Clinical Study Protocol

Study Intervention	Trastuzumab deruxtecan (T-DXd, AZD4552)
Study Code	D967RC00001
Version	5.0
Date	15 April 2024

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)

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s):

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

Protocol Number: D967RC00001

Amendment Number: 4

Study Intervention: Trastuzumab deruxtecan (T-DXd)

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

Study Phase: Phase 3

Short Title: Phase 3 neoadjuvant study of T-DXd or T-DXd followed by THP compared to ddAC-THP in participants with high-risk HER2+ early-stage breast cancer

Acronym: DESTINY-Breast11

Study Physician Name and Contact Information will be provided separately

International Co-ordinating Investigator

Prof. Dr. Nadia Harbeck

Director Breast Center

LMU Klinikum München

Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe

Marchioninistraße 15

81377 München

Germany

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 4	*15-April-2024*
Amendment 3	*28-July-2023*
Amendment 2	*15-July-2022*
Amendment 1	*05-August-2021*
Original Protocol	*14-Jun-2021*

Amendment [4] (15-April-2024)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

CCI [redacted]

Other minor changes were made to align with product specific safety requirements and to correct errors.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
CCI [redacted]			
Section 1.3 - Schedule of Activities	• Ophthalmologic assessments to be done at end of treatment visit • Troponin to be taken as clinically indicated	To align with product specific safety requirements	Non-substantial
Section 1.3 - Schedule of Activities	Concomitant medications to be collected up to safety follow-up visit	To align with Section 6.5	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
CCI			
Section 8.3.1 - Time Period and Frequency for Collecting AE and SAE Information	Description of SUSAR reporting in the EU	To comply with EU CTR	Non-substantial
CCI			
Appendix I 2 - Restricted, Prohibited, and Permitted Concomitant Medications/Therapies	Removal of hormone replacement therapy from allowed usage column of restricted medications table	Correction to align with rest of protocol, which correctly states that hormone replacement therapy is prohibited	Non-substantial
Appendix J 1 - Eligibility, Concomitant Medication, T-DXd Dose Modification and PK Sampling Text Relevant to COVID-19	Update of dose modification criteria for participants with confirmed or suspected COVID-19	To align with product specific safety requirements	Non-substantial

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3
TABLE OF CONTENTS 5
LIST OF FIGURES 9
LIST OF TABLES 9
1 PROTOCOL SUMMARY 11
1.1 Synopsis 11
1.2 Schema 16
1.3 Schedule of Activities 16
2 INTRODUCTION 35
2.1 Study Rationale 35
2.2 Background 35
2.2.1 Background on the Disease to be Treated 36
2.2.2 HER2-positive Early Breast Cancer 37
2.3 Benefit/Risk Assessment 38
2.3.1 Risk Assessment 38
2.3.1.1 Potential Risks of Clinical Significance for T-DXd 38
2.3.1.2 Potential Risks of HER2-targeted Agents 40
2.3.1.3 Potential Risks of Topoisomerase I Inhibitors 41
2.3.1.4 Potential Risks of T-DXd Followed by THP 41
2.3.2 Benefit Assessment 42
2.3.2.1 Potential Benefits of T-DXd in HER2-positive Breast Cancer 42
2.3.2.2 Potential Benefits of T-DXd Followed by THP in HER2 Positive Breast Cancer 43
2.3.3 Overall Benefit: Risk Conclusion 44
3 OBJECTIVES AND ENDPOINTS 45
4 STUDY DESIGN 49
4.1 Overall Design 49
4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis 50
4.2 Scientific Rationale for Study Design 51
4.2.1 Rationale for Study Design 51
4.2.2 Rationale for Participant Population 51
4.2.3 CCI 52
4.2.4 Rationale for ddAC-THP as Control Arm 52
4.2.5 Rationale for T-DXd Monotherapy Treatment Arm 52
4.2.6 Rationale for T-DXd followed by THP Treatment Arm 52
4.3 Justification for Dose 52
4.3.1 T-DXd Dose Rationale 52
4.3.2 Paclitaxel Dose Rationale 53

4.3.3 Trastuzumab Dose Rationale 53
4.3.4 Pertuzumab Dose Rationale 53
4.4 End of Study Definition 53
5 STUDY POPULATION 54
5.1 Inclusion Criteria 54
5.2 Exclusion Criteria 57
5.3 Lifestyle Considerations 60
5.3.1 Tobacco 60
5.4 Screen Failures 60
6 STUDY INTERVENTION 61
6.1 Study Intervention(s) Administered 61
6.1.1 Investigational Products 61
6.2 Preparation/Handling/Storage/Accountability of Interventions 66
6.2.1 T-DXd Preparation, Administration and Storage 66
6.3 Measures to Minimise Bias: Randomisation and Blinding 68
6.3.1 Participant Enrolment and Randomisation 68
6.3.2 Procedures for Handling Incorrectly Randomised Participants 69
6.3.3 Methods for Assigning Treatment Groups (Randomisation) 70
6.3.4 Methods for Ensuring Blinding 70
6.4 Study Intervention Compliance 70
6.5 Concomitant Therapy 71
6.6 Dose Modification 72
6.6.1 T-DXd Dose Modification 72
6.6.2 THP (Arm B) 74
6.6.3 ddAC-THP (Arm C) 74
6.6.4 Dose Modification of a Component or Entire Regimen 74
6.7 Intervention after the End of the Study 75
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 75
7.1 Discontinuation of Study Intervention 75
7.1.1 Procedures for Premature Discontinuation of Study Treatment 77
7.1.2 Dose Discontinuation of a Component or Entire Regimen 77
7.1.3 Follow-up of Participants Post Discontinuation of Study Intervention 78
7.1.4 Follow-up for Recurrence and Survival 79
7.2 Participant Withdrawal from the Study 79
7.3 Lost to Follow-up 80
8 STUDY ASSESSMENTS AND PROCEDURES 81
8.1 Efficacy Assessments 82
8.1.1 Surgical Specimen Assessments 82
8.1.2 Surgical Assessments 84
8.1.3 Central Reading of Scans 84

8.1.3.1 Baseline Disease Staging 85
8.1.3.2 Ultrasound of the Breast and Axilla 85
8.1.3.3 Breast MRI 85
8.1.3.4 Bilateral Mammogram 85
8.1.4 Disease Follow-up and Confirmation of Disease Progression or Recurrence 86
8.1.5 Overall Survival 89
8.1.6 Determination of Menopausal Status 89
8.1.7 Clinical Outcome Assessments 89
8.1.7.1 EORTC QLQ-C30 93
8.1.7.2 PRO-CTCAE 93
8.1.7.3 PGI-TT 94
8.1.7.4 EORTC Item Library Short Forms 94
8.1.7.5 CCI 95
8.1.7.6 Administration of Electronic PRO (ePRO) Questionnaires 95
8.2 Safety Assessments 97
8.2.1 Physical Examinations 97
8.2.2 Vital Signs 98
8.2.3 Electrocardiograms 99
8.2.4 Clinical Safety Laboratory Assessments 99
8.2.5 Other Safety Assessments 101
8.2.5.1 Echocardiogram/Multigated Acquisition Scan 101
8.2.5.2 Pulmonary Assessments 102
8.2.5.3 CCI 103
8.2.5.4 ECOG Performance Status 104
8.2.5.5 Ophthalmologic Assessments 105
8.3 Adverse Events and Serious Adverse Events 105
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 105
8.3.2 Follow-up of AEs and SAEs 106
8.3.3 Causality Collection 107
8.3.4 Adverse Events Based on Signs and Symptoms 107
8.3.5 Adverse Events Based on Examinations and Tests 108
8.3.6 Heart Failure 108
8.3.7 Hy's Law 109
8.3.8 Disease Progression 109
8.3.9 Disease Recurrence 109
8.3.10 Disease Under Study 109
8.3.11 New Cancers 110
8.3.12 Deaths 110
8.3.13 Adverse Events of Special Interest 110
8.3.14 Safety Data to be Collected Following the Final Data Cut-off of the Study 111
8.3.15 Reporting of Serious Adverse Events 111
8.3.16 Pregnancy 112
8.3.16.1 Maternal Exposure 113
8.3.16.2 Paternal Exposure 113
8.3.17 Medication Error, Drug Abuse, and Drug Misuse 114
8.3.17.1 Timelines 114

8.3.17.2 Medication Error 114
8.3.17.3 Drug Abuse 114
8.3.17.4 Drug Misuse 114
8.4 Overdose 115
8.5 Human Biological Samples 115
8.5.1 Pharmacokinetics 116
8.5.1.1 Determination of Drug Concentration 116
8.5.2 Immunogenicity Assessments 116
8.5.3 Pharmacodynamics 117
8.5.4 Surgical Specimen Collection 117
8.6 Human Biological Sample Biomarkers 117
8.6.1 Collection of Mandatory Samples for Biomarker Analysis 117
8.6.2 Collection of Optional Biomarker Samples 120
8.6.3 Other Study-Related Biomarker Assessments 121
8.7 Optional Genomics Initiative Sample 121
8.8 Medical Resource Utilisation and Health Economics 122
9 STATISTICAL CONSIDERATIONS 122
9.1 Statistical Hypotheses 122
9.2 Sample Size Determination 123
9.3 Populations for Analyses 124
9.4 Statistical Analyses 125
9.4.1 General Considerations 125
9.4.2 Efficacy 127
9.4.2.1 Primary Endpoints (pCR) 127
9.4.2.2 Secondary Endpoint(s) 128
9.4.2.3 Tertiary/Exploratory Endpoints 130
9.4.3 Safety 131
9.4.4 Other Analyses 133
9.4.4.1 Clinical Outcome Assessments 133
9.4.4.2 Medical Resource Utilisation and Health Economics 134
9.4.4.3 Pharmacokinetics 134
9.4.4.4 Biomarkers 135
9.4.4.5 Immunogenicity Data 135
9.4.4.6 Residual Cancer Burden 135
9.5 Futility Analysis 135
9.6 Data Monitoring Committee 136
9.6.1 IDMC 136
9.6.2 ILD Adjudication Committee 137
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 138
11 REFERENCES 238

LIST OF FIGURES

Figure 1 Study Design 16
Figure 2 Dosing Schedule 65
Figure 3 CCI 123

LIST OF TABLES

Table 1 Schedule of Activities 18
Table 2 Objectives and Endpoints 45
Table 3 Parameters for Adequate Organ and Bone Marrow Function 55
Table 4 Investigational Products 62
Table 5 Dose Reduction Levels of T-DXd 72
Table 6 Definition and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Event at Follow-up 87
Table 7 Patient-reported Outcome Schedule of Activities during Neoadjuvant Treatment 91
Table 8 Patient-reported Outcome Schedule of Activities Post-Surgery 92
Table 9 Laboratory Safety Variables 100
Table 10 Spirometry Component 102
Table 11 New York Heart Association (NYHA) Functional Classification 109
Table 12 Populations for Analysis 124
Table 13 Summary of Outcome Variables and Analysis Populations 126
Table 14 Definitions of Responders vs Non-responders for pCR Assessments 127
Table 15 Summary of Imaging Modalities for Tumour Assessment 165
Table 16 RECIST 1.1 Evaluation of Target Lesions 172
Table 17 RECIST 1.1 Evaluation of Non-Target Lesions 173
Table 18 RECIST 1.1 Overall Visit Response 174
Table 19 Highly Effective Methods of Contraception (<1% Failure Rate) 179
Table 20 Restricted medications/therapies 194
Table 21 Prohibited medications/therapies 194
Table 22 Supportive medications/therapies 196
Table 23 Toxicity Management Guidelines for T-DXd 204

LIST OF APPENDICES

Appendix A Regulatory, Ethical, and Study Oversight Considerations 139
Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 148
Appendix C Handling of Human Biological Samples 154
Appendix D Optional Genomics Initiative Sample 157
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 160
Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours) 165
Appendix G Contraception Requirements 177
Appendix H Patient-reported Outcomes 180
Appendix I Concomitant Medications 193
Appendix J Instructions Related to SARS-COV-2 Infection 197
Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis 201
Appendix L Guidance for Management of Participants with Drug-Induced ILD/Pneumonitis 203
Appendix M Toxicity Management Guidelines 204
Appendix N ASCO/CAP Guidelines on HER2 Testing in Breast Cancer 211
Appendix O Protocol Amendment History 214
Appendix P Abbreviations 230
Appendix Q Country-specific Requirements 237

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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)

Short Title: Phase 3 neoadjuvant study of T-DXd or T-DXd followed by THP versus ddAC-THP in participants with early-stage high-risk HER2+ breast cancer

Rationale:

Current SOC for neoadjuvant treatment of HER2-positive EBC consists of dual HER2 targeted therapy with trastuzumab plus pertuzumab concurrently or in sequence with polychemotherapy, representing a heavy treatment burden of 4 to 5 different agents. These multi-agent regimens expose participants to short- and long-term toxicities, while a significant subset of participants still experience relapse and death. Furthermore, earlier neoadjuvant studies have demonstrated that participants with positive lymph nodes or with advanced primary tumours (T stage ≥ T3), as well as those with inflammatory breast cancer, have lower rates of pCR, demonstrating these characteristics classify participants as high-risk.

Replacing SOC with T-DXd or displacing anthracyclines with T-DXd followed by THP could reduce both the treatment burden and potentially the overall short- and long-term toxicities (such as cardiotoxicity, AML, and neuropathy) experienced by participants, while improving outcomes for participants who are not benefiting from the current SOC. In this Phase 3 study, the efficacy (pCR) of T-DXd monotherapy or T-DXd followed by THP will be compared to SOC, ddAC-THP, in participants with high-risk (T stage ≥ T3, node positive, or inflammatory) HER2-positive EBC.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• **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.

Objectives	Endpoints
Secondary	
• **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) following completion of neoadjuvant therapy.
• **EFS, IDFS, and 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.
• 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

Objectives	Endpoints
	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).

ADA = anti-drug antibody; AE = adverse event; ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; EBC = early breast cancer; ECG = electrocardiogram; ECHO = echocardiogram; EFS = event-free survival; EORTC = European Organization for the Research and Treatment of Cancer; HER2 = human epidermal growth factor receptor 2; H&E = hematoxylin & eosin; IDFS = invasive disease-free survival; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NYHA = New York Heart Association; 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; SAE = serious adverse event; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab; 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.

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

Overall Design

Disclosure Statement:

This is a Phase 3, randomised, multicentre, open-label, 3-arm study to determine the efficacy and safety of T-DXd monotherapy or T-DXd followed by THP compared with ddAC-THP in participants with high-risk HER2-positive EBC.

Participant Population:

The target population of interest in this study is participants with high-risk (T stage ≥ T3, node positive, or inflammatory) HER2-positive EBC.

Number of Participants:

Approximately CCI participants will be screened to achieve 900 randomised participants with HER2-positive EBC for the assessments of pCR.

See Section 9 for Statistical Considerations and Section 9.2 for Sample Size Determination.

Note: Potential participants who are screened for the purpose of determining eligibility for the

study but are not randomly assigned in the study are considered "screen failures", unless otherwise specified in the CSP.

Intervention Groups and Duration:

Participants will be randomised in a 1:1:1 ratio to one of the following intervention groups: T-DXd monotherapy (Arm A), T-DXd followed by THP (Arm B), or ddAC-THP (Arm C).

CCI

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 IHC3+ status).

Participants in Arm A will receive T-DXd (5.4 mg/kg IV Q3W) for 8 cycles.

Participants in Arm B will receive T-DXd (5.4 mg/kg IV Q3W) for 4 cycles, followed by paclitaxel (80 mg/m^2 IV QW on Days 1, 8, and 15) concurrent with trastuzumab (6 mg/kg IV Q3W on Day 1), and pertuzumab (840 mg IV loading dose followed by 420 mg IV Q3W on Day 1) for 4 cycles.

Participants in Arm C will receive doxorubicin (60 mg/m^2 Q2W) and cyclophosphamide (600 mg/m^2 IV Q2W) for 4 cycles, followed by paclitaxel (80 mg/m^2 IV QW on Days 1, 8, and 15) concurrent with trastuzumab (8 mg/kg IV loading dose followed by 6 mg/kg IV Q3W on Day 1), and pertuzumab (840 mg IV loading dose followed by 420 mg IV Q3W on Day 1) for 4 cycles.

Participants should continue treatment until 8 cycles of intervention have been completed or an intervention discontinuation criterion is met.

Follow-up of Participants Post Discontinuation of Study Treatment:

After the last dose of study treatment, assessments for survival and recurrence will be made every 3 months (± 28 days) for the first 3 years. For years 4 to 6 after the last dose of study treatment, follow-up visits will take place every 6 months (± 28 days) until study completion. Participants who discontinue due to disease progression during the neoadjuvant treatment phase will receive subsequent therapy per investigator discretion. Any participant who receives non-protocol therapy prior to surgery will be discontinued from study treatment and

will be managed per local practice.

See Section 6.7 for a description of assessments following study DCOs.

Data Monitoring Committees:

An IDMC comprised of independent experts will be convened to review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety or futility findings. Specific data listings pertinent to the ability of the participant to undergo surgery and complete neoadjuvant study treatment will be provided to the IDMC for their consideration in making recommendations regarding study conduct.

A futility analysis is planned when approximately CCI participants ([redacted]% of the intended population) are treated and have had the opportunity to be assessed for pCR or have discontinued or withdrawn from treatment. The IDMC will review unblinded study data and inform the study sponsor, AstraZeneca, as to whether the interim boundaries specified in Section 9.5 are met. Efficacy data will be made available to the IDMC upon request to evaluate the benefit-risk to participants. Full details of the IDMC procedures and processes will be defined in the IDMC Charter.

ILD Adjudication Committee:

An ILD Adjudication Committee comprising independent expert clinicians will be established to review all cases of potential ILD/pneumonitis. Further information can be found in Section 9.6.

Statistical Methods

The study will randomise approximately 900 participants (1:1:1) to 3 arms: T-DXd monotherapy (Arm A), T-DXd followed by THP (Arm B), or ddAC-THP (Arm C). The primary objective of this study is to assess the efficacy of T-DXd alone or in sequence with THP relative to ddAC-THP in terms of the rate of pCR. Assuming recruitment over [redacted] months, the data cut-off for the futility analysis is anticipated approximately [redacted] months after the first participant is randomised. The data cut-off for the primary analysis for pCR is anticipated approximately 39 months after the first participant is randomised, when all the participants have had the opportunity to be assessed for pCR. The participants will be followed for long-term benefit data. The last analysis intended for 3-year EFS will be performed when all participants have had the opportunity to be followed for 3 years, or have discontinued or withdrawn from the study.

To strongly control the overall type I error at the 2-sided [redacted]% level, the primary endpoints of improved pCR rate with either T-DXd monotherapy or T-DXd in sequence with THP will be tested simultaneously with split alpha values. A significance level of [redacted]% will be used for the

comparison between Arms B and C and a significance level of CCI % will be used for the comparison between Arms A and C. Assuming a CCI % pCR rate in Arm C, the critical values in terms of the differences of pCR rates are CCI % and CCI %, respectively, at the initial alpha levels for Arms A and B, respectively. The spent alpha values can be recycled between successfully rejected tests of pCR. Assuming CCI % of pCR in Arm C and CCI % improvement with either active treatment, the primary analysis will provide at least CCI % power to demonstrate statistical significance regarding difference in pCR rates at an overall CCI % alpha level (2-sided test) for the dual primary endpoint.

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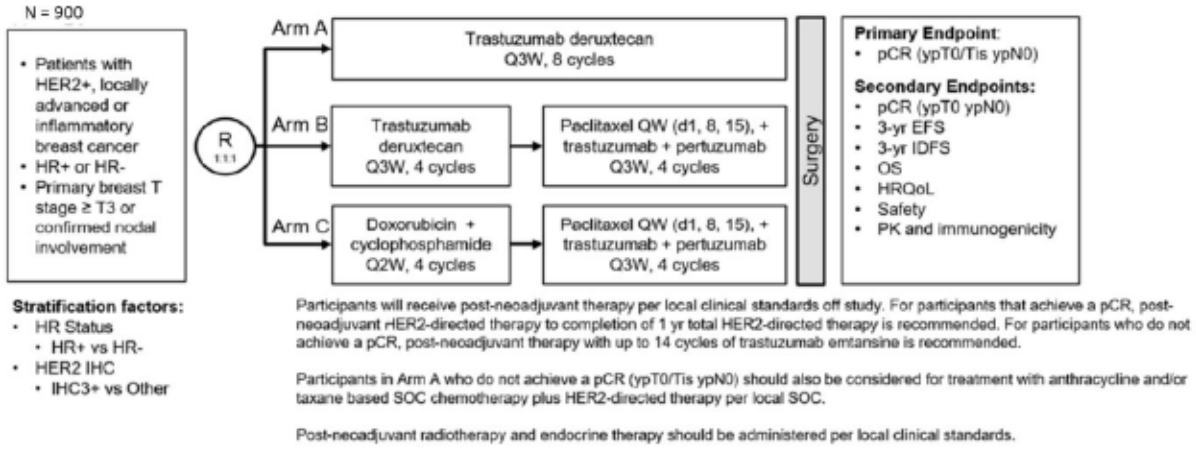
The sample size and the power of the study, for the analysis of pCR, were calculated using EAST 6.5.

1.2 Schema

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.

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1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Section 1.3).

Whenever vital signs and blood draws are scheduled for the same nominal time, the vital signs assessments should occur first. Whenever ECGs, vital signs, and blood draws are scheduled

for the same nominal time, ECG assessments should occur first, then vital signs assessments, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoA.

Unless all eligibility criteria have been met, participants must not be randomised and must not be treated. When participants do not receive study treatment, participants should undergo a physical examination and vital signs assessment with additional assessments at the discretion of the investigator. All samples are to be collected before infusion unless otherwise indicated.

Participants will be enrolled into the study after signing the main ICF and will begin screening/baseline procedures. Screening will take place for up to 28 days from the date of enrolment. At the end of screening/baseline procedures, participants who pass the eligibility criteria will be randomised. Every effort should be made to minimise the time between randomisation and dosing. Dosing should occur no more than 3 calendar days after treatment assignment. If it is anticipated that dosing cannot occur within 3 calendar days, a discussion with the AstraZeneca Study Physician is required. Participants who fail to meet the eligibility criteria will be termed "screen failures".

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Informed consent: main study	X													Section 6.3.1 and Appendix A
Informed consent: genetic sample and analysis (optional)	X												The sample for genetic testing will not be collected in China.	Section 6.3.1 and Appendix A
Study Procedures and Assessments														
Inclusion and exclusion criteria	X												Re-check clinical status before randomisation and/or first dose of study intervention.	Sections 5.1 and 5.2
Randomisation		X											Dosing should start within 3 days.	Section 6.3
Demography	X													Section 8
Full physical examination	X													Section 8.2.1

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Targeted physical examination		X	X	X	X	X			X	X	X	X	Within 3 days before dosing administration. Must include breast exam and tumour palpation.	Section 8.2.1
Height	X													Section 8.2.1
Weight	X	X	X	X	X	X			X		X		During intervention period, within 3 days before dosing administration.	Section 8.2.1
Medical history (includes substance usage and family history of premature CV disease)	X													Sections 5.1 and 5.2
ECOG performance status	X	X	X	X	X	X			X	X	X		During intervention period, within 3 days of dosing administration.	Section 8.2.5.4

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
12-lead ECG	X	X				X			X				ECGs will be performed in triplicate at screening and in triplicate subsequently only if an abnormality is noted. During C5-8, ECGs will be performed on C5D1 only.	Section 8.2.3
ECHO/MUGA (LVEF)	X					X			X				During screening, within 28 days prior to randomisation. During intervention period, within 3 days before C5D1 infusion. Note: In Germany, LVEF will be measured only by ECHO (see Appendix Q).	Section 8.2.5.1
Vital signs	X	X	X	X	X	X	X	X	X		X		During intervention period, within 3 days before infusion.	Section 8.2.2
SpO2	X	X	X	X	X	X	X	X	X		X		During intervention period, within 3 days before infusion.	Section 8.2.5.2

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Pulmonary function tests	X												During intervention period, if ILD/pneumonitis is suspected.	Section 8.2.5.2
ILD/pneumonitis investigation		If ILD/pneumonitis is suspected.												Section 8.2.5.3
Ophthalmologic assessments	X	As clinically indicated												Section 8.2.5.5
AE	At every clinic visit.												May be conducted by phone if not tied to a visit.	Section 8.3
Heart failure	Will be collected until the end of long-term follow-up.													Section 8.3.6
Concomitant medication	X	At every visit during treatment period and may be conducted by phone if not tied to a visit.												Section 6.5
Subsequent anticancer therapy (including surgery and radiation)									X		X	X		Section 4.1
Laboratory Assessments														
Serum/urine pregnancy test (WOCBP only)	X	X	X	X	X	X			X		X			Sections 5.1, 5.2, and 8.2.4

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Menopausal status assessments (including FSH, LH, and oestradiol); menstruation status	X								X		X	X	During long-term FU, assessments will be performed annually during years 1-3. For participants who are postmenopausal, at baseline only.	Section 8.1.6
Hepatitis B and C screening	X													Section 5.2
Clinical safety laboratory assessments (clinical chemistry, haematology)	X	X	X	X	X	X	X	X	X	X	X		If taken within 3 days before administration do not repeat at C1D1. In Arms B and C, laboratory assessments should be performed before every weekly taxane. For subsequent cycles after C1, can be done within 1 day prior to treatment administration.	Section 8.2.4
Coagulation	X									X			As clinically indicated.	Section 8.2.4

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Urinalysis	X									X			During intervention period, as clinically indicated.	Section 8.2.4
Troponin	X	As clinically indicated											To be taken if at any time a participant reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis.	Sections 8.2.4 and 8.2.5.1
Mandatory screening tumour sample for central HER2 confirmation and biomarker analysis	X												Two cores obtained CCI [redacted], to be provided as FFPE block(s) if possible, or 20 freshly-cut sections.	Section 8.6
CCI [redacted]														Section 8.6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
CCI	CCI												CCI	Section 8.6
CCI													Note: This blood sample will not be collected in China.	Section 8.6
CCI													Note: This blood sample will not be collected in China.	Section 8.6
CCI													Note: This blood sample will not be collected in China.	Section 8.6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
CCI	CCI												CCI Note: This blood sample will not be collected in China.	Section 8.6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
CCI	CCI												CCI Note: This blood sample will not be collected in China.	Section 8.6
CCI													CCI Note: This blood sample will not be collected in China.	Section 8.6
CCI													CCI Note: This blood sample will not be collected in China.	Section 8.6
Pre-dose blood sample for T-DXd PK testing (within 8 hours before infusion)		X	X		X				X				For T-DXd participants only.	Section 8.5.1

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Post-dose blood sample for T-DXd PK testing (+ 15 minutes)		X	X		X								For T-DXd participants only.	Section 8.5.1
Pre-dose blood sample for immunogenicity testing (within 8 hours before infusion)		X	X		X								For T-DXd participants only.	Section 8.5.2
Genomics initiative optional, exploratory genetic blood sample	CCI [redacted]												CCI [redacted] Note: This blood sample will not be collected in China.	Section 8.7 and Appendix D
Treatments														
Arm A														
Arm A - T-DXd IV (5.4 mg/kg Q3W CCI [redacted]		X	X	X	X	X							C1 should be administered within 3 days of randomisation.	Section 6
Arm B														
Arm B - T-DXd IV (5.4 mg/kg Q3W)		X	X	X	X								C1 should be administered within 3 days of randomisation.	Section 6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Arm B – Paclitaxel IV (80 mg/m^2 QW)						X	X	X						Section 6
Arm B - Trastuzumab IV (6 mg/kg Q3W)						X								Section 6
Arm B - Pertuzumab IV (840 mg loading dose followed by 420 mg Q3W)						X								Section 6
Arm C														
Arm C - Doxorubicin IV (60 mg/m^2 Q2W)		X	X	X	X								C1 should be administered within 3-days of randomisation.	Section 6
Arm C - Cyclophosphamide IV (600 mg/m^2 Q2W)		X	X	X	X								C1 should be administered within 3 days of randomisation.	Section 6
Arm C – Paclitaxel IV (80 mg/m^2 QW)						X	X	X						Section 6
Arm C - Trastuzumab IV (8 mg/kg loading dose followed by 6 mg/kg Q3W)						X								Section 6

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Arm C - Pertuzumab IV (840 mg loading dose followed by 420 mg Q3W)						X								Section 6
Definitive surgery										X			Participants should undergo surgery [redacted] following administration of the last cycle of treatment of the assigned neoadjuvant regimen.	Section 8.1.2
Imaging and Efficacy Assessments														
Ultrasound of the breast and axilla	X												Within 42 days prior to randomisation.	Section 8.1.3.2
Chest HRCT	X	Scans to be performed Q6W (at least 35 days, but not more than 42 days from previous scan) until EoT and if ILD/pneumonitis suspected.									X			Section 8.2.5.2
Breast MRI (RECIST 1.1 assessments)	X					X			X				During intervention period only before C5D1.	Section 8.1.3.3

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Bilateral mammogram	X											X	During screening, obtained any time between diagnosis and randomisation. During long-term FU, at 6 months post-surgery, then every 12 months up to 6 years, or until patient has recurrence or metastatic disease.	Section 8.1.3.4
Bone scan	X												Can be performed within 42 days prior to randomisation. After screening visit, as clinically indicated. PET/CT may be used as an alternative imaging technique and precludes the need for bone scan.	Section 8.1.3.1

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
CT or MRI chest, abdomen, pelvis	X												With IV contrast for CT. After screening visit, as clinically indicated. Can be performed within 42 days prior to randomisation.	Section 8.1.3.1
pCR assessment										X				Section 8.1.1
Surgical treatment plan	X								X				The participant should be evaluated for surgical treatment at baseline and the proposed surgical plan recorded in the eCRF. After completion of neoadjuvant treatment, the participant should be re-evaluated and the proposed surgical plan should be prospectively recorded.	Section 8.1.2

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[c]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Survival status									X		X	X	Every 3 months (± 28 days) for the first 3 years. For years 4 to 6 after the last dose of study treatment, follow-up visits will take place every 6 months (± 28 days) until study completion.	Section 8.1.5
PRO measures	See Table 7 and Table 8 (Section 8.1.7)													

Procedure	Screening (up to 28 days before Day 1)	Intervention Period[a]							Surgical Period		Post-intervention Follow-up Period		Notes	Details in CSP Section or Appendix
		C1	C2	C3	C4	C5–C8			EoT or E/D[b]	Pre-surgery/ Definitive surgery	Safety FU: 40 days + 7 from last dose of study treatment[c]	Long-term FU[e]: Q3M years 1-3 Q6M years 4-6 post-surgery		
Cycle day number		1	1	1	1	1	8	15						
Visit window (±days)	-28 to -1		± 2	± 2	± 2	± 2	± 1[d]	± 1[d]				± 28 days		
Additional Information Collected														
Healthcare resource used	At each scheduled visit, the site should review clinical notes for any non-study-related hospital admissions and visits that have occurred.													Section 8.8

[a] In general, assessments/procedures are performed on Day 1 of each cycle prior to dosing of any study treatment (or prior to weekly dosing of paclitaxel) unless otherwise specified. Each treatment cycle is 3 weeks (21 days), except for the dose dense AC portion of treatment for Arm C where each cycle is 2 weeks (14 days). If the treatment is delayed, all procedures should be performed based on the new dosing schedule.

[b] The EoT visit should be performed after completion of study treatment. For participants that complete neoadjuvant therapy, the EoT visit should be combined with the pre-surgery visit which takes place within 14 days of surgery. For participants that discontinue all study treatment before completing all cycles, the early discontinuation visit should take place within 7 days of the decision to discontinue treatment. If the early discontinuation visit is > 40 days (+7 days) after the last dose of study treatment, then the EoT/early discontinuation visit may be combined with the safety FU visit.

[c] The safety FU visit should be conducted 40 days + 7 after administration of last dose of study treatment. For participants that complete neoadjuvant study treatment, this should take place after definitive surgery. For participants that discontinue all study treatment prior to completion of all planned cycles, the timing of the safety FU visit is based on last administration of study treatment and could be conducted prior to surgery.

[d] ± 1 refers to weekly taxane use. If not taxane, must be ±2 days. Participants in Arm A (T-DXd monotherapy) are not required to attend visits on Days 8 and 15 of Cycles 5-8.

[e] Timing of long-term FU visits should be based on the safety FU visit or the date of surgery, whichever occurs later.

[f] CCI [redacted]

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

AC = doxorubicin + cyclophosphamide; ADA = anti-drug antibody; AE = adverse event; C = cycle; CSP = Clinical Study Protocol; CT = computerised tomography; CCI CCI CV = cardiovascular; D = day; ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; CCI CCI ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; E/D = Early Study Discontinuation; EoT = End of Treatment; exam = examination; FFPE = formalin-fixed and paraffin-embedded; FSH = follicle-stimulating hormone; FU = follow-up; HER2 = human epidermal growth factor receptor 2; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IV=intravenous; LH = luteinising hormone; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; CCI pCR = pathological complete response; PET = positron emission tomography; PK = pharmacokinetic; PRO = patient-reported outcome; Q3M = every 3 months; Q6M = every 6 months; QW = weekly; Q2W = every 2 weeks; Q3W = every 3 week; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumours, Version 1.1; CCI SAE = serious adverse event; SpO2 = pulse oximetry; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab; WOCBP = women of childbearing potential.

2 INTRODUCTION

Trastuzumab deruxtecan is a HER2-targeting ADC in development as a candidate therapy for breast cancer and other HER2-expressing tumours. The non-proprietary name for T-DXd is trastuzumab deruxtecan except in the US where it is fam-trastuzumab deruxtecan-nxki.

2.1 Study Rationale

Current SOC for neoadjuvant treatment of HER2-positive EBC consists of dual HER2 targeted therapy with trastuzumab plus pertuzumab concurrently or in sequence with polychemotherapy, representing a heavy treatment burden of 4 to 5 different agents. These multi-agent regimens expose participants to short- and long-term toxicities, while a significant subset of participants still experience relapse and death. Furthermore, earlier neoadjuvant studies have demonstrated that participants with positive lymph nodes or with advanced primary tumours (T stage ≥ T3), as well as those with inflammatory breast cancer, have lower rates of pCR, demonstrating these characteristics classify participants as high-risk.

Replacing SOC with T-DXd or displacing anthracyclines with T-DXd could reduce both the treatment burden and potentially the overall short- and long-term toxicities (such as cardiotoxicity, AML, and neuropathy) experienced by participants, while improving outcomes for participants who are not benefiting from the current SOC. In this Phase 3 study, the efficacy (pCR) of T-DXd monotherapy or T-DXd followed by THP will be compared to SOC, ddAC-THP, in participants with high-risk (T stage ≥ T3, node positive, or inflammatory) HER2-positive EBC.

2.2 Background

As of 28 March 2019, AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo) entered into a joint global development and collaboration agreement for T-DXd, a HER2 targeting ADC that is being developed as a therapeutic candidate for HER2-expressing tumours.

T-DXd is a HER2-targeted antibody and topoisomerase I inhibitor conjugate. The anti-HER2 component (mAb) has the same amino acid sequence as trastuzumab and is specifically targeted to HER2-expressing cells. The released DXd is a topoisomerase I inhibitor derivative of exatecan that is approximately 10 times more potent than the inhibitor SN-38, the active metabolite of irinotecan (Ogitani et al 2016a). DXd is cell-membrane permeable, giving the ability to penetrate and act in surrounding cells (Ogitani et al 2016b).

The mAb is covalently conjugated to a drug-linker (deruxtecan) that is composed of a cleavable maleimide tetrapeptide linker and the released drug DXd (Ogitani et al 2016a, Shiose et al 2007, Nakada et al 2016). The tetrapeptide linker is designed to be stable in plasma to reduce systemic exposure to DXd (Ogitani et al 2016a, Nagai et al 2019).

T-DXd binds specifically to, and is internalised by, HER2-expressing cells, after which the linker is cleaved by lysosomal enzymes such as cathepsins B and L (Shiose et al 2007), which are overexpressed in cancer cells (Aggarwal et al 2014, Niedergethmann et al 2004, Mohamed and Sloane 2006). The drug DXd is then released and exerts cytotoxic activity by inhibiting the activity of topoisomerase I, leading to inhibition of cell proliferation and apoptosis of the target tumour cells.

The released drug DXd has, by design, a short systemic half-life, and its active chemical moiety in the lactone form is present and active in the acidic tumoural environment, whereas the chemical moiety in the hydroxyl-acid form present in the neutral systemic environment is mostly inactive. As a result of the drug-linker design and site-specific conjugation, the DAR for T-DXd is approximately 8 compared to a DAR of 3 to 4 for other ADCs such as T-DM1 (Ogitani et al 2016a).

The mechanism of action of T-DXd is biologically relevant regardless of the sequence of prior anti-HER2 therapies and therefore, meaningful clinical activity from T-DXd is expected in participants with heterogenous anti-HER2 treatment history.

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

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

2.2.1 Background on the Disease to be Treated

Breast cancer is the second most common cancer in the world and the most frequent cancer in women with an estimated 2.2 million new cases globally in 2020 (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer with an estimated 685,000 deaths in 2020. In the US, approximately 1 in 8 women will be diagnosed with invasive breast cancer in their lifetime with 1 in 39 dying from it. According to 2020 estimates, over 276,000 women in the US were diagnosed with breast cancer and over 42,000 died from the disease (Breast Cancer Facts & Figures 2019-2020) while in Europe, over 531,000 patients were diagnosed with breast cancer and over 141,000 patients died from the disease (Globocan 2020). Breast cancer is most commonly diagnosed at the early-stage (63%) followed by locally advanced (30%) and metastatic disease (6%). Despite advances in treatment, up to 30% of women with early-stage non-metastatic breast cancer will develop distant metastatic disease (O'Shaughnessy 2005). Although treatable, MBC remains a virtually incurable disease with an estimated 5-year OS of only 25% (Cardoso et al 2018).

2.2.2 HER2-positive Early Breast Cancer

HER2-positive breast cancer, defined by amplification of the HER2 gene and/or overexpression at the protein level, comprises approximately 20% of all breast cancers (Arteaga et al 2011). The first HER2-targeted mAb, trastuzumab, which is approved for both the advanced (Slamon 2001) and early disease (Piccart-Gebhart et al 2005) settings, changed the natural history of the disease, significantly improving clinical outcomes.

In the EBC setting, adjuvant trastuzumab following chemotherapy reduced the risk of recurrence by 46% (hazard ratio = 0.54) with an absolute improvement in 2-year DFS of 8.4% compared to placebo (Piccart-Gebhart et al 2005). For operable EBC, the timing of systemic therapy before or after surgery has no effect on long-term outcomes (Gianni et al 2009, Rastogi et al 2008, Sikov et al 2015, von Minckwitz et al 2014); however, neoadjuvant treatment provides an opportunity to assess response to therapy via clinical assessment and pCR at time of surgery, which is of important prognostic value and can guide choice of therapy after surgery (Cortazar et al 2012). Furthermore, neoadjuvant treatment can lead to downstaging, which minimises the extent of surgery required, reducing the need for both mastectomy and ALND and its associated morbidities like lymphedema (Krag et al 2010).

The benefit of dual HER2 targeted therapy in EBC was initially demonstrated in the neoadjuvant NEOSPHERE trial where the addition of pertuzumab to trastuzumab plus docetaxel improved the rate of pCR from 21.5% to 39.3% (Gianni et al 2012). Later, the TRYPHAENA trial demonstrated that the benefit of dual HER2 targeted therapy with pertuzumab and trastuzumab was consistent when given with anthracycline-containing or anthracycline-free standard chemotherapy regimens, reporting pCR rates of 56.2% when combined with FEC (5-fluorouracil, epirubicin and cyclophosphamide), 54.6% when given sequentially after FEC, and 63.6% when given in combination regimens containing a taxane and a platinum agent (Schneeweiss et al 2013).

The long-term benefit of trastuzumab and pertuzumab concurrent with or in sequence with polychemotherapy was confirmed by the adjuvant APHINITY trial, which demonstrated an improvement in IDFS with chemotherapy (either anthracycline-based or combination regimens containing a taxane and a platinum agent) plus 1 year of trastuzumab plus pertuzumab compared to trastuzumab plus placebo (hazard ratio = 0.81) (von Minckwitz et al 2017). The absolute improvement in 3-year IDFS was 94.1% vs 93.2% for the combination vs trastuzumab in the ITT population, and 92.0% vs 90.2% in the cohort of participants with node positive disease (hazard ratio = 0.77).

The ability to tailor therapy post-surgery to improve long-term outcomes for participants with poor response to neoadjuvant therapy is a benefit that was only recently identified by conducting randomised trials in participants with residual disease at the time of surgery (Voort et al 2020). The benefit of treatment intensification with T-DM1 for participants that do

not achieve a pCR with neoadjuvant treatment was demonstrated in the KATHERINE trial which reported a hazard ratio of 0.50 and absolute improvement in 3-year EFS of 88.3% vs 77% (von Minckwitz et al 2014, von Minckwitz et al 2017, and von Minckwitz et al 2019). Therefore, post-neoadjuvant treatment with T-DM1 can help rescue participants that did not achieve a pCR, providing similar long-term outcomes to those seen in participants that achieve a pCR and receive post-neoadjuvant treatment with trastuzumab. The opportunity to rescue participants in the post-neoadjuvant setting has led to interest in de-escalation approaches that use regimens, such as THP, in the neoadjuvant setting to reduce the treatment burden. If pCR is not achieved, participants with residual disease can have treatment with T-DM1 or other agents in the post-neoadjuvant setting (File et al 2020).

While the add-on approach has led to great improvement in treatment outcomes for participants with HER2-positive EBC, these multi-agent treatment regimens expose participants to an ever-increasing treatment burden including both short- and long-term toxicities, while a significant subset of patients still experience relapse and death. The current treatment landscape would benefit from an option with an acceptable safety profile that reduces the overall treatment burden in the neoadjuvant setting while improving pCR rates and thus reducing the need for treatment intensification in the post-neoadjuvant setting.

2.3 Benefit/Risk Assessment

The potential risks of T-DXd and other HER2-targeting agents, as well as topoisomerase I inhibitors are provided in Sections 2.3.1.1, 2.3.1.2, and 2.3.1.3. Section 2.3.2 provides an assessment of the potential benefits that are associated with T-DXd.

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

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP guidelines and applicable regulatory requirements.

2.3.1 Risk Assessment

2.3.1.1 Potential Risks of Clinical Significance for T-DXd

Interstitial lung disease/pneumonitis and neutropenia, including febrile neutropenia, are considered important identified risks associated with administration of T-DXd. Left ventricular decrease and embryo-foetal toxicity are also considered important potential risks for T-DXd. Keratitis is considered a potential risk for T-DXd.

Other identified risks for T-DXd are infusion-related reactions, haematological AEs (anaemia, leukopenia, lymphopenia, thrombocytopenia), pulmonary/respiratory AEs (cough, dyspnoea, upper respiratory tract infection, epistaxis), gastrointestinal AEs (abdominal pain,

constipation, diarrhoea, dyspepsia, nausea, stomatitis, vomiting), hepatic AEs (hepatic function abnormality, ALT, AST, alkaline phosphatase and blood bilirubin increased), skin AEs (alopecia, rash, pruritis), pneumonia, dry eye, dehydration, hypokalaemia, decreased appetite, asthenia, dizziness, fatigue, malaise, peripheral oedema, and headache.

T-DXd has not been studied in subjects with severe/moderate hepatic impairment. Any patient could be at risk for ILD/pneumonitis, but a higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment at baseline. Patients with moderate renal impairment should be monitored carefully.

Summary of Data/Rationale for Risk

Based on the available pre-clinical data, review of the cumulative literature, and reported toxicities for the same class of agents, the important potential risks for T-DXd are LVEF decrease (re-labelled as 'Left ventricular dysfunction as the undesirable clinical outcome of LVEF reductions', in accordance with the Revision 2 of the EMA guidelines on Good Pharmacovigilance Practice [EMA GVP guidelines, Module V]). This re-labelling of the risk does not affect the nature or monitoring methods of the LVEF decrease as a potential risk associated with T-DXd and embryo-foetal toxicity.

T-DXd has demonstrated a generally acceptable safety profile in late-line MBC participants. In the DESTINY-Breast01 study, participants had received a median of 6 prior lines of treatments. The most common AEs of CTCAE Grade 3 or higher that occurred in more than 5% of the participants were decreased neutrophil count (20.7%), anaemia (8.7%), nausea (7.6%), decreased white blood-cell count (6.5%), decreased lymphocyte count (6.5%), and fatigue (6.0%). Twenty-eight participants (15.2%) discontinued treatment because of an AE (Modi et al 2020a). The risks associated with T-DXd have been communicated in the IB and appropriate risk minimisation measures are in place, and exploration of the safety of T-DXd in a larger set of earlier-line participants is warranted.

Mitigation Strategy

Specific inclusion/exclusion criteria (Section 5) and monitoring/management guidelines (Appendix M) are currently in place to mitigate the important identified risks of ILD/pneumonitis and neutropenia, including febrile neutropenia, and important potential risks of LVEF decrease and embryo-foetal toxicity.

Education about ILD/pneumonitis is to be re-emphasized in patients with moderate renal impairment. Physicians should consider more frequent patient contact in between visits (at least once in between cycles) in order to reinforce ILD/pneumonitis education and the importance of prompt reporting of symptoms, until the investigator is confident the patient is familiar with the requirements.

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

These identified and potential risks are generally manageable through dose modification (Section 6.6) and routine clinical practice.

2.3.1.2 Potential Risks of HER2-targeted Agents

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

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

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

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

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

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

Refer to Appendix M for T-DXd TMGs. Refer to local prescribing information or local practice guidelines for TMGs relating to the other treatments in this study.

2.3.1.3 Potential Risks of Topoisomerase I Inhibitors

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

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

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

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

2.3.1.4 Potential Risks of T-DXd Followed by THP

In Arm B of this study, patients will be treated with T-DXd for 4 cycles followed by THP for 4 cycles and thus may be exposed to the risks posed by both portions of that regimen.

THP is generally well tolerated relative to trastuzumab combined with a taxane (TH) and is associated with mild increases in the frequency of select side effects. In the randomised, double-blind, placebo-controlled Phase 3 CLEOPATRA trial (Baselga et al 2012), comparing TH to THP in 1L metastatic HER2-positive breast cancer, THP has been shown to increase the incidence of any grade diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin by at least 5 percentage points. The incidence of Grade 3 or higher neutropenia and

diarrhoea were higher by at least 2 percentage points.

While targeting the same HER2 pathway, THP does not seem to add significant cardiac toxicity compared to TH. The CLEOPATRA trial reported any grade left ventricular systolic dysfunction at higher rates in the TH arm compared to the THP arm (8.3% vs 4.4%). Similarly, left ventricular systolic dysfunction of Grade 3 or higher was reported in 2.8% of patients in the TH arm and 1.2% in the THP arm.

In HER2-positive EBC, THP has a similar safety profile to TH. In the Phase 2 neoadjuvant NEOSPHERE trial (Gianni et al 2012), the most frequently occurring AEs were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash, and mucosal inflammation. Most AEs were of Grades 1-2. The most common AEs of Grade 3 or higher for THP and TH were neutropenia (45% and 57%), febrile neutropenia (8% and 7%), and leucopenia (5% and 12%). The number of SAEs was 10% for THP and 17% for TH, the most common of which was febrile neutropenia (6% and 7%, respectively). In the NEOSPHERE study, no patients had an LVEF decrease to less than 40% at any time during the study. One patient in the TH arm and 3 in the THP arm showed LVEF declines of 10-15% from baseline to less than 50% during neoadjuvant treatment, but all patients had LVEF improvements to more than 50% and a decrease of less than 10% by Cycle 4.

2.3.2 Benefit Assessment

T-DXd is under development for the treatment of HER2-expressing cancers and HER2-mutant tumours. Based on preliminary clinical observations in a Phase 1 study (Study DS8201-A-J101 [Phase 1; NCT02564900]), Study DS8201-A-U201 (DESTINY-Breast01, Phase 2; NCT03248492), and the DESTINY-Gastric01 Phase 2 study (NCT03329690), T-DXd demonstrated antitumour activity in HER2-expressing cancers, including gastric cancer and breast cancer, and a generally acceptable safety profile in these populations. Data from the Phase 2 DS8201-A-U204 (DESTINY-Lung01; [NCT03505710]) study also provides encouraging preliminary evidence of antitumour activity of T-DXd in tumours with HER2 mutations.

2.3.2.1 Potential Benefits of T-DXd in HER2-positive Breast Cancer

In the recently published study DS8201-A-U201 (DESTINY-Breast01) a response to T-DXd therapy (5.4 mg/kg) was reported in 112 participants (60.9%; 95% CI, 13.8, 16.9) with HER2-positive MBC who had received previous treatment with T-DM1 and had median 6 lines of prior therapy. The median response duration was 14.8 months, and the median duration of PFS was 16.4 months. Estimated OS was 93.9% (95% CI: 89.3, 96.6) at 6 months and 86.2% (95% CI: 79.8, 90.7) at 12 months; the median OS was not reached at the time of the DCO (Modi et al 2020b). DESTINY-Breast01 also demonstrated activity of T-DXd in participants with stable brain metastases (CNS subgroup: n=24); 58.3% had a confirmed ORR (95% CI: 36.6%, 77.9%) and median PFS was 18.1 months (95% CI, 6.7, 18.1). Disease

progression in the CNS subgroup was 8% (Jerusalem et al 2020).

In an updated analysis of the DESTINY-Breast01 study with a DCO of 08 June 2020, results showed that, with an additional 9.4 months of follow-up, the median duration of response was 20.8 months and the estimated 12- and 18-month OS rates were 85% (95% CI: 79, 90) and 74% (95% CI: 67, 80), respectively. The median PFS was 19.4 months (95% CI: 14.1, not estimable) (Modi et al 2020b). It is noted that with the most recent DCO, data are still immature and include patients (> 60%) with censored data.

A key benefit of neoadjuvant treatment is downstaging, which can decrease the extent of surgery leading to improved surgical outcomes. Ideal treatment regimens in the neoadjuvant setting lead to deep responses while minimising the TTR. Based on these criteria, T-DXd could be well suited for the neoadjuvant setting given the high ORR (60.9%) and a 6.0% CR rate as well as a rapid TTR of 1.6 months demonstrated in heavily pre-treated participants (median 6 prior lines of therapy) with HER2-positive MBC in the DESTINY-Breast01 trial. These data compare favourably to other SOC options in MBC across different lines of therapy, which suggests that the responses could be substantial in earlier lines of metastatic treatment as well as in treatment-naïve participants in the neoadjuvant setting.

2.3.2.2 Potential Benefits of T-DXd Followed by THP in HER2 Positive Breast Cancer

Sequencing treatments with different mechanisms of action is a proven strategy in the neoadjuvant setting to maximise treatment benefit while minimising treatment-related adverse effects. Anthracycline-based regimens in sequence with THP are one of the main SOCs for treating neoadjuvant HER2-positive breast cancer. Pathological complete response rates improve when THP is given in sequence with additional chemotherapy regimens. The NEOSPHERE study reported a pCR rate for THP of 39.3% (Gianni et al 2012), while the TRYPHAENA study observed pCR rates of 54.6%, when sequencing 3 cycles of FEC with 3 cycles of THP. The BERENICE study observed pCR rates of 61.8% when 4 cycles of THP were administered after 4 cycles of ddAC (Swain et al 2018).

Further evidence supportive of the sequence approach is based on data from the Phase 2 NEOPEAKS study, which compared T-DM1 + pertuzumab regimens, TCHP followed by T-DM1 + pertuzumab, and SOC TCHP in people with HER2-positive primary breast cancer (Masuda et al 2020). The NEOPEAKS study observed pCR rates of 71.2% when 4 cycles of T-DM1+P were administered after 4 cycles of TCHP compared with 56.9% after 6 cycles of TCHP alone. While this was a small trial with 200 participants in 3 different treatment arms, the data suggest that sequencing different mechanisms of action may be important for improving pCR rates in disease historically less sensitive to existing treatment approaches.

2.3.3 Overall Benefit: Risk Conclusion

There is an unmet medical need for better therapies in neoadjuvant treatment of high-risk HER2-positive EBC. Current treatment options require multi-agent treatment regimens that expose participants to an ever-increasing treatment burden including both short- and long-term toxicities, with up to 30% of participants with EBC ultimately progressing to metastatic disease (O'Shaughnessy 2005). The current treatment landscape would benefit from an option with an acceptable safety profile that reduces the overall treatment burden in the neoadjuvant setting while improving pCR rates and thus reducing the need for treatment intensification in the post-neoadjuvant setting.

Given the promising T-DXd monotherapy efficacy seen in late-line HER2-positive participants, it is anticipated that T-DXd monotherapy or T-DXd in sequence with SOC will provide efficacy benefit in participants with EBC.

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

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

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

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints/Estimands
Primary	
• **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. The analysis will include all randomised participants according to the randomised neoadjuvant treatment. Participants who withdraw from treatment without pCR will not be included as responders in the primary pCR analysis (refer to Table 14 for details). The measure of interest is the difference in the rates of pCR between the experimental arms and the control arm.
Secondary	
• **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) following completion of neoadjuvant therapy. The analysis will include all randomised participants according to the randomised neoadjuvant treatment. Participants who withdraw from treatment without pCR will not be included as responders in the analysis (refer to Table 14 for details). The measure of interest is the difference in the rates of pCR between the experimental arms and the control arm.
• **EFS, IDFS, and 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.

Objectives	Endpoints/Estimands
	The EFS and OS analyses will include all randomised participants as randomised, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The IDFS analysis will include all randomised participants that complete surgery. Participants will be censored at the time they are last known to be alive and event free. The measure of interest is the hazard ratio of OS and the differences in the rate of 3-year EFS and 3-year IDFS.
• 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. The analysis will be performed using the SAF. Descriptive summary statistics will be provided. Missing data will not be imputed, and the analyses will be based on observed non-missing data.
• 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. The analysis will be performed using the SAF. Descriptive summary statistics will be provided. Missing data will not be imputed, and the analyses will be based on observed non-missing data.
• 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.
Safety	
• 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

Objectives	**Endpoints/Estimands**
	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).
Tertiary/Exploratory	
CCI	

Objectives	Endpoints/Estimands
CCI	

ADA = anti-drug antibody; AE = adverse event; CCI ddAC-THP = doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; CCI ECG = electrocardiogram; ECHO = echocardiogram; EFS = event-free survival; EORTC = European Organization for the Research and Treatment of Cancer; CCI HER2 = human epidermal growth factor receptor 2; H&E = hematoxylin & eosin; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; LVEF = left ventricular ejection fraction; CCI MUGA = multigated acquisition; NYHA = New York Heart Association; CCI OS = overall survival; pCR = pathological complete response; PGI-TT = Patient Global Impression of Treatment Tolerability; PK = pharmacokinetics; CCI 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; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab; 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 nodes.

4 STUDY DESIGN

4.1 Overall Design

DESTINY-Breast 11 is a global, open-label, multicentre, randomised, 3-arm Phase 3 study to determine the efficacy and safety of T-DXd monotherapy or T-DXd followed by THP as neoadjuvant treatment compared to ddAC-THP in participants with locally advanced or inflammatory HER2-positive, high-risk (lymph node positive [N1-3] or with a primary tumour stage T3-4) EBC. The study schema can be found in Section 1.2.

Participants will have core-needle biopsy tumour samples sent to a central laboratory for HER2 status confirmation. Participants who are determined eligible for the study will be randomised according to the following stratification factors:

- Hormone receptor status (ER and/or PgR positive vs ER and PR negative) by local assessment.
- Central assessment of HER2-positive status (IHC 3+ vs other; where 'other' is defined as ISH+ in the absence of IHC3+ status).

For multi-centric tumours, where multiple HER2 results should be available, the stratification will be based on the lowest IHC expression result (only patients with all lesions HER2 IHC3+ will be considered IHC3+ for stratification purposes). Approximately 900 participants will be randomised in a 1:1:1 ratio to the treatment arms below, all with IV administration:

- Arm A: T-DXd (5.4 mg/kg Q3W) × 8 cycles.
- Arm B: T-DXd (5.4 mg/kg Q3W) × 4 cycles followed by paclitaxel (80 mg/m^2 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/m^2 Q2W) and cyclophosphamide (600 mg/m^2 Q2W) × 4 cycles followed by paclitaxel (80 mg/m^2 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.

CCI

Note: For doxorubicin and cyclophosphamide, 1 cycle = 2 weeks; for all other treatments, 1 cycle = 3 weeks.

Eight cycles of neoadjuvant therapy will be administered for a total of 24 weeks (Arm A and Arm B) or 20 weeks (Arm C) per described schedules. During the intervention period and leading up to surgery, participants should only receive the assigned therapy per the designated schedule (unless patients are prematurely discontinued). Additional therapy after completion of neoadjuvant treatment and before surgery is not allowed. After initiation of study treatment and before surgery, participants will be monitored with breast MRIs to clinically assess tumour responses. In the event of disease progression, unacceptable toxicity, withdrawal of consent or study termination by the Sponsor, whichever comes first, neoadjuvant therapy will be discontinued. Participants who discontinue due to disease progression during the neoadjuvant treatment phase will receive subsequent therapy per investigator discretion.

Any participant who receives non-protocol therapy prior to surgery will be discontinued from study treatment, undergo an early withdrawal visit, be followed until study completion, and be managed per local practice.

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

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

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

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the participant's next contact with the study site).
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

- At-home study intervention administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the participants or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

This Phase 3 trial has 3 treatment arms to allow for determining whether T-DXd monotherapy or T-DXd followed by THP has superior efficacy compared with the SOC ddAC-THP treatment. No statistical testing between the T-DXd containing experimental arms (Arms A and B) is planned.

4.2.2 Rationale for Participant Population

The target population in this study is participants with high-risk (T stage ≥ T3, node positive, or inflammatory) HER2-positive EBC. Node positive disease and greater tumour burden are features consistently shown to be associated with higher rates of recurrence in EBC (Slamon et al 2011a). Specifically, in the neoadjuvant setting, participants with node positive disease at presentation are less likely to achieve a pCR and are more likely to experience a recurrence (van Ramshorst et al 2018). Subgroup analyses from the phase 3 TRAIN-2 trial, which investigated optimisation of chemotherapy regimens in combination with HP, showed that for participants who present with node positive disease, the pCR rate (ypT0/Tis ypN0) was 6% to 13% lower than the pCR rate for node negative participants. This represented the second largest intra-arm difference in pCR rates after HR status. When EFS was determined at 3-years of follow-up, the node positive participants accounted for 83% to 90% of reported events, making this subgroup represent the single largest number of events in each arm. Similarly, T stage of 3 or 4 was also associated with up to 5% lower rates of pCR (Voort et al 2020).

In addition to experiencing higher rates of recurrence, participants that present with node positive disease also have high unmet need because they are more likely to require extensive surgery, including ALND that is associated with significant morbidities including lymphedema which can cause life-long pain and functional impairment (Krag et al 2010). Therefore, participants with node positive disease represent both a high-risk and high unmet need population that would benefit from improved treatment options.

Participants with HER2-positive inflammatory breast cancer have lower rates of pCR compared to their counterparts without inflammatory features. A large US-based study of the National Cancer Database was used to analyse the outcomes of participants (n=8550) with

inflammatory breast cancer in the neoadjuvant setting. Participants with HER2-positive/HR-positive disease had a pCR rate of 13% and those with HER2-positive/HR-negative disease had a pCR rate of 27% (Biswas et al 2019). These results suggest that an improvement in the neoadjuvant treatment in these participants would reduce the need of post-neoadjuvant treatment escalation and ultimately disease recurrences.

4.2.3 CCI

CCI

4.2.4 Rationale for ddAC-THP as Control Arm

Dose dense doxorubicin + cyclophosphamide, followed by THP is the control arm because it is an accepted SOC for neoadjuvant disease globally, and endorsed by both NCCN and ESMO guidelines. In addition, ddAC-THP is the most appropriate regimen for the high-risk participant population in this study based on extrapolation from the adjuvant BCIRG006 study. BCIRG006 compared SOC AC-T with AC-TH or TCH and demonstrated that either trastuzumab-containing regimen improved DFS and OS compared to AC-T (Slamon et al 2011b). While no significant differences in long-term outcomes were seen between the 2 trastuzumab-containing regimens, AC-TH was numerically superior to TCH (Slamon et al 2011b). The safety and efficacy of the ddAC-THP in the standard neoadjuvant eligible participant population (T > 2 cm or node positive EBC) was investigated in the Phase 2 BERENICE trial, which reported a pCR rate for ddAC-THP of 61.8%.

4.2.5 Rationale for T-DXd Monotherapy Treatment Arm

Key anticipated benefits and rationale of T-DXd monotherapy out outlined in Section 2.3.2.1.

4.2.6 Rationale for T-DXd followed by THP Treatment Arm

Key anticipated benefits and rationale of T-DXd followed by THP are outlined in Section 2.3.2.2.

4.3 Justification for Dose

4.3.1 T-DXd Dose Rationale

The dose of T-DXd for this study is 5.4 mg/kg due to the better benefit-risk profile seen in breast cancer at the 5.4 mg/kg dose compared to higher doses, and is the confirmed dose for

future clinical development in breast cancer. This is based on data from the results in Study DS8201-A-J101 and the Phase II DS8201-A-U201 study (DESTINY-Breast01), which led to accelerated approval in the US and is under review in other regions.

4.3.2 Paclitaxel Dose Rationale

Taxanes are the backbone of the treatment of HER2-positive EBC. Docetaxel and paclitaxel are used interchangeably paired with trastuzumab and pertuzumab. While the registrational trials leading to the approval of pertuzumab, TRYPHAENA (Schneeweiss et al 2013) and NEOSPHERE (Gianni et al 2012) both used docetaxel, other trials, such as BERENICE (Swain et al 2018) have used paclitaxel administered weekly for 12 doses (4 cycles with a 3-week cycle). In this study, paclitaxel will be administered at a SOC dose of 80 mg/m^2 every week as opposed to the labelled paclitaxel dose in breast cancer of 175 mg/m^2 Q3W. A QW dose of 80 mg/m^2 was chosen based on the improved efficacy and safety profile demonstrated in an adjuvant breast cancer trial comparing QW paclitaxel, QW docetaxel, Q3W docetaxel, and Q3W paclitaxel (Sparano et al 2008).

4.3.3 Trastuzumab Dose Rationale

Trastuzumab will be dosed with initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30- to 90-minutes IV infusion Q3W, as per the trastuzumab prescribing information, except in Arm B (T-DXd followed by THP), where an initial loading dose is not needed as the antibody portion of T-DXd is the identical amino acid sequence of trastusumab (all doses given 6 mg/kg).

4.3.4 Pertuzumab Dose Rationale

For pertuzumab, the initial dose is 840 mg administered as a 60-minute IV infusion, followed Q3W thereafter by 420 mg administered as a 30- to 60-minute IV infusion, as per pertuzumab prescribing information.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

- **European Union requirements** define study completion as the last visit of the last subject for any protocol related activity.
- **Food and Drug Administration requirements** defines 2 completion dates:
  - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome

measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

– Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last expected visit/contact or the last scheduled procedure shown in the SoA (Section 1.3), including EFS/OS determination.

The study may be stopped if, in the judgement of AstraZeneca, study participants are placed at undue risk because of clinically significant findings or futility findings. The study may be terminated at individual centres if the study procedures are not being performed according to ICH GCP guidelines, or if recruitment rate does not allow the study to be completed in the planned timeframe.

At the time of study completion, the clinical database will close to new data; however, SAEs must continue to be reported via paper form (refer to Section 8.3.15 for details). Participants may be withdrawn from the study at this time. See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

The target population of interest in this study is previously untreated participants with histologically documented HER2-positive resectable, locally advanced, or inflammatory breast cancer with a primary tumour stage ≥ T3 and N0-3, or a primary tumour of any size with positive lymph nodes (any T and N1-3). Participants must be ≥ 18 years of age and have an ECOG performance status of 0 or 1 at randomisation.

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

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

5.1 Inclusion Criteria

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

Age

1 Male or female participants ≥ 18 years of age.

Type of Participant and Disease Characteristics

2 Histologically documented HER2-positive EBC participants with:

(a) Locally assessed HER2-positive (IHC 3+ or ISH+) according to ASCO-CAP guidelines (see Appendix N) and prospectively centrally confirmed as HER2-positive (Wolff et al 2018) based on a tumour sample.

(b) Unifocal and multifocal tumours (> 1 tumour confined to the same quadrant as the primary tumour) must have 1 focus sampled and centrally confirmed as HER2-positive.

(c) Multi-centric tumours (multiple tumours involving > 1 quadrant of the breast) must have 1 lesion from each involved quadrant sampled and centrally confirmed as HER2-positive. All quadrants tested must be centrally confirmed as HER2 positive.

(d) Tumours documented as HR-positive (either ER and/or PgR positive [ER or PgR ≥ 1%]) or HR-negative (ER and PgR negative) by local assessment per ASCO-CAP guidelines (Allison et al 2020).

(e) Clinical stage at presentation (based on mammogram or breast MRI assessment): T0-4 (inclusive of inflammatory breast cancer), N1-3, M0 or ≥ T3, N0, M0 as determined by the AJCC staging system, 8th edition (Hortobagyi et al 2017).

(f) Pathologic confirmation of nodal involvement with malignancy as determined by fine-needle aspiration or core-needle biopsy, when applicable.

3 Must have an adequate FFPE tumour tissue sample available for assessment of HER2 by central laboratory (either from an archival diagnostic biopsy or a newly obtained biopsy). At least 2 cores must be provided in the form of FFPE tissue blocks (for additional details on baseline tumour sample requirements, refer to Section 8.6.1).

4 ECOG performance status of 0 or 1 at randomisation.

5 Adequate organ and bone marrow function during screening:

Table 3 Parameters for Adequate Organ and Bone Marrow Function

Adequate bone marrow function	
Platelet count	≥ 100,000/mm^3. (Platelet transfusion or platelet growth factors are not allowed within 1 week prior to screening assessment)
Haemoglobin	≥ 9.0 g/dL **NOTE**: Participants requiring ongoing transfusions or growth factor support to maintain haemoglobin ≥ 9.0 g/dL are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count	≥ 1500/mm^3. (Granulocyte-colony stimulating factor administration is not allowed within 1 week prior to screening assessment)
Adequate hepatic function	

Table 3 Parameters for Adequate Organ and Bone Marrow Function

Adequate bone marrow function	
Alanine aminotransferase and aspartate aminotransferase	≤ 1.5 × ULN
Total bilirubin	≤ ULN or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia)
Serum albumin	≥ 2.5 g/dL
Adequate renal function	
Calculated creatinine clearance	≥ 30 mL/min as determined by Cockcroft Gault (using actual body weight)
Adequate blood clotting function	
International normalised ratio or prothrombin time and either partial thromboplastin or activated partial thromboplastin time	≤ 1.5 × ULN

ULN = upper limit of normal.

6 LVEF ≥ 50% within 28 days before randomisation.

Reproduction

7 Negative pregnancy test (serum) for women of childbearing potential who are sexually active with a non-sterilised male partner.

8 Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of non-hormonal birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). For women who are on hormone replacement therapy, please refer to Appendix G. Women of childbearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of non-hormonal birth control from the time of screening to 7 months after the last dose of study treatment or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment (see Appendix G for complete list of highly effective non-hormonal birth control methods). Female participants must refrain from egg cell donation and breastfeeding while on study and for 7 months after the last dose of study treatment or as dictated by prescribing information for SOC treatments received after neoadjuvant treatment. Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.

9 Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception (see Appendix G) from the time of screening throughout the total duration of the study and for

6 months after the last dose of study intervention or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study (or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment) is an acceptable practice if this is the preferred usual lifestyle of the participant; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Informed Consent

10 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1 Prior history of invasive breast cancer.

2 Stage IV breast cancer as determined by AJCC staging system, 8th edition (Hortobagyi et al 2017).

3 Any primary malignancy within 3 years, except adequately resected non-melanoma skin cancer, or curatively treated in situ disease.
Note: This includes a second current breast primary malignancy (ie, bilateral breast cancer).

4 History of DCIS, except for participants treated with mastectomy only > 5 years prior to current diagnosis.

5 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including ongoing or active infection, uncontrolled hypertension, renal transplant and active bleeding diseases, serious chronic gastrointestinal conditions associated with diarrhoea) which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.

6 Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

7 Active hepatitis C infection. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Participants with current active or history of hepatitis B infection with either HBsAg(+) or anti-HBc(+) are not eligible.

8 Active primary immunodeficiency or known to have tested positive for HIV or active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).

9 Participants with a medical history of myocardial infarction within 6 months before enrolment, symptomatic CHF (NYHA Class II to IV), unstable angina pectoris, or a recent (< 6 months) cardiovascular event including stroke. Participants with troponin levels above ULN at screening (as defined by the manufacturer), and without any myocardial related symptoms, should have a cardiologic consultation before enrolment to rule out myocardial infarction.

10 Investigator judgement of 1 or more of the following:

(a) Mean resting corrected QTcF interval > 470 ms (females) or > 450 ms (males), obtained from triplicate ECGs performed at screening.

(b) History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and cause TdP.

(c) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

11 History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the Study Physician.

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

13 Lung criteria:

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

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

(c) Prior pneumonectomy.

Prior/Concomitant Therapy

14 Prior systemic therapy for the treatment of breast cancer.

15 Previous treatment with anthracyclines, cyclophosphamide, or taxanes for any malignancy. Treatment with cyclophosphamide for non-cancer conditions is allowed if the last dose was > 6 months prior to the current diagnosis.

16 Ineligible for any medication in control arm (anthracycline, cyclophosphamide, taxane, trastuzumab, pertuzumab): participants with contraindications to these agents per local prescribing information cannot be enrolled into this study.

17 Receipt of live, attenuated vaccine within 30 days prior to the first dose study intervention. Note: Participants, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of study treatment.

18 Prior exposure, without adequate treatment washout period before randomisation, to chloroquine / hydroxychloroquine: ≥ 14 days.

19 Any concurrent anticancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is allowed.

20 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

Prior/Concurrent Clinical Study Experience

21 Previous randomisation in the present study.

22 Concurrent enrolment in another clinical study unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study.

23 Participants with a known hypersensitivity to study treatment or any of the study treatment excipients or other mAbs.

Diagnostic Assessments

24 Sentinel lymph node biopsy or axillary lymph node dissection prior to initiation of neoadjuvant therapy.

Other Exclusions

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

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

27 Currently pregnant (confirmed with positive pregnancy test) or breastfeeding, or who are planning to become pregnant.

5.3 Lifestyle Considerations

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

1 Participants must follow the contraception requirements outlined in Appendix G.
2 Participants should not donate blood or blood components while participating in this study and through 40 (+ 7 days) after the last dose of T-DXd for participants who receive T-DXd alone or for 90 days after the last dose of pertuzumab for participants in Arms B and C (or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment).
3 Preservation of ova or sperm should be considered prior to enrolment in this study.

Restrictions relating to concomitant therapies are described in Appendix I 2.

5.3.1 Tobacco

Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Any prior or current use of these products should be recorded in the eCRF (see Appendix I for further details).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. However, patients cannot be re-screened if there is a valid HER2 central negative result. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

All assessments must be repeated for rescreening unless they are within 28 days of randomisation, except for those noted per the SoA (Section 1.3). The additional samples for biomarker assessment, if already collected on initial screening, do not need to be collected on re-screening.

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

Participant enrolment and randomisation is described in Section 6.3.

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

All investigational medicinal products will only be supplied by AstraZeneca during the neoadjuvant period. For information on the study treatments to be administered in this study, please refer to Table 4. AstraZeneca will supply T-DXd.

Doxorubicin, cyclophosphamide, paclitaxel, and pertuzumab, will be supplied locally, where possible. Central supply of doxorubicin, cyclophosphamide, paclitaxel, and pertuzumab is only for markets where sites cannot supply these and there is no approved local vendor available in that market.

In this study, trastuzumab biosimilar Herzuma will be centrally supplied in all countries where it is approved for use. In countries where Herzuma is not approved, participants may be treated with Herceptin which will be supplied locally or centrally (central supply is only for markets where sites cannot supply these and there is no local vendor available in that market). One exception is the US, where Herzuma will be supplied locally by the sites. Where possible, participants should remain on a single product, Herzuma or Herceptin, for the duration of their treatment.

Dose modifications are described in Section 6.6.

Table 4 Investigational Products

Intervention Name	T-DXd	Paclitaxel	Trastuzumab	Pertuzumab	Doxorubicin	Cyclophosphamide
ARM Name	A: T-DXd monotherapy B: T-DXd then THP	B: T-DXd then THP C: ddAC-THP	B: T-DXd then THP C: ddAC-THP	B: T-DXd then THP C: ddAC-THP	C: ddAC-THP	C: ddAC-THP
Type	ADC	Taxane	Monoclonal antibody	Monoclonal antibody	Anthracycline	Alkylating agent
Dose Presentation	Vial	As sourced locally[a]	As sourced locally[a]	As sourced locally[a]	As sourced locally[a]	As sourced locally[a]
Unit Dose Strength	Powder for concentrate for solution for infusion [redacted] mg/vial	Variable	Variable	Variable	Variable	Variable
Dosage Levels	5.4 mg/kg Q3W	80 mg/m^2 QW	8 mg/kg loading dose (Arm C only) then 6 mg/kg Q3W	840 mg loading dose then 420 mg Q3W	60 mg/m^2 Q2W	600 mg/m^2 Q2W
Route of Administration	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Use	Experimental	Experimental (Arm B) Active-comparator (Arm C)	Experimental (Arm B) Active-comparator (Arm C)	Experimental (Arm B) Active-comparator (Arm C)	Active-comparator	Active-comparator
IMP	IMP	IMP	IMP	IMP	IMP	IMP

Table 4 Investigational Products

Sourcing	Provided centrally by the Sponsor	Provided locally [a]	Herzuma will be provided centrally by AstraZeneca in countries where it has regulatory approval. In countries where Herzuma is not approved, Herceptin will either be provided locally or centrally by AstraZeneca if none of the aforementioned options are available.	Provided locally[a]	Provided locally[a]	Provided locally[a]
Packaging and Labelling	Study intervention will be provided in [redacted] mg vials in carton. Each vial and carton will be labelled as required per country requirements [b]	If provided by AstraZeneca, study treatment will be labelled as required per country requirements.				
Current/Former Name(s) or Alias(es)	DS-8201a	N/A	Herceptin and Herzuma	Perjeta	N/A	N/A

[a] Under certain circumstances when local sourcing is not feasible, paclitaxel, trastuzumab, pertuzumab, doxorubicin, and cyclophosphamide treatments may be supplied centrally through AZ.

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

ADC = antibody-drug conjugate; ddAC-THP = doxorubicin + cyclophosphamide then paclitaxel + trastuzumab + pertuzumab; IMP = investigational medicinal product; IV = intravenous; N/A = not applicable; Q2W = every 2 weeks; Q3W = every 3 weeks; QW = weekly; T-DXd = trastuzumab deruxtecan; THP = paclitaxel + trastuzumab + pertuzumab.

Study Interventions

Participants in Arm A will receive T-DXd (5.4 mg/kg IV Q3W) for 8 cycles.

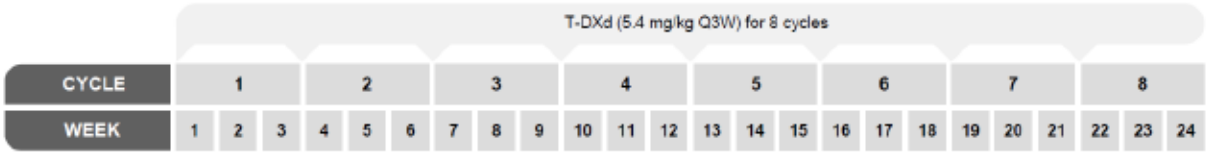
Participants in Arm B will receive T-DXd (5.4 mg/kg IV Q3W) for 4 cycles, followed by paclitaxel (80 mg/m^2 IV QW on Days 1, 8, and 15) concurrent with trastuzumab (6 mg/kg IV Q3W on Day 1), and pertuzumab (840 mg IV loading dose followed by 420 mg IV Q3W on Day 1) for 4 cycles.

Participants in Arm C will receive doxorubicin (60 mg/m^2 Q2W) and cyclophosphamide (600 mg/m^2 IV Q2W) for 4 cycles, followed by paclitaxel (80 mg/m^2 IV QW on Days 1, 8, and 15) concurrent with trastuzumab (8 mg/kg IV loading dose followed by 6 mg/kg IV Q3W on Day 1), and pertuzumab (840 mg IV loading dose followed by 420 mg IV Q3W on Day 1) for 4 cycles.

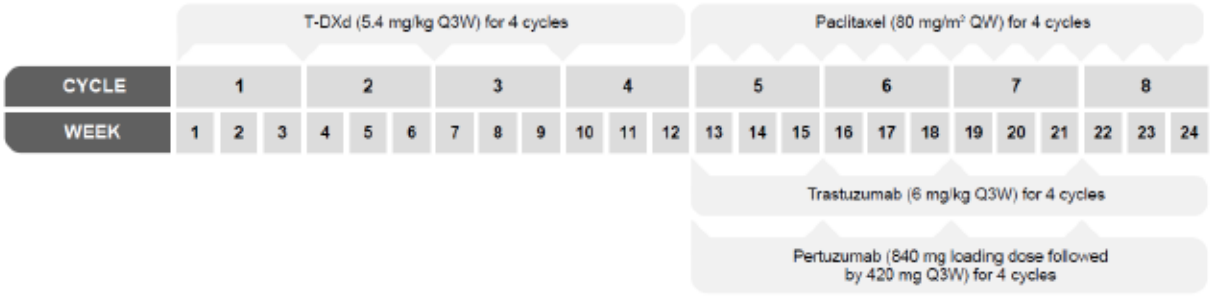
Note: 1 cycle = 3 weeks, except in Arm C, where 1 cycle = 2 weeks during doxorubicin and cyclophosphamide treatment.

Figure 2 Dosing Schedule

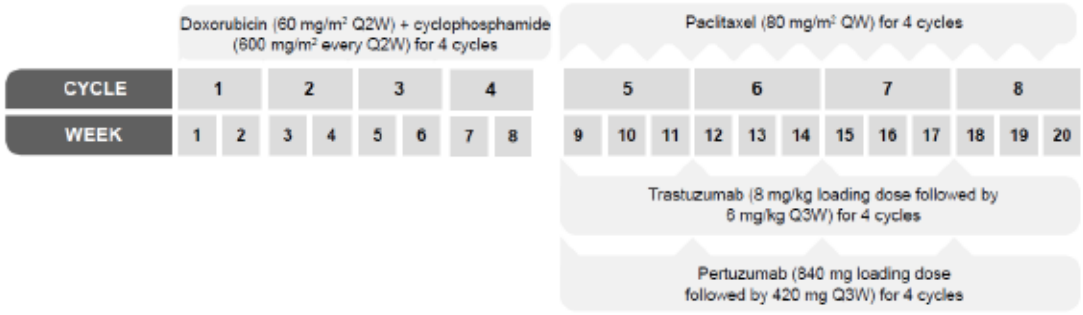
Arm A



Arm B



Arm C



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

Duration of Treatment

Participants will be administered 8 cycles of neoadjuvant therapy for a total of 24 weeks (Arm A and Arm B) or 20 weeks (Arm C) as described above. During the intervention period and leading up to surgery, participants should only receive the assigned therapy per the designated schedule (unless patients are prematurely discontinued). Additional therapy after completion of neoadjuvant treatment and before surgery is not allowed. In the event of disease progression, unacceptable toxicity, withdrawal of consent or study termination by the Sponsor, whichever comes first, neoadjuvant therapy will be discontinued. Participants who discontinue due to disease progression during the neoadjuvant treatment phase will receive subsequent therapy per investigator discretion.

Following surgery, participants will have their treatment determined by their investigator and administered as part of SOC. For further details, please see Section 4.1.

6.2 Preparation/Handling/Storage/Accountability of Interventions

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

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

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

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

THP (experimental in Arm B) will be handled per prescribing information, as outlined below.

Doxorubicin and Cyclophosphamide (as Part of ddAC-THP Regimen), Paclitaxel, Trastuzumab, and Pertuzumab (as Part of ddAC-THP and T-DXd-THP Regimens)

The SOC agents will either be locally sourced by the study site or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the drug, which will be labelled with local language translated text in accordance with regulatory guidelines.

For SOC storage information, refer to the prescribing information.

6.2.1 T-DXd Preparation, Administration and Storage

T-DXd will be supplied by AstraZeneca as a CCI mg/vial lyophilised powder for concentrate for solution for infusion. Following reconstitution with sterile water for injection the solution contains 20 mg/mL CCI

The reconstituted product is a CCI CCI

Preparation of T-DXd

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

puncture of the T-DXd vial to the start of administration must not exceed:

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

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

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

Administration of T-DXd

T-DXd is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of T-DXd, patients should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

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

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

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

Monitoring of T-DXd Administration

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

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

Storage of T-DXd

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

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

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Participant Enrolment and Randomisation

All participants will be centrally assigned to randomised study intervention using an IRT. Before the study is initiated, the call/log-in directions and user guides for the IRT will be provided to each site. Participants will be stratified by their HR status (positive vs negative), and HER2 status (IHC3+ vs other). The stratification factors will be recorded in the IRT system by site personnel and/or results may be directly integrated in IRT.

Study intervention will be dispensed at the study visits summarised in SoA or per SOC after surgery.

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

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

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

- Obtain signed informed consent. If laboratory or imaging procedures were performed prior to signing consent, these can be used for screening purposes with consent of the participant.
- Participants will be identified to the IRT per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IRT in the following format (PPD PPD PPD). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Obtain sample and send for centralised HER2 testing.

- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional). Participants who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.

At randomisation, once the participant is confirmed to be eligible, the investigator or suitably trained delegate will:

- Assign a randomised treatment group via the IRT. Randomisation codes will be assigned PPD within each stratum and site/country/region as participants become eligible for randomisation. The system will randomise the eligible participant to 1 of the 3 treatment groups.

If the participant is ineligible and not randomised, the IRT should be accessed to terminate the participant in the system.

Participants will begin treatment on Day 1. Every effort should be made to minimise the time between randomisation and dosing. Dosing should occur within 3 calendar days of randomisation. If it is anticipated that dosing cannot occur within 3 calendar days, a discussion with the AstraZeneca Study Physician is required. Once randomised, participants must continue on their assigned arm throughout the duration of the study. Crossover to another arm is not permitted. Participants must not be randomised and treated unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Randomised Participants

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

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

Randomised participants that have been withdrawn from the study are not eligible for re-screening.

6.3.3 Methods for Assigning Treatment Groups (Randomisation)

The actual treatment given to participants will be determined by the randomisation scheme in the IRT. The randomisation scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. A blocked randomisation will be generated, and randomisation will be balanced within the IRT at the site/country/region/central level.

Randomisation codes will be assigned PPD , within each stratum (refer to stratification factors in Section 4.1), as participants become eligible for randomisation. The IRT will provide the kit identification number to be allocated to the participant at the randomisation visit and subsequent treatment visits. If study medication is provided locally, IRT will not provide kit numbers.

6.3.4 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites; however, the trial will be conducted as "Sponsor-blind" and the specific treatment to be taken by a participant will be assigned using an IRT (see Section 6.3.1 for details). To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint. Before the first participant is randomised, a Trial Integrity Document should be generated, in which data access levels for relevant AstraZeneca personnel will be pre-specified.

6.4 Study Intervention Compliance

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

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Any changes in the dosing schedule such as dose interruptions, dose reductions, dose delays, and dose discontinuations should be recorded in the source documentation and eCRF. The reason should also be documented.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention. The site must retain records of all study treatments administered to the participants. The Study Monitor will check these records to confirm compliance with protocol.

6.5 Concomitant Therapy

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

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

During the intervention period, concomitant medication information may be collected by phone if not tied to a visit. The AstraZeneca Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

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

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

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix I 2.

For agents other than T-DXd, refer to the local prescribing information regarding warnings, precautions, and contraindications.

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

Drug-drug Interactions

Drug-drug interactions with T-DXd, either pre-clinically or in participants indicate that the impact is not clinically meaningful. There may be a hypothetical interaction between T-DXd and hydroxychloroquine and/or chloroquine, therefore concomitant treatment with hydroxychloroquine or chloroquine is not allowed during the study treatment.

For agents other than T-DXd, refer to the local prescribing information regarding potential drug-drug interactions.

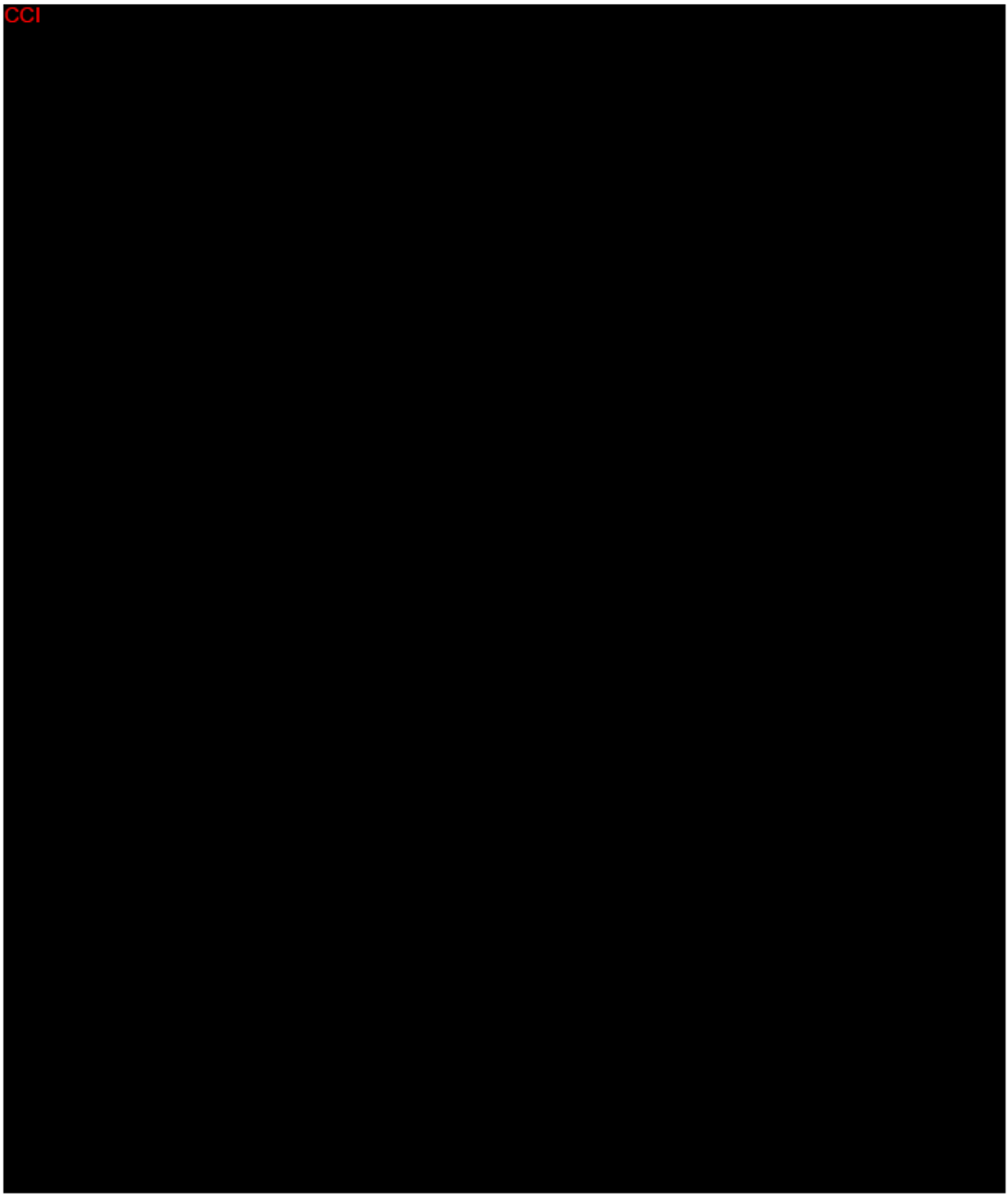
Guidance regarding potential interactions with concomitant medications is provided in

Appendix I 1.

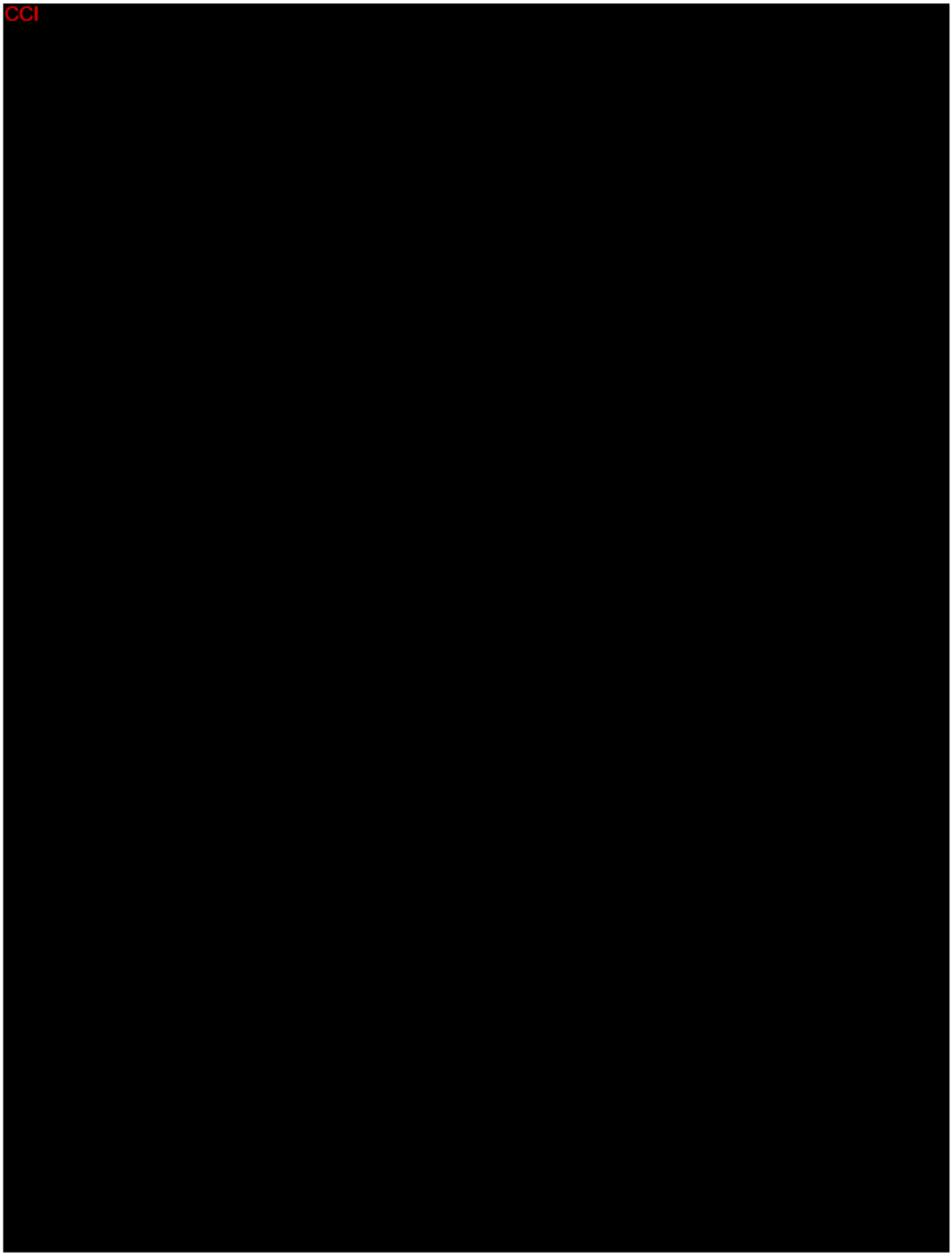
6.6 Dose Modification

6.6.1 T-DXd Dose Modification

CCI



CCI



6.6.2 THP (Arm B)

For management of toxicities due to THP following T-DXd administration, it is appropriate to refer to the locally approved prescribing information or manage in accordance with institutional guidelines. However, it is worth noting that there is currently no data on the safety of THP following administration of T-DXd. The administration of THP after T-DXd dosing may increase the risk or severity of toxicities that can be associated with both T-DXd and THP (eg, ILD/pneumonitis or haematologic toxicities). Furthermore, there is potential for new, unanticipated toxicities. Investigators must monitor for any unanticipated toxicities or more severe toxicities.

6.6.3 ddAC-THP (Arm C)

For management of toxicities due to SOC (ddAC-THP), refer to the locally approved prescribing information or manage in accordance with institutional guidelines.

6.6.4 Dose Modification of a Component or Entire Regimen

While administering part of a combination, if ≥ 1 component must be delayed (eg, due to toxicity) please follow the guidance below:

THP (Arm B and Arm C)

- If a dose of weekly paclitaxel cannot be administered, it should be skipped (and 0 mg recorded). Skipped doses of paclitaxel should not be made up later in the treatment course.
- If paclitaxel dosing is skipped, the HER2 targeted study interventions (H+P) may be administered per investigator discretion.
- If dosing for either of the HER2 targeted study interventions (H or P) must be delayed, the whole cycle (including paclitaxel) must be delayed. The delay must not exceed 9 weeks from the last administered dose. The numbering of cycles will remain consecutive.

ddAC (Arm C)

For dose delays for either doxorubicin or cyclophosphamide:

- Follow local standard clinical practice.
- If one of the agents must be delayed, and if compatible with local practice, the other must also be delayed. The delay must not exceed 6 weeks from the last administered dose. Numbering of the cycles will remain consecutive.

6.7 Intervention after the End of the Study

As described in Section 4.4, the study will remain open until all participants have completed their last expected visit/contact. After the final DCO for this study participants should continue appropriate treatment at the discretion of the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed. Note that discontinuation from study treatment is NOT the same thing as a withdrawal from the study.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention (ie, prior to completion of 8 cycles of study treatment). If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for pCR and other secondary endpoints including EFS, IDFS, and OS. The investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the

reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

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

Participants must be discontinued (ie, prior to completion of 8 cycles of study treatment) from study intervention in the following situations.

- Disease progression, as evaluated by MRI, mammogram, ultrasound, or clinical examination (refer to Section 8.1.4).
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6) or as defined in the local prescribing information for the SOC agents.
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant.
- Initiation of subsequent anticancer therapy, including another investigational agent.

If disease progression is suspected (eg, based on symptomatic deterioration), every effort should be made to document progression through use of objective criteria. If the investigator is not able to confirm disease progression by objective criteria and is considering discontinuing the patient, a discussion with the AstraZeneca Study Physician is required.

Please see Section 7.1.2 for guidance if a participant discontinues any components of or the entire treatment regimen offered in this study. Note: a participant continuing at least 1 investigational medicinal product will not be considered discontinued from study treatment and will continue to assessments per the SoA.

See the SoA for data to be collected at the time of intervention discontinuation (ie, the EoT visit) and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for Premature Discontinuation of Study Treatment

A participant who decides to discontinue study treatment will be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF. Discontinuation of study treatment does not impact the participant's participation in the study. The participant should continue attending subsequent study visits, per the SoA, and data collection should continue until the end of the study.

Participants who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment. EoT is described as the date that the investigator makes the decision to discontinue the participant from all study treatment in a treatment arm and not the last date that the participant received study treatment. For participants that complete neoadjuvant therapy, the EoT visit should be combined with the pre-surgery visit which takes place within 14 days of surgery. For participants that discontinue all study treatment before completing all cycles, the early discontinuation visit should take place within 7 days of the decision to discontinue treatment. If the early discontinuation visit is > 40 days (+7 days) after the last dose of study treatment, then the EoT/early discontinuation visit may be combined with the safety follow-up visit. For participants that complete neoadjuvant study treatment, the safety follow-up visit should take place after definitive surgery. For participants that discontinue all study treatment prior to completion of all planned cycles, the timing of the safety follow-up visit is based on last administration of study treatment and could be conducted prior to surgery.

7.1.2 Dose Discontinuation of a Component or Entire Regimen

While administering part of a combination or sequenced regimen, if ≥ 1 component must be discontinued due to toxicity, please follow the guidance below:

T-DXd Monotherapy (Arm A)

- If T-DXd is discontinued (eg, due to toxicity, disease progression), participants can proceed to surgery at the discretion of the investigator.
- Investigators at their discretion may choose to treat participants with other regimens following T-DXd monotherapy discontinuation prior to surgery. Please refer to Table 14 for information on how these participants will be handled in terms of efficacy analysis.

T-DXd Followed by THP (Arm B)

- If T-DXd is discontinued (eg, due to toxicity), participants should proceed to THP if clinically reasonable and not contraindicated.
- If THP is discontinued (eg, due to toxicity), the date of surgery can be brought forward, and participants can proceed to surgery at the discretion of the investigator.

- If paclitaxel must be discontinued before completion of the planned 4 cycles (eg, due to toxicity), the HER2-targeted study interventions (trastuzumab + pertuzumab) should be continued to completion of 4 cycles if clinically reasonable.
- If trastuzumab and pertuzumab must be discontinued before completion of the planned 4 cycles, paclitaxel should be continued to completion of 4 cycles if clinically reasonable.
- If pertuzumab must be discontinued, trastuzumab should be continued to completion of 4 cycles if clinically reasonable and not contraindicated.
- If trastuzumab must be discontinued, pertuzumab dosing must also be discontinued.

ddAC-THP (Arm C)

- If ddAC is discontinued (eg, due to toxicity), participants should proceed to THP if clinically reasonable and not contraindicated.
- If either doxorubicin or cyclophosphamide is discontinued (e.g., due to toxicity), the investigator can choose to continue the remaining agent if clinically reasonable and not contraindicated before proceeding to THP.
- If THP is discontinued (eg, due to toxicity), the date of surgery can be brought forward, and participants can proceed to surgery at the discretion of the investigator.
- If paclitaxel must be discontinued before completion of the planned 4 cycles (eg, toxicity), the HER2 targeted study interventions (trastuzumab + pertuzumab) should be continued to completion of 4 cycles if clinically reasonable and not contraindicated.
- If trastuzumab and pertuzumab must be discontinued before completion of the planned 4 cycles, paclitaxel should be continued to completion of 4 cycles if clinically reasonable.
- If pertuzumab must be discontinued, trastuzumab should be continued to completion of 4 cycles if clinically reasonable and not contraindicated.
- If trastuzumab must be discontinued, pertuzumab dosing must also be discontinued.

All actions taken regarding dose modification/dose discontinuation for regimens, including discontinuation of an entire regimen, must be clearly documented in the appropriate CRFs.

7.1.3 Follow-up of Participants Post Discontinuation of Study Intervention

Safety follow-up should be conducted 40 days + 7 after administration of last dose of study treatment. For participants that complete neoadjuvant study treatment, this will take place after definitive surgery. For participants that discontinue all study treatment prior to completion of all planned cycles, the timing of the safety follow-up visit is based on last administration of study treatment and could be conducted prior to surgery. Assessments to be performed at the time of the safety follow-up visit are detailed in the SoA. For ILD/pneumonitis, safety follow-up will continue until the resolution of ILD/pneumonitis.

7.1.4 Follow-up for Recurrence and Survival

Per SOC, assessments for recurrence and survival will begin after the post-surgery follow-up visit and be made every 3 months (± 28 days) for the first 3 years. For years 4 to 6 after the last dose of study treatment, follow-up visits will take place every 6 months (± 28 days) until study completion. For the first year after surgery, in-office visits for long-term follow-up should coincide with in-office visits for any SOC post-neoadjuvant therapy.

Additional tests/investigations/imaging assessments for recurrent or metastatic disease will be at the discretion of the participant's treating physician per local SOC. Participants who have recurrence or metastatic disease at any time during the neoadjuvant treatment phase, or during long-term follow-up, who are unable to come for in-clinic visits, will be followed by telephone every 6 months (±1 month) for overall survival until consent withdrawal from trial, becoming lost to follow-up, death or end of the study, whichever is earlier. Participants on treatment or in survival follow-up will be contacted following the DCO for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO. Please refer to the SoA for complete details.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to help ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 40 days [+ 7 days] after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records). All patients are to be encouraged to be monitored for OS.
- At the time of withdrawal from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before the participants' withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she is still agrees for existing samples to be used in line with the original consent. If he/she requests

withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

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

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

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

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

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

In order to support key efficacy endpoints of EFS, IDFS, and OS analyses, the survival status of all participants in the FAS and the SAF should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up".

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.3).

Screening

Screening procedures will be performed according to the SoA (Section 1.3).

Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. Once the ICF is signed, all AEs and SAEs must be collected.

At screening, consenting participants are assessed to ensure that they meet study eligibility criteria (see Section 5.1 and 5.2). Demographic data and other characteristics will be recorded and will include date of birth or age, gender, smoking history, and race and/or ethnicity (according to local regulations).

Baseline assessment of the primary tumour and regional lymph nodes should include placement of image-detectable markers to demarcate the tumour bed for surgical management after neoadjuvant treatment.

A biopsy sample of the primary tumour is required prior to study treatment administration and can be obtained from the previously collected diagnostic biopsy. A core-needle biopsy or fine-needle aspirate is required to confirm suspicious lymph nodes. It is recommended that any confirmed malignant lymph node be marked for targeted dissection at surgery. At baseline, the participant should be evaluated for feasible and most appropriate surgical treatment and a proposed surgical plan made.

Confirmation of HER2 status on FFPE samples will be performed via a central laboratory. Eligibility for the study will be determined by central testing of HER2 status (see Laboratory Manual for details). Central testing will be carried out in laboratories operating according to GCP guidelines and with pathology staff fully trained by the diagnostic manufacturer to reproducibly score samples at all relevant HER2 IHC and ISH cut-offs.

Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Data Collection Following Study Analysis until the End of the Study

Following the DCO for the primary efficacy endpoint, assessments for survival and recurrence will be performed as indicated in the SoA (Section 1.3).

After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.14).

8.1 Efficacy Assessments

This study will evaluate the primary endpoint of pCR (ypT0/Tis ypN0) in the FAS. Efficacy assessments of pCR (secondary definition: ypT0 ypN0), EFS, and OS in the FAS will also be investigated and IDFS will be investigated in the population of participants that complete surgery (see Section 8.1.2 for definitions of each of these endpoints).

8.1.1 Surgical Specimen Assessments

For participants with clinically negative axillary nodes at baseline, the recommended axillary surgical management after completion of neoadjuvant therapy is SLNB. If SLNB is

conducted, all patients with positive micro- or macrometastases in sentinel nodes should undergo ALND regardless of number of positive nodes.

For participants presenting with clinically positive axillary nodes at baseline (palpable or suspicious on imaging), a nodal biopsy (core-needle biopsy or fine need aspiration acceptable) must be obtained prior to randomisation, and it is recommended that the positive node be marked prior to initiating therapy. Re-staging after completion of neoadjuvant treatment at time of definitive surgery with SLNB or ALND is acceptable. SLNB should only be performed if nodes are clinically non-palpable at time of surgery. For patients with positive lymph nodes marked prior to therapy, a localisation procedure to retrieve the nodes that have been clipped or marked at time of biopsy, immunohistochemistry for pathological analysis, and harvesting at least 2 sentinel nodes is strongly recommended. All patients who remain node positive at time of surgery should undergo ALND regardless of the number of positive nodes.

Surgical specimens, including primary tumours, lymph nodes and margins should be locally assessed first before sending them for central assessment of pathological response together with the local pathology report (please refer to the Pathology Manual). The surgical specimen should be mapped and sampled as outlined in the Pathology Manual. Local assessment should include the result of the pathology re-staging margin and lymph node assessment (plus cytology if applicable).

CCI [redacted]

The primary efficacy endpoint (pCR: ypT0/Tis ypN0) will be measured by blinded central review. However, post-neoadjuvant treatment decisions should be based on local assessment. Results of these independent reviews will not be communicated to investigators and results of investigator assessments will not be shared with the central reviewers. Tissue specimens must be collected and stored as outlined in the Pathology Manual.

Any participant that does not undergo breast surgery or axillary surgery (SLNB or ALND) will be counted as no pCR. All central pathologists reviewing and interpreting surgical specimens for assessment of pCR are required to be blinded to treatment. Tissue specimens must be collected and stored as outlined in the Pathology Manual.

For central assessment, the percentage of residual viable tumour that was identified on routine H&E staining after mapping of the surgical specimen will be evaluated. Participants with no viable tumour in the breast or lymph nodes at the time of resection (ypT0/Tis ypN0) will be considered to have had a pCR. Refer to the Pathology Charter for further assessment details.

The samples may also be used for exploratory research and diagnostic development (except in China and other selected countries and study sites, as per local regulations).

8.1.2 Surgical Assessments

Participants should undergo surgery [redacted] following administration of the last cycle of treatment of the assigned neoadjuvant regimen. Details regarding date of surgery, type of surgery, tumour resectability, etc. will be recorded in the appropriate eCRF. At baseline, the participant should be evaluated for surgical treatment. The proposed surgical plan based on the surgeon's opinion of what is technically feasible and most appropriate should be recorded in the eCRF. After completion of neoadjuvant treatment, the participant should be re-evaluated and the proposed surgical plan should be prospectively recorded. Both the surgeon's proposed plan and the final agreed upon plan should be documented and reported in the eCRF.

Post-surgery

Post-neoadjuvant therapy will be determined by the investigator and administered as part of a participant's SOC. It is strongly recommended that participants receive systemic therapy determined by their pathological response at definitive surgery. Participants from any arm that achieve a pCR are strongly recommended to receive trastuzumab with or without pertuzumab for up to 1 year (a maximum of 18 cycles of HER2-directed therapy, inclusive of any cycles administered neoadjuvantly) as per local SOC. Participants who do not achieve a pCR are recommended to receive treatment with T-DM1 (3.6 mg/kg Q3W for up to 14 cycles). Due to the omission of SOC treatment elements in the neoadjuvant phase participants in Arm A who do not achieve a pCR should be considered for treatment with anthracycline and/or taxane based chemotherapy in combination with standard HER2-directed therapy.

After completion of surgery, all participants should receive radiotherapy. It is recommended that HER2-directed therapy be administered concomitantly with radiotherapy (Tan-Chiu et al 2005). The sequence of radiotherapy and chemotherapy, as needed, will be determined as per standard practice.

Participants with ER-positive and/or PgR positive tumours should receive adjuvant endocrine therapy as per local clinical standards.

8.1.3 Central Reading of Scans

HRCT and breast MRI, including unscheduled visit scans, will be collected on an ongoing basis, and sent to an AstraZeneca-appointed iCRO for quality control and storage. Digital copies of all original scans should be stored at the investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images may be performed at the discretion of AstraZeneca. Results of these independent

reviews will not be communicated to investigators, and results of investigator tumour assessments will not be shared with the central reviewers.

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

8.1.3.1 Baseline Disease Staging

Evidence of absence of metastatic disease is required prior to randomisation and must include a bone scan and diagnostic CT or MRI of the chest, abdomen, and pelvis (Note: PET/CT scan may be used as alternative imaging technique and precludes the need for bone scan). The baseline disease staging can be performed outside of the 28-day screening period (within 42 days prior to randomisation).

8.1.3.2 Ultrasound of the Breast and Axilla

Ultrasound of breast and axilla is mandated at baseline within 42 days prior to randomisation. If on ultrasound examination there is evidence of suspicious axillary lymph nodes at the baseline examination, then fine-needle aspiration or core-needle biopsy is required. It is recommended that any confirmed malignant lymph nodes be marked for targeted dissection at surgery.

8.1.3.3 Breast MRI

Breast MRIs, when available, will be performed in all participants at 3 timepoints: screening, before Cycle 5 Day 1 (within 3 days before treatment administration), and at the end of treatment visit within 14 days prior to definitive surgery during the neoadjuvant treatment phase. For participants that complete neoadjuvant therapy, the EoT visit should be combined with the pre-surgery visit which takes place within 14 days of surgery. In case of early discontinuation, breast MRIs should be performed within 7 days of decision to discontinue all study treatment. Breast MRIs performed as part of routine clinical management are acceptable for use as the screening tumour imaging if they are of diagnostic quality and were performed within 28 days prior to the first dose of trial treatment.

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

8.1.3.4 Bilateral Mammogram

Bilateral mammogram must be obtained during screening any time between diagnosis and randomisation, at 6 months post-surgery, and then every 12 months during the long-term follow-up period up to 6 years, or until patient has recurrence or metastatic disease. Additional mammograms can be performed per the investigator's discretion. Participants who have

undergone mastectomy do not require mammograms of reconstructed breast(s).

8.1.4 Disease Follow-up and Confirmation of Disease Progression or Recurrence

During the neoadjuvant treatment, diagnosis of disease progression or second primary breast cancer should be supported by clinical, laboratory, radiological, and/or histological findings. If the investigator is not able to confirm disease progression by objective criteria and is considering discontinuing the patient, a discussion with the AstraZeneca Study Physician is required. In cases where discordant results regarding disease progression are obtained by physical examination, imaging, biopsy and/or surgery, surgical results will overrule those obtained from biopsy, imaging, and physical examination.

Post-operatively, all participants must be followed to assess disease recurrence and survival. The designation of disease recurrence, whether local, regional, or distant can be made only when clinical, laboratory, radiological and/or histological findings support the diagnosis (see Table 6 for details).

During the post-operative portion of this study, disease status should be assessed per local practice every 3 months for the first 3 years and then every 6 months thereafter. The diagnosis of a breast cancer progression, recurrence, or second primary tumour should be confirmed histologically whenever clinically possible.

The earliest date of diagnosis of disease progression, recurrent disease, or a diagnosis of a second primary cancer should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence.

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. While ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or recurrent disease, these events should be recorded in the appropriate eCRF. For participants who develop second primary non-breast cancers, these events should be recorded as adverse events as appropriate per Section 8.3.11. Participants who have a diagnosis of in situ breast disease or second (non-breast) malignancies should be maintained on a regular follow-up schedule whenever possible in order to fully capture any subsequent recurrent disease events.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are provided in Table 6.

Table 6 Definition and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Event at Follow-up

Local invasive recurrence	Ipsilateral breast after previous lumpectomy	• Defined as evidence of invasive tumour (except DCIS and lobular carcinoma in situ, both of which will be recorded but not counted as events for EFS or IDFS) in the ipsilateral breast after lumpectomy. Participants who develop clinical evidence of tumour recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. • Confirmed by positive histology or cytology.
	Ipsilateral breast after previous mastectomy	• Defined as evidence of invasive tumour in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence. • Confirmed by positive histology or cytology.
Regional recurrence	• Defined as the development of tumour in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes, or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumour in the opposite breast. • Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT scan or MRI if no biopsy was performed).	

Distant recurrence	Defined as evidence of tumour in all areas, except for those described in local invasive recurrence and regional recurrence above. Confirmed by the following criteria: **Skin, subcutaneous tissue, and lymph nodes (other than local or regional)** • Positive cytology, aspirate, or biopsy, or radiological (CT scan, MRI, PET scan, or ultrasound) evidence of metastatic disease. **Bone** • X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, or bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), or Biopsy proof of bone metastases or cytology. **Bone marrow** • Positive cytology or histology or MRI. **Lung** • Radiologic (CT or PET scan) evidence of multiple pulmonary nodules consistent with pulmonary metastases. • Positive cytology or histology in case of diagnostic doubt (particularly for solitary lung lesions) if a biopsy is not performed. Serial scans should be obtained, if possible, to document stability or progression. • Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy. **Liver** • Radiologic evidence consistent with liver metastases, or liver biopsy or fine-needle aspiration. NOTE: If radiological findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained, if possible, to document stability or progression. **CNS** • Positive MRI or CT scan, usually in a participant with neurologic symptoms, or biopsy or cytology in case of inconclusive imaging (eg, for a diagnosis of meningeal involvement) and, depending on the general status of the participant, additional investigations (including cytology of the cerebrospinal fluid).
Contralateral invasive breast cancer	• Confirmed by positive cytology or histology.
Death from any cause	• Any death due to any cause is considered an event for the following endpoints: EFS, IDFS, CCI and OS.

CNS = central nervous system; CT = computed tomography; DCIS = ductal carcinoma in situ; CCI EFS = event-free survival; IDFS = invasive disease-free survival; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography.

8.1.5 Overall Survival

Assessments for survival will be conducted at EoT, at the post-surgery follow-up visit, and every 3 months (± 28 days) after the post-surgery follow-up for the first 3 years, then every 6 months (± 28 days) during years 4 to 6 until study completion. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.3.

8.1.6 Determination of Menopausal Status

Assessments to determine menopausal status i.e. menstruation and laboratory tests to measure follicle-stimulating hormone (FSH), luteinising hormone (LH), and oestradiol levels will be performed at baseline, at the EoT, at the post-surgery follow-up visit, and then annually during years 1-3. For postmenopausal patients, menopausal status will be assessed at baseline only.

8.1.7 Clinical Outcome Assessments

Patient-reported outcomes are one type of clinical outcome assessment, and generally refer to all symptoms and outcomes that are directly reported by the participant, without interpretation of the participant's response by a clinician or any other individual. Participants will be asked to complete assessments (questionnaires) that measure a variety of core outcomes that inform or contextualise treatment benefit and risk (Kluetz et al 2018), including data that can be used to compare the efficacy and tolerability of individual treatments. These instruments allow the participant to contribute valuable data regarding the presence and severity of cancer-related symptoms, symptomatic adverse events (patient-felt side effects) associated with study treatment, and physical function impacts. CCI [redacted] Patient-reported outcome assessments will be administered during neoadjuvant treatment and at the time of treatment discontinuation, per the PRO-specific SoA (Table 7). Patient-reported outcomes during post-surgical follow-up are presented in Table 8. Patient-reported outcome assessments will only be completed by participants if a linguistically validated version is available in their language for the country in which they live.

Participant burden is a critical consideration, therefore all PRO assessments included within the study are directly linked to a specific study objective, will only be administered when relevant to the participant's current stage of study treatment, and only at the frequency necessary to evaluate an endpoint for that objective. To further reduce participant burden, customised short-form assessments (such as those developed from the EORTC Item Library) have been developed for use to measure select items from longer instruments, such as the EORTC QLQ-C30, in order to ensure participants do not complete any superfluous items that can be assessed less frequently. Approximately 9-14 minutes will be required for participants to complete the questionnaires at any given assessment.

The following PRO instruments will be administered in this study: The EORTC QLQ-C30, short forms developed using the EORTC Item Library (123, 124, 125, and 19), the PRO-CTCAE, the PGI-TT, and the CCI .

Table 7 Patient-reported Outcome Schedule of Activities during Neoadjuvant Treatment

Study Day	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162[a]	EoT
PRO-CTCAE, PGI-TT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC-IL123, EORTC QLQ-C30	X				X				X				X				X				X				X
EORTC-IL124, EORTC-IL19		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X		X	X	X	
CCI	X								X				X								X				X

[a] Patients who do not discontinue treatment prior to Day 169 (for example, due to dose delay) will continue to complete weekly PRO assessments according to a repeating schedule based on the period from Day 141 through Day 168 until study EoT.

Note: Baseline PRO questions should be completed after informed consent and before the first dose of the study drug at Cycle 1 Day 1.

Note: Approximately 9-14 minutes will be required for participants to complete the questionnaires at any given assessment.

EORTC = European Organisation for Research and Treatment of Cancer; EORTC-IL = European Organization for the Research and Treatment of Cancer Item Library Form; EoT = End of Treatment; CCI 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.

Table 8 Patient-reported Outcome Schedule of Activities Post-Surgery

Instrument	Safety FU	3 Months	6 Months	9 Months	12 Months	15–36 Months
PGI-TT	Same as EoT visit (see Table 7)	X	X	X	X	Every 3 months
PRO-CTCAE; EORTC-IL123 or EORTC-IL125		X	X	X	X	
EORTC QLQ-C30 (including physical function)			X		X	Every 3 months
EORTC-IL19		X		X		
CCI			X		X	Every 6 months

EoT = end of treatment; EORTC = European Organisation for Research and Treatment of Cancer; EORTC-IL19 = European Organization for the Research and Treatment of Cancer Item Library physical functioning subscale; CCI FU = follow-up; PGI-TT = Patient Global Impression of Treatment Tolerability; PRO-CTCAE = Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 = 30 item core quality of life questionnaire.

8.1.7.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC QoL Group in 1993. It consists of 30 items and measures symptoms, functioning, and global health status/QoL (Aaronson et al 1993) for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer participants (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea), and 1 item on the financial impact of the disease.

8.1.7.2 PRO-CTCAE

The PRO-CTCAE system was developed by the NCI and is included to assess tolerability from the participants' perspective. The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. PRO-CTCAE is an item library of symptoms experienced by participants while undergoing treatment of their cancer. It has been carefully and systematically developed based on the NCI CTCAE to provide patient-reported assessment of common adverse effects of cancer treatments, including a library of 124 items, representing 78 symptomatic toxicities. The items have previously undergone extensive qualitative and quantitative evaluation to support their validity and reliability (Basch et al 2014, Dueck et al 2015, Hay et al 2014). For each symptomatic AE (eg, headache), there are up to 3 questions related to key symptom attributes, including the symptom frequency, severity, and interference with daily activities. Each question uses a 7-day recall with a 5-point ordinal response scale. The items pre-selected for this study are based on expected treatment-related symptoms, and in consideration of symptoms that are already captured in the other PRO instruments in order to minimise participant burden. During the on-treatment period, the following PRO-CTCAE items will be administered in this study: mouth/throat sores, taste changes, rash, hair loss, numbness and tingling, headache, aching muscles, joint pain, insomnia, increased sweating, and nosebleeds. In the follow-up period, the following PRO-CTCAE items will include taste changes, numbness and tingling, aching muscles, and joint pain. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

The PRO-CTCAE is intended to enhance the precision and reproducibility of AE reporting to provide data that complements and extends the information provided by clinician-reporting using CTCAE, and to represent the participant perspective of the experience of symptomatic AEs. Signs and symptoms assessed with the PRO questionnaires will not be considered AEs unless entered as such into the eCRF. Use of PRO-CTCAE is limited to describing in aggregate the safety and tolerability of the study interventions and does not include the use of PRO-CTCAE for diagnostic, prognostic, or therapeutic purposes in human subjects, or the use of PRO-CTCAE to assess the efficacy of the study interventions.

8.1.7.3 PGI-TT

The PGI-TT item is included to assess how a participant perceives the overall bother of treatment-related side effects of cancer treatment over the past 1 week. Participants will be asked to choose the response that best describes the severity of their overall cancer symptoms over the past week. The response options are: "not at all", "a little bit", "somewhat", "quite a bit", and "very much". This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment-related side effects.

8.1.7.4 EORTC Item Library Short Forms

Study endpoints that refer to "short form scales developed using the EORTC Item Library" will be referred to individually in the future using unique identifiers (ILXXX) in accordance with required EORTC naming conventions; however these have not yet been generated and assigned by EORTC. EORTC requirements dictate that any unique combination of items included within a single form must be designated as a separate and unique instrument. Therefore, select short forms with overlapping items will each be assigned a unique EORTC identifier, however they will never be administered at the same time. This is necessary to a) minimise participant burden by excluding irrelevant or superfluous items, b) ensure duplicate items are never administered to a participant at a single time point (for example, a symptom item from the EORTC QLQ-C30 that is included in a separate short form for administration at intermediate timepoints), and c) facilitate consistent measurement of symptoms and function associated with a study objective.

In total, 4 EORTC short form scales will be included in this study:

- **EORTC-IL19:** This form consists of the 5-item physical functioning scale from the EORTC QLQ-C30. It will be administered at intermediate timepoints where physical function data is necessary to fulfil a study objective, without requiring administration of the full EORTC QLQ-C30 instrument. EORTC-IL19 is the identifier assigned by EORTC and will not be updated in a subsequent amendment.
- **EORTC-IL123:** This form consists of symptomatic AE (treatment-related symptom) items to supplement the PRO-CTCAE and EORTC QLQC30. Items included in this form are not found in the EORTC QLQ-C30 and are either a) unavailable within the PRO-CTCAE library or b) better suited to characterise the symptomatic AE of interest than the equivalent PRO-CTCAE item. It will only be administered at timepoints where the full EORTC QLQ-C30 is also being administered.
- **EORTC-IL124:** This form contains all items included in the EORTC-IL123, in addition to any individual EORTC QLQ-C30 items that measure a symptomatic AE of interest. It will only be administered at timepoints where the full EORTC QLQ-C30 is <u>not</u> being administered.

- **EORTC-IL125:** This form contains a subset of symptoms drawn from the EORTCIL124 that measure symptomatic AEs of interest during study follow up. It will only be administered at timepoints during long-term follow-up where the full EORTCQLQ-C30 is not being administered.

8.1.7.5 CCI

CCI

CCI

8.1.7.6 Administration of Electronic PRO (ePRO) Questionnaires

Baseline PRO questions should be completed after informed consent and before the first dose of the study drug at Cycle 1 Day 1. While on treatment, PRO questionnaires will be self-administered electronically at home by the participants using handheld devices at the time points indicated in the SoA. Participants should complete the ePROs prior to or at the sites if the assessment time point coincides with a scheduled site visit. Alerts will remind participants when ePRO assessments should be completed.

Participants must be instructed to bring the device to all visits.

During follow-up, participants will complete the ePRO assessments using an electronic device during clinic visits at the time points indicated in the SoA. In the event of device unavailability during a site visit, paper questionnaires may be used at that visit. Questionnaires will be administered to participants in their local language. If questionnaires are not available in the local language of the participant, these will not be required for completion. A web back-up may be available to answer the questionnaires if there are technical problems with the device.

Each site must allocate the responsibility for the administration of the ePRO instruments to a specific individual (eg, a research nurse or study co-ordinator) and, if possible, assign a back-up person to cover if that individual is absent.

Approximately 9-14 minutes will be required for participants to complete the questionnaires.

The below instructions should be followed when collecting PRO data:

- The research nurse or appointed site staff should explain to participants the value and relevance of these data, so they are motivated to comply with questionnaire completion. Inform the participant that these questions are being asked to find out, directly from them, how their disease and treatment impacts how they feel and function.
- It is vital that the ePRO reporting is initiated at randomisation, as specified in the SoA to capture the effect of the study intervention. The ePRO device must be charged and fully functional at the beginning of the baseline visit (Cycle 1, Day 1) to ensure that the PROs can be completed at the start of the visit.
- Site staff must ensure that a participant completes baseline PRO questionnaires before revealing the treatment arm allocated to the participant.
- The participant should bring the ePRO device to each site visit so the research nurse or appointed site staff can check if there are available PRO questionnaires to be completed and that the device is functioning properly.
- PRO questionnaires completed at the sites must be completed prior to treatment administration or any other study procedures performed at the site and ideally before any discussions of health status (following informed consent), including medication treatments, and before discussion of PD to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimise bias.
- On completion of the questionnaire at the site, the device should be handed back to the research nurse or appointed staff, who should check that all questionnaires were completed.
- PRO questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO device using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the participant is completing the ePRO at home.
- All PRO questionnaires are to be completed using an ePRO device. If technical or other device-related issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.

- The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items.
- The participant must not receive help from relatives, friends, or clinic staff deciding on answers to the ePRO questionnaires. The responses are the participant's alone.
- Participants should be instructed to bring visual aids for reading (eg, glasses or contact lenses) to the baseline visit and all subsequent visits. If a participant uses visual aids (eg, glasses or contact lenses) for reading and does not have them when he or she attends the site visit, the participant may be exempted from completing the PRO questionnaires at that site visit.
- Site staff must not read or complete the ePRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate), that participant is exempted from completing PRO questionnaires but may still participate in the study. Participants exempted in this regard should be flagged appropriately by the site staff in the source documents and in the designated eCRF.
- Questions must not be translated from an available language in the device into the language for the participant speaks.
- Reminders should be provided to participants as needed to ensure compliance with the assessment schedules.
- The research nurse or appointed site staff must monitor compliance since minimising missing data is a key aspect of the study success.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a participant could not complete assessments, in the source documents and in the designated eCRF. If the site receives an email notification regarding the participant's compliance, appropriate action will be taken (eg, discussion with participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). A solution to enhance/resolve compliance should be discussed with the participant. Discussion and compliance review should be reflected in source documents.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

- A complete physical examination will be performed at screening and will include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems.

- Targeted physical examinations will be performed at subsequent visits after screening as described in the SoA and are to be used by the investigator on the basis of clinical observations and symptomatology. If screening assessments have been performed within 3 days prior to starting study treatment, they do not have to be repeated at Cycle 1 Day 1 if the participants condition has not changed. During neoadjuvant treatment, targeted physical examinations must be performed within 3 days before the next dose of study treatment.
- All physical examinations (complete and targeted) must include breast exam and tumour palpation.

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

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA. For participants receiving weekly paclitaxel during Cycles 5-8, vital signs assessments on Days 8 and 15 after Cycle 1 are performed per local standard practice and will need to be recorded only as clinically indicated. During the intervention period, vital signs must be performed within 3 days before dosing administration at the time points indicated in the SoA.

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

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

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

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; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 3 hours at room temperature.

Based on a 90-minute infusion period, vital signs, which includes blood pressure, pulse rate, temperature, and respiratory rate, will be collected at each cycle:

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]).
- At the end of the infusion (after approximately 90 minutes ± 5 minutes).

Based on a 30-minute infusion period, vital signs, which includes blood pressure, pulse rate, temperature, and respiratory rate, will be collected at each cycle:

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- At the end of the infusion (after approximately 30 minutes ± 5 minutes)

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

8.2.3 Electrocardiograms

Triplicate ECGs will be performed at screening. Subsequent ECGs will be performed in triplicate only if abnormalities are noted. Single 12-lead ECGs will be performed at the times specified in the SoA after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. If an ECG has been performed within 3 days prior to starting study treatment, it does not need to be collected again at Cycle 1 Day 1 if the participant's condition has not changed. If indicated, ECGs must be performed within 3 days before dosing administration at the time points indicated in the SoA.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

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

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

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

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

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

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

Pregnancy tests will be conducted within 72 hours before randomisation for all female participants of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours before infusion of each cycle, at EoT and at the safety follow-up visit. A negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine beta-human chorionic gonadotropin pregnancy test prior to each administration of study intervention. If the screening assessment for pregnancy was performed within 3 days prior to starting study treatment, it does not have to be repeated at Cycle 1 Day 1.

The following laboratory variables will be measured.

Table 9 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Haemoglobin	Creatinine
Leukocyte count	Creatinine clearance
Leukocyte differential count (absolute count; neutrophils, lymphocytes, monocytes, eosinophils, basophils)	Bilirubin, total
Platelet count	Alkaline phosphatase
Absolute neutrophil count	AST
Absolute lymphocyte count	ALT
Total red blood cell count	Albumin
Haematocrit	Potassium
	Calcium, total
	Sodium
	Bicarbonate (if available)

Table 9 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Urinalysis	Lactate dehydrogenase
Haemoglobin/Erythrocytes/Blood	Protein, total
Protein/Albumin	Urea/blood urea nitrogen depending on local practice
Glucose	Troponin
Specific gravity	Magnesium
Coagulation	Chloride
Coagulation variables (aPTT or PTT, and PT or INR)	GGT

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; INR = international normalised ratio; PT = prothrombin time; PTT = partial thromboplastin time.

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

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

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

8.2.5 Other Safety Assessments

8.2.5.1 Echocardiogram/Multigated Acquisition Scan

An ECHO or MUGA scan to assess LVEF will be performed at the visits as shown in SoA (Section 1.3). The screening ECHO or MUGA scan must be performed within 28 days prior to randomisation. During neoadjuvant treatment, the ECHO or MUGA scan is only assessed once within 3 days before dosing administration of Cycle 5 Day 1. The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO scan is used for the screening assessment for a given participant, then ECHO scan should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, accurate to 1% and not estimated to 5%). All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

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

Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening and if at any time a participant reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. If an additional troponin sample is taken, then an ECG also needs to be performed.

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

Note: In Germany, LVEF will be measured only by ECHO (see Appendix Q).

8.2.5.2 Pulmonary Assessments

Pulse oximetry should be evaluated by investigator or the delegate physician prior to the administration of study intervention at the time points indicated in the SoA (Section 1.3). For participants receiving weekly paclitaxel during Cycles 5-8, pulse oximetry assessments on Days 8 and 15 after Cycle 1 are performed per local standard practice and will need to be recorded only as clinically indicated.

Pulmonary function tests will be performed at screening and should include basic spirometry at a minimum with optional additional components as mentioned in Table 10.

Table 10 Spirometry Component

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

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

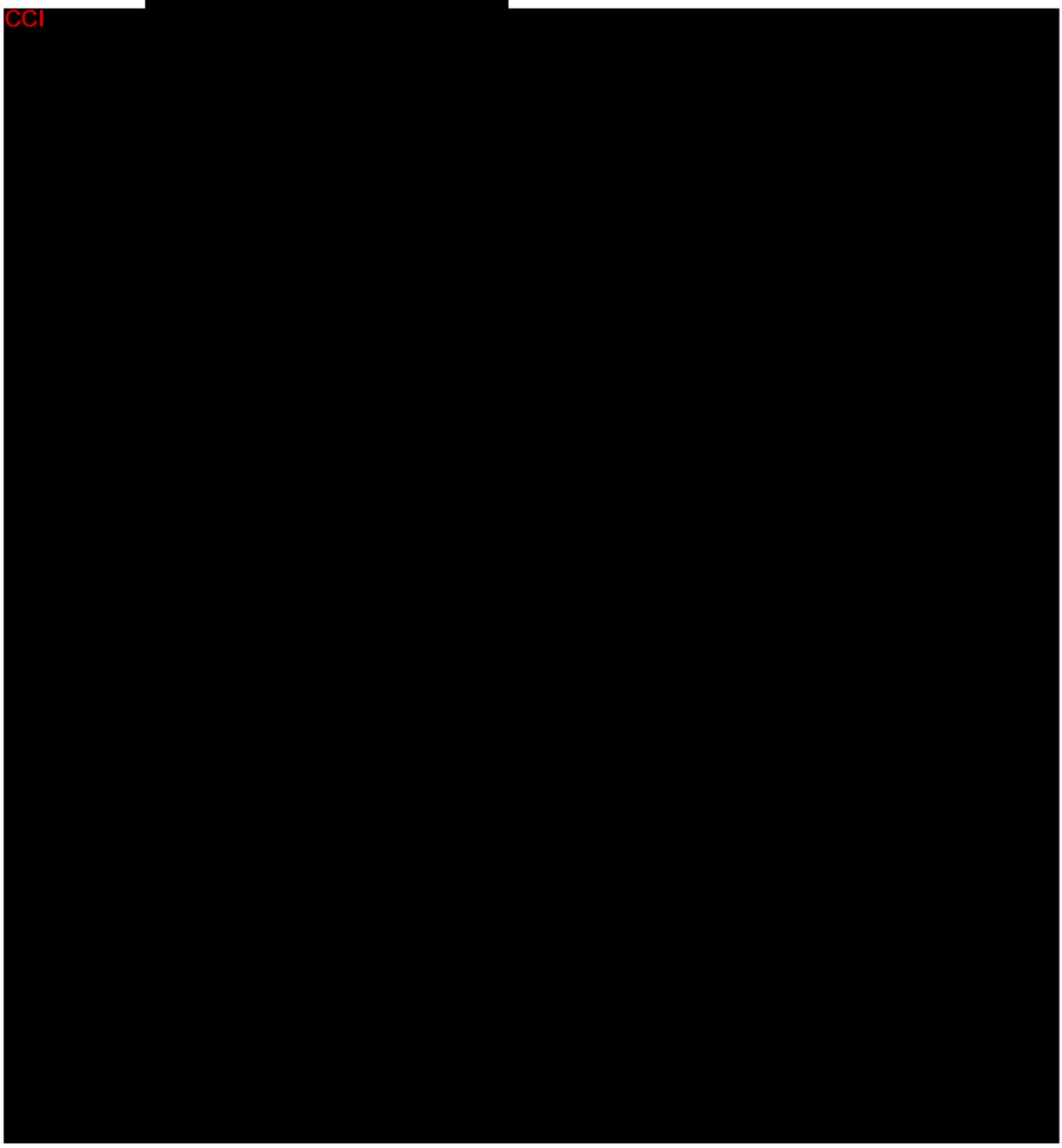
DLCO will be performed/encouraged if feasible, but for participants with prior severe and/or prior clinically significant pulmonary disorders, DLCO is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.2.5.3 additional pulmonary assessments.

HRCT (otherwise non-contrast CT is acceptable) of the chest will be performed at screening,

and then Q6W (at least 35 days, but not more than 42 days from previous scan) until EoT, at the 40-day (+ 7 days) safety follow-up, and if ILD/pneumonitis is suspected, for all participants. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of T-DXd. At screening, if both a non-contrast chest HRCT scan for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumour response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT should be performed first.

8.2.5.3 CCI

CCI



8.2.5.4 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the times specified in the SoA (Section 1.3). If ECOG performance status information has been collected within 3 days prior to starting study treatment, it does not need to be collected again at Cycle 1 Day 1 if the participant's condition has not changed. ECOG performance status must be collected within 3 days before dosing administration in each cycle. ECOG performance status is based on the following:

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

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

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

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

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

5 Dead.

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

8.2.5.5 Ophthalmologic Assessments

Ophthalmologic assessments will be performed as specified in the SoA (Section 1.3) and will include visual acuity testing, slit lamp examination and fundoscopy.

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs (other than ILD/pneumonitis and heart failure information which will be collected in the post-surgery setting) will be collected from the time of signature of the ICF, throughout the treatment period and including the safety follow-up period (which is 40 + 7 days after the discontinuation of all study interventions).

For ILD/pneumonitis, safety follow-up will be continued until resolution of ILD/pneumonitis events with an onset from randomisation to the safety follow-up period. Heart failure AEs will be collected and recorded until the end of the study (up to 6 years follow-up).

If an event that starts post the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study intervention, then it should be reported as an AE or SAE as applicable. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.14.

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

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

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

- SAEs.
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD/pneumonitis is described by the Event Adjudication Site Manual).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) $\geq 3 \times$ ULN and an elevated TBL $\geq 2 \times$ ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either a serious adverse event, a nonserious adverse event, or no adverse event occurs and is considered by the investigator as clinically relevant, ie, poses an actual or potential risk to the subject.
- Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. Adverse events can either be serious or non-serious. Details of the overdose including T-DXd dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within EDC.

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the EU CTR 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.3.2 Follow-up of AEs and SAEs

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim).
- The date when the AE started and stopped.
- Initial CTCAE grade, plus any changes in CTCAE grade.
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the study intervention(s) (yes or no).

- Action taken with regard to study intervention(s).
- Administration of treatment for the AE.
- Outcome.

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

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

The grading scales found in the National Cancer Institute CTCAE v5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When

collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

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

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

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

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

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

8.3.6 Heart Failure

Heart failure occurring during the study must be collected and recorded until the end of the study (up to 6 years follow-up). If the diagnosis is heart failure, it should be reported as such and not as individual signs and symptoms. In addition to CTCAE grading, heart failure should be graded according to NYHA classification as per Table 11.

Table 11 New York Heart Association (NYHA) Functional Classification

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

8.3.7 Hy's Law

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

8.3.8 Disease Progression

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

8.3.9 Disease Recurrence

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. Disease recurrence should be captured as efficacy assessment data only, and not be recorded as AEs. Events which are unequivocally due to disease recurrence should not be reported as an AE during the study. The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are provided in Table 6.

8.3.10 Disease Under Study

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

discontinuation of the study intervention.

8.3.11 New Cancers

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

8.3.12 Deaths

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

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

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

8.3.13 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of T-DXd safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Serious AESIs will be recorded and reported as per Section 8.3.15.

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

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 following events are considered to be AESIs:

Interstitial Lung Disease/Pneumonitis

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

Left Ventricular Ejection Fraction Decrease

Left ventricular ejection fraction (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.

8.3.14 Safety Data to be Collected Following the Final Data Cut-off of the Study

All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants after the final DCO which are considered by the investigator to be late-onset toxicities to the study treatments must be reported as detailed in Section 8.3.15.

8.3.15 Reporting of Serious Adverse Events

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

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

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

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

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

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

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

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

The reference documents for definition of expectedness/listedness for the study treatments used in this study are:

- The current IB for T-DXd.
- The label of the current effective version of the SmPC for pertuzumab, Roche Products Limited.
- The label of the current effective version of the SmPC for trastuzumab, Roche Products Limited.
- The label of the current effective version of the SmPC for paclitaxel, Hospira UK Limited.
- The label of the current effective version of the SmPC for cyclophosphamide, Sandoz Limited.
- The label of the current effective version of the SmPC for doxorubicin hydrochloride, Accord Healthcare Limited.

8.3.16 Pregnancy

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

8.3.16.1 Maternal Exposure

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

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.15) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.16.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 6 months after the last dose of study intervention for T-DXd or per local prescribing information for SOC treatments received after neoadjuvant treatment.

Participants in the SOC (ddAC-THP) group should follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SOC group.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of study intervention until 6 months after the last dose of study intervention (or per local prescribing information for SOC treatments administered after neoadjuvant treatment) should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry

site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

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

8.3.17 Medication Error, Drug Abuse, and Drug Misuse

8.3.17.1 Timelines

If an event of medication error, drug abuse or drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or **5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.15) and **within 30 days** for all other events.

8.3.17.2 Medication Error

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

The full definition and examples of a Medication Error can be found in Appendix B 4.

8.3.17.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of study intervention for perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.17.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorised product information, or for unauthorised study intervention(s), outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of Drug Misuse can be found in Appendix B 4.

8.4 Overdose

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

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.15) and within 30 days for all other overdoses.

For participants receiving SOC (ddAC-THP), refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.5 Human Biological Samples

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

Samples will be stored for a maximum of 15 years from the end of the study (as defined in the protocol) in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic (PK) samples will be disposed of within 6 months after finalisation of the Bioanalytical Report, unless consented for future analyses.
  - Pharmacokinetic (PK) samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
  - Pharmacokinetic (PK) and ADA samples collected in China will be stored and disposed of according to local laws and regulations. Pharmacokinetic (PK) samples

collected in China will be destroyed within 6 months after finalisation of the Bioanalytical Report, and ADA samples collected in China will be destroyed within 1 year of CSR publication. AstraZeneca, as a Foreign Entity, will not biobank in China, in line with Human Genetic Resources regulations.

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years post CSR publication. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

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

8.5.1 Pharmacokinetics

- Whole blood samples will be collected for measurement of serum concentrations of T-DXd, anti-HER2 antibody, and DXd for participants receiving T-DXd, as specified in the SoA.
- In addition, if feasible, a blood sample should be collected for PK analysis as soon as possible when a participant is suspected of having ILD/pneumonitis (see Section 8.2.5.3 and Appendix J).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, for example, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Blood samples collected for PK analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5.1.1 Determination of Drug Concentration

Samples for determination of concentration of T-DXd, anti-HER2 antibody, and DXd in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

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

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be collected for subjects receiving

T-DXd, per the SoA (Section 1.3). Samples will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response. In addition, the presence of neutralising antibodies could be tested for all ADA-positive samples using a validated assay.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.5.4 Surgical Specimen Collection

The surgical specimen collected during surgical resection (following neoadjuvant treatment) is required for pCR assessment as well as diagnostic and exploratory testing. Refer to the Pathology Manual for further details.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study. Samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Section 1.3). The following mandatory samples will be collected from all participants, including screen failures where possible.

Mandatory Tumour Sample at Study Entry

At study entry, participants must provide an adequate tissue sample consisting of 2 cores from either an archival biopsy taken using a core-cut or tru-cut device as a standard hospital diagnostic procedure CCI [redacted], or from a new biopsy.

If the archival biopsy was taken CCI [redacted] or is not likely to provide adequate tissue for the biomarker assays (eg, technical artefact or too little tumour present in the diagnostic core) then 2 cores from a new biopsy are required. New biopsy samples must not be taken from a previously irradiated lesion. Samples with limited tumour content or fine-needle aspirate samples are NOT acceptable.

Archival or newly obtained biopsy samples should be provided in the form of FFPE tissue blocks where local regulations allow. If local regulations do not permit the submission of tissue blocks, then a minimum of 20 freshly-cut sections containing 2 cores must be submitted. For cases of multi-centric tumours, 2 cores per discrete lesion in each affected quadrant or 20 freshly cut sections containing 2 cores must be submitted. If blocks are

incomplete or fewer than 20 slides are available, participants may be eligible following discussion with the AstraZeneca Study Physician.

Tumour samples at study entry will be used for central laboratory confirmation of HER2-positive status per inclusion criteria to determine study eligibility using assays selected by AstraZeneca. To meet the requirement of regulatory approval of a companion diagnostic, sections of the tumour may be retained in all regions that allow this for potential additional studies, as requested by the regulatory authorities, to support potential test approval.

Samples with limited tumour content and fine-needle aspirate specimens are NOT acceptable (see Laboratory Manual for further details). Cytology samples (slides or cell blocks) including fine-needle aspirates, transbronchial needle aspirates, bronchial washings, bronchial lavage, bone marrow aspirates, and expectorated sputum are NOT acceptable samples and should not be sent.

CCI

Note: Tumour samples collected for HER2 testing from Chinese participants will be destroyed or repatriated maximally within 1 year of CSR publication. For specific details regarding sample requirements in China, please refer to the Laboratory Manual for further information.

CCI

CCI

CCI

Blood Sample Collection (Collected Pre-dose)

The following blood samples will be collected as specified in the SoA (Section 1.3):

- CCI

CCI

- Blood sample for the isolation of plasma to enable analysis and interpretation of CCI
  CCI

  Note: This blood sample will not be collected in China.
- The buffy coat layer obtained during the plasma isolation process of the baseline sample may be taken to enable assessment, analysis, and interpretation of CCI :
  - CCI
  - CCI

    Note: This sample will not be collected in China.
- Blood sample for CCI

  Note: This blood sample will not be collected in China.
- Blood sample for CCI

  Note: This blood sample will not be collected in China.
- Blood sample for the assessment of CCI

  Note: This blood sample will not be collected in China.

- Blood sample for CCI

  Note: This blood sample will not be collected in China.
- Blood sample to determine menopausal status, including analysis of FSH, LH, and oestradiol levels.

Comparisons will be made between baseline and other measures to determine if CCI CCI

Blood samples for CCI

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

8.6.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker assessment is also part of this study as specified in the SoA and is subject to agreement to optional consent.

Where local regulations permit, optional samples will be tested for exploratory biomarkers which may include, but are not limited to, CCI

CCI Participants will not be excluded from the study if these samples are not collected.

CCI This sample will not be collected in China.

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

8.6.3 Other Study-Related Biomarker Assessments

CCI [redacted]

Additional exploratory analyses may be undertaken on participants' samples to identify other biomarkers of CCI [redacted] to study interventions and our CCI [redacted] CCI [redacted].

CCI [redacted]

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

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the ICF addendum. The sample for genetic research will be obtained at CCI [redacted]. If, for any reason, the sample is not drawn at CCI [redacted]. Only 1 sample should be collected per participant for genetics during the study.

CCI [redacted] Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the storage and destruction of Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

The sample for genetic testing will not be collected in China.

8.8 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics data associated with medical encounters will be collected in the eCRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The assessment of HcRU will increase the understanding regarding the relationship between treatment and tumour-related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction or bleeding. This will be captured and analysed to inform submissions to payers.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalisation (total days or length of stay, including duration by wards [eg, intensive care unit]).

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared by the time the first participant is randomised. The final amendment of the SAP will be completed prior to database lock for the primary endpoint.

CCI [redacted]

9.1 Statistical Hypotheses

One primary hypothesis of interest with regards to the efficacy is:

- H0: No difference between T-DXd (Arm A) and ddAC-THP (Arm C).
- H1: T-DXd (Arm A) improves pCR rate compared to ddAC-THP (Arm C) in the ITT population.

The other primary hypothesis of interest is:

- H0: No difference between T-DXd in sequence with THP (Arm B) and ddAC-THP (Arm C).
- H1: T-DXd in sequence with THP (Arm B) improves pCR rate compared to ddAC-THP (Arm C) in the ITT population.

Figure 3 CCI
CCI

α = alpha; pCR = pathological complete response.

9.2 Sample Size Determination

Approximately CCI participants will be screened to achieve 900 randomised participants with HER2-positive EBC for the assessments of pCR.

Assuming recruitment over CCI months, the data cut-off for the futility analysis is anticipated approximately CCI months after the first participant is randomised. The data cut-off for the primary analysis for the primary pCR endpoint will be anticipated approximately 39 months after the first participant is randomised, when all the participants have had the opportunity to be assessed for pCR. The study will be considered successful if either test for the observed

difference in pCR rates is significant. This assumes [redacted]% of pCR in Arm C and [redacted]% improvement with either active treatment. The primary analysis will provide at least [redacted]% power to demonstrate statistical significance regarding difference in pCR rates at an overall [redacted]% alpha level (2-sided test) for the dual primary endpoints.

The participants will be followed for long-term benefit data after the completion of the pCR analysis. The last analysis intended for 3-year EFS will be performed when all participants have had the opportunity to be followed for 3 years, or have discontinued or withdrawn from the study. [redacted]

The sample size and the power of the study, for the analysis of pCR, were 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.

9.3 Populations for Analyses

The following populations are defined (Table 12):

Table 12 Populations for Analysis

Population/Analysis Set	Description
FAS (ITT)	All participants who are randomised in the study. The FAS will be used for all the efficacy analyses (including PROs). Treatment groups will be compared on the basis of randomised study intervention, regardless of the treatment actually received. Participants who were randomised but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomised.
Resected analysis set	All participants in the FAS who had surgical resection following neoadjuvant treatment and who do not have positive margins. The resected analysis set will be used for IDFS endpoint.
Safety analysis set	All participants who have received at least 1 dose of IMP (at least 1 study intervention [T-DXd, paclitaxel, trastuzumab, pertuzumab, doxorubicin, and cyclophosphamide]). Erroneously treated subjects (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A subject who has received any dose of the experimental investigational product will be classified as in the experimental investigational product treatment group.

Table 12 Populations for Analysis

Population/Analysis Set	Description
PK analysis set	All participants randomly assigned to study intervention who take at least 1 dose of T-DXd therapy per protocol for whom any post-dose PK data are available.

FAS = full analysis set; IDFS = invasive disease-free survival; IMP = investigational medicinal product; ITT = intent-to-treat; PK = pharmacokinetic; PRO = patient-reported outcome.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock for the primary endpoint and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

A summary of outcome variables any analysis populations is provided in Table 13.

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Efficacy data	
pCR	FAS
EFS, CCI , OS	FAS
IDFS	Resected analysis set
CCI	CCI
CCI	CCI
PROs (EORTC QLQ-C30 [all scores] and CCI])	FAS
Study population/Demography data	
Demography characteristics	FAS
Baseline and disease characteristics	FAS
Important deviations	FAS
Medical/surgical history	FAS
Previous anticancer therapy	FAS
Concomitant medications/procedures	FAS
Subsequent anticancer therapy	FAS
PK data	
PK data	PK analysis set
Immunogenicity data	
Immunogenicity data	Listings will be based on the SAF. Summaries will be based on participants who have non-missing baseline ADA and at least one non-missing post-baseline ADA results.
Safety data	
Exposure	SAF
PROs (symptomatic AE, side-effect bother, physical function, and HcRU)	SAF
AEs	SAF
Laboratory measurements	SAF
Vital signs	SAF
ECGs	SAF

ADA = anti-drug antibody; AE = adverse event; CCI CCI ECG = electrocardiogram; EFS = event-free survival; EORTC = European Organization for the Research and Treatment of Cancer; CCI FAS = Full Analysis Set; CCI IDFS = invasive disease-free survival; ECG = electrocardiogram; CCI OS = overall survival; pCR = pathological complete response; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = 30 item core quality of life questionnaire; SAF = safety analysis set.

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

9.4.2 Efficacy

9.4.2.1 Primary Endpoints (pCR)

The dual primary endpoints of the study are pCR rates (ypT0/Tis ypN0) for the comparisons of T-DXd vs ddAC-THP (Arm A vs Arm C) and T-DXd in sequence with THP vs ddAC-THP (Arm B vs Arm C).

The 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. The analysis will be performed on all randomised participants according to their randomised neoadjuvant treatment. The measure of interest is the difference in the rates of pCR between the experimental arms and the control arm.

Analysis Methods

The primary analysis will be performed using the FAS. Definitions of participants who will be considered responders or non-responders for the primary analysis of pCR are presented in Table 14. A supplementary analysis will be performed, accounting for all responders regardless of whether the participants receive any subsequent therapy. Further supplementary and sensitivity analyses to explore the robustness of the primary pCR endpoint will be documented in the SAP.

Table 14 Definitions of Responders vs Non-responders for pCR Assessments

Situation	Primary Analysis
Participants that only received randomised study treatment (at least 1 dose) and achieved pCR	Responder
Participants discontinued randomised study treatment, received any subsequent neoadjuvant cancer treatment, and achieved pCR	Non-responder
Participants had disease progression or died from any cause prior to surgery	Non-responder

Situation	Primary Analysis
Participants with no valid records regarding pCR status due to any reason (including but not limited to withdrawal from the study, PD or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist)	Non-responder
All other randomised participants	Non-responder

pCR = pathological complete response; PD = progression of disease.

The stratified Miettinen and Nurminen's method will be used for the primary analysis comparing the pCR rates between the active treatment arms (Arms A and B) and the control arm (Arm C). The difference in pCR rate, together with its 95% CI and the p-value, will be reported using the stratified Miettinen and Nurminen's method with strata weighting by sample size (ie, Mantel-Haenszel weights). The stratification variables will be defined according to data from the IRT. The active treatments will be considered superior to the control if the difference in the pCR rates is significantly bigger than zero.

In addition, a complementary analysis will be provided reporting 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 Miettinen-Nurminen method (Miettinen and Nurminen 1985).

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

9.4.2.2 Secondary Endpoint(s)

pCR (ypT0 ypN0)

A secondary definition of pCR (ypT0 ypN0) will be analysed using the stratified Miettinen-Nurminen method as described for the primary endpoint (Section 9.4.2.1). Definitions of participants who will be considered responders or non-responders for the secondary analysis of pCR are the same as for the primary analysis and are presented in Table 14.

EFS, IDFS, and OS

The long-term benefit of T-DXd alone or in sequence with THP relative to ddAC-THP in neoadjuvant setting will be assessed using EFS, IDFS, and OS. The EFS and OS analyses will include all randomised participants, regardless of whether the participant withdraws from therapy or receive another anticancer therapy. The analysis for IDFS will include all randomised participants that complete surgery (ie, the resected analysis set). The participants will be censored at the time they are last known to be alive and event free.

EFS is defined as the time from randomisation until disease progression precluding surgery, invasive disease recurrence (local, regional, distant, or contralateral) based on local assessments or death from any cause. Positive margins in the surgical sample do not count as an event for EFS.

IDFS is defined as the time from surgery until invasive disease recurrence (local, regional, distant, or contralateral) based on local assessments or death from any cause. Participants with positive margins will not count as disease-free after surgery, and therefore will be excluded from IDFS analysis.

OS is defined as the time from randomisation to death from any cause.

All these endpoints will be analysed using a log rank test stratified by HR status (positive vs negative) and HER2 status (IHC3+ vs other). If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified in the SAP. The hazard ratio together with its 95% CI and p-value will be presented (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.

The stratification variables will be defined according to data from the IRT.

Kaplan-Meier plots for each endpoint will be presented by treatment group. Summaries of the number and percentage of participants experiencing an event of interest and the type of event (eg, disease progression or death) will be provided for each treatment. The proportion of participants experience no events up to 3 years from randomisation (i.e., 3-year landmark rate) will be summarised for each endpoint by treatment group.

Subgroup Analysis

Subgroup analyses will be conducted for pCR, EFS, IDFS, CCI , and OS comparing the efficacy between T-DXd and ddAC-THP as well as the efficacy between T-DXd in sequence with THP and ddAC-THP in the following subgroups of the FAS (but not limited to):

- 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
  - Clinical tumour stage (T0-2 vs T3-4)
  - Tumour grade

- Geographical region
- Baseline ECOG
- Menopausal status

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.

The subgroup analyses for the stratification factors as well as for all other factors will be based on values recorded on the eCRF, or from the third-party vendor data.

For time-to-event endpoints, 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 descriptive summaries will be provided.

For a binary endpoint, if there are less than 10 patients in each treatment arm for a subgroup, it is not considered appropriate to present analyses; therefore, the subgroup for that endpoint will not be analysed. In this case, only descriptive summaries will be provided.

Additional subgroups of interest and analysis methods will be outlined in the SAP.

9.4.2.3 Tertiary/Exploratory Endpoints

CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI [redacted]

CCI

CCI

CCI

9.4.3 Safety

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

Baseline

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

Adverse Events

AEs will be coded using the most recent version of MedDRA that will be released for execution at AstraZeneca and NCI CTCAE v5.0.

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

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

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

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

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

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

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

A TEAE listing will cover details for each individual TEAE.

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

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of participants (n), mean, standard deviation, median, Min. and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

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

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

Laboratory Parameters

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of participants (n), mean, standard deviation, median, Min. and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

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

Elevation in liver parameters for assessment of Hy's Law will be performed and reported as appropriate.

A frequency table for urinalysis will be presented with number of participants reporting at least one treatment emergent increase in baseline category. A shift table for urinalysis will be presented with baseline assessment against the maximum on treatment category.

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

Details of laboratory summaries will be provided in the SAP.

Percentage of NYHA Classification

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 using descriptive statistics. The analysis will be performed using the SAF.

Percentage of LVEF Decrease

The percentage of participants with decrease in LVEF of at least 10% from baseline and to below 50% during neoadjuvant treatment period will be summarised using descriptive statistics. The analysis will be performed using the SAF.

9.4.4 Other Analyses

9.4.4.1 Clinical Outcome Assessments

Patient-reported outcomes will be analysed as secondary and exploratory endpoints. Details of all statistical analyses will be described in full in the SAP.

Study endpoints intended to evaluate treatment benefit using data from PRO assessments will be analysed using the FAS population, unless stated otherwise in the study SAP. Study endpoints intended to evaluate detriment resulting from treatment using PRO data, such as patient-reported symptomatic AEs and overall side-effect bother, will be performed using the SAF. Missing data in the PRO assessments will not be imputed and the analyses will be based on observed non-missing data.

All PRO assessments with developer-defined scoring algorithms (such as the EORTC QLQ-C30) will be analysed in accordance with these guidelines except when otherwise indicated in the study SAP. Instruments without developer-defined scoring guidelines will be analysed using raw item-level values as presented in the item response scale, except when otherwise indicated in the study SAP.

Descriptive analyses will be performed using methods appropriate for the scale of measurement and study objective and will be defined in the study SAP. The analysis of selected PRO scales may include change from baseline using a mixed-model for repeated measurements. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs may be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value. Additional analyses may include time to deterioration (hazard ratio and Kaplan-Meier curves), descriptive statistics (absolute and unadjusted change from baseline scores), or graphical presentations, as applicable. Where possible, analyses should report missing data as a percentage of the FAS or SAF population, according to the study objective.

CCI [redacted]

CCI [redacted]

9.4.4.2 Medical Resource Utilisation and Health Economics

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

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

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 intervention if the start of study intervention is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Participants 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 intensive care unit stay will be calculated using the same method.

The potential impact of the disease and treatment on health care resource use will be analysed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each treatment group on the different types of hospital admissions, the length of stay for participants admitted into hospital for at least 1 overnight stay, and the length of stay for participants admitted to intensive care/high dependency units, as well as the primary sign or symptom the participant presents with.

9.4.4.3 Pharmacokinetics

Pharmacokinetic data will be summarised using the PK analysis set. Serum concentration data for T-DXd, total anti-HER2 antibody, and DXd will be listed for each sampling time for each participant and each dosing day, for all evaluable participants. Descriptive statistics may be calculated.

CCI [redacted] Details of these analyses will be described in the SAP finalised before database lock. CCI [redacted]

9.4.4.4 Biomarkers

CCI [redacted]

9.4.4.5 Immunogenicity Data

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

The effect of immunogenicity as well as the effect of its neutralising properties on PK, efficacy, and safety will be evaluated, if the data allow.

9.4.4.6 Residual Cancer Burden

The RCB, which is a categorized score based on the residual viable tumour identified on routine H&E staining after mapping of the surgical specimen (Symmans et al 2007), will be summarised using the FAS. A summary will be provided of the percentage of participants by RCB class after central pathological evaluation.

9.5 Futility Analysis

A futility analysis for pCR will be performed when approximately CCI participants (CCI% of the intended population) are treated and have had the opportunity to be assessed for pCR or have discontinued or withdrawn from treatment. Assuming recruitment over CCI months, the data cut-off of the futility analysis is anticipated approximately CCI months after the first participant is randomised.

The proportion of pCR in Arm A and Arm B will each be compared to the proportion of pCR in Arm C. CCI [redacted] The suggestion to stop a T-DXd-containing treatment arm will be considered if the rate of pCR in a T-DXd treatment arm is lower than the rate of pCR in the SOC arm by more than CCI%, ie, ΔpCR CCI%. CCI [redacted]

CCI

CCI

9.6 Data Monitoring Committee

9.6.1 IDMC

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 participants have been randomised, whichever occurs first, to review safety data and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter until the last participant has completed neoadjuvant treatment. The IDMC will review unblinded safety data. Specific data listings pertinent to the ability of the participant to undergo surgery and complete neoadjuvant study treatment will be provided to the IDMC for their consideration in making recommendations regarding study conduct.

The IDMC will also specifically monitor the following parameters:

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

Should the IDMC identify a potential safety signal, they have the option to request efficacy data to evaluate the overall benefit-risk to participants. Full details of the IDMC procedures, and processes can be found in the IDMC Charter.

For the pCR-based futility analysis the IDMC will review unblinded study data and inform the study sponsor, AstraZeneca, as to whether the futility boundaries specified in Section 9.5 are met.

Furthermore, the AstraZeneca study team physician or delegate will review on a regular basis participant accrual and safety data such as AEs, including ILD/pneumonitis events. Based on these reviews, if deemed necessary, AstraZeneca can recommend an ad hoc IDMC meeting.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be

addressed; for instance, this could involve amendments to the CSP and letters to investigators.

9.6.2 ILD Adjudication Committee

An independent ILD Adjudication Committee and Charter will be established to review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database may be provided to the adjudication committee to fully characterise medical history (eg, smoking, radiation, and pulmonary history), diagnostic evaluation, treatment, and outcome of the event. Further details can be found in the ILD Adjudication Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable regulatory authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned regulatory authority. This responsibility may be delegated to a Contract Research Organisation but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

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

review and then file it along with the IB or other relevant documents and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via EMA CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.

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

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the

processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

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

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

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored, or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The investigator should have a process in place to:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- ensure that any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

[1] The **Data Controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will

be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

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

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EMA CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study.

- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention And Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

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

- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

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

The first act of recruitment is the first site open/activation date to allow recruitment of a potential participant and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

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

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

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

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

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

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

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

Life-threatening

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

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

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

Intensity Rating Scale:

The grading scales found in the revised NCI CTCAE v5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

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

B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.

- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IRT errors).
- Wrong drug administered to participant (excluding IRT errors).

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

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

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error. Any events of medication error, with or without associated AEs, are to be captured and forwarded to the DES using the Medication Error Report Form.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of study intervention for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorised product information, or for unauthorised study interventions, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

The investigator:

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

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

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are, for example, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

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

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

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

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

- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on T-DXd continues but no longer than 15 years from the end of the study (as defined in the protocol) or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection.

Withdrawal of Consent for Genetic Research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

The blood sample for this genetic research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate

in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP may be prepared where appropriate.

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

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver abnormalities can be found in Section 8.3.6 and Appendix M of the CSP.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

PHL

Aspartate aminotransferase or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

HL

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, where no other reason, other than the

study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT $\geq 3 \times$ ULN.
- AST $\geq 3 \times$ ULN.
- TBL $\geq 2 \times$ ULN.

Local Laboratories

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition.
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the 3 Liver eCRF Modules as information becomes available.

#**A "significant" change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently

whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now "Hy's Law case") ensuring causality assessment is related to study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH PT INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc
	HBsAg HCV DNA[a] IgM and IgG anti-HCV HCV RNA[a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate-deficient transferrin[b]
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin[b] Transferrin saturation

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.
[b] Carbohydrate-deficient transferrin and transferrin are not available in China.

CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgG = immuno-globulin G; IgM = immuno-globulin M; INR = international normalised ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RNA = ribonucleic acid.

E 7 References

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

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

Introduction

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

Imaging Modalities and Acquisition Specifications for RECIST 1.1

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

Table 15 Summary of Imaging Modalities for Tumour Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose-PET/CT

CT=computed tomography; PET/CT=positron emission tomography/CT; MRI=magnetic resonance imaging.

Computed Tomography and Magnetic Resonance Imaging

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

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of

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

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

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

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

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

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

1. Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred).
2. Chest CT without IV contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study.

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

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

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

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

Chest X-ray

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

Plain X-ray

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

Isotopic Bone Scan

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new

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

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

^{18}F-fluoro-deoxyglucose positron emission tomography(PET)/CT scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[2] not present on baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the ^{18}F-fluoro-deoxyglucose-PET scan. The PET portion of the PET/CT introduces additional data that may bias an investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior ^{18}F-fluoro-deoxyglucose-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

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

Ultrasound

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

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

Other Tumour Assessments

Clinical Examination

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

Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Histology and Cytology

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

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

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

Measurability of Tumour Lesions at Baseline

RECIST 1.1 Measurable Lesions at Baseline

A tumour lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[3] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatis lymph nodes.

Non-measurable Lesions at Baseline

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component).
  - Leptomeningeal disease.
  - Ascites, pleural effusion, or pericardial effusion.

[3] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

  - Inflammatory breast disease.
  - Lymphangitic involvement of skin or lung.
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline).[4]
- Previously irradiated lesions.[5]
- Brain metastasis.

Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions:
  - Bone scan, PET scan, or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL Selection at Baseline

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

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

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

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

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

Special Cases for TL Assessment at Baseline

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

RECIST 1.1 NTL Selection at Baseline

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

Evaluation of Tumour Response and Progression

RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumour visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified

previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

Special Cases for TL Assessment at Follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 CRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 16 RECIST 1.1 Evaluation of Target Lesions

CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.

PD	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir). This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

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

RECIST 1.1 NTL Assessment at Follow-up

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

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 17 RECIST 1.1 Evaluation of Non-Target Lesions

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of 1 or more NTLs.
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when 1 or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable	Only relevant if no NTLs present at baseline.

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

RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour. If a NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

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

RECIST 1.1 Evaluation of Overall Visit Response at Follow-up

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

Table 18 RECIST 1.1 Overall Visit Response

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

Non-CR/Non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
CR = complete response; NA = not applicable (only relevant if there were no TLs at baseline or NTLs at baseline), NE = not evaluable; NED = no evidence of diseases (only relevant if there were neither target lesions nor non-target lesions at baseline); NTL = non-target lesion; PD = progression of disease; PR = partial response; SD = stable disease; TL = target lesion.

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

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

Evaluation of Scans Subsequent to RECIST 1.1-defined Progression

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

- ≥20% increase and at least a 5 mm increase in the sum of diameters of TLs compared with the nadir sum of diameters at 2 consecutive visits, and a further increase of ≥5 mm in the sum of diameters at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of NTLs at the follow-up scan time point compared with the immediate prior time point.
- Significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan time point compared with the immediate prior time point.
- Additional brand-new unequivocal lesions at the follow-up scan time point.

Central Imaging

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

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

F 1 Reference

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

Appendix G Contraception Requirements

Contraception requirements for this study are as follows.

G 1 Female Participants

Women not of childbearing potential are defined as those who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have LH and FSH levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non-sterilised male partner must use at least 1 highly effective non-hormonal method of contraception (Table 19). They should be on their chosen method of birth control from the time of screening and continue to use it throughout the total duration of the drug treatment and the drug washout period (7 months after the last dose of study intervention or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment).

Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial or as dictated by local prescribing information for SOC treatments received after neoadjuvant treatment. Female participants should refrain from breastfeeding throughout this period. Women must not donate, or retrieve for their own use, ova from the time of the first dose of study intervention, throughout the study treatment period, and for at least 7 months after the final study intervention administration or as dictated by local prescribing information for SOC treatments received

after neoadjuvant treatment.

G 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (6 months after the last dose of study intervention or as dictated by prescribing information for SOC treatments received after neoadjuvant treatment) to prevent pregnancy in a partner.

Not engaging in sexual activity for the duration of the study (or as dictated by prescribing information for SOC treatments received after neoadjuvant treatment) is an acceptable practice. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout this period. Preservation of sperm should be considered prior to enrolment in this study.

Vasectomised males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table 19).

G 3 Highly Effective Methods of Contraception

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

Participants in the SOC (ddAC-THP) group: Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SOC (ddAC-THP) group.

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

Non-Hormonal Methods (female participants and female partners [of childbearing potential] of male participants)	**Hormonal Methods (female partners [of childbearing potential] of male participants ONLY)**
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Bilateral tubal occlusion • Intrauterine device (provided coils are copper banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Levonorgestrel-releasing intrauterine system (eg, Mirena®) • Progesterone T intrauterine device • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low-dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Mini pill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

Note: for hormonal methods to be considered "highly effective" they must inhibit ovulation.

Appendix H Patient-reported Outcomes

EORTC QLQ-C30

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights.

Patient Reported Outcomes Questionnaire: EORTC QLQ-C30 was removed due to copyrights.

PRO-CTCAE (on-treatment)

Patient Reported Outcomes Questionnaire: PRO-CTCAE was removed due to copyrights.

Patient Reported Outcomes Questionnaire: PRO-CTCAE was removed due to copyrights.

PRO-CTCAE (follow up)

Patient Reported Outcomes Questionnaire: PRO-CTCAE was removed due to copyrights.

Patient Reported Outcomes Questionnaire: PRO-CTCAE was removed due to copyrights.

Patient Global Impression of Treatment Tolerability (PGI-TT)

Patient Reported Outcomes Questionnaire: PGI-TT was removed due to copyrights.

EORTC-IL19

Patient Reported Outcomes Questionnaire: EORTC-IL19 was removed due to copyrights.

EORTC-IL123

Patient Reported Outcomes Questionnaire: EORTC-IL123 was removed due to copyrights.

EORTC-IL124

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EORTC-IL125

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Appendix I Concomitant Medications

I 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Paclitaxel

In a Phase 1 trial using escalating doses of paclitaxel (110–200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (ie, paclitaxel before cisplatin). PK data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin. The metabolism of paclitaxel is catalysed by CYP isoenzymes CYP2C8 and CYP3A4.

Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials. Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

I 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 20, Table 21, and Table 22. Refer also to the dose modification guidelines for management of study intervention-related toxicities in Section 6.6, and to local prescribing information for SOC treatments. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Table 20 Restricted medications/therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it is allowed)
Tobacco products, e-cigarettes and vaping	Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Any prior or current use of these products should be recorded in the eCRF.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is discouraged, but not prohibited.
Hormonal therapy	For non-cancer-related conditions only.

eCRF = electronic case report form.

With the exception of medications that are under investigation in the study (eg, SOC, comparators, or combination therapies), the medications in Table 21 are considered exclusionary during the study. The Sponsor must be notified if a participant receives any of these during the study.

Table 21 Prohibited medications/therapies

Prohibited medication/class of drug/therapy	Usage
Chloroquine or hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment.
Any concurrent chemotherapy, anticancer study intervention or biologic, radiotherapy or hormonal therapy for cancer treatment	Must not be given concomitantly while the participant is on study intervention. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes) is acceptable.

Table 21 Prohibited medications/therapies

Prohibited medication/class of drug/therapy	Usage
Immunosuppressive medications, including corticosteroids	T-DXd cannot be administered when the participant is taking immunosuppressive medications, including corticosteroids with the exception of: • Short-term courses (< 2 weeks) • Low to moderate dose (< 10 mg prednisolone per day or equivalent) • Long-term, alternate-day treatment with short-acting preparations • Maintenance physiologic doses (replacement therapy) • Administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection • Prevention or treatment of hypersensitivity reactions to radiographic contrast agents A temporary period of steroid treatment will be allowed for different indications after discussion with the Sponsor Study Physician (eg, chronic obstructive pulmonary disease, radiation, nausea, etc). Participants with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study. Use of immunosuppressive medications for the management of study intervention-related AEs or in participants with contrast allergies is acceptable. Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumour necrosis factor-alpha blockers.
Herbal and natural remedies that may interfere with interpretation of study results	Must not be given concomitantly unless agreed by the Sponsor.
Live vaccine	Participants, if assigned treatment, should not receive live vaccine during the study and up to 30 days after the last dose of study intervention. Participants who have received live, attenuated vaccine within 30 days prior to the first dose of T-DXd will be excluded. Note: mRNA and replication deficient adenoviral vaccines are not considered live, attenuated vaccines.
Hormonal contraception	Are contraindicated for female study participants and must not be given concomitantly.

COVID-19 = coronavirus disease 2019; mRNA = messenger ribonucleic acid; T-DXd = trastuzumab deruxtecan.

Table 22 Supportive medications/therapies

Supportive medication/class of drug/therapy	Usage
Prophylactic anti-emetic agents	Trastuzumab deruxtecan is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of T-DXd, patients should be premedicated with a combination regimen of 2 or 3 medicinal products (eg, dexamethasone with either a 5 HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.
Haematopoietic growth factors	May be used for prophylaxis or treatment based on the clinical judgement of the investigator.
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate adverse event management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 21.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table 21.
Inactivated viruses, such as those in the influenza vaccine	Permitted.
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 21.
Bisphosphonates and/or denosumab	Permitted for treatment of osteoporosis.
GnRH agonists	Permitted for the protection of ovarian function.

GnRH = gonadotropin-releasing hormone; NK1 = neurokinin 1; T-DXd = trastuzumab deruxtecan; 5-HT3 = 5-hydroxytryptamine 3.

Appendix J Instructions Related to SARS-COV-2 Infection

J 1 Eligibility, Concomitant Medication, T-DXd Dose Modification and PK Sampling Text Relevant to COVID-19

Inclusion Criteria

The following inclusion criterion has been added (see Section 5.1):

- Has adequate treatment washout period before randomisation, defined as:
  - Chloroquine/Hydroxychloroquine: ≥ 14 days

Prior and Concomitant Medications

In addition to Section 6.5, the following text is relevant for participants with COVID-19:

Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required for COVID-19, study intervention must be interrupted.

Due to the potential impact of COVID-19 (due to SARS CoV-2), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with trastuzumab deruxtecan. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

SARS-CoV-2 Infection Assessment(s)

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, infection should be confirmed via NAAT (nucleic acid amplification test such as RT-PCR [reverse transcription polymerase chain reaction]) or rapid antigen testing. SARS-CoV-2 antigen testing can be used to confirm infection, but not to rule it out.

Serum samples will be used for COVID-19 testing from each subject who provides consent. Samples will be collected prior to the study intervention infusion, shipped to a central laboratory, and stored there until the tests become available.

If participants consent, the remaining serum samples will also be stored for future analysis.

Sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Dose Modification Criteria for Suspected or Confirmed SARS-CoV-2 Infection

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. Dose modifications will be based on the worst CTCAE grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. **Please use CTCAE v5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria

If asymptomatic or symptomatic COVID-19 is suspected, interrupt T-DXd and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidelines as outlined in the CE protocol template.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, follow dose modification as outlined below and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no respiratory signs/symptoms of COVID-19, and completely or nearly resolved chest CT findings which are equivalent to CT Severity Score of 1 (CT Severity Score of 1 = Subtle Ground Glass Opacities and very few findings)*. Then follow below dose modifications:

** Luger, Anna K., et al. "Chest CT of lung injury 1 year after COVID-19 Pneumonia: The CovILD study." Radiology (2022).*

COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	**Schedule Modification for trastuzumab deruxtecan**
Grade 1	After recovery, resume study treatment(s)at the same dose
Grade 2	After recovery, resume study treatment(s) at the same dose if chest CT findings are completely resolved Reduce by 1 dose level if chest CT findings are nearly resolved (equivalent to CT Severity Score of 1)

Grade 3	After recovery, reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

COVID-19 = coronavirus disease 2019; CT = computed tomography; CT Severity Score of 1 = Subtle Ground Glass Opacities and very few findings; CTCAE = Common Terminology for Adverse Event Criteria; NCI = National Cancer Institute.

Closely monitor signs/symptoms after resuming T-DXd, initially with a weekly phone call phone call or site visit for 6 weeks.

- In addition to the recommendations outlined in the table above, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.
- If an event is suspected to be drug related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline.

J 2 Benefit-Risk Considerations for COVID-19

The emergence of COVID-19 presents a potential safety risk for participants. Several risk mitigation factors have been implemented in this study. Notably, the eligibility criteria will exclude participants with COVID-19 infections (see CSP Section 5.20).

Moreover, with the outbreak of COVID-19, there is the potential for increased use of chloroquine and hydroxychloroquine to treat severely symptomatic participants, or even for prophylactic use. Chloroquine and hydroxychloroquine have shown in vitro to substantially affect the pH of the lysosome, a key intracellular compartment involved in the trafficking and payload release of T-DXd. As it is unknown whether chloroquine/hydroxychloroquine may affect the safety and efficacy of T-DXd, to be eligible for this clinical trial, use of chloroquine and hydroxychloroquine treatment must be completed at least 14 days prior to the first dose of T-DXd (see CSP Section 5.1). During study treatment, chloroquine and hydroxychloroquine are considered prohibited concomitant medications. Lastly, due to the potential overlapping impact of T-DXd and COVID-19 on the lung, the Sponsor has also provided in this Appendix, a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with T-DXd.

With these measures in place, it is considered the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks.

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

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

Reconsent of Study Participants During Study Interruptions

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

Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participants home / or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

Telemedicine Visit to Replace On-site Visit (where applicable)

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

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

At-home or Remote Location Study Intervention Administration Instructions

If a site visit is not possible, at-home or remote location administration of study intervention may be performed [by a qualified HCP, provided this is acceptable within local

regulation/guidance, or by the participant or his / her caregiver]. The option of at home or remote location study intervention administration ensures participants safety in cases of a pandemic where participants may be at increased risk by travelling to the site/clinic. This will also minimise interruption of study intervention administration during other study disruptions, eg, site closures due to natural disaster.

At-home or Remote Location Study Intervention Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service may administer the study intervention at the participant's home or other remote location according to the CSP and the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis, and if allowed by local SOPs, as applicable. All necessary supplies and instructions for administration and documentation of study intervention administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

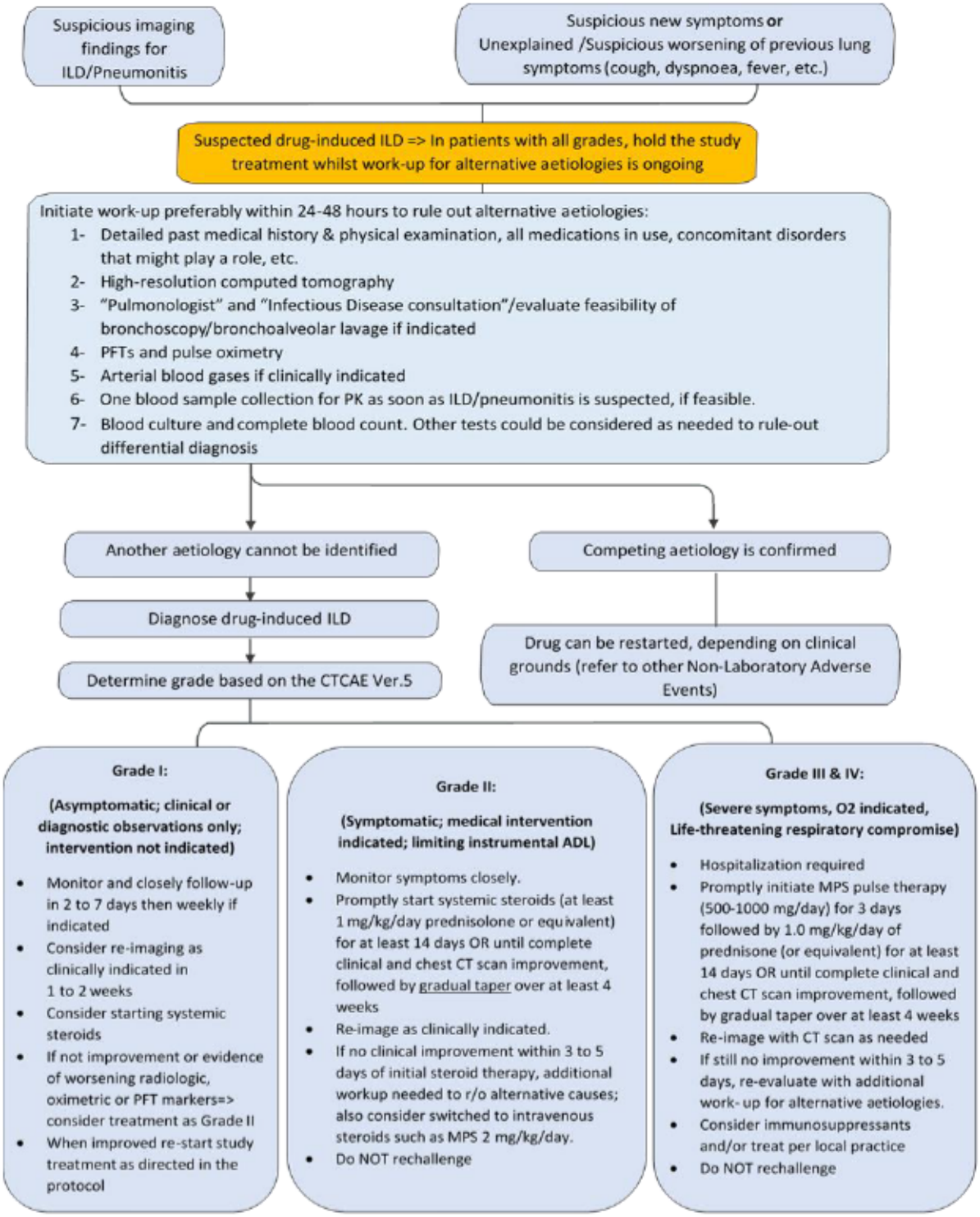
At-home or Remote Location Study Intervention Administration by the Participant or His / Her Caregiver

Prior to at-home or remote location study intervention administration the investigator must assess the participant or his / her caregiver to determine whether they are appropriate for at home or remote location administration of study intervention. Once the participant or his / her caregiver is deemed appropriate for at-home or remote location administration, he / she must receive appropriate training. All necessary supplies and instructions for administration and documentation of study intervention administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

Appendix L Guidance for Management of Participants with Drug-Induced ILD/Pneumonitis



Appendix M Toxicity Management Guidelines

Table 23 Toxicity Management Guidelines for T-DXd

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Table 23 Toxicity Management Guidelines for T-DXd

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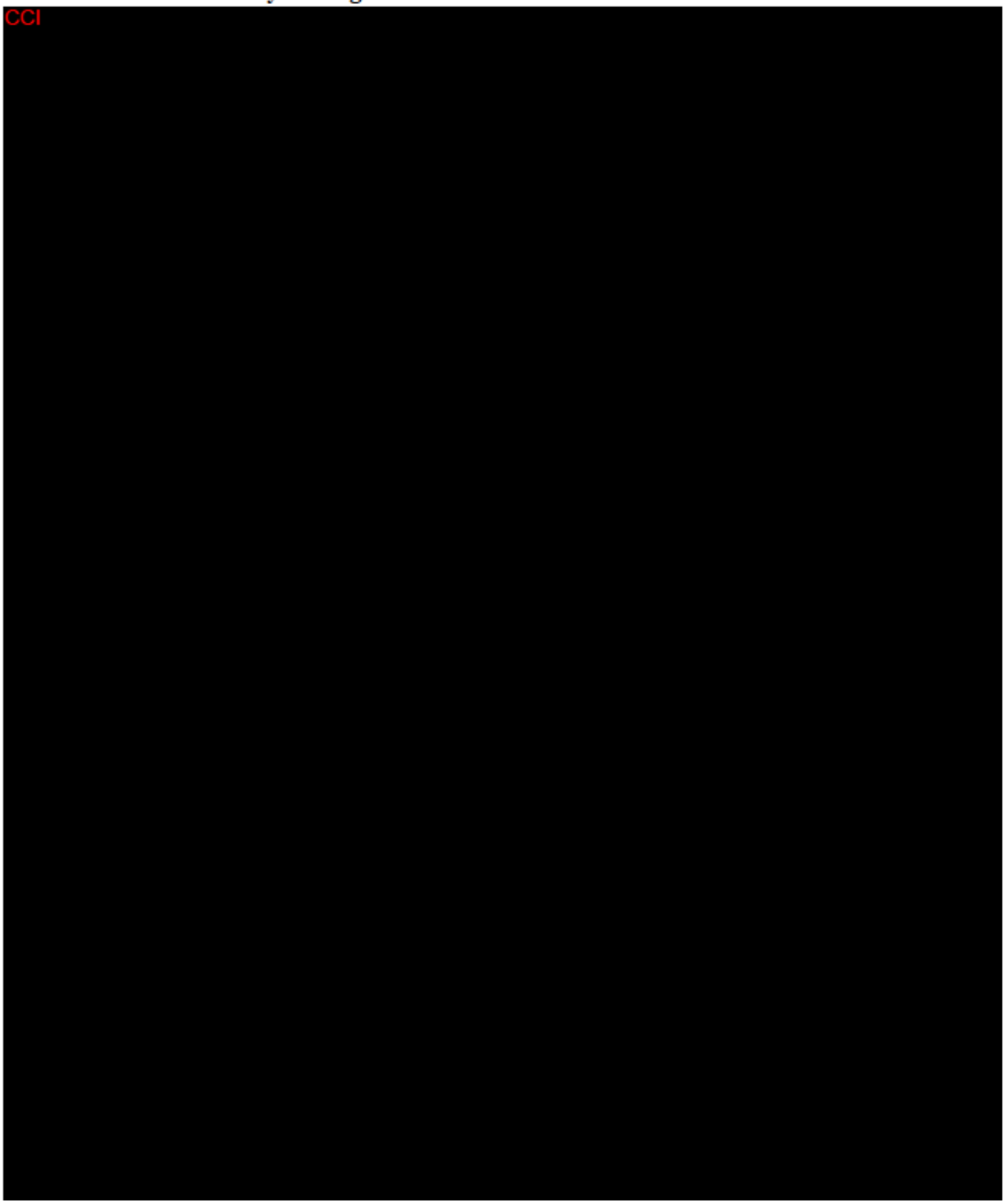

Table 23 Toxicity Management Guidelines for T-DXd

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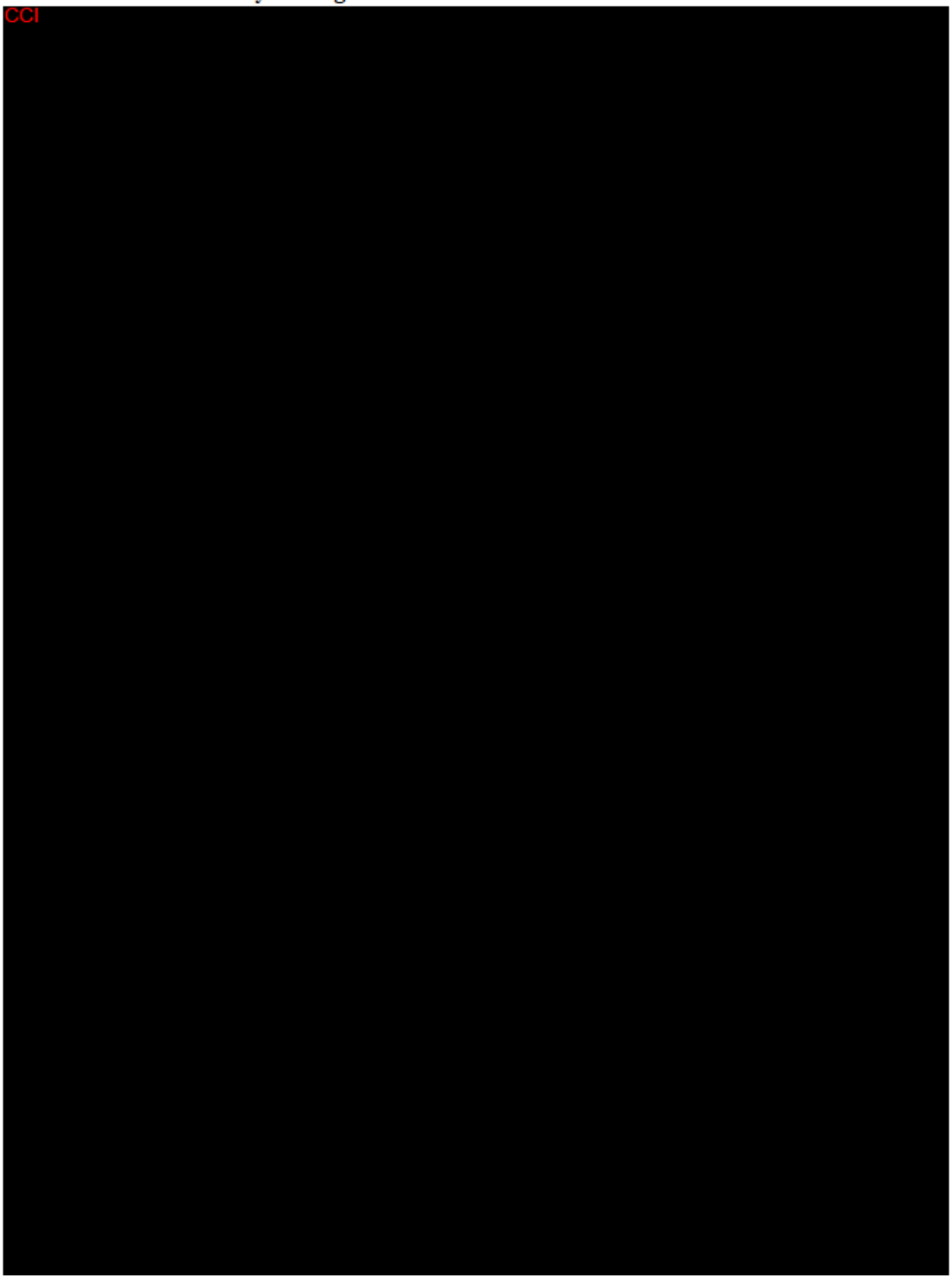

Table 23 Toxicity Management Guidelines for T-DXd

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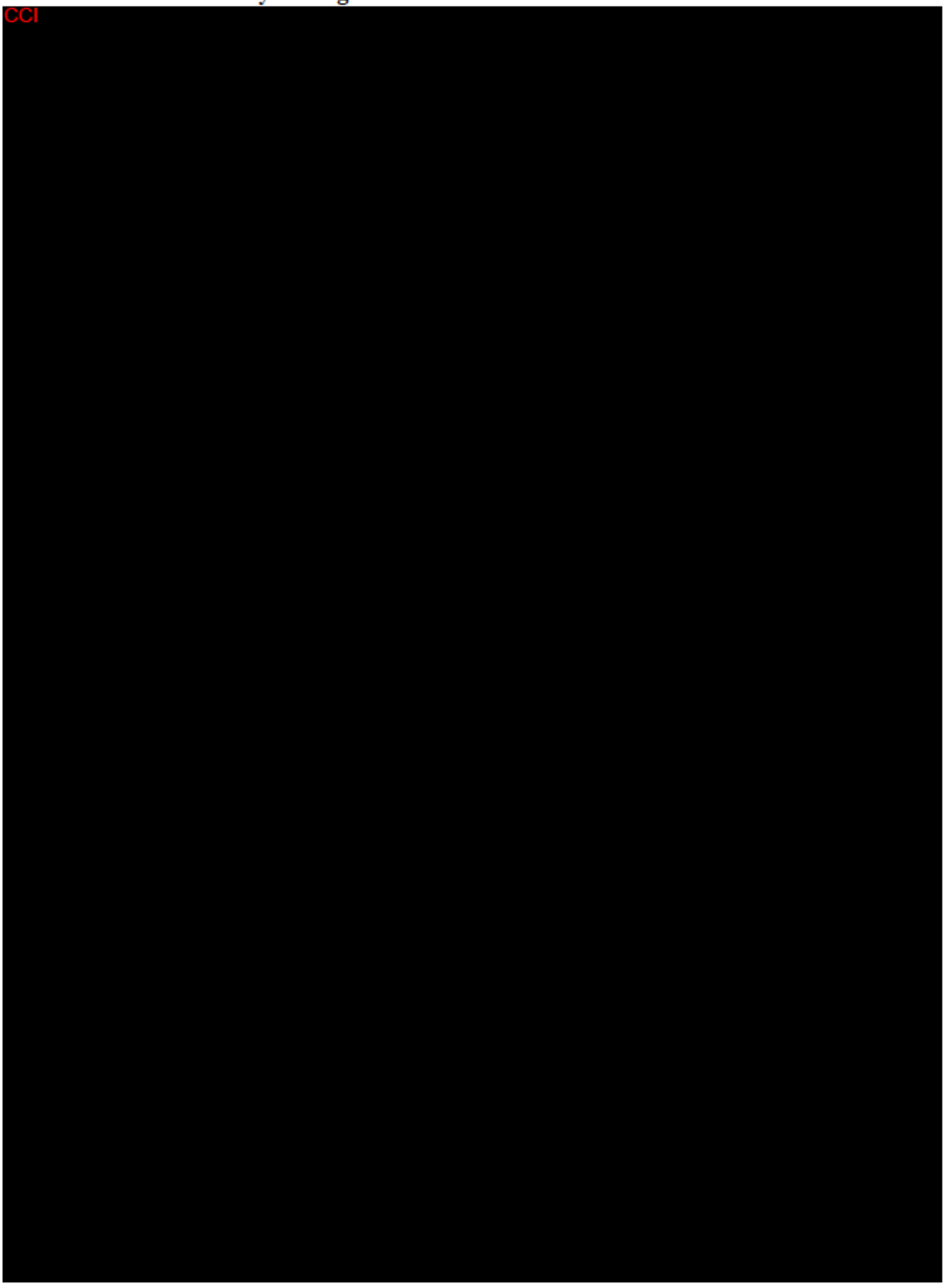

Table 23 Toxicity Management Guidelines for T-DXd

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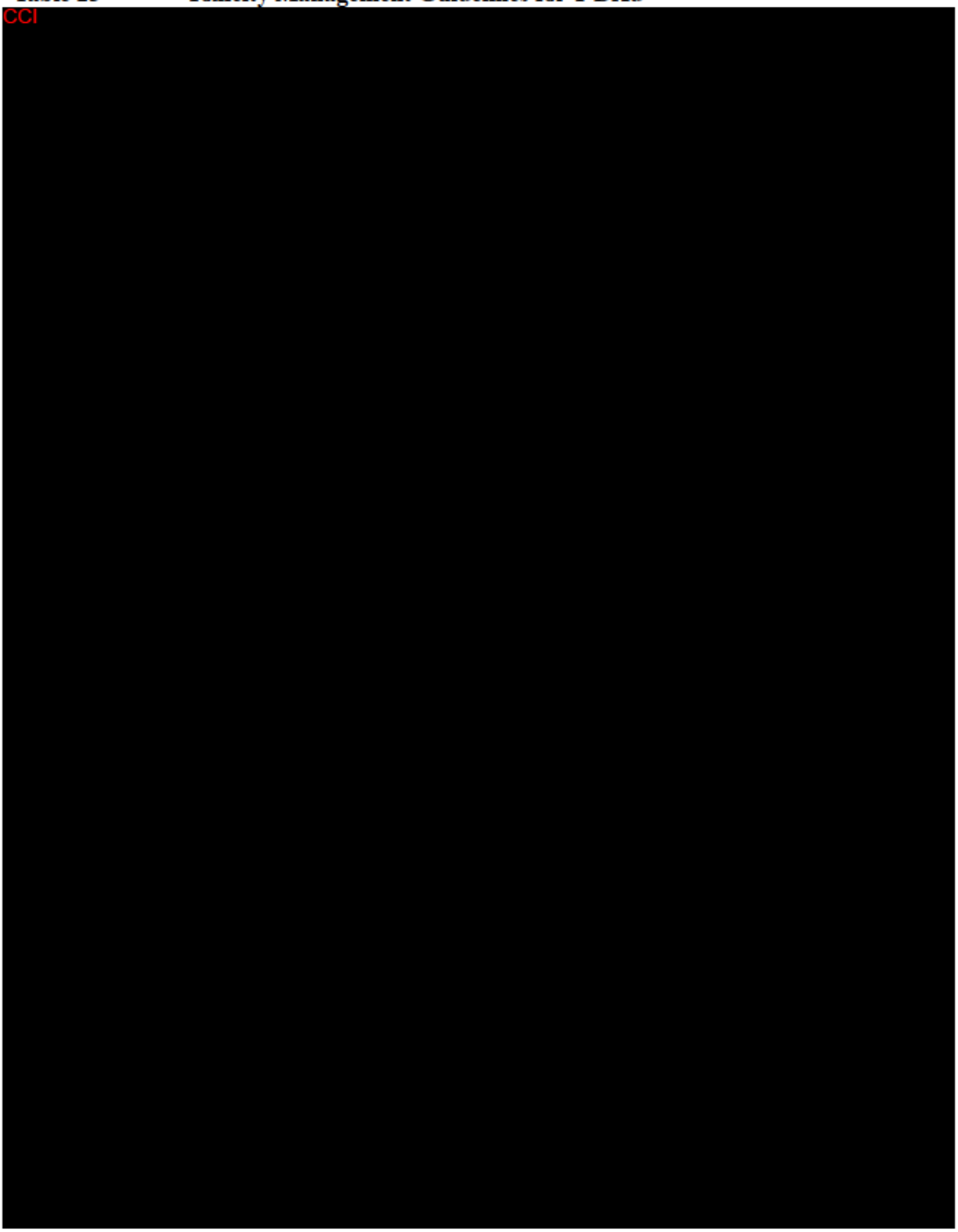

Table 23 Toxicity Management Guidelines for T-DXd

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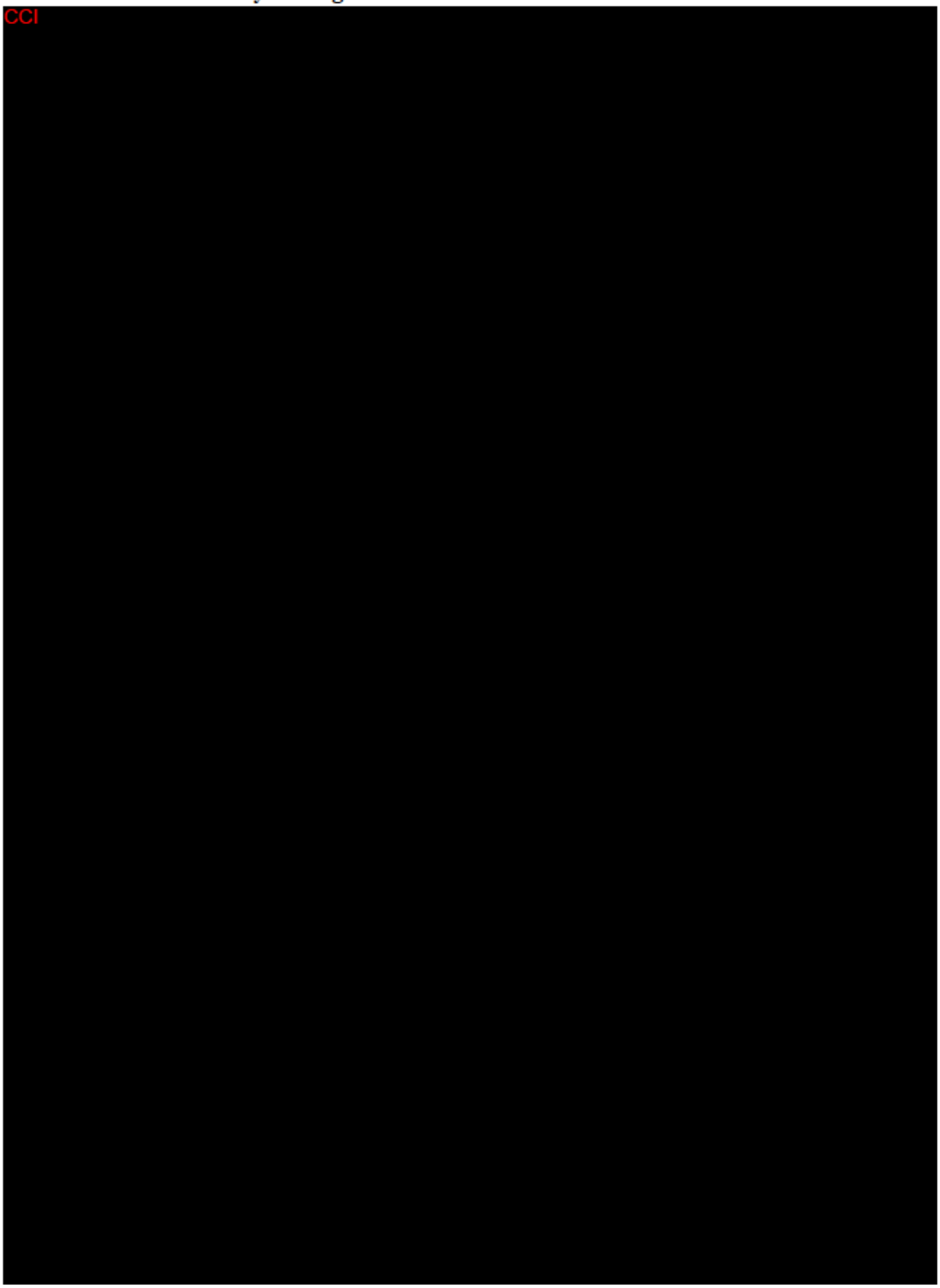

Table 23 Toxicity Management Guidelines for T-DXd

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[redacted]

[a] CCI

[b] See Section 6.6

Note: All dose modifications should be based on the worst preceding toxicity.
AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count; CHF = congestive heart failure; CRP = C-reactive protein; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DI = drug-induced; DLCO = diffusion capacity of the lungs for carbon monoxide; FVC = forced vital capacity; hrs = hours; ILD = interstitial lung disease; IMP = investigational medicinal product; IV = intravenous; LVEF = left ventricular ejection fraction; NSAID = non-steroidal anti-inflammatory drug; PK = pharmacokinetics; SpO2 = pulse oximetry; TBL = total bilirubin; TdP = Torsades de Pointes; T-DXd = trastuzumab deruxtecan; TMGs = toxicity management guidelines; ULN = upper limit of normal; WBC = white blood cell count.

Appendix N ASCO/CAP Guidelines on HER2 Testing in Breast Cancer

This protocol will determine HER2 status using guidelines from the American Society of Clinical Oncology (Table 24, per ASCO/CAP 2018 guidelines).

Table 24 Summary of Guideline Recommendations

Procedure	Recommendations
Optimal algorithm for HER2 testing	HER2 is positive if IHC 3+. HER2 IHC 2+ is equivocal (the revised definition of IHC 2+ [equivocal] is invasive breast cancer with "Weak to moderate complete membrane staining observed in > 10% of tumour cells") and triggers ISH testing. Diagnostic criteria by ISH is defined by HER2 copy number (signals/cell) and, for dual probe assay, by HER2/CEP17 ratio: For dual probe assay, HER2-positive is defined as: • (Group 1) or (Group 2 AND concurrent IHC 3+) OR (Group 3 AND concurrent IHC 2+ or 3+) OR (Group 4 AND concurrent IHC 3+) Where Groups 1-4 are defined: • Group 1: ratio ≥ 2.0 and ≥ 4.0 signals/cell • Group 2: ratio ≥ 2.0 and < 4.0 signals/cell • Group 3: ratio < 2.0 and ≥ 6.0 signals/cell • Group 4: ratio < 2.0 and ≥ 4.0 to < 6.0 signals/cell • Group 5: ratio < 2.0 and < 4.0 signals/cell For tumours in groups 2-4 by dual probe assay, definitive diagnosis will be made based on additional work-up as detailed in ASCO/CAP guidelines 2018. For single probe assay, HER2-positive is defined as: • (HER2 copy number ≥ 6.0 signals/cell) or (HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+) or (HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent dual probe Group 1). • All other tumours will be defined as HER2- as defined by ASCO/CAP 2018. These definitions depend on laboratory documentation of the following: 1. Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2 2. Ongoing internal QA procedures 3. Participation in external proficiency testing 4. Current accreditation by valid accrediting agency

Procedure	**Recommendations**
ISH rejection criteria	Fixation for fewer than 6 hours or longer than 48 hours is not recommended. Test is rejected and repeated if: • Controls are not as expected • Observer cannot find and count at least 2 areas of invasive tumour • > 25% of signals are unscorable due to weak signals • > 10% of signals occur over cytoplasm • Nuclear resolution is poor • Autofluorescence is strong Interpretation done by counting at least 20 cells; a pathologist must confirm that counting involved invasive tumour Sample is subjected to increased counting and/or repeated if equivocal; report must include guideline-detailed elements
IHC rejection criteria	Fixation for fewer than 6 hours or longer than 48 hours is not recommended. Test is rejected and repeated or tested by FISH if: • Controls are not as expected • Artefacts involve most of sample • Sample has strong membrane staining of normal breast ducts (internal controls) • Interpretation follows guideline recommendation • Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in > 30% of invasive tumour • Interpreters have method to maintain consistency and competency Sample is subjected to confirmatory FISH testing if equivocal based on initial results. Report must include guideline-detailed elements.
Optimal tissue handling requirements	• Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in 10% neutral buffered formalin for 6-72 hours. Samples should be sliced at 5-10 mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin • Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation or storage conditions • Time to fixation and duration of fixation if available should be recorded for each sample • Any exception to this process must be included in report

Procedure	Recommendations
Optimal internal validation procedure	• Validation of test must be done before test is offered • Initial test validation requires 25-100 samples tested by alternative validated method in the same laboratory or by validated method in another laboratory • Proof of initial testing validation in which positive and negative HER2 categories are 95% concordant with alternative validated method or same validated method for HER2 • Ongoing validation should be done biannually
Optimal internal QA procedures	• Initial test validation • Ongoing quality control and equipment maintenance • Initial and ongoing laboratory personnel training and competency assessment • Use of standardised operating procedures including routine use of control materials • Revalidation of procedure if changed • Ongoing competency assessment and education of pathologists
Optimal external proficiency assessment	• Participation in external proficiency testing programme with at least 2 testing events (mailings)/year • Satisfactory performance requires at least 90% correct responses on graded challenges for either test • Unsatisfactory performance will require laboratory to respond according to accreditation agency programme requirements
Optimal laboratory accreditation	• On-site inspection every other year with annual requirement for self-inspection • Reviews laboratory validation, procedures, QA results and processes, results and reports • Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method

ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; CEP17, chromosome 17 centromere; FISH = fluorescent in situ hybridisation; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH – in situ hybridisation; QA, quality assurance.

N 1 Reference

Wolff et al 2018
Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American pathologists clinical practice guideline focused update. Arch Pathol Lab Med 2018;142(11):1364-82.

Appendix O Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment [3] (28-July-2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment:

CCI [redacted] This amendment is to also align with the current project-level requirements for T-DXd study protocols and to transition the study from the EU Directive to EU CTR.

Additional modifications, along with more clarifications, specifically in Section 9, are also made as described in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
Title Page Section 1.1 – Synopsis	Inclusion of "Regulatory Agency Identifier Number(s)" table with study EudraCT, EU CT, and IND registration numbers	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
CCI [redacted]			
Section 1.1 – Synopsis Section 9.2 – Sample Size Determination	Language regarding accounting for a 5% dropout rate was removed	The dropout rate was not used for sample size calculation and was added inadvertently in the previous version of the protocol.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
CCI [redacted]			
Section 1.3 – Schedule of Activities Related sections as applicable	Removal of the following: • ADA at safety follow-up visit under "pre-dose blood sample for immunogenicity testing (within 8 hours before infusion)" • Ophthalmologic assessment at end of treatment visit • Troponin sample collection at end of treatment visit	To align with sample collection requirements.	Non-substantial
Section 1.1 – Synopsis Section 1.3 – Schedule of Activities Section 3 – Objectives and Endpoints Related sections as applicable	Long-term FU updated from 4 years and 5 years post surgery to 4 to 6 years post surgery	To reflect the change in sample size	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
Section 1.3 – Schedule of Activities	Inclusion of footnote for long-term FU to clarify that timing of long-term FU visits should be based on the safety FU visit or the date of surgery, whichever occurs later	To clarify activities in the event that surgery occurs after safety FU visit	Non-substantial
Section 2.3.1.1 – Potential Risks of Clinical Significance for T-DXd	ILD/pneumonitis risk, monitoring, and education in patients with moderate renal impairment at baseline	To provide clear guidance to Investigators regarding ILD/pneumonitis, and to align with the current project-level requirements for T-DXd study protocol	Substantial
CCI			
Section 4.4 – End of Study Definition	Clarified definition of the end of study according to European Union and Food and Drug Administration requirements	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
Section 6.1.1 – Investigational Products – Table 4	Minor change to labelling and packaging requirements	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
Section 6.6.1 – T-DXd Dose Modification	Updated wording to state that details regarding all ECG measurements will be recorded in the eCRF	Clarification	Non-substantial
Section 7.2 – Participant Withdrawal from the Study	Added that all patients are to be encouraged to be monitored for OS	Clarification	Non-substantial
CCI			
Section 8.1.4 – Disease Follow-up and Confirmation of Disease Progression	For definition for death from any cause, added "due to any cause" and removed "occurring without	Corrected definition for death from any cause	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
or Recurrence Table 6	prior breast cancer recurrence or second (non-breast) malignancy"		
Section 8.1.7 – Clinical Outcome Assessments (and relevant subsections) Table 7 Appendix H – Patient-Reported Outcomes	• Clarified ePRO activities and timelines • Included PRO questionnaires in appendix	Updated to provide clear guidance on ePRO implementation	Non-substantial
Section 8.2.4 – Clinical Safety Laboratory Assessments	Added that Grade 3 or 4 laboratory values will be as per CTCAE	Clarification	Non-substantial
CCI			
Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE Information	Removal of "SAE with onset or worsening 48 days or more after the last dose of study intervention, are also TEAEs."	Changes made to comply with latest T-DXd-specific protocol template	Non-substantial
Section 8.3.15 – Reporting of Serious Adverse Events	Updated wording regarding reference documents for IMPs in this study	To align with latest AstraZeneca-specific protocol template	Non-substantial
Section 8.3.17 – Medication Error, Drug Abuse, and Drug Misuse Appendix B4 – Medication Error, Drug Abuse, and Drug Misuse	• Updated title to include drug abuse and drug misuse • Included new subsections • Added definitions of drug abuse and drug misuse	To align with the latest AstraZeneca-specific protocol template	Non-substantial
Section 8.5 – Human Biological Samples Section 8.6.1 – Collection of Mandatory Samples	Revised sample retention timelines	To be compliant with ICH GCP, China Human Genetic Resources regulations, and AstraZeneca HBS global standards and policies for sample storage and retention	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
for Biomarker Analysis			
CCI [redacted]			
Section 9.3 – Populations for Analyses, Table 12 Section 9.4.2.1 – Primary Endpoints (pCR)	Removal of Efficacy Analysis Set (EAS)	Not applicable to this study	Non-substantial
Section 9.3 – Populations for Analyses, Table 12	Added "and who do not have positive margins" to the Resected Analysis Set definition	To refine Resected Analysis Set definition	Non-substantial
Section 9.3 – Populations for Analyses, Table 12	Clarification of PK analysis set definition	Available PK data will be used for analysis	Non-substantial
Section 9.4.2.1 – Primary Endpoints (pCR)	Specified that Mantel-Haenszel weights will be used as the weighting strategy in stratified Miettinen and Nurminen's method for pCR rate analysis	Detail provided for more clarification	Non-substantial
Section 9.4.2.1 – Primary Endpoints (pCR)	Corrected "primary PFS endpoint" to "primary pCR endpoint"	Typo	Non-substantial
Section 9.4.2.2 – Secondary Endpoint(s) – EFS, IDFS, and OS	Updated definition of 3-year landmark rate	To add more clarification.	Non-substantial
Section 9.4.2.2 – Secondary Endpoint(s) – EFS, IDFS, and OS	• Clarification of subgroup list • Removal of reference to subgroup analysis by post-baseline factors	Statistical clarification – post-baseline factors should not be used as subgroups in the subgroup analyses. Subgroup analyses are	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
		planned for primary and key secondary endpoints	
Section 9.4.2.2 – Secondary Endpoint(s) – EFS, IDFS, and OS	Clarification that subgroup analyses for stratification factors, as well as for all other factors, will be based on values recorded in the eCRF or from third-party vendor data	This will ensure that the subgroup analyses will be based on more current data from the eCRF or third-party vendor rather than IRT data which can have mis-stratification	Non-substantial
Section 9.4.2.2 – Secondary Endpoint(s) – EFS, IDFS, and OS	Added the minimum number of patients in each treatment arm in a subgroup for pCR subgroup analyses	Adding minimum number of patients will ensure a balanced comparison within a subgroup	Non-substantial
Section 9.4.2.2 – Secondary Endpoint(s) – EFS, IDFS, and OS	Removal of "non-invasive" from EFS definition	Correction to ensure definition is consistent throughout the CSP	Non-substantial
Section 9.4.4.6 – Residual Cancer Burden	Added new subsection for RCB	Included details on planned analysis of RCB	Non-substantial
Appendix A1 – Regulatory and Ethical Considerations	Added text that investigators will be responsible for providing oversight study conduct at site, and adherence to 21 CFR 312.120, ICH guidelines, IRB/IEC, European Regulation 536/2014 as applicable, and all other applicable local regulations	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
Appendix A1 – Regulatory and Ethical Considerations	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches" and related guidance	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
Appendix A4 – Data Protection	Added bullet points with regard to informing participants of collection of data for business needs and data pseudonymisation	To align with most recent AstraZeneca-specific protocol template	Non-substantial
Appendix A4 – Data Protection	Added sub-heading "Personal Data Breaches" and related guidance	To address EU CTR RFI concerns relating to personal data breaches	Non-substantial
Appendix A6 – Dissemination of Clinical Study Data	Updated information about timelines for submission of trial results summaries to EMA CTIS	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
Appendix A7 – Data Quality Assurance	• Inclusion of quality tolerance limits and medical oversight details • Clarification on medical oversight process • Updated information about retention timelines of records and documents to "25 years after study archiving or as required by local regulations"	Update required to comply with regulatory requirement (eg, EU CTR)	Non-substantial
Appendix E6 – Laboratory Tests	Added footnote to state that tests for carbohydrate-deficient transferrin and transferrin are not available in China	Clarification	Non-substantial
Appendix I – Concomitant Medications, Table 21	• Removal of the following: ° Hydroxychloroquine and chloroquine treatment for COVID-19 ° Hormone replacement therapy as acceptable treatment • Clarification that mRNA and replication-deficient adenoviral vaccines are not considered live, attenuated vaccines	To align with the current project-level requirements for T-DXd study protocols, and to align with study protocol	Non-substantial
Appendix J – Instructions Related to SARS-COV-2 Infection	• Revised name of appendix to "Instructions Related to SARS-COV-2 Infection" • Removed pharmacokinetic sampling • Added other clarifications and changes	To align with project-specific safety requirements	Non-substantial
Appendix J2 – Benefit-Risk Considerations for COVID-19	Removed hydroxychloroquine and chloroquine treatment for COVID 19	To align with project-specific safety requirements	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
Appendix M – Toxicity Management Guidelines	Included the following: • CCI • CCI • CCI	To align with project-specific safety requirements	Non-substantial
Appendix O – Protocol Amendment History	Moved protocol amendment history to new appendix	To comply with the latest AstraZeneca-specific protocol template	Non-substantial
Appendix P – Abbreviations	Minor modifications to list of abbreviations	To align with study protocol	Non-substantial
Appendix Q – Country-specific Requirements All sections as required	Included the following: • New appendix for country-specific requirements • Clarifications throughout protocol for country-specific requirements	Update required to comply with EU CTR (EU CTR submissions only allow one version of the protocol used by all EU/EEA countries)	Non-substantial
All sections as required	Correction of typographical and grammatical errors	Typographical change	Non-substantial

ADA = anti-drug antibody; CFR = Code of Federal Regulations; COVID-19 = coronavirus disease 2019; CR = complete response; CSP = Clinical Study Protocol; CTCAE = Common Terminology Criteria for Adverse Events; EAS = efficacy analysis set; EBC = early breast cancer; ECG = electrocardiogram; eCRF = electronic case report form; EEA = European Economic Area; EFS = event-free survival; ePRO = electronic patient-reported outcome; EMA = European Medicines Agency; EU CTR = European Union Clinical Trial Regulation; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; FU = follow-up; GCP = Good Clinical Practice; HER2 = human epidermal growth factor receptor 2; ICH = International Council for Harmonisation; IDFS = invasive disease-free survival; ILD = interstitial lung disease; IMP = investigational medicinal product; IND = Investigational New Drug; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; CCI CCI pCR = pathological complete response; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RCB = residual cancer burden; RECIST = Response Evaluation Criteria in Solid Tumours; RFI = request for information; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; T-DXd = trastuzumab deruxtecan; TEAE = treatment emergent adverse event.

Amendment [2] (15-July-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for the Amendment:

The primary reason for Amendment 2 is to CCI

CCI [redacted]

Additional modifications were also made as described in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 - Schedule of Activities Section 8.2.5.1, Echocardiogram/Multigated Acquisition Scan	Corrected the ECHO or MUGA scan to be assessed once within *28 days* prior to randomisation.	Typographical oversight.	Non-substantial
Section 1.3 – Schedule of Activities Note section for "Menopausal status assessments (including FSH, LH, and oestradiol); **menstruation status**" Section 8.1.6, Determination of Menopausal Status	Included the collection of menstruation status along with menopausal status for premenopausal women.	Updated to capture menstruation status during study to help potentially identify oncofertility issues.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 – Schedule of Activities Note section for "Menopausal status assessments (including FSH, LH, and oestradiol); **menstruation status**"	Replaced reference to premenopausal participants. with postmenopausal participants.	Administrative clarification. Menopausal status is required to be confirmed for postmenopausal women at baseline only.	Non-substantial
Section 1.3 - Schedule of Activities Section 8.2.4, Clinical Safety Laboratory Assessments	Removed HIV screening.	To reconcile with exclusion criterion 8.	Non-substantial
Section 1.3 - Schedule of Activities Section 8.2.4, Clinical Safety Laboratory Assessments	Removed allowance for laboratory assessments to be performed within 3 days of treatment administration.	Administrative clarification to reconcile with Section 1.3 - Schedule of Activities.	Non-substantial
Section 1.3 - Schedule of Activities	Added pre-dose blood sample to be taken for T--DXd PK testing and removed the blood sample for immunogenicity testing at the Early Study Discontinuation/End of Treatment visit of the surgical period.	Administrative clarification. Typographical error.	Substantial
CCI			
Section 1.3 - Schedule of Activities Section 7.1.4 Follow-up for Recurrence and Survival Section 8.1.3.4 Bilateral Mammogram	Removed requirement for Bilateral Mammogram after patient has recurrence or metastatic disease. Added clarification on when follow-up via phone will be done after patient has recurrence or metastatic disease	Bilateral mammogram not clinically relevant once patient has recurrence or metastatic disease	Non-Substantial
Section 5.1 Inclusion Criterion 8	Removed requirement for the participant to be stable on their chosen method of birth control *for*	Administrative clarification. Only non-hormonal	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Appendix G, Contraception Requirements G1, Female Participants	*a minimum of 3 months* before entering the study.	methods of birth control are accepted in this study.	
Section 5.2 Exclusion Criterion 3	Added a second current breast primary malignancy.	Administrative clarification.	Substantial
Section 5.4, Screen Failures	Added that patients cannot be re-screened if there is a valid HER2 central negative result.	Administrative clarification.	Non-substantial
Section 6.2.1, T-DXd Preparation, Administration and Storage	Updated Administration of T-DXd wording to align with current standard.	To provide updated guidance on premedication prior to administering T-DXd	Non-substantial
Section 6.6.4, Dose Modification of a Component or Entire Regimen THP (Arm B and Arm C)	Added clarifications in the event that a dose of weekly paclitaxel cannot be administered and regarding skipped paclitaxel doses. Added text to provide clarification on the dose modification of other components of regimen in the case a single HER2 targeted intervention agent is delayed.	To provide additional dosing guidance to sites.	Substantial
Section 6.6.4, Dose Modification of a Component or Entire Regimen ddAC (Arm C)	Added text to take into account the requirement to delay either doxorubicin or cyclophosphamide.	To provide additional dosing guidance to sites.	Substantial
Section 8.2.2, Vital Signs	Revised "oral temperature" to read as "body temperature".	Other forms of temperature are acceptable.	Non-substantial
Section 8.2.2, Vital Signs	Provided clarification regarding timing of vital signs for a 30-minute infusion.	To ensure clarity for subsequent infusions.	Non-substantial
Section 8.2.4, Clinical Safety Laboratory Assessments	Added that a pregnancy test should be performed at the safety follow-up visit.	Administrative clarification to reconcile with Section 1.3 -	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		Schedule of Activities.	
Section 8.2.4, Clinical Safety Laboratory Assessments Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information Section 8.3.7. Hy's Law Appendix E, Actions Required in Cases of Increases in Liver Biochemistry and Evaluation Appendix M, Toxicity Management Guidelines	Updated TBL requirements to meet Hy's Law from "TBL >2×ULN" to "TBL ≥2×ULN".	Updated as per FDA feedback.	Non-substantial
CCI [redacted]			
Appendix F, Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)	Reordered the additional options for chest-abdomen (-pelvis) imaging when participants have sensitivity to IV contrast or have compromised renal function.	To conform to the imaging vendor's imaging acquisition guidelines.	Non-substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Appendix G, Contraception Requirements G 1, Female Participants	Replaced that women must not donate or retrieve ova from the "time of screening" to "the first dose of study intervention".	To provide flexibility to the site without compromising participant safety.	Non-substantial
Appendix G, Contraception Requirements G 2, Male Participants with a Female Partner of Childbearing Potential	Corrected the period that non-sterilised male participants must use an acceptable form of contraception to *6* months after the last dose of study intervention or as dictated by prescribing information for SOC treatments received after neoadjuvant treatment.	Typographical oversight.	Non-substantial

CCI

[redacted]

Amendment [1] (05-August-2021)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU

Overall Rationale for the Amendment:

The primary reason for Amendment 1 is to modify Exclusion Criterion 7 such that participants with active hepatitis C infections or active or prior hepatitis B infections are excluded from participation in this study. Additional modifications were also made as described in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 – Schedule of Activities, Section 8.1.3.3 – Breast MRI	Added additional text to section 8.1.3.3 to specify breast MRIs should only be performed at 3 timepoints.	Clarify that breast MRIs should only be performed at 3 timepoints (during screening, before Cycle 5 Day 1, and at the end of treatment).	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
CCI			
Section 4.1 - Overall Design	Changed text to remove multifocal tumours	To clarify only multi-centric tumors will have multiple samples for central HER2 testing, and multi-centric tumors must have 1 lesion from each involved quadrant sampled according to the inclusion criteria.	Non-substantial
Section 4.1 - Overall Design	Modified text to reflect that in cases of multi-centric tumours where multiple HER2 results should be available, only patients with all lesions HER2 IHC3+ will be considered IHC3+ for stratification purposes	Clarified considerations for stratification	Non-substantial
Section 4.1 - Overall Design	Added text to reflect that, during the intervention period and leading up to surgery, participants should only receive the assigned therapy per the designated schedule (unless patients are prematurely discontinued).	Clarify that bridge therapy (after neoadjuvant but before surgery) is not allowed	Non-substantial
Section 5.1 Inclusion Criteria 2 (b)	Added text to include unifocal tumours	Clarify the requirement for unifocal tumours.	Non-substantial
Section 5.1 Inclusion Criterion 2(e); Section 5.2 Exclusion	Changed Kueng and Gershenwald 2020 to Hortobagyi et al. 2017	Corrected reference	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Criterion 2, Section 11 References			
Section 5.2 - Exclusion criterion 7	Modified text: Active hepatitis C infection. Participants positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Participants with current active or history of hepatitis B infection with either HBsAg(+) or anti-HBc(+) are not eligible.	Amended such that participants with active hepatitis C infections or active or prior hepatitis B infections are excluded	Substantial
Section 6.1.1 Investigational products	Added text to reflect that participants should only receive the assigned therapy per the designated schedule (unless patients are prematurely discontinued). Additional therapy after completion of neoadjuvant treatment and before surgery is not allowed.	Clarify that bridge therapy (after neoadjuvant but before surgery) is not allowed	Non-substantial
Section 8.2.4 – Clinical Safety Laboratory Assessments	Changed text from "During Cycle 1, laboratory assessments should be performed within 3 days of treatment administration. During subsequent cycles, these assessments can be done within 1 day prior to treatment administration." To "Laboratory assessments should be performed within 3 days of treatment administration on D1 of each cycle."	Window should be 3 days prior for each administration cycle. Change made to align with SoA.	Non-substantial
Section 8.6.1 - Collection of Mandatory Samples for Biomarker Analysis	Edited text as follows: "For cases of ~~multifocal or~~ multi-centric tumours, 2 cores per discrete lesion in each affected quadrant or 20 freshly cut sections	To prevent confusion on requirements for multifocal tumours	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	containing 2 cores must be submitted"		

Appendix P Abbreviations

Abbreviation or Special Term	Explanation
AC	doxorubicin + cyclophosphamide
AC-T	doxorubicin + cyclophosphamide followed by docetaxel
AC-TH	AC-T + trastuzumab
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALND	axillary lymph node dissection
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
aPTT	activated partial thromboplastin time
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
CCI	CCI
BICR	Blinded Independent Central Review
C	cycle
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disorder
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Special Term	Explanation
CCI	CCI
CTIS	Clinical Trials Information System
CV	cardiovascular
CYP	cytochrome P450
D	day
DAR	drug-antibody ratio
DCIS	ductal carcinoma in situ
DCO	data cut-off
ddAC-THP	doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab
DES	Data Entry Site
DFS	disease-free survival
DILI	drug-induced liver injury
DLCO	diffusion capacity of the lungs for carbon monoxide
CCI	CCI
DNA	deoxyribonucleic acid
DXd	deruxtecan
EBC	early breast cancer
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EoT	end of treatment
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
EU CTR	European Union Clinical Trial Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
exam	examination

Abbreviation or Special Term	Explanation
FAS	Full Analysis Set
FEC	5 fluorouracil + epirubicin + cyclophosphamide
FEV/1/6	forced expiratory volume/1 second/6 seconds
FFPE	formalin-fixed and paraffin-embedded
FISH	fluorescent in situ hybridisation
FSH	follicle-stimulating hormone
FU	follow-up
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GnRH	gonadotropin-releasing hormone
HAV	hepatitis A virus
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care professional
HcRU	healthcare resource utilisation
HCV	hepatitis C virus
HER1	human epidermal growth factor receptor 1
HER2	human epidermal growth factor receptor 2
H&E	hematoxylin & eosin
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HL	Hy's Law
HP	trastuzumab + pertuzumab
HR	hormone receptor
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
hrs	hours
HSV	herpes simplex virus
5-HT3	5-hydroxytryptamine 3
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation or Special Term	Explanation
iCRO	imaging Contract Research Organisation
IDFS	invasive disease-free survival
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immuno-globulin G
IgM	immuno-globulin M
IHC	Immunohistochemistry
International co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally.
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalised ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISH	in situ hybridisation
ITT	Intent-to-treat
IV	intravenous
KL-6	Krebs von den Lungen-6
L	Litre
LDH	lactate dehydrogenase
LH	luteinising hormone
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
Max.	maximum
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
Min.	minimum
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
CCI	CCI
MUGA	multigated acquisition
NA	not applicable
NCCN	National Comprehensive Cancer Network

Abbreviation or Special Term	Explanation
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of diseases
NK1	Neurokinin 1
NL	new lesion
NSAID	nonsteroidal anti-inflammatory drugs
NTL	non-target lesion
NYHA	New York Heart Association
CCI	CCI
OS	overall survival
CCI	CCI
P	pertuzumab
PBMC	peripheral blood mononuclear cell
pCR	pathological complete response
PD	progression of disease
PEF	peak expiratory flow
PET	positron emission tomography
PFS	progression-free survival
PGI-TT	Patient Global Impression of Treatment Tolerability
PHL	public health laboratory
PgR	progesterone receptor
PHL	Potential Hy's Law
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QW	weekly
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
QTcF	QT interval corrected by Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1

Abbreviation or Special Term	Explanation
RCB	residual cancer burden
RNA	ribonucleic acid
RV	residual volume
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SLFN11	Schlafen Family Member 11
SLNB	sentinel lymph node biopsy
SmPC	summary of product characteristics
SoA	Schedule of Activities
SOC	standard of care
SOP	Standard Operating Procedure
SP-D	surfactant protein D
SpO2	peripheral capillary oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
TBL	total bilirubin
TCH	docetaxel + carboplatin + trastuzumab
TCHP	docetaxel + carboplatin + trastuzumab + pertuzumab
TdP	Torsades de Pointes
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TEAE	treatment emergent adverse event
THP	paclitaxel + trastuzumab + pertuzumab
TIL	tumour infiltrating lymphocytes
TL	target lesion
TLC	total lung capacity
TMG	toxicity management guideline
TPV	third party verification
TTR	time to response
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell count

Abbreviation or Special Term	Explanation
WOCBP	women of childbearing potential
w/v	weight per volume
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

Appendix Q Country-specific Requirements

European Union Country Specific Requirements

Q 1 Germany

Section # and Name	Description of Change with Reason
Section 1.3 – Schedule of Activities Section 6.6.1 – T-DXd Dose Modification Section 8.2.5.1 – Echocardiogram/Multigated Acquisition Scan Section 8.3.5 – Adverse Events Based on Examinations and Tests	Left ventricular ejection fraction (LVEF) will be measured only by echocardiogram (ECHO). Multiple gated acquisition (MUGA) scan will not be allowed in Germany to avoid unnecessary exposure to radiation. This has already been discussed during previous studies and is in accordance with Federal Office for Radiation Protection (BfS) in Germany.

T-DXd = trastuzumab deruxtecan.

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