CLINICAL STUDY PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED TRIAL OF TRASTUZUMAB DERUXTECAN (T-DXd), AN ANTI-HER2-ANTIBODY DRUG CONJUGATE (ADC), VERSUS TREATMENT OF PHYSICIAN'S CHOICE FOR HER2-LOW, UNRESECTABLE AND/OR METASTATIC BREAST CANCER SUBJECTS (DESTINY-Breast04)

DS8201-A-U303

IND NUMBER 127553

EudraCT NUMBER 2018-003069-33

VERSION 5.0, 12 October 2020

Daiichi Sankyo Inc.

DOCUMENT HISTORY

Version Number	Version Date
5.0	12 October 2020
4.0	23 April 2020
3.0	24 April 2019
2.0	23 November 2018
1.0	23 August 2018

INVESTIGATOR AGREEMENT

A Phase 3, multicenter, randomized, open-label, active-controlled trial of trastuzumab deruxtecan (T-DXd), an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects (DESTINY-Breast04)

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo Inc. representative listed below.

PPD	PPD
Print Name	**Signature**
Senior Director, Global Oncology R&D	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives, and relevant Regulatory Authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 5.0 (dated 12 Oct 2020) vs. protocol Version 4.0 (dated 23 Apr 2020) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U303 clinical study protocol (Version 5.0) by section.

Amendment Rationale:

This amendment (Version 5.0) includes the addition of new timepoints for overall survival (OS) analyses. The study was originally designed to perform OS analysis at the same time as the final progression-free survival (PFS) analysis. This early analysis would not have provided adequate follow up and statistical power to detect a statistically significant difference in OS. The protocol is now amended to include OS as a key secondary endpoint with adequate follow-up to provide statistical power to detect meaningful improvement in overall survival between the 2 treatment arms.

In addition, progression-free survival on the next line of therapy (PFS2) is added as an exploratory objective and endpoint.

To evaluate the impact of the global pandemic caused by coronavirus disease 2019 (COVID-19), biomarker analysis is added to identify patients affected by COVID-19, and the analysis plan is updated to identify the impact of COVID-19 on safety, efficacy, and study conduct. Other changes and rationale for each change are noted in the table below.

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 European Union.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

All locations (Section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in the Summary of Changes.

Minor edits, such as an update to language that does not alter original meaning, an update to version numbering, formatting, a change in font color, a correction to a typographical error, the use of abbreviations, moving verbiage within a section or table, a change in style or numbering, or a change in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Throughout all sections	Updated the investigational product name from trastuzumab deruxtecan to T-DXd.	To align with the program compound terminology.
Title Page Investigator Agreement Protocol Synopsis	Added "DESTINY-Breast04" to the study name.	To provide clarification.
Investigator Agreement	Updated the Daiichi Sankyo Inc. study representative.	The Daiichi Sankyo Inc. study representative was updated.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis 2.1.2. Key Secondary Objectives 2.1.3. Other Secondary Objectives 2.3.2. Key Secondary Efficacy Endpoints 2.3.3. Other Secondary Efficacy Endpoints 3.2.1. Duration of the Study 3.2.3. Definition of the End of the Study 7.1.2. Key Secondary Efficacy Endpoints 7.1.3. Other Secondary Efficacy Endpoints 7.2. Appropriateness of Selected Efficacy Assessments 11.1 General Statistical Considerations 11.4.2 Key Secondary Efficacy Analyses 11.6. Interim Analyses 11.7. Sample Size Determination 17.9.1. Sweden Only	Updated to include overall survival (OS) power consideration and planned analyses.	The study was originally designed to perform OS analysis at the same time as final PFS analysis. This early analysis would not have provided adequate follow up and statistical power to detect a statistically significant difference in OS. The protocol is now amended to include OS as a key secondary endpoint with adequate follow-up to provide statistical power to detect meaningful improvement in overall survival between the 2 treatment arms. The relevant sections of the protocol were updated to describe the changes.
Protocol Synopsis 2.1.4. Exploratory Objectives 2.3.4. Exploratory Efficacy Endpoints 7.1.4. Exploratory Efficacy Endpoints 11.4.5.2. Analyses of Exploratory Efficacy Endpoints 17.9.1. Sweden Only	Progression-free survival on the next line of therapy (PFS2) was added as an objective and endpoint.	PFS2 was added to provide additional information on the impact of study intervention on the subsequent therapy in terms of a second progression event as captured by the PFS2 endpoint.
Protocol Synopsis	Updated the timing of the primary analyses from 18 months to now occur at approximately 28 months.	Based on updated enrollment information.
5.4.1.1. Dose Interruptions and Reductions for T-DXd, Table 5.3 17.1. Schedule of Events, Table 17.1 17.1. Schedule of Events, Table 17.2	Removed dose modification guidelines for troponin.	The removal of the dose modification guidelines for elevated troponin was driven by updated safety data from T-DXd clinical studies, showing no association between asymptomatic troponin increase with left ventricular dysfunction or any other cardiac events reported in the program.
6.2. Screening	Updated human immunodeficiency virus (HIV) testing language for screening to clearly state the test is	Clarification of HIV testing language.

Section # and Title	Description of Change	Brief Rationale
	not mandatory unless required by local regulations or Institutional Review Board/Institutional Ethics Committee.	
6.2. Screening	Added clarification that subjects who have a positive hepatitis C virus (HCV) antibody test will require a negative polymerase chain reaction for HCV RNA.	Clarification of HCV testing.
6.2. Screening 6.4.1.2. Day 1 Before Dosing (All Cycles, Unless Otherwise Noted). 6.5. End of Study Treatment 17.1. Schedule of Events, Table 17.1 and Table 17.2 17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	COVID-19 serology testing guidance was added.	To provide guidance on serum sample collection related to COVID-19.
6.6.2. Long-term/Survival Follow-up 10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45	Timing of completion of specific HEOR outcomes questionnaires was specified.	To provide clarification.
8.1 Pharmacokinetic Assessments 17.1. Schedule of Events, Table 17.2 17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	Schedule of PK Sample Collection in Case of Chloroquine or Hydroxychloroquine Treatment and descriptions of testing conditions were added.	To monitor potential drug-drug interactions between investigational/study drug treatment and COVID 19 specific treatment.
9.5. Adverse Events and Adverse Event of Special Interest Reporting–Procedures For Investigators	Clarification added regarding reporting of urgent safety query follow-up information.	To provide clarification regarding urgent safety query reporting.
11.5.7. Immunogenicity (Anti-Drug Antibody) Analyses	Clarification added for the immunogenicity (anti-drug antibody) analyses.	To further define the analyses.
17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	Updated management guidance.	To align with the latest management guidelines for COVID-19.
17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	Added statistical analysis to assess the impact of COVID-19, if deemed appropriate.	To assess the impact of COVID-19.

PROTOCOL SYNOPSIS

EudraCT:	2018-003069-33
IND Number:	127553
Protocol Number:	DS8201-A-U303 (DESTINY-Breast04)
Investigational Product:	Trastuzumab deruxtecan (T-DXd; DS-8201a; also known as fam-trastuzumab deruxtecan-nxki)
Active Ingredients:	Trastuzumab deruxtecan (T-DXd; DS-8201a) consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a
Study Title:	A Phase 3, multicenter, randomized, open-label, active-controlled trial of trastuzumab deruxtecan (T-DXd), an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects (DESTINY-Breast04)
Study Phase:	Phase 3
Indication Under Investigation:	Unresectable and/or metastatic breast cancer that is human epidermal growth factor receptor 2 (HER2)-low
Study Objectives:	Primary Objective: • To compare the progression-free survival (PFS) benefit of T-DXd to physician's choice in HER2-low, hormone receptor (HR)-positive breast cancer, based on blinded independent central review (BICR) Key Secondary Objectives: • To compare the PFS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive, and HR-negative breast cancer), based on BICR • To compare the overall survival (OS) benefit of T-DXd to physician's choice in HER2-low, HR-positive breast cancer • To compare the OS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive and HR-negative breast cancer) **In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.**

	Other Secondary Objectives: • To evaluate efficacy of T-DXd compared to physician's choice on the following parameters: – Progression-free survival (PFS) in HR-positive subjects, based on Investigator assessment – Confirmed objective response rate (ORR), based on BICR and Investigator assessment in HR-positive subjects – Duration of response (DoR), based on BICR in HR-positive subjects – Confirmed ORR, and DoR in all subjects, regardless of HR status. • To determine pharmacokinetics (PK) of T-DXd • To evaluate safety of T-DXd compared to physician's choice of treatment • To evaluate Health Economics and Outcomes Research (HEOR) endpoints for T-DXd compared to physician's choice **In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.** Exploratory Objectives: • To evaluate clinical benefit rate (CBR; the sum of complete response [CR] rate, partial response [PR] rate, and greater than or equal to 6 months' stable disease rate) based on BICR • To evaluate disease control rate (DCR), based on BICR • To evaluate time to response (TTR), based on BICR • To evaluate progression-free survival on the next line of therapy (PFS2) • To evaluate potential biomarkers of response/resistance • To evaluate exposure-response relationships for efficacy and safety endpoints • To evaluate PFS, OS, confirmed ORR, and DoR in HR-negative subjects
Study Design:	This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of T-DXd versus the physician's choice in HER2-low, unresectable and/or metastatic breast cancer subjects. Subjects to be enrolled:

- Not more than 240 HR-positive subjects who have not had prior therapy with a cyclin-dependent kinase (CDK) 4/6 inhibitor
- At least 240 HR-positive subjects who have had prior therapy with a CDK4/6 inhibitor
- ~60 HR-negative subjects.

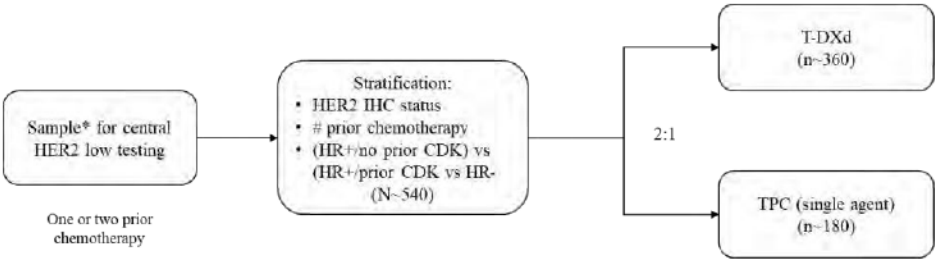
The ~540 subjects will be randomized 2:1 to T-DXd (~360) versus the physician's choice (~180) with one of the following drugs:

- Capecitabine
- Eribulin
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

Randomization will be stratified by:

- HER2 immunohistochemistry (IHC) status of tissue samples assessed by a central laboratory: HER2 IHC 1+ vs. HER2 IHC 2+/in situ hybridization [ISH]-
- Number of prior lines of chemotherapy: 1 vs. 2
- HR/CDK status: HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative.

Study Design Schema of DS8201-A-U303



CDK = cyclin-dependent kinase, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, TPC = treatment of physician's choice
*See Section 6.1 and Section 6.2 for details.

There will be follow-up visits after permanent discontinuation of study treatment to obtain information about subsequent treatment(s) and survival status.

Study Duration:	Enrollment is planned to occur over approximately 16 months from the randomization date of the first subject. The data cutoff for the primary analysis of PFS is planned when approximately 318 PFS events per BICR have been observed in the HR-positive subjects, and data cut for the final analysis of the key secondary endpoint of OS is planned when approximately 333 OS events have been documented in the HR-positive subjects. There will be a 40-Day (+7 days) Follow-up after the last study treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up every 3 months (±14 days) from the date of the 40-Day (+7 days) Follow-up, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.
Study Centers and Location:	Approximately 225 sites, including but not limited to, North America, Western Europe, and Asia.
Subject Eligibility Criteria:	<u>Key Inclusion Criteria</u> The Investigator should follow the label approved in the country of drug administration for the individual treatment options (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) for eligibility criteria if the subject is randomized to the arm of treatment of physician's choice. The inclusion criteria include: • Men or women ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old.) • Pathologically documented breast cancer that: – Is unresectable or metastatic. – Has a history of low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested). – Is assessed as low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ according to ASCO-CAP 2018 HER2 testing guidelines (adapted by Daiichi Sankyo Inc. and Ventana) evaluated at a central laboratory. – Is HR-positive or HR-negative. Approximately 60 HR-negative subjects are to be enrolled; the remaining subjects will be HR-positive. – If HR-positive, is documented refractory to endocrine therapy, defined as having progressed on at least 1 endocrine therapy and determined by the Investigator that subject would no longer benefit from further treatment from endocrine therapy.

  - If HR-positive, has or has not been treated with a CDK4/6 inhibitor. Not more than 240 HR-positive subjects who have not had prior therapy with a CDK4/6 inhibitor and at least 240 HR-positive subjects who have had prior therapy with a CDK4/6 inhibitor will be enrolled.
  - Has been treated with at least 1 and at most 2 prior lines of chemotherapy in the metastatic setting. If recurrence occurred within 6 months of adjuvant chemotherapy, adjuvant therapy would count as 1 line of chemotherapy.
    - Was never previously HER2-positive (IHC 3+ or IHC2+/ISH+) on prior pathology testing (per ASCO-CAP - guidelines) or was historically HER2 IHC 0 only.
  - Was never previously treated with anti-HER2 therapy.
- Documented radiologic progression (during or after most recent treatment).
- Must have an adequate archival tumor tissue sample available for assessment of HER2 status by central laboratory (based on most recent available tumor tissue sample). If archival tumor tissue is not available, a fresh tumor tissue biopsy is required. See Section 6.1 for details.
- All subjects must have a recent tumor tissue sample after the most recent treatment regimen or agree to undergo a tissue biopsy prior to randomization. See Section 6.2 for details.
- Presence of at least 1 measurable lesion based on computed tomography (CT) or magnetic resonance imaging (MRI), per modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1.
  - Brain lesions will be considered as non-target lesions only.
- Left ventricular ejection fraction (LVEF) ≥50%
- Adequate renal function, defined as:
  - Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation
- Adequate hepatic function, defined as:
  - Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤5 × upper limit of normal (ULN)
  - Total bilirubin ≤1.5 × ULN) if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome

(unconjugated hyperbilirubinemia) or liver metastases at baseline

- Males and females of reproductive/childbearing potential must agree to follow instructions for method(s) of contraception

Key Exclusion Criteria

The Investigator should follow the label approved in the country of drug administration for the individual treatment options (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) if the subject is randomized to the arm of treatment of physician's choice. The exclusion criteria include:

- Ineligible for the declared physician's choice comparator because of previously receiving treatment with the same comparator in the metastatic setting or the comparator is contraindicated. Subjects are eligible if there is a comparator with which they have not previously been treated.
- Has medical history of myocardial infarction within 6 months before randomization
- Has history of symptomatic congestive heart failure (New York Heart Association Class II to IV)
- Has corrected QT interval (QTc) prolongation to >470 ms (females) or >450 ms (male) based on average of Screening triplicate 12-lead electrocardiograms (ECGs)
- Has a history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
- Has spinal cord compression or clinically active central nervous system metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
  - Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.

Dosage Form, Dose, and Route of Administration:	T-DXd for injection 100 mg, Lyo-DP: A T-DXd lyophilized powder containing 100 mg of T-DXd in a glass vial.

	T-DXd for intravenous (IV) infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight. The study treatment will be administered at a dose of 5.4 mg/kg as an IV infusion every 21 days, initially for approximately 90 minutes, then, if there is no infusion related reaction, for a minimum of 30 minutes thereafter. Physician's choice comparative therapy will be administered in accordance with the label approved in the country of drug administration or the NCCN guidelines[1] (see Table 5.1). The physician's choice needs to be predefined, prior to randomization, from the following options: • Capecitabine • Eribulin • Gemcitabine • Paclitaxel • Nab-paclitaxel
Study Endpoints:	Primary Efficacy Endpoint: • PFS, based on BICR, in HR-positive breast cancer subjects Key Secondary Efficacy Endpoint: • PFS, based on BICR, in all randomized subjects • OS in HR-positive breast cancer subjects • OS in all randomized subjects **In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.** Other Secondary Efficacy Endpoints: • PFS, based on Investigator assessment • Confirmed ORR, based on BICR and Investigator assessment • DoR, based on BICR **In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.** Exploratory Efficacy Endpoints: • CBR, based on BICR • DCR, based on BICR • TTR, based on BICR

- PFS2

Health Economic and Outcomes Research Endpoints:

- European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)
    - C30
    - BR45
- EuroQol 5 dimensions 5 levels [of severity] (EQ-5D-5L)
- Hospitalization-related endpoints

Pharmacokinetic Endpoints:

- Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a

Biomarker Endpoints:

- Serum biomarkers (eg, HER2 extracellular domain)
- Other potential biomarkers of response/resistance (eg, deoxyribonucleic acid [DNA] profiling in cell free DNA, RNA expression profiling, mutations)

Safety Endpoints:

- Serious adverse events (SAEs)
- Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
- Adverse events of special interest (AESIs)
- Discontinuations associated with adverse events
- Physical examination findings
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Vital sign measurements
- Standard clinical laboratory parameters
- ECG parameters
- Echocardiogram (ECHO)/multigated acquisition (MUGA) scan findings
- Anti-drug antibodies

Planned Sample Size:	The target sample size will be approximately 540 subjects, randomized in a 2:1 ratio into 2 treatment arms (T-DXd vs. physician's choice). Up to ~40 T-DXd subjects and up to ~20 physician's choice subjects will be HR-negative.
Statistical Analyses:	The primary analyses for PFS will be performed when ~318 PFS events per BICR have been observed in the HR-positive population, which is expected to occur in ~28 months from the randomization date of the first subject. <u>Efficacy Analyses</u> The primary efficacy endpoint is PFS per BICR. The primary efficacy analyses of PFS per BICR will be performed for the HR-positive cohort of the Full Analysis Set (FAS). Progression-free survival per BICR is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression based on BICR or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cutoff date for PFS analysis will be censored at the date of their last evaluable tumor assessment. The primary efficacy analysis will compare PFS of HR-positive subjects between the 2 treatment arms using a stratified log-rank test. Stratification factors used for primary analysis will be from the randomization. The PFS will be tested for statistical significance at a 2-sided alpha of 0.05. Kaplan-Meier estimates and survival curves will also be presented for each treatment arm. The median event times and 2-sided 95% confidence intervals (CIs) for the medians will be provided using Brookmeyer and Crowley method for each treatment arm. The hazard ratios and their 95% CIs will be estimated, using stratified Cox proportional hazards regression models. Group sequential testing will be used to compare OS between the 2 treatment groups hierarchically, provided the PFS analysis is statistically significant. Kaplan-Meier estimates and survival curves will also be presented for each treatment group. The median survival times and 2-sided 95% CIs for the medians will be provided using Brookmeyer and Crowley method for each treatment arm. In addition, Kaplan-Meier estimates at fixed time points, along with their 2-sided 95% CIs, will be provided for each treatment arm. The HR and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by stratification factors per Interactive Web/Voice Response System. Up to 3 analyses of OS will be performed:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant), at which point a total of approximately 162 OS events (49% information fraction) in HR-positive subjects are expected.
- If the first OS interim analysis is not significant, a second interim analysis for OS is planned when approximately 233 OS events (70% information fraction) in HR-positive subjects have been documented.
- If the second OS interim analysis is not significant, a final analysis for OS after approximately 333 OS events in HR-positive subjects have been documented.

Duration of response is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression, based on BICR, or death. Duration of response will be measured for responding subjects (PR or CR) only. Subjects who are progression-free and alive at the time of the analyses will be censored at the date of the last evaluable tumor assessment.

Duration of response will be summarized with median event times and its 2-sided 95% CIs using Brookmeyer and Crowley method for each treatment arm.

The Cochran–Mantel–Haenszel test will be used to compare confirmed ORR between the treatment arms. The estimates of confirmed ORR and its 2-sided 95% exact CI will be provided using the Clopper-Pearson method.

Health Economic and Outcomes Research Analyses

Health economic and outcomes research endpoints based on the hospitalization-related data collection form and the following PRO questionnaires will be summarized by treatment arm: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L. A detailed analysis plan of QoL endpoints, including control of type I error regarding QoL analyses, will be provided in the SAP.

Pharmacokinetic Analyses

Descriptive statistics will be provided for all serum concentration data (T-DXd, total anti-HER2 antibody, and MAAA-1181a) at each time.

The population-PK (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of T-DXd, and if appropriate, total anti-HER2 antibody and MAAA-1181a, will be characterized, including available PK data from other T-DXd studies. After establishment of the pop-PK model, a pop-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and safety

endpoints. The results of the nonlinear mixed effects pop-PK and pop-PK/pharmacodynamic models may be reported separately from the clinical study report.

Biomarker Analyses

A tumor tissue biopsy after the completion of the subject's most recent treatment regimen is required for retrospective assessment. If the tumor tissue sample provided for HER2 status testing was collected after completion of the last treatment regimen, an additional new biopsy is not required. If the tumor tissue sample provided for HER2 status testing was collected before completion of the last treatment regimen, an additional new biopsy is required. Optional fresh tissue samples may additionally be obtained during and after study treatment.

Biomarkers will be summarized by treatment arm using descriptive statistics, when applicable.

Safety Analyses

Safety endpoints will include SAEs, TEAEs, AESIs, discontinuations associated with AEs, physical examination findings, ECOG PS, vital signs measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA scan findings, and anti-drug antibodies. The TEAEs will be graded according to the NCI CTCAE version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

TABLE OF CONTENTS

DOCUMENT HISTORY 2
INVESTIGATOR AGREEMENT 3
SUMMARY OF CHANGES 4
PROTOCOL SYNOPSIS 7
LIST OF ABBREVIATIONS 28
1. INTRODUCTION 32
1.1. Background 32
1.1.1. Investigational Product 33
1.1.1.1. Name 33
1.1.1.2. Description 33
1.1.1.3. Intended Use Under Investigation 33
1.1.1.4. Comparators (Physician's Choice) 34
1.1.1.5. Nonclinical Studies of T-DXd 34
1.1.1.6. Clinical Experience 35
1.1.1.7. Benefit/Risk Assessment 38
1.1.1.8. Summary of Clinical Pharmacokinetics 39
1.2. Study Rationale 40
2. STUDY OBJECTIVES AND HYPOTHESIS 42
2.1. Study Objectives 42
2.1.1. Primary Objective 42
2.1.2. Key Secondary Objectives 42
2.1.3. Other Secondary Objectives 42
2.1.4. Exploratory Objectives 42
2.2. Study Hypothesis 43
2.3. Study Endpoints 43
2.3.1. Primary Efficacy Endpoint 43
2.3.2. Key Secondary Efficacy Endpoints 43
2.3.3. Other Secondary Efficacy Endpoints 43
2.3.4. Exploratory Efficacy Endpoints 43
2.3.5. Health Economic and Outcomes Research Endpoints 44
2.3.6. Pharmacokinetic/Biomarker Endpoints 44

2.3.6.1. Pharmacokinetic Endpoints 44
2.3.6.2. Biomarker Endpoints 44
2.3.7. Safety Endpoints 44
3. STUDY DESIGN 45
3.1. Overall Design 45
3.2. Discussion of Study Design 46
3.2.1. Duration of the Study 47
3.2.2. Duration of Subject Participation 47
3.2.3. Definition of the End of the Study 47
4. STUDY POPULATION 48
4.1. Inclusion Criteria 48
4.2. Exclusion Criteria 51
4.3. Subject Replacement 53
4.4. Subject Re-screening Procedures 53
5. STUDY TREATMENTS 54
5.1. Assigning Subjects to Treatments and Blinding 54
5.1.1. Treatment Groups 54
5.1.2. Method of Treatment Allocation 54
5.1.3. Blinding 54
5.1.4. Emergency Unblinding Procedure 55
5.2. Study Drug 55
5.2.1. Description 55
5.2.2. Labeling and Packaging 55
5.2.3. Preparation 55
5.2.4. Administration 55
5.2.5. Storage 56
5.2.6. Drug Accountability 56
5.3. Control Treatment 56
5.4. Guidelines for Dose Modification 57
5.4.1. Dose Interruptions and Reductions 57
5.4.1.1. Dose Interruptions and Reductions for T-DXd 58
5.4.1.2. Dose Interruptions and Reductions for Physician's Choice 66

5.5. Method of Assessing Treatment Compliance....66
5.6. Prior and Concomitant Medications and Treatments....66
5.6.1. Prohibited Medications and Treatments....67
5.7. Study Drug Discontinuation and Discontinuation from the Study....68
5.7.1. Discontinuation of Study Drug....68
5.7.2. Subject Withdrawal/Discontinuation from the Study....69
6. STUDY PROCEDURES....71
6.1. Tissue Screening....71
6.2. Screening....72
6.3. Randomization....74
6.4. Treatment Period....74
6.4.1. Cycle 1 to 4 and Subsequent Cycles....74
6.4.1.1. Between -3 Days Before Dosing Through Immediately Before Dosing (All Cycles)....74
6.4.1.2. Day 1 Before Dosing (All Cycles, Unless Otherwise Noted)....75
6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted)....76
6.4.1.4. Day 8 (±1 day) and Day 15 (±1 day) (Cycle 1 Only)....77
6.4.2. Every 4 Cycles (±7 days) After Cycle 1....77
6.4.3. Every 6 Weeks (±7 days)....77
6.5. End of Study Treatment....78
6.6. Follow-up....79
6.6.1. 40-Day (+7 days) Follow-up....79
6.6.2. Long-term/Survival Follow-up....80
7. EFFICACY ASSESSMENTS....82
7.1. Assessments for Efficacy Endpoints....82
7.1.1. Primary Efficacy Endpoint....82
7.1.2. Key Secondary Efficacy Endpoints....82
7.1.3. Other Secondary Efficacy Endpoints....82
7.1.4. Exploratory Efficacy Endpoints....82
7.2. Appropriateness of Selected Efficacy Assessments....83
8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS....85
8.1. Pharmacokinetic Assessments....85
8.2. Pharmacodynamic Assessment(s)....85

8.3. Biomarker Assessments 85
8.3.1. Tumor Tissue Sampling 86
8.3.2. Blood Sampling 86
8.3.3. Additional Biomarker Assessments 86
8.3.4. Disclosure of the Results of Additional Biomarker Assessments 86
8.4. Immunogenicity 86
8.5. Pharmacogenomic Analysis 87
8.5.1. Genomic or Genetic Banking and Analysis 87
8.5.1.1. Disclosure of the Results of Genomic or Genetic Analysis 87
8.5.1.2. Storage and Disposal of Specimens for Genomic or Genetic Analysis 87
9. SAFETY EVALUATION AND REPORTING 88
9.1. Assessment of Safety Endpoint(s) 88
9.2. Adverse Event Collection and Reporting 88
9.3. Adverse Events of Special Interest 89
9.3.1. Interstitial Lung Disease/Pneumonitis 89
9.3.1.1. Clinical Summary 89
9.3.1.2. Management Guidance 89
9.3.1.3. Interstitial Lung Disease Adjudication Committee 90
9.3.2. Left Ventricular Ejection Fraction Decrease 90
9.3.2.1. Clinical Summary 90
9.3.2.2. Management Guidance 90
9.4. Adverse Event 90
9.4.1. Definition of Adverse Event 90
9.4.2. Serious Adverse Event 91
9.4.3. Grade Assessment 91
9.4.4. Causality Assessment 92
9.4.5. Action Taken Regarding Study Drug(s) 92
9.4.6. Other Action Taken for Event 93
9.4.7. Adverse Event Outcome 93
9.5. Adverse Events and Adverse Event of Special Interest Reporting–Procedures For Investigators 93
9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Institutional Ethics Committee 95

9.7. Exposure in Utero During Clinical Studies 95
9.8. Clinical Laboratory Evaluations 95
9.9. Vital Signs 96
9.10. Electrocardiograms 96
9.11. Physical Examinations 97
9.12. Other Examinations 97
9.12.1. Cardiac Assessments 97
9.12.2. Pulmonary Assessments 97
10. OTHER ASSESSMENTS 98
10.1. Patient Reported Outcomes 98
10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45 98
10.1.2. EuroQoL Five Dimensions Five Levels Patient Reported Outcome Questionnaire 99
10.2. Health-related QoL Endpoints 99
10.2.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endpoints 99
10.2.2. EuroQoL Five Dimensions Five Levels Endpoints 100
10.3. Pharmacoeconomic Assessments 100
10.3.1. Hospitalization-Related Endpoint 100
11. STATISTICAL METHODS 101
11.1. General Statistical Considerations 101
11.2. Analysis Sets 101
11.2.1. Full Analysis Set 101
11.2.2. Safety Analysis Set 101
11.2.3. Per-protocol Analysis Set 101
11.2.4. Pharmacokinetic Analysis Set 101
11.3. Study Population Data 102
11.4. Efficacy Analyses 102
11.4.1. Primary Efficacy Analyses 102
11.4.2. Key Secondary Efficacy Analyses 102
11.4.3. Other Secondary Efficacy Analyses 103
11.4.4. Analyses of Health Economic and Outcomes Research Endpoints 103

11.4.4.1. EuroQoL Five Dimensions Five Levels 103
11.4.4.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45 103
11.4.4.3. Hospitalization-Related Endpoints 104
11.4.5. Exploratory Efficacy Analyses 104
11.4.5.1. Subgroup Analyses 104
11.4.5.2. Analyses of Exploratory Efficacy Endpoints 104
11.4.6. Pharmacokinetic and Pharmacodynamic Analyses 105
11.4.6.1. Pharmacokinetic Analyses 105
11.4.6.2. Pharmacodynamic Analyses 105
11.4.7. Biomarker Analyses 105
11.5. Safety Analyses 105
11.5.1. Adverse Event Analyses 106
11.5.2. Clinical Laboratory Evaluation Analyses 106
11.5.3. Vital Sign Analyses 106
11.5.4. Electrocardiogram Analyses 106
11.5.5. Physical Examination Analyses 107
11.5.6. Concomitant Medication Analyses 107
11.5.7. Immunogenicity (Anti-Drug Antibody) Analyses 107
11.5.8. Other Safety Analyses 107
11.6. Interim Analyses 107
11.7. Sample Size Determination 108
11.8. Statistical Analysis Process 109
12. DATA INTEGRITY AND QUALITY ASSURANCE 110
12.1. Monitoring and Inspections 110
12.2. Data Collection 110
12.3. Data Management 111
12.4. Study Documentation and Storage 111
12.5. Record Keeping 112
13. FINANCING AND INSURANCE 113
13.1. Finances 113
13.2. Reimbursement, Indemnity, and Insurance 113
14. PUBLICATION POLICY 114

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION 115
15.1. Compliance Statement, Ethics, and Regulatory Compliance 115
15.2. Subject Confidentiality 115
15.3. Informed Consent 115
15.4. Regulatory Compliance 116
15.5. Protocol Deviations 116
15.6. Supply of New Information Affecting the Conduct of the Study 117
15.7. Protocol Amendments 117
15.8. Study Termination 118
15.9. Data Monitoring Committee 118
15.10. Address List 118
16. REFERENCES 119
17. APPENDICES 123
17.1. Schedule of Events 123
17.2. Cockcroft-Gault Equation 132
17.3. New York Heart Association 133
17.4. Eastern Cooperative Oncology Group (ECOG) Performance Status 134
17.5. Modified Response Evaluation Criteria in Solid Tumors (version 1.1) 135
17.5.1. Measurability of Tumor at Baseline 135
17.5.1.1. Definitions 135
17.5.1.2. Specifications by Methods of Measurements 136
17.5.2. Tumor Response Evaluation 136
17.5.2.1. Assessment of Overall Tumor Burden and Measurable Disease 136
17.5.2.2. Baseline Documentation of 'Target' and 'Nontarget' Lesions 136
17.5.2.3. Response Criteria 137
17.5.2.4. Evaluation of Target Lesions 137
17.5.2.5. Evaluation of Non-target Lesions 138
17.5.2.6. New Lesions 139
17.5.2.7. Evaluation of Best Overall Response 140
17.5.2.8. Frequency of Tumor Re-evaluation 141
17.6. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45 143

17.6.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) 143
17.6.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire BR45 145
17.7. EuroQoL Five Dimensions Five Levels 148
17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19) 151
COVID-19 Serum Biomarker Assessment(s) 152
17.9. Country-Specific Protocol Text 153
17.9.1. Sweden Only 153
17.9.2. Portugal Only 154
17.9.3. Germany Only 156

LIST OF TABLES

Table 1.1: Efficacy Results in HER2-positive and HER2-low Breast Cancer Subjects from DS8201-A-J101 (5.4 mg/kg or 6.4 mg/kg T-DXd) as of 01 Feb 2019 36
Table 1.2: Mean Pharmacokinetic Parameters of T-DXd (± Standard Deviation) 39
Table 1.3: Mean Pharmacokinetic Parameters of Total Antibody (± Standard Deviation) 39
Table 1.4: Mean Pharmacokinetic Parameters of MAAA-1181a (± Standard Deviation) 40
Table 5.1: Dose Regimens for Physician's Choice per the NCCN Guidelines[1] 57
Table 5.2: Dose Reduction Levels of T-DXd 58
Table 5.3: Dose Modification for T-DXd 59
Table 8.1: Blood Sampling for Pharmacokinetic Analysis 85
Table 11.1: Stopping Boundaries at OS Interim and Final Analyses 108
Table 17.1: Schedule of Events – Tissue Screening and Screening Period 124
Table 17.2: Schedule of Events – Treatment and Follow-up Period 127
Table 17.3: New York Heart Association Functional Classification 133
Table 17.4: Eastern Cooperative Oncology Group Performance Status Scale Grade Description 134
Table 17.5: Time Point Response: Subjects with Target (+/–Non-target) Disease 140

LIST OF FIGURES

Figure 1.1: Anti-tumor Effect of T-DXd Against Patient-derived Breast Cancer Xenograft in Nude Mice: ST910 (HER2 IHC 1+, FISH Negative) 34

Figure 3.1: Study Design Schema 46

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCO-CAP	American Society of Clinical Oncology – College of American Pathologists
AST	aspartate aminotransferase
AUC	area under the plasma/serum concentration-time curve
$AUC_{0\text{-}21d}$	area under the plasma/serum concentration-time curve from time 0 to 21 days
AUC_{∞}	area under the plasma/serum concentration-time curve from time 0 extrapolated to infinity
BI	before infusion or dosing
BICR	blinded independent central review
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
cfDNA	cell free deoxyribonucleic acid
CHO	Chinese hamster ovary
CI	confidence interval
C_{max}	maximum plasma/serum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response

ABBREVIATION	DEFINITION
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EIU	Exposure in Utero
EOI	end of infusion or dosing
EORTC QLQ	European Organization for Research and Treatment of Cancer quality of life questionnaire(s)
EOT	end of treatment
EQ-5D-5L	EuroQol 5 dimensions 5 levels [of severity]
FAS	Full Analysis Set
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
HCV	hepatitis C virus
HEOR	Health Economics and Outcomes Research
HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of HER2
HIV	human immunodeficiency virus
HR	hormone receptor
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Institutional Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IRB	Institutional Review Board
ISH	in situ hybridization
IUO	investigational use only

ABBREVIATION	DEFINITION
IV	intravenous(ly)
IXRS	Interactive Web/Voice Response System
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors (version 1.1)
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	nonsteroidal anti-inflammatory drug
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PK	pharmacokinetic
pop-PK	population pharmacokinetics
PPS	Per-protocol Analysis Set
PR	partial response
PRO	patient reported outcome
PT	preferred term
QoL	quality of life
QTc	corrected QT interval
QTcF	QT intervals corrected for heart rate by Fridericia's formula
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan

ABBREVIATION	DEFINITION
SAVER	Serious Adverse Event Report
SD	stable disease
SID	subject identification
SMQ	Standardised MedDRA Query
SOP	standard operating procedure
SpO2	peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma/serum concentration (C_{max})
TPC	treatment of physician's choice
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
V_{ss}	volume of distribution at steady state

1. INTRODUCTION

1.1. Background

Breast cancer is a life-threatening disease and remains the most common cancer and the first leading cause of cancer mortality in women globally.[2] Evidence on the global burden of metastatic breast cancer is limited, and statistics on metastatic recurrences, which account for the largest proportion of metastatic breast cancer patients, are not routinely collected. The following evidence therefore relates to estimated incidence, mortality, and prevalence rates for breast cancer cases overall.

Breast cancer has a higher incidence rate in women (43.3 per 100,000) than any other cancer. There were an estimated 1,676,633 new cases (25% of all cancers in women) and 521,817 breast cancer deaths (15% of all cancer deaths in women) in 2012. In terms of prevalence rates, according to the World Health Organization, breast cancer is the most prevalent cancer, with 6,255,391 survivors diagnosed within the previous 5 years.[2]

In approximately 20% of breast cancer cases, overexpression of human epidermal growth factor receptor 2 (HER2) occurs. Several anti-HER2 targeted therapies such as trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and lapatinib have improved outcomes in HER2-positive breast cancer patients. On the other hand, current preferred National Comprehensive Cancer Network (NCCN) treatment guidelines for HR-positive, HER2-negative breast cancer are for 3 rounds of endocrine therapy with the inclusion of a CDK 4/6 inhibitor. Once a tumor is endocrine refractory, single-agent chemotherapies are recommended.[1]

Among HER2-negative patients, HER2-low (immunohistochemistry [IHC] 2+, in situ hybridization [ISH]- or IHC 1+) tumors comprise approximately 45% of all breast cancers and treatment options for HR-positive, HER2-low metastatic breast cancer follow HR-positive, HER2-negative population, therefore remain limited, with no targeted therapy specifically approved for endocrine refractory disease. In this setting, recommended treatment options include single-agent chemotherapies with limited efficacy. Due to the lack of clear superiority, no specific agent is currently endorsed by the NCCN guidelines.[1] Of note, eribulin is the most recent chemotherapy approved for this patient population. Approval was based on results of the EMBRACE trial in which subjects previously treated with 2 to 5 prior chemotherapy regimens were randomized 2:1 to eribulin versus treatment of physician's choice. The most common agents chosen as comparators were vinorelbine, gemcitabine, capecitabine, taxanes, and anthracyclines. In this trial, efficacy of eribulin versus physician's choice showed an objective response rate (ORR) of 12% versus 5%, progression-free survival (PFS) 3.7 versus 2.2 months, and overall survival (OS) of 13.1 versus 10.6 months.[3] In an earlier line setting of 1 to 3 prior chemotherapy regimens, a Phase 3 trial comparing eribulin to capecitabine showed ORR 11% versus 11.5%, PFS of 4.2 versus 4.1 months, and OS of 15.9 versus 14.5 months.[4] Other trials have shown similar results for single-agent chemotherapies in this setting. Therefore, a highly unmet medical need exists and new treatment options need to be developed to improve outcomes for patients with disease progression for HER2-low breast cancer.

Trastuzumab deruxtecan (T-DXd; DS-8201a) is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody conjugated to a drug-linker carrying a topoisomerase I payload. T-DXd was studied in the Phase 1 DS8201-A-J101 study for HER2-expressing solid tumors and Study

DS8201-A-U201 for HER2-positive metastatic breast cancer previously treated with T-DM1. Based on the results of these studies, T-DXd (Enhertu®) obtained accelerated approval in the US on 20 December 2019 for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting based on the results of Study DS8201-A-U201. On 25 March 2020, T-DXd (ENHERTU) obtained approval under the conditional early approval system in Japan for the treatment of patients with HER2-positive unresectable or recurrent breast cancer after prior chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments).

1.1.1. Investigational Product

1.1.1.1. Name

Trastuzumab deruxtecan (T-DXd; DS-8201a)

1.1.1.2. Description

T-DXd consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker to a drug component MAAA-1181a. MAAL-9001 is an in-house humanized immunoglobulin G1 monoclonal antibody having the same amino acid sequence as trastuzumab. MAAA-1181a, an exatecan derivative, is a topoisomerase I inhibitor that is cell membrane permeable and more potent than SN-38 (the active metabolite of irinotecan).[5,6,7] This antibody drug conjugate achieves a high drug-to-antibody ratio (approximately 8) with homogeneous conjugation with MAAA-1181a.[8] After binding to HER2 and internalization, T-DXd is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm.

The lyophilized powder (Lyo-DP) form of T-DXd will be administered in this study.

CCI

[redacted]

1.1.1.3. Intended Use Under Investigation

This study will compare the activity of T-DXd in subjects with HER2-low, unresectable and/or metastatic breast cancer versus physician's choice options that are currently part of guideline recommendations for this line of therapy.

1.1.1.4. Comparators (Physician's Choice)

Subjects enrolled in this trial may be randomized to the treatment of physician's choice arm. The treating physician will specify choice of comparator prior to randomization by selecting 1 of the following options:

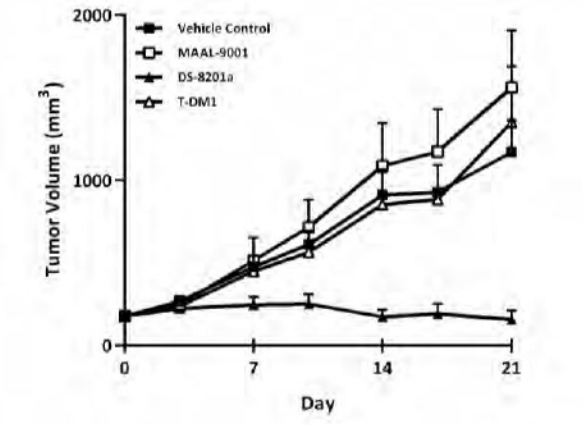
- Capecitabine
- Eribulin
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

The description of these can be found within their label approved in the country of drug administration. Please refer to the label approved in the country of drug administration or the NCCN guidelines[1] (see Table 5.1) for the dosing regimens.

1.1.1.5. Nonclinical Studies of T-DXd

The pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of T-DXd have been examined in nonclinical studies. One example of nonclinical pharmacology study results indicates that T-DXd inhibits tumor growth in patient-derived HER2-low tumor xenograft that is insensitive to T-DM1.

Figure 1.1: Anti-tumor Effect of T-DXd Against Patient-derived Breast Cancer Xenograft in Nude Mice: ST910 (HER2 IHC 1+, FISH Negative)



FISH = fluorescence in-situ hybridization; HER2 = human epithelial growth factor 2; IHC = immunohistochemistry.
Data represent the mean + standard error of the mean (n = 5).
Mice were subcutaneously implanted with ST910 patient-derived xenografts. T-DXd, MAAL-9001, or T-DM1 at the dose of 10 mg/kg was administered on Day 0.
The tumor volume of each mouse was calculated according to the following equation:
Tumor volume (mm^3) = 0.52 × length × $width^2$

For details of these experiments, please see the latest version of the Investigator's Brochure (IB).[9]

1.1.1.6. Clinical Experience

As of 08 Jun 2019, T-DXd has been evaluated in 12 company-sponsored clinical studies (11 monotherapy studies and 1 combination therapy study), with an estimated 1036 subjects exposed to at least 1 dose of T-DXd.[9] Three studies are complete (have finalized clinical study reports reporting the results for the study primary objective), and 9 studies are ongoing.[9] For updated results, please refer to the latest version of the IB.[9]

The T-DXd first-in-human study (Protocol DS8201-A-J101) is an open-label, dose finding study to assess the safety and tolerability of T-DXd in subjects with advanced solid tumors. Part 1 (dose escalation) enrolled subjects with either advanced breast cancer or gastric/gastroesophageal junction (GEJ) adenocarcinoma that is refractory or intolerant to standard treatment, or for which no standard treatment is available. Part 2 is the expansion phase and focuses on T-DM1-treated HER2-overexpressing breast cancer, trastuzumab-treated HER2-overexpressing gastric/GEJ adenocarcinoma, and HER2-low breast cancer, as well as other HER2 expressing solid cancers.

For the latest enrollment in this and other T-DXd studies, please refer to the latest version of the IB.[9]

Results from breast cancer subjects treated with 5.4 and 6.4 mg/kg T-DXd across Parts 1 and 2 of Study DS8201-A-J101 demonstrated that the majority of subjects experienced tumor shrinkage and durable treatment duration. Evaluable subjects for confirmed response were those who had 2 post-baseline scans or discontinued treatment for any reason prior to second post-baseline scan. Confirmed responses are summarized in Table 1.1.

As of the data cut-off date of 01 Feb 2019, at doses of 5.4 mg/kg or 6.4 mg/kg for subjects with HER2-positive breast cancer, median duration of follow-up was 15.5 months (range: 0.1 months to 34.4 months).[9] In the Enrolled Analysis Set, a confirmed ORR by ICR of 52.5% was observed in all subjects with HER2-positive breast cancer (Table 1.1). In all subjects with HER2-positive breast cancer, 62 subjects had best overall responses by ICR of complete response (10 [8.5%] subjects) or partial response (52 [44.1%] subjects). The median duration of confirmed response by ICR is 13.3 months.

As of the data cutoff date of 01 Feb 2019, at doses of 5.4 mg/kg or 6.4 mg/kg for subjects with HER2-low breast cancer, median duration of follow-up was 6.3 months (range: 2.5 months to 29.3 months).[9] In the Enrolled Analysis Set, confirmed ORR by ICR of 37.0% was observed in subjects with HER2-low breast cancer (Table 1.1). In all subjects with HER2-positive breast cancer, 20 subjects had best overall responses by ICR of partial response (20 [37.0%] subjects). The median duration of confirmed response by ICR is 10.4 months.

Table 1.1: Efficacy Results in HER2-positive and HER2-low Breast Cancer Subjects from DS8201-A-J101 (5.4 mg/kg or 6.4 mg/kg T-DXd) as of 01 Feb 2019

Efficacy Variable	Subjects with Breast Cancer	
	HER2-low BC (N=54)	HER2-positive BC (N=118)
Confirmed ORR n (%) (95% CI[a])		
ORR by ICR	20 (37.0) (24.3, 51.3)	62 (52.5) (43.1, 61.8)
ORR by Investigator	24 (44.4) (30.9, 58.6)	71 (60.2) (50.7, 69.1)
ORR by ICR, n/N	20/49 (40.8) (27.0, 55.8)	60/102 (58.8) (48.6, 68.5)
Confirmed Best Overall Response by ICR (n, %)		
CR	0	10 (8.5)
PR	20 (37.0)	52 (44.1)
SD	27 (50.0)	47 (39.8)
PD	6 (11.1)	5 (4.2)
NE	1 (1.9)	4 (3.4)
Confirmed Best Overall Response by Investigator (n, %)		
CR	0	5 (4.2)
PR	24 (44.4)	66 (55.9)
SD	21 (38.9)	38 (32.2)
PD	9 (16.7)	6 (5.1)
NE	0	3 (2.5)
Confirmed DoR Median Months[c] (95% CI)		
DoR by ICR	10.4 (8.8, -)	13.3 (9.5, -)
DoR by Investigator	11.0 (4.5, 12.8)	17.1 (9.8, 20.0)
Confirmed DCR[b] (n, %) (95% CI[a])		
DCR by ICR	47 (87.0) (75.1, 94.6)	109 (92.4) (86.0, 96.5)
DCR by Investigator	45 (83.3) (70.7, 92.1)	109 (92.4) (86.0, 96.5)
Time to Confirmed Response by ICR, Median Months[c] (95% CI)	2.6 (1.3, 3.1)	2.8 (1.5, 2.8)
Duration of Confirmed Stable Disease by ICR, Median Months[c] (95% CI)	10.9 (4.2, -)	10.5 (8.2, -)
Progression-free Survival (PFS)		
PFS by ICR		
Events (n, %)	24 (44.4)	50 (42.4)
Median Months[c] (95% CI)	11.1 (7.6, -)	13.7 (9.4, 19.4)
PFS by Investigator		
Events (n, %)	30 (55.6)	48 (40.7)
Median Months[c] (95% CI)	8.0 (5.6, 13.9)	16.6 (11.3, 22.1)

Efficacy Variable	Subjects with Breast Cancer	
	HER2-low BC (N=54)	HER2-positive BC (N=118)
Overall survival		
Events (n, %)	15 (27.8)	23 (19.5)
Median Months[c] (95% CI)	29.4 (12.9, 29.4)	- (26.4, -)
Survival at 6 months, % (95% CI[d])	86.2 (73.1, 93.2)	94.7 (88.7, 97.6)
Survival at 12 months, % (95% CI[d])	77.7 (61.7, 87.6)	84.4 (75.7, 90.2)
Survival at 18 months, % (95% CI[d])	66.4 (47.7, 79.7)	77.6 (67.3, 85.0)
Survival at 24 months, % (95% CI[d])	53.1 (24.8, 75.1)	74.8 (63.1, 83.2)

BC = breast cancer; CI = confidence interval; CR = complete response; DCR = disease control rate; DoR = duration of response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; ORR = objective response rate; NE = non-evaluable; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

[a] 95% exact binomial CI

[b] DCR was calculated as the proportion of subjects demonstrating CR, PR, or SD for a minimum of 6 weeks (±1week) from the first dosing date

[c] Median is from Kaplan-Meier Estimate. CI for median was computed using the Brookmeyer-Crowley method.

[d] CI for the rate at a fixed time point was computed by applying asymptotic normality to the log-log transformation of the rate

The range includes the censored observations where using "+" after value indicates censoring. Months were calculated as Days*12/365.25.

Part 1 (5.4 mg/kg and 6.4 mg/kg) and Part 2 subjects are included.

Data cutoff date: 01 February 2019

The safety dataset included all subjects who had received at least 1 dose of study drug in DS8201-A-J101 as of 01 Feb 2019 (n=289).[9] No dose-limiting toxicity was observed, and the maximum tolerated dose was not reached in the dose escalation part of DS8201-A-J101. The recommended dose levels for the expansion were 5.4 mg/kg and 6.4 mg/kg based on tolerability, efficacy, PK data, and exposure-response analysis.

As of 01 Feb 2019, 288 (99.7%) subjects experienced at least 1 treatment-emergent adverse event (TEAE).[9] The most common (>20%) adverse events (AEs) reported were: nausea (222 subjects [76.8%]), decreased appetite (168 subjects [58.1%]), vomiting (133 subjects [46.0%]), alopecia (120 subjects [41.5%]), anemia (118 subjects [40.8%]), fatigue (111 subjects [38.4%]), diarrhea (102 subjects [35.3%]), constipation and platelet count decreased (100 subjects [34.6%] each), neutrophil count decreased (91 subjects [31.5%]), white blood cell count decreased (82 [28.4%]), aspartate aminotransferase (AST; 63 subjects [21.8%]), malaise (62 subjects [21.5%]), pyrexia (60 subjects [20.8%]), and stomatitis (58 subjects [20.1%]).

A total of 168 subjects (58.1%) experienced at least 1 Grade 3 or above TEAE, of which 139 (48.1%) were related to T-DXd per Investigator assessment. The most common (>5%) Grade 3 or higher TEAEs were anemia (60 subjects [20.8%]), neutrophil count decreased (53 subjects [18.3%]), white blood cell count decreased (37 subjects [12.8%]), platelet count decreased (33 subjects [11.4%]), and hypokalemia (18 subjects [6.2%]).

1.1.1.7. Benefit/Risk Assessment

T-DXd is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. Based on the preliminary clinical observations in the Phase 1 study (Study DS8201-A-J101), T-DXd demonstrates antitumor activity in HER2-expressing cancers, including breast cancer and gastric cancer (Section 1.1.1.6).

As of 01 February 2019, from the ongoing study DS8201-A-J101, the overall efficacy results in subjects with HER2-positive breast cancer at 5.4 mg/kg or 6.4 mg/kg demonstrated a confirmed ORR by ICR of 52.5%. Among the subjects with HER2-low breast cancer, confirmed ORR by ICR was 37.0%. The overall efficacy results in subjects with HER2-positive gastric/GEJ cancer at 5.4 mg/kg or 6.4 mg/kg demonstrated a confirmed ORR by ICR of 29.5%. The overall efficacy results in subjects with other cancers demonstrated a confirmed ORR by ICR of 29.5%.

As of 08 Jun 2019, based on the cumulative review of the safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished) and taking into consideration biological plausibility, ILD, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease are classified as important identified risks. LVEF decrease is classified as an important potential risk. Infusion related reactions, which were previously classified as an important potential risk, are reclassified as an identified risk. QT prolongation is no longer considered an important potential risk and has been removed from the list of safety concerns for T-DXd.

In the T-DXd clinical program, the inclusion/exclusion criteria and monitoring/management guidelines are currently in place in all protocols to mitigate the important identified risks of ILD, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease, and important potential risk of LVEF decrease.

ILD is a known serious risk of T-DXd, and cases with fatal outcomes have been reported. Most events were Grade 1 or Grade 2 and were manageable by dose modification and following clinical treatment guidelines for drug-induced ILD, with specific recommendations including close monitoring of signs/symptoms of ILD (eg, cough, fever, and dyspnea) to identify potential ILD and proactively managing ILD with dose modification and treatment (eg, steroids). ILD requires proper monitoring, dose modification, and supportive care instituted in a timely fashion.

Other identified risks of T-DXd in order of descending frequencies are nausea, decreased appetite, alopecia, vomiting, fatigue, constipation, diarrhoea, WBC count decrease, stomatitis, aspartate aminotransferase increased, cough, headache, abdominal pain, alanine aminotransferase increased, hypokalaemia, epistaxis, dyspnoea, dyspepsia, dizziness, dry eye, upper respiratory tract infection, asthenia, and infusion related reactions.

These identified risks were generally manageable through dose modification and routine clinical practice.

T-DXd has demonstrated a generally acceptable safety profile in the treated populations.

In conclusion, given the data available on the efficacy and safety of T-DXd, the overall benefit/risk remains positive for clinical development.

For further details related to the efficacy and safety of T-DXd reported from clinical studies, please see the latest version of the IB.[9]

1.1.1.8. Summary of Clinical Pharmacokinetics

Table 1.2: Mean Pharmacokinetic Parameters of T-DXd (± Standard Deviation)

CCI							

AUC = area under the plasma/serum concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from time 0 to 21 d; AUC_{∞} = AUC from time 0 extrapolated to infinity; CL = clearance; C_{max} = maximum plasma/serum concentration; N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to reach C_{max}; V_{ss} = volume of distribution at steady state.

Table 1.3: Mean Pharmacokinetic Parameters of Total Antibody (± Standard Deviation)

CCI					

AUC = area under the plasma/serum concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from time 0 to 21 d; AUC_{∞} = AUC from time 0 extrapolated to infinity; C_{max} = maximum plasma/serum concentration; N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to reach C_{max}.

Table 1.4: Mean Pharmacokinetic Parameters of MAAA-1181a (± Standard Deviation)

CCI					

AUC = area under the plasma/serum concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from time 0 to 21 d; AUC_{∞} = AUC from time 0 extrapolated to infinity; C_{max} = maximum plasma/serum concentration; N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to reach C_{max}.

1.2. Study Rationale

Recent guidelines for treatment for metastatic breast cancer are divided based on HER2 and HR status. Current American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) 2018 HER2 testing guidelines (adapted by Daiichi Sankyo Inc. and Ventana) set forth criteria for IHC status, defining IHC 3+ as positive, IHC 2+ as equivocal (for which ISH is used for the final determination), and combining IHC 0 and IHC 1+ as negative for HER2.[10] These definitions were based on studies that correlated IHC cutoffs to HER2 gene amplification status. Multiple trials have demonstrated a role for anti-HER2 therapy in the HER2-positive setting (IHC 3+ or IHC 2+/ISH+) and several drugs have been approved for treatment of HER2-positive disease.[11,12,13] However, no anti-HER2 therapy has been approved for tumors with lower levels of HER2 expression (IHC 1+ or IHC 2+/ISH-). The Sponsor proposes to define a new HER2-low population in this trial including tumors with HER2 IHC 1+ and HER2 IHC 2+,ISH-.

Several studies have attempted to use ASCO-CAP HER2 testing criteria to define a patient population combining IHC 2+/ISH- tumors with IHC 1+. In a retrospective analysis of The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial, 9.7% (174 of 1795) subjects enrolled were HER2-negative on central lab testing despite being HER2-positive on local laboratory enrollment. However, these HER2-negative subjects still showed a disease-free survival benefit from addition of trastuzumab. To follow up on the hypothesis that trastuzumab could benefit HER2-low patients, the NSABP B-47 trial randomized 3270 subjects to adjuvant treatment with or without trastuzumab. In the B-47 trial, 56.2% were IHC 1+ and 43.8% were IHC 2+/ISH-,[14] but no advantage of addition of anti-HER2 therapy was observed.

T-DXd has shown efficacy for subjects with IHC 1+ as well as IHC 2+ disease. In the DS8201-A-J101 trial, as of 01 Feb 2019, confirmed ORR by ICR was 37.0% (20 of 54) for HER2-low breast cancer tumors.[15]

To define the upper boundary of low HER2 expression, the Sponsor plans to use the adapted ASCO-CAP 2018 HER2 testing guidelines (adapted by Daiichi Sankyo Inc. and Ventana) IHC definitions.[16] The distinction between IHC 2+ and 3+ has been well-defined because of the differences in treatment algorithm in which multiple HER2 targeted agents have been shown to benefit HER2-positive patients. However, partly due to treatment with anti-HER2 therapy, changes in tumor HER2 status have been described to occur over time.[17] In addition,

discordance between laboratories has also been shown to occur with up to 8% difference in HER2 status even when read by central laboratories.[18] To prevent heterogeneity in HER2 status, the Sponsor therefore proposes to exclude potential subjects who have previously tested positive for HER2 (IHC 3+ or IHC 2+/ISH+) or been treated with anti-HER2 therapy.

To define low HER2 expression, it is necessary to clarify the boundary between IHC 0 and IHC 1+. The ASCO-CAP suggests a definition for IHC 1+ as incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells. The IHC 0 is defined as no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells.[10] Because there is no difference in treatment algorithm for subjects with IHC 0 and IHC 1+ readings, several commercial HER2 tests use alternative cutoffs. To standardize this boundary, the Sponsor proposes to use the adapted ASCO-CAP cutoffs to provide the lower boundary for low HER2 expression.

Hormone Receptor Status

The other key determinant of treatment pathway in breast cancer is HR status. The HR-positive breast cancers are generally luminal type whereas HR-negative, HER2-low tumors would currently be characterized as triple negative disease. In terms of prevalence, although HR positivity is negatively correlated with HER2 positivity, HR is positively correlated with HER2 status within the HER2-negative spectrum. Combined with the overall lower incidence of triple negative disease, these correlations result in the majority of HER2-low breast cancers being HR-positive. In the NSABP B-47 trial, 82.8% of subjects were HR-positive.[14] Similarly, as of 16 Feb 2018, of 33 HER2-low subjects enrolled in the DS8201-A-J101 study, 29 (87.9%) were HR-positive. In addition to a difference in prevalence, significant differences are seen in gene signature between luminal and triple negative disease, outcomes, and response to therapy.

For both HER2-negative, HR-positive breast cancers refractory to endocrine therapy and HR-negative breast cancers, guidelines from the NCCN recommend sequential treatment with single-agent chemotherapies.[1] To delineate the unmet medical need of subjects in this trial, inclusion criteria require at least 1 and at most 2 prior lines of chemotherapy.

To best characterize the unmet need and address the role of T-DXd in this patient population, the Sponsor recognizes that there are a relatively large number of agents and potential sequences of treatment. Another important criterion is to clearly define the boundaries for HER2 status. To ensure a homogenous patient population, the Sponsor will take extra steps to fully characterize HER2-low status and number of prior therapies.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to compare the PFS benefit of T-DXd to physician's choice in HER2-low, HR-positive breast cancer, based on blinded independent central review (BICR).

2.1.2. Key Secondary Objectives

The key secondary objectives are:

- To compare the PFS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive, and HR-negative breast cancer), based on BICR
- To compare the OS benefit of T-DXd to physician's choice in HER2-low, HR-positive breast cancer
- To compare the OS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive and HR-negative breast cancer)

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

2.1.3. Other Secondary Objectives

The other secondary objectives are:

- To investigate the efficacy of T-DXd compared to physician's choice on the following parameters (definitions of these endpoints are included in Section 7.1.3):
  - PFS in HR-positive subjects, based on Investigator assessment
  - Confirmed ORR, based on BICR and Investigator assessment in HR-positive subjects
  - DoR, based on BICR in HR-positive subjects
  - Confirmed ORR, and DoR in all subjects, regardless of HR status
- To determine PK of T-DXd
- To evaluate safety of T-DXd compared to physician's choice
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for T-DXd compared to physician's choice

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

2.1.4. Exploratory Objectives

The exploratory objectives are to evaluate the following:

- Clinical benefit rate (CBR; the sum of complete response [CR] rate, PR rate, and greater than or equal to 6 months' stable disease [SD] rate), based on BICR in HR-positive subjects and all subjects regardless of HR status

- Disease control rate (DCR), based on BICR in HR-positive subjects and in all subjects regardless of HR status
- Time to response (TTR) in HR-positive subjects and all subjects regardless of HR status, based on BICR
- Progression-free survival on the next line of therapy (PFS2)
- Potential biomarkers of response/resistance
- Exposure-response relationships for efficacy and safety endpoints
- PFS, OS, confirmed ORR, and DoR in HR-negative subjects

2.2. Study Hypothesis

T-DXd confers a significant benefit in PFS in HER2-low, HR-positive breast cancer subjects compared to physician's choice.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, based on BICR, in HR-positive breast cancer subjects.

2.3.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- PFS, based on BICR, in all randomized subjects
- OS in HR-positive breast cancer subjects
- OS in all randomized subjects

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

2.3.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- PFS, based on Investigator assessment
- Confirmed ORR, based on BICR and Investigator assessment
- DoR, based on BICR

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

2.3.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- CBR, based on BICR
- DCR, based on BICR

- TTR, based on BICR
- PFS2

2.3.5. Health Economic and Outcomes Research Endpoints

The HEOR endpoints include:

- European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ)
  - C30
  - BR45
- EuroQol 5 dimensions 5 levels [of severity] (EQ-5D-5L)
- Hospitalization-related endpoints

2.3.6. Pharmacokinetic/Biomarker Endpoints

2.3.6.1. Pharmacokinetic Endpoints

The PK endpoints include:

- Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a

2.3.6.2. Biomarker Endpoints

The biomarker endpoints include:

- Serum biomarkers (eg, extracellular domain of HER2 [HER2ECD])
- Other potential biomarkers of response/resistance (eg, deoxyribonucleic acid [DNA] profiling in cell free DNA [cfDNA], RNA expression profiling, mutations)

2.3.7. Safety Endpoints

The safety endpoints include:

- Serious adverse events (SAEs)
- TEAEs, graded according to the National Cancer Institute (NCI) CTCAE version 5.0
- AESIs
- Discontinuations associated with AEs
- Physical examination findings
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Vital sign measurements
- Standard clinical laboratory parameters
- Electrocardiogram (ECG) parameters
- Echocardiogram (ECHO)/multigated acquisition (MUGA) scan findings
- Anti-drug antibodies (ADAs)

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of T-DXd versus the physician's choice in HER2-low, unresectable and/or metastatic breast cancer subjects. Figure 3.1 shows the study design.

T-DXd for injection, 100 mg, will be administered IV at a dose of 5.4 mg/kg every 3 weeks.

The comparator for this study is called physician's choice. Approximately 540 subjects will be randomized in a 2:1 ratio to T-DXd or 1 of the following physician's choice treatments:

- Capecitabine
- Eribulin
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

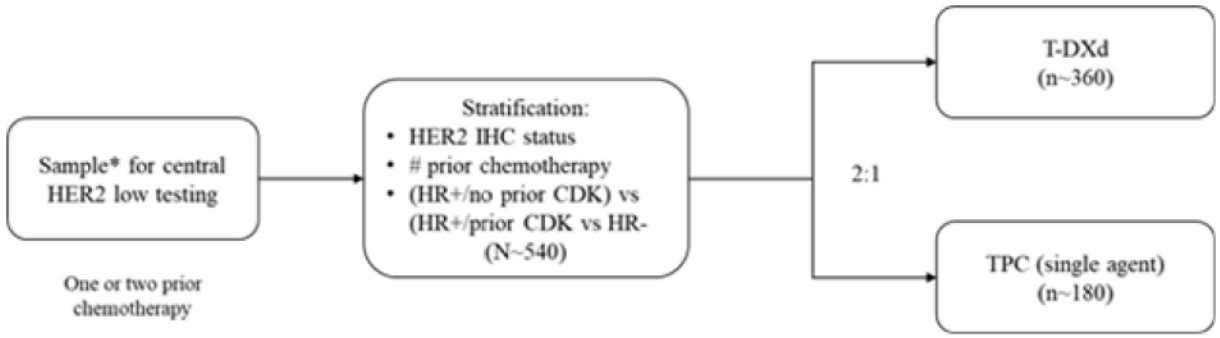
If a subject receives a comparator with a regimen other than a 21-day cycle, the Investigator should ensure that the subject follows the study-defined Schedule of Events per a 28-day cycle (see Section 17.1). However, tumor assessments and CT/MRI of the brain must be performed every 6 weeks $\pm$7 days from randomization date. Laboratory and safety assessment before drug administration should be appropriately performed according to the label approved in the country of drug administration.

Randomization will be stratified by:

- HER2 IHC status of tissue samples assessed by a central laboratory: HER2 IHC 1+ vs. HER2 IHC 2+/ISH-
- Number of prior lines of chemotherapy: 1 vs. 2
- HR/CDK status: HR-positive with prior CDK4/6 inhibitor treatment vs. HR-positive without prior CDK4/6 inhibitor treatment vs. HR-negative

The study treatment will be continued according to the dosing criteria in the absence of withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity (see Section 5.7 for other reasons why a subject may be withdrawn from study treatment). If the study treatment is delayed more than 28 days from the planned date of administration, the subject will be withdrawn from the study treatment (see Section 5.7).

Figure 3.1: Study Design Schema



CDK = cyclin-dependent kinase, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, TPC = treatment of physician's choice.
*See Section 6.1 and Section 6.2 for details.

3.2. Discussion of Study Design

This trial is designed to compare the use of T-DXd versus treatment of physician's choice for unresectable/metastatic breast cancer that is HER2-low.

HER2-low is a new category of HER2 status for which no targeted therapy is currently approved. To define the upper boundary of low HER2 expression, the Sponsor plans to use the adapted ASCO-CAP 2018 HER2 testing guidelines (adapted by Daiichi Sankyo Inc. and Ventana). The distinction between IHC 2+ and 3+ has been well defined because of the differences in treatment algorithm in which multiple HER2-targeted agents have been shown to benefit HER2-positive patients. However, partly as a response to anti-HER2 therapy, changes in tumor HER2 status have been described to occur over time.[17] In addition, discordance between laboratories has also been shown to occur with up to 8% difference in HER2 status even when read by central laboratories.[18] To prevent heterogeneity in HER2 status, the Sponsor therefore proposes to exclude potential subjects who have previously tested positive for HER2 or been treated with anti-HER2 therapy.

To define low HER2 expression, it is necessary to clarify the boundary between IHC 0 and IHC 1+. The ASCO-CAP suggests a definition for IHC 1+ as incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells. The IHC 0 is defined as no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells.[10] Because there is no difference in treatment algorithm for subjects with IHC 0 and IHC 1+ readings, several commercial HER2 tests use alternative cutoffs. To standardize this boundary, the Sponsor proposes to use the adapted ASCO-CAP cutoffs to provide the lower boundary for low HER2 expression.

This study will be conducted in approximately 225 sites including but not limited to North America, Western Europe, and Asia.

The target sample size will be approximately 540 subjects randomized in a 2:1 ratio into 2 treatment arms (T-DXd versus physician's choice).

3.2.1. Duration of the Study

Enrollment is planned to occur over approximately 16 months from the randomization date of the first subject. The data cutoff for the primary efficacy analysis of PFS is planned when approximately 318 PFS events per BICR have been observed in the HR-positive subjects.

The Sponsor will monitor the number of PFS events and will make projections of the data cutoff date for PFS analysis. The primary analysis will use all events accrued on or before the cutoff date. All data before or on the cutoff date will be used for analysis.

The final data cutoff for the key secondary efficacy endpoint OS is planned when approximately 333 OS events have been observed in HR-positive subjects.

For each subject there will be a 40-Day (+7 days) Follow-up after the last study drug treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up every 3 months (±14 days) from the date of 40-Day (+7 days) Follow-up, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

The Sponsor may terminate the study at any time and study termination may also be requested by (a) competent authority(ies).

3.2.2. Duration of Subject Participation

The Screening period is up to 28 days. For T-DXd, each cycle of treatment will be 21 days. The number of treatment cycles with T-DXd is not fixed. Upon commencing study treatment, subjects may continue receiving study treatment until the occurrence of any of the events defined in Section 5.7.

For the physician's choice comparator arm, if a subject receives a comparator with a regimen other than 21 days, the Investigator should ensure that the subject follows the study-defined Schedule of Events per a 28-day cycle (see Section 17.1). However, tumor assessments and CT/MRI of the Brain must be performed every 6 weeks ±7 days from randomization date. Laboratory and safety assessment before drug administration should be appropriately performed according to the label approved in the country of drug administration.

After study treatment discontinuation, all subjects may be contacted at the 40-Day (+7 days) Follow-up and every 3 months until death or until follow-up data collection is no longer of scientific value or otherwise needed (at the Sponsor's discretion), to obtain information about subsequent treatment(s) and survival status (Section 5.7.1). If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.

3.2.3. Definition of the End of the Study

The study closure is defined as the date when the last subject discontinues study treatment and applicable follow-up occurs, or the study is ended by the Sponsor.

4. STUDY POPULATION

Each subject will sign study Informed Consent Form(s) (ICF[s]) provided by the site. A subject is considered enrolled in the study upon the Investigator or designee obtaining written informed consent from the subject (Section 15.3) at the time of Screening and upon determination that all inclusion and exclusion criteria have been satisfied.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited subject information and outcome of Screening process (ie, enrollment in the study, reason for ineligibility, withdrew consent).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification (SID) code list. This confidential list of the names of all subjects, allocated study numbers on enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study. The Investigator should follow the label approved in the country of drug administration for the individual treatment options (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) for eligibility criteria if the subject is randomized to the arm of treatment of physician's choice. The inclusion criteria include:

1. Must be competent and able to comprehend, sign, and date an Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) approved ICF before performance of any study-specific procedures or tests.
2. Men or women ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old.)
3. Pathologically documented breast cancer that:
    a. Is unresectable or metastatic.
    b. Has a history of low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested)
    c. Assessed as low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ according to ASCO-CAP 2018 HER2 testing guidelines (adapted by Daiichi Sankyo Inc. and Ventana) evaluated at a central laboratory.
    d. Is HR-positive or HR-negative. Approximately 60 HR-negative subjects are to be enrolled, the remaining subjects will be HR-positive (positive for estrogen receptor or progesterone receptor if finding of ≥1% of tumor cell nuclei are immunoreactive).
    e. If HR-positive, is documented refractory to endocrine therapy, defined as having progressed on at least 1 endocrine therapy and determined by the Investigator that subject would no longer benefit from further treatment with endocrine therapy.
    f. If HR-positive, has or has not been treated with a CDK4/6 inhibitor. Not more than 240 HR-positive subjects who have not had prior therapy with a CDK4/6 inhibitor and at least 240 HR-positive subjects who have had prior therapy with a CDK4/6 inhibitor will be enrolled.

g. Has been treated with at least 1 and at most 2 prior lines of chemotherapy in the recurrent or metastatic setting. If recurrence occurred within 6 months of (neo)adjuvant chemotherapy, (neo)adjuvant therapy would count as 1 line of chemotherapy. Targeted agents (such as mTOR inhibitors, PARP inhibitors, PD-L inhibitors, PD-L1 inhibitors, histone deacetylase inhibitors, or CDK4/6 inhibitors) and endocrine therapies on their own do not contribute to the count of prior lines of chemotherapy, although regimens with such agents in combination with chemotherapy would still count as 1 line of chemotherapy.
h. Was never previously HER2-positive (IHC 3+ or IHC2+/ISH+) on prior pathology testing (per ASCO-CAP guidelines) or was historically HER2 IHC 0 only.
i. Was never previously treated with anti-HER2 therapy.

4. Documented radiologic progression (during or after most recent treatment).
5. Must have an adequate archival tumor tissue sample available for assessment of HER2 status by central laboratory (based on most recent available tumor tissue sample). If archival tumor tissue is not available, a fresh tumor tissue biopsy is required. See Section 6.1 for details.
6. All subjects must have a recent tumor tissue sample after the most recent treatment regimen or agree to undergo a tissue biopsy prior to randomization. See Section 6.2 for details.
7. Presence of at least 1 measurable lesion based on computed tomography (CT) or magnetic resonance imaging (MRI) per modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 (see Section 17.5).[19]
   - Brain lesions will be considered as non-target lesions only.
8. ECOG PS 0 or 1.
9. LVEF ≥50% within 28 days prior to randomization.
10. Adequate bone marrow function within 14 days before randomization, defined as:
    - Platelet count ≥100,000/mm^3 (Platelet transfusion is not allowed within 1 week prior to Screening assessment)
    - Hemoglobin level ≥9.0 g/dL (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)
11. Adequate renal function within 14 days before randomization, defined as:
    - Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation (see Section 17.2; $\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ {× 0.85 for females}).
12. Adequate hepatic function within 14 days before randomization, defined as:
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤5 × upper limit of normal (ULN)

- Total bilirubin ≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline

13. Adequate blood clotting function within 14 days before randomization, defined as:
    - International normalized ratio/prothrombin time ≤1.5 × ULN and either partial thromboplastin or activated partial thromboplastin time
14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and after the last dose of T-DXd for at least 7 months for females or 4.5 months for males or according to the label approved in the country of drug administration for the physician's choice treatments.[20] Male subjects must agree to inform all female partners that they are participating in a clinical trial that may cause birth defects. Methods considered as highly effective methods of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
    - The reliability of complete sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Subjects in this study should refrain from heterosexual intercourse during and upon completion of the study and for at least 7 months for females or 4.5 months for males after the last dose of T-DXd or according to the label approved in the country of drug administration for the physician's choice treatment. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

    Non-childbearing potential is defined as premenopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous

amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.
In Portugal only, please see Section 17.9.2 for text applicable to sites in Portugal.

15. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 months after the final study treatment administration or according to the label approved in the country of drug administration for the physician's choice treatments. Preservation of sperm should be considered prior to enrollment in this study.
16. Female subjects must not donate ova, or retrieve for their own use, from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study treatment administration or according to the label approved in the country of drug administration for the physician's choice treatments.
17. Has adequate treatment washout period before randomization/enrollment, defined as chloroquine/hydroxychloroquine >14 days.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study. The Investigator should follow the label approved in the country of drug administration for the individual treatment options (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) for eligibility criteria if the subject is randomized to the arm of treatment of physician's choice. The exclusion criteria include:

1. Ineligible for the declared physician's choice comparator because of previously having received treatment with the same comparator in the metastatic setting or the comparator is contraindicated. Subjects are eligible to be treated with a comparator with which they have not previously been treated.
2. Prior treatment with antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor including prior participation in a study involving an ADC produced by Daiichi Sankyo and/or AstraZeneca.
3. Uncontrolled or significant cardiovascular disease, including any of the following:
    a. History of myocardial infarction within 6 months before randomization, troponin levels consistent with myocardial infarction as defined according to the manufacturer 28 days prior to randomization
    b. History of symptomatic congestive heart failure (New York Heart Association Class II to IV)

c. Corrected QT interval (QTc) prolongation to >470 ms (females) or >450 ms (male) based on average of Screening triplicate 12 lead ECGs

4. Has a history of (noninfectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
5. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
   - Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.
6. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or contralateral breast cancer.
7. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
8. Has a history of severe hypersensitivity reactions to other monoclonal antibodies.
9. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
10. Substance abuse or medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
11. Social, familial, or geographical factors that would interfere with study participation or follow-up.
12. Has known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to randomization if required by local regulations or IRB/IEC.
    In Portugal only, please see Section 17.9.2 for text applicable to sites in Portugal.
13. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).
14. Therapeutic radiation therapy or major surgery within 4 weeks before study treatment or palliative stereotactic radiation therapy within 2 weeks before study treatment.
15. Systemic treatment with anticancer therapy (immunotherapy [non-antibody-based therapy], retinoid therapy,) or hormonal therapy within 3 weeks before study treatment; antibody-based-anticancer-therapy within 4 weeks before randomization; or treatment

with nitrosoureas or mitomycin C within 6 weeks before study treatment; or treatment with small-molecule targeted agents within 2 weeks, or 5 half-lives, whichever is longer.

17. Participation in a therapeutic clinical study within 3 weeks before study treatment (for small-molecule targeted agents, this nonparticipation period is 2 weeks or 5 half-lives, whichever is longer), current participation in other therapeutic investigational procedures or prior participation in this investigational trial.
18. Is pregnant or breastfeeding, or planning to become pregnant.
19. Subject must not be study site personnel or Sponsor employee directly involved in the clinical trial, or an immediate family member of someone directly involved.
20. Otherwise considered inappropriate for the study by the Investigator.
21. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within three months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion etc), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjögren's, sarcoidosis etc), or prior pneumonectomy.

4.3. Subject Replacement

Randomized subjects will not be replaced.

4.4. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The SID number **must remain the same** at the time of re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who was re-screened (see Study Manual for details).

5. STUDY TREATMENTS

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Groups

There will be 2 treatment arms, T-DXd and physician's choice. There are 5 options within physician's choice:

- Capecitabine
- Eribulin
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

The option chosen must be declared for each individual subject before randomization. Once assigned, subjects will remain on study in their treatment arm and will not change arms. Within physician's choice, the subject must remain on the declared option for his/her duration within the study.

5.1.2. Method of Treatment Allocation

Prior to randomization of a subject, the ICF must be signed and all eligibility criteria must be met.

Subjects will be randomized into 1 of the 2 treatment arms (T-DXd versus physician's choice) in a 2:1 ratio. The randomization will be stratified by

- HER2 IHC status of tissue samples assessed by a central laboratory: HER2 IHC 1+ vs. HER2 IHC 2+/ISH-
- Number of prior lines of chemotherapy: 1 vs. 2
- HR/CDK status: HR-positive with prior CDK4/6 inhibitor treatment vs.HR-positive without prior CDK4/6 inhibitor treatment vs.HR-negative.

Randomization will be managed through an Interactive Web/Voice Response System (IXRS) for subjects meeting all eligibility criteria. The directions on how to use the system will be provided in the IXRS Quick Reference Manual.

All subjects will have physician's choice treatment declared and recorded in the IXRS prior to randomization.

5.1.3. Blinding

It is not feasible to blind treatment allocations for individual subjects because of different routes of administration, different treatment schedules, and different AE profiles between T-DXd and physician's choice therapy. The primary endpoint of PFS will be based on BICR. The study team will not perform or have access to efficacy analysis/summary during the study.

An independent biostatistician will generate the randomization schedule per the randomization specification.

5.1.4. Emergency Unblinding Procedure

Not applicable as the study is open label.

5.2. Study Drug

5.2.1. Description

Lyophilized powder (Lyo-DP)

T-DXd for injection 100 mg Lyo-DP will be provided as a lyophilized powder containing 100 mg of T-DXd in a glass vial. Each glass vial should be reconstituted to a concentration of 20 mg/mL. Each vial is designed for single use only and is not to be used to treat more than 1 subject.

The starting dose of 5.4 mg/kg will be based on body weight.

5.2.2. Labeling and Packaging

T-DXd for injection 100 mg Lyo-DP will be supplied by the Sponsor. T-DXd for injection 100 mg will be packaged and labeled in compliance with regulatory requirements. The packaging will clearly display the name of the study treatment, the lot number, storage condition, and other required information in accordance with local regulations.

5.2.3. Preparation

T-DXd for IV infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight. Prepared study treatment infusion solutions should be prepared and used as directed in the pharmacy instructions. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site.

5.2.4. Administration

T-DXd will be administered at a body weight–based dose of 5.4 mg/kg initially as an IV infusion over 30 to 90 minutes every 21 days (±2 days). The initial dose of T-DXd will be infused for approximately 90 minutes. If there is no infusion related reaction, after the initial dose, the next doses of T-DXd will be infused for a minimum of 30 minutes. The subject's weight at Screening (baseline) will be used to calculate the initial dose. If during the course of treatment, the subject's weight changes by ≥±10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of T-DXd.

T-DXd should only be initiated by a physician or healthcare professional experienced in the administration of cytotoxic chemotherapy. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use.

5.2.5. Storage

T-DXd for injection 100 mg must be stored in a secure, limited-access storage area under the storage conditions listed below:

- Stored at 2°C to 8°C (protected from light) for lyophilized powder

If storage conditions are not maintained per specified requirements, the Sponsor or contract research organization (CRO) should be contacted.

For storage of the infusion solutions, see pharmacy instructions.

5.2.6. Drug Accountability

When a drug shipment is received from the Sponsor, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, check drug expiration date, and acknowledge receipt in IXRS. In addition, the Investigator or designee will contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for study treatment (T-DXd/physician's choice). The record must be kept current and should contain the following:

- Dates and quantities of drug received
- Subject's SID and/or initials or supply number (as applicable)
- The date and quantity of study treatment dispensed and remaining (if from individual subject drug units)
- Initials of the dispenser

At the study closure, or as directed, all study treatment, including unused, partially used, or empty containers, will be returned to a designee as instructed by Sponsor. Study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation included in the shipment. At study closure, a final study drug reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. See pharmacy instructions for details.

Unused study drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor, the Sponsor has received copies of the study site's drug handling and disposition SOPs, and it is assured that the Sponsor will receive copies of the certificate of destruction that is traceable to the study treatment.

All investigational product inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and Regulatory Agency inspectors.

5.3. Control Treatment

Subjects randomized to physician's choice will be treated with 1 of the following agents:

- Capecitabine
- Eribulin
- Gemcitabine

- Paclitaxel
- Nab-paclitaxel

Accountability for Investigator's choice medications will follow the T-DXd procedures (Section 5.2.6). Storage for all medications must follow storage instructions printed on the product label. Dosage, regimen, and dose modification must follow the label approved in the country of drug administration or the NCCN guidelines[1] (see Table 5.1). A 21-day cycle regimen is recommended if there are multiple options in the label approved in the country of drug administration or the NCCN guidelines.[1] If a subject receives a comparator with a regimen other than 21 days, the Investigator should ensure that the subject follows the study-defined schedule of event (see Section 17.1) interval per a 28-day cycle. However, tumor assessments and CT/MRI of the brain must be performed every 6 weeks ±7 days from randomization date. Laboratory and safety assessment before drug administration should be appropriately performed according to the label approved in the country of drug administration. Treatment of physician's choice will be supplied by the local pharmacy or site and reimbursed by the Sponsor where necessary. Medication will be centrally supplied by the Sponsor or delegated vendor in the event that a particular country or site cannot locally source the approved medications.

Administration and dose modification should be done according to the label approved in the country of drug administration or the NCCN guidelines[1] (see Table 5.1).

Table 5.1: Dose Regimens for Physician's Choice per the NCCN Guidelines[1]

Comparator	Dosing Regimen
Capecitabine	1000-1250 mg/m^2 PO twice daily Days 1-14; cycled every 21 days
Eribulin	1.4 mg[a]/m^2 IV Days 1 and 8; cycled every 21 days
Gemcitabine	800-1200 mg/m^2 IV Days 1, 8, and 15; cycled every 28 days
Paclitaxel	Option 1: 175 mg/m^2 IV Day 1; cycled every 21 days Option 2: 80 mg/m2 IV Day 1 weekly
Nab-paclitaxel	Option 1: 260 mg/m^2 IV; cycled every 21 days Option 2: 100 mg/m^2 or 125 mg/m^2 IV Days 1, 8, and 15; cycled every 28 days

[a] Refers to eribulin mesylate. 1.23 mg eribulin base = 1.4 mg eribulin mesylate

5.4. Guidelines for Dose Modification

5.4.1. Dose Interruptions and Reductions

The Investigator will evaluate which toxicities are attributed to the study treatment and adjust the dose of the drug as recommended in Section 5.4.1.1 for T-DXd and as per label approved in the country of drug administration for physician's choice treatment (see Section 5.4.1.2). All dose modifications should be based on the worst preceding toxicity (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). All interruptions or modifications must be recorded on the AE and drug administration electronic case report form (eCRF). Appropriate clinical experts should be consulted as deemed necessary.

Investigators may consider dose reductions or discontinuations of the study treatment according to the subject's condition and after discussion with and approval from the Sponsor Medical Monitor or designee.

For Grade 3 or Grade 4 events assessed as related to use of T-DXd by the Investigator(s), monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 days until the AE is determined to be resolving.

Prophylactic or supportive treatment for expected toxicities, including management of study treatment–induced AEs will be as per treating physician discretion and institutional guidelines.

5.4.1.1. Dose Interruptions and Reductions for T-DXd

NOTE: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 5.3.

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity (CTCAE version 5.0).

Specific criteria for interruption, re-initiation, dose reduction, and/or discontinuation of T-DXd are **applicable only to TEAEs that are assessed as related** to the use of T-DXd by the investigator(s). For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

Two dose reductions will be permitted. The adjustment for reduced dosing of T-DXd depends on the initial starting dose, as shown in Table 5.2.

Table 5.2: Dose Reduction Levels of T-DXd

Starting Dose	Dose Level -1	Dose Level -2
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

Once the dose of T-DXd has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. **If toxicity continues after 2 dose reductions, the subject will be withdrawn from the study treatment.** Refer to Section 5.7 for withdrawal/discontinuation procedures.

T-DXd dose increases are not allowed in the study.

Dose Interruption and Modification/Toxicity Management Guidelines:

A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 days, the subject will be withdrawn from the study. **Refer to Section 5.7 for withdrawal/discontinuation procedures.**

Treatment cycles for a subject for whom T-DXd dosing is temporarily withheld for any reason may have future cycles scheduled based on the date that T-DXd dosing was resumed.

All confirmed or suspected coronavirus disease 2019 (COVID-19) infection events must be recorded in the eCRF. Please refer to Section 17.8 for additional information on dose modification.

Table 5.3: Dose Modification for T-DXd

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for T-DXd**
No Toxicity	Maintain dose and schedule
Infusion related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours)	• Administration of T-DXd should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of T-DXd should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation, etc, should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	• Delay dose until resolved to ≤ Grade 2 • Reduce dose 1 level
Febrile Neutropenia (Absolute neutrophil count <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	• Delay dose until resolved • Reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	• No dose modification
Grade 4 (<0.2 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2:

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
	– If resolved in ≤14 days from day of onset, maintain dose – If resolved in >14 days from day of onset, reduce dose 1 level
Anaemia	
Grade 3 (Hemoglobin <8.0 g/dL); transfusion indicated	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated	• Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (Platelets <50 to 25 × 10^9/L)	• Delay dose until resolved to ≤ Grade 1: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (Platelets <25 × 10^9/L)	• Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure	• Discontinue subject from study treatment
Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	• Continue treatment with T-DXd
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	• Continue treatment with T-DXd • Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% and decrease is 10-20% (absolute value) from baseline	• Interrupt T-DXd dosing • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment • If LVEF recovers to within 10% from baseline, resume study drug treatment and maintain dose
LVEF <40% or >20% (absolute value) decrease from baseline	• Interrupt T-DXd dosing • Repeat LVEF assessment within 3 weeks • If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
Electrocardiogram QT Prolonged	
Grade 3 (Average QTc >500 ms or >60 ms change from baseline)	• Delay dose until resolved to ≤ Grade 1 (QTc ≤480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then – if attributed to T-DXd, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Discontinue subject from study treatment
Pulmonary Toxicity	If a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • High resolution CT, • Pulmonologist consultation (infectious disease consultation as clinically indicated) • Blood culture and CBC. Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests and pulse oximetry (SpO2) • Arterial blood gases if clinically indicated • One blood sample collection for PK (central laboratory) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD, follow the ILD management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Management Guidelines for T-DXd**
Grade 1	The administration of T-DXd must be interrupted for any ILD events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade 1 events, T-DXd can be restarted only if the event is fully resolved to Grade 0, then: • If resolved in ≤28 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose 1 level However, if the event Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given.
Grade 2	Permanently discontinue subject from study treatment. • Promptly start and treat with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone). – Re-consider additional work-up for alternative etiologies as described above. – Escalate care as clinically indicated.
Grade 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
	• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, – Re-consider additional work-up for alternative etiologies as described above. – Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	• Delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, maintain dose. – If resolved in >7 days from day of onset, reduce dose 1 level.
Grade 4	• Discontinue subject from study treatment
Blood Creatinine Increased	
Grade 3 (>3 to 6 × ULN)	• Delay dose until resolved to ≤Grade 2 or baseline, then reduce dose 1 level
Grade 4 (>6 × ULN)	• Discontinue subject from study treatment
Hepatic Toxicity	
AST or ALT With Simultaneous Total Bilirubin	
AST/ALT ≥3.0 × ULN with simultaneous total bilirubin >2.0 × ULN	• Delay study medication until drug-induced liver injury can be ruled out. • If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study treatment may occur after discussion between the Investigator and Sponsor. • If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. • Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
AST or ALT Increased	
Grade 2 (>3.0 to 5.0 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal)	• No action for Grade 2 AST/ALT
Grade 3 (>5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 × ULN	• Repeat testing within 3 days. Delay dose until resolved to ≤Grade 1 if baseline ≤ 3 × ULN, otherwise delay dose until resolved to ≤ baseline, then: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Grade 3 (>8.0 to 20.0 × ULN if baseline was normal; >8.0 to 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was >3 × ULN	• Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	• Discontinue subject from study treatment
Total Bilirubin Increased	
Grade 2 (>1.5 to 3.0 × ULN if baseline was normal; >1.5 to 3.0 × baseline if baseline was abnormal)	• If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level • If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 to 10.0 × ULN if baseline was normal; >3.0 to 10.0 × baseline if baseline was abnormal)	• If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 1: – If resolved in ≤7 days from day of onset, reduce dose 1 level – If resolved in >7 days from day of onset, discontinue T-DXd

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
	• If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 2: – If resolved in ≤7 days from day of onset, reduce dose 1 level – If resolved in >7 days from day of onset, discontinue T-DXd
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	• Discontinue subject from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 (>5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × baseline if baseline was abnormal), or Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	• No modification unless determined by the Investigator to be clinically significant or life-threatening
Gastrointestinal	
Nausea	
Grade 3	• Delay dose until resolved to ≤Grade 1 – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	• Delay dose until resolved to ≤Grade 1 – If resolved in ≤3 days from day of onset, maintain dose – If resolved in >3 days from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment
Other Laboratory AEs	
Grade 3	• Delay dose until resolved to ≤Grade 1 or baseline level: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
Other Non-laboratory Adverse Events	
Grade 3	• Delay dose until resolved to ≤Grade 1 or baseline: – If resolved in ≤7 days from day of onset, maintain dose – If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment

All dose modifications should be based on the worst preceding toxicity.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; QTc = corrected QT interval; ULN = upper limit of normal.

In addition, Investigators may consider dose reductions or discontinuations of the study treatment according to the subject's condition and after discussion with the Sponsor Medical Monitor or designee.

5.4.1.2. Dose Interruptions and Reductions for Physician's Choice

Dose adjustments for physician's choice treatment should be made in accordance with the label approved in the country of drug administration or the NCCN guidelines.[1] Changes in medication dosage, timing, etc, will be documented in the eCRF. Physician's choice treatment can be interrupted for up to 28 days from the planned date of administration. If a subject requires a dose delay longer than 28 days (49 days from the last infusion date), the subject will permanently discontinue study treatment and will be followed for survival.

5.5. Method of Assessing Treatment Compliance

T-DXd and physician's choice treatment will be administered to subjects participating in the study and under the supervision of clinical study personnel at the site. Start and stop times of dosing and amount of drug administered are to be recorded by clinical study personnel.

For orally administered physician's choice treatments, treatment compliance will be reported by the subject or clinical study personnel.

5.6. Prior and Concomitant Medications and Treatments

Medications used from the time the subject signs the Main ICF to 40 days (+7 days) after the last administration of T-DXd or control treatment will be recorded. Concomitant medications and therapies include all prescription, over-the-counter, and herbal remedies. All concomitant medications will be recorded on the eCRF.

Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator, except for within 1 week prior to Screening (see Section 4.1).

Prophylactic or supportive treatment of study treatment–induced AEs will be otherwise as per Investigator's discretion and institutional guidelines.

Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor antagonists or Neurokinin-1 receptor antagonists and/or steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged but not prohibited. Concomitant use of e-cigarettes and vaping is strongly discouraged but not prohibited.

5.6.1. Prohibited Medications and Treatments

With the exception of medications that are under investigation in the study (eg, standard of care, comparators, or combination therapies), the following medications, treatment, and procedures will be prohibited during the treatment period (see Section 4.2 for required washout periods). The Sponsor must be notified if a subject receives any of these during the study.

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable);
  - Use of bisphosphonates or RANKL pathway inhibitors for the prevention or treatment of skeletal-related events is acceptable.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Section 17.8 for further details.;
- Other investigational therapeutic agents;
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification section);
- Radiotherapy to the thorax;
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs (inhaled steroids or intra-articular steroid injections are permitted in this study);
  - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.

For subjects randomized to Investigator's choice:

- Refer to the approved label in the country of drug administration or the NCCN guidelines[1] for capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel for medications prohibited during treatment with the applicable product.

5.7. Study Drug Discontinuation and Discontinuation from the Study

5.7.1. Discontinuation of Study Drug

Subjects may be discontinued from study treatment for the following reasons:

- PD per criteria set forth in mRECIST version 1.1 (Section 17.5);
- Clinical progression (definitive clinical signs of PD), but a recent radiographic assessment did not meet the criteria for PD according to mRECIST version 1.1;
- AE;
- Death;
- Pregnancy;
- Withdrawal by subject (**to discontinue study drug**) Note: this section only refers to withdrawal from treatment with study drug, which is not the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including survival follow-up);
- Lost to follow-up;
- Protocol deviation;
- Physician decision;
- Study terminated by Sponsor;
- Other, specify.

Procedures for Discontinuation from Study Drug

If there is evidence that the subject is receiving benefit from treatment even though the subject has met a criterion for discontinuation as listed above, the subject may remain on study treatment after discussion with and approval from the Sponsor Medical Monitor.

All subjects who are discontinued from study treatment should complete protocol-specified EOT assessments (Section 6.5), withdrawal procedures and follow-up procedures (Section 6.6). The investigator must discuss with the subject that even though study treatment has stopped, the subject will continue into the follow-up period for study visits. If a subject withdraws consent from study treatment, the investigator must discuss with the subject that their decision to permanently discontinue study treatment does not mean follow-up visits should be discontinued as well.

Record the last dose date and reason for any subject who discontinues study treatment on the eCRF. Discontinued subjects will be followed for survival, either through direct contact or by collecting public records (eg, death certificates) as allowed by local laws. If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.

If the subject is withdrawn because of an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

If a subject does not agree to continue to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options

The following modified follow-up options can be offered to the subject who does not agree to study visits at the study site.

- Study personnel contacting the subject by telephone to collect study information based on the follow-up schedule
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information (eg, doctor's notes, hospital records) at the study site or other location)

Dates of the modified follow-up contact(s) should be recorded. See Section 5.7.2 for definition of withdrawal by subject from the study (ie, withdrawal of consent).

5.7.2. Subject Withdrawal/Discontinuation from the Study

The duration of subject participation in the study will be until 1 of the following occurs:

- Subject dies;
- Study termination;
- Withdrawal by subject (**from the study**) NOTE: this indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival;
- Subject is lost to follow-up;
- Other, specify.

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel accessing and reviewing the subject's medical information (at study site or other location)

If the subject refuses all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow up, the investigator will document this as a withdrawal of consent (from the interventional portion and follow-up). The Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal. For these

subjects, survival status information will be collected by public records (eg death certificates) unless prohibited by local laws.

Procedures for Withdrawal/Discontinuation From Study

Withdrawal from the study will entail discontinuation of all follow-up procedures.

Subjects will be followed for survival status by collecting public records (eg, death certificates) unless prohibited by local laws.

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained during the EOT assessments and the 40-Day (+7 days) Follow-up assessments conducted after the last administration of study treatment (Section 6.5 and Section 6.6.1).

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 17.1 for the Tissue Screening and Screening period and in Table 17.2 for the treatment and follow-up periods.

6.1. Tissue Screening

To determine eligibility, subjects must have breast cancer that has been assessed as having low HER2 expression as determined by the FDA approved VENTANA PATHWAY Anti-HER-2/neu (4B5) IHC assay, additionally validated to investigational use only (IUO) for the HER2 IHC 1+ category, according to ASCO-CAP 2018 HER2 testing guidelines(adapted by Daiichi Sankyo Inc. and Ventana)[10] evaluated at a central laboratory. The assay methodology will be the same as described in the package insert. The only difference between the IUO version of the assay used in this study and the approved assay will be the investigational scoring algorithm for the lower cut point bound on the HER2 IHC 1+ category. HER2 ISH testing will follow the scoring criteria specified in the package insert of Ventana INFORM Dual ISH kit.

Note: Subjects may continue on prior therapy while tissue testing takes place.

A sequential screening process must be followed. Tissue screening must be followed by the main screening procedures in Section 6.2.

Please refer to the study laboratory manual for required tumor sample specifications and shipping instructions.

Fine Needle Aspirate (FNA) and bone biopsies will not be accepted for tissue samples.

The following procedures will be conducted:

- Obtain a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue.
- Obtain adequate archived or recent tumor tissue sample for HER2 testing. The biopsy used for central HER2 testing can be an archived sample that was obtained prior or after the last treatment regimen. Refer to the study laboratory manual for preparation, number of slides required, storage, and shipment procedures. If the most recent tissue sample is unavailable:
  - Document the reason why the most recent tissue sample is unavailable and submit another prior tissue specimen.
- If archival tumor tissue is not available, collect a fresh tumor tissue sample.
- If a tumor biopsy is needed, report any SAEs directly related to tissue screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.
- Send the samples to the central laboratory to assess HER2 status.
- Assign SID.

6.2. Screening

A sequential screening process must be followed. Tissue screening (see Section 6.1) must be complete before the main screening procedures below.

The duration of the screening/baseline period is up to 28 days. Informed consent will be obtained from the subject before any study-specific procedures are initiated.

The following activities and/or assessments will be performed **within 28 days before randomization** during the screening period:

- Unless required by local regulations or IRB/IEC, an HIV antigen/antibody test is not required prior to randomization/enrollment.
  In Portugal only, please see Section 17.9.2 for text applicable to sites in Portugal.
- Perform a hepatitis B surface antigen/hepatitis C antibody test. Subjects who have a positive HCV antibody test will require a negative polymerase chain reaction for HCV RNA.
- Perform ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy.
- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study).
  In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.
- Perform tumor assessment by CT or MRI scans of the chest, abdomen, pelvis, and any other sites of disease. A CT or MRI of the brain is to be included for all subjects.
- A tumor tissue biopsy after the completion of the subject's most recent treatment regimen is required for retrospective assessment. If the tumor tissue provided for HER2 status testing was collected after completion of the last treatment regimen, an additional new biopsy is not required. If the tumor tissue provided for HER2 status testing was collected before completion of the last treatment regimen, an additional new biopsy is required. The detailed procedures for preparing and submitting tumor tissue samples will be provided in the laboratory manual. FNA and bone biopsies will not be accepted for tissue samples.
- Additional tissue samples for exploratory biomarker assessment are required unless prohibited by local regulations (see the study laboratory manual). It is preferred if the slides are from the same block as the tissue sample sent for central laboratory HER2 testing.

If there are screening procedures that are performed within 28 days of randomization during the standard treatment of the subject, these procedure results can be used for the trial even if conducted prior to consent as they were performed during the normal course of subject care.

Note: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use it as comparator for subsequent measurement. Therefore, all lesions (target and non-target) have to be assessed at Screening according to mRECIST version 1.1 (Section 17.5).

The following activities and/or assessments will be performed during the screening period **within 14 days before randomization** except as indicated:

- Confirm subject eligibility.
- Obtain:
  - Demographics (eg, birth date, sex, race, ethnicity);
  - Medical (including smoking) and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, estrogen/progesterone receptor status, and previous cancer therapies (including prior radiation therapy);
  - Oncology surgical history.
- Perform a physical examination (see Section 9.11), including weight and height.
- Assess functional status using the ECOG PS (Section 17.4).
- Record concomitant medications, AEs, and hospitalization-related records at every visit (from the time the subject signed the Main ICF). For details on AE collection and reporting, refer to Section 9.2.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature; Section 9.9) and peripheral oxygen saturation (SpO2; Section 9.12.2).
- Perform triplicate 12-lead ECG.
- The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points (Section 9.10).
  - Note that subsequent ECGs will be performed in triplicate only if an abnormality is noted.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
  - Coagulation (should also be performed as clinically indicated throughout the study)
  - Troponin (preferably high-sensitivity troponin-T); the test used to test troponin should be the same at Screening and at EOT. In addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing. If ECG is abnormal, follow institutional guidelines.
  - Serum biomarkers (eg, HER2ECD), exploratory biomarkers (eg, cfDNA in plasma), see Section 8.3.2, and COVID-19 serology, see Section 17.8.

- Obtain urine sample for urinalysis (protein, glucose, blood, microscopy assessment [if indicated], and specific gravity; Section 9.8).
- For women of childbearing potential (criteria for non-childbearing potential are defined in Section 4.1), within 72 hours before randomization perform a serum or urine pregnancy test and document the results; a positive urine pregnancy test result must be immediately confirmed using a serum test.

6.3. Randomization

Eligible subjects will be randomized by the IXRS in a 2:1 ratio into the treatment arms: T-DXd vs. physician's choice, which has 5 available treatment paradigms (refer to Section 5.1.1).

Subjects to be enrolled:

- Not more than 240 HR-positive subjects who have not had prior therapy with a cyclin-dependent kinase (CDK) 4/6 inhibitor
- At least 240 HR-positive subjects who have had prior therapy with a CDK4/6 inhibitor
- ~60 HR-negative subjects.

Randomization will be stratified by

- HER2 IHC status of tissue samples assessed by a central laboratory: HER2 IHC 1+ vs. HER2 IHC 2+/ISH-
- Number of prior lines of chemotherapy: 1 vs.2
- HR/CDK status: HR-positive with prior CDK4/6 inhibitor treatment vs.HR-positive without prior CDK4/6 inhibitor treatment vs.HR-negative.

Investigators will choose 1 of the control treatments for every subject before randomization.

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 17.2 and further described below. Procedures are to be performed within 3 days of the Day 1 visit of each cycle unless otherwise specified. Cycles for T-DXd are 21 days in duration; cycles for physician's choice should be 21 days in duration if there are multiple options in the label approved in the country of drug administration or the NCCN guidelines.[1]

A subject's first dose at Cycle 1 Day 1 should occur within 7 days after the date the subject is randomized.

6.4. Treatment Period

6.4.1. Cycle 1 to 4 and Subsequent Cycles

6.4.1.1. Between -3 Days Before Dosing Through Immediately Before Dosing (All Cycles)

- Perform a physical examination (Section 9.11), including weight. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

- Assess functional status using the ECOG PS (Section 17.4).
- Record concomitant medications, AEs, and hospitalization-related records at every visit. For details on AE collection and reporting, refer to Section 9.2.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) and SpO2 (Section 9.12.2). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Perform 12-lead ECG. ECGs will be performed in triplicate if an abnormality is noted. The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points (Section 9.10).
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
- For all female subjects of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test within 72 hours prior to the beginning of dosing and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects who are of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.

Note: Vital signs (including SpO2) evaluations, clinical laboratory tests, physical examination, weight, ECG ECOG PS, and HEOR outcome questionnaires need not be repeated if they were performed within 3 days of the first dose in each cycle.

6.4.1.2. Day 1 Before Dosing (All Cycles, Unless Otherwise Noted)

- The subject must complete the HEOR outcomes: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done on the day of clinic visit (Section 10.1) at Cycle 1, Cycle 2, and Cycle 3 and then every 2 cycles during the treatment period.
- Obtain blood samples for:
  - Pharmacogenetic assessment (Section 8.5), Cycle 1 only, if the subject provides consent by signing the pharmacogenetics sample banking ICF. (This sample is not required for study participation.)
  - Serum biomarkers (eg, HER2ECD [Section 8.3.2]; COVID-19 serology [Section 17.8]) assessments will be collected on Cycle 3 Day 1 and every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc), see Section 8.3.2.
    - COVID-19 testing will be performed on the serology samples **only** starting from Cycle 5 and every 4 cycles thereafter.
  - Only subjects randomized to T-DXd:

  - PK assessment before infusion (within 8 hours) on Day 1 of each cycle through Cycle 4 and then every 2 cycles until Cycle 8 (ie, Cycle 1, 2, 3, 4, 6, 8); see Section 8.1;
  - ADA (within 8 hours before infusion) at Cycles 1, 2 and 4, then every 4 cycles (ie, Cycles 8, 12, 16, etc); see Section 8.4.
- Obtain blood samples for exploratory biomarkers, such as cfDNA in plasma, before treatment on Day 1 of Cycle 1 and every 3 cycles thereafter (eg, Cycles 4, 7, etc) until EOT; see Section 8.3.2.
- An optional fresh tumor tissue biopsy may be collected at Cycle 3 Day 1 (±7 days); see Section 8.3.1.
- Record concomitant medications, AEs, and hospitalization-related records at every visit.

6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted)

T-DXd should only be initiated and administered by a healthcare professional experienced in the administration of cytotoxic chemotherapy. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use. Comparator treatments should be administered and monitored as per label approved in the country of drug administration or the NCCN guidelines.[1]

- For T-DXd treatment, administer study treatment IV infusion approximately 90 minutes for the initial dose and, if no infusion related reaction after the initial dose, infuse subsequent doses over 30 minutes. Record start and stop times of any study treatment and amount of drug administered. T-DXd and physician's choice treatments are to be administered every 21 days ±2 days.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) (all cycles before and for the T-DXd arm only after infusion) and SpO2 (all cycles before and for the T-DXd arm only after infusion) (Section 9.12.2). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- At Cycle 1 Day 1, perform ECG testing at 5 hours after the start of drug administration (±2 hours) for T-DXd-treated subjects.
  - If an abnormality is noted, perform triplicate ECG.
- Collect blood samples for:
  - For subjects randomized to T-DXd, PK analysis on Day 1 of each cycle through Cycle 4 and then every 2 cycles until Cycle 8 (ie, Cycle 1, 2, 3, 4, 6, 8) preferably within 15 minutes or as soon as possible after end of infusion. The actual time of sampling should be accurately recorded. In addition, for Cycle 1 Day 1 only, collect sample at 5 hours after the start of drug administration (±2 hours); see Section 8.1.

- If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis, collect blood samples for troponin (preferably high-sensitivity troponin-T) testing and perform ECG in triplicate. If ECG is abnormal, follow institutional guidelines. See details in Table 5.3.

Note that end of infusion assessments are not required for subjects on capecitabine.

6.4.1.4. Day 8 (±1 day) and Day 15 (±1 day) (Cycle 1 Only)

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) (before and for the T-DXd arm only after infusion) and SpO2 (before and for the T-DXd arm only after infusion) (Section 9.12.2). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
- Record concomitant medications, AEs, and hospitalization-related records at every visit.

6.4.2. Every 4 Cycles (±7 days) After Cycle 1

- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study) before infusion at Cycle 5, 9, 13, etc.
  In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.

6.4.3. Every 6 Weeks (±7 days)

- Tumor assessments, based on sites of disease identified at Screening and any additional newly suspected sites of PD, will be conducted every 6 weeks (±7 days) from randomization, independent of treatment cycle. A CT or MRI (CT or MRI with ≤5 mm cuts) of chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. The same assessment modality should be used throughout the study for all assessments for each subject unless prior approval is obtained from Sponsor or its designee. Unscheduled tumor assessments may be performed if progression is suspected.
- A CT or MRI of the brain is mandatory for all subjects who were enrolled with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for subsequent tumor assessments unless clinically indicated.

Imaging results will be reviewed by an independent radiologic facility.

6.5. End of Study Treatment

The EOT is defined as the date the Investigator decides to discontinue study treatment and the visit should occur within 7 days of the decision. All assessments required as part of EOT must occur within 7 days from the date the Investigator decides to discontinue study treatment. The following procedures will be performed as specified in Table 17.2. If the EOT assessments have been performed within 30 days (±7 days) of their last treatment, they can be considered to be the EOT data and there is no need to repeat them; otherwise, these assessments need to be repeated.

- The subject must complete the HEOR outcomes EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done on the day of clinic visit.
- For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test and document the results. For subjects who are of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.
- Perform a physical examination (Section 9.11), including weight.
- Perform ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy.
- Assess functional status using the ECOG PS (Section 17.4).
- Record concomitant medications, AEs, and hospitalization-related records at every visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) and SpO2 (Section 9.12.2).
- Perform 12-lead ECGs.
  - If an abnormality is noted, perform triplicate ECG. The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points (Section 9.10).
- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study).
  In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.
- Blood sample for troponin (preferably high-sensitivity troponin-T). In addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing. If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3.

  If Grade 1:

  - Repeat troponin testing at 3±1 hours after initial troponin test. If repeat troponin level at 3±1 hours rises significantly per institutional guidelines,

- Perform ECG in triplicate;
- Repeat troponin testing at 6±1 hours after initial troponin test;
- Follow institutional guidelines for management of detectable troponin testing.

  - If repeat troponin level at 3±1 hours does not rise significantly per institutional guidelines, repeat troponin testing at 6±1 hours or at 24±2 hours after initial troponin test.

  If Grade 3:

  - Perform ECG in triplicate.
  - Repeat troponin testing at 6±1 hours and 12±1 hours after initial troponin test.
  - Follow institutional guidelines for management of detectable troponin testing.

- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
  - Coagulation
  - Serum biomarkers (eg, HER2ECD [Section 8.3.2]; COVID-19 serology [Section 17.8]).
- Blood sample for exploratory biomarkers, such as cfDNA analysis in plasma, will be collected.
- An optional fresh tumor tissue biopsy may be collected.
- Tumor assessments should include all sites of disease identified at Screening and any other locations where PD is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged, per mRECIST version 1.1. If the previous scan was within the last 6 weeks (±7 days) from the date of EOT, this assessment does not need to be performed at EOT. If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.
- A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need brain scan for tumor assessment unless clinically indicated.

6.6. Follow-up

6.6.1. 40-Day (+7 days) Follow-up

Forty days (+7 days) after last study treatment administration or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in

Table 17.2. If EOT is >40 days (+7 days) after last treatment, then the EOT assessments can also function as the 40-Day (+7 days) Follow-up assessments.

- The subject must complete the HEOR outcomes EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done on the day of clinic visit.
- For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test and document the results. For subjects who are of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.
- Perform a physical examination (Section 9.11), including weight.
- Assess functional status using the ECOG PS (Section 17.4).
- Record concomitant medications, AEs, and hospitalization-related records.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) and SpO2 (Section 9.12.2).
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
- Obtain blood samples for ADA, only for subjects randomized to T-DXd.

  See Section 6.6.2 for information on subjects with positive ADA at the 40-Day (+7 days) Follow-up.

6.6.2. Long-term/Survival Follow-up

After completion of the 40-Day (+7 days) Follow-up assessments, the Long-term/Survival Follow-up assessments will be performed every 3 months (±14 days) from the date of 40-Day (+7 days) Follow-up assessments until death, withdrawal of consent from the study, loss to follow-up, or study closure, whichever occurs first.

The following activities will take place during Long-term/Survival Follow-up at the study site or by telephone contact:

- The subject must complete the HEOR outcomes EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day (only at first 3 months, which will be the last data collection point for HEOR questionnaires).
- For subjects with positive ADA at the 40-Day (+7 days) Follow-up assessment, additional serum ADA samples may be collected every 3 months (±1 month) up to 1 year from the last dose of study drug, until the ADA becomes negative, until the ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), until the subject starts another therapy for cancer or withdraws consent from the study, whichever occurs first.
- Record subsequent anticancer treatments, their outcomes, and survival.

- Further follow-up may be required for ongoing AEs (see Section 9.2).
- All subjects will be followed for survival until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

If direct contacts are not possible because of withdrawal of consent or the subject becomes lost to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws. See Section 5.7.1 for further details on how subjects will be followed for survival status if they withdraw consent.

Note that if a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoints

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, based on BICR, in HR-positive breast cancer subjects. Progression-free survival based on BICR is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via BICR according to mRECIST version 1.1 or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cutoff date for PFS analysis will be censored at the date of their last evaluable tumor assessment. Detailed censoring rules for PFS based on BICR will be specified in the Statistical Analysis Plan (SAP).

7.1.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- PFS, based on BICR, in all randomized subjects
- OS in HR-positive breast cancer subjects
- OS in all randomized subjects

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

OS is defined as the time from the date of randomization to the date of death for any cause. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

7.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints include:

- PFS, based on Investigator assessment
- Confirmed ORR, defined as the sum of CR rate and PR rate, based on BICR and Investigator assessment, and confirmed by a second assessment.
- DoR, defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression, based on BICR, or death. Duration of response will be measured for responding subjects (PR or CR) only. Subjects who are progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment.

In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.

Detailed censoring rules for applicable secondary efficacy endpoints will be specified in the SAP.

7.1.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- CBR, defined as the sum of CR rate, PR rate, and greater than or equal to 6 months' SD rate, based on BICR.
- DCR, defined as the sum of CR rate, PR rate, and SD rate, based on BICR
- TTR, defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), based on BICR. Time to response will be measured for responding subjects (CR or PR) only.
- PFS2, defined as the time from date of randomization to the first documented progression on next-line therapy* or death due to any cause, whichever occurs first. The first documented progression on next-line therapy is based on investigator assessment of PD. PFS2 will be censored if no PFS2 event is observed during next line therapy before the analysis cutoff date; the censoring date will be the last contact date in cases where there is no next-line therapy. In the case that a second anti-cancer therapy is introduced prior to a PFS2 event, then PFS2 date will be censored at the end date of the first next-line therapy.
  - Any death occurring prior to the start of next-line therapy will be considered a PFS2 event.
  - Any death following the next line of therapy will be a PFS2 event if no second new line of therapy is initiated.
  - PFS and PFS2 may be identical in the case that a subject starts the next line anti-neoplastic therapy prior to progression on the trial therapy and tumor assessments continue after start of the new therapy.

  * Next-line therapy is defined as the first new systemic anticancer therapy initiated after discontinuation of study treatment regardless of EOT reason.

7.2. Appropriateness of Selected Efficacy Assessments

The primary endpoint of this study is PFS based on mRECIST version 1.1, which will be determined by independent review of baseline and follow-up assessments obtained every 6 weeks from randomization date. Progression-free survival has served as the basis of several recent approvals in the metastatic breast cancer setting including pertuzumab (CLEOPATRA study),[12] palbociclib (PALOMA studies),[21,22] ribociclib (MONALEESA-2),[23] and abemaciclib (MONARCH 2).[24] Sample size has been calculated to ensure the study is adequately powered to detect a clinically meaningful PFS benefit.

Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess overall survival, it is usually the preferred endpoint.[25,26] The guidelines recommend estimating the treatment effect on OS when the primary endpoint is something other than OS. Addition of OS as a key secondary endpoint is expected to help demonstrate the overall favorable risk-benefit profile of the study treatment.

Patients with metastatic breast cancer face an illness associated with significant symptoms. Moreover, they are also aware that despite the availability of various treatments, it is ultimately incurable. The success of modern therapies in achieving better disease control and prolonged survival means that more women with metastatic breast cancer can receive several lines of

treatment and in the process the key goals are to prolong survival and to improve health-related quality of life (QoL). That is why it is particularly valuable to involve subjects in clinical studies by asking them to provide assessment of their health and QoL. In recent years, a growing number of clinical studies in metastatic breast cancer have been reporting on health-related QoL, the most common patient reported outcome (PRO) being used is the EORTC QLQ-C30 with or without the breast cancer supplement EORTC QLQ-BR45, followed by FACT-B.[27]

The index scores from the PROs will be used to show changes in overall health related quality of life and clinically meaningful changes in specific aspects of subject's wellbeing over time. In addition, the outcomes will be used in further analyses and economic models to generate evidence to support access and reimbursement.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessments

Blood samples for PK assessments will be collected from subjects randomized to T-DXd at multiple time points in the study, as outlined in Table 8.1 and Table 17.2. In addition, if feasible, a blood sample should be collected for PK analysis as soon as possible when a subject is suspected of having ILD/pneumonitis.

Table 8.1: Blood Sampling for Pharmacokinetic Analysis

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 1	Day 1	BI (within 8 hours) EOI: Preferably within 15 minutes or as soon as possible after EOI 5 hours after the start of drug administration (±2 hours)
Cycles 2, 3, 4, 6, and 8	Day 1	BI (within 8 hours) EOI: Preferably within 15 minutes or as soon as possible after EOI

BI = before infusion; EOI = end of infusion

At each time point, blood will be collected for T-DXd, total anti-HER2 antibody, and MAAA-1181a PK analysis. The actual time of study treatment administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF.

Details for blood sampling, processing, storage, and shipment to central laboratory for PK samples will be provided in the study laboratory manual.

Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a will be measured using validated assays at the bioanalytical laboratory.

If chloroquine or hydroxychloroquine is administered for COVID-19 infection, additional PK serum samples should be collected from each subject who provides consent as described in Section 17.8 and at the time points specified in the Schedule of Events (Table 17.2).

8.2. Pharmacodynamic Assessment(s)

Not applicable.

8.3. Biomarker Assessments

In this study, biomarker analyses will be used to investigate the effect of T-DXd at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the study laboratory manual.

8.3.1. Tumor Tissue Sampling

In addition to the tumor tissue sample required for assessment of HER2 status, an additional tissue sample for exploratory biomarker analysis needs to be submitted, if allowed by local laws. An additional tumor tissue biopsy after the completion of the subject's most recent treatment regimen is required for retrospective assessment. If this tumor tissue sample was collected after completion of the last treatment regimen, an additional tumor tissue biopsy is not required. If this tumor tissue sample was collected before completion of the last treatment regimen, an additional tumor tissue biopsy is required. Optional fresh tissue samples may additionally be obtained during and after study treatment. The detailed instructions for the handling and shipping of tumor samples are included in the study laboratory manual. FNA and bone biopsies will not be accepted for tissue samples.

8.3.2. Blood Sampling

The HER2ECD in serum may be measured by a central laboratory. Other exploratory biomarkers, such as cfDNA in plasma, may be measured.

8.3.3. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, optional exploratory biomarker research may be conducted on available additional samples. These studies would extend the search for other potential biomarkers of response/resistance that may correlate with clinical benefit. This may include the development of ways to detect, monitor, or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability. If the subject agrees, the remaining samples (tumor tissues, blood, and plasma) may be stored for up to 15 years at the longest, according to the regulation in each country or region, respectively, and further analyzed to address scientific questions related to T-DXd and/or cancer.

8.3.4. Disclosure of the Results of Additional Biomarker Assessments

See ICF for details on disclosure.

8.4. Immunogenicity

Blood samples for ADA analyses will be collected only for subjects randomized to T-DXd and at the time points specified in Table 17.2. A blood sample will be drawn at each time point. Serum concentrations of T-DXd and/or total anti-HER2 antibody may be measured using the same ADA samples for purpose of ADA assessment.

Details for ADA serum sampling, processing, storage, and shipment for ADA samples will be provided in the study laboratory manual.

The ADA testing will be performed using a validated ADA assay following tiered assay steps including screening, confirmatory, and titer determination testing. Samples confirmed ADA positive will be analyzed by neutralizing antibody assay.

8.5. Pharmacogenomic Analysis

8.5.1. Genomic or Genetic Banking and Analysis

A single blood sample for pharmacogenomics analysis will be collected from each subject who consents to this test, predose on Cycle 1 Day 1. Participation in this part of the study is optional for all subjects.

The DNA samples will be extracted from the blood sample for pharmacogenomics analysis. The pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of T-DXd. Additionally, samples may be analyzed for genes involved in T-DXd related signaling pathways or to examine diseases or physiologic processes related to T-DXd. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study treatment, as well as helping in the development of new drugs or improvement of existing drugs.

Specimen shipping and handling details will be included in the study laboratory manual.

8.5.1.1. Disclosure of the Results of Genomic or Genetic Analysis

See ICF for details on disclosure.

8.5.1.2. Storage and Disposal of Specimens for Genomic or Genetic Analysis

Samples will be retained for up to 15 years at the longest, according to the regulation in each country or region respectively, or until the sample has been exhausted or until the Sponsor instructs the laboratory for sample storage and/or analysis to destroy the sample (in accordance with laboratory procedures). During the period of storage, the samples will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

However, the data will not be discarded if the genetic analysis has been completed before the subject withdraws consent.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will include SAEs, TEAEs, AESIs, discontinuations associated with AEs, physical examination findings, ECOG PS, vital signs measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ADAs. All AEs will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded using National Cancer Institute (NCI) CTCAE version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

9.2. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the Main ICF and up to 40 days (+7 days) after last treatment (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. All SAEs occurring after subject signs the Main ICF and up to 40 days (+7 days) after last treatment will be recorded on the eCRF. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

If a tumor biopsy is needed, report any SAEs directly related to tissue screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

All AEs, SAEs, and AESIs are to be reported according to the procedures in Section 9.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital signs findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose interruption or reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator will determine whether or not any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

The Investigator should always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, the primary sign or symptom should be reported as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, they should be reported as individual entries of AE or SAE.

For events that are considered serious because of hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently, should not be reported as an AE or SAE. However, when a subject dies from PD with no other immediate causes, "disease progression" should be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

9.3. Adverse Events of Special Interest

For the T-DXd clinical program, based on the available preclinical data, review of the cumulative literature, reported toxicities for the same class of agents, and biological plausibility, ILD and LVEF decrease are considered to be AESIs.

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

Interstitial lung disease/pneumonitis is considered to be an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD AC, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[9]

9.3.1.2. Management Guidance

Interstitial lung disease/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated "Other Non-laboratory Adverse Events" dose modification section of the study protocol (Section 5.4).

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation (infectious disease consultation as clinically indicated), blood culture and CBC (other blood tests could be considered as needed), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests and pulse oximetry (SpO2), arterial blood gases if clinically indicated, and one blood sample collection for PK (central laboratory) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed.

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of the study protocol (Table 5.3).

All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

9.3.1.3. Interstitial Lung Disease Adjudication Committee

An independent ILD AC for the T-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection will be triggered for AEs reported using the selected 42 preferred terms (PTs) (all from the ILD Standardised MedDRA Query [SMQ]) plus the 2 PTs of acute respiratory failure and respiratory failure.

9.3.2. Left Ventricular Ejection Fraction Decrease

9.3.2.1. Clinical Summary

LVEF decrease in association with T-DXd are considered to be important potential risks based on the available nonclinical data, literature, and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[9]

9.3.2.2. Management Guidance

Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.
In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.

Troponin will be measured at Screening and EOT and as needed based on subject-reported cardiac signs and symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter will be recorded in the eCRF.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Conference on

Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).[28]

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings that should be considered AEs.

9.4.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).[28]

Medical and scientific judgment should be exercised in deciding whether or not expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Grade Assessment

The severity of AEs will be graded using the NCI CTCAE version 5.0. For each episode, the highest severity grade attained should be reported.

The NCI CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI CTCAE guidelines should be followed closely.

- Grade 1: Mild AE

- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event; however, the event itself may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global regulatory definition for reporting SAEs to Regulatory Agencies. For example, the NCI CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grade may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the Investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that immediately makes the event serious based upon hospitalization without regard to the Investigator assessment of severity.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made
- Drug Withdrawn: The study drug was permanently stopped
- Dose Reduced: The dosage of study drug was reduced
- Drug Interrupted: The study drug was temporarily stopped

- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment

9.4.6. Other Action Taken for Event

- None: No treatment was required
- Medication required: Prescription and/or over-the-counter medication was required to treat the AE
- Other

9.4.7. Adverse Event Outcome

- Recovered/Resolved: The subject fully recovered from the AE with no residual effect observed.
- Recovered/Resolved with Sequelae: The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- Recovering/Resolving: The AE has improved but has not fully resolved.
- Not Recovered/Not Resolved: The AE itself is still present and observable.
- Fatal: Fatal should be used when death is a direct outcome of the AE.
- Unknown: Unknown should be used if subject is lost to follow-up before an outcome can be determined.

9.5. Adverse Events and Adverse Event of Special Interest Reporting– Procedures For Investigators

All AEs, SAEs, AESIs, and overdoses will be reported in the eCRF.

Additional relevant information regarding the AESIs ILD/pneumonitis and LVEF decrease for the T-DXd clinical program, regardless of seriousness, is to be collected through the targeted questionnaires built within the applicable eCRFs in the clinical study database. Only the AESIs ILD/pneumonitis targeted questionnaire is to be collected for the comparator arm.

For broad surveillance of LVEF decrease, relevant AEs under the MedDRA SMQs of Cardiac Failure and Myocardial Infarction are included for enhanced data collection; additional data for these AEs are collected via targeted questionnaires of heart failure or myocardial infarction.

For broad surveillance of ILD, the selected 42 PTs (all from the ILDSMQ) plus the 2 PTs of respiratory failure and acute respiratory failure are included for enhanced data collections.

Serious events that are also efficacy endpoints (eg, PD) and/or safety endpoints will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, “disease progression” should be reported as an SAE and captured on designated eCRF. These events are clinically anticipated events in the target treatment population, and will be periodically reviewed

by the Daiichi Sankyo safety teams to ensure prompt identification of any clinically concerning safety issues.

The following types of events should be reported by the Investigator in electronic data capture (EDC) within 24 hours of awareness:

- SAEs (see Section 9.4.2 for definition).
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of PTs)
- Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is in-built as an 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 an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the 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. AEs can either be serious or non-serious. Details of the overdose including T-DXd dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within electronic data capture.

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether or not an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries and follow-up information, such as those upgraded to a fatal/life-threatening case, must be followed and addressed promptly. The investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information. Other follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up. In the event that eCRF is unavailable, report SAEs by faxing the paper Serious Adverse Event Report (SAVER) Form to the CRO using the provided fax cover sheet and the appropriate fax number provided for your country. Once eCRF becomes available, please enter SAEs reported on the SAVER Form

into eCRF as soon as possible. Please refer to eCRF Completion Guide for additional instructions.

Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Institutional Ethics Committee

Daiichi Sankyo and/or the CRO will inform Investigators, IRBs/IECs, and Regulatory Authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study sites or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or the CRO will comply with any additional local safety reporting requirements.

In the United States (US), upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's responsibility to report SUSARs to all IECs and Regulatory Authorities.

9.7. Exposure in Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 7 months of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure in Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, postpartum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

1. Hematology tests
    - Red blood cell count, hemoglobin, hematocrit, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count

2. Blood chemistry tests
    - Total protein, albumin, alkaline phosphatase, ALT, AST, total bilirubin, blood urea nitrogen/urea, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium.
    - Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.2).
    - A coagulation test will be performed (international normalized ratio/prothrombin time ≤1.5 × ULN and either partial thromboplastin or activated partial thromboplastin time).
    - Troponin will be analyzed for each sample at Screening, EOT, and as needed based on subject-reported signs or symptoms.
3. Urinalysis
    - Protein, glucose, blood, microscopy assessment (if indicated), and specific gravity.

In addition, pregnancy test (serum or urine) for all female subjects of childbearing potential will be performed at the visits indicated in the Schedule of Events (Table 17.1 and Table 17.2). A positive urine pregnancy test result must be confirmed immediately using a serum test.

All laboratory values must be appraised by the Investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the Investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, relevant procedures must be followed (see Section 9.5). Abnormal laboratory values (NCI CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Information will be entered in the eCRF on whether or not measured, date of measurement, and measurement results for the following items: systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

9.10. Electrocardiograms

ECGs will be taken in triplicate at screening. Thereafter, singular ECGs will be performed. If an abnormality is noted, ECGs should then be performed in triplicate. Standard supine/semi-recumbent 12-lead ECGs should preferably be taken prior to blood draws and will be performed as described in the Schedule of Events (Table 17.1 and Table 17.2). When taken in triplicate, ECGs should be taken in close succession. Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities.

9.11. Physical Examinations

Physical examination findings will evaluate the following body systems/organs: general appearance; dermatological; head; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Weight and height will also be recorded in kilograms and centimeters, respectively.

9.12. Other Examinations

9.12.1. Cardiac Assessments

Either ECHO or MUGA will be performed as described in the Schedule of Events (Table 17.1 and Table 17.2); LVEF will be measured.
In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.

9.12.2. Pulmonary Assessments

The SpO2 will be collected as indicated in the Schedule of Events (Table 17.1 and Table 17.2). For more details, please refer to Section 6 of the protocol.

An ILD AC will review all cases of (potential) ILD/pneumonitis on an ongoing basis. Description of the ILD AC is available in Section 9.3.1.3.

10. OTHER ASSESSMENTS

10.1. Patient Reported Outcomes

Patient reported outcomes will be used to evaluate study treatment. The impact of breast cancer symptoms will be assessed based upon the EORTC QLQ-BR45 and EORTC QLQ-C30 (version 3.0), and EQ-5D-5L questionnaires (Section 17.6 and Section 17.7, respectively).

10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45

The QLQ-C30 is a QoL instrument for cancer patients developed in 1987 by EORTC. Since then it has undergone several revisions and its current version is 3.0.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items - no item occurs in more than 1 scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Due to limitations inherent in its generic focus, the EORTC QLQ-C30 is supplemented by disease specific modules such as the EORTC QLQ-BR45, which are designed to be administered in addition to the core questionnaire. The EORTC QLQ-BR45 is specific for breast cancer.

The EORTC QLQ-C30 with EORTC QLQ-BR45 will be used in the study as the disease-specific instruments to assess the health-related QoL of subjects. They will be administered before any other assessments or procedures are done that day. Complete before infusion on Day 1 of Cycle 1, Cycle 2, and Cycle 3 and then every 2 cycles thereafter, and at the EOT assessments. Subjects will be followed up at Day 40 (+7 days) and at the first of the Long-term/Survival Follow-up Visit 3 months after, which will be the last data collection point for the questionnaires. Reporting will follow closely the Consolidated Standards of Reporting Trials (CONSORT) extension on reporting PROs.[29]

Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30 and in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

Further, time to deterioration on the “breast symptoms” and “arm symptoms” subscales of the EORTC QLQ-BR45 and the pain symptom subscale of the EORTC QLQ-C30 will be assessed. On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores.

Further details on the scoring of these scales, including missing items, will be provided in the SAP.

10.1.2. EuroQoL Five Dimensions Five Levels Patient Reported Outcome Questionnaire

Study subjects will be asked to complete the EQ-5D-5L questionnaire, a generic measure of standardized health status, before any other study procedures are performed before infusion on Day 1 of Cycles 1, Cycle 2, and Cycle 3 and then every 2 cycles thereafter, and at the EOT assessments. Data collection will continue at the 40-Day (+7 days) Follow-up assessments and the first Long-term/Survival Follow-up assessments 3 months after, which will be the last data collection point for the questionnaires.

The EQ-5D-5L is self-administered and consists of 2 parts, the EQ-5D-5L descriptive system, and the EQ-5D visual analogue scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems.[30] The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. The numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score.

The EQ-5D VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D-5L will be administered before the first cycle and every 2 cycles after that until EOT as defined in the protocol. Subjects will be followed up at Day 40 (±7 days) and at the first Long-term/Survival Follow-up Visit 3 months after that (last measurement). Reporting will follow closely the CONSORT extension on reporting PROs.[29]

10.2. Health-related QoL Endpoints

10.2.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endpoints

- Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), and the 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30.
- Time to deterioration on the pain symptom subscale of the EORTC QLQ-C30 will be assessed.
- Changes from baseline over time will be assessed in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

- Time to deterioration on the "breast symptoms" and "arm symptoms" subscales of the EORTC QLQ-BR45 will be assessed.
- On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores.[31]

10.2.2. EuroQoL Five Dimensions Five Levels Endpoints

- VAS as a measure of self-rated health status
- Response by dimension
- Index score change from baseline using United Kingdom value set
- Index score by disease state

10.3. Pharmacoeconomic Assessments

10.3.1. Hospitalization-Related Endpoint

Time to hospitalization will be assessed. Each hospitalization event will prompt the completion, by the site, of a detailed hospitalization eCRF containing the following components:

- Date of admission to hospital.
- Date of discharge from hospital.
- Primary reason for hospitalization.
- Discharge status from hospital (died, discharged home, discharged to home health care, discharged to nursing home care, discharged to long-term care, other).
- Use of intensive care unit (ICU) services in hospital (Yes/No).
  - If yes, date of admission to ICU.
  - If yes, date of discharge from ICU.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary efficacy analyses of PFS per BICR will be performed for the HR-positive cohort and Full Analysis Set (FAS) when approximately 318 PFS events per BICR have been observed in the HR-positive cohort of FAS. Up to 3 analyses of OS could be performed for the HR-positive cohort and FAS when approximately 162, 233, and 333 OS events, respectively, have been observed in the HR-positive cohort, if the PFS analyses are statistically significant. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values (as well as geometric means and geometric coefficient of variation for the PK parameters of C_{max} and AUC). Categorical variables will be summarized using frequency counts and percentages.

Assessment of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of the study treatment will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Efficacy analyses will be performed on the HR-positive cohort and FAS. Safety analyses will be performed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. Analyses for all other exploratory endpoints will be performed based on the HR-positive cohort.

11.2. Analysis Sets

11.2.1. Full Analysis Set

The FAS will include all subjects randomized into the study, including those who did not receive a dose of study treatment. Subjects will be analyzed according to the treatments assigned at randomization.

11.2.2. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of study treatment. Subjects will be summarized according to treatment actually received.

11.2.3. Per-protocol Analysis Set

The PPS will include all subjects in the FAS who complied with the protocol sufficiently with respect to exposure to study treatment, availability of tumor assessment, and absence of major protocol violations likely to impact efficacy outcome. Details will be specified in the SAP.

11.2.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who received at least 1 dose of T-DXd and had measurable serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a.

11.3. Study Population Data

Subject disposition will be summarized for subjects in the FAS and HR-positive cohort of FAS. The total number of subjects for each defined analysis set will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the HR-positive cohort, FAS, PPS, and Safety Analysis Set. Study treatment exposure and treatment duration will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Efficacy Analyses

11.4.1. Primary Efficacy Analyses

The primary efficacy endpoint is PFS, based on BICR, in HR-positive breast cancer subjects. One analysis for the primary endpoint is planned. The PFS analysis will be performed after observing 318 BICR-assessed PFS events.

The primary efficacy analysis will compare the distribution of PFS between the 2 treatment arms in the HR-positive cohort using a stratified log-rank test. Stratification factors used for primary analysis will be from the randomization. The PFS will be tested using stratified log-rank test for statistical significance at a 2-sided alpha of 0.05. Kaplan-Meier (KM) estimates and KM curves will also be presented for each treatment arm. The median survival times and 2-sided 95% confidence intervals (CIs) for the medians based on the Brookmeyer and Crowley method will be provided for each treatment arm. The hazard ratios and their 95% CIs will be estimated, using stratified Cox proportional hazards regression models with the stratification factors per IXRS.

11.4.2. Key Secondary Efficacy Analyses

The same analysis as specified above for primary efficacy endpoint will be performed for the key secondary endpoints: PFS based on BICR in the FAS, OS in the HR-positive cohort, and OS in the FAS. If the test of the primary endpoint, PFS based on BICR, is statistically significant, the key secondary endpoints will be tested. Group sequential testing with 2 interim analyses are planned for OS analyses. The first OS interim analysis is planned at time of the PFS analysis (expecting approximately 162 OS events or 49% of the targeted 333 OS events) and the second OS interim analysis will be performed when approximately 233 OS events have been documented (70% of the planned 333 OS events) in the HR-positive cohort. The data cut-off for the final OS analysis will occur after approximately 333 OS events have been documented in HR-positive cohort. The OS interim analysis will allow the study to stop early for outstanding efficacy. Additional details of the interim analyses are in Section 11.6.

To control the overall family-wise type-I error, the primary efficacy endpoint and the key secondary efficacy endpoints, will be tested hierarchically in the order below to maintain the overall 2-sided type-I error rate to 0.05 or less:

1. PFS based on BICR in the HR-positive cohort
2. PFS based on BICR in the FAS
3. OS in the HR-positive cohort (up to 3 analyses)
4. OS in the FAS (up to 3 analyses)

The statistical testing for a key secondary endpoint will be performed only when the analyses in the hierarchy above the current endpoint have demonstrated statistical significance.

11.4.3. Other Secondary Efficacy Analyses

Duration of response will be summarized with median survival times and its 2-sided 95% CIs using Brookmeyer and Crowley method for each treatment arm.

The Cochran–Mantel–Haenszel test will be used to compare confirmed ORR between the treatment arms. The estimates of confirmed ORR and its 2-sided 95% exact CI based on the Clopper-Pearson method will be provided.

Additional sensitivity analyses of PFS per BICR and analysis of PFS per investigator assessment will be specified in the SAP.

11.4.4. Analyses of Health Economic and Outcomes Research Endpoints

Health economic and outcomes research endpoints based on the hospitalization-related data collection form and the following PRO questionnaires will be summarized by treatment arm: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L. A detailed analysis plan of QoL endpoints, including control of type I error regarding QoL analyses, will be provided in the SAP. Some descriptive analysis will be performed as follows.

11.4.4.1. EuroQoL Five Dimensions Five Levels

Based on results of the EQ-5D-5L assessment, the EQ-5D-5L summary index score across disease states will be assessed. Descriptive statistics for the actual value and change from baseline will be computed for the EQ-5D-5L health profile utilities and EQ-5D VAS by scheduled time of evaluation (including EOT) for all subjects. Results of the EQ-5D VAS will be presented as a measure of overall self-rated health status.

11.4.4.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45

Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), and 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30 and in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

Time to deterioration on the “breast symptoms” and “arm symptoms” subscales of the EORTC QLQ-BR45 and the pain symptom subscale of the EORTC QLQ-C30 will also be assessed. On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the EORTC QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores.

Further details on the scoring of these scales, including missing items, will be provided in the SAP.

11.4.4.3. Hospitalization-Related Endpoints

For hospitalization-related endpoints: time to hospitalization as well as reason, discharge diagnosis, ICU stay, and length of stay will be reported.

11.4.5. Exploratory Efficacy Analyses

11.4.5.1. Subgroup Analyses

Subgroup analyses for PFS based on BICR, and OS will be performed for the HR-positive cohort and the FAS.

Subgroups will include:

- HER2 status (HER2 IHC 1+, HER2 IHC 2+/ISH-) assessed by a central laboratory
- Number of prior lines of chemotherapy (1, 2)
- Prior CDK4/6 (Yes, No)
- Age (<65, ≥ 65 years)
- Race (Asian, Rest of World)
- Region (Asia, North American, Europe, Rest of World)
- Lines of endocrine therapy received in the metastatic setting (0, 1, 2, ≥3)
- Best response to prior cancer systemic therapy
- History of CNS metastases (yes, no)
- Renal impairment at baseline (within normal range, mild/moderate impairment)
- Hepatic impairment at baseline (within normal range, mild impairment)
- History of visceral disease (yes, no)
- ECOG PS (0, 1)

The subgroups are based on baseline values (ie, the last non-missing values before the first drug administration). These results will be considered exploratory because of smaller sample sizes. Subgroup analyses will be performed only if at least 10 relevant events in each subgroup. Details about statistical method for subgroup analyses will be specified in SAP.

11.4.5.2. Analyses of Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

- CBR and DCR, based on BICR
- TTR, based on BICR

Rates and 95% CIs for CBR and DCR and descriptive statistics for TTR (based on BICR) will be provided by treatment arm. Analyses will be conducted based on the HR-positive cohort and based on the FAS, respectively.

The survival distribution of PFS2 will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS2 and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS2 rates at fixed time points (eg, 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the treatment group as model factor and the randomization stratification factors from IXRS as strata variables.

Exposure-response relationships will be explored.

11.4.6. Pharmacokinetic and Pharmacodynamic Analyses

11.4.6.1. Pharmacokinetic Analyses

Descriptive statistics will be provided for all serum concentration data (T-DXd, total anti-HER2 antibody, and MAAA-1181a) at each time.

The population PK (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of T-DXd, and, if appropriate, total anti-HER2 antibody and MAAA-1181a will be characterized, including available PK data from other T-DXd studies. After establishment of the pop-PK model, a pop-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and safety endpoints. The results of the nonlinear mixed effects pop-PK and pop-PK/pharmacodynamic models may be reported separately from the clinical study report.

11.4.6.2. Pharmacodynamic Analyses

Not applicable.

11.4.7. Biomarker Analyses

A tumor tissue biopsy after the completion of the subject's most recent treatment regimen is required for retrospective assessment. If the tumor tissue sample provided for HER2 status testing was collected after completion of the last treatment regimen, an additional new biopsy is not required. If the tumor tissue sample provided for HER2 status testing was collected before completion of the last treatment regimen, an additional new biopsy is required. Optional fresh tissue samples may additionally be obtained during and after study treatment.

Biomarkers will be summarized by treatment arm using descriptive statistics, when applicable.

11.5. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set and subjects will be analyzed according to their actual treatment received.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

11.5.1. Adverse Event Analyses

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after initiating study drug up until 47 days after last dose of the study drug. SAEs with an onset 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs. Treatment-emergent AEs will be coded using MedDRA and assigned grades based on version 5.0 of NCI CTCAE. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class, PT, relationship to the study treatment, and the worst NCI CTCAE grade. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by treatment arm, as well as TEAEs leading to discontinuation of the study treatments.

A by-subject AE (including TEAE) data listing including but not limited to the verbatim terms, system organ class, PT, NCI CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, AESIs, and other significant AEs, including those leading to discontinuation of the study treatments, will be listed.

Treatment-emergent AEs will also be summarized by treatment arm for the subgroups described in the SAP.

11.5.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by treatment arm at each scheduled time of evaluation, including EOT, maximum post-treatment value, and minimum post-treatment value.

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting 2-way frequency tabulation for baseline and the worst post-treatment value according to NCI CTCAE grade, will be provided for clinical laboratory tests.

All clinical laboratory test results and abnormal clinical laboratory test results of Grade 3 or 4 will be listed.

11.5.3. Vital Sign Analyses

Descriptive statistics will be provided by treatment arm for the vital signs measurements and changes from baseline by scheduled time of evaluation, including EOT and the maximum and minimum post-treatment values. All vital signs data will also be listed.

11.5.4. Electrocardiogram Analyses

Descriptive statistics will be provided by treatment arm for ECG parameters and changes from baseline by scheduled time of evaluation, including EOT and the maximum post-treatment value. In addition, the number and percentage of subjects with the maximum post-baseline ECG interval values and change from baseline meeting the categorical criteria per ICH E14 guidance[32] will be tabulated (see details in the SAP).

The QT intervals corrected by Fridericia's formula, $QTcF = QT/[RR]^{1/3}$, will be used for assessing the effect of treatment on QT. The ECG data will also be listed.

11.5.5. Physical Examination Analyses

Physical examination findings and ECOG PS will be listed.

11.5.6. Concomitant Medication Analyses

Concomitant medications will be coded using the World Health Organization Drug Reference List Dictionary. Number and percentage of subjects taking concomitant medications will be summarized. Concomitant medications will also be listed.

11.5.7. Immunogenicity (Anti-Drug Antibody) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. The number and percentage of subjects will be calculated for the presence or absence of development of ADA after the start of administration, defining subjects who are negative for ADA at all time points as negative and subjects who are positive for ADA at least 1 time point after drug treatment as positive. The raw values and change from baseline for ADA titers will be summarized by time point and treatment arm using descriptive statistics. The treatment-emerging ADA incidence will be calculated. A treatment-emergent ADA-positive subject will be defined as subjects who are ADA negative at baseline and become ADA positive post-treatment, those who are ADA positive at baseline and post-treatment but have an increase in ADA titer from baseline to post-treatment, or those who have missing ADA data at baseline but become ADA positive posttreatment. The number and percentage of subjects positive for neutralizing anti-drug antibody of T-DXd may be reported.

11.5.8. Other Safety Analyses

All other safety endpoints (eg, ECHO/MUGA) will be listed.

11.6. Interim Analyses

No interim analysis is planned for PFS.

Up to 3 analyses of OS are planned:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant), at which point a total of approximately162 OS events (49% information fraction) in HR-positive subjects are expected.
- If the first OS interim analysis is not significant, a second interim analysis for OS is planned when approximately 233 OS events (70% information fraction) in HR-positive subjects have been documented.
- If the second OS interim analysis is not significant, a final analysis for OS after approximately 333 OS events in HR-positive subjects have been documented.

OS will be compared between the 2 treatment groups at either interim or final analysis, provided superiority in PFS is demonstrated for both the HR-positive cohort and the FAS. A hierarchical testing procedure, as described in Section 11.4.2, will be adopted in this study.

A group sequential design, utilizing 3-look Lan-DeMets alpha spending function with O'Brien - Fleming type stop boundary will be used to construct the efficacy stopping boundaries[33] with an

overall 2-sided significance level of 0.05. The trial allows for the early stopping of the study for a superior OS, provided the log-rank test for PFS has demonstrated statistical significance in both HR-positive cohort and FAS. The same interim efficacy stopping boundaries will be used for OS hypotheses testing with HR-positive cohort and FAS. If the study continues to final analysis, the efficacy stopping boundaries at the final OS analysis to control the 2-sided significance level of the repeated testing at 0.05 will be derived separately for HR-positive cohort and FAS based on the actual number of OS events documented at the cut-off date, and the actual information fractions and the alpha already spent at the interim analyses. This will ensure the overall significance level at 0.05 (2-sided) across the 2 OS hypotheses testing with HR positive cohort and FAS, and the repeated testing of the OS hypotheses at the interim and the final analyses, provided the log-rank test for PFS has demonstrated statistical significance in both the HR-positive cohort and FAS.[34]

The stopping boundaries in p-value and hazard ratio scales, as well as the minimal detectable median OS differences and the cumulative statistical powers, are summarized in Table 11.1.

Table 11.1: Stopping Boundaries at OS Interim and Final Analyses

Analysis Time (months)*	Number of OS Events (information fraction)	HR (p-value) Superiority Boundary[a]	Minimal Detectable Difference in Median OS vs 15 for Control Arm (months)[b]	Cumulative Power when True HR=0.72	Cumulative Power when True HR=0.68
28.3 (FA PFS)	162 (0.49)	0.605 (0.001)	9.8	0.150	0.244
35.2 (IA OS)	233 (0.70)	0.711 (0.007)	6.1	0.466	0.628
49.3 (FA OS)	333 (1.00)	0.792 (0.023)	3.9	0.800	0.909

FA = final analysis; IA = interim analysis; HR= hazard ratio; OS = overall survival; PFS = progression-free survival
* From randomization date of the first subject.
[a] The derived O'Brien-Fleming type superiority stopping boundary.
[b] Minimal detectable differences in median OS are derived based on the hazard ratio boundaries and the median OS for the control arm of 15 months, assuming exponential distributions for OS.

It is recognized that the information fractions at the interim analyses may not be as planned. The stopping boundary will be updated based on the actual information fraction at the interim analyses.

An independent statistician from the designated vendor will perform the interim analyses for the data monitoring committee (DMC) review. For further details, see the DMC Charter.

11.7. Sample Size Determination

This is a prospectively randomized open-label trial to compare the primary endpoint of PFS between the 2 treatment arms, T-DXd and physician's choice with a randomization ratio of 2:1.

Assuming a true hazard ratio of 0.68 (corresponding an improvement in median PFS from the physician's choice arm of 4.2 months [NCT00337103] to a median PFS in T-DXd arm of 6.2 months), a total of 318 PFS events per BICR in HR-positive cohort will be needed to ensure at least 90% power of log-rank test to reject the null hypothesis of no difference in PFS distributions at 2-sided alpha of 0.05 in HR-positive cohort (primary analysis). A total of ~480 HR-positive subjects (~320 T-DXd and ~160 physician's choice) and ~60 HR-negative

subjects (~40 T-DXd and ~20 physician's choice) will be randomized, for a total enrollment of ~540 subjects (~360 T-DXd and ~180 physician's choice).

The primary efficacy analyses will be event driven, and the primary analyses for PFS will be performed when approximately 318 PFS events per BICR have been observed in the HR-positive population. The expected data cutoff dates for the final analyses of PFS will be approximately 28.3 months after the first subject is randomized, based on updated enrollment rates.

The key secondary endpoint of OS will be compared between the 2 treatment groups, provided that the log-rank tests for comparison of PFS in both the HR-positive cohort and the FAS demonstrate statistical significance. Assuming a median OS of 15 months in the control arm[35,36,37,38,39,40] and a hazard ratio of 0.72, a total of 333 OS events is needed to ensure 80% power of a log-rank test to reject a null hypothesis of no difference in OS distributions at an overall 2-sided significance level of 0.05 under a 3-look group sequential design using Lan-DeMets alpha spending function with O'Brien-Fleming type superiority stopping boundary provided PFS is statistically significant. Final OS analysis is projected in approximately 49.3 months from the date of first subject randomized when 333 OS events have been documented in the HR-positive cohort. Approximately 162 (49%) and 233 (70%) out of the target total OS events are projected at the first and the second OS interim analyses in the HR-positive cohort.

The sample size computation was performed using the EAST 6.4.

11.8. Statistical Analysis Process

Statistical analyses of the study will be performed by the designated CRO.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

All statistical analyses will be performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The Sponsor/CRO monitor and Regulatory Authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a Regulatory Authority informs the Investigator that it intends to conduct an inspection, the Sponsor will be notified immediately.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection drug administration, AEs, and final evaluation.

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study.

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedures. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs (or SAEs as appropriate). All study-related data for these subjects will be maintained in the medical records at the site.

The Investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or designee. Data will be vetted both electronically and manually for eCRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness, and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference List Dictionary.

Data that may potentially unblind the treatment assignment (ie, study treatment serum concentrations, ADA, treatment allocation, and study treatment preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent audits.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/IEC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution, and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable Regulatory Authorities. Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/IEC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records, and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All study-related essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the Sponsor or the CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance will be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

Daiichi Sankyo Inc. is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. We will comply with US, European Union, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. We follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)," and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors.[41]

In order to ensure that we are in compliance with the public disclosure policies and the International Council of Medical Journal Editors recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the Sponsor prior to submission.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor, and Welfare Ordinance No. 28 of 27 Mar 1997 and/or;
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal product for human use and/or;
- Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the Regulatory Agency(ies), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study treatments are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB/IEC prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator and/or Sponsor must submit and, where necessary, obtain approval from the IEC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IEC or IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to Regulatory Authorities and implementation of these changes are made only after approval by the relevant regulatory bodies, as needed.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority(ies) in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP noncompliance of which the Investigator becomes aware.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the Regulatory Authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRBs/ECs of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, IECs/IRBs, and Regulatory Authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether or not the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/IEC. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to Regulatory Authorities.

A global protocol amendment will affect study conduct at all study sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/IEC and by Regulatory Authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The Sponsor has the right to terminate the study at any time and study termination may also be requested by (a) competent authority(ies).

15.9. Data Monitoring Committee

An independent DMC will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring the progress and results. The DMC will comprise qualified physicians and scientists who are not Investigators in the study and not otherwise directly associated with the Sponsor.

The DMC will periodically review unblinded safety data in this study. The details about the reviews of the study data and other DMC processes will be described in the DMC charter.

The DMC may recommend modification of the study protocol or study to the Steering Committee based on pre-specified rules described in the DMC charter.

15.10. Address List

A list of key study personnel (including personnel at the Sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and regularly updated as necessary.

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17. APPENDICES

17.1. Schedule of Events

Table 17.1: Schedule of Events – Tissue Screening and Screening Period

Visit	Tissue Screening	Screening	
Window (Days)		**-28 to -1**	**-14 to -1 or as noted**
Procedures			
Tissue Screening Informed Consent [a]	●		
Tumor Tissue Sample for HER2 Status	● [b]		
Main Informed Consent [a]		●	
Tumor Tissue Biopsy (may collect sample anytime between completion of most recent treatment regimen and randomization)		● [c]	
Tumor Tissue Mandatory Exploratory Biomarker		● [d]	
Inclusion/Exclusion			●
Demographics			●
Medical (including smoking) and Surgical History (including target disease)			●
Physical Examination			●
Weight			●
Height			●
ECOG PS			●
Adverse Events	● [e]		●
Concomitant Medications			●
Hospitalization-related Records			●
Vital Signs			●
SpO2			●
12-lead ECG in Triplicate [f]			●
ECHO or MUGA (LVEF) [g]		●	
Ophthalmologic Assessment [h]		●	

Visit	Tissue Screening	Screening	
Window (Days)		**-28 to -1**	**-14 to -1 or as noted**
Procedures			
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease) [i]		●	
CT/MRI of the Brain		●	
Hematology, Clinical Chemistry [j]			●
Coagulation			●
Urinalysis			●
Troponin [k]			●
Sample for Serum Biomarkers (eg, HER2ECD, COVID-19 serology) and Exploratory Biomarkers (eg, cfDNA in plasma)			●
HIV Antibody Test (as required by local regulations or IRBs/IECs) **In Portugal only, please see Section 17.9.2 for text applicable to sites in Portugal**		●	
Hepatitis B/C Serology		●	
Pregnancy Test (urine or serum) [l]			●
Assign Subject Identification Number	●		
Physician Selection of Physician's Choice Paradigm, then Randomization			●

AE = adverse event; COVID-19 = coronavirus disease 2019; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); SAE = serious adverse event; SpO2 = peripheral oxygen saturation.

[a] Tissue screening informed consent must be signed before tumor tissue screening assessments. The main informed consent form must be signed and central HER2 testing confirmed HER2-low status before initiating all other screening assessments. See Section 6.2.

[b] Archived tumor tissue sample appropriate for central laboratory HER2 testing. If archived tumor tissue is not available, a fresh tumor tissue biopsy is required. A sequential screening process should be followed. Tissue screening (see Section 6.1) should be complete before the main screening procedures.

[c] A tumor tissue biopsy after the completion of the subject's most recent treatment regimen is required for retrospective assessment. If the tumor tissue provided for HER2 status testing was collected after completion of the last treatment regimen, an additional new biopsy is not required. If the tumor tissue sample provided for HER2 status testing was collected before completion of the last treatment regimen, an additional new biopsy is required. See Section 6.2 for details.

[d] Additional slides are required for exploratory biomarker analysis. It is preferred if the slides are from the same block as the tissue sample sent for central laboratory HER2 testing.

[e] For subjects who sign only the Informed Consent Form for tumor tissue screening, only SAEs directly related to tissue screening procedure (ie, tumor tissue biopsy) will be reported. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor tissue biopsy will be recorded during tumor tissue screening.

[f] ECG will be taken in triplicate at screening. Subsequent ECGs will be performed in triplicate if an abnormality is noted. ECGs will be taken in close succession while in a supine/semi-recumbent position. ECGs should preferably be performed before blood draws at respective time points.

[g] ECHO or MUGA scan assessments will be performed at Screening. Note that the same test must be used for the subject throughout the study.
In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.

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

[i] A previous tumor assessment scan performed according to standard of care after progression on the previous treatment can be used if performed within 28 days of randomization regardless of date of signed informed consent

[j] Hematology tests include red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils); clinical chemistry tests include total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen/urea, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium.

[k] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening, EOT, and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. An additional sample should be submitted for central laboratory troponin-T testing, and perform ECG. If ECG is abnormal, follow institutional guidelines.

[l] Within 72 hours before randomization for all female subjects of childbearing potential (criteria for non-childbearing potential are defined in Section 4.1) ; a positive urine pregnancy test result must be immediately confirmed using a serum test.

Table 17.2: Schedule of Events – Treatment and Follow-up Period

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Every 6 weeks (±7 d)	EOT[b]	40-Day F/U[c]	Long-term / Survival F/U (±14 d)[d]
	Day 1		Day 8 (±1 d)	Day 15 (±1 d)	Day 1±2 d		Day 1±2 d		Day 1±2 d					
Study Day (Window)	BI[a]	EOI			BI	EOI	BI	EOI	BI	EOI				
Fresh Tumor Tissue Biopsy[e]							●					●		
HEOR Outcomes: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L [f]	●[h]				●[h]		●[h]		●[h]			●	●	●[g]
Physical Examination	●[h]				●[h]		●[h]		●[h]			●	●	
Weight	●[h]				●[h]		●[h]		●[h]			●	●	
ECOG PS	●[h]				●[h]		●[h]		●[h]			●	●	
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	—	→	
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	—	→	
Hospitalization-related Records	←	—	—	—	—	—	—	—	—	—	—	—	→	
Vital Signs [i]	●[h]	●[j]	●	●	●[h]	●[j]	●[h]	●[j]	●[h]	●[j]		●	●	
SpO2	●[h]	●[j]	●	●	●[h]	●[j]	●[h]	●[j]	●[h]	●[j]		●	●	
12-lead ECG [k]	●[h]	●			●[h]		●[h]		●[h]			●		
ECHO or MUGA (LVEF) [l]									●			●		
Ophthalmologic Assessment [m]												●		
Pregnancy Test [n]	●				●		●		●			●	●	

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Every 6 weeks (±7 d)	EOT[b]	40-Day F/U[c]	Long-term / Survival F/U (±14 d)[d]
	Day 1		Day 8 (±1 d)	Day 15 (±1 d)	Day 1±2 d		Day 1±2 d		Day 1±2 d					
Study Day (Window)	BI[a]	EOI			BI	EOI	BI	EOI	BI	EOI				
Hematology & Blood Chemistry Tests [o]	● [h]		●	●	● [h]		● [h]		● [h]			●	●	
Coagulation												●		
Troponin [p]												●		
PK Blood (Serum) Sample only for T-DXd Arm	● [q]	●[r,s]			● [q]	● [r]	● [q]	● [r]	● [q]	● [r]				
PK Sampling for CQ/HCQ Administration[bb]	If CQ or HCQ is administered for COVID-19, additional PK blood samples should be collected at the following visits: • Prior to the first CQ or HCQ dose (Day 1) • Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) • Last day of the CQ/HCQ treatment prior to CQ/HCQ dose (within 4h) The day of T-DXd resumption, after the CQ/HCQ washout period[cc], (within 8h BI of T-DXd)													
ADA Blood Sample only for T-DXd Arm	● [t]				● [t]				● [t]				● [u]	● [u]
Serum Biomarkers (eg, HER2ECD, COVID-19 serology[dd]) Sample							● [v]		● [v,ee]			●		
Exploratory Biomarker Blood Samples [w]	●[h]								●			●		
Pharmacogenomics Blood Sample [x]	●													

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Every 6 weeks (±7 d)	EOT[b]	40-Day F/U[c]	Long-term / Survival F/U (±14 d)[d]
	Day 1		Day 8 (±1 d)	Day 15 (±1 d)	Day 1±2 d		Day 1±2 d		Day 1±2 d					
Study Day (Window)	BI[a]	EOI			BI	EOI	BI	EOI	BI	EOI				
Administer Study Treatment, as Appropriate [y]	•				•		•		•					
Tumor Assessment [y,z]											•	•		•
CT/MRI of the Brain [y,aa]											•	•		
Survival Follow-up														•

ADA = anti-drug antibody; BI = before infusion or dosing; cfDNA = cell free deoxyribonucleic acid; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; d = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion or dosing; EORTC QLQ = European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-5L = EuroQol 5 dimensions 5 levels [of severity]; EOT = end of treatment; F/U = follow-up; HCQ = hydroxychloroquine; HEOR = Health Economics and Outcomes Research; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PK = pharmacokinetic; SpO2 = peripheral oxygen saturation.

[a] First dose at Cycle 1 Day 1 should occur within 7 days after the date the subject is randomized.

[b] All assessments required as part of EOT must occur within 7 days from the date the Investigator decides to discontinue study treatment. See Section 6.5 for whether new tests need to be conducted.

[c] 40 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. See Section 6.6.1 to determine whether new tests need to be conducted. If EOT assessments occur >40 days (+7 days) after last treatment, then the EOT assessments can also function as the 40-Day (+7 days) Follow-up assessments.

[d] Long-term/Survival Follow-up visits will be performed every 3 months (±14 days) from the date of 40-Day (+7 days) Follow-up assessments until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

[e] Participation is optional for all subjects. The optional fresh tumor tissue biopsy during treatment should be performed at Cycle 3 Day 1 (±7 days) and EOT.

[f] Done at Cycle 1, Cycle 2, and Cycle 3 and then every 2 cycles (eg, Cycles 5, 7, 9, etc) during the treatment period. Subject must complete the HEOR outcomes questionnaires before any other assessments or procedures are done on the day of clinic visit.

[g] Performed only 3 months after the 40-Day (+7 days) Follow-up assessments.

[h] Within 72 hours before administration.

[i] Vital signs and SpO2 will be done at all cycles before and after an infusion. For the comparator arm, vital signs and SpO2 is required only at Day 1 of each cycle. For capecitabine, no end of infusion assessment is required.

[j] T-DXd arm only

[k] At Cycle 1 Day 1 for T-DXd subjects only, record ECG 5 hr (± 2 hr) after start of drug administration. If at any time during the study an abnormality is noted, perform ECG. ECGs will be taken in close succession while subject is in a supine/semi-recumbent position. ECGs should preferably be performed before blood draws at respective time points.

[l] For ECHO or MUGA scan assessments (**Note:** The same test must be used for the subject throughout the study) will be performed BI on Day 1 of every 4 cycles (±7 days) (Cycle 5, 9, 13, etc).
In Germany only, please see Section 17.9.3 for text applicable to sites in Germany.

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

[n] For female subjects of childbearing potential, perform a urine or serum pregnancy test. A positive urine pregnancy test result must immediately be confirmed using a serum test. Must be performed within 72 hours of drug administration.

[o] Laboratory tests: Hematology tests include red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and chemistry tests include total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen/urea, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium.

[p] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening, EOT, and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction (MI), or other causes of myocyte necrosis. An additional sample should be submitted for central laboratory troponin-T testing. Perform ECG. If ECG is abnormal, follow institutional guidelines.

[q] For T-DXd subjects only, PK samples should be obtained within 8 hours BI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8.

[r] For T-DXd subjects only, preferably within 15 minutes or as soon as possible after EOI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8.

[s] For T-DXd subjects only, 5 hours (±2 hours) after the start of drug administration.

[t] For T-DXd subjects only, ADA samples should be taken within 8 hours BI on Day 1 in Cycles 1, 2, and 4, and then every 4 cycles (Cycles 8, 12, 16, etc)

[u] For subjects with positive ADA at the 40-Day (+7 days) F/U assessment, additional serum ADA samples may be collected every 3 months (±1 month) up to 1 year from the last dose of study drug, until the ADA becomes negative, until the ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), until the subject starts another therapy for cancer or withdraws consent from the study, whichever occurs first.

[v] Before administration at every 2 cycles from Cycle 3 (Cycle 3, 5, 7, 9, etc).

[w] Samples will be collected at Cycle 1 and then every 3 cycles (Cycles 4, 7, etc) until EOT for exploratory biomarkers such us cfDNA in plasma.

[x] A single blood sample for pharmacogenomics analysis will be collected from each subject who consents to this test, predose on Day 1 of Cycle 1 Day 1. Participation in this part of the study is optional for all subjects.

[y] T-DXd is to be administered every 21 days ±2 days unless dose interruption/modification or discontinuation is required. For the control treatment arm, if a subject receives a comparator with a regimen other than a 21-day cycle, the Investigator should ensure that the subject follows the study-defined Schedule of Events per a 28-day cycle. However, tumor assessments and CT/MRI of the brain must be performed every 6 weeks ±7 days from randomization date. Laboratory and safety assessment before drug administration should be appropriately performed according to label approved in the country of drug administration.

[z] If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.

[aa] CT or MRI of the brain is mandatory for all subjects who were enrolled with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated. CT/MRI will be performed every 6 weeks ±7 days from randomization date, and at EOT.

[bb] If subject provides consent, samples should be collected.

[cc] A washout period of more than14 days since last dose of CQ/HCQ is required before restarting T-DXd. See Section 17.8.

[dd] If subject provides consent, samples should be collected prior to study drug infusion. For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 17.8.

[ee] COVID-19 serology testing to be performed starting at Cycle 5, Day 1 and every 4 cycles thereafter.

For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending evaluation.

Evaluations should include:

- High resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests and pulse oximetry (SpO2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK (central laboratory) analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

17.2. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl) rate (mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight (1 kilogram = 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units – serum creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

17.3. New York Heart Association

Table 17.3: New York Heart Association Functional Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American heart Association. Classification of Functional Capacity and Objective Assessment. Available from:
http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

17.4. Eastern Cooperative Oncology Group (ECOG) Performance Status

Table 17.4: Eastern Cooperative Oncology Group Performance Status Scale Grade Description

0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

17.5. Modified Response Evaluation Criteria in Solid Tumors (version 1.1)

17.5.1. Measurability of Tumor at Baseline

17.5.1.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

17.5.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by computed tomography (CT)/ magnetic resonance imaging (MRI) scan (CT scan slice thickness no greater than 5 mm).
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up (ie, all on-study measurements), only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.5.1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly non-measurable lesions are considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

17.5.1.1.3. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

17.5.1.1.3.1. Bone lesions

Bone scan, positron emission tomography scan or plain films 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, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

17.5.1.1.3.2. Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.5.1.1.3.3. Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion since the therapy.

17.5.1.2. Specifications by Methods of Measurements

17.5.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before randomization.

17.5.1.2.2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. The MRI is also acceptable in certain situations (eg, for body scans).

17.5.2. Tumor Response Evaluation

17.5.2.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

In this study, only subjects with measurable disease at baseline should be included in the study.

17.5.2.2. Baseline Documentation of 'Target' and 'Nontarget' Lesions

When more than 1 measurable lesion is present at baseline all lesions up to a total of 2 lesions per organ and a maximum of 5 lesions total (representative of all involved organs, with a maximum of 2 per organ) should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum of lesion diameters. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Up to 2 nodal target lesions can be recorded. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded.

A sum of the diameters (longest diameter for non-nodal lesions, short-axis diameter for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

17.5.2.3. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

17.5.2.4. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum of diameters must also

demonstrate an absolute increase of at least 5 mm. (**Note:** The appearance of one or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR (taking as reference the sum of diameters at baseline) nor sufficient increase to qualify for PD (taking as reference the smallest sum of diameters while on study).

17.5.2.4.1. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure.' When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (**Note:** It is less unlikely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro-peritoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness.) The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

17.5.2.5. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Progressive Disease: Unequivocal progression (see comments below) of existing non-target lesions. (**Note:** The appearance of one or more new lesions is also considered progression.)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

17.5.2.5.1. Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions 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 PR of target disease will therefore be rare.

When the subject has only non-measurable disease: The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in "volume" [which is equivalent to a 20% increase diameter in a measurable lesion]). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that time point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

17.5.2.6. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of brain that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan that indicated its presence.

17.5.2.7. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

17.5.2.7.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.5 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 17.5: Time Point Response: Subjects with Target (+/–Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Time Point Response[1]
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR[2]
PR	NE	No	PR[2]
PR	CR	No	PR
PR	Non-CR/Non-PD	No	PR
SD	NE	No	SD[2]
SD	CR	No	SD
SD	Non-CR/Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	NA[4]	No	CR
PR	NA[4]	No	PR
SD	NA[4]	No	SD
NA[3]	Non-CR/Non-PD	No	Non-CR/Non-PD
NA[3]	CR	No	CR
NA[3]	NE	No	NE
NA[3]	NA[4]	No	NE

CR = complete response; NA = not applicable; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[1] Identification of new lesions at a post-Baseline time point will result in a time point response (TPR) of PD. If an identified new lesion subsequently becomes NE, the TPR will be recorded as PD unless the new lesion has proven to have resolved. Note: TPRs assessed after a progression event will not contribute to the determination of the Best Response.

[2] If a non-target lesion is classified as NE, a designation of PR or SD may be assigned based on information from the target lesions.

[3] No target lesions identified at Baseline.

[4] No non-target lesions identified at Baseline.

17.5.2.7.2. Missing Assessments and Non-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

17.5.2.7.3. Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known.

The best overall response is the best response recorded from the start of the study treatment until the EOT. When SD is believed to be best response, it must also meet the protocol-specified minimum time of 5 weeks from Cycle 1 Day 1. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second, and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered non-evaluable.

17.5.2.7.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR might not have a total sum of diameters of "zero" on the eCRF.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

17.5.2.8. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at Screening, and then at the intervals specified or sooner if clinically indicated. Tumor measurement will be performed during the EOT assessments if it was not done within the previous 6 weeks (±7 days) or the previous assessment demonstrated disease progression.

Baseline tumor assessments must be performed within 28 days of randomization.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of chest, abdomen, and pelvis at Screening period. A CT or MRI of the brain is mandatory for all subjects included with baseline

stable brain metastases. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. Follow-up evaluations should include all sites of disease identified at Screening and any other locations if PD is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

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

17.6. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45

17.6.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

17.6.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire BR45

ENGLISH

EORTC QLQ-BR45

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Have you had a dry mouth?	1	2	3	4
32.	Have food and drink tasted different than usual?	1	2	3	4
33.	Have your eyes been painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you have lost any hair: Have you been upset by the loss of your hair?	1	2	3	4
36.	Have you felt ill or unwell?	1	2	3	4
37.	Have you had hot flushes?	1	2	3	4
38.	Have you had headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
41.	Have you had problems looking at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Have you worried about your health in the future?	1	2	3	4

During the past four weeks:		Not at All	A Little	Quite a Bit	Very Much
44.	Have you been interested in sex?	1	2	3	4
45.	Have you been sexually active (with or without intercourse)?	1	2	3	4
46.	Has sex been enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Have you had any pain in your arm or shoulder?	1	2	3	4
48.	Have you had a swollen arm or hand?	1	2	3	4
49.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Has the area of your affected breast been swollen?	1	2	3	4
52.	Has the area of your affected breast been oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4
54.	Have you sweated excessively?	1	2	3	4
55.	Have you had mood swings?	1	2	3	4
56.	Have you been dizzy?	1	2	3	4
57.	Have you had soreness in your mouth?	1	2	3	4
58.	Have you had any reddening in your mouth?	1	2	3	4
59.	Have you had pain in your hands or feet?	1	2	3	4
60.	Have you had any reddening on your hands or feet?	1	2	3	4
61.	Have you had tingling in your fingers or toes?	1	2	3	4
62.	Have you had numbness in your fingers or toes?	1	2	3	4
63.	Have you had problems with your joints?	1	2	3	4
64.	Have you had stiffness in your joints?	1	2	3	4
65.	Have you had pain in your joints?	1	2	3	4
66.	Have you had aches or pains in your bones?	1	2	3	4
67.	Have you had aches or pains in your muscles?	1	2	3	4
68.	Have you gained weight?	1	2	3	4
69.	Has weight gain been a problem for you?	1	2	3	4

Please go on to the next page

During the past four weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
70. Have you had a dry vagina?	1	2	3	4
71. Have you had discomfort in your vagina?	1	2	3	4

Please answer the following two questions only if you have been sexually active:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
72. Have you had pain in your vagina during sexual activity?	1	2	3	4
73. Have you experienced a dry vagina during sexual activity?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
74. Have you been satisfied with the cosmetic result of the surgery?	1	2	3	4
75. Have you been satisfied with the appearance of the skin of your affected breast (thoracic area)?	1	2	3	4

Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the past week?	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
76. _____	1	2	3	4
77. _____	1	2	3	4
78. _____	1	2	3	4

17.7. EuroQoL Five Dimensions Five Levels

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

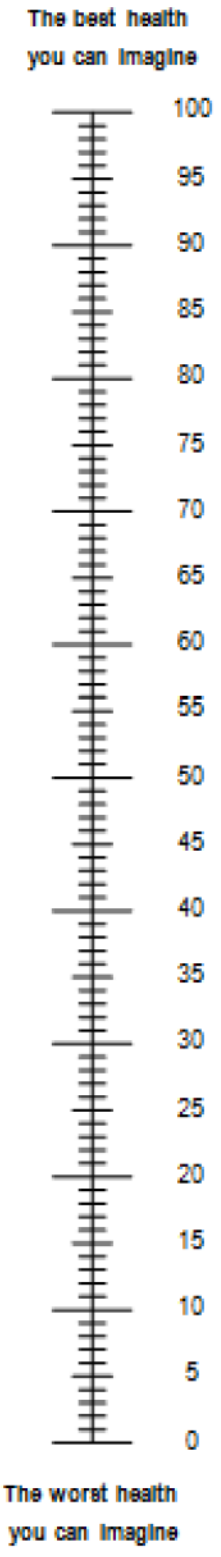
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)

Inclusion criterion

- Has adequate treatment washout period before randomization/enrollment, defined as chloroquine/hydroxychloroquine: >14 days

Prior and Concomitant Medications

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 treatment must be interrupted. If chloroquine or hydroxychloroquine is administered, then a washout period of >14 days is required before restarting study treatment.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected from each subject who provides consent, if chloroquine or hydroxychloroquine is administered for COVID-19, at the time points specified in the Schedule of Events (Table 17.2).

The chloroquine or hydroxychloroquine administration and the exact time of blood sample collection for PK analysis must be recorded on the eCRF (Table 17.2).

Dose modification criteria for suspected or confirmed COVID-19

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.**

Dose modification criteria

If COVID-19 infection is suspected, interrupt T-DXd and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 5.3.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, manage COVID-19 per local guidance until recovery of COVID-19, defined as no signs/symptoms, at least 1 negative real-time polymerase chain reaction (RT-PCR) test result,[a] and nearly or completely resolved chest CT findings. Then follow below dose modifications:
  - If Grade 1, resume T-DXd at the same dose;
  - If Grade 2,
    - Maintain same dose if chest CT findings are completely resolved;[b]
    - Reduce dose 1 level if chest CT findings are nearly resolved.[b]
  - If Grade 3,
    - Reduce dose 1 level if chest CT findings are completely resolved;[b]
    - Discontinue study drug if chest CT findings are **not** completely resolved;
  - If Grade 4, discontinue study treatment.

[a] All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT PCR test is not available at the site, the participant must not have any signs or symptoms of COVID-19 infection for at least 2 weeks and nearly or completely resolved chest CT findings. Alternatively, a sample kit may be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory.

[b] Closely monitor signs/symptoms after restarting T-DXd, initially with a telephone call every 3 days for the first week, and then with a weekly telephone call thereafter, for a total of 6 weeks.

In addition to the recommendations outlined 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 a drug-related ILD, manage per protocol ILD management guideline.

COVID-19 Serum Biomarker Assessment(s)

Serum samples will be used for COVID-19 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, will be shipped to a central laboratory and stored there until the tests become available.

If subjects consent, the remaining serum samples will also be stored for future analysis.

Serum sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of COVID-19

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the statistical analysis plan.

17.9. Country-Specific Protocol Text

This appendix lists protocol text italicized, underlined, and bolded that applies only to 1 country as specified below. Protocol text removed in only 1 country is shown in strikethrough as specified below.

17.9.1. Sweden Only

The italicized, underlined, and bolded text below is applicable to sites in Sweden.

In each section below in the secondary efficacy objectives and endpoints, HER2-low subjects are specified. Text specific to Sweden is shown italicized, underlined, and bolded below and all other text remains the same.

Section 2.1.2 Key Secondary Objectives

The key secondary objectives ***for HER2-low (IHC 1+ or IHC 2+/ISH-) subjects*** are:

- To compare the PFS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive, and HR-negative breast cancer), based on BICR
- To compare the OS benefit of T-DXd to physician's choice in HER2-low, HR-positive breast cancer
- To compare the OS benefit of T-DXd to physician's choice in all randomized subjects (HER2-low, HR-positive, and HR-negative breast cancer)

Section 2.1.3 Other Secondary Objectives

- To investigate the efficacy of T-DXd compared to physician's choice ***for HER2-low (IHC 1+ or IHC 2+/ISH-) subjects*** on the following parameters:
  - PFS in HR-positive subjects, based on Investigator assessment
  - Confirmed ORR, based on BICR in HR-positive subjects
  - DoR, based on BICR in HR-positive subjects
  - Confirmed DoR in all subjects, regardless of HR status.

Section 2.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints ***for HER2-low (IHC 1+ or IHC 2+/ISH-) subjects*** are:

- PFS, based on BICR, in all randomized subjects
- OS in HR-positive breast cancer subjects
- OS in all randomized subjects

Section 2.3.3 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints ***for HER2-low (IHC 1+ or IHC 2+/ISH-) subjects*** are:

- PFS, based on Investigator assessment
- Confirmed ORR, based on BICR and Investigator assessment

- DoR, based on BICR

Section 7.1.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints ***for HER2-low subjects*** are:

- PFS, based on BICR, in all randomized subjects
- OS in HR-positive breast cancer subjects
- OS in all randomized subjects

Section 7.1.3 Other Secondary Efficacy Endpoints

In the other secondary efficacy endpoints, HER2-low subjects are specified. Text specific to Sweden is shown italicized, underlined, and bolded below and all other text remains the same.

Other secondary efficacy endpoints ***for HER2-low subjects*** include:

- PFS, based on Investigator assessment
- Confirmed ORR, defined as the sum of CR rate and PR rate, based on BICR and Investigator assessment, and confirmed by a second assessment.
- DoR, defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression, based on BICR, or death. Duration of response will be measured for responding subjects (PR or CR) only. Subjects who are progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment.

17.9.2. Portugal Only

The italicized, underlined, and bolded text below is applicable to sites in Portugal.

Section 4.1 Inclusion Criteria

Inclusion criterion #14 is amended to specify that subjects with hormone receptor (HR)-positive tumors must not use hormonal contraceptives to prevent pregnancy and must choose one of the other methods listed. Text specific to Portugal is shown italicized, underlined, and bolded below and all other text remains the same.

14 Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and after the last dose of T-DXd for at least 7 months for females or 4.5 months for males or according to the label approved in the country of drug administration for the physician's choice treatments.[20] ***Subjects with HR-positive tumors must not choose hormonal contraceptives to prevent pregnancy and must choose one of the other methods listed below.*** Male subjects must agree to inform all female partners that they are participating in a clinical trial that may cause birth defects. Methods considered as highly effective methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral

  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- The reliability of complete sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Subjects in this study should refrain from heterosexual intercourse during and upon completion of the study and for at least 7 months for females or 4.5 months for males after the last dose of T-DXd or according to the label approved in the country of drug administration for the physician's choice treatment. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Non-childbearing potential is defined as premenopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Section 4.2 Exclusion Criteria

Testing for human immunodeficiency virus (HIV) is amended to specify HIV testing is required. In the exclusion criterion #12, text is removed as shown in strikethrough below and all other text remains the same.

12. Has known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Subjects should be tested for HIV prior to randomization ~~as required by local regulations or IRB/IEC~~.

Section 6.2 Screening

Testing for human immunodeficiency virus (HIV) is amended to specify HIV testing is required. In the screening procedures, text is removed as shown in strikethrough below and all other text remains the same.

The following activities and/or assessments will be performed **within 28 days before randomization** during the screening period:

- Perform an HIV antibody test~~Unless required by local regulations or IRB/IEC, an HIV antigen/antibody test is not required prior to randomization/enrollment.~~

Section 17.1 Schedule of Events

Testing for human immunodeficiency virus (HIV) is amended to specify HIV testing is required. In the Table 17.1, text is removed as shown in strikethrough below and all other text remains the same.

HIV Antibody Test ~~(as required by local regulations or IRBs/IECs)~~		•	

17.9.3. Germany Only

The italicized, underlined, and bolded text below is applicable to sites in Germany.

In each section below, clarification is added that echocardiogram (ECHO) is the preferred LVEF assessment modality. A multigated acquisition (MUGA) scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement).

Text specific to Germany is shown italicized, underlined, and bolded. Deleted text is shown in strikethrough. All other text remains the same.

Section 6.2 Screening

- Perform an ECHO ~~or MUGA~~. **Note:** The same test must be used for the subject throughout the study. ***ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Section 6.4.2 Every 4 Cycles (±7 days) After Cycle 1

- Perform an ECHO ~~or MUGA (**Note:** The same test must be used for the subject throughout the study)~~ before infusion at Cycle 5, 9, 13, etc. ***Note: The same test must be used for the subject throughout the study. ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Section 6.5 End of Study Treatment

- Perform an ECHO ~~or MUGA~~. **Note:** The same test must be used for the subject throughout the study. ***ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Section 9.3.2.2 Management Guidance

Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. ***Note: The same test must be used for the subject throughout the study. ECHO will be the preferred LVEF assessment modality, as a less invasive procedure* avoiding *study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Section 9.12.1 Cardiac Assessments

Either ECHO or MUGA will be performed as described in the Schedule of Events (Table 17.1 and Table 17.2); LVEF will be measured. ***Note: The same test must be used for the subject throughout the study. ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Section 17.1 Schedule of Events

Table 17.1 Schedule of Events – Tissue Screening and Screening Period

[e] ECHO ~~or MUGA scan~~ assessments will be performed at Screening. Note that the same test must be used for the subject throughout the study. ***ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***

Table 17.2 Schedule of Events – Treatment and Follow-up Period

[k] ECHO ~~or MUGA scan~~ assessments will be performed BI on Day 1 of every 4 cycles (±7 days) (Cycle 5, 9, 13, etc). Note that the same test must be used for the subject throughout the study. ***ECHO will be the preferred LVEF assessment modality, as a less invasive procedure avoiding study subjects' exposure to ionizing radiation. MUGA scan may be used only if ECHO examination is not indicated per subject's clinical condition (eg, higher accuracy and reproducibility of assessment are required per investigator's judgement). In case MUGA is the assessment modality of choice, a sound medical rationale for selecting it must be provided and properly documented.***