

Protocol

Protocol for: Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022;387:9-20. DOI: 10.1056/NEJMoa2203690

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

CLINICAL STUDY PROTOCOL

**A PHASE 3, MULTICENTER, RANDOMIZED,
OPEN-LABEL, ACTIVE-CONTROLLED TRIAL OF
DS-8201A, AN ANTI-HER2-ANTIBODY DRUG
CONJUGATE (ADC), VERSUS TREATMENT OF
PHYSICIAN'S CHOICE FOR HER2LOW,
UNRESECTABLE AND/OR METASTATIC BREAST
CANCER SUBJECTS**

DS8201-A-U303

IND NUMBER 127553

EudraCT NUMBER 2018-003069-33

VERSION 1.0, 23 August 2018

Daiichi Sankyo Inc.

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CRITICAL STUDY CONTACT LIST

Sponsor (United States)	Daiichi Sankyo Inc. 211 Mt Airy Rd Basking Ridge, NJ 07920 USA
Sponsor (Japan)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan

INVESTIGATOR AGREEMENT

A Phase 3, multicenter, randomized, open-label, active-controlled trial of DS-8201a, an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects

Sponsor Approval:

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

PPD

PPD

Print Name

Signature

Director, Global Oncology R&D

27 Aug 2018

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)

PROTOCOL SYNOPSIS

EudraCT:	2018-003069-33
IND Number:	127553
Protocol Number:	DS8201-A-U303
Investigational Product:	DS-8201a
Active Ingredients:	DS8201a consists of an antibody component, MAAL9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA1181a
Study Title:	A Phase 3, multicenter, randomized, open-label, active-controlled trial of DS-8201a, an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects
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:	<p><u>Primary Objective:</u></p> <ul style="list-style-type: none">• To compare the progression-free survival (PFS) benefit of DS-8201a to physician's choice in HER2-low, hormone receptor (HR)-positive breast cancer, based on blinded independent central review (BICR) <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none">• To investigate the efficacy of DS-8201a compared to physician's choice on the following parameters:<ul style="list-style-type: none">PFS in HR-positive subjects, based on Investigator assessmentOverall survival (OS) in HR-positive subjectsConfirmed objective response rate (ORR), based on BICR and Investigator assessment in HR-positive subjectsDuration of response (DoR), based on BICR and Investigator assessment in HR-positive subjectsPFS, OS, ORR, and DoR in all subjects, regardless of HR

status.

- To determine pharmacokinetics (PK) of DS8201a
- To evaluate safety of DS8201a compared to physician's choice of treatment
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for DS8201a compared to physician's choice

Exploratory Objectives:

- To evaluate clinical benefit rate (CBR; the sum of complete response [CR] rate, partial response [PR] rate, and longer than 6 months' stable disease rate) based on BICR and Investigator assessment
- To evaluate disease control rate (DCR), based on BICR and Investigator assessment
- To evaluate time to response (TTR), based on BICR and Investigator assessment
- To evaluate potential biomarkers of response/resistance
- To evaluate exposure-response relationships for efficacy and safety endpoints

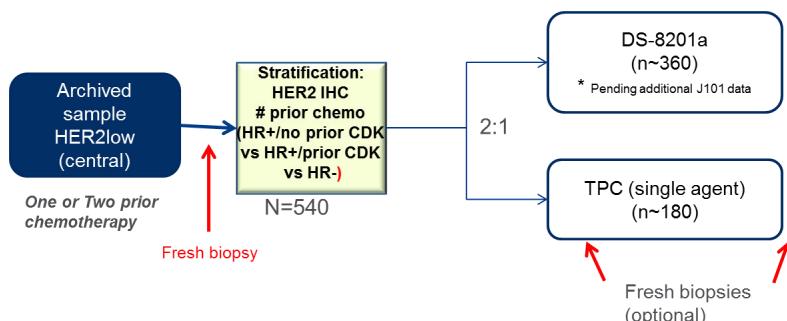
Study Design:	<p>This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of DS8201a versus the physician's choice in HER2-low, unresectable and/or metastatic breast cancer subjects.</p> <p>The study is expected to enroll ~360 DS-8201a subjects and ~180 physician's choice subjects. After ~60 HR-negative subjects have been enrolled, further enrollment will be limited to only subjects who have HR-positive disease. After ~240 HR-positive subjects who have not had prior therapy with a cyclin-dependent kinase (CDK) 4/6 inhibitor have been enrolled, further enrollment will be limited to only subjects who have had prior therapy with a CDK4/6 inhibitor.</p> <p>The ~540 subjects will be randomized 2:1 to DS8201a versus the physician's choice of 1 of the following drugs:</p> <ul style="list-style-type: none">• Capecitabine• Eribulin• Gemcitabine• Paclitaxel
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- Nab-paclitaxel

Randomization will be stratified by:

- HER2 immunohistochemistry (IHC) status of archived 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

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. The end of the study hypothesis-testing period is defined as the date when approximately 318 PFS events per BICR have been observed in the HR-positive population. There will be a 40-Day (+7 days) Follow-up Visit after the last study treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up visits every 3 months (± 14 days) from the date of the 40-Day (+7 days) Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.
Study Centers and Location:	Approximately 161 sites, including but not limited to, North America, Western Europe, and Asia.

Subject Eligibility Criteria:	<p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none">• 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:<ul style="list-style-type: none">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 American Society of Clinical Oncology College of American Pathologists (ASCO-CAP) guidelines evaluated at a central laboratory.Is HR-positive or HR-negative. After ~ 60 HR-negative subjects are enrolled, further enrollment will be limited to only subjects who are HR-positive (either estrogen receptor positive or progesterone receptor positive per ASCO-CAP guidelines)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. After ~ 240 HR-positive subjects have been enrolled who have not had prior therapy with a CDK4/6 inhibitor, further enrollment of HR-positive subjects will be limited to subjects who have had prior therapy with a CDK4/6 inhibitor.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 ISH+) on prior pathology testing (per ASCO-CAP guidelines).Was never previously treated with anti-HER2 therapy.• Documented radiologic progression (during or after most recent treatment).• Must have an adequate archival tumor sample available for assessment of HER2 status by central laboratory (based on most recent available tumor tissue sample). If archival tissue is
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not available, a fresh biopsy is required.

- All subjects must have a recent tumor sample after the most recent treatment regimen or agree to undergo a tissue biopsy prior to randomization.
- 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
- Left ventricular ejection fraction (LVEF) $\geq 50\%$
- Adequate renal function, defined as:

Creatinine clearance ≥ 30 mL/min, as calculated using the CockcroftGault equation
- Adequate hepatic function, defined as:

Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) $\leq 5 \times$ upper limit of normal (ULN)
Total bilirubin $\leq 1.5 \times$ ULN if no liver metastases or $< 3 \times$ 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:

- Ineligible for all 5 of the options in the physician's choice arm either because of previously receiving treatment in the metastatic setting with the comparator or having a contraindication to treatment
 - 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 12lead 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 and 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:	DS-8201a for injection 100 mg, CCI DP: A DS-8201a CCI containing 100 mg of DS-8201a in a glass vial. DS-8201a 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 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 locally approved label. The physician's choice needs to be predefined, prior to randomization, from the following options: <ul style="list-style-type: none">• Capecitabine• Eribulin• Gemcitabine• Paclitaxel• Nab-paclitaxel
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Study Endpoints:	<u>Primary Efficacy Endpoint:</u> <ul style="list-style-type: none">• PFS, based on BICR <u>Secondary Efficacy Endpoints:</u> <ul style="list-style-type: none">• PFS, based on Investigator assessment• OS• Confirmed ORR, based on BICR and Investigator assessment• DoR, based on BICR and Investigator assessment <u>Exploratory Efficacy Endpoints:</u> <ul style="list-style-type: none">• CBR, based on BICR and Investigator assessment
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- DCR, based on BICR and Investigator assessment
- TTR, based on BICR and Investigator assessment

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 DS-8201a, total anti-HER2 antibody, and MAAA-1181a

Biomarker Endpoints:

- Serum biomarkers (eg, HER2 extracellular domain)
- Other potential biomarkers (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 due to 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 (DS8201a vs. physician's choice). Up to ~40 DS-8201a subjects and up to ~20 physician's choice subjects will be HR-negative.
Statistical Analyses:	<p>The primary analyses for PFS will be performed when ~318 PFS events per BICR are observed in the HR-positive population, which is expected to occur in ~16 months.</p> <p>Efficacy Analyses</p> <p>The primary efficacy analyses will be performed for the Intent-to-treat Analysis Set that consists of all randomized HR-positive subjects, including those who did not receive a dose of study treatment. The primary efficacy endpoint is PFS per BICR.</p> <p>Progressionfree 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 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.</p> <p>The primary efficacy analysis will compare PFS of HR-positive subjects between the 2 treatment arms in the ITT HR-positive Analysis Set using a stratified log-rank test. Stratification factors used for primary analysis will be pre-specified in the Statistical Analysis Plan. The PFS will be tested for statistical significance at a 1-sided alpha of 0.025. KaplanMeier estimates and survival curves will also be presented for each treatment arm. The median event times and 2sided 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.</p> <p>Analysis of the secondary efficacy endpoints is described in the following paragraphs. To control the overall type-I error, endpoints will be tested in the following order:</p> <ul style="list-style-type: none">• PFS per BICR based on ITT (HR-positive)• PFS per BICR based on ITT (Total)• OS based on ITT (HR-positive)• OS based on ITT (Total) <p>Overall survival is defined as the time from the date of randomization to the date of death for any cause. If there is no</p>

death reported for a subject before the data cutoff date for PFS analysis, OS will be censored at the last contact date at which the subject is known to be alive. Overall survival will be compared using a stratified log-rank test. Kaplan-Meier estimates and survival curves will also be presented for each treatment arm.

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 and Investigator assessment, 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

The HEOR endpoints based on the following patient reported outcome questionnaires will be summarized descriptively. For EORTC QLQ-C30 and EORTC QLQ-BR45: changes from baseline over time on the global quality of life scale, the functioning scales, symptom scales, and single item scales of the QLQC30 and in each of the subscales of BR45. Time to deterioration will be assessed for key symptoms. For EQ5D5L: visual analogue scale, all 5 dimensions and associated utility scores; and for health care resource utilization: time to hospitalization as well as reason, discharge diagnosis, intensive care unit stay, and length of stay will be reported.

Pharmacokinetic Analyses

Descriptive statistics will be provided for all serum concentration data (DS-8201a, 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 DS-8201a, and if appropriate, total anti-HER2 antibody and MAAA-1181a, will be characterized, including available PK data from other DS-8201a 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 popPK- and pop-PK/pharmacodynamic models may be reported separately from the clinical study report.

Biomarker Analyses

A mandatory fresh tissue sample will be obtained after discontinuation of the most recent prior treatment regimen and before treatment with DS-8201a, and 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 due to 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.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibody
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 _{0-21d}	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
BICR	blinded independent central review
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
cfDNA	cell free deoxyribonucleic acid
CCI	CCI
CI	confidence interval
C _{max}	maximum plasma/serum concentration
CONSORT	Consolidated Standards of Reporting Trials
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
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]
GCP	Good Clinical Practice
GEJ	gastric/gastroesophageal junction
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
ITT	intent-to-treat
IV	intravenous(ly)
IXRS	Interactive Web/Voice Response System
LVEF	left ventricular ejection fraction
CCI	CCI

ABBREVIATION	DEFINITION
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
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
pop-PK	population pharmacokinetics
PPS	Per-protocol Analysis Set
PR	partial response
PRO	patient reported outcome
PT	preferred term
RES	Response Evaluable Set
QoL	quality of life
QTc	corrected QT interval
QTcF	QT intervals corrected for heart rate by Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	stable disease
SID	subject identification
SOP	standard operating procedure
SpO ₂	peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction

ABBREVIATION	DEFINITION
t _½	terminal elimination half-life
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
T _{max}	time to 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.¹ 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.¹

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 hormone receptor (HR)-positive, HER2-negative breast cancer are for 3 rounds of endocrine therapy with the inclusion of a cyclin-dependent kinase (CDK) 4/6 inhibitor. Once a tumor is endocrine refractory, single-agent chemotherapies are recommended.

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.² 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.

1.1.1. Investigational Product

1.1.1.1. Name

DS-8201a

1.1.1.2. Description

DS-8201a 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 DS-8201a is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm after it binds to the HER2 receptor and gets internalized in tumor cells.

The [REDACTED] CCI DP) form of DS-8201a will be administered in this study.

The DS-8201a Phase 1 clinical study DS8201-A-J101 was initiated with the antibody component, MAAL-9001, [REDACTED] CCI DP1). To support new clinical studies, [REDACTED] CCI transition was made to MAAL-[REDACTED] CCI DP2). Analytic comparison of the 2 [REDACTED] CCI products has shown comparability across a wide range of variables. Minor differences have been observed in glycan profile, charge variants, size variants, FcγRIIA binding, FcRn binding, and antibody-dependent cellular cytotoxic activity. Following single intravenous (IV) administration of DS-8201a to cynomolgus monkeys, mean maximum plasma/serum concentration (C_{max}) of DS-8201a was similar while the area under the plasma/serum concentration-time curve (AUC) was about 22% lower for [REDACTED] CCI DP2 material as compared to [REDACTED] CCI DP1 material. However, in a xenograft study, no difference was seen in [REDACTED] CCI between the 2 products.

1.1.1.3. Intended Use Under Investigation

This study will compare the activity of DS-8201a 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

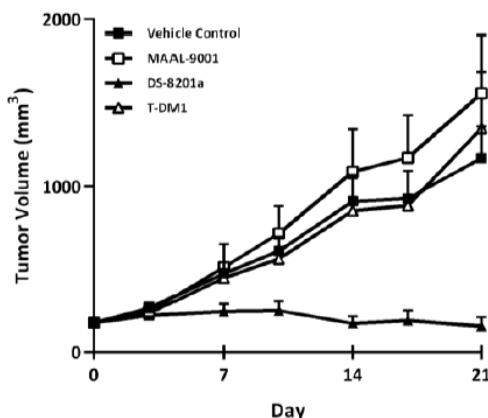
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

The description of these can be found within their locally approved labels. Please refer to the local package insert for the dosing regimen.

1.1.1.5. Nonclinical Studies of DS-8201a

The pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of DS-8201a have been examined in nonclinical studies. One example of nonclinical pharmacology study results indicate that DS-8201a inhibits tumor growth in patient-derived HER2-low tumor xenograft that is insensitive to T-DM1.

Figure 1.1: Anti-tumor Effect of DS-8201a 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. DS-8201a, 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 (mm³) = 0.52 × length × width²

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

1.1.1.6. Clinical Experience

The DS-8201a first-in-human study (Protocol DS8201-A-J101) is an open-label, dose finding study to assess the safety and tolerability of DS-8201a 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 DS-8201a studies, please refer to the latest version of the IB.⁹

Unlike currently approved HER2 targeted therapies, DS-8201a has shown efficacy for subjects with both HER2-positive and HER2-low breast cancer. As of 16 Feb 2018, in the DS8201-A-J101 trial, DS-8201a achieved a confirmed ORR of 58.8% (50/85) for HER2-positive metastatic breast cancer in the salvage line setting with an estimated median PFS not reached. The HER2-low breast cancer subjects were also enrolled in this study and demonstrated an overall confirmed ORR of 51.6% (16/31) including 4 confirmed partial responses (PRs) among 13 subjects with IHC 1+ disease, with estimated median PFS of 13.6 months. Response was seen in both IHC 2+ and IHC 1+ disease (Table 1.1).

Table 1.1: Escalation Confirmed Objective Response Rate from DS8201-A-J101 Part 2 (Dose Expansion) as of 13 Dec 2017

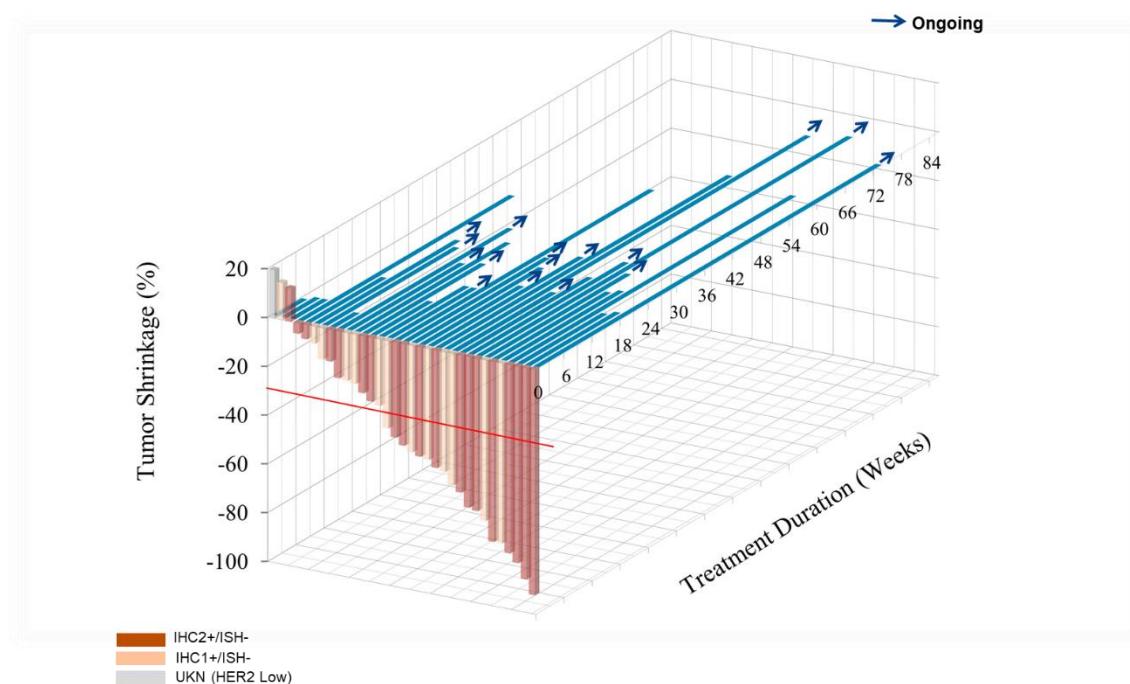
	Complete Response (CR)	Partial Response (PR)	Objective Response Rate (CR + PR)	Stable Disease (SD)	Disease Control Rate (CR + PR + SD)	Median Duration of Response (DOR)	Median Progression-Free Survival (PFS)
All breast cancer (n=134) ^a	1.7% (2/118)	55.1% (65/118)	56.8% (67/118)	35.6% (42/118)	92.4% (109/118)	11.0 mo	13.7 mo
HER2-positive breast cancer (n=100) ^a	2.4% (2/85)	56.5% (48/85)	58.8% (50/85)	35.3% (30/85)	94.1% (80/85)	Not reached	Not reached
HER2-low breast cancer (n=32) ^a	0.0% (0/31)	51.6% (16/31)	51.6% (16/31)	38.7% (12/31)	90.3% (28/31)	11.0 mo	13.6 mo

CR = complete response; DOR = duration of response; HER2 = human epithelial growth factor 2;

PFS = progression-free survival; PR = partial response; SD = stable disease.

^a Analysis set: efficacy evaluable subjects for time to event. Number of evaluable subjects for confirmed overall response at least 2 post-baseline scans is separately described in the table.

Figure 1.2: Best Percentage Change from Baseline in Tumor Size and Treatment Duration, Breast Cancer HER2-low (5.4 + 6.4 mg/kg) in DS8201-A-J101 as of 16 Feb 2018



HER2 = human epithelial growth factor 2; IHC = immunohistochemistry; ISH = in-situ hybridization;
UKN = unknown.

As of 13 Dec 2017, the safety dataset included all subjects who received at least 1 dose of study drug in DS8201-A-J101 (n 212). 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 safety, tolerability, efficacy, and PK.

In Part 1, a total of 24 subjects received DS-8201a, 3 in the 0.8 mg/kg cohort, 3 in the 1.6 mg/kg cohort, 3 in the 3.2 mg/kg cohort, 6 in the 5.4 mg/kg cohort, 6 in the 6.4 mg/kg cohort, and 3 in the 8.0 mg/kg cohort. A total of 17 breast cancer subjects, 6 gastric cancer subjects and 1 GEJ cancer subject, have been enrolled. No dose-limiting toxicities (defined as occurring during Cycle 1) have been reported in any subject. The doses of 5.4 mg/kg and 6.4 mg/kg were chosen for expansion in Part 2.

In Part 2, a total of 188 subjects received at least 1 dose of DS-8201a, 81 in Part 2a, 41 in Part 2b, 20 in Part 2c, 25 in Part 2d, and 21 in Part 2e. Of these 188 subjects, 54 subjects received 5.4 mg/kg (37 subjects in Part 2a and 17 subjects in Part 2b), and the other 134 subjects received 6.4 mg/kg of DS-8201a. In Part 2d, 12 colorectal cancer subjects and 6 non-small cell lung cancer subjects have been enrolled.

The safety dataset for DS-8201a as of 13 Dec 2017 included all subjects who received at least 1 dose of study drug in DS8201-A-J101 (n 212). Of the 95 HER2-positive breast cancer subjects dosed with DS-8201a 5.4 and 6.4 mg/kg in Part 1, Part 2a, and Part 2e, 67 subjects were still on treatment, 16 discontinued study treatment because of disease

progression, 3 subjects withdrew study treatment, 1 discontinued because of clinical progression, and the remaining 8 subjects because of the following adverse events (AEs): 4 interstitial lung disease (ILD; 3 Grade 1 and 1 Grade 3), 1 pneumonitis (Grade 4), 1 organizing pneumonia (Grade 2), 1 anemia (Grade 3), and 1 constipation (Grade 2). A total of 15 subjects had dose reductions because of the events of bronchopneumonia, decreased appetite, febrile neutropenia, lung infection, malaise, nausea, organizing pneumonia, pneumonia, and platelet count decreased. The safety profiles in the breast cancer subjects described above were similar to the overall safety data observed from both Part 1 and 2 described below.

For the 212 subjects who received at least 1 dose of DS-8201a in the DS8201-A-J101 study as of 13 Dec 2017, the most common treatment-emergent AEs (TEAEs) of any grades were nausea (72.6%), decreased appetite (58.5%), vomiting (39.2%), anemia (34.4%), alopecia (34.4%), platelet count decreased (30.7%), diarrhea (29.2%), constipation (29.2%), neutrophil count decreased (26.9%), white blood cell count decreased (25.5%), fatigue (25.0%), and malaise (24.1%). The majority of the TEAEs were of Grade 1 or 2 severity; 94 of 212 subjects (44.3%) experienced Grade 3 or above TEAEs regardless of causality.

As of 13 Dec 2017, there was 1 fatal case of ILD and 1 fatal case of pneumonitis, both of which have been confirmed by the ILD Adjudication Committee (AC) as ILD and related to DS-8201a.

Based on a comprehensive cumulative review of the available DS-8201a safety data from the DS8201-A-J101 study, as well as the results of potential ILD/pneumonitis cases reviewed by the ILD AC, available data from epidemiology/literature, biological plausibility, and safety information from drugs of similar class, the previously classified important potential risk of ILD/pneumonitis has been reclassified as an important identified risk for DS-8201a. While ILD/pneumonitis has been reclassified to an important identified risk, the benefit-risk profile of DS-8201a remains positive.

Cardiotoxicity in association with DS-8201a is considered to be an important potential risk based on the available nonclinical data, literature, and safety information for drugs of similar class.

As with any therapeutic antibodies, there is the possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions following the administration of DS-8201a. Immune responses causing allergic or anaphylactic reactions are considered to be an AE of special interest (AESI) for the DS-8201a clinical program.

Based on a review of the cumulative safety data as of 13 Dec 2017 with 212 subjects enrolled, DS-8201a demonstrates an acceptable and manageable safety profile.

For further details related to the efficacy and safety of DS-8201a reported from clinical studies, please see the latest version of the IB.⁹

1.1.1.7. Summary of Clinical Pharmacokinetics

Pharmacokinetics were evaluated in 24 subjects who received DS-8201a. Following a single IV administration, the systemic exposure increased approximately in proportion to

the dose. The PK parameters at 5.4, 6.4, and 8.0 mg/kg are shown in Table 1.2. The C_{\max} of DS-8201a at 6.4 mg/kg was achieved with a median time to C_{\max} (T_{\max}) of 2.16 hours. The C_{\max} and AUC from time 0 to 21 days (AUC_{0-21d}) at 6.4 mg/kg were 181 $\mu\text{g}/\text{mL}$ and 901 $\mu\text{g}\cdot\text{d}/\text{mL}$, respectively (Table 1.2). The systemic exposure at 6.4 mg/kg in subjects in Cycle 1 was observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation. At this dose, the mean terminal elimination half-life ($t_{1/2}$) of DS-8201a was 7.33 days at 6.4 mg/kg, and the volume of distribution at steady state (V_{ss}) was 58.6 mL/kg, which is similar to the serum volume.

The PK parameters of total antibody were close to that of DS-8201a (Table 1.3).

The C_{\max} and AUC for the dosing interval (AUC_{0-21d}) of MAAA-1181a, which were quite low, were 6.80 ng/mL and 31.0 ng·d/mL at 6.4 mg/kg, respectively (Table 1.4). The $t_{1/2}$ of MAAA-1181a was similar to that of DS-8201a.

For further details related to the clinical PK of DS-8201a, please see the latest version of the IB.⁹

Table 1.2: Mean Pharmacokinetic Parameters of DS-8201a (\pm Standard Deviation)

Dose (mg/kg)	C_{\max} ($\mu\text{g}/\text{mL}$)	T_{\max} (h) median (range)	AUC_{0-21d} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	$t_{1/2}$ (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
5.4 (N 6)	127 \pm 17.2	1.92 (1.92, 2.16)	544 \pm 165	590 \pm 186	6.03 \pm 0.603	10.1 \pm 3.90	75.2 \pm 24.2
6.4 (N 6)	181 \pm 33.1	2.16 (1.44, 4.08)	901 \pm 155	1030 \pm 209	7.33 \pm 1.64	6.41 \pm 1.12	58.6 \pm 11.0
8.0 (N 3)	216 \pm 52.0	1.92 (1.92, 2.16)	914 \pm 235	1020 \pm 279	6.97 \pm 0.357	8.17 \pm 1.93	69.7 \pm 13.1

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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; $t_{1/2}$ = terminal elimination half-life; T_{\max} = time to C_{\max} ; V_{ss} = volume of distribution at steady state.

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

DS-8201a Dose (mg/kg)	C_{\max} ($\mu\text{g}/\text{mL}$)	T_{\max} (h) median (range)	AUC_{0-21d} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	$t_{1/2}$ (d)
5.4 (N 6)	116 \pm 13.9	1.92 (1.92, 6.96)	609 \pm 151	682 \pm 172	6.78 \pm 2.39
6.4 (N 6)	146 \pm 18.9	3.84 (2.16, 6.96)	878 \pm 97.1	1050 \pm 149	8.25 \pm 2.16
8.0 (N 3)	178 \pm 18.5	2.16 (1.92, 6.72)	1090 \pm 213	1270 \pm 296	7.35 \pm 0.417

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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; $t_{1/2}$ = terminal elimination half-life; T_{\max} = time to C_{\max} .

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

DS-8201a Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h) median (range)	AUC _{0-21d} (ng·d/mL)	AUC _∞ (ng·d/mL)	t _½ (days)
5.4 (N 6)	10.8 \pm 7.56	5.28 (3.84, 23.76)	40.6 \pm 19.8	43.6 \pm 21.2	6.11 \pm 0.811
6.4 (N 6)	6.80 \pm 1.72	6.72 (4.08, 7.20)	31.0 \pm 5.11	34.2 \pm 5.63	6.28 \pm 1.17
8.0 (N 3)	9.25 \pm 3.18	6.72 (6.72, 6.96)	39.4 \pm 6.43	43.4 \pm 9.16	6.36 \pm 1.53

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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 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) guidelines 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. 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 IHC 1+ and IHC 2+/ISH- HER2 expression.

Several studies have attempted to use ASCO-CAP 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.

DS-8201a has shown efficacy for subjects with IHC 1+ as well as IHC 2+ disease. In the DS8201-A-J101 trial, as of 16 Feb 2018, confirmed ORR reached 51.6% (16 of 31, 5 confirmed PRs from IHC 1+ disease) for HER2-low breast cancer tumors.

To define the upper boundary of low HER2 expression, the Sponsor plans to use the standard ASCO-CAP definitions. 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.¹⁵ 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.¹⁶ 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 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.² 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 DS-8201a 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 Objectives

The primary objective is to compare the PFS benefit of DS-8201a to physician's choice in HER2-low, HR-positive breast cancer, based on blinded independent central review (BICR).

2.1.2. Secondary Objectives

The secondary objectives are:

- To investigate the efficacy of DS-8201a compared to physician's choice on the following parameters (definitions of these endpoints are included in Section 7.1.2):
 - PFS in HR-positive subjects, based on Investigator assessment
 - Overall survival (OS) in HR-positive subjects
 - Confirmed objective response rate (ORR), based on BICR and Investigator assessment in HR-positive subjects
 - Duration of response (DoR), based on BICR and Investigator assessment in HR-positive subjects
 - PFS, OS, confirmed ORR, and DoR in all subjects, regardless of HR status
- To determine PK of DS-8201a
- To evaluate safety of DS-8201a compared to physician's choice
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for DS-8201a compared to physician's choice

2.1.3. Exploratory Objectives

The exploratory objectives are to evaluate the following:

- Clinical benefit rate (CBR; the sum of complete response [CR] rate, PR rate, and longer than 6 months' stable disease [SD] rate), based on BICR and Investigator assessment in HR-positive subjects and all subjects regardless of HR status
- Disease control rate (DCR), based on BICR and Investigator assessment 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 and Investigator assessment
- Potential biomarkers of response/resistance

- Exposure-response relationships for efficacy and safety endpoints

2.2. Study Hypothesis

DS-8201a confers a significant benefit in PFS in HER2-low, HR-positive breast cancer subjects compared to physician's choice.

2.3. Study Endpoints

The efficacy endpoints will be based on central assessments unless otherwise stated.

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, based on BICR.

2.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

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

2.3.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- CBR, based on BICR and Investigator assessment
- DCR, based on BICR and Investigator assessment
- TTR, based on BICR and Investigator assessment.

2.3.4. 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

2.3.5. Pharmacokinetic/Biomarker Endpoints

2.3.5.1. Pharmacokinetic Endpoints

The PK endpoints include:

- Serum concentrations of DS-8201a, total anti-HER2 antibody, and MAAA-1181a

2.3.5.2. Biomarker Endpoints

The biomarker endpoints include:

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

2.3.6. Safety Endpoints

The safety endpoints include:

- Serious adverse events (SAEs)
- TEAEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
- AESIs
- Discontinuations due to 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 DS-8201a versus the physician's choice in HER2-low, unresectable and/or metastatic breast cancer subjects. [Figure 3.1](#) shows the study design.

DS-8201a for injection, 100 mg, will be administered IV at a dose to be defined based on results from the DS8201-A-J101 and DS8201-A-U201 studies.

The comparator for this study is called physician's choice. Approximately 540 subjects will be randomized in a 2:1 ratio to DS-8201a or 1 of the following physician's choice treatments:

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

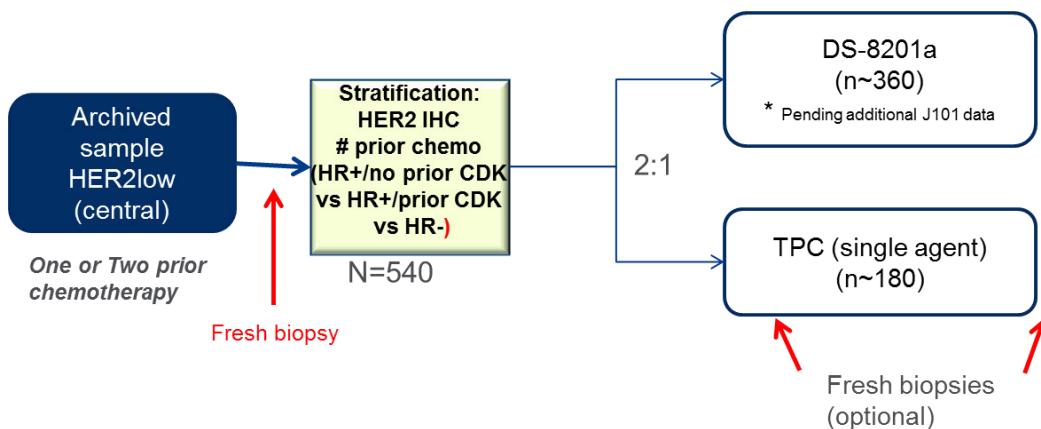
For subjects randomized to comparator, the treatment will be in cycles of 21 days. If a subject receives a comparator with a regimen other than a 21-day cycle, the Investigator should ensure that the subject follows the study-defined Schedule of Events (see Section [17.1](#)).

Randomization will be stratified by:

- HER2 IHC status of archived 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 [5.7.3.1](#) 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 (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.

3.2. Discussion of Study Design

This trial is designed to compare the use of DS-8201a 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 standard ASCO-CAP definitions. 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.¹⁵ 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.¹⁶ 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 ASCO-CAP cutoffs to provide the lower boundary for low HER2 expression.

This study will be conducted in approximately 161 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 (DS-8201a versus physician's choice).

3.2.1. Duration of the Study

Enrollment is planned to occur over approximately 16 months. The end of the study hypothesis-testing period is defined as the date when approximately 318 PFS events per BICR have been observed in the HR-positive population.

The Sponsor will monitor the number of PFS events and will make projections of the data cutoff date for PFS analysis. The data cutoff date will be made at a time when the number of reported PFS events is 90% or less of the planned required number of events. 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.

For each subject there will be a 40-Day (+7 days) Follow-up Visit after the last study drug treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up visits every 3 months (± 14 days) from the date of 40-Day (+7 days) Follow-up Visit, 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 DS-8201a, each cycle of treatment will be 21 days. The number of treatment cycles with DS-8201a 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 subjects randomized to physician's choice, treatment cycles will be on the same 21-day cycles. 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 (see Section [17.1](#)).

After study treatment discontinuation, all subjects may be contacted at the 40-Day (+7 days) Follow-up Visit 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 [5.7.3](#)).

3.2.3. Definition of the End of the Study

The end of the study hypothesis-testing period is defined as the date when approximately 318 PFS events per BICR have been observed in the HR-positive population. 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:

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 American Society of Clinical Oncology College of American Pathologists (ASCO-CAP) guidelines evaluated at a central laboratory.
 - d. Is HR-positive or HR-negative. After ~ 60 HR-negative subjects are enrolled, further enrollment will be limited to only subjects who are HR-positive per ASCO-CAP guidelines (positive for estrogen receptor or progesterone receptor if finding of $\geq 1\%$ of tumor cell nuclei are immunoreactive).
 - e. 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. After ~ 240 HR-positive subjects have been enrolled who have not had prior therapy with a CDK4/6 inhibitor, further enrollment of HR-positive subjects will be limited to subjects who have had prior therapy with a CDK4/6 inhibitor.
 - 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

- adjuvant chemotherapy, adjuvant therapy would count as 1 line of chemotherapy.
- h. Was never previously HER2-positive (IHC 3+ or ISH+) on prior pathology testing (per ASCO-CAP guidelines).
 - 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 sample available for assessment of HER2 status by central laboratory (based on most recent available tumor tissue sample). If archival tissue is not available, a fresh biopsy is required.
 6. All subjects must have a recent tumor sample after the most recent treatment regimen or agree to undergo a tissue biopsy prior to randomization.
 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 17.6).¹⁷
 8. ECOG PS 0 or 1.
 9. Left ventricular ejection fraction (LVEF) $\geq 50\%$ within 28 days prior to randomization.
10. Adequate bone marrow function within 14 days before randomization, defined as:
- Platelet count $\geq 100,000/\text{mm}^3$ (Platelet transfusion is not allowed within 1 week prior to Screening assessment)
 - Hemoglobin level $\geq 9.0 \text{ g/dL}$ (red blood cell transfusion is not allowed within 1 week prior to Screening assessment)
 - Absolute neutrophil count $\geq 1500/\text{mm}^3$ (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 $\geq 30 \text{ mL/min}$, as calculated using the Cockcroft-Gault equation (see Section 17.2; $[\{140 - \text{age in y}\} \times \{\text{weight in kg}\}]$ divided by $[\{72 \times \text{serum creatinine in mg/dL}\}]$ multiply by 0.85 if female]).
12. Adequate hepatic function within 14 days before randomization, defined as:
- Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 5 \times$ upper limit of normal (ULN)
 - Total bilirubin $\leq 1.5 \times$ ULN if no liver metastases or $< 3 \times$ 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 and activated partial thromboplastin time $\leq 1.5 \times$ ULN

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 for at least 4.5 months after the last dose of DS-8201a or according to the locally approved labels for the physician's choice treatments.¹⁸ 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
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study treatment. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method 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.

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 locally approved labels 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 4.5 months after the final study treatment administration or according to the locally approved labels for the physician's choice treatments.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Ineligible for all 5 of the options in the physician's choice arm either because of previously having received treatment in the metastatic setting with the comparator or having a contraindication to treatment.
2. Prior treatment with antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor.
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 and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
 - Subjects with clinically inactive brain metastases may be included in the study.
 - 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 nonmelanoma 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 would, in the opinion of the Investigator, increase the safety risk to the subject or 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 should be tested for HIV prior to randomization if required by local regulations or IRB/IEC.
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 (other than abdominal radiation) within 2 weeks before study treatment.
15. Systemic treatment with anticancer therapy, antibody-based therapy, retinoid therapy, or hormonal therapy within 3 weeks before study treatment; 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 before study treatment, whichever is longer.
16. Current treatment with strong cytochrome P450 (CYP3A4) and organic anion transporting polypeptide (OATP) inhibitors (see Section 17.5) and any monoclonal antibody treatment (washout period of ≥ 3 elimination half-lives of the inhibitor/antibody is required).
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), or current participation in other investigational procedures.
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.

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, DS-8201a 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 (DS-8201a versus physician's choice) in a 2:1 ratio. The randomization will be stratified by

- HER2 IHC status of archived 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 DS-8201a 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, not otherwise part of the Sponsor study team, will generate the randomization schedule.

5.1.4. Emergency Unblinding Procedure

Not applicable as the study is open label.

5.2. Study Drug

5.2.1. Description

CCI [REDACTED] DP)

DS-8201a for injection 100 mg CCI [REDACTED]

[REDACTED] Each vial is designed for single use only and is not to be used to treat more than 1 subject.

5.2.2. Labeling and Packaging

DS-8201a for injection 100 mg CCI [REDACTED] DP will be supplied by the Sponsor. DS-8201a 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

DS-8201a 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

DS-8201a will be administered initially as an IV infusion over 30 to 90 minutes every 21 days (± 2 days). The initial dose of DS-8201a will be infused for approximately 90 minutes. If there is no infusion-related reaction, after the initial dose, the next doses of DS-8201a 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 $\pm 10\%$ 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 DS-8201a.

5.2.5. Storage

DS-8201a for injection 100 mg must be stored in a secure, limited-access storage area under the storage conditions listed below:

- CCI

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, 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 (DS-8201a/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 DS-8201a procedures (Section 5.2.6). Storage for all medications must follow the locally approved label. Dosage, regimen, and dose modification in locally approved label and/or local guideline should be used. A 21-day cycle regimen is strongly recommended. 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), regardless of treatment/rest interval. Treatment of physician's choice will be either supplied by the local pharmacy or site and reimbursed by the Sponsor where necessary, or centrally supplied by the Sponsor or delegated vendor in the event that a particular country or site is unable to supply material.

Administration and dose modification should be done according to the package insert or local practice.

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 DS-8201a and as per locally approved label 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, 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 or subject is discontinued at end of treatment (EOT).

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 DS-8201a

NOTE: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in [Table 5.1](#).

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

Once the dose of DS-8201a 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.**

Dose Interruption and Modification/Toxicity Management Guidelines:

A dose can be delayed for up to 28 days 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.

Treatment cycles for a subject for whom DS-8201a dosing is temporarily withheld for any reason may have future cycles scheduled based on the date that DS-8201a dosing was resumed.

Table 5.1: Dose Modification for DS-8201a

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
No Toxicity	Maintain dose and schedule
Infusion-related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• Administration of DS-8201a 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)	<ul style="list-style-type: none">• Administration of DS-8201a should be discontinued immediately and permanently.• Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
	inhalation, etc., should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2, then maintain dose
Grade 4	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2 Reduce dose 1 level
Febrile Neutropenia (Absolute neutrophil count $<1 \times 10^9/L$, fever $>38.3^\circ\text{C}$ or a sustained temperature of $\geq 38^\circ\text{C}$ for more than 1 hour)	<ul style="list-style-type: none"> Delay dose until resolved Reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	<ul style="list-style-type: none"> No dose modification
Grade 4 ($<0.2 \times 10^9/L$)	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2: <ul style="list-style-type: none"> If resolved in ≤ 14 days from day of onset, maintain dose If resolved in >14 days from day of onset, reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin $<8.0 \text{ g/dL}$); transfusion indicated	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2, then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (Platelets <50 to $25 \times 10^9/L$)	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 1: <ul style="list-style-type: none"> 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 $<25 \times 10^9/L$)	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure	<ul style="list-style-type: none"> Discontinue subject from study treatment

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	<ul style="list-style-type: none"> Continue treatment with DS-8201a
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	<ul style="list-style-type: none"> Continue treatment with DS-8201a Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% and decrease is ≥10% (absolute value) from baseline	<ul style="list-style-type: none"> Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks If LVEF has not recovered to within 10% from baseline, discontinue subject from study treatment
LVEF <40% or >20% (absolute value) decrease from baseline	<ul style="list-style-type: none"> Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment
QTc Prolongation	
Grade 3 (QTc >500 ms on 2 separate ECGs or >60 ms change from baseline)	<ul style="list-style-type: none"> 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, then If attributed to DS-8201a, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Pulmonary Toxicity	<p>If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis.</p> <p>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.</p> <p>If the AE is suspected to be ILD/pneumonitis, treatment with study treatment should be interrupted pending further evaluations.</p> <p>Evaluations should include:</p> <ul style="list-style-type: none"> High resolution CT, Pulmonologist consultation,

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
	<ul style="list-style-type: none"> One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. <p>Other evaluations could include:</p> <ul style="list-style-type: none"> Pulmonary function tests including diffusing capacity of the lungs for carbon monoxide, peripheral oxygen saturation, and arterial blood gases, Serum marker testing (eg, KL-6, surfactant protein D, or others), Or other tests as needed. <p>As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (refer to drug-induced lung disease guideline).¹⁹</p> <ul style="list-style-type: none"> If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below.
Grade 1	<ul style="list-style-type: none"> Delay dose until resolved to Grade 0, then: <ul style="list-style-type: none"> If resolved in ≤ 28 days from day of onset, maintain dose If resolved in > 28 days from day of onset, reduce dose 1 level For further management, see guidance above.
Grade 2, 3, or 4	<ul style="list-style-type: none"> Discontinue subject from study treatment. For further management, see guidance above.
Troponin Increased	
Grade 1 (Levels above the ULN and below the level of myocardial infarction as defined by the manufacturer)	<p>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.</p> <p>Repeat troponin testing at 3 hours ± 1 hour after initial troponin test.</p> <ul style="list-style-type: none"> If repeat troponin level at 3 hours ± 1 hour rises significantly per institutional guidelines, <ul style="list-style-type: none"> Perform ECG in triplicate Repeat troponin testing at 6 hours ± 1 hour after initial troponin test Follow institutional guidelines for

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
	<ul style="list-style-type: none"> management of detectable troponin testing. If repeat troponin level at 3 hours ± 1 hour does not rise significantly per institutional guidelines, <p style="margin-left: 40px;">Repeat troponin testing 6 hours ± 1 hour or 24 hours ± 2 hours after initial troponin test</p> <p style="margin-left: 40px;">Continue treatment with DS-8201a.</p>
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	<ul style="list-style-type: none"> Perform ECG in triplicate Repeat troponin testing at 6 hours ± 1 hour and 12 hours ± 1 hour after initial troponin test. Follow institutional guidelines for management of detectable troponin testing. If acute myocardial infarction is confirmed, discontinue subject from study treatment. Otherwise, delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level.
Ocular	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose. If resolved in $>$7 days from day of onset, reduce dose 1 level.
Grade 4	<ul style="list-style-type: none"> Discontinue subject from study treatment
Renal Toxicity (Serum Creatinine)	
Grade 3 (>3 to $6 \times$ ULN)	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 2 or baseline, then reduce dose 1 level
Grade 4 ($>6 \times$ ULN)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Hepatic Toxicity	
AST or ALT With Simultaneous Total Bilirubin	
AST/ALT $\geq 3.0 \times$ ULN with simultaneous total bilirubin $> 2.0 \times$ ULN	<ul style="list-style-type: none"> 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

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
	<p>resumption of study treatment may occur after discussion between the Investigator and Sponsor.</p> <ul style="list-style-type: none"> • 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.
AST or ALT Increased	
Grade 2 (>3.0 to $5.0 \times$ ULN if baseline was normal; >3.0 to $5.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> • No action for Grade 2 AST/ALT
Grade 3 (>5.0 to $20.0 \times$ ULN if baseline was normal; >5.0 to $20.0 \times$ baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level $\leq 3 \times$ ULN	<ul style="list-style-type: none"> • Repeat testing within 3 days. Delay dose until resolved to \leqGrade 1, then: <ul style="list-style-type: none"> 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 $20.0 \times$ ULN if baseline was normal; >8.0 to $20.0 \times$ baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was $>3 \times$ ULN	<ul style="list-style-type: none"> • Repeat testing within 3 days. Delay dose until resolved to \leq baseline level, then: <ul style="list-style-type: none"> 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 ($>20.0 \times$ ULN if baseline was normal; $>20.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> • Discontinue subject from study treatment
Total Bilirubin Increased	
Grade 2 (>1.5 to $3.0 \times$ ULN if baseline was normal; >1.5 to $3.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> • If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> 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 $10.0 \times$ ULN if baseline was normal; >3.0 to $10.0 \times$ baseline if	<ul style="list-style-type: none"> • If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
baseline was abnormal)	<p>3 days. Delay dose until resolved to \leqGrade 1: If resolved in \leq7 days from day of onset, reduce dose 1 level If resolved in $>$7 days from day of onset, discontinue DS-8201a</p> <ul style="list-style-type: none"> If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to \leqGrade 2: If resolved in \leq7 days from day of onset, reduce dose 1 level If resolved in $>$7 days from day of onset, discontinue DS-8201a
Grade 4 ($>10.0 \times$ ULN if baseline was normal; $>10.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Alkaline Phosphatase Increased	
Grade 3 (>5.0 to $20.0 \times$ ULN if baseline was normal; >5.0 to $20.0 \times$ baseline if baseline was abnormal), or Grade 4 ($>20.0 \times$ ULN if baseline was normal; $>20.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> No modification unless determined by the Investigator to be clinically significant or life-threatening
Gastrointestinal	
Nausea	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1 If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1 If resolved in \leq3 days from day of onset, maintain dose If resolved in $>$3 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> Discontinue subject from study treatment

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Dose or Schedule Modification for DS-8201a
Other Laboratory AEs	
Grade 3	<ul style="list-style-type: none"> • Delay dose until resolved to \leqGrade 1 or baseline level: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> • Discontinue subject from study treatment
Other Non-laboratory Adverse Events	
Grade 3	<ul style="list-style-type: none"> • Delay dose until resolved to \leqGrade 1 or baseline: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> • 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 locally approved label and/or local guideline for that medication. 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, the subject will permanently discontinue study treatment and will be followed for survival.

5.5. Method of Assessing Treatment Compliance

DS-8201a 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 DS-8201a 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.

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

5.6.1. Prohibited Medications and Treatments

The following medications, treatment, and procedures will be prohibited during the treatment period (see Section 4.2 for required washout periods):

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment;
- 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.

- CYP3A4 strong inhibitors (eg, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, saquinavir, telaprevir, telithromycin, voriconazole). Consult with your local resources as needed to evaluate potential CYP3A4 inhibitors (see Section 17.5 for a more extensive list).

If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying DS-8201a treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is

co-administered and DS-8201a treatment cannot be delayed, subjects should be closely monitored for adverse reactions.

- OATP inhibitors include but are not limited to: atazanavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir, rifampin, ritonavir, and simeprevir. Consult with your local resources as needed to evaluate potential OATP inhibitors (see Section 17.5 for a more extensive list).

If concomitant use of OATP inhibitors is unavoidable, consider delaying DS-8201a treatment until the OATP inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) as long as possible.

If an OATP inhibitor is co-administered and DS-8201a treatment cannot be delayed, subjects should be closely monitored for adverse reactions.

- Foods or beverages containing grapefruit.
- For the control arm, please refer to the package insert of the chemotherapy.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

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

- Subject dies;
- Study termination;
- Subject withdraws consent to participate in study procedures;
- Subject is lost to follow-up;
- Other, specify.

5.7.2. Withdrawal Procedures

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.

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

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

5.7.3. Procedures for Discontinuation from Study Treatment and Post-Treatment Follow-up

5.7.3.1. Procedures for Discontinuation from Study Treatment

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

- PD per criteria set forth in mRECIST version 1.1 (Section 17.6);
- 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 of consent by subject;
- Lost to follow-up;
- Protocol deviation;
- Physician decision;
- Study terminated by Sponsor;
- Other, specify.

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 withdrawn from study treatment should complete protocol-specified withdrawal procedures (Section 5.7.2) and follow-up procedures (Section 6.6).

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.

5.7.3.2. Procedures for Discontinuation From the Study

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

All subjects will be followed for survival status even after consent for study procedures is withdrawn. Subjects discontinued from the study because of withdrawal of consent will be followed for survival by collecting public records (eg, death certificates) unless prohibited by local laws.

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 according to ASCO-CAP guidelines¹⁰ evaluated at a central laboratory.

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

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

The following procedures will be conducted:

- Obtain a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue and/or performing a biopsy as needed.
- Obtain adequate archived or recent tumor tissue sample for HER2 testing. 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 it is unavailable and submit another prior tissue specimen.
- If archival tissue is not available, collect a fresh 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.
- Additional slides for optional exploratory biomarker assessment are requested (see the study laboratory manual).
- Assign SID.

6.2. Screening

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:

- Perform an HIV antibody test as required by local regulations or IRB/IEC.

- Perform a hepatitis B surface antigen/hepatitis C antibody test.
- 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).
- 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 fresh tumor biopsy must be obtained after discontinuation of the most recent treatment regimen and before randomization. The detailed procedures for preparing and submitting tumor samples will be provided in the laboratory manual. There is no need to perform fresh tumor biopsy if a subject already has an adequate tumor sample that was taken after the completion of the most recent treatment regimen and available to be submitted. The fresh tumor biopsy may be collected any time after completion of the most recent prior treatment regimen and prior to randomization.

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 17.6).

The following activities and/or assessments will be performed during the screening period **within 14 days of starting study treatment except as indicated:**

- Confirm subject eligibility.
- Obtain:
 - Demographics (eg, birth date, sex, race, ethnicity);
Medical 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 ECGs. The ECGs will be taken in close succession, initiated approximately 3 minutes apart, while in a supine/semi-recumbent position. The ECGs should 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

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) and exploratory biomarkers (eg, cfDNA in plasma), see Section 8.3.2.

- 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), perform a serum or urine pregnancy test 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.

6.3. Randomization

Eligible subjects will be randomized by the IXRS in a 2:1 ratio into the treatment arms: DS-8201a vs. physician's choice, which has 5 available treatment paradigms (refer to Section 5.1.1).

The study is expected to enroll ~360 DS-8201a subjects and ~180 physician's choice subjects. After ~60 HR-negative subjects have been enrolled, further enrollment will be limited to only subjects who have HR-positive disease. After ~240 HR-positive subjects who have not had prior therapy with a CDK4/6 inhibitor have been enrolled, further enrollment will be limited to only subjects who have had prior therapy with a CDK4/6 inhibitor.

Randomization will be stratified by

- HER2 IHC status of archived 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 DS-8201a are 21 days in duration; cycles for physician's choice should be 21 days in duration unless discussed with the Sponsor.

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 triplicate 12-lead ECGs. The ECGs will be taken in close succession, initiated approximately 3 minutes apart, while in a supine/semi-recumbent position. The ECGs should 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, and ECOG PS 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)

- 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) assessment will be collected on Cycle 3 Day 1 and every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc.), see Section 8.3.2.

Only subjects randomized to DS-8201a:

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 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)

- For DS-8201a 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 a minimum of 30 minutes. Record start and stop times of any study treatment and amount of drug administered. DS-8201a 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) (Cycles 1, 2, and 3) and SpO₂

(Cycle 1) (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 in triplicate at 5 hours after the start of drug administration (± 2 hours) for DS-8201a-treated subjects.
- Collect blood samples for:

For subjects randomized to DS-8201a, 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) within 15 minutes after end of infusion. 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 5.1.

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) and SpO₂ (Day 8 only) (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 2 Cycles

- 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 (Section 10.1).

6.4.3. 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.

6.4.4. 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 Cycle 1 Day 1, 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 Visit

The EOT is defined as the date the Investigator decides to discontinue study treatment (± 7 days). 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.
- 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 triplicate 12-lead ECGs. The ECGs will be taken in close succession, initiated approximately 3 minutes apart, while in a supine/semi-recumbent position. The ECGs should 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).

- 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).

- Blood sample for exploratory biomarkers, such as cfDNA analysis in plasma, will be collected.
- An optional fresh tissue biopsy may be collected.
- Tumor assessments 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, per mRECIST version 1.1. If the previous scan was within the last 6 weeks (± 7 days), this assessment does not need to be performed at the EOT Visit.

- 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 Visit.

- 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.
- 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 DS-8201a.

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

6.6.2. Long-term/Survival Follow-up

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

The following activities will take place during Long-term/Survival Follow-up visits 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 (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 Visit, 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), or 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 5.7.3 for further details on how subjects will be followed for survival status if they withdraw consent.

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoints

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on BICR. 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. Secondary Efficacy Endpoints

Secondary efficacy endpoints noted below that will be assessed by BICR review will be based on mRECIST version 1.1. Secondary efficacy endpoints include:

- PFS, based on Investigator assessment
- OS, 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.
- 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 and Investigator assessment, 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.

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

7.1.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are

- CBR, defined as the sum of CR rate, PR rate, and more than 6 months' SD rate, based on BICR and Investigator assessment.
- DCR, defined as the sum of CR rate, PR rate, and SD rate, based on BICR and Investigator assessment

- 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 and Investigator assessment. Time to response will be measured for responding subjects (CR or PR) only.

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. 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),^{20,21} ribociclib (MONALEESA-2),²² and abemaciclib (MONARCH 2).²³ Sample size has been calculated to ensure the study is adequately powered to detect a clinically meaningful PFS benefit.

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.²⁴

The index scores will be used in further analyses and economic models to generate evidence for access and reimbursement purposes.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessments

Blood samples for PK assessments will be collected from subjects randomized to DS-8201a 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: Within 15 minutes 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: Within 15 minutes after EOI

BI = before infusion; EOI = end of infusion

At each time point, blood will be collected for DS-8201a, 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 for PK samples will be provided in the study laboratory manual.

Serum concentrations of DS-8201a, total anti-HER2 antibody, and MAAA-1181a will be measured using validated assays at the bioanalytical laboratory.

8.2. Pharmacodynamic Assessment(s)

Not applicable.

8.3. Biomarker Assessments

In this study, biomarker analyses will be used to investigate the effect of DS-8201a 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 Sampling

In addition to the tumor sample required for assessment of HER2 status, if the subject agrees, additional slides for optional exploratory biomarker analysis are requested. A mandatory fresh tissue sample will be obtained after discontinuation of the most recent

prior treatment regimen and before treatment with DS-8201a, and 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.

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 any samples. These studies would extend the search for other potential biomarkers relevant to the effects of DS-8201a, cancer, and/or the resistance to the treatment. 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 DS-8201a 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 DS-8201a and at the time points specified in [Table 17.2](#). A blood sample will be drawn at each time point. Serum concentrations of DS-8201a 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 positive will be banked until availability of the neutralizing ADA assay, and sample storage time will not exceed 15 years.

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 DS-8201a. Additionally, samples may be analyzed for genes involved in DS-8201a related signaling pathways or to examine diseases or physiologic processes related to DS-8201a. 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 due to 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 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

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

As of 13 Dec 2017, 3 clinical studies have subjects dosed with DS-8201a: DS8201-A-J101, DS8201-A-U201, and DS8201-A-J202. There have been no events of ILD/pneumonitis reported in the DS8201-A-U201 and DS8201-A-J202 studies. Due to the limited number of subjects dosed and short treatment duration in these 2 studies, ILD/pneumonitis data has been summarized from the DS8201-A-J101 study.

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 DS8201-A-J101 clinical study 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 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, study treatment should be interrupted pending diagnostic evaluation, which should include high resolution CT and pulmonologist consultation. Other evaluations could include pulmonary function tests

such as diffusing capacity of the lungs for carbon monoxide and SpO₂, arterial blood gases, serum marker testing (eg, KL-6, SP-D, or others), or other tests as needed. One blood sample for PK analysis should also be collected as soon as ILD/pneumonitis is suspected, if feasible. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines.¹⁹

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 (Section 5.4).

9.3.1.3. Interstitial Lung Disease Adjudication Committee

An independent ILD AC for the DS-8201a 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 MedDRA preferred terms (PTs) from the current ILD Standardised MedDRA Query.

9.3.2. Cardiotoxicity (Cardiac-related Events Including QT Prolongation and Left Ventricular Ejection Fraction Decrease)

9.3.2.1. Clinical Summary

Cardiotoxicity in association with DS-8201a is considered to be an important potential risk based on the available nonclinical data, literature, and available safety information for drugs of similar class. Refer to the current 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. Troponin will be measured at Screening and EOT and as needed based on subject-reported cardiac symptoms. Triplicate 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.

9.3.3. Infusion-related Reactions

9.3.3.1. Clinical Summary

As with any therapeutic antibodies, there is a possibility of infusion-related reactions, and immune responses causing allergic or anaphylactic reactions following the administration of DS-8201a. Immune responses causing allergic or anaphylactic reactions are

considered to be an AESI for the DS-8201a clinical program. Refer to the current IB for a summary of preliminary clinical study data.⁹

9.3.3.2. Management Guidance

Subjects receiving DS-8201a should be monitored by means of vital signs, physical examination, and signs and symptoms of infusion-related reaction (ie, fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain) usually of mild to moderate severity that may lead to shortness of breath and severe lowering of blood pressure.

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).²⁵

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).²⁵

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
- Hospitalization or prolongation of hospitalization required: Hospitalization was required or prolonged due to the AE, regardless of whether medication was required
- 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. Serious 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 cardiotoxicity (cardiac-related events including QT prolongation and LVEF) for the DS-8201a clinical program, regardless of seriousness, is to be collected through the targeted questionnaires built within the applicable eCRFs in the clinical study database.

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).
- Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria defined as an elevated (ALT or AST) $\geq 3 \times$ ULN and an elevated total bilirubin $> 2 \times$ ULN that may occur at different time points 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.

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 must be followed and addressed promptly. 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 4.5 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 (prothrombin time and 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).

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

Standard supine/semi-recumbent 12-lead ECGs in triplicate (taken in close succession, initiated approximately 3 minutes apart) will be performed as described in the Schedule of Events ([Table 17.1](#) and [Table 17.2](#)). 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.

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 17.7 and Section 17.8, 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 infusion on Day 1 of Cycle 1, every 2 cycles thereafter, and at the EOT visit. 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.²⁶

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, every 2 cycles thereafter, and at the EOT Visit. Data collection will continue at the 40-Day (+7 days) Follow-up Visit and the first Long-term/Survival Follow-up Visit 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.²⁷ 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.²⁶

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.²⁸

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 analyses for PFS will be performed when approximately 318 PFS events per BICR are observed in HR-positive subjects.

Summary statistics will be presented by treatment arm. 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 intent-to-treat (ITT) HR-positive and overall ITT Analysis Sets. Some efficacy analyses such as ORR analysis will also be performed on the Response Evaluable Set (RES) and/or Per-protocol Analysis Set (PPS). Safety analyses will be performed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the ITT Analysis Set.

No interim analysis is planned for this study.

11.2. Analysis Sets

11.2.1. Intent-to-treat Analysis Set – HR-positive Population

The ITT Analysis Set will include all HR-positive subjects randomized into the study, including those who did not receive a dose of study treatment. The ITT Analysis Set (HR-positive) will be the primary analysis set for all efficacy analysis of the HR-positive subjects. Subjects will be analyzed according to the treatments assigned at randomization.

11.2.2. Intent-to-treat Analysis Set – Total Population

The ITT Analysis Set will include all subjects randomized into the study, including those who did not receive a dose of study treatment. The ITT Analysis Set (Total) will be the primary analysis set for all efficacy analysis of all randomized subjects. Subjects will be analyzed according to the treatments assigned at randomization.

11.2.3. 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.

11.2.4. Response Evaluable Set

The RES includes randomized subjects who took at least 1 dose of study treatment and had measurable disease at baseline per BICR.

11.2.5. Per-protocol Analysis Set

The PPS will include all subjects in the ITT Analysis Set who complied with the protocol sufficiently in exposure to study treatment, availability of tumor assessment, and absence of major protocol violations. Details will be specified in the SAP.

11.2.6. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who received at least 1 dose of DS-8201a and had measurable serum concentrations of DS-8201a, total anti-HER2 antibody, and MAAA-1181a.

11.3. Study Population Data

Subject disposition will be summarized for subjects in the ITT and ITT HR-positive Analysis Sets. 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 ITT Analysis Set, ITT HR-positive Analysis Set, RES, 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.

The primary efficacy analysis will compare PFS between the 2 treatment arms in the ITT HR-positive Analysis Set using a stratified log-rank test. Stratification factors used for primary analysis will be pre-specified in the SAP. The PFS will be tested for statistical significance at a 1-sided alpha of 0.025. Kaplan-Meier estimates and survival curves will also be presented for each treatment arm. The median survival 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.

11.4.2. Secondary Efficacy Analyses

The secondary efficacy endpoints are:

- PFS, based on Investigator assessment

- OS
- Confirmed ORR, based on BICR and Investigator assessment
- DoR, based on BICR and Investigator assessment.

To control the overall type-I error, these endpoints will be tested in the following order:

- Primary efficacy analysis (PFS per BICR based on ITT [HR-positive])
- PFS per BICR based on ITT (Total)
- OS based on ITT (HR-positive)
- OS based on ITT (Total)

Progression-free survival assessed by the Investigator and OS will be compared between the 2 treatment arms in the ITT and the ITT HR-positive Analysis Sets, using a stratified log-rank test. Kaplan-Meier estimates and survival curves will also be presented for each treatment arm.

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 will be provided using the Clopper-Pearson method.

Sensitivity analysis of PFS will be specified in the SAP.

11.4.3. 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.

11.4.3.1. 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 Visit) for all subjects. Results of the EQ-5D VAS will be presented as a measure of overall self-rated health status.

11.4.3.2. 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.

11.4.3.3. 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.

11.4.4. Exploratory Efficacy Analyses

11.4.4.1. Subgroup Analyses

Subgroup analyses for PFS (based on BICR), OS, confirmed ORR (based on BICR), DoR (based on BICR), and DCR (based on BICR) will be performed for the ITT HR-positive Analysis Set. Subgroups will include:

- HER2 IHC status (HER2 IHC 1+, HER2 IHC 2+/ISH-) of archived samples assessed by a central laboratory
- Number of prior lines of chemotherapy (1, 2)
- Prior CDK4/6 (Yes, No)

The subgroups are based on baseline values (ie, the last non-missing values before the first drug administration). In each subgroup defined above, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of smaller sample sizes.

11.4.4.2. Analyses of Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

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

Rates and 95% CIs for CBR and DCR and descriptive statistics for TTR (based on BICR and Investigator assessment) will be provided by treatment arm. Analyses will be conducted based on the ITT HR-positive Analysis Set and based on the ITT analysis Set, respectively.

Exposure-response relationships will be explored.

11.4.5. Pharmacokinetic and Pharmacodynamic Analyses

11.4.5.1. Pharmacokinetic Analyses

Descriptive statistics will be provided for all serum concentration data (DS-8201a, 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 DS-8201a, and, if appropriate, total anti-HER2 antibody and MAAA-1181a will be characterized, including available PK data from other DS-8201a 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.

11.4.5.2. Pharmacodynamic Analyses

Not applicable.

11.4.6. Biomarker Analyses

A mandatory fresh tissue sample will be obtained after discontinuation of the most recent prior treatment regimen and before treatment with DS-8201a, and 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 emerges during the treatment period (from date of first dose until 47 days after the last dose of the study treatment), having been absent at pretreatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment related to the pretreatment state, when the AE is continuous. Serious AEs related to study drug, regardless of onset date, will be considered to be 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 the EOT Visit, 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 the EOT Visit 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 the EOT Visit and the maximum post-treatment value. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc \leq 450 ms, >450 to \leq 480 ms, >480 ms to \leq 500 ms, and >500 ms). The QT intervals will be corrected for heart rate by Fridericia's formula ($QTcF = QT/[RR]^{1/3}$). 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.

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 this study.

11.7. Sample Size Determination

This is a prospectively randomized open-label trial comparing the primary endpoint of PFS in HR-positive subjects between the 2 treatment arms, DS-8201a and physician's choice with a randomization ratio of 2:1.

Assuming that the expected hazard ratio equals 0.68 (median PFS in the physician's choice arm is 4.2 months [NCT00337103] and median PFS in DS-8201a arm is 6.2 months), a total of 318 PFS events are needed to detect a HR of 0.68 for PFS with 1-sided alpha of 0.025 and power of 90%. Assuming an enrollment rate of 33.75 subjects per month on average and considering the effect of 2:1 randomization ratio on event rate by treatment arm, ~480 HR-positive subjects (~320 DS-8201a and ~160 physician's choice) and ~60 HR-negative subjects (~40 DS-8201a and ~20 physician's choice) will be randomized, for a total enrollment of ~540 subjects (~360 DS-8201a 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 are observed in the HR-positive population.

The expected data cutoff dates for the final analyses of PFS will be approximately 18 months after the first subject is randomized.

The sample size computation was performed using the EAST 6.4 procedure, “Design: Survival Endpoint: Two-Sample Test Parallel Design Logrank Given Accrual Duration and Accrual Rates.”

11.8. Statistical Analysis Process

The clinical study will be analyzed by the Sponsor or its agent/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.²⁹

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 data monitoring committee (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.

16. REFERENCES

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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)		-14 to -1 or as noted
Procedures		
Tissue Screening Informed Consent	•	
Tumor Sample for HER2 Status and Optional Biomarker	• ^a	
Fresh Tissue Biopsy (may collect any time between end of most recent treatment regimen and randomization)		• ^b
Main Informed Consent (may collect from 28 days to 1 day prior to randomization)		•
Inclusion/Exclusion		•
Demographics		•
Medical and Surgical History (including target disease)		•
Physical Examination		•
Weight		•
Height		•
ECOG PS		•
Adverse Events	• ^c	•
Concomitant Medications		•
Hospitalization-related Records		•
Vital Signs		•
SpO2		•
12-lead ECG in Triplicate ^d		•
ECHO or MUGA (LVEF) ^e (may collect from 28 days to 1 day prior to randomization)		•
Ophthalmologic Assessment ^f (may collect from 28 days to 1 day prior to randomization)		•

Visit	Tissue Screening	Screening
Window (Days)		-14 to -1 or as noted
Procedures		
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease; may collect from 28 days to 1 day prior to randomization)		•
CT/MRI of the Brain (may collect from 28 days to 1 day prior to randomization)		•
Hematology, Clinical Chemistry ^g		•
Coagulation		•
Urinalysis		•
Troponin ^h		•
Sample for Serum Biomarkers (eg, HER2ECD) and Exploratory Biomarkers (eg, cfDNA in plasma)		•
HIV Antibody Test (as required by local regulations or IRBs/IECs; may collect from 28 days to 1 day prior to randomization)		•
Hepatitis B Surface Antigen/Hepatitis C Antibody Test (may collect from 28 days to 1 day prior to randomization)		•
Pregnancy Test (urine or serum) ⁱ		•
Assign Subject Identification Number	•	
Physician Selection of Physician's Choice Paradigm, then Randomization		•

AE = adverse event; 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; IEC = Institutional Ethics Committee; IRB = Institutional Review Board; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); SAE = serious adverse event; SpO₂ = peripheral oxygen saturation.

^a Archived tissue appropriate for central laboratory HER2 testing. If archived tissue is not available, a fresh biopsy is required. Additional slides are requested for optional biomarker analysis.

^b A fresh tissue biopsy will be collected for retrospective assessment after the completion of the subject's most recent treatment regimen. For subjects who sign only the Informed Consent Form for tissue screening, only SAEs directly related to tissue screening procedure (ie, tumor biopsy) will be reported. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

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

^d ECGs will be taken in close succession, approximately 3 minutes apart, while in a supine/semi-recumbent position. ECGs should be performed before blood draws at respective time points.

^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.

^f Ophthalmologic assessments include visual acuity testing, slit lamp examination, and fundoscopy.

^g 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.

^h 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 in triplicate. If ECG is abnormal, follow institutional guidelines. 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.

ⁱ Within 72 hours before randomization for all female subjects of childbearing potential; a positive urine pregnancy test results 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 Tissue Biopsy ^e							•					•		
HEOR Outcomes: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L ^f	•						•		•			•	•	• ^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	• ^h	•	•	•	• ^h	•	• ^h	•	• ^h			•	•	
SpO ₂	• ^h	•	•		• ^h		• ^h		• ^h			•	•	
12-lead ECG (in triplicate) ⁱ	• ^h	•			• ^h		• ^h		• ^h			•		
ECHO or MUGA (LVEF) ^j									•			•		

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	BI	EOI						
Ophthalmologic Assessment ^k											•					
Pregnancy Test ^l	• ^h				• ^h		• ^h		• ^h			•	•			
Hematology & Blood Chemistry Tests ^m	• ^h		•	•	• ^h		• ^h		• ^h			•	•			
Coagulation												•				
Troponin ⁿ												•				
PK Blood (Serum) Sample	• ^o	• ^{p,q}			• ^o	• ^p	• ^o	• ^p	• ^o	• ^p						
ADA Blood Sample	• ^r				• ^r				• ^r			• ^r	• ^s			
Serum Biomarkers (eg, HER2ECD) Sample							• ^t		• ^t			•				
Exploratory Biomarker Blood Samples ^u	• ^h								•			•				
Pharmacogenomics Blood Sample ^v	•															
Administer Study Treatment, as Appropriate ^w	•			•		•		•								
Tumor	•										•	•				

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	BI	EOI						
Assessment ^x																
CT/MRI of the Brain ^y											•	•				
Survival Follow-up														•		

ADA = anti-drug antibody; BI = before infusion; cfDNA = cell free deoxyribonucleic acid; 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; 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; HEOR = Health Economics and Outcomes Research; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; 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 The date the Investigator decides to discontinue study treatment (+7 days). 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 is >40 days (+7 days) after last treatment, then the EOT assessments can also function as the 40-Day (+7 days) Follow-up Visit.

^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 Visit 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 tissue biopsy during treatment should be performed at Cycle 3 Day 1 (± 7 days).

^f Done every 2 cycles during the treatment period. Subject must complete the HEOR outcomes questionnaires before any other assessments or procedures are done.

^g Performed only 3 months after the 40-Day (+7 days) Follow-up Visit.

^h Within 72 hours before administration.

ⁱ ECGs will be taken in close succession, approximately 3 minutes apart, while subject is in a supine/semi-recumbent position. ECGs should be performed before blood draws at respective time points. At Cycle 1 Day 1, record ECG in triplicate 5 hours (± 2 hours) after start of drug administration. At Cycle 1 Day 1, ECGs will be required for DS-8201a-treated subjects only.

^j 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).

^k Ophthalmologic assessments include visual acuity testing, slit lamp examination, and fundoscopy.

^l 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.

^m 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.

ⁿ 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 in triplicate. If ECG is abnormal, follow institutional guidelines. If troponin levels are above the upper limit of normal and below the level of MI as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3.

^o PK samples should be obtained from DS-8201a subjects only within 8 hours BI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8.

^p Within 15 minutes of EOI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8. ^q 5 hours (± 2 hours) after the start of drug administration.

^r Within 8 hours BI on Day 1 in Cycles 1, 2, and 4, and then every 4 cycles (Cycles 8, 12, 16, etc) only for subjects randomized to DS-8201a.

^s For subjects with positive ADA at the 40-Day (+7 days) F/U visit, 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), or until the subject starts another therapy for cancer or withdraws consent from the study, whichever occurs first.

^t Before administration at every 2 cycles from Cycle 3 (Cycle 3, 5, 7, 9, etc).

^u 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.

^v 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.

^w DS-8201a is to be administered every 21 days ± 2 days unless dose interruption/modification or discontinuation is required.

^x Investigator's tumor assessment will be performed according to mRECIST version 1.1 BI on Cycle 1 Day 1, every 6 weeks ± 7 days, and at EOT.

^y An 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. For suspected interstitial lung disease (ILD)/pneumonitis, study drug should be interrupted pending evaluation, which should include: high resolution CT, pulmonologist consultation, 1 blood sample collected for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other evaluations could include pulmonary function tests including diffusing capacity of the lungs for carbon monoxide, pulse oximetry, and arterial blood gases; serum markers testing (eg, KL-6, SP-D, or others); other tests, as needed. CT/MRI will be performed every 6 weeks ± 7 days, and at EOT.

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 $\mu\text{mol/L}$:

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. Strong Cytochrome P450 3A4 and Organic Anion Transporting Polypeptide/Organic Anion Transporting Polypeptide 1B Inhibitors

CYP3A4 strong inhibitors	Boceprevir Clarithromycin Conivaptan Indinavir Itraconazole Ketoconazole Lopinavir/ritonavir Mibepradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Voriconazole
OATP1B inhibitors	Atazanavir Cyclosporine Eltrombopag Gemfibrozil Lopinavir Rifampin (single-dose) Ritonavir Saquinavir Tipranavir Clarithromycin Erythromycin Simeprevir

Please consult with your local resources as needed to evaluate potential cytochrome P450 (CYP3A4) and organic anion transporting polypeptide inhibitors.

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

17.6.1. Measurability of Tumor at Baseline

17.6.1.1. Definitions

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

17.6.1.1.1. 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.

17.6.1.1.2. 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.

17.6.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.6.1.1.3.1. 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.

17.6.1.1.3.2. 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.

17.6.1.1.3.3. 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.

17.6.1.2. Specifications by Methods of Measurements

17.6.1.2.1. 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 the beginning of the treatment.

17.6.1.2.2. 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).

17.6.2. Tumor Response Evaluation

17.6.2.1. 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.

17.6.2.2. 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 \times 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’).

17.6.2.3. Response Criteria

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

17.6.2.4. 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).

17.6.2.4.1. 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.”

17.6.2.5. 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).

17.6.2.5.1. 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.

17.6.2.6. 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.

17.6.2.7. 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.

17.6.2.7.1. 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

Target Lesions	Non-target Lesions	New Lesions	Time Point Response ¹
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.

17.6.2.7.2. 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.

17.6.2.7.3. 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.

17.6.2.7.4. 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.

17.6.2.8. 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 visit 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.

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

17.7.1. 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:

10 of 10

Your birthdate (Day, Month, Year):

31

Today's date (Day, Month, Year):

	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 <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> 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:

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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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

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



17.7.2. 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:

70. Have you had a dry vagina?

	Not at All	A Little	Quite a Bit	Very Much
70.	1	2	3	4

71. Have you had discomfort in your vagina?

71.	1	2	3	4
-----	---	---	---	---

Please answer the following two questions only if you have been sexually active:

72. Have you had pain in your vagina during sexual activity?

	Not at All	A Little	Quite a Bit	Very Much
72.	1	2	3	4

73. Have you experienced a dry vagina during sexual activity?

73.	1	2	3	4
-----	---	---	---	---

During the past week:

74. Have you been satisfied with the cosmetic result of the surgery?

	Not at All	A Little	Quite a Bit	Very Much
74.	1	2	3	4

75. Have you been satisfied with the appearance of the skin of your affected breast (thoracic area)?

75.	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?

76. _____

76.	1	2	3	4
-----	---	---	---	---

77. _____

77.	1	2	3	4
-----	---	---	---	---

78. _____

78.	1	2	3	4
-----	---	---	---	---

17.8. EuroQoL Five Dimensions Five Levels



Health Questionnaire

English version for the USA

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trademark of the EuroQol Group

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

MOBILITY

- | | |
|----------------------------------|--------------------------|
| I have no problems walking | <input type="checkbox"/> |
| I have slight problems walking | <input type="checkbox"/> |
| I have moderate problems walking | <input type="checkbox"/> |
| I have severe problems walking | <input type="checkbox"/> |
| I am unable to walk | <input type="checkbox"/> |

SELF-CARE

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have slight problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I have severe problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

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

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have slight problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I have severe problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

PAIN / DISCOMFORT

- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | <input type="checkbox"/> |
| I have slight pain or discomfort | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have severe pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort | <input type="checkbox"/> |

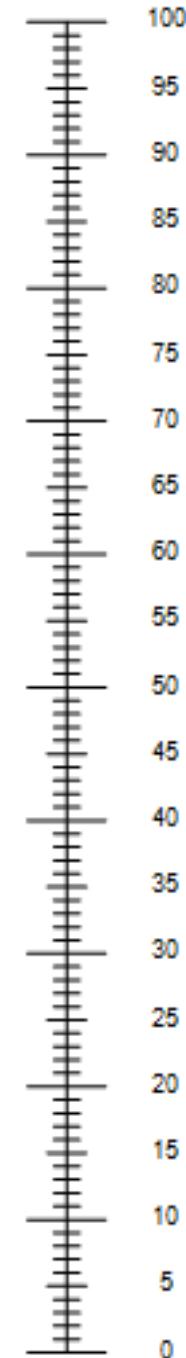
ANXIETY / DEPRESSION

- | | |
|--------------------------------------|--------------------------|
| I am not anxious or depressed | <input type="checkbox"/> |
| I am slightly anxious or depressed | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am severely anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed | <input type="checkbox"/> |

- 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 =

The best health
you can Imagine



The worst health
you can Imagine

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.

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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	Digitally signed by PPD
Print Name	Signature	Date: 2020.10.12 14:59:10 -04'00'
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:	<p><u>Primary Objective:</u></p> <ul style="list-style-type: none">• 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) <p><u>Key Secondary Objectives:</u></p> <ul style="list-style-type: none">• 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)
<p><u>In Sweden only, please see Section 17.9.1 for text applicable to sites in Sweden.</u></p>	

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.

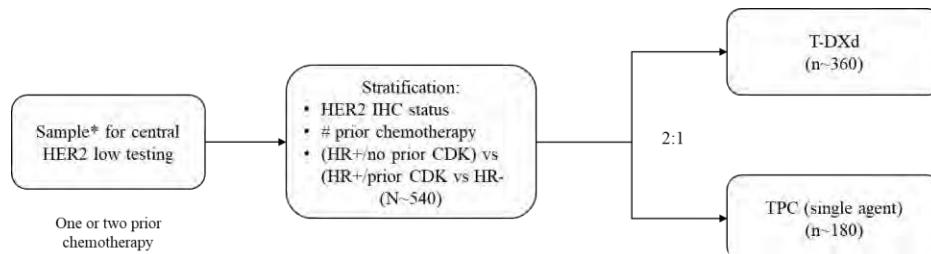
The ~540 subjects will be randomized 2:1 to T-DXd (~360) versus the physician's choice (~180) with one of the following drugs:

- 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:	<p>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.</p> <p>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 (\pm14 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.</p>
Study Centers and Location:	Approximately 225 sites, including but not limited to, North America, Western Europe, and Asia.
Subject Eligibility Criteria:	<p><u>Key Inclusion Criteria</u></p> <p>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:</p> <ul style="list-style-type: none">• Men or women \geq18 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:<ul style="list-style-type: none">– 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) $\geq 50\%$
 - 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) $\leq 5 \times$ upper limit of normal (ULN)
 - Total bilirubin $\leq 1.5 \times$ ULN if no liver metastases or $< 3 \times$ 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, **CC1** DP: A T-DXd **CC1**
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 guidelines¹ (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:	<p>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.</p> <p><u>Efficacy Analyses</u></p> <p>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).</p> <p>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.</p> <p>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.</p> <p>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:</p>

- 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.

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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 _{0-21d}	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
CCI [REDACTED]	CCI [REDACTED]
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
CCI	CCI
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
SpO ₂	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 CCI [REDACTED] DP) form of T-DXd will be administered in this study.

The T-DXd Phase 1 clinical study DS8201-A-J101 was initiated with the antibody component, MAAL-9001, CCI [REDACTED] DP1). To support new clinical studies, CCI [REDACTED] transition was made to MAAL-9001 CCI [REDACTED] DP2). Analytic comparison of the 2 CCI [REDACTED] products has shown comparability across a wide range of variables. Minor differences have been observed in glycan profile, charge variants, size variants, Fc_gR_{IIIA} binding, FcR_n binding, and antibody-dependent cellular cytotoxic activity. Following single intravenous (IV) administration of T-DXd to cynomolgus monkeys, mean maximum plasma/serum concentration (C_{max}) of T-DXd was similar while the area under the plasma/serum concentration-time curve (AUC) was about 22% lower for CCI [REDACTED] DP2 material as compared to CCI [REDACTED] DP1 material. However, in a xenograft study, no difference was seen in CCI [REDACTED] between the 2 products.

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:

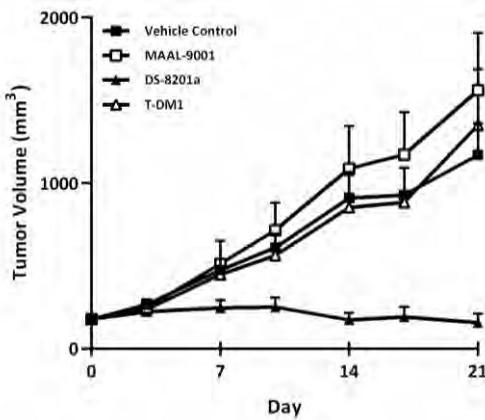
- Capecitabine
- Eribulin
- Gemcitabine
- Paclitaxel
- Nab-paclitaxel

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 guidelines¹ (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 (mm³) = 0.52 × length × width²

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 (± 1 week) 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

Pharmacokinetics were evaluated in 24 subjects who received T-DXd. Following a single IV administration, the systemic exposure increased approximately in proportion to the dose. The PK parameters at 5.4, 6.4, and 8.0 mg/kg are shown in [Table 1.2](#). The C_{max} of T-DXd at 6.4 mg/kg was achieved with a median time to reach C_{max} (T_{max}) of 2.16 hours. The C_{max} and AUC from time 0 to 21 days (AUC_{0-21d}) at 6.4 mg/kg were 181 $\mu\text{g}/\text{mL}$ and 901 $\mu\text{g}\cdot\text{d}/\text{mL}$, respectively ([Table 1.2](#)). The systemic exposure at 6.4 mg/kg in subjects in Cycle 1 was observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation. At this dose, the mean terminal elimination half-life ($t_{1/2}$) of T-DXd was 7.33 days at 6.4 mg/kg, and the volume of distribution at steady state (V_{ss}) was 58.6 mL/kg, which is similar to the serum volume.

The PK parameters of total antibody were close to that of T-DXd ([Table 1.3](#)).

The C_{max} and AUC for the dosing interval (AUC_{0-21d}) of MAAA-1181a, which were quite low, were 6.80 ng/mL and 31.0 ng \cdot d/mL at 6.4 mg/kg, respectively ([Table 1.4](#)). The $t_{1/2}$ of MAAA-1181a was similar to that of T-DXd.

For further details related to the clinical PK of T-DXd, please see the latest version of the IB.⁹

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

Dose (mg/kg)	C_{max} ($\mu\text{g}/\text{mL}$)	T_{max} (h) median (range)	AUC_{0-21d} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	$t_{1/2}$ (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
5.4 (N=6)	127 \pm 17.2	1.92 (1.92, 2.16)	544 \pm 165	590 \pm 186	6.03 \pm 0.603	10.1 \pm 3.90	75.2 \pm 24.2
6.4 (N=6)	181 \pm 33.1	2.16 (1.44, 4.08)	901 \pm 155	1030 \pm 209	7.33 \pm 1.64	6.41 \pm 1.12	58.6 \pm 11.0
8.0 (N=3)	216 \pm 52.0	1.92 (1.92, 2.16)	914 \pm 235	1020 \pm 279	6.97 \pm 0.357	8.17 \pm 1.93	69.7 \pm 13.1

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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; $t_{1/2}$ = 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 (\pm Standard Deviation)

T-DXd Dose (mg/kg)	C_{max} ($\mu\text{g}/\text{mL}$)	T_{max} (h) median (range)	AUC_{0-21d} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{d}/\text{mL}$)	$t_{1/2}$ (d)
5.4 (N=6)	116 \pm 13.9	1.92 (1.92, 6.96)	609 \pm 151	682 \pm 172	6.78 \pm 2.39
6.4 (N=6)	146 \pm 18.9	3.84 (2.16, 6.96)	878 \pm 97.1	1050 \pm 149	8.25 \pm 2.16
8.0 (N=3)	178 \pm 18.5	2.16 (1.92, 6.72)	1090 \pm 213	1270 \pm 296	7.35 \pm 0.417

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to reach C_{max} .

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

T-DXd Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h) median (range)	AUC _{0-21d} (ng·d/mL)	AUC _∞ (ng·d/mL)	t _{1/2} (days)
5.4 (N=6)	10.8 \pm 7.56	5.28 (3.84, 23.76)	40.6 \pm 19.8	43.6 \pm 21.2	6.11 \pm 0.811
6.4 (N=6)	6.80 \pm 1.72	6.72 (4.08, 7.20)	31.0 \pm 5.11	34.2 \pm 5.63	6.28 \pm 1.17
8.0 (N=3)	9.25 \pm 3.18	6.72 (6.72, 6.96)	39.4 \pm 6.43	43.4 \pm 9.16	6.36 \pm 1.53

AUC = area under the plasma/serum concentration-time curve; AUC_{0-21d} = 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_{1/2} = 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

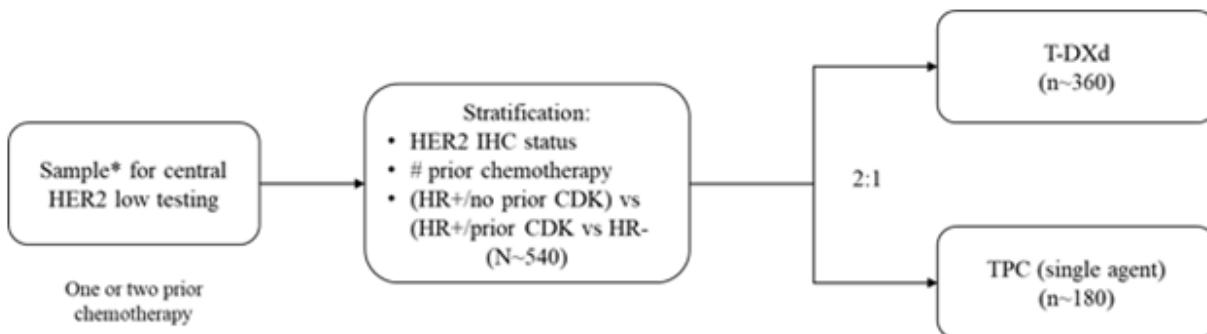
If a subject receives a comparator with a regimen other than a 21-day cycle, the Investigator should ensure that the subject follows the study-defined Schedule of Events per a 28-day cycle (see Section [17.1](#)). However, tumor assessments and CT/MRI of the brain must be performed every 6 weeks \pm 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 (\pm 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 \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.

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 $\geq 1\%$ 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-L1 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 $\geq 50\%$ within 28 days prior to randomization.
10. Adequate bone marrow function within 14 days before randomization, defined as:
 - Platelet count $\geq 100,000/\text{mm}^3$ (Platelet transfusion is not allowed within 1 week prior to Screening assessment)
 - Hemoglobin level $\geq 9.0 \text{ g/dL}$ (red blood cell transfusion is not allowed within 1 week prior to Screening assessment)
 - Absolute neutrophil count $\geq 1500/\text{mm}^3$ (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 $\geq 30 \text{ mL/min}$, as calculated using the Cockcroft-Gault equation (see Section 17.2; CLcr (mL/min) = $\frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ { $\times 0.85$ for females}).
12. Adequate hepatic function within 14 days before randomization, defined as:
 - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 5 \times$ upper limit of normal (ULN)

- Total bilirubin $\leq 1.5 \times$ ULN if no liver metastases or $< 3 \times$ 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 $\leq 1.5 \times$ 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

CCl [REDACTED] DP)

T-DXd for injection 100 mg CCl [REDACTED]

[REDACTED] 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 CCl 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 $\geq \pm 10\%$ 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:

- CCI [REDACTED]

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 guidelines¹ (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 \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. 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 guidelines¹ (see Table 5.1).

Table 5.1: Dose Regimens for Physician's Choice per the NCCN Guidelines¹

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/m ² 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2, then maintain dose
Grade 4	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2 Reduce dose 1 level
Febrile Neutropenia (Absolute neutrophil count $<1 \times 10^9/L$, fever $>38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than 1 hour)	<ul style="list-style-type: none"> Delay dose until resolved Reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	<ul style="list-style-type: none"> No dose modification
Grade 4 ($<0.2 \times 10^9/L$)	<ul style="list-style-type: none"> Delay dose until resolved to \leq Grade 2:

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
	<ul style="list-style-type: none"> – If resolved in \leq14 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	<ul style="list-style-type: none"> • Delay dose until resolved to \leq Grade 2, then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated	<ul style="list-style-type: none"> • Delay dose until resolved to \leq Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (Platelets <50 to $25 \times 10^9/L$)	<ul style="list-style-type: none"> • Delay dose until resolved to \leq Grade 1: <ul style="list-style-type: none"> – If resolved in \leq7 days from day of onset, maintain dose – If resolved in $>$7 days from day of onset, reduce dose 1 level
Grade 4 (Platelets $<25 \times 10^9/L$)	<ul style="list-style-type: none"> • Delay dose until resolved to \leq Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure	<ul style="list-style-type: none"> • Discontinue subject from study treatment
Decrease in LVEF 10% to 20% (absolute value), but LVEF $>45\%$	<ul style="list-style-type: none"> • Continue treatment with T-DXd
LVEF 40% to $\leq 45\%$ and decrease is $<10\%$ (absolute value) from baseline	<ul style="list-style-type: none"> • Continue treatment with T-DXd • Repeat LVEF assessment within 3 weeks
LVEF 40% to $\leq 45\%$ and decrease is 10-20% (absolute value) from baseline	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> if attributed to T-DXd, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Pulmonary Toxicity	<p>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.</p> <p>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.</p> <p>If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations.</p> <p>Evaluations should include:</p> <ul style="list-style-type: none"> 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. <p>Other tests could be considered, as needed.</p> <p>If the AE is confirmed to be ILD, follow the ILD management guidance as outlined below.</p> <p>All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.</p>

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
Grade 1	<p>The administration of T-DXd must be interrupted for any ILD events regardless of grade.</p> <ul style="list-style-type: none"> • 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.* <p>For Grade 1 events, T-DXd can be restarted only if the event is fully resolved to Grade 0, then:</p> <ul style="list-style-type: none"> • If resolved in ≤ 28 days from day of onset, maintain dose • If resolved in > 28 days from day of onset, reduce dose 1 level <p>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.</p> <p>* If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given.</p>
Grade 2	<p>Permanently discontinue subject from study treatment.</p> <ul style="list-style-type: none"> • 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 <u>gradual taper</u> 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, <ul style="list-style-type: none"> – 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	<p>Permanently discontinue subject from study treatment.</p> <ul style="list-style-type: none"> • Hospitalization required.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Management Guidelines for T-DXd
	<ul style="list-style-type: none"> 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 <u>gradual taper</u> over at least 4 weeks. Re-image as clinically indicated. If still no improvement within 3 to 5 days, <ul style="list-style-type: none"> Re-consider additional work-up for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose. If resolved in $>$7 days from day of onset, reduce dose 1 level.
Grade 4	<ul style="list-style-type: none"> Discontinue subject from study treatment
Blood Creatinine Increased	
Grade 3 (>3 to $6 \times$ ULN)	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 2 or baseline, then reduce dose 1 level
Grade 4 ($>6 \times$ ULN)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Hepatic Toxicity	
AST or ALT With Simultaneous Total Bilirubin	
AST/ALT $\geq 3.0 \times$ ULN with simultaneous total bilirubin $>2.0 \times$ ULN	<ul style="list-style-type: none"> 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 $5.0 \times$ ULN if baseline was normal; >3.0 to $5.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> No action for Grade 2 AST/ALT
Grade 3 (>5.0 to $20.0 \times$ ULN if baseline was normal; >5.0 to $20.0 \times$ baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level $\leq 3 \times$ ULN	<ul style="list-style-type: none"> Repeat testing within 3 days. Delay dose until resolved to \leqGrade 1 if baseline $\leq 3 \times$ ULN, otherwise delay dose until resolved to \leq baseline, then: <ul style="list-style-type: none"> 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 $20.0 \times$ ULN if baseline was normal; >8.0 to $20.0 \times$ baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was $>3 \times$ ULN	<ul style="list-style-type: none"> Repeat testing within 3 days. Delay dose until resolved to \leq baseline level, then: <ul style="list-style-type: none"> 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 ($>20.0 \times$ ULN if baseline was normal; $>20.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Total Bilirubin Increased	
Grade 2 (>1.5 to $3.0 \times$ ULN if baseline was normal; >1.5 to $3.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> 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 $10.0 \times$ ULN if baseline was normal; >3.0 to $10.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to \leqGrade 1: <ul style="list-style-type: none"> 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
	<ul style="list-style-type: none"> If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to \leqGrade 2: <ul style="list-style-type: none"> If resolved in \leq7 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 \times$ ULN if baseline was normal; $>10.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> Discontinue subject from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 (>5.0 to $20.0 \times$ ULN if baseline was normal; >5.0 to $20.0 \times$ baseline if baseline was abnormal), or Grade 4 ($>20.0 \times$ ULN if baseline was normal; $>20.0 \times$ baseline if baseline was abnormal)	<ul style="list-style-type: none"> No modification unless determined by the Investigator to be clinically significant or life-threatening
Gastrointestinal	
Nausea	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1 <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1 <ul style="list-style-type: none"> If resolved in \leq3 days from day of onset, maintain dose If resolved in $>$3 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> Discontinue subject from study treatment
Other Laboratory AEs	
Grade 3	<ul style="list-style-type: none"> Delay dose until resolved to \leqGrade 1 or baseline level: <ul style="list-style-type: none"> If resolved in \leq7 days from day of onset, maintain dose If resolved in $>$7 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> • Delay dose until resolved to \leqGrade 1 or baseline: <ul style="list-style-type: none"> – If resolved in \leq7 days from day of onset, maintain dose – If resolved in $>$7 days from day of onset, reduce dose 1 level
Grade 4	<ul style="list-style-type: none"> • 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 guidelines¹ 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.
- o 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:

- o Perform ECG in triplicate.
 - o Repeat troponin testing at 6 ± 1 hours and 12 ± 1 hours after initial troponin test.
 - o 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) $\geq 3 \times$ ULN and an elevated total bilirubin $> 2 \times$ 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 $\leq 1.5 \times \text{ULN}$ 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, \geq 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, \geq 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 guidance³² 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 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.

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 boundaries³³ 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.

16. REFERENCES

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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) <u>In Portugal only, please see Section 17.9.2 for text applicable to sites in Portugal</u>		•	
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	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)	40-Day 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: <ul style="list-style-type: none">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)	40-Day EOT ^b	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 (\pm 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 (\pm 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 (\pm 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 (\pm 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 \pm 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 \pm 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 than 14 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 $\mu\text{mol/L}$:

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.

17.5.1.3.2. 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.

17.5.1.3.3. 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 \times 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

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
2. Do you have any trouble taking a long walk?
3. Do you have any trouble taking a short walk outside of the house?
4. Do you need to stay in bed or a chair during the day?
5. Do you need help with eating, dressing, washing yourself or using the toilet?

Not at All	A Little	Quite a Bit	Very Much
------------	----------	-------------	-----------

1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4

During the past week:

6. Were you limited in doing either your work or other daily activities?
7. Were you limited in pursuing your hobbies or other leisure time activities?
8. Were you short of breath?
9. Have you had pain?
10. Did you need to rest?
11. Have you had trouble sleeping?
12. Have you felt weak?
13. Have you lacked appetite?
14. Have you felt nauseated?
15. Have you vomited?
16. Have you been constipated?

Not at All	A Little	Quite a Bit	Very Much
------------	----------	-------------	-----------

1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4
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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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

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 OLO-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?

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 | <input type="checkbox"/> |
| I have slight problems walking | <input type="checkbox"/> |
| I have moderate problems walking | <input type="checkbox"/> |
| I have severe problems walking | <input type="checkbox"/> |
| I am unable to walk | <input type="checkbox"/> |

SELF-CARE

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have slight problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I have severe problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

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

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have slight problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I have severe problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

PAIN / DISCOMFORT

- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | <input type="checkbox"/> |
| I have slight pain or discomfort | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have severe pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort | <input type="checkbox"/> |

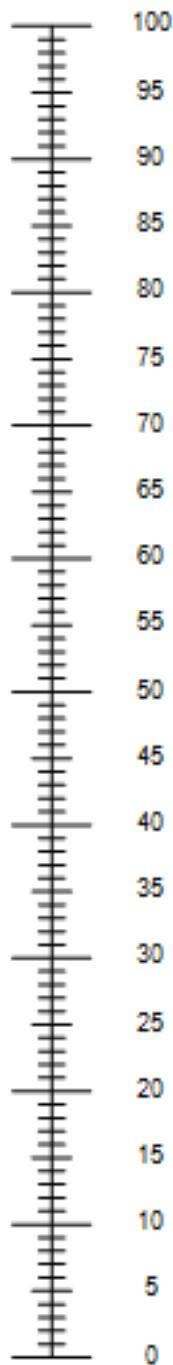
ANXIETY / DEPRESSION

- | | |
|--------------------------------------|--------------------------|
| I am not anxious or depressed | <input type="checkbox"/> |
| I am slightly anxious or depressed | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am severely anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed | <input type="checkbox"/> |

- 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 =

The best health
you can imagine



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. 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.

**STATISTICAL ANALYSIS PLAN
(SAP)**

**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 HER2LOW,
UNRESECTABLE AND/OR METASTATIC BREAST
CANCER SUBJECTS
(DESTINY-Breast04)**

DS8201-A-U303

VERSION 1.0, 6 NOVEMBER 2020

DAIICHI SANKYO INC.

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SAP APPROVAL FORM

Prepared By:

PPD

Print Name

Signature

Date

Director, Biostatistics

Title

PPD

Print Name

Signature

Date

Senior Principal Biostatistician, Covance

Title

Approved By:

PPD

Print Name

Signature

Date

Executive Director, Biostatistics

Title

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ADA	anti-drug antibody(ies)
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
BICR	blinded independent central review
DCR	disease control rate
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
cfDNA	cell free deoxyribonucleic acid
CI	confidence interval
Cmax	maximum plasma/serum concentration
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAE	discontinuation due to adverse events
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
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
HEOR	health economics and outcomes research

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HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of HER2
HR	hormone receptor
IHC	immunohistochemistry
ISH	in situ hybridization
ITT	intent-to-treat
IV	Intravenous(ly)
IXRS	Interactive Web/Voice Response System
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PK	pharmacokinetic
PopPK	population pharmacokinetics
PPS	Per-protocol Analysis Set
PR	partial response
PT	preferred term
RES	Response Evaluable Set
RR	respiratory rate
QoL	quality of life
QTc	corrected QT interval
QTcF	QT intervals corrected for heart rate by Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class

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SpO2	peripheral oxygen saturation
TBL	Total Bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TPR	time point response
TTR	time to response
VAS	visual analogue scale
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the efficacy, safety, pharmacokinetic, pharmacodynamics, health economics and outcomes research endpoints for the clinical study report (CSR) of the study protocol DS8201-A-U303, 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. The contents of the SAP are based on protocol Version 5.0 (12 October 2020). All decisions regarding final analysis, as defined in the SAP document, will be made prior to database lock and unblinding of study data. Specifications for tables, listings, and figures are contained in a separate document.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan (T-DXd) to physician's choice in human epidermal growth factor receptor 2 (HER2)-low, hormone receptor (HR)-positive breast cancer, based on blinded independent central review (BICR).

2.2. Key Secondary Objectives

The key secondary objectives are:

- To compare 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)

2.3. Other Secondary Objectives

The other secondary objectives are:

- To investigate the efficacy of T-DXd compared to physician's choice on the following parameters:
 - 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

2.4. Exploratory Objectives

The exploratory objectives are to evaluate the following:

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

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- Disease control rate (DCR), based on BICR and Investigator assessment 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 and Investigator assessment.
- 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

3. STUDY DESIGN AND METHODS

3.1. General Study Design and Plan

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 (see [Figure 3.1](#) for study design schema).

Approximately 540 subjects (including approximately 480 HR-positive subjects and 60 HR-negative subjects) will be randomized in a 2:1 ratio into 2 treatment groups (T-DXd versus physician's choice).

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

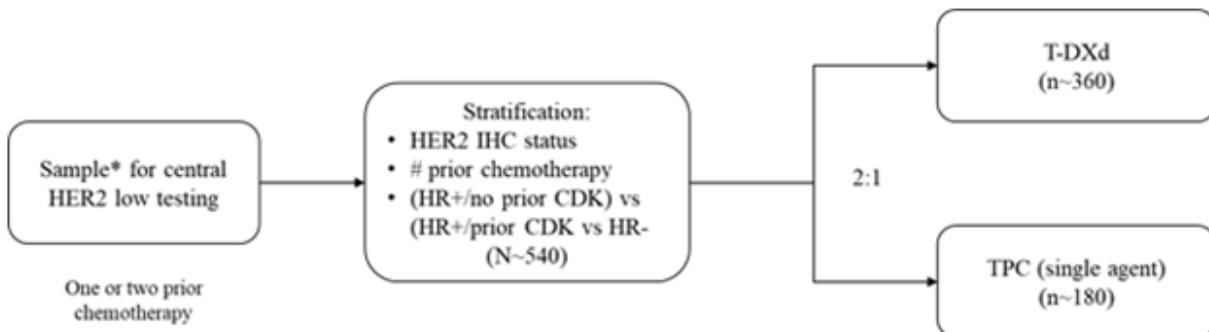
The comparator for this study is the physician's choice with the options being one of the following:

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

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.

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 3.1 and Section 3.2 of the protocol (v5, 12 Oct 2020) for details.

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. If the study treatment is delayed more than 28 days from the planned date of administration, the subject will be withdrawn from the study.

After study treatment discontinuation, all subjects may be contacted at the 40-Day (+7 days) Follow-up Visit, 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. 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.

Progression free survival (PFS) based on BICR, in HR-positive breast cancer subjects is the primary endpoint in this study. The primary efficacy analysis is planned to be performed after approximately 318 BICR PFS events in the HR-positive subjects have been documented in the study.

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 if study continues after OS interim analyses.

An independent Data Monitoring Committee (DMC) will monitor unblinded safety data accruing in the trial. A separate DMC SAP describes the analyses for the DMC reviews.

3.2. Randomization

The target sample size of approximately 480 HR-positive subjects and approximately 60 HR-negative subjects will be randomized in a 2:1 ratio to the 2 treatment arms (T-DXd versus the comparator of physician's choice).

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

3.3. Blinding

This study is an open-label study as it is not feasible to blind treatment allocations for individual subjects because of different routes of administration, different treatment schedules, between T-DXd and investigator's choice therapy.

3.4. Schedule of Events

Refer to Section 17.1 of DS8201-A-U303 protocol for schedule of events.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

Detailed specifications of efficacy endpoints are provided in Section 8 below.

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, based on BICR, in HR-positive subjects. PFS 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 according to mRECIST version 1.1 or death due to any cause. If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the last adequate tumor evaluation date before the cut-off date. See Section 8.2 for details related to censoring rules. Discontinuation associated with disease progression, without supporting objective evidence satisfying progression criteria per mRECIST 1.1 will not be considered as a PFS event.

4.1.2. Key Secondary Efficacy Endpoint

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

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.

4.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are:

- PFS, based on investigator assessment
- Confirmed ORR, defined as the proportion of subjects with best overall response of confirmed complete response (CR) or partial response (PR), 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 (confirmed 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 (confirmed CR or PR) only. Subjects who are progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment.

4.1.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- CBR, defined as the sum of CR rate, PR rate, and more than 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 (confirmed CR or PR), based on BICR. Time to response will be measured for responding subjects (confirm 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.

4.2. Safety Endpoints

4.2.1. Adverse Events

The AE safety endpoints include:

- Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
- Serious adverse events (SAEs)
- Adverse events of special interest (AESIs)
- TEAEs associated with dose reduction and dose interruptions
- TEAEs associated with discontinuations of study treatment
- TEAEs associated with death as outcome

4.2.2. Clinical Laboratory Evaluations

Standard clinical laboratory parameters are included as a safety endpoint. Refer to Section 7.3.4 for details.

4.2.3. Vital Signs

Vital sign measurements are included as safety endpoints. Refer to Section 7.3.5 for details.

4.2.4. Electrocardiogram

Electrocardiogram (ECG) parameters are included as safety endpoints. Refer to Section 7.3.6 for details.

4.2.5. Other Safety Endpoints

Other safety endpoints include:

- Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
- Echocardiogram (Echo)/multi-gated acquisition scan (MUGA) findings
- Anti-drug antibodies (ADA)
- Neutralizing ADA

4.3. Pharmacokinetic Endpoints

The PK endpoints include serum concentrations of T-DXd, total anti-HER2 antibody and DXd.

4.4. Pharmacodynamics Endpoint

Not applicable in this study.

4.5. Biomarkers

Biomarker endpoints may be added in the future when applicable.

4.6. Health Economics and Outcomes Research Endpoints

The Heath Economics and Outcomes Research (HEOR) endpoints include:

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

5. SAMPLE SIZE DETERMINATION

A total of approximately 480 HR-positive subjects will be randomized (approximately 320 T-DXd and approximately 160 physician's choice). In addition, approximately 60 HR-negative subjects (approximately 40 T-DXd and approximately 20 physician's choice) will be enrolled for exploratory purpose.

Assuming a median PFS of 4.2 months in the physician's choice arm in HR-positive subjects, it is hypothesized that treatment with T-DXd will result in a hazard ratio of 0.68, a 32% reduction in the hazard rate of PFS (disease progression or death) that would correspond to a 47% improvement in median PFS from 4.2 months in the physician's choice arm to 6.2 months in the T-DXd arm under the exponential model assumption.

The final PFS analysis will occur after approximately 318 PFS events have been documented in HR-positive subjects. With 318 PFS events, the study will have approximately 90% power of a log-rank test to reject the null hypothesis of no difference in PFS distributions at an overall 2-sided significance level of 0.05, assuming a hazard ratio of 0.68.

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 have demonstrated statistical significance. Assuming a median OS of 15 months in the control arm in HR-positive subjects¹²³⁴⁵⁶⁷, it is hypothesized that treatment with T-DXd will result in a hazard ratio of 0.72 in OS that would correspond to a 39% improvement in median OS from 15 months in the physician's choice arm to 20.8 months in the T-DXd arm under the exponential model assumption. With a total of 333 OS events, the study will have approximately 80% power of a log-rank test (conditional on PFS being significant) to reject the null hypothesis at an overall 2-sided significance level of 0.05 under a 3-look group sequential design with O'Brien-Fleming superiority boundary⁸ of Lan-DeMets alpha spending function⁹ (see Section 6.2 for further details), assuming a hazard ratio of 0.72. If the true hazard ratio is 0.72, it is estimated that approximately 162 (49%) and 233 (70%) of the targeted OS events will be documented in HR-positive subjects at the times of the 2 OS interim analyses (the first OS interim analysis performed at the time of PFS final analysis).

The sample size calculation was performed using the EAST version 6.4¹⁰.

6. GENERAL STATISTICAL CONSIDERATIONS

Summary statistics will be presented by treatment group, T-DXd and physician's choice.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

For efficacy evaluations, the last available assessment on or before the date of randomization will be used as the "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include patient reported outcomes. If there is no patient reported outcome prior or on the randomization date, the assessment prior or on the first drug administration date and closest to the randomization date will be used as baseline assessment.

For safety evaluations (e.g. laboratory, ECG and vital signs), the last available assessment before start of study treatment will be used as the 'baseline' assessment. If subjects have no value as defined above, the baseline results will be set to missing.

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. 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 HR-positive cohort and FAS. Sensitivity analysis of primary efficacy endpoint may be performed on per-protocol analysis set (PPS). Safety analyses will be performed using the safety analysis set. PK analysis will be based on the PK analysis set. All other exploratory analyses will be performed based on the HR-positive cohort and FAS.

6.1. Analysis Sets

6.1.1. 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 and stratum assigned at randomization.

6.1.2. 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.

6.1.3. Per-Protocol Analysis Set (PPS)

The PPS will include all subjects in the HR-positive cohort who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumor assessment, and absence of major protocol violations likely to impact efficacy outcome. To be eligible for inclusion in the PPS, subjects must meet the following criteria:

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- Received at least one dose of study drug as assigned by randomization
- Had at least one evaluable post-baseline tumor assessments or died more than 14 weeks of randomization without post-baseline scans
- Absence of major protocol violations as described below.

Major protocol deviations that lead to exclusion from the PPS are as follows:

- Did not sign informed consent
- Eligibility Criteria

A subject who violates any of the following inclusion and/or exclusion criteria will be classified as a major protocol deviation likely to impact efficacy outcome:

Inclusion Criteria (per protocol):

- IC #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 American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines evaluated at a central laboratory;
 - e. is documented refractory to endocrine therapy If HR-positive, 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;
 - 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.

IC #4. Documented radiologic progression (during or after most recent treatment).

IC #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.

Exclusion Criteria (per protocol):

EC #1. Ineligible for a comparator in the physician's choice arm either because of previously having received treatment in the metastatic setting with the same comparator or having a contraindication to treatment.

EC #2. Prior treatment with antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor.

- A subject who received a study drug regimen that was not assigned by randomization, i.e., the alternative treatment was received throughout the study.

The PPS will be determined by the study team and documented in the data handling plan prior to database lock.

6.1.4. Pharmacokinetic (PK) Analysis Set

The PK analysis set will include all subjects who received at least 1 dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and DXd.

6.2. Interim Analyses and Data Monitoring

No formal interim analysis is planned for PFS.

Up to three analyses of OS are planned:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant in both HR-positive cohort and FAS), at which point a total of 162 OS events (49% information fraction) in HR-positive cohort 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 cohort 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 cohort 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 is adopted as described in Section 6.3 below.

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 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 HR-positive cohort and FAS.

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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 6.1](#).

Table 6.1: Stopping Boundaries at OS Interim and Final analyses

Analysis time (month)*	Number of OS events (Information fraction)	HR (p-value) superiority boundary ^a	Minimal detectable difference in median OS vs 15 for control arm (month) ^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

* 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 month, 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.

6.3. Multiple Comparisons/Multiplicity

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

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.

7. STATISTICAL ANALYSIS

7.1. Summary of Study Data

7.1.1. Subject Disposition

Subject disposition will be summarized and listed for all screened subjects. Number of screen failures will be presented. The total number of subjects for each defined analysis set will also be tabulated.

7.1.2. Protocol Deviations

Major protocol deviations will be summarized by treatment arm and by category for subjects in FAS. All protocol deviations will be listed by treatment group.

7.1.3. Demographic and Baseline Characteristics

The demographic and baseline disease characteristics will be summarized descriptively and listed for the HR-positive cohort, and FAS.

Discrepancies between randomization stratification information (obtained from IXRS) and strata formed based on baseline factors collected on eCRFs will be tabulated and listed.

7.1.3.1. Diagnosis and Extent of Cancer

Summary statistics will be tabulated for diagnosis and extent of cancer using HR-positive cohort and FAS.

According to the data collected on the eCRF, this analysis will include the following: histological grade, stage at initial diagnosis, stage at study entry, grade, HER2 expression (IHC), HER2 gene amplification (ISH), estrogen receptor status, progesterone receptor status, BRCA1 status, BRCA2 status, time since initial diagnosis, and presence/absence of target and non-target lesions.

A listing will be provided for FAS.

7.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHOdrug). Concomitant medications will be summarized by ATC2 class and preferred term for the safety analysis set. Prior medications will be summarized for the HR-positive cohort. Within each level of summarization, a subject will be counted once if he/she takes one or more medications.

Prior medications are defined as those with a stop date prior to the date of first dose of study drug. Concomitant medications are defined as those with a start date greater than or equal to the date of first dose of study drug, or with a start date prior to the date of first dose of study drug and a stop date either after the date of first dose of study drug or marked as “ongoing” or

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“continuing”. Medications taken prior to the first dose of study drug, but with a missing stop date or with a stop date either on or after the date of the first dose of study drug or marked as “ongoing” or “continuing” will also be considered concomitant medications for the summary. Medications started after the 47-day visit or after start of new anticancer therapy are not considered as concomitant medications. A listing of prior and concomitant medications by subject will also be provided.

7.2. Efficacy Analyses

7.2.1. Analysis of PFS

7.2.1.1. Primary Efficacy Analysis

The primary efficacy analysis will be the comparison of the distribution of PFS per BICR in HR-positive cohort between the two treatment groups using stratified log-rank test, with stratification factors from IXRS, at two-sided significance level of 0.05, under statistical hypotheses:

$$H_0: S_T(t) = S_C(t) \text{ vs. } H_a: S_T(t) \neq S_C(t), t \geq 0$$

where $S_T(t)$ is the survival distribution function of PFS with the treatment of T-DXd and $S_C(t)$ is the survival distribution function of PFS with the control treatment group.

The primary efficacy analysis will be performed using HR-positive cohort based on the data up to the data cut-off date when approximately 318 BICR-assessed PFS events are observed. If a patient has not progressed or died, at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date (See Section [8.2.1.1](#) for additional details regarding censoring rules). Discontinuation associated with disease progression, without supporting objective evidence satisfying progression criteria per mRECIST version 1.1, will not be considered as a PFS event.

The hypothesis will be tested using a stratified log-rank test at two-sided significance level of 0.05. The stratification factors will be the randomization stratification factors taken from IXRS. The distribution of PFS will be estimated using the Kaplan-Meier (K-M) method for each treatment arm, and the results will be presented graphically by treatment group.

The median PFS and the two-sided 95% confidence intervals (CIs) using Brookmeyer and Crowley method¹¹ will be provided for each treatment group. In addition, PFS rates at fixed time points (e.g., 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group.

The hazard ratio of PFS and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with treatment group as model factor and the stratification factors from IXRS as strata.

7.2.1.2. Supportive and Sensitivity Analyses

As a sensitivity analysis to assess the impact of stratification on primary efficacy analysis, the two treatment groups will be compared using an unstratified log-rank test. The same censoring rules used for the primary efficacy analysis will be applied. The hazard ratio together with associated 95% CI will also be estimated using unstratified Cox proportional hazards regression model.

The primary efficacy analyses will be repeated for FAS and PPS if the PPS and the full analysis sets differ.

A stratified Cox regression model with strata collected through IXRS as stratification factor will be fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio. This model will include the following key prognostic factors as covariates: ECOG performance status (0, 1), lines of endocrine therapy received in the metastatic setting (0, 1, 2, ≥ 3), history CNS metastases (yes, no), and age (<65 , ≥ 65 years old). The p-value associated with treatment and with each of the baseline covariates will be presented. The hazard ratio along with the associated 95% CI will also be presented for each covariate.

In addition to the above, the sensitivity analyses of the primary efficacy endpoint will be performed to assess the impact of censoring rules used for the primary efficacy analysis. The following test statistics will be provided: stratified log-rank test p-values, K-M estimates of survival distribution, estimate of the median PFS along with 95% confidence interval, and hazard ratio obtained using stratified Cox proportional hazards model. Sensitivity analyses include the following:

- Using the BICR-assessed PFS data on the HR-positive cohort, and including PFS events whenever they occurred, i.e. not censoring for missing 2 consecutive tumor assessments
- Using the BICR PFS data on the HR-positive cohort, but censoring for new anticancer therapy
- Backdating PFS analysis: repeat primary analysis of the primary efficacy endpoint but backdate PFS event time in the case that PFS event occurred after missing one or more tumor assessments. In such cases, the PFS event date would be considered to be 6 weeks after last evaluable tumor assessment occurring prior to progression/death.

Additional supportive analyses will include:

- Number of subjects and number of events by treatment arm within each stratum will be presented along with hazard ratio obtained using unstratified cox regression model, provided enough events are observed within each stratum. K-M estimates of median survival and 95% CIs will be presented for each treatment group. No formal statistical comparison will be carried out within stratum.
- If there is $\geq 10\%$ discrepancy between strata constructed through the eCRF data and those obtained through IXRS, a sensitivity analysis may be performed where the treatment

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effect HR will be estimated along with the 95% CI using a stratified cox regression model, where the stratum is derived based on the eCRF data. No inferential statistics (p-values) will be presented.

7.2.1.3. Censoring Pattern of PFS

Number of subjects in the PFS analysis and the number of subjects with a PFS event will be summarized for HR-positive cohort and FAS. In addition, a summary of reasons for censoring will be provided by treatment based on the following reasons:

- No baseline tumor assessments
- No post-baseline tumor assessments
- Event after ≥ 2 missing tumor assessments
- No PD or death

Details on the PFS censoring rules are given in Section 8.2.1.1.

7.2.1.4. Concordance Analysis of PFS

Concordance analysis will be performed for FAS.

Cross-tabulation of 'PFS by BICR' vs. 'PFS by investigator' by PFS event type (i.e., 'death', 'PD', and 'censor' for each of the two sources resulting in a 3-by-3 table) and by treatment will be constructed to assess concordance between the two sources on a patient-by-patient basis.

Discrepancy (%) rate between 'BICR assessed' and 'Investigator-assessed' PFS status (event vs censor) will be calculated and presented (by treatment group) as follows: $100 \times (n_{13} + n_{23} + n_{31} + n_{32}) / N$.

Comparison Between PFS Investigator and BICR Assessments in HR-positive cohort

<i><Treatment group> N=XXX</i>			
Investigator PFS result	BICR PFS result		
	Death	PD	Censor
Death	n11	n12	n13
PD	n21	n22	n23
Censor	n31	n32	n33

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A cross-tabulation will be produced displaying the PFS timings for the local investigators' assessment compared to the BICR assessment. For progression assessments, the frequency and percent of subjects with complete agreement [occurring on the same date plus or minus 7 days of each other], progression later, progression earlier, and cases where progression was called by one method and censored by the other will be displayed. Similarly, if censoring was recorded, the frequency and percent of subjects with complete agreement, censoring called later, censoring called earlier, and cases where censoring was called by one method and progression was called by the other method will be displayed.

Comparison of PFS Event Times between Investigator and BICR Assessments in HR-positive cohort

		< Treatment arm > (N = XXX)			
Investigator	BICR	Same time n (%)	BICR after Investigator n (%)	BICR before Investigator n (%)	Total
PD	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	Death	xx (xx.x)	-	-	xx (xx.x)
Censor	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Death	-	xx (xx.x)	-	XX (xx.x)
Death	PD	-	-	xx (xx.x)	xx (xx.x)
Death	Censor	-	-	xx (xx.x)	xx (xx.x)
Censor	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Censor	Death	-	xx (xx.x)	-	xx (xx.x)
Total		xx (xx.x)	xx (xx.x)	xx (xx.x)	xxx(100.00)

7.2.1.5. Subgroup Analysis of BICR-assessed PFS

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

For each of these subgroups, the median PFS and the two-sided 95% confidence intervals (CIs) using the K-M method as well as the estimated HR and 95% CI obtained using the unstratified Cox regression model will be presented. Subgroup analyses will be performed only if at least 10 PFS events in both treatment group. A forest plot will be used to depict the estimated treatment effects.

Subgroups 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 (USA, CAN), Europe (AUT, CHE, BEL, ESP, FRA, GBR, GRC, HUN, ISR, ITA, PRT, RUS, SWE)+ Israel, Rest-of-World (RoW))
- Lines of endocrine therapy received in the metastatic setting (0, 1, 2, >=3)
- Best Response to prior cancer systemic therapy
- Reported history of CNS metastases (yes, no)
- Clinically inactive central nervous system (CNS) metastases (Yes, No)
- Renal impairment at baseline (within normal range, mild/moderate impairment)

Renal impairment status is determined by the baseline creatinine clearance as calculated using the Cockcroft-Gault equation:

- Normal renal function: creatinine clearance ≥90 mL/min
- Mild renal impairment: creatinine clearance ≥60, <90 mL/min
- Moderate renal impairment: creatinine clearance ≥30, <60 mL/min
- Severe renal impairment: creatinine clearance ≥15, <30 mL/min
- End stage renal disease: creatinine clearance <15 not on dialysis or requiring dialysis
- Hepatic impairment at baseline (within normal range, mild impairment)
 - Normal hepatic function:
 - Total bilirubin ≤ upper limit of normal (ULN) and (AST ≤ULN) except for subjects with Gilbert syndrome (preferred term [PT]: 10018267)

- Total bilirubin \leq 3.0 xULN and (AST \leq ULN) for subjects with Gilbert syndrome
- Mild dysfunction:
 - Total bilirubin >ULN, \leq 1.5 xULN and any AST except for subjects with Gilbert syndrome
 - Total bilirubin >ULN, \leq 3.0 xULN and (AST >ULN) for subjects with Gilbert syndrome
 - Total bilirubin \leq ULN and (AST >ULN) regardless of Gilbert Syndrome
- Moderate dysfunction:
 - Total bilirubin >1.5 xULN, \leq 3.0 xULN and any AST except for subjects with Gilbert syndrome
- Severe dysfunction:
 - Total bilirubin >3.0 xULN and any AST regardless of Gilbert Syndrome
- Baseline visceral disease (yes, no)

Visceral disease is determined with any target or non-target tumor except “Breast”, “Skin”, “Lymph Node”, and “Bone” in the location on the “Target/Non-Target Tumor Assessments (Imaging Baseline)” CRF page. A detail list of the locations to be included/excluded is provided in Appendix 11.4.
- ECOG PS (0, 1)

The subgroups are based on baseline values (i.e., the last non-missing values before the first drug administration). Note that HR-negative cohort will be added in subgroup analysis of PFS for FAS.

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. No inferential statistics (p-values) will be presented for the subgroups.

7.2.2. Analysis of OS

OS is defined as the time from the date of randomization to the date of death due to any cause. Subjects without an OS event are censored at date of last contact when subjects are known to be alive. Derivation of date of last contact is provided in Section 8. The analysis of OS will be performed for HR-positive cohort and FAS.

Overall survival will be compared between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at 2-sided significance level adjusting for alpha spending, provided superiority in PFS per BICR is demonstrated in both HR-positive cohort and FAS. The survival distribution of OS will be estimated by Kaplan-Meier method and results will be presented graphically. The median survival time and the 2-sided 95% CI for the median will be provided using Brookmeyer and Crowley method for each treatment group. In addition, Kaplan-Meier estimates of OS rate at fixed time points (e.g., 3, 6, 9, 12, 18, 24, 36, 48 months) along with their 2-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its 95% CI will be estimated, using stratified Cox

proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

7.2.2.1. Supportive Analyses for OS

If the analysis of OS is significant, a Cox regression model stratified by the IXRS stratification factors will be fitted to evaluate the effect of the same prognostic factors as specified earlier for the Cox regression analysis for PFS.

7.2.2.2. Censoring Pattern of OS

The pattern of censored data will be presented by treatment group. Reasons for censoring (“Alive”, “Lost to follow-up”) will be summarized. In addition, survival status, reasons for censoring, and causes of death will be listed. Subjects not known to have died will be censored due to lost to follow-up if the time interval between the last contact date and analysis cut-off date is longer than the protocol-defined 3 months interval of survival follow-up plus 2 weeks.

7.2.2.3. Subgroup Analysis for OS

Subgroup analyses of OS will be performed for HR-positive cohort and FAS using the same subgroups defined for the PFS analysis and using the same methodology, provided PFS analyses are significant for both HR-positive cohort and FAS. Note that HR-negative cohort will be added in subgroup analysis of OS for FAS.

7.2.2.4. Currentness of PFS and OS Follow-up

Time from last tumor assessment to data cut-off in weeks will be summarized by treatment arm for HR-positive cohort. Subjects who have a PFS event will be considered as current for this analysis. The currentness of PFS follow-up will be categorized into the following categories: 0-6 weeks, 6-12 weeks, and > 12 weeks. The median follow-up duration for PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group using the Kaplan-Meier method by reversing the PFS censoring and event indicators.

Currentness of OS follow-up will be summarized in months, by computing the time from “last known alive” date to data cut-off date. Subjects who have a death event will be considered as current for this analysis. The currentness of follow-up will be categorized into the following categories: 0-3 months, 3-6 months, and > 6 months. The median follow-up duration for OS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group using the Kaplan-Meier method by reversing the OS censoring and event indicators.

7.2.3. Analysis of Other Secondary Efficacy Endpoints

Analysis of other secondary efficacy endpoints will be performed based on HR-positive cohort of FAS and the FAS at the time of primary PFS analysis.

Other efficacy endpoints include PFS based on investigator assessment, confirmed objective response rate based on BICR and investigator assessment, and duration of response based on BICR and investigator assessment.

7.2.3.1. PFS Based on Investigator Assessment

The survival distribution of PFS based on investigator assessment will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (e.g., 3, 6, 9, 12, 18, 24 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 same stratification factors as the randomization stratification factors taken from IXRS. The survival distribution of PFS based on investigator assessment between the two treatment groups will be compared at a two-sided significance level of 0.05, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at the time when primary analysis of PFS per BICR is statistically significant.

7.2.3.2. Confirmed Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with best overall response of confirmed complete response (CR) or partial response (PR) according to mRECIST version 1.1 criteria. ORR will be calculated based on the data from the full analysis set based on BICR assessment of tumor scans. Subjects with only non-measurable disease at baseline will be included in the numerator only if a complete response was observed.

Number and proportion of subjects in each response category of BOR will be provided by treatment group. ORR (based on BICR and investigator assessment) will be summarized by treatment group along with the two-sided 95% CIs using the Clopper-Pearson method. The difference of ORR between the two treatment groups will be summarized and the 95% CI will be calculated using continuity correction. The Cochran-Mantel-Haenszel test stratified by the randomization stratification factors per IXRS will be used to compare ORR at two-sided significance level of 0.05.

As a supportive analysis, ORR will also be summarized by using the investigator review of tumor data.

7.2.3.3. Duration of Response

Duration of response (DoR) is defined as the time from date of initial response (confirmed CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. DoR (based on BICR and investigator assessment, respectively) will be summarized with median duration and its two-sided 95% CI for the median using Brookmeyer and Crowley method for each treatment group. K-M estimates of the distribution of DoR will be calculated and presented graphically by treatment group. The same censoring rules will be applied as for the primary analysis of PFS based on BICR or based on investigator assessments, respectively. DOR will be calculated only for subjects with a best overall response of confirmed CR or PR.

7.2.4. Analysis of Exploratory Efficacy Endpoints

Analysis of exploratory efficacy endpoints will be performed based on HR-positive cohort of FAS and the FAS at the time of primary PFS analysis.

The exploratory endpoints include clinical benefit rate (CBR) based on BICR, disease control rate (DCR) based on BICR, time to response (TTR) based on BICR, best percent change in the sum of the diameters of measurable tumors based on BICR, and PFS2.

7.2.4.1. Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as proportion of subjects with best overall response of CR, PR, or more than 6 months Stable Disease (SD). The analyses for ORR will be repeated for CBR based on BICR assessment.

7.2.4.2. Disease Control Rate

Disease control rate (DCR) per BICR is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) according to mRECIST version 1.1. The analyses for ORR will be repeated for DCR.

7.2.4.3. Time to Response

Time to response (confirmed CR or PR, based on BICR) is defined as the time between date of randomization until the first documented response (confirmed CR or PR). Patients with a confirmed CR or PR will be included in the time to response calculation. Descriptive statistics will be used to summarize time to response.

7.2.4.4. Change of Sum of Diameters from baseline to post-baseline minimum

Descriptive statistics for percent change from baseline to the best (minimum) post-baseline sum of the diameters (based on BICR) will be provided by treatment group. A waterfall plot of the best percent change from baseline to post-baseline minimum in the sum of the diameters for each subject will be presented for each treatment group with vertical lines representing the sorted values of percent changes. Only subjects with measurable target lesions at baseline will be included for this analysis. All measurable assessments up to start of new anticancer therapy or progressive disease will be included.

7.2.4.5. PFS2

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.

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 (e.g., 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 taken from IXRS as strata variables. Analysis of PFS2 will be performed for HR-positive cohort and FAS.

7.3. Safety Analyses

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

7.3.1. Dosing and Extent of Exposure

Study treatment exposure and treatment duration will be summarized by treatment group using descriptive statistics for the safety analysis set. In addition, the total number of cycles initiated will be summarized using descriptive statistics. The number and percentage of subjects who continued the treatment at fixed time points (e.g., 3, 6, 9, 12 months) will be tabulated. T-DXd dosing status will be summarized to show the number and percentage of subjects with and without dose reductions or interruptions. For subjects with dose reductions, delays, or interruptions, the reasons will be provided.

All study drug administration data will be listed by subject.

The following definitions will be used.

- Duration of exposure (day)
 - Duration of exposure (day) for therapies with daily dose
= Last dose date – First dose date + 1
 - Duration of exposure (day) for 7 day-cycle based therapies
= Date of first dose of last cycle – First dose date + 7
 - Duration of exposure (day) for 21 day-cycle based therapies
= Date of first dose of last cycle – First dose date + 21
 - Duration of exposure (day) for 28 day-cycle based therapies
= Date of first dose of last cycle – First dose date + 28
- Planned cumulative dose (mg/kg)
= Total amount of dose planned to be taken per protocol for the duration of exposure in question
- Cumulative dose (mg/kg)
= Total amount of doses actually taken (mg/kg)
- Dose intensity (DI) (mg/kg/3 weeks)
= Cumulative dose (mg/kg) / Duration of exposure/21
- Planned dose intensity (PDI) (mg/kg/3 weeks) = Planned cumulative dose (mg/kg)/Duration of exposure (day)/21
- Relative dose intensity (RDI) (%)
= (Dose intensity (DI) / Planned dose intensity (PDI))*100,

7.3.2. Adverse Events

A TEAE is defined as an AE that occurs 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 the MedDRA with the current version at database lock. AE grades will be based on NCI-CTCAE v5.0.

A high level summary of the number of subjects with TEAEs will be presented by treatment group, including the number and percentage of subjects with any TEAEs, treatment emergent serious adverse events (TESAEs), TEAEs related to study treatment, and TEAEs associated with dose interruption, dose-reduction, or discontinuation of study treatment.

The number and percentage of subjects reporting TEAEs will be tabulated by System Organ Class (SOC), Preferred Term (PT), relationship to the study treatment, and the worst CTCAE grade for all and treatment related TEAEs. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by treatment group, as well as TEAEs associated with interruption, dose-reduction, or discontinuation of the study treatments.

A by-subject AE (including TEAE) data listing including but not limited to the verbatim terms, SOC, PT, NCI-CTCAE grade, and relationship to study treatment, will be provided.

If more than one AE occurs with the same PT for the same subject, the subject will be counted only once for that PT using the worst grade and most related occurrence for the summarizations by grade and by relationship to study treatment. Additional safety endpoint derivations for missing data are described in SAP Section 8.1.2.

Treatment-emergent AEs will also be summarized by treatment group for the subgroups described in the SAP Section 7.3.2.4.

7.3.2.1. Overall Summary of Treatment-Emergent Adverse Events

An overall summary of TEAEs by treatment group will be provided for each of the follow TEAE categories:

- TEAEs
- Treatment Related TEAEs
- Serious TEAEs
- Treatment Related Serious TEAEs
- TEAEs of special interest

The number and percentage of subjects with the following criteria will be summarized by treatment group:

- CTCAE grade ≥ 3
- Associated with death as an outcome
- Associated with study treatment discontinuation
- Associated with study treatment dose interruption

- Associated with study treatment dose reduction

7.3.2.2. Treatment-Emergent Adverse Events Classified by SOC, PT and NCI CTCAE grade

The number and percentage of subjects with the following TEAEs will be summarized by treatment group as follows:

- TEAEs by SOC, PT and Worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- TEAEs by PT (in descending frequency)
- Serious TEAEs by SOC, PT and Worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Serious TEAEs by PT (in descending frequency)
- Treatment-related TEAEs by SOC, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Treatment-related TEAEs by PT (in descending frequency)
- Treatment-related serious TEAEs by SOC, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Treatment-related serious TEAEs by PT (in descending frequency)
- TEAEs associated with study drug discontinuation by SOC, PT
- Treatment-related TEAEs associated with study drug discontinuation by SOC, PT
- TEAEs associated with drug interruption by SOC, PT
- Treatment-related TEAEs associated with drug interruption by SOC, PT
- TEAEs associated with dose reduction by SOC, PT
- Treatment-related TEAEs associated with dose reduction by SOC, PT
- TEAEs associated with death as outcome by SOC, PT
- Treatment-related TEAEs associated with death as outcome by SOC, PT

TEAE by grouped PT and worst CTCAE grade will be summarized by treatment. A list of grouped PTs will be provided in a separate file.

7.3.2.3. Adverse Events of Special Interest

Interstitial lung disease (ILD)/pneumonitis and left ventricular ejection fraction (LVEF) decrease have been identified as AEs of special interest (AESI) for the DS-8201a program. An external ILD Adjudication Committee (AC) was established for the program and adjudicates all events of potential ILD/pneumonitis reported by investigators on an ongoing basis. ILD will be summarized based on the ILD adjudicated outcomes based on the ILD AC charter. To conduct a comprehensive review, a list of PTs is selected from relevant Standardized MedDRA Queries (SMQs) for each AESI. Case definitions for each of the AEs are described in Section 11.2.

The number and percentage of subjects with the following AESIs will be summarized according to treatment group per the criteria as follows:

- AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and \geq 3)
- Serious AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and \geq 3)
- Treatment-related AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and \geq 3)
- AESIs associated with discontinuation of study treatment by AESI category, PT
- AESIs associated with dose reduction of study treatment by AESI category, PT
- AESIs associated with drug interruption of study treatment by AESI category, PT
- AESIs associated with death as outcome by AESI category, PT

In addition, ILD event adjudicated outcomes will be summarized by CTC grade and a shift table will be provided for ILD events reported by adjudicated by the ILD AC. The adjudicated outcome of the worst ILD event will also be summarized.

The number and percentage of subjects with TEAEs will be summarized by selected PTs by cycle as well.

7.3.2.4. Subgroup Analysis of Treatment-Emergent Adverse Events

The following subgroup analyses for the TEAEs will be performed in the following subgroups for the safety analysis set. The number and percentage of subjects with TEAEs will be summarized by PT. Some of these subgroup categories may be combined if there are not enough subjects.

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (Asia, North American (USA, CAN), Europe (AUT, CHE, BEL, ESP, FRA, GBR, GRC, HUN, ISR, ITA, PRT, RUS, SWE)+ Israel, Rest-of-World (RoW))
- Age (<65, \geq 65 years)
- ECOG performance status (0, 1)
- Renal impairment at baseline (within normal range, mild/moderate impairment)
- Hepatic impairment at baseline (within normal range, mild)

7.3.2.5. Recurrent Treatment-Emergent Adverse Events Classified by SOC and PT

The number and percentage of subjects with recurrent selected TEAEs will be summarized by SOC and PT. The selected PTs include, but not limited to, nausea, vomiting, decreased appetite, constipation, diarrhea, anemia, platelet count decreased, white blood cell count decreased, neutrophil count decreased, fatigue, and malaise. The recurrent TEAEs are defined as one or more occurrences of TEAE with the same PT after the first event.

7.3.2.6. Time to and Duration of First Treatment-Emergent Adverse Events of Special Interest

Time to the first treatment emergent AEs of Special Interest (AESI) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum) for subjects who had a treatment emergent AESI.

Duration of the first treatment emergent AESI will be summarized using K-M approach and estimates of the quartiles will be calculated with the 95% CI. For ongoing AEs in the database, stop date is censored at the earliest of following:

- Death date
- Start of new anticancer therapy
- Last date of treatment + 47 days
- Last contact date

7.3.3. Death

Death will be summarized by treatment group. All deaths will be listed, and post-treatment deaths after last dose + 47 days will be flagged. It should be noted that the death summaries and listings (as with all safety analyses) will be based on the safety analysis set and could be different from the number of deaths reported in the efficacy analyses.

7.3.4. Clinical Laboratory Evaluations

Data from all sources (central and local laboratories, as applicable) will be reported. The summaries will include all laboratory assessments collected up to the safety follow-up date (up to 47 days after the last study treatment administration). Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by treatment group at each scheduled time of evaluation, including EOT, maximum post-treatment value, and minimum post-treatment value. All laboratory assessments will be listed, and those collected beyond the safety follow-up period will be flagged.

The following summaries will be produced for hematology and biochemistry laboratory data (by local laboratory parameter and treatment group):

- Summary of laboratory test results and changes from baseline
- Shift tables using CTCAE grades to compare baseline values to worst post-baseline values

The following listings of lab parameters from all sources will be produced for laboratory data:

- Subjects with hematology laboratory values outside the laboratory normal ranges with values flagged to show the corresponding CTCAE grades and the classification relative to the laboratory normal range. Abnormal laboratory values collected outside the on-treatment period (between first dose of study treatment and 47 days after last dose of study treatment) will also be reported in the listings and flagged accordingly.
- A similar listing for biochemistry laboratory data.

- A similar listing for urinalysis, coagulation and troponin.

7.3.4.1. Liver Function Parameters

Subjects with elevated post-treatment ALT, AST, ALP, or total bilirubin that fall into the following categories will be identified and listed. The number and percentage of these subjects will be tabulated. An eDISH plot will be presented.

Table 7-1: Elevated Liver Function Category

Clinical Laboratory Parameter	Category
ALT or AST	$\geq 3 \times \text{ULN}$; $\geq 5 \times \text{ULN}$; $\geq 8 \times \text{ULN}$; $\geq 10 \times \text{ULN}$; $\geq 20 \times \text{ULN}$
Total Bilirubin (TBL)	$\geq 1.5 \times \text{ULN}$; $\geq 2 \times \text{ULN}$; $\geq 3 \times \text{ULN}$
ALP	$\geq 1.5 \times \text{ULN}$; $\geq 2 \times \text{ULN}$
Concurrent TBL elevation with ALT or AST elevation ^a	(ALT or AST $\geq 3 \times \text{ULN}$) and (TBL $\geq 2 \times \text{ULN}$)
Concurrent TBL elevation with ALT or AST elevation and ALP $< 2 \times \text{ULN}$ ^a	(ALT or AST $\geq 3 \times \text{ULN}$) and ALP $< 2 \times \text{ULN}$ and (TBL $\geq 2 \times \text{ULN}$)

^a Concurrent is defined as these abnormalities occurred within a 28-day window.

7.3.5. Vital Signs

Descriptive statistics will be provided by treatment group for the vital sign measurements and changes from baseline by scheduled time of evaluation, including the EOT Visit and the maximum and minimum post-treatment values. All vital sign data will also be listed. Box-Whisker plots will be presented for selected parameters (e.g., systolic and diastolic blood pressure, pulse rate, and SpO₂) at each scheduled time of evaluation.

7.3.6. ECG

Descriptive statistics will be provided by treatment group for ECG parameters (e.g., heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval) and changes from baseline by scheduled time of evaluation, including the EOT Visit and the maximum post-treatment value. For descriptive statistics at each visit, the mean of the triplicate assessments is used.

In addition, the following criteria of notable post-baseline ECG interval values are defined:

QT and QTcF:

- New > 450 ms
- New > 480 ms
- New > 500 ms
- Increase from baseline > 30 ms
- Increase from baseline > 60 ms

PR:

- An increase > 25% from baseline and PR > 200 ms

QRS:

- An increase >25% from baseline and QRS > 100 ms

HR:

- A decrease >25% from baseline and HR < 50 bpm
- An increase >25% from baseline and HR > 100 bpm

Note that “New” implies a newly occurring ECG abnormality. It is defined as an abnormal ECG finding at post-baseline that is not present at baseline (e.g., QT New>480 m implies QT>480 ms post-baseline and QT≤480 ms at baseline). The last non-missing value before the first dose of study drug will be used as the baseline value for each item.

QTc interval will be calculated using Fridericia’s ($QTcF = QT/[RR]^{1/3}$) correction (with RR in seconds). If RR is not available, it will be replaced with 60/(heart rate) in the correction formula and computed as $QTcF = QT \times (HR/60)^{1/3}$.

Summaries of QTcF interval, without and with the imputation by heart rate when RR interval is missing, will be performed.

A subject with multiple occurrences of a new occurring abnormality is counted only once per abnormality.

Maximum value any time during study will also be summarized, as well as maximum change from baseline and will include any unscheduled assessments

Box-Whisker plots will be presented for QTcF interval at each scheduled time of evaluation.

ECG data will be listed.

7.3.7. Immunogenicity (Anti-Drug Antibody Analyses)

Immunogenicity will be assessed through characterization of incidence and titer of ADA for all subjects who received at least one dose of study drug and who had at least one baseline or post-baseline immunogenicity assessment.

The number and percentage of subjects who have a positive ADA result will be summarized with regards to:

- Baseline prevalence of ADA (prior to dosing with T-DXd)
- Post-baseline prevalence of ADA (for all subjects and subjects with positive result at baseline)
- ADA positive at baseline or post-baseline (percentages will be based on the number of subjects who had a baseline or post-baseline assessment)
- Treatment-emergent incidence of ADA (positive post-baseline result where baseline result was negative or missing, or ADA titer increased following positive baseline result)
- Treatment-boosted ADA incidence (ADA titer increased following positive baseline result)

- Treatment-induced ADA incidence (positive post-baseline result where baseline result was negative or missing)

The number and percentage of subjects who are positive for neutralizing antibody (NAb) of trastuzumab deruxtecan, if analyzed, will also be summarized.

Descriptive statistics will also be presented for the following:

- ADA titer at each scheduled visit
- Highest ADA titer in treatment-emergent ADA positive subjects
- Time to first ADA positive sample in treatment-emergent ADA positive subjects
- Time to last immunogenicity sample

A summary table by scheduled visit will be provided for prevalence of ADA/NAb.

A listing of all ADA/NAb assessments and raw values of ADA titers will be provided by scheduled visit.

7.3.8. Other Safety Analysis

A shift table will be provided for ECOG PS and LVEF. LVEF values at baseline and EOT visit, the minimum post-treatment values, and the change from baseline will be summarized as well. A Box-Whisker plot will be presented for LVEF values at each scheduled visit. All other safety endpoints (e.g., physical examination findings, ophthalmologic findings) will be listed.

7.4. Pharmacokinetic and Pharmacodynamic Analyses

7.4.1. Pharmacokinetic Analyses

Descriptive statistics and listing will be provided for all serum concentration data (T-DXd, total anti-HER2 antibody and DXd) at each time point for the PK analysis set. The time course of serum concentrations for T-DXd, total anti-HER2 antibody and DXd will be plotted in each subject and for mean-SD using descriptive statistics at each time point on linear axis and semi-log axis. The same analysis will be performed by region/country (e.g. China (CHN/HKG/TWN) vs Non-China, JPN vs Non-JPN, KOR vs Non KOR, and Asian vs Non-Asian. etc).

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

7.5. Biomarkers Analysis

Biomarker endpoints will be summarized by treatment group for each time point using descriptive statistics if data are available.

7.6. Health Economics and Outcome Research Endpoint(s) Analysis

Health economic and outcomes research endpoints based on the hospitalization-related data collection form and the following patient reported outcomes (PRO) questionnaires will be summarized by time point for each treatment group: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L.

The global health status/global QoL scale score of the EORTC QLQ-C30 is identified as the primary PRO variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR45, and the index score of the EQ-5D-5L are identified as secondary PRO variables of interest. High scores in the EORTC QLQ-C30 and QLQ-BR45 represent 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.

Higher scores in the EQ-5D-5L also correspond to better health states. The HR-positive cohort of FAS will be used for all PRO summaries and listings.

The number of subjects completing QoL data and the number of subjects missing/expected to have QoL assessments will be summarized by each treatment group for scheduled assessment time points (the number of on-going patients will be used as denominator). Furthermore, the amount and the pattern of missing data may be explored by treatment group and over time using summary statistics. The following categories will be used to describe whether the questionnaire was completed at a specific time point:

- yes, fully completed
- yes, partially completed
- no, subject missed scheduled assessment visit

Scoring of raw data and methods for handling of missing items or missing assessments will be handled according to scoring manuals for each respective subject questionnaire.

Subject data listings will be provided for all HEOR data in accordance with this SAP.

Derivations are detailed in SAP Section 8.2.3.

7.6.1. 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, 40-day Follow-up, and Long-term/Survival Follow-up Visits) for all subjects using the HR-positive cohort of FAS.

Results of the EQ VAS will be presented as a measure of overall self -rated health status.

7.6.2. 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 quality of life (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.

Change from baseline in all sub-scales obtained from EORTC QLQ-C30 and QLQ-BR45 will be analyzed using a linear mixed effect model for longitudinal data to assess the treatment effect over time including terms for treatment, randomization stratification factors, nominal visit, treatment by time of visit interaction, and baseline score. The differences in least square means between treatment and control group, and the corresponding two-sided 95% CI at selected time points will be presented. For the mixed effects model, patients with baseline and at least one non-missing post-baseline assessment will be included. This analysis will only include assessments up to the time point where there are at least 50 patients on each of the treatments. As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. In the event of the statistical model failing to converge or other presenting issues with the model, the covariance structure will be modified to an autoregressive (AR(1)) covariance matrix. Furthermore, in the case where the AR(1) model also fails to converge, a compound symmetric (CS) covariance structure will be used.

Time to definitive deterioration on the ‘breast symptoms’ and ‘arm symptoms’ subscales of the EORTCQLQ-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, a definitive deterioration event will be defined as an increase of 10 points or more (compared to baseline) on the symptom subscale score in question. Time to definitive deterioration is the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event (as defined above) is first seen. If a patient has not had a definitive deterioration event prior to analysis cut-off or start of new anticancer therapy, loss to follow-up, or withdrawal of consent, the time to definitive deterioration will be censored at the date of the last evaluation of the symptom subscale score in question. Only assessments collected while the patient is on treatment and on or before the 40-day visit will be included in the PRO ‘time to definitive deterioration’ analysis. Death is considered as deterioration of symptoms/QoL if it occurs within twice the planned period between two assessments from last available assessment. Patients who die after more than twice the planned period between two assessments since the last assessment are censored at the date of their last available questionnaire. If a definitive deterioration is observed after two or more missing assessments, the patient will be censored at the date of their last available assessment (questionnaire), prior to the definitive deterioration.

Time to definitive deterioration will be compared between the two treatment groups in the HR-positive cohort of FAS using the stratified log-rank test (strata determined by the randomization stratification factors collected from IXRS) and at two-sided type I error rate of 5%. The survival distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier analysis, including the median time to definitive deterioration and the proportion of patients without definitive deterioration at specific time-points will be reported. A stratified Cox regression model will be used to estimate the HR of time to definitive deterioration, along with 95% confidence interval (using the same strata information as above).

As a sensitivity analysis, a pattern mixture model (PMM) may be fit to address potential departures from the assumption that the data are missing at random for global health

status/global QoL scale score of the EORTC QLQ-C30. For the PMM, patterns will be determined using the neighboring case missing value (NCMV) method. In addition, to address unmeasured uncertainty (e.g., standard errors and confidence intervals), the pattern mixture model will be combined with multiple imputation⁶. For each imputed timepoint T_j , this approach uses the observations for which T_j is observed and T_{j+1} is missing. If the data do not follow a monotone missing data pattern, a monotonic structure will be obtained using the Markov chain Monte Carlo (MCMC) method. After missing data have been made monotone, a regression model will be used to perform the imputations within each treatment group. The stratification variables assigned at randomization will also be included in the model. Estimates from this model will be compared to those from the mixed model repeated measures analysis. A discrepancy between the two approaches would support the conclusion that the data are missing not at random (MNAR).

7.6.3. Hospitalization-related Endpoints

The following hospitalization-related endpoints:

- Reason for hospitalization
- Discharge diagnosis
- Length of hospital stay (days)
- Length of ICU stay (days)
- Time to first hospitalization, defined as the time from the date of randomization to the date of the first hospitalization during the study treatment (from date of first dose to 47 days after last dose)

will be summarized using descriptive statistics.

7.7. Other analysis

7.7.1. COVID-19 Analyses

Additional analyses may be performed to explore the impact of implemented contingency measures (eg, subjects discontinued from study treatment and/or study, alternative procedures used to collect critical safety and/or efficacy data, protocol deviations related to COVID-19) on the safety and efficacy results reported for the study. The following may be explored:

- Sensitivity analyses of overall summary for key safety endpoints (TEAE, treatment-related TEAE, serious TEAE, treatment-related serious TEAE, AESI, and treatment-related AESI) and primary analysis (no P-values) of PFS by excluding data from subjects from sites that are closed out due to COVID-19.
- Overall summary for key safety endpoints (as described above) separately for subjects affected by COVID-19, identified using data from eCRF pages
- Summary of deaths and TEAEs attributed to COVID-19 pandemic

In addition, the following listings may be provided for

- subjects who discontinued treatment due to the COVID-19 pandemic

- subjects with protocol deviations related to COVID-19 and the reasons for the protocol deviation

8. GENERAL STATISTICAL METHODOLOGY, STUDY ENDPOINT DERIVATION DETAILS, DATA HANDLING, AND REPORTING CONVENTIONS

8.1. General Statistical Methodology

8.1.1. Time-to-Event Analyses

The following sections describe general statistical methodology to be used for analyzing the following time-to-event variables:

- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (DoR)
- Time to response (TTR)
- Time to definitive deterioration of PRO scores
- Progression-free survival on the next line of therapy (PFS2)

Hypothesis and test statistic

The primary efficacy analysis will be the comparison of the distribution of PFS per BICR in HR-positive cohort between the two treatment groups using a stratified log-rank test at two-sided 5% significance level.

The stratified log-rank test (strata based on the randomization factor) will be implemented as follows: for each of the strata, the LIFETEST procedure will be run with the STRATA statement including only the treatment variable. The TIME statement will include the survival time and a (right) censoring variable.

```
PROC LIFETEST data=dataset METHOD=KM ;
  TIME survtime*censor(1);
  STRATA stratum 1 stratum 2 stratum 3 / group = trt;
  RUN;
/* stratum represents stratum variable (to be included for stratified analysis only);
survtime represents variable containing event/censor times;
censor represents censoring variable (1=censored, 0=event);
trt represents treatment group variable; */
```

Kaplan-Meier estimates

The survival function in each treatment group will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST (see examples above). Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the loglog option available within PROC LIFETEST, Kaplan-Meier estimates of survival rates with 95% confidence intervals at specific time points will be summarized.

Hazard ratio

The hazard ratio will be derived from the Cox proportional hazards model using SAS procedure PHREG with TIES=EXACT option in the MODEL statement. The stratified and unadjusted Cox model will be used (where the baseline hazard function is allowed to vary across strata) for the primary analysis, i.e. the MODEL statement will include only the treatment group variable as a covariate and the STRATA statement will include stratification variable(s).

General SAS code for the stratified Cox model

```
PROC PHREG data=dataset;
  MODEL survtime*censor(1)=trt / TIES=EXACT;
  STRATA stratum 1 stratum 2 stratum 3;
  RUN;
/* survtime represents variable containing event/censor times;
censor represents censoring variable (1=censored, 0=event);
trt represents treatment group variable;
stratum 1, stratum 2 and stratum 3 represent stratification variables */
```

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Note: Since score test based confidence intervals are not available in SAS procedure PHREG, Wald test based intervals will be used instead.

8.2. Study Endpoints Derivation Details

8.2.1. Efficacy Endpoints Derivation Details

8.2.1.1. PFS Event and Censoring Rules

Progression-free survival (PFS) is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cut-off date for PFS analysis will be censored at the date of their last evaluable tumor assessment.

Event or censoring for primary PFS analyses are described in the Table below.

Case Scenario	Event/Censor (Event or Censoring Description)	Event or Censoring Date
No baseline evaluable tumor assessment	Censored (no baseline tumor assessment)	Date of randomization
No post-baseline tumor assessment	Censored (no post-baseline assessment)	Date of randomization
Early death (within 14 weeks of randomization) regardless of tumor assessment	Event (death)	Date of death
Radiographic disease progression or death without missing two or more consecutive tumor assessments immediately preceding the event	Event (progression or death)	Date of progressive disease assessment or date of death
Disease progression or death after missing ≥ 2 consecutive scheduled tumor assessments (i.e., more than 14 weeks)	Censor (event after missing 2 or more consecutive tumor assessments)	Date of last evaluable tumor assessment (prior to earliest of death/progression date and analysis cut-off date)
At least one post-baseline response assessment, subject with no death or objective documentation of radiographic disease progression (progression-free)	Censor (lost to follow-up; withdraw consent; ongoing without event; adequate tumor assessment no longer available**)	Date of last evaluable tumor assessment (prior to analysis cut-off date, NOT coded as "inevaluable")
Anti-cancer therapy started prior to disease progression, death or analysis cut-off date (*)	Censor (anti-cancer therapy)	Date of last evaluable tumor assessment prior to anti-cancer therapy (other than study drug)

* This censoring rule will be used for sensitivity analysis

** Censoring reason will be lost to follow-up if date of lost to follow-up from end of treatment page or post-treatment follow-up page is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be withdraw consent if date of withdraw of consent from end of treatment page is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be ongoing without progression if cutoff date is within 2 consecutive tumor assessments from last adequate tumor assessment; Otherwise censoring reason will be adequate assessment no longer available.

Analysis of PFS per investigator assessments will use the same censoring rules.

8.2.1.2. OS Event and Censoring Rules

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.

The last contact date at which the subject was known to be alive will be the latest date among the following:

- Last non-missing assessment/onset date captured under the following eCRF pages (or if a date of assessment/onset is not available the “date of visit” for the eCRF page can be used): adverse events, vital signs, physical examination, ECOG PS, ECG, clinical laboratory test, tumor assessment, and also PK/biomarker/other specimen sample collection date.
- Last dosing date of study drug, last date of concomitant medications, and last date of non-drug treatments/procedures.
- Last date of subsequent anti-cancer therapy administered after study treatment discontinuation.
- Date of Last Contact collected on the survival follow up page of the eCRF.

8.2.1.3. Evaluation of Best Overall Response

The best overall response is the best confirmed response recorded from the start of the study treatment until PD/death or start of new anticancer therapy whichever is earlier.

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.

Confirmation of CR/PR is required for this study.

The best overall response of PD corresponds to disease progression (assessment based upon tumor measurements and recorded on the electronic case report form (eCRF) page “overall tumor assessment”) for the first on-treatment tumor assessment. The best overall response of CR/PR cannot be determined unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response of CR/PR is first suspected.

If there is no on-treatment tumor assessment, the best overall response will be assigned as “Inevaluable (NE)”.

When SD is believed to be best response, it must also meet the protocol-specified minimum time of 5 weeks from date of randomization. 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.

If there is no next tumor assessment, the best overall response will be assigned as “Not evaluable (NE)”. The tumor assessment at the Screening Visit will be used as the baseline tumor assessment.

Best overall response with confirmation of CR/PR is as follows:

First Time Point Response**	Subsequent Time Point Response	Confirmed Response (Best Response)*
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	NE **	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	NE **	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

*A Best Response of SD can only be made after the subject is on-study for a minimum of five (5) weeks (35 days). If the subject is on-study less than thirty-five (35) days, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third time point response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR). Note: in the following scenario, PR SD NE PR, the first PR is not a confirmed PR.

- (1) Best response will be SD if the first TPR is after five (5) weeks (35 days). Otherwise, the best response will be PD.
- (2) Best response will be SD if the first TPR is after five (5) weeks (35 days). Otherwise, the best response will be NE.
- (3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.

Subjects without on-treatment tumor assessment will be included in the denominators of best overall response and ORR (as best overall response of “Inevaluable (NE)”).

8.2.1.4. Other Efficacy Endpoint Derivation and Censoring

ORR: ORR is defined as the proportion of subjects with best overall response of confirmed CR or PR.

DoR: DoR is defined as the time from the date of the first documentation of objective response (confirmed CR or PR) to the date of the first documentation of disease progression or death due

to any cause. Duration of response will be measured for responding subjects (confirmed PR or CR) only. Censoring rules for PFS analysis are applied for DoR analysis.

CBR: CBR is defined as the proportion of subjects with best overall response of confirmed CR, PR, or more than 6 months Stable Disease (SD)

Both of the following conditions must be met for ‘more than 6 months SD’

- Best overall response is SD
- Duration of SD ≥ 183 days

DCR: Disease control rate (DCR) per BICR is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD)

TTR: TTR is defined as the time from the date of randomization to the date of the first documentation of objective response (confirmed CR or PR). Patients with a confirmed PR or CR will be included in TTR calculation.

Best percent change in the sum of the diameters: Best percent change in the sum of the diameters of measurable tumors will be based on BICR and on investigator assessment respectively. The tumor measurement at the Screening Visit will be used as the baseline tumor measurement.

Time to hospitalization: Time to hospitalization is defined as the time from the date of randomization to the date of the first hospitalization during the study treatment. Study treatment period is defined as the period from the date of first dose up to 47 days after the last dose of treatment. Note, only hospitalizations during the defined treatment period are included for this analysis. Time to hospitalization will be summarized using descriptive statistics.

PFS2: PFS2 is 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 cut-off date; censoring date will be the last contact date. In case a 2nd anti-plastic therapy is introduced prior to 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 as PFS2 event.
- Any death following the next line of therapy will be a PFS2 event if no 2nd new line of therapy is initiated.
- PFS and PFS2 may be identical in case a patient 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 anti-cancer therapy initiated after discontinuation of study treatment regardless of EoT reason.

8.2.2. Safety Endpoints Derivation Details

8.2.2.1. Adverse Events

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or worsened in severity or seriousness after the initiating the study drug 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. All AEs will be graded (1 to 5) according to the latest NCI-CTCAE version 5.0.

For Treatment-Emergent adverse event toxicity tables tabulated on subject level, a subject with two or more TEAEs with the same preferred term will be counted only once for that term with the highest CTCAE grade. For a given subject, if the toxicity grade is missing for all TEAEs with the same preferred term, the TEAEs will be counted only once for that term under the “Missing” CTCAE toxicity category. In the presence of a subject who has both missing and non-missing CTCAE toxicity grades for AEs with the same preferred term, the missing CTCAE toxicity of the AE will be treated as the lowest toxicity grade. In addition, a subject who reported two or more TEAEs with the same system organ class will be counted only once in the system organ class total, and subjects with 2 or more TEAEs in different SOCs will be counted only once in the overall total.

8.2.3. Health Economic and Outcomes Research Endpoints

8.2.3.1. EQ-5D-5L

The EQ-5D-5L will be assessed using the index scored according to the EQ-5D-5L UK value set as well as the response on the Visual Analogue Scale (VAS) question. The value set will be used to assign a baseline index value as well as a value at each nominal time point, based on the health state indicated on the questionnaire. The index score will be derived according to the EQ-5D-5L UK value set, for example, the index score will be 0.483 for a value set of 11234.

The following endpoints will be tabulated or derived at each nominal time point. For descriptive system, missing values are coded as 9 and ambiguous values (2 levels checked in one dimension) are treated as missing; index score will be derived as missing.

- Response by dimension
- Index score by disease state
- Index score change from baseline
- VAS as a measure of self-rated health status
 - 100 is the best health subject can imagine
 - 0 is the worst health subject can imagine
- VAS change from baseline

8.2.3.2. EORTC QLQ-C30

EORTC QLQ-C30 (version 3.0) consists of a total of 30 questions related to QoL, scored on a 4-point Likert scale for the first 28 questions (1=not at all, 4=very much) and scored on a scale of 1 (very poor) to 7 (excellent) for the final two questions that probe the patient’s overall health and QoL. It is composed of both multi-item scales and single-item measures. These include five

functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status and a number of single items assessing additional symptoms (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and financial difficulties. The following explains the scoring procedure.

Table 8-1: Scoring the EORTC QLQ-C30

	Scale	Item range ^a	Item Numbers	Raw Score ^b
Global health status/QoL	QL2	6	29,30	(Q29+Q30)/2
Functional Scales				
Physical Functioning	PF2	3	1 to 5	(Q1+Q2+Q3+Q4+Q5)/5
Role Functioning	RF2	3	6,7	(Q6+Q7)/2
Emotional Functioning	EF	3	21 to 24	(Q21+Q22+Q23+Q24)/4
Cognitive Functioning	CF	3	20,25	(Q20+Q25)/2
Social Functioning	SF	3	26,27	(Q26+Q27)/2
Symptom Scales				
Fatigue	FA	3	10,12,18	(Q10+Q12+Q18)/3
Nausea and Vomiting	NV	3	14,15	(Q14+Q15)/2
Pain	PA	3	9,19	(Q9+Q19)/2
Dyspnea	DY	3	8	Q8
Insomnia	SL	3	11	Q11
Appetite Loss	AP	3	13	Q13
Constipation	CO	3	16	Q16
Diarrhea	DI	3	17	Q17
Financial Difficulties	FI	3	28	Q28

^a Item range is the difference between the possible maximum and the minimum response to individual items.

^b Raw score is the mean of the component items

Once the raw scores are calculated, a linear transformation to 0-100 is applied to obtain the particular score as follows:

For functional scales: Score = {1-(Raw score-1)/Range}*100

For all other scales/items: Score = {(Raw score-1)/Range}*100

Each scale has a range of 0-100%. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high level of functioning. A high score for a symptom scale represents a high level of symptomatology/problem.

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. So, for example, if the fatigue scale is missing Q10, the average of Q12 and Q18 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

8.2.3.3. EORTC QLQ-B45 (QLQ-BR23)

EORTC QLQ-BR45 consists of a total of 45 questions related to QoL. As QLQ-BR45 is still undergoing validation, analysis will be performed on QLQ-BR23 scoring.

EORTC QLQ-BR23 consists of a total of 23 questions related to QoL, scored on a 4-point Likert scale (1=not at all, 4=very much). It is composed of questions citing the extent to which the subject has experienced symptoms or problems during the past week and during the past four weeks.

These include four functional scales (body image, sexual functioning, sexual enjoyment, future perspective), and four symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss).

The following explains the scoring procedure.

The 23 questions are numbered as Items 31-53 in the eCRF.

	Scale name	Number of items	Item range	QLQ-BR23 items numbers (per eCRF)
Functional scales				
Body image	BRBI	4	3	39, 40, 41, 42
Sexual functioning	BRSEF	2	3	44, 45
Sexual enjoyment	BRSEE	1	3	46
Future perspective	BRFU	1	3	43
Symptom scales / items				
Systemic therapy side effects	BRST	7	3	31, 32, 33, 34, 36, 37, 38
Breast symptoms	BRBS	4	3	50, 51, 52, 53
Arm symptoms	BRAS	3	3	47, 48, 49
Upset by hair loss	BRHS	1	3	35

Item range is the difference between the possible maximum and the minimum response to individual items; values are from 1 to 4, giving range = 3.

Once the raw scores are calculated, a linear transformation to 0-100 is applied to obtain the particular score as follows:

For functional scales: Score = {1-(Raw score-1)/Range}*100

For symptom scales/items: Score = {(Raw score-1)/Range}*100

Each scale has a range of 0-100%. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

Remarks

- Sexual enjoyment (BRSEE) is not applicable if item 45 is scored “not at all.”
- Upset by hair loss (BRHL) is not applicable if item 34 is “not at all.”

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. So,

for example, if the breast symptom scale is missing Q50, the average of Q51, Q52, Q53 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

8.2.3.4. Censoring Rules for Time to Definitive Deterioration

Time to definitive deterioration is defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event is first seen. Event or censoring rules are as follows:

Case Scenario		Event/Censor (Event or Censoring Description)	Event or Censoring Date
No baseline evaluable QoL and/or no post-baseline tumor assessment	Death by the first survival FU (3 months from 40-day visit)	Event (death)	Date of death
	Others	Censored (no baseline or post-baseline assessment)	Date of randomization
Patients with baseline and at least 1 post-baseline QoL assessments	Increase of 10 points or more (compared to baseline) at two or more consecutive time points on the symptom subscale score in question (confirmed)	Event (Definitive deterioration)	Date of first deterioration of the consecutive assessments with an increase of 10 point or more
	Increase of 10 points or more (compared to baseline) at last assessment on the symptom subscale score in question	Event (Definitive deterioration)	Date of last assessment if that is the last one
	Death by the first survival FU (3 months from 40-day visit)	Event (Death)	Date of death
	Others	Censor (No definitive deterioration)	Date of last assessment

8.2.4. Other Derivations for Endpoint Analysis

8.2.4.1. Hormone Receptors

Estrogen Receptors	Progesterone Receptors	Hormone Receptors
---------------------------	-------------------------------	--------------------------

negative	Negative	negative
negative	Positive	positive
negative	indeterminate	indeterminate
positive	Negative	positive
positive	Positive	positive
positive	indeterminate	positive
indeterminate	Negative	indeterminate
indeterminate	Positive	positive
indeterminate	indeterminate	indeterminate

8.2.4.2. Prior and Post Anti-cancer Therapy

For the summaries of prior cancer therapy, prior cancer surgery, and post anti-cancer therapy, review of the relevant clinical terms will be performed after every data snapshot to accurately classify and identify the correct groupings. The steps to be followed are as below.

- The unique terms from the reported prior cancer therapy (or prior cancer surgery or post anti-cancer therapy) data are extracted from the study database and put into an excel spreadsheet without any accompanying subject-level information.
- The spreadsheet is reviewed by the clinical team and the terms are classified under the different groupings.

The updated spreadsheet with the grouping information is then merged with the study database to derive variables in the associated ADaM data sets

8.3. Data Handling Conventions

In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified in this section.

8.3.1. Definition and Use of Visit Windows

For data analysis and display purposes, Study Day is defined as the number of days from (positive) or prior (negative) to the day of randomization, with the day of randomization as Study Day 1. The Screening Period is defined as any days prior to day of randomization. Day -1 is the day prior to randomization.

Detailed Visit Windows for each assessment are defined in the protocol Schedule of Events. Visit IDs are recorded in the eCRF. No visit windowing will be derived for purposes of analysis; the nominal visits will be used in the summaries, except for ECOG and PRO analyses.

8.3.1.1. Time Window to Scheduled Timepoint of ECOG

ECOG assessments should be collected on Day 1 of each cycle during study treatment period, EOT, and 40-day safety follow-up visits.

The following time based intervals will be used to group the ECOG data over time:

	Time Interval
Cycle 1/Baseline	The latest assessment within 28 days prior to or on the randomization date/the first dose (Cycle 1 Day 1) date, whichever occurs later.
Cycle 2,3,4,..., before EOT	+11/-10 days centered around the planned assessment date
EOT	Assessment taken for the end of treatment visit
40-day safety FU post EOT	Assessment taken for the 40-day safety FU visit

Note: 1 Cycle = 21 days

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments are within a time window are equidistant from the target date (or if the closest assessment to the target date has two questionnaires filled out on the same date), then the worst of all non-missing items for these assessments will be used.

8.3.1.2. Time Window to Scheduled Timepoint of PRO

PRO assessments should be collected at visits: Day 1 of each cycle during study treatment period, EOT, 40-day safety follow-up post EOT, and every 3-months during long-term follow-up.

The following time based intervals will be used to group the PRO data over time:

	Time Interval
Baseline	The latest assessment within 28 days prior to or on the randomization date/the first dose (Cycle 1 Day 1) date, whichever occurs later.
Cycle 2,3,4,..., before EOT	+11/-10 days centered around the planned assessment date
EOT	Assessment taken for the end of treatment visit
40-day safety FU post EOT	Assessment taken for the 40-day safety FU visit
3m, 6m, ... during long-term FU	±45 days centered around the planned assessment date

Note: 1 Cycle = 21 days

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used.

If 2 assessments are within a time window are equidistant from the target date, then the assessment obtained prior to target date will be considered. If the closest assessment to the target date has two questionnaires filled out on the same date, then the worst score of these assessments will be used for each subscale score.

8.3.2. Repeated or Unscheduled Assessments of Safety Parameters

It is possible that repeat or unscheduled assessments are made for some safety endpoints (e.g., clinical laboratory tests, vital signs, ECGs, etc.). It is also possible that multiple measurements are available within the same window for summary, whether they are scheduled or not. In this case, the following rule should be applied for statistical summary unless otherwise justified:

- If a subject has repeated assessments before the initiation of study treatment administration, then the results from the final assessment made prior to the initiation of study treatment administration, will be used as baseline assessment.
- If a subject has repeated assessments during treatment, the value obtained on the day (and/or time) closest to the scheduled measurement time point should be selected. If there are two or more measurements collected on days (and/or times) that are equidistant from the scheduled time point, the later will be used for analysis.

8.3.3. Missing Date or Incomplete Date

8.3.3.1. Missing or Incomplete Date Information of Study Treatment

When the date of the last dose of study treatment is missing or incomplete for a subject in the safety analysis set, all efforts should be made to obtain the date from the investigator.

8.3.3.2. Incomplete Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing and year is available) start dates. Incomplete stop dates may also be imputed when the calculation of the duration of an AE is required by the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete, then impute the start date first.

Incomplete Start Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date, assuming year is available. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study treatment, then the day and month of the date of the first dose of study treatment will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of study treatment, then January 1 will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of study treatment, then December 31 will be assigned to the missing fields.

Missing Month Only

- The day will remain the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study treatment, then the day of the date of the first dose of study treatment will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study treatment or if both years are the same but the month is before the month of the date of the first dose of study treatment, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of study treatment or if both years are the same but the month is after the month of the date of the first dose of study treatment, then the first day of the month will be assigned to the missing day.

Incomplete Stop Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the missing numerical fields, assuming year is available. If the date of the last dose of study treatment is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of study treatment, then the day and month of the date of the last dose of study treatment will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of study treatment, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of study treatment, then January 1 will be assigned to the missing fields.

Missing Month Only

- The day will be the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study treatment, then the day of the date of the last dose of study treatment will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of study treatment or if both years are the same but the month is before the month of the date of the last dose of study treatment, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the last dose of study treatment or if both years are the same but the month is after the month of the date of the last dose of study treatment, then the first day of the month will be assigned to the missing day.

8.3.3.2.1. Missing Severity Assessment for Adverse Events

Missing CTCAE grade is not imputed. For TEAE derivation, missing grade for AEs prior to first dose will be treated as grade 1.

8.3.3.2.2. Missing Relationship to Study Treatment for Adverse Events

If the relationship to study treatment is missing for a TEAE starting on or after the date of the first dose of study treatment, a causality of “related” will be assigned. The imputed values of relationship to study treatment will be used for incidence summaries, while the actual values will be presented in data listings.

8.3.3.3. Incomplete Date Information for Prior and Concomitant Medications

For prior or concomitant medications, follow the imputation rules presented in Section 8.3.3.2 for incomplete (i.e., partially missing) start and stop dates.

8.3.3.4. Incomplete Date Information for Determination of Time Since Diagnosis

To calculate time since disease diagnosis, the date of diagnosis must have at least a non-missing year. A partially missing date of diagnosis will be assigned the middle of the year (July 1) if month is missing, and the 15th of the month if only the day is missing. If the year of diagnosis is the same as the randomization/registration year, then January 1 will be assigned if the month is missing, and the 1st of the month will be assigned if only the day of month is missing.

8.3.4. Character Values of Clinical Laboratory Tests and Below Limit of Quantification Values

If the reported value for a clinical laboratory test cannot be used in a statistical summary and analysis due to, for example, a character string being reported for a numerical value, an imputed value may be used in the statistical analysis according to the conventions described below.

- A character field represents a value below a number (e.g., <XX), the imputed value will be calculated as half of the numerical cut-off, i.e. XX/2.
- A character field represents a value greater than a number (e.g., >XX), the imputed value will be calculated as XX.

Details of the imputation algorithm will be provided in ADaM specifications document after reviewing the dry run lab listing prior to database lock.

Actual values as recorded in the database (i.e., the character field) will be presented in data listings.

8.4. Statistical Summary and General Reporting Conventions

8.4.1. Computing Methods

Statistical analyses will be performed using Version 9.3 or newer of SAS®¹² on a suitably qualified environment.

8.4.2. Statistical Summary Conventions

Continuous endpoints will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum, unless otherwise stated. The frequency and percentage of observed levels will be reported for categorical measures. In general, all data will be listed, sorted by subject and, when appropriate, by study day and study hour within a subject.

8.4.3. General Reporting Conventions

P-values will be reported to four decimal places; p-values less than 0.0001 will be reported as p<0.0001. The rounding of p-values to four decimal places will occur after comparing to significance level. The mean and median will be reported up to one decimal place and the standard deviation up to two decimal places greater than the original (raw) value, unless otherwise specified. The precision for reporting of summary statistics for demographics and baseline characteristics will be limited to two decimal places for the standard deviation and one decimal place for everything else.

**9. SUMMARY OF CHANGES TO THE STATISTICAL ANALYSES
SPECIFIED IN PROTOCOL**

This SAP for Protocol DS8201-A-U303 incorporates Amendments.

Protocol Version	Approval Date	Salient Changes, if any*

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11. APPENDICES

11.1. Overall Response: Subjects with Target (+/-Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Time point Response
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 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.

11.2. Adverse events of special interest

Case definitions for each of the AESIs are described in the table below. This list of AESIs will be periodically reviewed and updated by safety team.

AESIs	Case definition
ILD (Selected PTs from Interstitial lung disease (SMQ 20000042))	ILD will be summarized based on the ILD adjudicated outcomes based on 44 PTs defined in the ILD AC charter.
LVEF decrease (Selected PTs from Cardiac failure (SMQ 20000004))	LVEF as a case definition refers to a subject who experienced any of the pre-selected PTs and corresponding MedDRA codes: Acute left ventricular failure (10063081), Acute right ventricular failure (10063082), Cardiac failure (10007554), Cardiac failure acute (10007556), Cardiac failure chronic (10007558), Cardiac failure congestive (10007559), Chronic left ventricular failure (10063083), Chronic right ventricular failure (10063084), Ejection fraction decreased (10050528), Left ventricular failure (10024119) Right ventricular failure (10039163), and ventricular failure (10060953).

11.3. Lesion Locations for Baseline Visceral Disease Derivation

Baseline visceral disease is determined with any target or non-target tumor in the lesion locations on “Target/Non-Target Tumor Assessments (Imaging Baseline)” eCRF page as listed in the table below.

Lesion Location	Visceral Disease	Not Visceral Disease
Abdominal Cavity	Y	
Adrenal gland	Y	
Ascites	Y	
Back		N
Bile Duct	Y	
Biliary/Gall Bladder	Y	
Bone		N
Brain	Y	
Breast		N
Cervical Vertebra		N
Cervix uteri	Y	
Chest wall		N
Colon	Y	
Esophagus	Y	
Extremity		N
Eye	Y	

Fallopian tube	Y	
Gastroesophageal Junction	Y	
Head		N
Head (excluding Oral Cavity)		N
Heart	Y	
Kidney	Y	
Larynx		N
Liver	Y	
Lumbar Vertebra		N
Lung	Y	
Lymph Nodes		N
Mediastinum	Y	
Muscle		N
Nasopharynx		N
Neck		N
Nose		N
Oropharynx		N
Other		N
Ovary	Y	
Pancreas	Y	
Pelvic Bone		N
Penis		N
Pericardial effusion	Y	
Peritoneum/Omentum	Y	
Pleura	Y	
Pleural effusion	Y	
Prostate	Y	
Rectum	Y	
Retroperitoneum	Y	
Rib		N
Skin		N
Skull		N
Small Intestine	Y	
Soft Tissue		N
Spinal	Y	
Spleen	Y	
Stomach	Y	
Subcutaneous		N
Testis	Y	
Thoracic Vertebra		N
Urinary Bladder	Y	
Uterus	Y	
Vagina	Y	

**STATISTICAL ANALYSIS PLAN
(SAP)**

**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 (TPC) FOR HER2LOW,
UNRESECTABLE AND/OR METASTATIC BREAST
CANCER SUBJECTS
(DESTINY-Breast04)**

DS8201-A-U303

**VERSION 2.0, JAN 4, 2022
VERSION 1.0, 6 NOVEMBER 2020**

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SAP APPROVAL FORM

Prepared By:

PPD

Print Name

Signature

Date

Director, Biostatistics

Title

PPD

Print Name

Signature

Date

Senior Statistician, Covance

Title

Approved By:

PPD

Print Name

Signature

Date

Executive Director, Biostatistics

Title

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AC	adjudication committee
ADA	anti-drug antibody(ies)
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ASCO-CAP	American society of clinical oncology – college of American pathologists
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BICR	blinded independent central review
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
DCR	disease control rate
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
cfDNA	cell free deoxyribonucleic acid
CI	confidence interval
COVID	coronavirus disease
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DMC	data monitoring committee
DoR	duration of response
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	eastern cooperative oncology group performance status
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity

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ABBREVIATION	DEFINITION
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
HEOR	health economics and outcomes research
HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of HER2
HR	hormone receptor
IHC	immunohistochemistry
ILD	interstitial lung disease
ISH	in situ hybridization
IV	intravenous(ly)
IXRS	interactive web/voice response system
LV	left ventricular
LVEF	left ventricular ejection fraction
K-M	Kaplan-Meier
MedDRA	medical dictionary for regulatory activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
NCI	national cancer institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PK	pharmacokinetic
PopPK	population pharmacokinetics
PPS	per-protocol Analysis Set
PR	partial response
PR interval	time from the beginning of the P wave (atrial depolarization) to the beginning of the QRS complex

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ABBREVIATION	DEFINITION
PRO	patient-reported outcome
PT	preferred term
RR	respiratory rate
QoL	quality of life
QLQ	quality of life questionnaire
QT interval	time from the start of the Q wave to the end of the T wave
QTc	corrected QT interval
QTcF	QT intervals corrected for heart rate by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
TBL	Total Bilirubin
T-DXd	trastuzumab deruxtecan
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TPC	treatment of physician's choice
TPR	time point response
TTR	time to response
VAS	visual analogue scale
ULN	upper limit of normal
WHOdrug	world health organization drug dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the efficacy, safety, pharmacokinetic, pharmacodynamics, health economics and outcomes research endpoints for the clinical study report (CSR) of the study protocol DS8201-A-U303, a phase 3, multicenter, randomized, open-label, active-controlled trial of trastuzumab deruxtecan (T-DXd), an anti-HER2 (human epidermal growth factor receptor 2)-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects. The contents of the SAP are based on protocol Version 5.0 (12 October 2020). All decisions regarding final analysis, as defined in the SAP document, will be made prior to database lock and unblinding of study data. Specifications for tables, listings, and figures are contained in a separate document.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan (T-DXd) to physician's choice (TPC) in human epidermal growth factor receptor 2 (HER2)-low, hormone receptor (HR)-positive breast cancer, based on blinded independent central review (BICR).

2.2. Key Secondary Objectives

The key secondary objectives are:

- To compare PFS benefit of T-DXd to TPC in all randomized subjects (HER2-low, hormone receptor positive and hormone receptor negative breast cancer), based on BICR
- To compare overall survival (OS) benefit of T-DXd to TPC in HER2-low, hormone receptor positive breast cancer.
- To compare the OS benefit of T-DXd to TPC in all randomized subjects (HER2-low, hormone receptor positive and hormone receptor negative breast cancer)

2.3. Other Secondary Objectives

The other secondary objectives are:

- To investigate the efficacy of T-DXd compared to TPC on the following parameters:
 - PFS in hormone receptor positive subjects, based on Investigator assessment
 - Confirmed objective response rate (ORR), based on BICR and Investigator assessment in hormone receptor positive subjects and hormone receptor negative subjects
 - DoR (duration of response), based on BICR in hormone receptor positive subjects and hormone receptor negative subjects
 - Confirmed ORR, and DoR in all subjects, regardless of hormone receptor status
- To determine pharmacokinetics (PK) of T-DXd
- To evaluate safety of T-DXd compared to TPC
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for T-DXd compared to TPC

2.4. Exploratory Objectives

The exploratory objectives are to evaluate the following:

- Clinical benefit rate (CBR; the sum of complete response [CR] rate, partial response [PR] rate, and longer than 6 months' stable disease [SD] rate) based on BICR and

Investigator assessment in hormone receptor positive subjects and all subjects regardless of hormone receptor status.

- Disease control rate (DCR), based on BICR and Investigator assessment in hormone receptor positive subjects and in all subjects regardless of HR status.
- Time to response (TTR) in hormone receptor positive subjects and all subjects regardless of hormone receptor status, based on BICR and Investigator assessment.
- 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 hormone receptor negative subjects
- Best percent change in the sum of the diameter of measurable tumors based on BICR

3. STUDY DESIGN AND METHODS

3.1. General Study Design and Plan

This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of T-DXd versus the TPC in HER2-low, unresectable and/or metastatic breast cancer subjects (see [Figure 3.1](#) for study design schema).

Approximately 540 subjects (including approximately 480 hormone receptor positive subjects and 60 hormone receptor negative subjects) will be randomized in a 2:1 ratio into 2 treatment groups (T-DXd versus TPC).

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

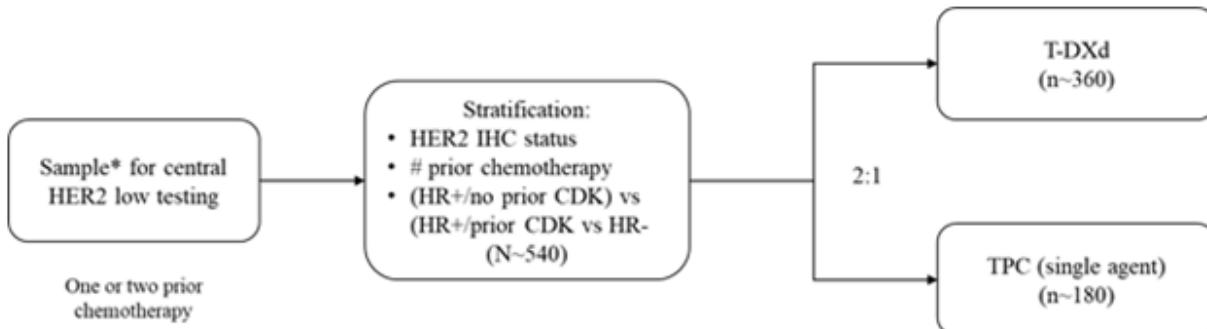
The comparator for this study is the TPC with the options being one of the following:

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

Randomization will be stratified by:

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

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 3.1 and Section 3.2 of the protocol (v5, 12 Oct 2020) for details.

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. If the study treatment is delayed more than 28 days from the planned date of administration, the subject will be withdrawn from the study.

After study treatment discontinuation, all subjects may be contacted at the 40-Day (+7 days) Follow-up Visit, 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. 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.

Progression free survival (PFS) based on BICR, in hormone receptor positive breast cancer subjects is the primary endpoint in this study. The primary efficacy analysis is planned to be performed after approximately 318 BICR PFS events in the hormone receptor positive subjects have been documented in the study.

The final data cutoff for the key secondary efficacy endpoint OS is planned when approximately 333 OS events have been observed in hormone receptor positive subjects if study continues after OS interim analyses.

An independent Data Monitoring Committee (DMC) will monitor unblinded safety data accruing in the trial. A separate DMC SAP describes the analyses for the DMC reviews.

3.2. Randomization

The target sample size of approximately 480 hormone receptor positive subjects and approximately 60 hormone receptor negative subjects will be randomized in a 2:1 ratio to the 2 treatment arms (T-DXd versus the comparator of TPC).

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
- hormone receptor /CDK status: hormone receptor positive with prior CDK4/6 inhibitor treatment vs. hormone receptor positive without prior CDK4/6 inhibitor treatment vs. hormone receptor 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. A subject's first dose/Cycle 1 Day 1 should occur within 7 days after the date the subject is randomized.

3.3. Blinding

This study is an open-label study as it is not feasible to blind treatment allocations for individual subjects because of different routes of administration, different treatment schedules, between T-DXd and investigator's choice therapy.

3.4. Schedule of Events

Refer to Section 17.1 of DS8201-A-U303 protocol for schedule of events.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

Detailed specifications of efficacy endpoints are provided in Section 8 below.

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, based on BICR, in hormone receptor positive subjects. PFS 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 according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 or death due to any cause. If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the last adequate tumor evaluation date before the cut-off date. See Section 8.2 for details related to censoring rules. Discontinuation associated with disease progression, without supporting objective evidence satisfying progression criteria per mRECIST 1.1 will not be considered as a PFS event. Details on time point responses per mRECIST 1.1 can be found in Appendix 11.1.

4.1.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints are:

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

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.

4.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are:

- PFS, based on investigator assessment
- Confirmed ORR, defined as the proportion of subjects with best overall response of confirmed complete response (CR) or partial response (PR), 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 (confirmed 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 (confirmed CR or PR) only. Subjects who are progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment.

4.1.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- CBR, defined as the sum of CR rate, PR rate, and more than 6 months' SD rate, based on BICR
- DCR, defined as the sum of CR rate, PR rate, and SD rate, based on BICR and investigator assessment
- TTR, defined as the time from the date of randomization to the date of the first documentation of objective response (confirmed CR or PR), based on BICR. Time to response will be measured for responding subjects (confirm CR or PR) only.
- PFS2, defined as the time from date of randomization to the first documented progression on next-line therapy based on investigator assessment or death due to any cause, whichever occurs first.
- PFS, OS, confirmed ORR, and DoR based on BICR in the hormone receptor-negative cohort
- Best percent change in the sum of the diameter of measurable tumors based on BICR

4.2. Safety Endpoints

4.2.1. Adverse Events

The AE safety endpoints include:

- Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
- Serious adverse events (SAEs)
- Adverse events of special interest (AESIs)
- TEAEs associated with dose reduction and drug interruptions
- TEAEs associated with discontinuations of study treatment
- TEAEs associated with outcome of death

4.2.2. Clinical Laboratory Evaluations

Standard clinical laboratory parameters are included as a safety endpoint. Refer to Section [7.3.4](#) for details.

4.2.3. Vital Signs

Vital sign measurements are included as safety endpoints. Refer to Section [7.3.5](#) for details.

4.2.4. Electrocardiogram

Electrocardiogram (ECG) parameters are included as safety endpoints. Refer to Section [7.3.6](#) for details.

4.2.5. Other Safety Endpoints

Other safety endpoints include:

- Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
- Echocardiogram (Echo)/multi-gated acquisition scan (MUGA) findings
- Anti-drug antibodies (ADA)
- Neutralizing ADA

4.3. Pharmacokinetic Endpoints

The PK endpoints include serum concentrations of T-DXd, total anti-HER2 antibody and DXd.

4.4. Pharmacodynamics Endpoint

Not applicable in this study.

4.5. Biomarkers

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)

4.6. Health Economics and Outcomes Research Endpoints

The Heath Economics and Outcomes Research (HEOR) endpoints include:

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

5. SAMPLE SIZE DETERMINATION

A total of approximately 480 hormone receptor positive subjects will be randomized (approximately 320 T-DXd and approximately 160 TPC). In addition, approximately 60 hormone receptor negative subjects (approximately 40 T-DXd and approximately 20 TPC) will be enrolled for exploratory purpose.

Assuming a median PFS of 4.2 months in the TPC arm in hormone receptor positive subjects, it is hypothesized that treatment with T-DXd will result in a hazard ratio of 0.68, a 32% reduction in the hazard rate of PFS (disease progression or death) that would correspond to a 47% improvement in median PFS from 4.2 months in the TPC arm to 6.2 months in the T-DXd arm under the exponential model assumption.

The final PFS analysis will occur after approximately 318 PFS events have been documented in hormone receptor positive subjects. With 318 PFS events, the study will have approximately 90% power of a log-rank test to reject the null hypothesis of no difference in PFS distributions at an overall 2-sided significance level of 0.05, assuming a hazard ratio of 0.68.

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 hormone receptor positive cohort and the FAS (full analysis set) have demonstrated statistical significance. Assuming a median OS of 15 months in the control arm in hormone receptor positive subjects^{1 2 3 4 5 6}, it is hypothesized that treatment with T-DXd will result in a hazard ratio of 0.72 in OS that would correspond to a 39% improvement in median OS from 15 months in the TPC arm to 20.8 months in the T-DXd arm under the exponential model assumption. With a total of 333 OS events, the study will have approximately 80% power of a log-rank test (conditional on PFS being significant) to reject the null hypothesis at an overall 2-sided significance level of 0.05 under a 3-look group sequential design with O'Brien-Fleming superiority boundary⁷ of Lan-DeMets alpha spending function⁸ (see Section 6.2 for further details), assuming a hazard ratio of 0.72. If the true hazard ratio is 0.72, it is estimated that approximately 162 (49%) and 233 (70%) of the targeted OS events will be documented in hormone receptor positive subjects at the times of the 2 OS interim analyses (the first OS interim analysis performed at the time of PFS final analysis).

The sample size calculation was performed using the EAST version 6.4⁹.

6. GENERAL STATISTICAL CONSIDERATIONS

Summary statistics will be presented by treatment group, T-DXd and TPC.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

For efficacy evaluations, the last available assessment on or before the date of randomization will be used as the “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include patient reported outcomes, for which the baseline is defined as the latest assessment prior to or on the randomization date/the first dose (Cycle 1 Day 1) date, whichever occurs later.

For safety evaluations (e.g. laboratory, ECG and vital signs), the last available assessment before start of study treatment will be used as the ‘baseline’ assessment. If subjects have no value as defined above, the baseline results will be set to missing.

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. 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 hormone receptor positive cohort and FAS. Sensitivity analysis of primary efficacy endpoint may be performed on per-protocol analysis set (PPS).

Safety analyses will be performed using the safety analysis set. PK analysis will be based on the PK analysis set. All other exploratory analyses will be performed based on the hormone receptor positive cohort and FAS.

6.1. Analysis Sets

6.1.1. 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 and strata assigned at randomization.

The hormone receptor positive cohort of FAS, according to baseline hormone receptor status per IXRS, will be the primary analysis set for efficacy analyses.

6.1.2. 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.

6.1.3. Per-Protocol Analysis Set (PPS)

The PPS will include all subjects in the hormone receptor positive cohort who complied sufficiently with the protocol with respect to exposure to study treatment, availability of tumor assessment, and absence of major protocol violations likely to impact efficacy outcome. To be eligible for inclusion in the PPS, subjects must meet the following criteria:

- Received at least one dose of study drug as assigned by randomization
- Had at least one evaluable post-baseline tumor assessments or died less than 14 weeks of randomization without post-baseline scans
- Absence of major protocol violations as described below.

Major protocol deviations that lead to exclusion from the PPS are as follows:

- Did not sign main informed consent
- Eligibility Criteria

A subject who violates any of the following inclusion and/or exclusion criteria will be classified as a major protocol deviation likely to impact efficacy outcome:

Inclusion Criteria (per protocol):

IC #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 American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines evaluated at a central laboratory;
- d. is documented refractory to endocrine therapy If hormone receptor positive, 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;
- e. 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;
- f. was never previously treated with anti-HER2 therapy.

IC #4. Documented radiologic progression (during or after most recent treatment).

IC #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.

Exclusion Criteria (per protocol):

EC #1. Ineligible for a comparator in the TPC arm either because of previously having received treatment in the metastatic setting with the same comparator or having a contraindication to treatment.

EC #2. Prior treatment with antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor.

- A subject who received a study drug regimen that was not assigned by randomization, i.e., the alternative treatment was received throughout the study.

6.1.4. Pharmacokinetic (PK) Analysis Set

The PK analysis set will include all subjects who received at least 1 dose of T-DXd and had any measurable post-dose serum concentrations of T-DXd, total anti-HER2 antibody, and DXd.

6.2. Interim Analyses and Data Monitoring

No formal interim analysis is planned for PFS.

Up to three analyses of OS are planned:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant in both hormone receptor positive cohort and FAS), at which point a total of 162 OS events (49% information fraction) in hormone receptor positive cohort 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 hormone receptor positive cohort have been documented.
- If the second OS interim analysis is not significant, a final analysis for OS after approximately 333 OS events in hormone receptor positive cohort 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 hormone receptor positive cohort and the FAS. A hierarchical testing procedure is adopted as described in Section [6.3](#) below.

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 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 hormone receptor positive cohort and FAS. The same interim efficacy stopping boundaries will be used for OS hypotheses testing with hormone receptor 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 hormone receptor 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 hormone receptor 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 hormone receptor positive cohort and FAS.

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 6.1](#).

Table 6.1: Stopping Boundaries at OS Interim and Final analyses

Analysis time (month)*	Number of OS events (Information fraction)	HR (p-value) superiority boundary ^a	Minimal detectable difference in median OS vs 15 for control arm (month) ^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

* 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 month, 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.

6.3. Multiple Comparisons/Multiplicity

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

1. PFS based on BICR in the hormone receptor positive cohort
2. PFS based on BICR in the FAS
3. OS in the hormone receptor 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.

7. STATISTICAL ANALYSIS

7.1. Summary of Study Data

7.1.1. Subject Disposition

Subject disposition will be summarized and listed for all screened subjects. Number of screen failures will be presented. The total number of subjects for each defined analysis set will also be tabulated.

7.1.2. Protocol Deviations

Major protocol deviations will be summarized by treatment arm and by category for subjects in FAS. All protocol deviations will be listed by treatment group.

7.1.3. Demographic and Baseline Characteristics

The demographic and baseline disease characteristics will be summarized descriptively and listed for the hormone receptor positive cohort, PPS, FAS, safety analysis set.

Discrepancies between randomization stratification information (obtained from IXRS) and strata formed based on baseline factors collected on eCRFs will be tabulated and listed.

7.1.3.1. Diagnosis and Extent of Cancer

Summary statistics will be tabulated for diagnosis and extent of cancer using hormone receptor positive cohort and FAS.

According to the data collected on the eCRF, this analysis will include the following: histology, tumor stage at initial diagnosis, grade, HER2 expression (IHC), HER2 gene amplification (ISH), estrogen receptor status, progesterone receptor status, BRCA1 status, BRCA2 status, and time since initial diagnosis.

A listing will be provided for FAS.

7.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHOdrug). Concomitant medications will be summarized by ATC2 class and preferred term for the safety analysis set. Prior medications will be summarized for the hormone receptor positive cohort and FAS. Within each level of summarization, a subject will be counted once if he/she takes one or more medications.

Prior medications are defined as those with a stop date prior to the date of first dose of study drug. Concomitant medications are defined as those with a start date greater than or equal to the date of first dose of study drug, or with a start date prior to the date of first dose of study drug and a stop date either after the date of first dose of study drug or marked as “ongoing” or “continuing”. Medications taken prior to the first dose of study drug, but with a missing stop date or with a stop date either on or after the date of the first dose of study drug or marked as “ongoing” or “continuing” will also be considered concomitant medications for the summary. Medications started after the 47-day visit or after start of new anticancer therapy are not

considered as concomitant medications. A listing of prior and concomitant medications by subject will also be provided.

7.1.5. Prior Breast Cancer Systemic Therapy

Frequency and percent of subjects with prior breast cancer systemic therapy will be summarized for the following class/subclass and medication:

- Any Prior Systemic Cancer Therapy Intended for
 - Neo-Adjuvant
 - Adjuvant
 - Locally Advanced
 - Metastatic
 - Preventive
 - Maintenance
 - Other
- Any Prior Systemic Cancer Therapy
- Targeted Therapy
 - CDK 4/6 inhibitor
 - Immunotherapy
 - Other
- Endocrine Therapy
- Chemotherapy

In addition, frequency and percent of subjects for following derived variables will be summarized:

- Lines of Prior Systemic Therapy (0, 1, 2, >=3) in Any Setting
- Lines of Prior Systemic Therapy (0, 1, 2, >=3) in Metastatic Setting - derived
- Lines of Prior Chemotherapy (0, 1, 2, >=3) in Any Setting
- Lines of Prior Chemotherapy (0, 1, 2, >=3) in Metastatic Setting - Derived
- Lines of Prior Endocrine Therapy (0, 1, 2, >=3) in Any Setting
- Line of Prior Endocrine Therapy (0, 1, 2, >=3) in Metastatic Setting – Derived

Derivation of the variables is specified below:

Variable	Derivation
Lines of Prior Systemic Therapy (0, 1, 2, >=3) in Any Setting	<p>Total number of the unique regimen ID, regardless what intended for), if Any Prior Cancer Systemic Therapy = “Yes”</p> <ul style="list-style-type: none"> Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
Lines of Prior Systemic Therapy (0, 1, 2, >=3) in Metastatic Setting - derived	<p>Total number of regimens of systemic cancer therapies, intended for “Locally Advanced”, “Metastatic”, or “Other” (palliative), if Any Prior Cancer Systemic Therapy = “Yes”</p> <ul style="list-style-type: none"> Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
Lines of Chemotherapy (0, 1, 2, >=3) in Any Setting	<ul style="list-style-type: none"> Class = Chemotherapy Count the number of the unique regimen ID, regardless what intended for Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
Lines of Prior Chemotherapy (0, 1, 2, >=3) in Metastatic Setting - Derived	<ul style="list-style-type: none"> Class = Chemotherapy Count the number of the unique regimen ID, intended for “Locally Advanced” or “Metastatic” or “other” (palliative) Count the number of the unique regimen ID, intended for “Neo-Adjuvant”, “Adjuvant”, or “Maintenance”, with PD within 6 months since the end of the therapy (only if end of therapy date and PD date are present after imputation) Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
Lines of Prior Endocrine Therapy (0, 1, 2, >=3) in Any Setting	<ul style="list-style-type: none"> Class = Endocrine therapy Count the number of the unique regimen ID, regardless what intended for Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.
Line of Prior Endocrine Therapy (0, 1, 2, >=3)	<ul style="list-style-type: none"> Class = Endocrine Therapy

Variable	Derivation
in Metastatic Setting - Derived	<ul style="list-style-type: none"> Count the number of the unique regimen ID, intended for “Locally Advanced” or “Metastatic” or “other” (palliative) Any regimens in sequential lines of therapy according to eCRF entry with identical combination of agent names will be subtracted.

A worksheet on drug class/subclass will be provided in a separate file.

7.2. Efficacy Analyses

7.2.1. Analysis of PFS

7.2.1.1. Primary Efficacy Analysis

The primary efficacy analysis will be the comparison of the distribution of PFS per BICR in hormone receptor positive cohort between the two treatment groups using stratified log-rank test, with stratification factors from IXRS, at two-sided significance level of 0.05, under statistical hypotheses:

$$H_0: S_T(t) = S_C(t) \text{ vs. } H_a: S_T(t) \neq S_C(t), t \geq 0$$

where $S_T(t)$ is the survival distribution function of PFS with the treatment of T-DXd and $S_C(t)$ is the survival distribution function of PFS with the TPC group.

The primary efficacy analysis will be performed using hormone receptor positive cohort based on the data up to the data cut-off date when approximately 318 BICR-assessed PFS events are observed. If a patient has not progressed or died, at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date (See Section 8.2.1.1 for additional details regarding censoring rules). Discontinuation associated with disease progression, without supporting objective evidence satisfying progression criteria per mRECIST version 1.1, will not be considered as a PFS event.

The hypothesis will be tested using a stratified log-rank test at two-sided significance level of 0.05. The stratification factors will be the randomization stratification factors taken from IXRS. The distribution of PFS will be estimated using the Kaplan-Meier (K-M) method for each treatment arm, and the results will be presented graphically by treatment group.

The median PFS and the two-sided 95% confidence intervals (CIs) using Brookmeyer and Crowley method¹⁰ will be provided for each treatment group. In addition, PFS rates at fixed time points (e.g., 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group.

The hazard ratio of PFS and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with treatment group as model factor and the stratification factors from IXRS as strata.

7.2.1.2. Supportive and Sensitivity Analyses

As a sensitivity analysis to assess the impact of stratification on primary efficacy analysis, the two treatment groups will be compared using an unstratified log-rank test. The same censoring rules used for the primary efficacy analysis will be applied. The hazard ratio together with associated 95% CI will also be estimated using unstratified Cox proportional hazards regression model.

The primary efficacy analyses will be repeated for FAS and PPS if the PPS and the full analysis sets differ.

A stratified Cox regression model with strata collected through IXRS as stratification factor will be fitted to evaluate the effect of other baseline demographic or disease characteristics on the estimated hazard ratio. This model will include the following key prognostic factors as covariates: ECOG performance status (0, 1), lines of endocrine therapy received in the metastatic setting (0, 1, ≥ 1), history CNS metastases (yes, no), and age (<65 , ≥ 65 years old). The p-value associated with treatment and with each of the baseline covariates will be presented. The hazard ratio along with the associated 95% CI will also be presented for each covariate.

In addition to the above, the sensitivity analyses of the primary efficacy endpoint will be performed to assess the impact of censoring rules used for the primary efficacy analysis. The following test statistics will be provided: stratified log-rank test p-values, K-M estimates of survival distribution, estimate of the median PFS along with 95% confidence interval, and hazard ratio obtained using stratified Cox proportional hazards model. Sensitivity analyses include the following:

- Using the BICR-assessed PFS data on the hormone receptor positive cohort, and including PFS events whenever they occurred, i.e. not censoring for missing 2 consecutive tumor assessments
- Using the BICR PFS data on the hormone receptor positive cohort, but censoring for new anticancer therapy
- Backdating PFS analysis: repeat BICR PFS analysis not censoring for missing tumor assessment, but backdate PFS event time in the case that PFS event occurred after missing one or more tumor assessments. In such cases, the PFS event date would be considered to be 6 weeks after last evaluable tumor assessment occurring prior to progression/death.

Additional supportive analyses will include:

- Number of subjects and number of events by treatment arm within each stratum will be presented along with hazard ratio obtained using unstratified cox regression model, provided enough events are observed within each stratum. K-M estimates of median survival and 95% CIs will be presented for each treatment group. No formal statistical comparison will be carried out within stratum.
- If there is $\geq 10\%$ discrepancy between strata constructed through the eCRF data and those obtained through IXRS, a sensitivity analysis may be performed where the

treatment effect HR will be estimated along with the 95% CI using a stratified cox regression model, where the stratum is based on the eCRF data. No inferential statistics (p-values) will be presented.

If the number of BICR PFS events by the data cutoff date is more than 328 (3% over the target number of PFS events), a sensitivity analysis using the data up to the target 318 BICR PFS events will be carried out following the primary analysis approach.

7.2.1.3. Censoring Pattern of PFS

Number of subjects in the PFS analysis and the number of subjects with a PFS event will be summarized for hormone receptor positive cohort and FAS. In addition, a summary of reasons for censoring will be provided by treatment based on the following reasons:

- No baseline tumor assessments
- No post-baseline tumor assessments
- Event after ≥ 2 missing tumor assessments
- No PD or death

Details on the PFS censoring rules are given in Section [8.2.1.1](#).

7.2.1.4. Concordance Analysis of PFS

Concordance analysis will be performed for FAS.

Cross-tabulation of 'PFS by BICR' vs. 'PFS by investigator' by PFS event type (i.e., 'death', 'PD', and 'censor' for each of the two sources resulting in a 3-by-3 table) and by treatment will be constructed to assess concordance between the two sources on a patient-by-patient basis.

Discrepancy (%) rate between 'BICR assessed' and 'Investigator-assessed' PFS status (event vs censor) will be calculated and presented (by treatment group) as follows: $100 \times (n_{13} + n_{23} + n_{31} + n_{32}) / N$.

Comparison Between PFS Investigator and BICR Assessments in Hormone Receptor Positive Cohort

<Treatment group> N=XXX			
Investigator PFS result	BICR PFS result		
	Death	PD	Censor
Death	n11	n12	n13
PD	n21	n22	n23
Censor	n31	n32	n33

A cross-tabulation will be produced displaying the PFS timings for the local investigators' assessment compared to the BICR assessment. For progression assessments, the frequency and percent of subjects with complete agreement [occurring on the same date plus or minus 7 days of each other], progression later, progression earlier, and cases where progression was called by one method and censored by the other will be displayed. Similarly, if censoring was recorded, the frequency and percent of subjects with complete agreement, censoring called later, censoring called earlier, and cases where censoring was called by one method and progression was called by the other method will be displayed.

Comparison of PFS Event Times between Investigator and BICR Assessments in Hormone Receptor Positive Cohort

		< Treatment arm > (N = XXX)			
Investigator	BICR	Same time n (%)	BICR after Investigator n (%)	BICR before Investigator n (%)	Total
PD	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	Death	xx (xx.x)	-	-	xx (xx.x)
Censor	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Censor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD	Death	-	xx (xx.x)	-	XX (xx.x)
Death	PD	-	-	xx (xx.x)	xx (xx.x)
Death	Censor	-	-	xx (xx.x)	xx (xx.x)
Censor	PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Censor	Death	-	xx (xx.x)	-	xx (xx.x)
Total		xx (xx.x)	xx (xx.x)	xx (xx.x)	xxx(100.00)

7.2.1.5. Subgroup Analysis of BICR-assessed PFS

Subgroup analyses for PFS based on BICR will be performed for the hormone receptor positive cohort and the FAS.

For each of these subgroups, the median PFS and the two-sided 95% confidence intervals (CIs) using the K-M method as well as the estimated HR and 95% CI obtained using the unstratified Cox regression model will be presented. Subgroup analyses will be performed only for the category of the subgroup if at least 10 PFS events in both treatment arms. A forest plot will be used to depict the estimated treatment effects.

Subgroups include:

- HER2 status (HER2 IHC 1+, HER2 IHC 2+/ISH-) based on baseline value from EDC
- Number of prior lines of chemotherapy (1, >=2) in the metastatic setting
- Prior CDK4/6 (Yes, No), derived based on baseline value from EDC
- Age (<65, ≥ 65 years; <75, ≥ 75 years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (Asia (CHN, JPN, KOR, TWN), North American (USA, CAN), Europe (AUT, CHE, BEL, ESP, FRA, GBR, GRC, HUN, ITA, PRT, RUS, SWE)+ Israel)
- Number of lines of endocrine therapy received in the metastatic setting (0, 1, 2, >=3)
- Best Response to last prior cancer systemic therapy

- Reported history of CNS metastases (yes, no)
- Baseline CNS metastases (Yes, No)
- Renal function at baseline (normal function, mild, moderate impairment)
Renal function is determined by the baseline creatinine clearance:
 - Normal renal function: creatinine clearance ≥ 90 mL/min
 - Mild renal impairment: creatinine clearance $\geq 60, < 90$ mL/min
 - Moderate renal impairment: creatinine clearance $\geq 30, < 60$ mL/min
 - Severe renal impairment: creatinine clearance $\geq 15, < 30$ mL/min
 - End stage renal disease: creatinine clearance < 15
- Hepatic function at baseline (normal function, mild impairment)
 - Normal hepatic function:
 - Total bilirubin \leq upper limit of normal (ULN) and (AST \leq ULN) except for subjects with Gilbert syndrome (preferred term [PT]: 10018267)
 - Total bilirubin $\leq 3.0 \times$ ULN and (AST \leq ULN) for subjects with Gilbert syndrome
 - Mild impairment:
 - Total bilirubin $>$ ULN, $\leq 1.5 \times$ ULN and any AST except for subjects with Gilbert syndrome
 - Total bilirubin $>$ ULN, $\leq 3.0 \times$ ULN and (AST $>$ ULN) for subjects with Gilbert syndrome
 - Total bilirubin \leq ULN and (AST $>$ ULN) regardless of Gilbert Syndrome
 - Moderate impairment:
 - Total bilirubin $> 1.5 \times$ ULN, $\leq 3.0 \times$ ULN and any AST except for subjects with Gilbert syndrome
 - Severe impairment:
 - Total bilirubin $> 3.0 \times$ ULN and any AST regardless of Gilbert Syndrome
- Baseline visceral disease (yes, no)
Visceral disease is determined with any target or non-target tumor except “Breast”, “Skin”, “Lymph Node”, and “Bone” in the location on the “Target/Non-Target Tumor Assessments (Imaging Baseline)” CRF page. A detail list of the locations to be included/excluded is provided in Appendix [11.3](#).
- ECOG PS (0, 1)

The subgroups are based on baseline values (i.e., the last non-missing values before the first drug administration). Note that hormone receptor group based on baseline hormone receptor status will be added in subgroup analysis of PFS for FAS.

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. No inferential statistics (p-values) will be presented for the subgroups.

The algorithm for number of prior lines of chemotherapy in the metastatic setting, (1, >=2) and number of prior lines of endocrine therapy received in the metastatic setting (0, 1, 2, >=3) is provided in Section 7.1.5.

7.2.2. Analysis of OS

OS is defined as the time from the date of randomization to the date of death due to any cause. Subjects without an OS event are censored at date of last contact when subjects are known to be alive. Derivation of date of last contact is provided in Section 8. The analysis of OS will be performed for hormone receptor positive cohort and FAS.

Overall survival will be compared between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at 2-sided significance level adjusting for alpha spending, provided superiority in PFS per BICR is demonstrated in both hormone receptor positive cohort and FAS. The survival distribution of OS will be estimated by Kaplan-Meier method and results will be presented graphically. The median survival time and the 2-sided 95% CI for the median will be provided using Brookmeyer and Crowley method for each treatment group. In addition, Kaplan-Meier estimates of OS rate at fixed time points (e.g., 3, 6, 9, 12, 18, 24, 36, 48 months) along with their 2-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

7.2.2.1. Supportive Analyses for OS

If the analysis of OS is significant, a Cox regression model stratified by the IXRS stratification factors will be fitted to evaluate the effect of the same prognostic factors as specified earlier for the Cox regression analysis for PFS.

7.2.2.2. Censoring Pattern of OS

The pattern of censored data will be presented by treatment group. Reasons for censoring that will be based on subject outcome of survival follow-up CRF page or as “Alive” for subject still on treatment will be summarized. In addition, survival status, reasons for censoring, and causes of death will be listed.

7.2.2.3. Subgroup Analysis for OS

Subgroup analyses of OS will be performed for hormone receptor positive cohort and FAS using the same subgroups defined for the PFS analysis and using the same methodology, provided PFS and OS analyses are significant for both hormone receptor positive cohort and FAS. Note that hormone receptor negative cohort will be added in subgroup analysis of OS for FAS.

7.2.2.4. Currentness of PFS and OS Follow-up

Time from the PFS end date to data cut-off in weeks will be summarized by treatment arm for hormone receptor positive cohort. Subjects who have a PFS event will be considered as current for this analysis. The currentness of PFS follow-up will be categorized into the following categories: 0-6 weeks, 6-12 weeks, and > 12 weeks. The median follow-up duration for PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group using the Kaplan-Meier method by reversing the PFS censoring and event indicators.

Currentness of OS follow-up will be summarized in months, by computing the time from “last known alive” date to data cut-off date. Subjects who have a death event will be considered as current for this analysis. The currentness of follow-up will be categorized into the following categories: 0-3 months, 3-6 months, and > 6 months. The median follow-up duration for OS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group using the Kaplan-Meier method by reversing the OS censoring and event indicators.

7.2.3. Analysis of Other Secondary Efficacy Endpoints

Analysis of other secondary efficacy endpoints will be performed based on hormone receptor positive cohort of FAS and the FAS at the time of primary PFS analysis.

Other efficacy endpoints include PFS based on investigator assessment, confirmed objective response rate based on BICR and investigator assessment, and duration of response based on BICR and investigator assessment.

7.2.3.1. PFS Based on Investigator Assessment

The survival distribution of PFS based on investigator assessment will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (e.g., 3, 6, 9, 12, 18, 24 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 same stratification factors as the randomization stratification factors taken from IXRS. The survival distribution of PFS based on investigator assessment between the two treatment groups will be compared at a two-sided significance level of 0.05, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at the time when primary analysis of PFS per BICR is statistically significant.

7.2.3.2. Confirmed Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with best overall response of confirmed complete response (CR) or partial response (PR) according to mRECIST version 1.1 criteria. ORR will be calculated based on the data from the full analysis set based on BICR assessment of tumor scans. Subjects with only non-measurable disease at baseline will be included in the numerator only if a complete response was observed.

Number and proportion of subjects in each response category of BOR will be provided by treatment group. ORR (based on BICR and investigator assessment) will be summarized by treatment group along with the two-sided 95% CIs using the Clopper-Pearson method. The difference of ORR between the two treatment groups will be summarized and the 95% CI will be calculated using continuity correction. The Cochran-Mantel-Haenszel test stratified by the randomization stratification factors per IXRS will be used to compare ORR at two-sided significance level of 0.05.

As a supportive analysis, ORR will also be summarized by using the investigator review of tumor data.

7.2.3.3. Duration of Response

Duration of response (DoR) is defined as the time from date of initial response (confirmed CR or PR) to the date of disease progression or death due to any cause for subjects with a confirmed CR or PR. DoR (based on BICR and investigator assessment, respectively) will be summarized with median duration and its two-sided 95% CI for the median using Brookmeyer and Crowley method for each treatment group. K-M estimates of the distribution of DoR will be calculated and presented graphically by treatment group. The same censoring rules will be applied as for the primary analysis of PFS based on BICR or based on investigator assessments, respectively. DOR will be calculated only for subjects with a best overall response of confirmed CR or PR.

7.2.4. Analysis of Exploratory Efficacy Endpoints

Analysis of exploratory efficacy endpoints will be performed based on hormone receptor positive cohort of FAS and the FAS at the time of primary PFS analysis.

The exploratory endpoints include clinical benefit rate (CBR) based on BICR, disease control rate (DCR) based on BICR, time to response (TTR) based on BICR, best percent change in the sum of the diameters of measurable tumors based on BICR, and PFS2.

7.2.4.1. Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as proportion of subjects with best overall response of CR, PR, or more than 6 months Stable Disease (SD). The analyses for ORR will be repeated for CBR based on BICR assessment.

7.2.4.2. Disease Control Rate

Disease control rate (DCR) per BICR is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) according to mRECIST version 1.1. The analyses for ORR will be repeated for DCR.

7.2.4.3. Time to Response

Time to response (confirmed CR or PR, based on BICR) is defined as the time between date of randomization until the first documented response (confirmed CR or PR). Patients with a confirmed CR or PR will be included in the time to response calculation. Descriptive statistics will be used to summarize time to response.

7.2.4.4. Change of Sum of Diameters from baseline to post-baseline minimum

A waterfall plot of the best percent change from baseline to post-baseline minimum in the sum of the diameters for each subject will be presented for each treatment group with vertical lines representing the sorted values of percent changes. Only subjects with measurable target lesions at baseline will be included for this analysis. All measurable assessments up to start of new anticancer therapy or progressive disease will be included.

7.2.4.5. PFS2

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.

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 (e.g., 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 taken from IXRS as strata variables. Analysis of PFS2 will be performed for hormone receptor positive cohort and FAS.

7.2.4.6. Others

Confirmed BICR ORR, and DoR will be summarized for hormone receptor negative subjects.

Analyses of PFS and OS in hormone receptor negative cohort are included in subgroup analysis using FAS.

7.3. Safety Analyses

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

7.3.1. Dosing and Extent of Exposure

Study treatment exposure and treatment duration will be summarized by treatment group using descriptive statistics for the safety analysis set. In addition, the total number of cycles initiated will be summarized using descriptive statistics. The number and percentage of subjects who continued the treatment at fixed time points (e.g., 3, 6, 9, 12 months) will be tabulated. T-DXd dosing status will be summarized to show the number and percentage of subjects with and without dose reductions or drug interruptions. For subjects with dose reductions, delays, or drug interruptions, the reasons will be provided.

All study drug administration data will be listed by subject.

The following definitions will be used.

- Duration of exposure (day)
 - Duration of exposure (day) for therapies
 - = Treatment duration end date – First treatment dose date

The treatment duration end date is defined as:

1. T-DXd arm: minimum (the date of last T-DXd dose + 21, the start date of new anticancer therapy if applicable, and death date if applicable)
 2. TPC arm: details are provided in Appendix [11.4](#).
- Planned cumulative dose (unit for the treatment)

Infusion = the sum of total amount of dose planned to be taken per protocol at each dosing record in CRF over the duration of exposure in question

Capecitabine = Planned the total dose of first dosing day x the duration of exposure (day)

Note that for capecitabine, the planned doses are between 1000-1250 mg/m² as per protocol, but not collected in CRF. The planned dose for capecitabine can be derived by total daily dose of the first dosing day /BSA, and the derived planned dose will be used in calculation of Planned Total Amount of Dose and Planned Dose Intensity.

- Cumulative dose (unit for the treatment)
 - = Total amount of doses actually taken (unit)
- Dose intensity (DI) (mg/kg/cycle)
 - = Cumulative dose (mg/kg) / Duration of exposure (day) /cycle length in day
- Planned dose intensity (PDI) (mg/kg/cycle) = Planned cumulative dose (mg/kg)/Duration of exposure (day)/cycle length in day
- Relative dose intensity (RDI) (%)
 - = (Dose intensity (DI) / Planned dose intensity (PDI))*100,

7.3.2. Adverse Events

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or worsened in severity or seriousness after initiating study drug up until 47 days after last dose of the study drug. SAEs with an onset or worsening 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 the MedDRA with the current version at database lock. AE grades will be based on NCI-CTCAE v5.0.

A high level summary of the number of subjects with TEAEs will be presented by treatment group, including the number and percentage of subjects with any TEAEs, treatment emergent serious adverse events (TESAEs), TEAEs related to study treatment, and TEAEs associated with study drug interruption, dose-reduction, or discontinuation of study treatment.

The number and percentage of subjects reporting TEAEs will be tabulated by System Organ Class (SOC), Preferred Term (PT), relationship to the study treatment, and the worst CTCAE grade for all and treatment related TEAEs. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by treatment group, as well as TEAEs associated with study drug interruption, dose-reduction, or discontinuation of the study treatments.

A by-subject AE (including TEAE) data listing including but not limited to the verbatim terms, SOC, PT, NCI-CTCAE grade, and relationship to study treatment, will be provided.

If more than one AE occurs with the same PT for the same subject, the subject will be counted only once for that PT using the worst grade and most related occurrence for the summarizations by grade and by relationship to study treatment. Additional safety endpoint derivations for missing data are described in SAP Section 8.2.2.

Treatment-emergent AEs will also be summarized by treatment group for the subgroups described in the SAP Section 7.3.2.4.

7.3.2.1. Overall Summary of Treatment-Emergent Adverse Events

An overall summary of TEAEs by treatment group will be provided for each of the follow TEAE categories:

- TEAEs
- Treatment Related TEAEs
- Serious TEAEs
- Treatment Related Serious TEAEs

The number and percentage of subjects with the following criteria will be summarized by treatment group:

- CTCAE grade ≥ 3
- Associated with outcome of death
- Associated with study drug discontinuation
- Associated with study drug interruption
- Associated with dose reduction

7.3.2.2. Treatment-Emergent Adverse Events Classified by SOC, PT and NCI CTCAE grade

The number and percentage of subjects with the following TEAEs will be summarized by treatment group as follows:

- TEAEs by SOC, PT and Worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- TEAEs by PT (in descending frequency)
- Serious TEAEs (TESAE) by SOC, PT and Worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)

- Serious TEAEs (TESAE) by PT (in descending frequency)
- Drug-related TEAEs by SOC, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Drug-related TEAEs by PT (in descending frequency)
- Drug-related serious TEAEs by SOC, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Drug-related serious TEAEs by PT (in descending frequency)
- TEAEs associated with study drug discontinuation by PT
- Drug-related TEAEs associated with study drug discontinuation by PT
- TESAEs associated with study drug discontinuation by PT
- TEAEs associated with study drug interruption by PT
- Drug-related TEAEs associated with study drug interruption by PT
- TESAEs associated with study drug interruption by PT
- TEAEs associated with dose reduction by PT
- Drug-related TEAEs associated with dose reduction by PT
- TESAEs associated with dose reduction by PT
- TEAEs associated with outcome of death by PT
- Drug-related TEAEs associated with outcome of death by PT
- TESAEs associated with outcome of death by PT

TEAE by selected TEAE and worst CTCAE grade will be summarized by treatment. A list of selected TEAEs will be provided in a separate file. Selected TEAEs are specified in Appendix [11.6](#).

7.3.2.3. Adverse Events of Special Interest

Interstitial lung disease (ILD)/pneumonitis and left ventricular (LV)dysfunction have been identified as AEs of special interest (AESI) for the DS-8201a program. An external ILD Adjudication Committee (AC) was established for the program and adjudicates all events of potential ILD/pneumonitis reported by investigators on an ongoing basis. Events of potential ILD/pneumonitis from PTs triggering adjudication are based on the current MedDRA version for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and respiratory failure and acute respiratory failure

ILD will be summarized based on the ILD adjudicated outcomes based on the ILD AC charter. Case definitions for each of the AEs are described in Appendix [11.2](#).

The number and percentage of subjects with the following AESIs will be summarized according to treatment group per the criteria as follows:

- AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Serious AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- Drug-related AESIs by AESI category, PT and worst NCI CTCAE grade (1, 2, 3, 4, 5, and ≥ 3)
- AESIs associated with study drug discontinuation by AESI category, PT
- AESIs associated with dose reduction by AESI category, PT
- AESIs associated with study drug interruption by AESI category, PT
- AESIs associated with outcome of death by AESI category, PT

For the AESI summaries listed above, ILD/pneumonitis will include all events adjudicated as drug-related by the adjudication committee.

In addition, ILD event adjudicated outcomes will be summarized by CTC grade and a shift table indicating CTCAE grade by investigator vs adjudication committee will be provided all events adjudicated as drug-related by the ILD AC. The adjudicated outcome of the worst ILD event will also be summarized.

The number and percentage of subjects with TEAEs will be summarized by selected PTs by 3-week periods as well.

Time to and Duration of First Treatment-Emergent Adverse Events of Special Interest

Time to the first treatment emergent AEs of Special Interest (AESI) and duration of AESI will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum) for subjects who had a treatment emergent AESI.

LVEF (left ventricular ejection fraction)

Summary statistics for time to first LV dysfunction and duration of first LV dysfunction per investigator will provided.

The frequency and percentage of worst LVEF grade post-baseline, together with the proportion of subjects who recovered to $\geq 90\%$ baseline since worst grade will be provided

Summary statistics will be provided for LVEF measurement at baseline, EOT (end of treatment) value, minimum postbaseline value, and maximum postbaseline value (Mean, SD, Median, Min-Max, 40% - 49%, 20% - 39%, <20%), as well as change from baseline to EOT, minimum, and maximum postbaseline value (Mean, SD, Median, Min-Max, 10% - 19% decrease, $\geq 20\%$ decrease, 10% - 19% increase, $\geq 20\%$ increase).

ILD

Summary statistics will be provided for ILD reported by the ILD adjudication committee and investigator below:

- Number of subjects (%) of ILD events
- Adjudicated as ILD by worst CTCAE grade
- Adjudicated as not ILD
- Adjudicated as drug-related ILD by worst CTCAE grade
- Adjudicated as not study drug-related ILD by worst CTCAE grade

In addition, the characteristics of ILD by the ILD adjudication committee and investigator will be summarized:

- Time to first adjudicated drug-related ILD onset date
- Time to first investigator reported ILD onset date
- Duration of first investigator reported ILD
- Outcome of the worst grade ILD event

Subgroup analysis of ILD characteristics of study drug-related ILD reported by the ILD adjudication committee will be performed.

7.3.2.4. Subgroup Analysis of Treatment-Emergent Adverse Events

The following subgroup analyses for the TEAEs will be performed in the following subgroups for the safety analysis set. The number and percentage of subjects with TEAEs will be summarized by PT. Some of these subgroup categories may be combined if there are not enough subjects.

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (Asia, North American (USA, CAN), Europe (AUT, CHE, BEL, ESP, FRA, GBR, GRC, HUN, ITA, PRT, RUS, SWE)+ Israel)
- Country (Japan, Non-Japan)
- Age (<65, ≥ 65 years; <75, ≥ 75 years)
- ECOG performance status (0, 1)
- Renal function at baseline (normal function, mild, moderate impairment)
- Hepatic function at baseline (normal function, mild)

7.3.2.5. Selected Treatment-Emergent Adverse Events

The selected TEAEs include, but not limited to, nausea, vomiting, decreased appetite, constipation, diarrhea, and febrile neutropenia, and the grouped terms as specified in Section 11.6.

For the selected TEAE, following summary will be provided:

- Summary of any selected TEAE number of subjects, worst NCI CTCAE grade, outcome of the worst selected TEAE, time to first onset (days), duration of first event (days)
- Drug-related selected TEAEs by Preferred Term and worst NCI CTCE grade
- Serious selected TEAEs by Preferred Term
- Grade ≥ 3 selected TEAEs by Preferred Term
- Selected TEAEs associated with study drug discontinuation by Preferred Term and worst NCI CTCAE grade
- Selected TEAEs associated with dose reduction by Preferred Term and worst NCI CTCAE grade
- Selected TEAEs associated with study drug interruption by Preferred Term and worst NCI CTCAE grade
- Selected TEAEs associated with outcome of death by Preferred Term
- Recurrent TEAEs by selected TEAE and episode

The recurrent TEAEs are defined as one or more occurrences of TEAE with the same PT after the first event. Episodes are counted with both initial record of TEAE and recurrent records of TEAEs in each subject.

7.3.2.6. Exposure-Adjusted Incidence Rate of Treatment-Emergent Adverse Events

Subjects who are exposed to study treatment for a longer period of time tend to have a higher incidence of AEs. The exposure-adjusted incidence rate (EAIR) adjusts for the number of incidences by the length of exposure to study medication.

The EAIR for a given AE event is calculated as the ratio of the number of subjects with at least 1 incidence of the event divided by the sum of the total subject-years of exposure.

Total subject-years of exposure are calculated as follows is the total of treatment duration of all subjects within each treatment group, with year as unit. This will be used as the denominator for EAIR.

Note that dose reduction and interruption will be ignored in calculation subject-year exposure.

The EAIR by treatment will be provided for

- TEAEs
- TEAE of CTCAE grade ≥ 3
- TESAEs
- AESI
 - Adjudicated drug-related ILD – worst grade post-baseline 1, 2, 3, 4, 5
 - LV dysfunction – worst grade post-baseline 2, 3, 4 (from AE panel)

7.3.2.7. Overall Summary of Treatment-Emergent Adverse Events by Individual Study Drug

An overall summary of TEAEs by study drugs (T-DXd, capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel) will be provided for:

- TEAEs
- Treatment Related TEAEs
- Serious TEAEs
- Treatment Related Serious TEAEs.

7.3.3. Death

Death will be summarized by treatment group. All deaths will be listed, and post-treatment deaths after last dose + 47 days will be flagged. It should be noted that the death summaries and listings (as with all safety analyses) will be based on the safety analysis set and could be different from the number of deaths reported in the efficacy analyses.

7.3.4. Clinical Laboratory Evaluations

The summaries will include all laboratory assessments collected up to the safety follow-up date (up to 47 days after the last study treatment administration). Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by treatment group at each scheduled time of evaluation, including EOT, maximum post-treatment value, and minimum post-treatment value. All laboratory assessments will be listed, and those collected beyond the safety follow-up period will be flagged.

The following summaries will be produced for hematology and biochemistry laboratory data (by local laboratory parameter and treatment group):

- Summary of laboratory test results and changes from baseline
- Shift tables using CTCAE grades to compare baseline values to worst post-baseline values

The following listings of lab parameters from all sources will be produced for laboratory data:

- Subjects with hematology laboratory values outside the laboratory normal ranges with values flagged to show the corresponding CTCAE grades and the classification relative to the laboratory normal range. Abnormal laboratory values collected outside the on-treatment period (between first dose of study treatment and 47 days after last dose of study treatment) will also be reported in the listings and flagged accordingly.
- A similar listing for biochemistry laboratory data.
- A similar listing for urinalysis, coagulation and troponin.

The hematology and biochemistry laboratory variables are specified in Appendix [11.5](#).

7.3.4.1. Liver Function Parameters

Subjects with elevated post-treatment ALT, AST, ALP, or total bilirubin that fall into the following categories will be identified and listed. The number and percentage of these subjects will be tabulated. An eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) plot will be presented.

Table 7.1: Elevated Liver Function Category

Clinical Laboratory Parameter	Category
ALT or AST	$\geq 3 \times \text{ULN}$; $\geq 5 \times \text{ULN}$; $\geq 8 \times \text{ULN}$; $\geq 10 \times \text{ULN}$; $\geq 20 \times \text{ULN}$
Total Bilirubin (TBL)	$\geq 1.5 \times \text{ULN}$; $\geq 2 \times \text{ULN}$; $\geq 3 \times \text{ULN}$
ALP	$\geq 1.5 \times \text{ULN}$; $\geq 2 \times \text{ULN}$
Concurrent TBL elevation with ALT or AST elevation ^a	(ALT or AST $\geq 3 \times \text{ULN}$) and (TBL $\geq 2 \times \text{ULN}$)
Concurrent TBL elevation with ALT or AST elevation and ALP $< 2 \times \text{ULN}$ ^a	(ALT or AST $\geq 3 \times \text{ULN}$) and ALP $< 2 \times \text{ULN}$ and (TBL $\geq 2 \times \text{ULN}$)

^a Concurrent is defined as these abnormalities occurred within a 28-day window.

7.3.5. Vital Signs

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

7.3.6. ECG

Descriptive statistics will be provided by treatment group for ECG parameters (e.g., heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval) and changes from baseline by scheduled time of evaluation, including the EOT Visit and the maximum post-treatment value. For descriptive statistics at each visit, the mean of the triplicate assessments is used.

In addition, the following criteria of notable post-baseline ECG interval values are defined:

QT and QTcF:

- New > 450 ms (male) / New > 470 ms (female)
- New > 480 ms
- New > 500 ms
- Increase from baseline > 30 ms
- Increase from baseline > 60 ms

PR:

- An increase > 25% from baseline and PR > 200 ms

QRS:

- An increase > 25% from baseline and QRS > 100 ms

HR:

- A decrease > 25% from baseline and HR < 50 bpm
- An increase > 25% from baseline and HR > 100 bpm

Note that “New” implies a newly occurring ECG abnormality. It is defined as an abnormal ECG finding at post-baseline that is not present at baseline (e.g., QT New > 480 m implies QT > 480 ms post-baseline and QT ≤ 480 ms at baseline). The last non-missing value before the first dose of study drug will be used as the baseline value for each item.

QTc interval will be calculated using Fridericia’s ($QTcF = QT/[RR]^{1/3}$) correction (with RR in seconds). If RR is not available, it will be replaced with 60/(heart rate) in the correction formula and computed as $QTcF = QT \times (HR/60)^{1/3}$.

A subject with multiple occurrences of a new occurring abnormality is counted only once per abnormality.

Maximum value any time during study will also be summarized, as well as maximum change from baseline and will include any unscheduled assessments

Box-Whisker plots will be presented for QTcF interval at each scheduled time of evaluation.
ECG data will be listed.

7.3.7. Immunogenicity (Anti-Drug Antibody Analyses)

Immunogenicity will be assessed through characterization of incidence and titer of ADA for all subjects who received at least one dose of study drug and who had at least one baseline or post-baseline immunogenicity assessment.

The number and percentage of subjects who have a positive ADA result will be summarized with regards to:

- Baseline prevalence of ADA (prior to dosing with T-DXd)
- Post-baseline prevalence of ADA (for all subjects and subjects with positive result at baseline)
- ADA positive prevalence at baseline or post-baseline (percentages will be based on the number of subjects who had a baseline or post-baseline assessment)
- Treatment-emergent incidence of ADA (positive post-baseline result where baseline result was negative or missing, or ADA titer increased following positive baseline result)
- Treatment-boosted ADA incidence (ADA titer increased following positive baseline result)
- Treatment-induced ADA incidence (positive post-baseline result where baseline result was negative or missing)

The number and percentage of subjects who are positive for neutralizing antibody (NAb) of trastuzumab deruxtecan, if analyzed, will also be summarized.

Descriptive statistics will also be presented for the following:

- ADA titer at each scheduled visit
- Highest ADA titer in treatment-emergent ADA positive subjects
- Time to first ADA positive sample in treatment-emergent ADA positive subjects
- Time to last immunogenicity sample

A summary table by scheduled visit will be provided for prevalence of ADA/NAb.

A listing of all ADA/NAb assessments and raw values of ADA titers will be provided by scheduled visit.

7.3.8. Other Safety Analysis

A shift table will be provided for ECOG PS and LVEF.

A Box-Whisker plot will be presented for LVEF values at each scheduled visit. All other safety endpoints (e.g., physical examination findings, ophthalmologic findings) will be listed.

7.4. Pharmacokinetic and Pharmacodynamic Analyses

7.4.1. Pharmacokinetic Analyses

Descriptive statistics and listing will be provided for all serum concentration data (T-DXd, total anti-HER2 antibody and DXd) at each time point for the PK analysis set. The time course of serum concentrations for T-DXd, total anti-HER2 antibody and DXd will be plotted for mean-SD using descriptive statistics at each time point on linear axis and semi-log axis.

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

7.5. Biomarkers Analysis

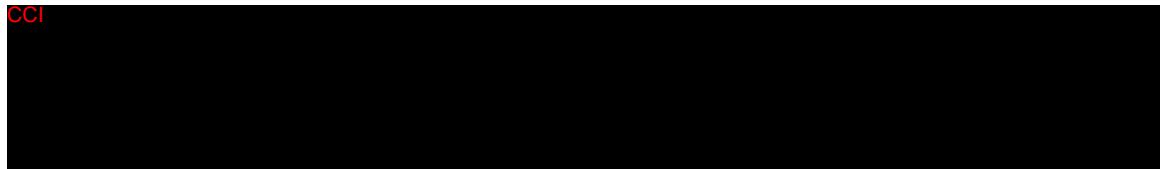
Biomarker endpoints will be summarized by treatment group for each time point using descriptive statistics if data are available.

7.6. Health Economics and Outcome Research Endpoint(s) Analysis

Health economic and outcomes research endpoints based on the hospitalization-related data collection form and the following patient reported outcomes (PRO) questionnaires will be summarized by time point for each treatment group: European organization for research and treatment of cancer quality of life questionnaire ((EORTC QLQ)-C30, EORTC QLQ-BR45, and EQ-5D-5L.

The global health status/global quality of life (QoL) scale score of the EORTC QLQ-C30 is identified as the primary PRO variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR45, and the index score of the EQ-5D-5L are identified as secondary PRO variables of interest. Linear transformations will be applied to all subscales of EORTC QLQ-C30, and EORTC QLQ-BR45 as specified in Section 8.2.3 to harmonize the trend:

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Higher index scores in the EQ-5D-5L correspond to better health states and higher scores of EQ-5D-5L visual analog scale (VAS) represent better overall self-rated health status. The hormone receptor positive cohort of FAS will be used for all PRO summaries and listings.

The number of subjects completing QoL data and the number of subjects missing/expected to have QoL assessments will be summarized by each treatment group for scheduled assessment time points (the number of on-going patients will be used as denominator). Furthermore, the amount and the pattern of missing data may be explored by treatment group and over time using summary statistics. The following categories may be used to describe whether the questionnaire was completed at a specific time point:

- yes, fully completed
- yes, partially completed
- no, subject missed scheduled assessment visit

Scoring of raw data and methods for handling of missing items or missing assessments will be handled according to scoring manuals for each respective subject questionnaire.

Subject data listings will be provided for all HEOR data in accordance with this SAP.

Derivations are detailed in SAP Section 8.2.3.

7.6.1. 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, 40-day Follow-up, and Long-term/Survival Follow-up Visits) for all subjects in the hormone receptor positive cohort of FAS.

Results of the EQ VAS will be presented as a measure of overall self-rated health status.

7.6.2. 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 quality of life (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.

Change from baseline in all sub-scales obtained from EORTC QLQ-C30 and QLQ-BR45 will be analyzed using a linear mixed effect model for longitudinal data to assess the treatment effect over time including terms for treatment, randomization stratification factors, time of visit, treatment by time of visit interaction, and baseline score. Descriptive P-Values for the treatment, time of visit, and corresponding interactions will be presented. The differences in least square means between treatment and control group, and the corresponding two-sided 95% CI at selected time points will be presented. For the mixed effects model, patients with baseline and at least one non-missing post-baseline assessment will be included. This analysis will only include assessments up to the time point where there are at least 50 patients on each of the treatments. As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. In the event of the statistical model failing to converge or other presenting issues with the model, the covariance structure will be modified to an autoregressive (AR(1)) covariance matrix. Furthermore, in the case where the AR(1) model also fails to converge, a compound symmetric (CS) covariance structure will be used.

Time to definitive deterioration on the ‘breast symptoms’ and ‘arm symptoms’ subscales of the EORTCQLQ-BR45, and ‘pain symptom’, ‘global health status’, ‘physical functioning’, ‘emotional functioning’, ‘social functioning’ 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, a definitive deterioration event will be defined as an increase of 10 points or more (compared to baseline) on the symptom subscale score in question or ~~CCI~~ [REDACTED]

Time to definitive deterioration is the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event (as defined above) is first seen. If a patient has not had a definitive deterioration event prior to analysis cut-off or start of new anticancer therapy, loss to follow-up, or withdrawal of consent, the time to definitive deterioration will be censored at the date of the last evaluation of the symptom subscale score in question. Death is considered as deterioration of symptoms/QoL if it occurs by the first survival follow-up (3 months from 40-day follow-up visit). Patients who die after the first survival follow-up are censored at the date of their last available questionnaire.

The survival distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier analysis, including the median time to definitive deterioration and the proportion of patients without definitive deterioration at specific time-points will be reported. A stratified Cox regression model will be used to estimate the HR of time to definitive deterioration, along with 95% confidence interval (using the same strata information as above).

As a sensitivity analysis, a pattern mixture model (PMM) may be fit to address potential departures from the assumption that the data are missing at random for global health status/global QoL scale score of the EORTC QLQ-C30. For the PMM, patterns will be determined using the neighboring case missing value (NCMV) method. In addition, to address unmeasured uncertainty (e.g., standard errors and confidence intervals), the pattern mixture model will be combined with multiple imputation. For each imputed timepoint T_j , this approach

uses the observations for which T_j is observed and T_{j+1} is missing. If the data do not follow a monotone missing data pattern, a monotonic structure will be obtained using the Markov chain Monte Carlo (MCMC) method. After missing data have been made monotone, a regression model will be used to perform the imputations within each treatment group. The stratification variables assigned at randomization will also be included in the model. Estimates from this model will be compared to those from the mixed model repeated measures analysis.

7.6.3. Hospitalization-related Endpoints

The following hospitalization-related endpoints:

- Reason for hospitalization
- Discharge status
- Length of hospital stay (days)
- Length of ICU stay (days)
- Time to first hospitalization, defined as the time from the date of randomization to the date of the first hospitalization during the study treatment (from date of first dose to 47 days after last dose)

will be summarized using descriptive statistics.

7.7. Other analysis

7.7.1. COVID-19 Analyses

Additional analyses may be performed to explore the impact of implemented contingency measures (eg, subjects discontinued from study treatment and/or study, alternative procedures used to collect critical safety and/or efficacy data, protocol deviations related to COVID-19) on the safety and efficacy results reported for the study. The following may be explored:

- Sensitivity analyses of overall summary for key safety endpoints (TEAE, drug-related TEAE, serious TEAE, drug-related serious TEAE, AESI, and drug-related AESI) by excluding data from subjects from sites that are closed out due to COVID-19 for 3 months or more consecutively due to COVID-19.
- Summary for key safety endpoints (Overall TEAE, TEAE by PT, ILD, and LV dysfunction), treatment exposure, and demographics separately for subjects with de novo SARS-CoV-2 infection status by treatment group if at least 10% subjects with positive de novo SARS-CoV-2 in a treatment group, identified by COVID-19 serology test or PCR test.
- De novo SARS-CoV-2 is defined as positive serology testing anytime during study treatment with a negative test at baseline, or positive PCR testing by site anytime during study treatment.
- Summary of discontinuation from study drug treatment, discontinuation from the study, missing imaging visit/cycle, or delayed imaging visit/cycle attributed to COVID-19 pandemic by treatment group per COVID-19 CRF page.

Sensitivity analysis of primary analysis of PFS may be performed if there are considerable number of subjects who may have been impacted by COVID-19 and had delayed or missing tumor scan assessments by either excluding data from these subjects or not applying the censoring rule of missing two or more consecutive tumor assessments due to COVID-19 for PFS. No P-value will be presented for these sensitivity analyses. In addition, the following listings may be provided for

- subjects who discontinued from study drug treatment, discontinued from the study, had imaging visit/cycle missed, or had imaging visit/cycle delayed due to the COVID-19
- subjects with protocol deviations related to COVID-19 and the reasons for the protocol deviation
- subjects with TEAEs identified per COVID-19 PTs
- subjects with COVID-19 serology test

8. GENERAL STATISTICAL METHODOLOGY, STUDY ENDPOINT DERIVATION DETAILS, DATA HANDLING, AND REPORTING CONVENTIONS

8.1. General Statistical Methodology

8.1.1. Time-to-Event Analyses

The following sections describe general statistical methodology to be used for analyzing the following time-to-event variables:

- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (DoR)
- Time to response (TTR)
- Time to definitive deterioration of PRO scores
- Progression-free survival on the next line of therapy (PFS2)

Hypothesis and test statistic

The primary efficacy analysis will be the comparison of the distribution of PFS per BICR in hormone receptor positive cohort between the two treatment groups using a stratified log-rank test at two-sided 5% significance level.

The stratified log-rank test (strata based on the randomization factor) will be implemented as follows: for each of the strata, the LIFETEST procedure will be run with the STRATA statement including only the treatment variable. The TIME statement will include the survival time and a (right) censoring variable.

```
PROC LIFETEST data=dataset METHOD=KM ;  
    TIME survtime*censor(1);  
    STRATA stratum 1 stratum 2 stratum 3 / group = trt;  
RUN;  
/* stratum represents stratum variable (to be included for stratified analysis only);  
survtime represents variable containing event/censor times;  
censor represents censoring variable (1=censored, 0=event);  
trt represents treatment group variable; */
```

Kaplan-Meier estimates

The survival function in each treatment group will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST (see examples above). Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the loglog option available with in PROC LIFETEST, Kaplan-Meier estimates of survival rates with 95% confidence intervals at specific time points will be summarized.

Hazard ratio

The hazard ratio will be derived from the Cox proportional hazards model using SAS procedure PHREG with TIES=EXACT option in the MODEL statement. The stratified and unadjusted Cox model will be used (where the baseline hazard function is allowed to vary across strata) for the primary analysis, i.e. the MODEL statement will include only the treatment group variable as a covariate and the STRATA statement will include stratification variable(s).

General SAS code for the stratified Cox model

```
PROC PHREG data=dataset;  
  MODEL survtime*censor(1)=trt / TIES=EXACT;  
  STRATA stratum 1 stratum 2 stratum 3;  
  RUN;  
/* survtime represents variable containing event/censor times;  
censor represents censoring variable (1=censored, 0=event);  
trt represents treatment group variable;  
stratum 1, stratum 2 and stratum 3 represent stratification variables */
```

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Note: Since score test based confidence intervals are not available in SAS procedure PHREG, Wald test based intervals will be used instead.

8.2. Study Endpoints Derivation Details

8.2.1. Efficacy Endpoints Derivation Details

8.2.1.1. PFS Event and Censoring Rules

Progression-free survival (PFS) is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cut-off date for PFS analysis will be censored at the date of their last evaluable tumor assessment.

Event or censoring for primary PFS analyses are described in the Table below.

Case Scenario	Event/Censor (Event or Censoring Description)	Event or Censoring Date
No baseline evaluable tumor assessment	Censored (no baseline tumor assessment)	Date of randomization
No post-baseline tumor assessment	Censored (no post-baseline assessment)	Date of randomization
Early death (within 14 weeks of randomization) without baseline or postbaseline tumor assessment	Event (death)	Date of death
Radiographic disease progression or death without missing two or more consecutive tumor assessments immediately preceding the event	Event (progression or death)	Date of progressive disease assessment or date of death
Disease progression or death after missing ≥ 2 consecutive scheduled tumor assessments (i.e., more than 14 weeks)	Censor (event after missing 2 or more consecutive tumor assessments)	Date of last evaluable tumor assessment (prior to earliest of death/progression date and analysis cut-off date)
At least one post-baseline response assessment, subject with no death or objective documentation of radiographic disease progression (progression-free)	Censor (lost to follow-up; withdraw consent; ongoing without event; adequate tumor assessment no longer available*)	Date of last evaluable tumor assessment (prior to analysis cut-off date, NOT coded as “inevaluable”)
Anti-cancer therapy started prior to disease progression, death or analysis cut-off date (**)	Censor (anti-cancer therapy)	Date of last evaluable tumor assessment prior to anti-cancer therapy (other than study drug)

* Censoring reason will be lost to follow-up if date of lost to follow-up from end of treatment page or post-treatment follow-up page is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be withdraw consent if date of withdraw of consent from study is within 2 consecutive tumor assessments from last adequate tumor assessment; Censoring reason will be ongoing without progression if cutoff date is within 2 consecutive tumor assessments from last adequate tumor assessment; Otherwise censoring reason will be adequate assessment no longer available.

** This censoring rule will be used for sensitivity analysis

Analysis of PFS per investigator assessments will use the same censoring rules.

8.2.1.2. OS Event and Censoring Rules

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.

The last contact date at which the subject was known to be alive will be the latest date among the following:

- Last non-missing assessment/onset date captured under the following electronic case report form (eCRF) pages (or if a date of assessment/onset is not available the “date of visit” for the eCRF page can be used): adverse events, vital signs, physical examination, ECOG PS, ECG, clinical laboratory test, tumor assessment, and also PK/biomarker/other specimen sample collection date.
- Last dosing date of study drug, last date of concomitant medications, and last date of non-drug treatments/procedures.
- Last date of subsequent anti-cancer therapy administered after study treatment discontinuation.
- Date of Last Contact collected on the survival follow up page of the eCRF.

8.2.1.3. Reasons for censoring will be based on subject outcome of survival follow-up CRF page or specified as “Alive” for subject still on treatment. Evaluation of Best Overall Response

The best overall response is the best confirmed response recorded from the start of the study treatment until PD/death or start of new anticancer therapy whichever is earlier.

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.

Confirmation of CR/PR is required for this study.

The best overall response of PD corresponds to disease progression (assessment based upon tumor measurements and recorded on the electronic case report form (eCRF) page “overall tumor assessment”) for the first on-treatment tumor assessment. The best overall response of CR/PR cannot be determined unless it is confirmed, no earlier than 4 weeks (28 days) from the time a response of CR/PR is first suspected.

If there is no on-treatment tumor assessment and no tumor assessment prior to new anticancer therapy post end of study treatment, the best overall response will be assigned as “Inevaluable (NE)”.

When SD is believed to be best response, it must also meet the protocol-specified minimum time of 5 weeks from C1D1. 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.

If there is no next tumor assessment, the best overall response will be assigned as “Not evaluable (NE)”. The tumor assessment at the Screening Visit will be used as the baseline tumor assessment.

Best overall response with confirmation of CR/PR is as follows:

First Time Point Response**	Subsequent Time Point Response	Confirmed Response (Best Response)*
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD ^a
PR	PD	SD or PD ^a
SD	PD	SD or PD ^a
CR	CR	CR
CR	NE **	SD or NE ^b
PR	CR	PR
PR	PR	PR
PR	SD c**	SD
PR	NE **	SD or NE ^b
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE ^b
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE
NE	NED ^d	NE
NED ^d	NED ^d or NE	NE
NED ^d	PD	PD

* A Best Response of SD can only be made after the subject is on-study for a minimum of five (5) weeks (35 days). If the subject is on-study less than thirty-five (35) days, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third time point response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR). Note: in the following scenario, PR SD NE PR, the first PR is not a confirmed PR. In following scenario, with sequential PR records, e.g., PR, PR, PR or PR, PR, PR, PR, if interval between first PR and last PR records of sequential PR records is more than 28 days, the first PR is the confirmed PR.

a Best response will be SD if the first TPR is after five (5) weeks (35 days). Otherwise, the best response will be PD.

b Best response will be SD if the first TPR is after five (5) weeks (35 days). Otherwise, the best response will be NE.

c TPR is SD if the increase from the first to the second assessment does not qualify for PD.

d For subjects with tumor scan performed but no identified disease/lesion at baseline.

Subjects without on-treatment tumor assessment will be included in the denominators of best overall response and ORR (as best overall response of “Inevaluable (NE)”).

8.2.1.4. Other Efficacy Endpoint Derivation and Censoring

ORR: ORR is defined as the proportion of subjects with best overall response of confirmed CR or PR.

DoR: DoR is defined as the time from the date of the first documentation of objective response (confirmed CR or PR) to the date of the first documentation of disease progression or death due to any cause. Duration of response will be measured for responding subjects (confirmed PR or CR) only. Censoring rules for PFS analysis are applied for DoR analysis.

CBR: CBR is defined as the proportion of subjects with best overall response of confirmed CR, PR, or more than 6 months Stable Disease (SD)

Both of the following conditions must be met for ‘more than 6 months SD’

- Best overall response is SD
- Duration of SD ≥ 183 days

DCR: Disease control rate (DCR) per BICR is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD)

TTR: TTR is defined as the time from the date of randomization to the date of the first documentation of objective response (confirmed CR or PR). Patients with a confirmed PR or CR will be included in TTR calculation.

Best percent change in the sum of the diameters: Best percent change in the sum of the diameters of measurable tumors will be based on BICR and on investigator assessment respectively. The tumor measurement at the Screening Visit will be used as the baseline tumor measurement.

Time to hospitalization: Time to hospitalization is defined as the time from the date of randomization to the date of the first hospitalization during the study treatment. Study treatment period is defined as the period from the date of first dose up to 47 days after the last dose of treatment. Note, only hospitalizations during the defined treatment period are included for this analysis. Time to hospitalization will be summarized using descriptive statistics.

PFS2: PFS2 is 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 cut-off date; censoring date will be the last contact date. In case a 2nd anti-plastic therapy is introduced prior to 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 as PFS2 event.
- Any death following the next line of therapy will be a PFS2 event if no 2nd new line of therapy is initiated.
- PFS and PFS2 may be identical in case a patient 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 anti-cancer therapy initiated after discontinuation of study treatment regardless of EoT reason.

The event or censoring for PFS2 analyses are described in the Table below.

Case Scenario		Event/Censor (Event or Censoring Description)	Event or Censoring Date
Subject did not receive new systemic anti-cancer therapy	Death	Event (Death)	Date of death
	No death	Censored (No new systemic anti-cancer therapy)	Last contact date
Subject received new systemic anti-cancer therapy	Disease progression during next line therapy before/on the analysis cut-off date	Event (Progression)	Date of progressive disease assessment
	Death during next line therapy and before/on the analysis cut-off date	Event (Death)	Date of death
	No disease progression/death during next line therapy and received a second new systemic anti-cancer therapy before/on the analysis cut-off date	Censored (Second new systemic anti-cancer therapy)	End date of the first new systemic anti-cancer therapy
	No disease progression/death during next line therapy did not receive a second new systemic anti-cancer therapy before/on the analysis cut-off date	Censored (No progression/death on next-line therapy)	Last contact date

8.2.2. Safety Endpoints Derivation Details

8.2.2.1. Adverse Events

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or worsened in severity or seriousness after the initiating the study drug 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. All AEs will be graded (1 to 5) according to the latest NCI-CTCAE version 5.0.

For Treatment-Emergent adverse event toxicity tables tabulated on subject level, a subject with two or more TEAEs with the same preferred term will be counted only once for that term with the highest CTCAE grade. For a given subject, if the toxicity grade is missing for all TEAEs with the same preferred term, the TEAEs will be counted only once for that term under the “Missing” CTCAE toxicity category. In the presence of a subject who has both missing and non-missing CTCAE toxicity grades for AEs with the same preferred term, the missing CTCAE toxicity of the AE will be treated as the lowest toxicity grade. In addition, a subject who reported two or more TEAEs with the same system organ class will be counted only once in the system organ class total, and subjects with 2 or more TEAEs in different SOCs will be counted only once in the overall total.

8.2.3. Health Economic and Outcomes Research Endpoints

8.2.3.1. EQ-5D-5L

The EQ-5D-5L will be assessed using the index score according to the EQ-5D-5L UK value set as well as the response on the Visual Analogue Scale (VAS) question. The value set will be used to assign a baseline index value as well as a value at each nominal time point, based on the health state indicated on the questionnaire. The index score will be derived according to the EQ-5D-5L UK value set, for example, the index score will be 0.483 for a value set of 11234.

The following endpoints will be tabulated or derived at each nominal time point. For descriptive system, missing values are treated as missing; index score will be derived as missing.

- Response by dimension
- Index score
- Index score change from baseline
- VAS as a measure of self-rated health status
 - 100 is the best health subject can imagine
 - 0 is the worst health subject can imagine
- VAS change from baseline

8.2.3.2. EORTC QLQ-C30

EORTC QLQ-C30 (version 3.0) consists of a total of 30 questions related to QoL, scored on a 4-point Likert scale for the first 28 questions (1=not at all, 4=very much) and scored on a scale of 1 (very poor) to 7 (excellent) for the final two questions that probe the patient's overall health and QoL. It is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status and a number of single items assessing additional symptoms (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and financial difficulties. The following explains the scoring procedure.

Table 8.1: Scoring the EORTC QLQ-C30

	Scale name	Item range ^a	Item numbers	Raw score ^b
Global health status/QoL	QL2	6	29,30	(Q29+Q30)/2
Functional Scales				
Physical Functioning	PF2	3	1 to 5	(Q1+Q2+Q3+Q4+Q5)/5
Role Functioning	RF2	3	6,7	(Q6+Q7)/2
Emotional Functioning	EF	3	21 to 24	(Q21+Q22+Q23+Q24)/4
Cognitive Functioning	CF	3	20,25	(Q20+Q25)/2
Social Functioning	SF	3	26,27	(Q26+Q27)/2
Symptom Scales				
Fatigue	FA	3	10,12,18	(Q10+Q12+Q18)/3
Nausea and Vomiting	NV	3	14,15	(Q14+Q15)/2
Pain	PA	3	9,19	(Q9+Q19)/2
Dyspnea	DY	3	8	Q8
Insomnia	SL	3	11	Q11
Appetite Loss	AP	3	13	Q13
Constipation	CO	3	16	Q16
Diarrhea	DI	3	17	Q17
Financial Difficulties	FI	3	28	Q28

^a Item range is the difference between the possible maximum and the minimum response to individual items.

^b Raw score is the mean of the component items

Once the raw scores are calculated, a linear transformation to 0-100 is applied to obtain the particular score as follows:

For global health status/QoL: Score = {1-(Raw score-1)/Range}*100

For all other scales/items: Score = {(Raw score-1)/Range}*100

After the liner transformation, the score of each scale has a range of 0-100%. A high score represents a low level of functioning for a functional scale, and a high level of symptomatology/problem for a symptom scale.

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. So, for example, if the fatigue scale is missing Q10, the average of Q12 and Q18 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

8.2.3.3. EORTC QLQ-B45 (QLQ-BR23)

EORTC QLQ-BR45 consists of a total of 45 questions related to QoL. As QLQ-BR45 is still undergoing validation, analysis will be performed on QLQ-BR23 scoring.

EORTC QLQ-BR23 consists of a total of 23 questions related to QoL, scored on a 4-point Likert scale (1=not at all, 4=very much). It is composed of questions citing the extent to which the subject has experienced symptoms or problems during the past week and during the past four weeks.

These include four functional scales (body image, sexual functioning, sexual enjoyment, future perspective), and four symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss).

The following explains the scoring procedure.

The 23 questions are numbered as Items 31-53 in the eCRF.

	Scale name	Number of items	Item range ^a	Raw score ^b QLQ-BR23 items	Scale score ^c
Functional scales					
Body image	BRBI	4	3	(Q39+Q40+Q41+Q42)/4	{(Raw score-1)/Range}*100
Sexual functioning	BRSEF	2	3	(Q44+Q45)/2	{1-(Raw score-1)/Range}*100
Sexual enjoyment	BRSEE	1	3	Q46	{1-(Raw score-1)/Range}*100
Future perspective	BRFU	1	3	Q43	{(Raw score-1)/Range}*100
Symptom scales / items					
Systemic therapy side effects	BRST	7	3	(Q31+Q32+Q33+Q34+Q36+Q37+Q38)/7	{(Raw score-1)/Range}*100
Breast symptoms	BRBS	4	3	(Q50+Q51+Q52+Q53)/4	{(Raw score-1)/Range}*100
Arm symptoms	BRAS	3	3	(Q47+Q48+Q49)/3	{(Raw score-1)/Range}*100
Upset by hair loss	BRHS	1	3	Q35	{(Raw score-1)/Range}*100

^a Item range is the difference between the possible maximum and the minimum response to individual items.

^b Raw score is the mean of the component items

^c Scale score is a linear transformation of raw score to 0-100 scale

Once the raw scores are calculated, a linear transformation to 0-100 is applied to obtain the particular scale score as follows:

For functional scales: Score = {1-(Raw score-1)/Range}*100

For symptom scales/items: Score = {(Raw score-1)/Range}*100

After the liner transformation, the score of each scale has a range of 0-100%. A high score represents a low level of functioning for a functional scale, and a high level of symptomatology/problem for a symptom scale.

Remarks

- Sexual enjoyment (BRSEE) is not applicable if item 45 is scored “not at all.”
- Upset by hair loss (BRHL) is not applicable if item 34 is “not at all.”

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. So, for example, if the breast symptom scale is missing Q50, the average of Q51, Q52, Q53 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

8.2.3.4. Censoring Rules for Time to Definitive Deterioration

Time to definitive deterioration is defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event is first seen. Event or censoring rules are as follows:

Case Scenario	Event/Censor (Event or Censoring Description)	Event or Censoring Date	
No baseline evaluable QoL and/or no post-baseline tumor assessment	Death by the first survival FU (3 months from 40-day visit)	Event (death)	Date of death
	Others	Censored (no baseline or post-baseline assessment)	Date of randomization
Patients with baseline and at least 1 post-baseline QoL assessments	Increase of 10 points or more (compared to baseline) at two or more consecutive time points on the symptom subscale score in question (confirmed)	Event (Definitive deterioration)	Date of first deterioration of the consecutive assessments with an increase of 10 point or more
	Increase of 10 points or more (compared to baseline) at last assessment on the symptom subscale score in question	Event (Definitive deterioration)	Date of last assessment if that is the last one
	Death by the first survival FU (3 months from 40-day visit)	Event (Death)	Date of death
	Others	Censor (No definitive deterioration)	Date of last assessment

8.2.4. Other Derivations for Endpoint Analysis

8.2.4.1. Hormone Receptors

Estrogen Receptors	Progesterone Receptors	Hormone Receptors
negative	Negative	negative
negative	Positive	positive
negative	indeterminate	indeterminate
positive	Negative	positive
positive	Positive	positive
positive	indeterminate	positive
indeterminate	Negative	indeterminate
indeterminate	Positive	positive
indeterminate	indeterminate	indeterminate

8.2.4.2. Prior and Post Anti-cancer Therapy

For the summaries of prior cancer therapy, and post anti-cancer therapy, review of the relevant clinical terms will be performed after every data snapshot to accurately classify and identify the correct groupings. The steps to be followed are as below.

- The unique terms from the reported prior cancer therapy (or post anti-cancer therapy) data are extracted from the study database and put into an excel spreadsheet without any accompanying subject-level information.
- The spreadsheet is reviewed by the clinical team and the terms are classified under the different groupings.

The updated spreadsheet with the grouping information is then merged with the study database to derive variables in the associated ADaM data sets

8.3. Data Handling Conventions

8.3.1. Definition and Use of Visit Windows

For data analysis and display purposes, Study Day is defined as the number of days from (positive) or prior (negative) to

- For efficacy analysis: the day of randomization, with the day of randomization as Study Day 1. The Screening Period is defined as any days prior to day of randomization. Day -1 is the day prior to randomization.
- For safety analysis: the first study treatment date, with the first study treatment date as Study Day 1. Day -1 is the day prior to the first study treatment date.

Detailed Visit Windows for each assessment are defined in the protocol Schedule of Events. Visit IDs are recorded in the eCRF. No visit windowing will be derived for purposes of analysis; the nominal visits will be used in the summaries, except for ECOG and PRO analyses.

8.3.1.1. Time Window to Scheduled Timepoint of ECOG

ECOG assessments should be collected on Day 1 of each cycle during study treatment period, EOT, and 40-day safety follow-up visits.

The following time based intervals will be used to group the ECOG data over time:

	Time Interval
Cycle 1/Baseline	The latest assessment prior to or on the randomization date/the first dose (Cycle 1 Day 1) date, whichever occurs later.
Cycle 2 Day 1	For 21 Day Cycle (Cycle 2 Day 1=22): +10/-20 days centered around the planned assessment date (Day 2 to Day 32); Choose the one closest to the planned assessment date. For 28 Day Cycle (Cycle 2 Day 1=29): +13/-27 days centered around the planned assessment date (Day 2 to Day 42); Choose the one closest to the planned assessment date.
Cycle 3,4,..., before EOT	For 21 Day Cycle (Cycle $x \geq 3$): +10/-10 days centered around planned assessment date: Day $(x-1)*21+1-10$, Day $(x-1)*21+1+10$; Choose the closest assessment to the planned assessment dosing date. For 28 Day Cycle (Cycle $x \geq 3$) +13/-14 days centered around planned assessment date: Day $(x-1)*28+1-14$, Day $(x-1)*28+1+13$; Choose the closest assessment to the planned assessment dosing date.
EOT	Assessment taken for the end of treatment visit per CRF
40-day safety FU post EOT	Assessment taken for the 40-day safety FU visit per CRF

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used.

If 2 assessments are within a time window are equidistant from the target date (or if the closest assessment to the target date has two assessments on the same date), then the worst ECOG of these assessments will be used.

8.3.1.2. Time Window to Scheduled Timepoint of PRO

PRO assessments should be collected at visits: Day 1 of each cycle during study treatment period, EOT, 40-day safety follow-up post EOT, and every 3-months during log-term follow-up.

The following time based intervals will be used to group the PRO data over time:

	Time Interval
Baseline	The latest assessment within prior to or on the randomization date/the first dose (Cycle 1 Day 1) date, whichever occurs later.
Cycle 2 Day 1	<p>For 21 Day Cycle (Cycle 2 Day 1=22): $+10/-20$ days centered around the planned assessment date (Day 2 to Day 32); Choose the one closest to the planned assessment date.</p> <p>For 28 Day Cycle (Cycle 2 Day 1=29): $+13/-27$ days centered around the planned assessment date (Day 2 to Day 42); Choose the one closest to the planned assessment date.</p>
Cycle 3 Day 1	<p>For 21 Day Cycle (Cycle 3 Day 1=43): $+20/-10$ days centered around the planned assessment date (Day 33 to Day 63); Choose the one closest to the planned assessment date.</p> <p>For 28 Day Cycle (Cycle 3 Day 1=57): $+27/-14$ days centered around the planned assessment date (Day 43 to Day 84); Choose the one closest to the planned assessment date.</p>
Cycle 5,7,..., Day 1	<p>For 21 Day Cycle (Cycle $x \geq 5$): $+20/-21$ days centered around planned assessment date: Day $(x-1)*21+1-21$, Day $(x-1)*21+1+20$; Choose the closest assessment to the planned assessment dosing date.</p> <p>For 28 Day Cycle (Cycle $x \geq 5$): $+27/-28$ days centered around planned assessment date (For Cycle $x >= 3$): Day $(x-1)*28+1-28$, Day $(x-1)*28+1+27$; Choose the closest assessment to the planned assessment dosing date.</p>
EOT	Assessment taken for the end of treatment visit per CRF
40-day safety FU post EOT	Assessment taken for the 40-day safety FU visit per CRF
3m, 6m, ... during long-term FU	as collected per CRF

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used.

If 2 assessments are within a time window are equidistant from the target date, then the assessment obtained prior to target date will be considered. If the closest assessment to the target date has two questionnaires filled out on the same date, then the worst score of these assessments will be used for each subscale score.

8.3.2. Repeated or Unscheduled Assessments of Safety Parameters

It is possible that repeat or unscheduled assessments are made for some safety endpoints (e.g., clinical laboratory tests, vital signs, ECGs, etc.). It is also possible that multiple measurements are available within the same window for summary, whether they are scheduled or not. In this case, the following rule should be applied for statistical summary unless otherwise justified:

- If a subject has repeated assessments before the initiation of study treatment administration, then the results from the final assessment made prior to the initiation of study treatment administration, will be used as baseline assessment.
- If a subject has repeated assessments during treatment, the value obtained on the planned assessment date will be used for analysis. If there are two or more measurements collected on the same date, the earliest assessment will be used for analysis.

8.3.3. Missing Date or Incomplete Date

8.3.3.1. Missing or Incomplete Date Information of Study Treatment

When the date of the last dose of study treatment is missing or incomplete for a subject in the safety analysis set, all efforts should be made to obtain the date from the investigator.

8.3.3.2. Incomplete Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing and year is available) start dates. Incomplete stop dates may also be imputed when the calculation of the duration of an AE is required by the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete, then impute the start date first.

Incomplete Start Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date, assuming year is available. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study treatment, then the day and month of the date of the first dose of study treatment will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of study treatment, then January 1 will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of study treatment, then December 31 will be assigned to the missing fields.

Missing Month Only

- The day will remain the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study treatment, then the day of the date of the first dose of study treatment will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study treatment or if both years are the same but the month is before the month of the date of the first dose of study treatment, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of study treatment or if both years are the same but the month is after the month of the date of the first dose of study treatment, then the first day of the month will be assigned to the missing day.

Incomplete Stop Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the missing numerical fields, assuming year is available. If the date of the last dose of study treatment is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of study treatment, then the day and month of the date of the last dose of study treatment will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of study treatment, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of study treatment, then January 1 will be assigned to the missing fields.

Missing Month Only

- The day will be the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study treatment, then the day of the date of the last dose of study treatment will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of study treatment or if both years are the same but the month is before the month of the date of the last dose of study treatment, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the last dose of study treatment or if both years are the same but the month is after the month of the date of the last dose of study treatment, then the first day of the month will be assigned to the missing day.

8.3.3.2.1. Missing Severity Assessment for Adverse Events

Missing CTCAE grade is not imputed.

8.3.3.2.2. Missing Relationship to Study Treatment for Adverse Events

If the relationship to study treatment is missing for a TEAE starting on or after the date of the first dose of study treatment, a causality of “related” will be assigned. The imputed values of relationship to study treatment will be used for incidence summaries, while the actual values will be presented in data listings.

8.3.3.3. Incomplete Date Information for Prior and Concomitant Medications

For prior or concomitant medications, follow the imputation rules presented in Section [8.3.3.2](#) for incomplete (i.e., partially missing) start and stop dates.

8.3.3.4. Incomplete Date Information for Disease Progression on Post Anti-cancer Therapy

If disease progression date collected on the Post Anti-Cancer Treatment CRF page has a partial date with missing Day portion, then check:

- if disease progression occurs in the same month as post anti-cancer treatment end date, then set post anti-cancer treatment end date to date of disease progression.
- else if post anti-cancer treatment end date missing, then set post anti-cancer treatment start date to date of disease progression if at same month.
- else if month of disease progression is after post anti-cancer treatment start month, then set Day 1 of the month of disease progression date.

Post anti-cancer treatment start date and end date will be imputed if partial.

8.3.3.5. Incomplete Date Information for Determination of Time Since Diagnosis

To calculate time since disease diagnosis, the date of diagnosis must have at least a non-missing year. A partially missing date of diagnosis will be assigned the middle of the year (July 1) if month is missing, and the 15th of the month if only the day is missing. If the year of diagnosis is the same as the randomization/registration year, then January 1 will be assigned if the month is missing, and the 1st of the month will be assigned if only the day of month is missing.

8.3.3.6. Incomplete Death Date

If the day or month is missing, death date will be imputed to the maximum of the full (non-imputed) date of last contact (excluding the date of death) and the following:

- Missing day: 1st day of the month and year of death
- Missing month: January of the year of death
- If day, month and year of death date are missing, the death date will not be imputed.

8.3.3.7. Incomplete Last Known Alive Date

If the day or month is missing, last known alive date will be imputed to the maximum of the full (non-imputed) date of last contact (excluding the incomplete last known alive date) and the following:

- Missing day: 1st day of the month and year of last known alive
- Missing month: January of the year of last known alive
- Missing day and month: January 1st of the year of last known alive

If day, month and year of last known alive date are missing, the last known alive date will not be imputed.

8.3.4. Character Values of Clinical Laboratory Tests and Below Limit of Quantification Values

If the reported value for a clinical laboratory test cannot be used in a statistical summary and analysis due to, for example, a character string being reported for a numerical value, an imputed value may be used in the statistical analysis according to the conventions described below.

- A character field represents a value below a number (e.g., <XX), the imputed value will be calculated as half of the numerical cut-off, i.e. XX/2.
- A character field represents a value greater than a number (e.g., >XX), the imputed value will be calculated as XX.

Details of the imputation algorithm will be provided in ADaM specifications document after reviewing the dry run lab listing prior to database lock.

Actual values as recorded in the database (i.e., the character field) will be presented in data listings.

8.4. Statistical Summary and General Reporting Conventions

8.4.1. Computing Methods

Statistical analyses will be performed using Version 9.3 or newer of SAS®¹¹ on a suitably qualified environment.

8.4.2. Statistical Summary Conventions

Continuous endpoints will be summarized using the following descriptive statistics: mean, standard deviation, median, minimum, and maximum, unless otherwise stated. The frequency and percentage of observed levels will be reported for categorical measures. In general, all data will be listed, sorted by subject and, when appropriate, by study day and study hour within a subject.

8.4.3. General Reporting Conventions

P-values will be reported to four decimal places; p-values less than 0.0001 will be reported as $p<0.0001$. The rounding of p-values to four decimal places will occur after comparing to significance level. The mean and median will be reported up to one decimal place and the standard deviation up to two decimal places greater than the original (raw) value, unless otherwise specified. The precision for reporting of summary statistics for demographics and baseline characteristics will be limited to two decimal places for the standard deviation and one decimal place for everything else.

9. SUMMARY OF CHANGES TO THE STATISTICAL ANALYSES SPECIFIED IN PROTOCOL

This SAP for Protocol DS8201-A-U303 incorporates Amendments.

Protocol Version	Approval Date	Salient Changes, if any*
1.0	Nov 11, 2020	NA
1.1	Oct 10, 2021	<ul style="list-style-type: none">• Refine the safety analyses• Add summary for ORR and DoR for HR-negative cohort (exploratory objective, but no analyses were specified in SAP v1.0)• Provide algorithm for TPC duration of exposure• Specify algorithm for prior lines of chemotherapy and lines of endocrine therapy• Update PRO section• Add death date imputation rule• Refine the algorithm for time windows for ECOG and PRO• Clarify HR positive cohorts and HR negative cohort of FAS, is based on baseline HR status• Add censoring rules for PFS2

10. REFERENCES

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9. EAST version 6.4, (2018). Cytel, Waltham, MA
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11. APPENDICES

11.1. Overall Response: Subjects with Target (+/-Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Time point Response ^a
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR ^b
PR	NE	No	PR ^b
PR	CR	No	PR
PR	Non-CR/Non-PD	No	PR
SD	NE	No	SD ^b
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 ^d	No	CR
PR	NA ^d	No	PR
SD	NA ^d	No	SD
NA ^c	Non-CR/Non-PD	No	Non-CR/Non-PD
NA ^c	CR	No	CR
NA ^c	NE	No	NE
NA ^c	NA ^d	No	NE

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

^a Identification of new lesions at a post-Baseline time point will result in a 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.

^b 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.

^c No target lesions identified at Baseline.

^d No non-target lesions identified at Baseline.

11.2. Adverse events of special interest

Case definitions for each of the AESIs are described in the table below. This list of AESIs will be periodically reviewed and updated by safety team.

AESIs	Case definition
ILD (Selected PTs from Interstitial lung disease (SMQ 20000042))	ILD will be summarized based on the ILD adjudicated outcomes as defined in the ILD AC charter.
LV Dysfunction (Selected PTs from Cardiac failure (SMQ 20000004))	LV dysfunction as a case definition refers to a subject who experienced any of the pre-selected PTs and corresponding MedDRA (Medical Dictionary for Regulatory Activities) codes: Acute left ventricular failure (10063081), Acute right ventricular failure (10063082), Cardiac failure (10007554), Cardiac failure acute (10007556), Cardiac failure chronic (10007558), Cardiac failure congestive (10007559), Chronic left ventricular failure (10063083), Chronic right ventricular failure (10063084), Ejection fraction decreased (10050528), Left ventricular failure (10024119), Right ventricular failure (10039163), Left ventricular dysfunction (10049694), and ventricular failure (10060953).

11.3. Lesion Locations for Baseline Visceral Disease Derivation

Baseline visceral disease is determined with any target or non-target tumor in the lesion locations on “Target/Non-Target Tumor Assessments (Imaging Baseline)” eCRF page as listed in the table below.

Lesion Location	Visceral Disease	Not Visceral Disease
Abdominal Cavity	Y	
Adrenal gland	Y	
Ascites	Y	
Back		N
Bile Duct	Y	
Biliary/Gall Bladder	Y	
Bone		N
Brain	Y	
Breast		N
Cervical Vertebra		N
Cervix uteri	Y	
Chest wall		N
Colon	Y	
Esophagus	Y	
Extremity		N
Eye	Y	
Fallopian tube	Y	
Gastroesophageal Junction	Y	

Lesion Location	Visceral Disease	<u>Not</u> Visceral Disease
Head		N
Head (excluding Oral Cavity)		N
Heart	Y	
Kidney	Y	
Larynx		N
Liver	Y	
Lumbar Vertebra		N
Lung	Y	
Lymph Nodes		N
Mediastinum	Y	
Muscle		N
Nasopharynx		N
Neck		N
Nose		N
Oropharynx		N
Other		N
Ovary	Y	
Pancreas	Y	
Pelvic Bone		N
Penis		N
Pericardial effusion	Y	
Peritoneum/Omentum	Y	
Pleura	Y	
Pleural effusion	Y	
Prostate	Y	
Rectum	Y	
Retroperitoneum	Y	
Rib		N
Skin		N
Skull		N
Small Intestine	Y	
Soft Tissue		N
Spinal	Y	
Spleen	Y	
Stomach	Y	
Subcutaneous		N
Testis	Y	
Thoracic Vertebra		N
Urinary Bladder	Y	
Uterus	Y	
Vagina	Y	

11.4. Define Treatment Duration End Date for Drugs in TPC Arm

There are 5 different treatments in TPC arm in this study: Capecitabine, Eribulin, Gemcitabine, Paclitaxel, and Nab-paclitaxel.

The cycle length in days, number of dosing days in each cycle and algorithm to derived treatment duration end date are summarized in the Table below.

Comparator	Dosing Regimen	Cycle Length (day)	Number of dosing days within a cycle	Treatment end date
Capecitabine	1000-1250mg/m ² PO twice daily Days 1-14; cycled every 21 days	21	14	minimum (the date of the last Capecitabine dose + 7, the start date of the new anticancer therapy if applicable, and death date if applicable)
Eribulin	1.4 mg ^a /m ² IV Days 1 and 8; cycled every 21 days	21	2	minimum (the date of the last Eribulin dose + 14, the start date of the new anticancer therapy if applicable, and death date if applicable)
Gemcitabine	800-1200mg/m ² IV Option 1: Days 1 and 8; cycled every 21 days Option 2: Days 1, 8, and 15; cycled every 28 days	21 for option 1 28 for option 2	2 for option 1 3 for option 2	minimum (the date of the last Gemcitabine dose + 14, the start date of the new anticancer therapy if applicable, and death date if applicable)
Paclitaxel	Option 1: 175 mg/m ² IV Day 1; cycled every 21 days Option 2: 80 mg/m ² IV Day 1 weekly	21	1 for option 1 3 for option 2	Option 1. minimum (the date of the last Paclitaxel dose + 21, the start date of the new anticancer therapy if applicable, and death date if applicable) Option 2. minimum (the date of the last Paclitaxel dose + 7, the start date of the new anticancer therapy if applicable, and death date if applicable)
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	21 for option 1 28 for option 2	1 for option 1 3 for option 2	Option 1. minimum (the date of the last Nab-paclitaxel dose + 21, the start date of the new anticancer therapy if applicable, and death date if applicable) Option 2. minimum (the date of the last Nab-paclitaxel dose + 14, the start date of the new anticancer therapy if applicable, and death date if applicable)

11.5. Clinical Laboratory Tests

The following lab variables are to be summarized. All assessments will be performed by the local laboratory.

Test	Analytes	
Blood Chemistry	ALP Increased (U/L)	Hypermagnesemia (mmol/L)
	ALT Increased (U/L)	Hypernatremia (mmol/L)
	AST Increased (U/L)	Hypoalbuminemia (g/L)
	Blood Bilirubin Increased (umol/L)	Hypocalcemia (mmol/L)
	Creatinine Increased (umol/L)	Hypokalemia (mmol/L)
	Hypercalcemia (mmol/L)	Hypomagnesemia (mmol/L)
	Hyperkalemia (mmol/L)	Hyponatremia (mmol/L)
Hematology	Hemoglobin increased (g/L)	Lymphocyte Count Increased ($10^9/L$)
	Anaemia (g/L)	Lymphocyte Count Decreased ($10^9/L$)
	White Blood Cell Count Decreased ($10^9/L$)	Neutrophil Count Decreased ($10^9/L$)
		Platelet Count Decreased ($10^9/L$)

11.6. Grouped Terms

Grouped Term	Preferred Terms	PT Code (MedDRA version 23.0)	PT Code (MedDRA version 23.1)	PT Code (MedDRA 24.0)
Abdominal pain	Abdominal discomfort	10000059	10000059	10000059
	Abdominal pain	10000081	10000081	10000081
	Abdominal pain lower	10000084	10000084	10000084
	Abdominal pain upper	10000087	10000087	10000087
	Gastrointestinal pain	10017999	10017999	10017999
Anaemia	Haemoglobin decreased	10018884	10018884	10018884
	Red blood cell count decreased	10038153	10038153	10038153
	Anaemia	10002034	10002034	10002034
	Haematocrit decreased	10018838	10018838	10018838
Lymphopenia	Lymphocyte count decreased	10025256	10025256	10025256
	Lymphopenia	10025327	10025327	10025327
Neutropenia	Neutrophil count decreased	10029366	10029366	10029366
	Neutropenia	10029354	10029354	10029354
Thrombocytopenia	Platelet count decreased	10035528	10035528	10035528
	Thrombocytopenia	10043554	10043554	10043554
Stomatitis	Stomatitis	10042128	10042128	10042128
	Aphthous ulcer	10002959	10002959	10002959
	Mouth ulceration	10028034	10028034	10028034
	Oral mucosa erosion	10064594	10064594	10064594
	Oral mucosal blistering	10030995	10030995	10030995
	Oral mucosal eruption	10030997	10030997	10030997
Leukopenia	White blood cell count decreased	10047942	10047942	10047942
	Leukopenia	10024384	10024384	10024384

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Grouped Term	Preferred Terms	PT Code (MedDRA version 23.0)	PT Code (MedDRA version 23.1)	PT Code (MedDRA 24.0)
Upper respiratory tract infection	Influenza	10022000	10022000	10022000
	Influenza like illness	10022004	10022004	10022004
	Upper respiratory tract infection	10046306	10046306	10046306
	nasopharyngitis	10028810	10028810	10028810
	pharyngitis	10034835	10034835	10034835
	sinusitis	10040753	10040753	10040753
	rhinitis	10039083	10039083	10039083
Headache	Migraine	10027599	10027599	10027599
	Headache	10019211	10019211	10019211
	Sinus headache	10040744	10040744	10040744
Rash	Rash	10037844	10037844	10037844
	Rash pustular	10037888	10037888	10037888
	Rash maculo-papular	10037868	10037868	10037868
Fatigue	Fatigue	10016256	10016256	10016256
	Asthenia	10003549	10003549	10003549
	Malaise	10025482	10025482	10025482
	Lethargy	10024264	10024264	10024264
Transaminases increased	Transaminases increased	10054889	10054889	10054889
	Aspartate aminotransferase increased	10003481	10003481	10003481
	Alanine aminotransferase increased	10001551	10001551	10001551
	Gamma-glutamyltransferase increased	10017693	10017693	10017693
	Liver function test abnormal	10024690	10024690	10024690
	Hepatic function abnormal	10019670	10019670	10019670
Blood potassium decreased	Hypokalaemia	10021015	10021015	10021015
	Blood potassium decreased	10005724	10005724	10005724

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Grouped Term	Preferred Terms	PT Code (MedDRA version 23.0)	PT Code (MedDRA version 23.1)	PT Code (MedDRA 24.0)
Musculoskeletal pain	Back pain	10003988	10003988	10003988
	Myalgia	10028411	10028411	10028411
	pain in extremity	10033425	10033425	10033425
	Musculoskeletal pain	10028391	10028391	10028391
	muscle spasms	10028334	10028334	10028334
	bone pain	10006002	10006002	10006002
	neck pain	10028836	10028836	10028836
	musculoskeletal chest pain	10050819	10050819	10050819
	limb discomfort	10061224	10061224	10061224
Skin hyperpigmentation	Skin hyperpigmentation	10040865	10040865	10040865
	skin discolouration	10040829	10040829	10040829
	pigmentation disorder	10062080	10062080	10062080
Blood bilirubin increased	Blood bilirubin increased	10005364	10005364	10005364
	Hyperbilirubinaemia	10020578	10020578	10020578
	Bilirubin conjugated increased	10004685	10004685	10004685
	Blood bilirubin unconjugated increased	10005370	10005370	10005370

SUMMARY OF CHANGES

DESCRIPTION/RATIONALE OF EACH CHANGE	
Critical Study Contact List	Update the Sponsor on the Critical Study Contact List.
Investigator Agreement	Update Sponsor representative on the Investigator Agreement page.
Synopsis	Update description of the EuroQol 5 dimensions 5 levels [of severity] scale.
List of Abbreviations Section 17.1	Update before infusion and end of infusion definitions to include the phrase “or dosing”.
Section 1.1.1.6	Update DS8201-A-J101 efficacy and safety data.
Synopsis Section 2.1.3 Section 7.1.3	Update clinical benefit rate to include greater than or equal to 6 months’ stable disease rate.
Synopsis Section 3.1 Section 5.2.1 Section 5.2.4 Section 5.4.1.1	Add the starting dose of 5.4 mg/kg.
Synopsis Section 3.1	Update study design schema in the DS-8201a box to remove the statement pending additional J101 data.
Synopsis Section 1.2 Section 4.1 Section 6.1 Section 16	Update to clarify the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) 2018 guideline used.
Section 4.1	Update inclusion criterion #3g to clarify what is considered a prior line of therapy.
Synopsis Section 4.2	Update exclusion criterion #5 to clarify that subjects with untreated or symptomatic central nervous system metastases or inactive brain metastases are excluded from the study.
Section 4.2	Update exclusion criterion #14 to remove mention of abdominal radiation.
Section 4.2	Update exclusion criterion #15 to remove mention of before study treatment.
Section 4.2	Update exclusion criterion #16 to remove mention of monoclonal antibody treatment.
Section 4.2	Update exclusion criterion #17 to include prior participation in this investigational trial.
Synopsis Section 5.2.4 Section 6.4.1.3	Update initial DS-8201a infusion time to be at least 90 minutes.

Section 5.4.1.1	Add dose reduction levels and supporting text for DS-8201a, including that dose increases are not allowed.
Section 5.4.1.1	Minor clarifications to the dose modification table for DS-8201a.
Section 5.6.1	Update to clarify prohibited medications and treatments for DS-8201a and the comparator arm.
Section 6.2	Update screening text to within 14 days before randomization.
Section 6.4.1.2 Section 6.5 Section 6.6.1 Section 17.1	Add completion of the Health Economic and Outcomes Research Analyses outcomes EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires at Cycle 2 Day 1 and clarify the timing in regard to other assessments.
Section 6.4.1.3	Add statement that end of infusion assessments are not required for subjects on capecitabine.
Synopsis Section 3.2.1 Section 3.2.2 Section 5.7.2 Section 6.5 Section 6.6.1 Section 6.6.2 Section 10.1.2 Section 17.1	Clarify End of Study Treatment Visit timing and update the 40-Day Follow-up Visit and Long-term/Survival Follow-up visits to allow a window for the visit of plus or minus 7 days.
Section 9.3 Section 9.3.1.1 Section 9.3.2 Section 9.3.2.1	Update AESI wording to reflect the latest DS-8201a safety profile.
Section 9.5	Clarify that only the AESIs ILD/pneumonitis targeted questionnaire is to be collected for the comparator arm and clarify that AESI infusion-related reaction information is to be collected through narrative forms.
Section 17.1	Clarify in Table 17.1 the Screening procedures that could be performed from Day -28 to -1.
Section 17.1	Clarify in Table 17.2 that the PK blood (serum) sample and ADA blood sample are only for the DS-8201a arm.
Section 17.1	Updated Table 17.2 to remove the tumor assessment at Cycle 1 Day 1 as a tumor assessment is specified at screening.
Section 17.1	Clarify in Table 17.2 footnote i the timing of the assessment.
Section 17.1	Clarify in Table 17.2 footnote w the comparator arm treatment regimen instructions.
Section 17.1	Clarify in Table 17.2 footnote x that the tumor assessment will be performed every 6 weeks.
Section 17.1	Clarify in Table 17.2 footnote y the assessment is computed tomography or magnetic resonance imaging.

SUMMARY OF CHANGES

DESCRIPTION/RATIONALE OF EACH CHANGE	
Synopsis Section 3.1 Section 4.1 Section 5.1.2 Section 6.1 Section 6.2 Section 6.3 Section 6.4.1.2 Section 6.5 Section 8.3.1 Section 11.4.6 Section 17.1	Update tissue biopsy text to clarify archival and fresh sample requirements.
Synopsis Section 3.2	Update number of study centers to approximately 225 sites.
Synopsis Section 1.2 Sectoion 3.2 Section 4.1 Section 6.1	Update to clarify use of American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines and remove reference to the study laboratory manual.
Synopsis Section 4.1 Section 6.3	Update to clarify the number of hormone receptor (HR)-negative and HR-positive subjects with and without prior therapy with a cyclin-dependent kinase (CDK)4/6 inhibitor to be enrolled in the study.
Synopsis Section 4.1	Update Inclusion Criterion #3e to specify HR-positive subjects.
Section 1.1.1.6	Clarify that the 271 subjects referred to are enrolled on DS8201-A-J101 as of the data cut-off date in the paragraph.
Section 4.1	Update Inclusion Criterion #14 to add statement regarding female partners of male subjects and to update the definition of sexual abstinence.
Synopsis Section 4.1 Section 4.2	Include statement that the Investigator should follow the locally approved label for the individual treatment options if the subject is randomized to the physician's choice treatment arm.
Synopsis Section 4.2	Update Exclusion Criterion #1 to exclude subjects who previously received the same comparator treatment.
Section 5.2.4	Update body weight change requiring calculation to be $\geq\pm10\%$
Section 5.4.1	Update Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or Grade 4 adverse events monitoring timing.
Section 5.4.1.1 Section 9.3.1.2 Section 17.1	Amend interstitial lung disease (ILD) monitoring plan to include that pulmonary function tests and pulse oximetry should be conducted, and arterial blood gases should be conducted as clinically indicated, when evaluating potential ILD events.

Section 5.4.1.1 Section 9.3.1.2 Section 17.1	Clarify that ILD biomarkers (i.e., KL-6, SP-D) will not be used for diagnosis or monitoring of drug-induced ILD. Blood samples will be collected at the time of ILD event, if feasible, for pharmacokinetic (PK) and future exploratory analysis of biomarkers.
Section 5.4.1.1 Section 9.3.1.2 Section 17.1	Reword ILD dose modification language so it is clear that study drug should be interrupted for any ILD event regardless of CTCAE grade, and should be permanently discontinued in subjects demonstrating Grade 2, 3, or 4 toxicity .
Section 6.2 Section 17.1	Update medical history to include smoking history.
Section 6.4.1.3	Clarify administration of DS-8201a and comparator treatment details.
Section 9.3.1.2 Section 17.1	Add statement to clarify that ILD events regardless of severity or seriousness will be followed until resolution even after drug discontinuation.
Section 11.1	Clarify statistical presentations to be produced.
Section 17.1	Update Table 17.2 footnote regarding pregnancy to clarify testing within 72 hours of drug administration.
Section 17.1	Update Table 17.2 footnotes to correct footnote letters.
Section 17.1	Update Table 17.2 footnotes to clarify when the footnote applies to subjects randomized to DS-8201a treatment.
Synopsis Section 3.1 Section 4.2 Section 5.4.1.1 Section 6.6.2 Section 17.1	Correct typographical errors.

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 4.0 (dated 23 Apr 2020) vs. protocol Version 3.0 (dated 24 Apr 2019) 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 4.0) by section.

Amendment Rationale:

This amendment is primarily driven by the clarification that tumor assessments are to be conducted every 6 weeks from randomization and clarification regarding the Physician's Choice dose regimens. It also includes changes based on country-specific amendments and investigator feedback. Other changes 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 asset language to use trastuzumab deruxtecan (DS-8201a; also known as fam-trastuzumab deruxtecan).	International Non-proprietary Name (INN) was assigned.
Synopsis Section 1.1.1.4. Comparators (Physician's Choice) Section 4.1. Inclusion Criteria. Section 4.2. Exclusion Criteria Section 5.3. Control Treatment Section 5.4.1. Dose Interruptions and Reductions Section 5.4.1.2. Dose Interruptions and Reductions for Physician's Choice Section 5.6.1. Prohibited Medications and Treatments Section 6.3 Randomization	Clarified the dose regimen for the Physician's Choice arm and added Table 5.1 . Also clarified all other aspects related to comparator drug administration are according to the label approved in the country of drug administration or per the NCCN guidelines.	Modifications are for clarification.

Section # and Title	Description of Change	Brief Rationale
Section 6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted) Section 17.1. Schedule of Events, Table 17.2		
Synopsis Section 2.1.2. Secondary Objectives Section 7.1.2. Secondary Efficacy Endpoints Section 17.8.1. Sweden Only	Added Section 17.9.1 that contains protocol text that is country specific to Sweden only. A reference to the appendix was added in each applicable location in the protocol.	The protocol language specific to the country of Sweden was incorporated into the global protocol.
Synopsis Section 2.1.3. Exploratory Objectives	Added exploratory efficacy objective in HR-negative subjects.	To explore efficacy in the HR-negative subjects.
Synopsis Section 3.2.1. Duration of the Study Section 6.6.1. 40-Day (+7 days) Follow-up Section 6.6.2. Long-term/Survival Follow-up Section 9.2. Adverse Event Collection and Reporting Section 10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45 Section 10.1.2. EuroQoL Five Dimensions Five Levels Patient Reported Outcome Questionnaire Section 17.1. Schedule of Events, Table 17.2	Clarified the 40-Day Follow-up assessment timing to have a +7-day window.	This change establishes a window of 7 days for the 40-Day Follow-up assessments.
Synopsis Section 1.2. Study Rationale Section 3.2. Discussion of Study Design Section 4.1. Inclusion Criteria Section 6.1. Tissue Screening	Clarified utilization of the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) 2018 HER2 testing guidelines in the study and the assay methodology.	Modifications are for clarification.
Synopsis Section 4.1. Inclusion Criteria	Updated inclusion criterion #7 to clarify that brain lesions will be considered as non-target lesions only.	Modifications are for clarification.
Synopsis Section 4.2. Exclusion Criteria	Clarified exclusion criterion #1 eligibility for comparator treatments options in the physician's choice arm.	Subjects are eligible if there is a comparator with which they have not previously been treated and the comparator is not contraindicated.
Synopsis	Clarified statistical analyses that included items such as updating the	Clarification of the statistical analyses.

Section # and Title	Description of Change	Brief Rationale
Section 2.3.2. Secondary Efficacy Endpoints Section 2.3.3. Exploratory Efficacy Endpoints Section 3.2.1. Duration of the Study Section 7.1.2. Secondary Efficacy Endpoints Section 7.1.3. Exploratory Efficacy Endpoints Section 11.1. General Statistical Considerations Section 11.2.1. Full Analysis Set – HR-positive Population Section 11.2.2. Full Analysis Set – Total Population Section 11.2.4. Per-protocol Analysis Set Section 11.3. Study Population Data Section 11.4.1. Primary Efficacy Analyses Section 11.4.2. Secondary Efficacy Analyses Section 11.4.4.1. Subgroup Analyses Section 11.4.4.2. Analyses of Exploratory Efficacy Endpoints Section 11.5.4. Electrocardiogram Analyses Section 11.7. Sample Size Determination Section 11.8. Statistical Analysis Process	intent-to-treat analysis set to be the full analysis set (FAS) and removing the response evaluable analysis set. Change from 1-sided test at significance level of 0.025 to 2-sided test at 0.05.	For project level consistency.
Synopsis Section 8.3.1 Tumor Tissue Sampling Section 11.4.6. Biomarker Analyses Section 17.1. Schedule of Events, Table 17.1	Clarified the language regarding tumor tissue sampling.	Modifications are for clarification of tumor tissue sampling language.
Section 1.1 Background	Added statement regarding the recent approval of trastuzumab deruxtecan in the United States (US) and approval in Japan.	Updated to reflect recent approval.
Section 1.1.1.6. Clinical Experience	Updated data provided for clinical experience.	Clinical data were updated with data from the current Investigator's Brochure (IB).
Section 1.1.1.7. Benefit/Risk Assessment	Updated the risk/benefit analysis and added a separate section for this text.	The risk/benefit analysis was updated with data from the current IB.

Section # and Title	Description of Change	Brief Rationale
Section 3.1. Overall Design Section 3.2.2. Duration of Subject Participation Section 5.3. Control Treatment Section 6.3. Randomization Section 17.1. Schedule of Events, Table 17.2	Clarified the assessments and the schedule of events (Table 17.2) to allow the flexibility to permit visits to occur on a 28-day cycle except for the tumor assessments (CT or MRI) which will maintain their assessment schedule.	Modifications are to align with the cycle in use for a comparator dosing regimen.
Section 3.2.2. Duration of Subject Participation Section 5.7.1. Discontinuation of Study Drug Section 6.4.3. Every 6 Weeks (± 7 days) Section 6.5. End of Study Treatment Section 6.6.2. Long-term/Survival Follow-up Section 17.1. Schedule of Events, Table 17.2	Clarified that tumor assessments are conducted every 6 weeks from randomization and should be performed while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up. Scan dates should not be adjusted or rescheduled due to dose interruption of any type. 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.	Modifications are for clarification.
Section 4.1. Inclusion Criteria	Added criterion #3g clarification regarding therapies contributing to the count of prior lines of chemotherapy.	Modifications are for clarification.
Section 4.1. Inclusion Criteria	Added criterion #3h clarification to exclude pathologically documented breast cancer that was historically HER2 IHC 0 only.	Modifications are for clarification.
Section 4.1. Inclusion Criteria Section 9.8. Clinical Laboratory Evaluations	Updated inclusion criterion #13 and blood chemistry coagulation tests to specify either partial thromboplastin or activated partial thromboplastin time.	Modifications are for clarification
Section 4.1. Inclusion Criteria Section 9.7. Exposure in Utero During Clinical Studies	Updated contraception requirements and pregnancy notification after the last dose of trastuzumab deruxtecan.	Updated based on new compound level guidelines regarding contraception.
Section 4.1. Inclusion Criteria Section 4.2. Exclusion Criteria Section 6.2. Screening Section 17.1. Schedule of Events, Table 17.1 Section 17.8.2. Portugal Only	Added Section 17.9.2 that contains protocol text that is specific to Portugal only. A reference to the appendix was added in each applicable location in the protocol.	The protocol language specific to the country of Portugal was incorporated into the global protocol.

Section # and Title	Description of Change	Brief Rationale
Section 4.1. Inclusion Criteria Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan Section 5.6.1. Prohibited Medications and Treatments Section 17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	Added inclusion criterion #17 to include a washout period for chloroquine and hydroxychloroquine. Prohibited the use of chloroquine and hydroxychloroquine during the treatment period. Added an appendix with instructions related to coronavirus disease 2019 (COVID-19).	Prohibited because of potential drug-drug interaction based on the mechanism of action of both drugs.
Section 4.2. Exclusion Criteria Section 17.1. Schedule of Events, Table 17.1	Clarified exclusion criterion #12 to specify that subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.	Modifications are for clarification.
Section 4.2. Exclusion Criteria	Clarified exclusion criterion #15 to add immunotherapy and to specify non-antibody-based-therapy within 4 weeks before randomization.	Modifications are for clarification.
Section 4.2. Exclusion Criteria Section 5.6.1. Prohibited Medications and Treatments Section 17.5 Strong Cytochrome P450 3A4 and Organic Anion Transporting Polypeptide/Organic Anion Transporting Polypeptide 1B Inhibitors (deleted from previous version)	Removed cytochrome P450 (CYP3A4) strong inhibitors, organic anion transporting polypeptide (OATP) inhibitors as an exclusion criterion (#16) and food or beverages containing grapefruit from the list of prohibited medications during treatment due to new findings.	Results of Study DS8201-A-A104 show that there is no clinically meaningful impact of CYP3A4 and OATP inhibitors on trastuzumab deruxtecan.
Section 4.2. Exclusion Criteria	Added criterion #21 that excludes clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder, and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement, or prior pneumonectomy.	Updated based on ongoing review of data from the trastuzumab deruxtecan program.
Section 5.2.4. Administration	Clarified personnel who should initiate administration of drug as well as the equipment on site during administration.	Identify personnel who should administer study drug and the equipment needed on site during administration.
Section 5.4.1. Dose Interruptions and Reductions Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan	Clarified that criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are applicable only to treatment-emergent adverse events (TEAEs) that are assessed as related to	TEAEs that are assessed as related to the use of trastuzumab deruxtecan by the investigator will follow the criteria for interruption, re-initiation, dose reduction

Section # and Title	Description of Change	Brief Rationale
	use of trastuzumab deruxtecan by the investigator(s).	and/or discontinuation of trastuzumab deruxtecan.
Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan Section 5.4.1.2. Dose Interruptions and Reductions for Physician's Choice	Added the length of dose delay in relation to the last infusion date.	Clarified the length of dose delay in relation to the last infusion date.
Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan, Table 5.3	Clarified the left ventricular ejection fraction (LVEF) modification guideline.	Modifications are for clarification.
Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan, Table 5.3 Section 9.3.1.2. Management Guidance Section 9.5. Adverse Events and Adverse Event of Special Interest Reporting-Procedure for Investigators Section 17.1. Schedule of Events, Table 17.2	Updated the guidelines on monitoring and management of interstitial lung disease (ILD).	Updated based on ongoing review of data from the trastuzumab deruxtecan program.
Section 5.4.1.1. Dose Interruptions and Reductions for Trastuzumab Deruxtecan, Table 5.3	Minor clarifications to the table are added.	Modifications are for clarification.
Section 5.6. Prior and Concomitant Medications and Treatments	Added recommendation that subjects receive prophylactic antiemetic agents prior to infusion of trastuzumab deruxtecan.	Clarification based on request from clinical sites and align with NCCN guidelines.
Section 5.6. Prior and Concomitant Medications and Treatments	Added that concomitant use of e-cigarettes and vaping is strongly discouraged but not prohibited	Added after review of e-cigarette/vaping literature
Section 5.6.1. Prohibited Medications and Treatments	Clarified that the use of bisphosphonates or RANKL pathway inhibitors for the prevention or treatment of skeletal-related events is acceptable. Clarified medications under investigation and the use of concurrent hormones for noncancer-related conditions is acceptable.	Modifications are for clarification.
Section 5.7.1. Reasons for Withdrawal from the Study Section 5.7.2. Reasons for Discontinuation from Study Treatment	Clarified withdrawal from the study and withdrawal from study treatment as well as follow-up methods.	Modifications are for clarification.
Section 6.1. Tissue Screening Section 6.2. Screening Section 17.1 Schedule of Events, Table 17.1	Clarified that tissue screening should be performed before the rest of the screening procedures.	Tissue screening assessments will be performed before all other screening assessments.

Section # and Title	Description of Change	Brief Rationale
Section 6.1. Tissue Screening Section 6.2. Screening Section 8.3.1. Tumor Tissue Sampling Section 17.1 Schedule of Events, Table 17.1	Moved the collection of additional slides for optional exploratory biomarker assessment from tissue screening to the main screening procedures. Additional slides for optional exploratory biomarker assessment is changed to mandatory.	Modifications are for clarification.
Section 6.1. Tissue Screening Section 6.2. Screening Section 8.3.1. Tumor Tissue Sampling	Clarified that Fine Needle Aspirate and bone biopsies will not be accepted for tissue samples.	Modifications are for clarification.
Section 6.2. Screening Section 6.4.2. Every 4 Cycles (± 7 days) After Cycle 1 Section 6.5. End of Study Treatment Section 9.3.2.2. Management Guidance Section 9.12.1. Cardiac Assessments Section 17.1. Schedule of Events, Table 17.1 and Table 17.2 Section 17.8.3. Germany Only	Added Section 17.9.3 that contains protocol text that is specific to Germany only. A reference to the appendix was added in each applicable location in the protocol.	The protocol language specific to the country of Germany was incorporated into the global protocol.
Section 6.2. Screening Section 17.1 Schedule of Events, Table 17.1	Clarified that screening procedures performed within 28 days of randomization during the standard treatment of the subject can be used for the trial even if conducted prior to consent because they were performed during the normal course of subject care.	Allow screening procedures performed within 28 days of randomization during the standard treatment of the subject can be used for the trial.
Section 6.2. Screening Section 6.4.1.1. Between -3 Days Before Dosing Through Immediately Before Dosing (All Cycles) Section 6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted) Section 6.5. End of Study Treatment Section 9.3.2.2. Management Guidance Section 9.10. Electrocardiograms Section 17.1. Schedule of Events, Table 17.1 and Table 17.2	Clarified that ECG will be taken in triplicate at screening in close succession. Subsequent ECGs will be performed in triplicate if an abnormality is noted.	ECG will be taken in triplicate at screening with subsequent ECGs performed in triplicate if an abnormality is noted.
Section 6.2. Screening Section 9.8. Clinical Laboratory Evaluations Section 17.1. Schedule of Events, Table 17.1	Clarified pregnancy testing guidelines.	Pregnancy testing will be aligned across the protocol

Section # and Title	Description of Change	Brief Rationale
Section 6.4.1.1. Between -3 Days Before Dosing Through Immediately Before Dosing (All Cycles) Section 10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45 Section 10.1.2. EuroQoL Five Dimensions Five Levels Patient Reported Outcome Questionnaire Section 17.1. Schedule of Events, Table 17.2	Clarified that Health Economics and Outcomes Research (HEOR) outcome questionnaires need not be repeated if performed within 3 days of the first dose in each cycle and to align timing.	Modifications are for clarification.
Section 6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted) Section 6.4.1.4. Day 8 (± 1 day) and Day 15 (± 1 day) (Cycle 1 Only) Section 17.1. Schedule of Events, Table 17.2	Clarified SpO ₂ assessment timing to align with vital signs assessment and that after infusion assessment is only for the trastuzumab deruxtecan arm.	Modifications are for clarification.
Section 5.4.1.1 Dose Interruptions and Reductions for Trastuzumab Deruxtecan Table 5.3 Section 6.4.1.3. Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted) Section 8.1. Pharmacokinetic Assessments Section 9.3.1.2 Management Guidance Section 17.1. Schedule of Events, Table 17.2	Clarified the blood sample collection timing for PK analysis and clarified the use of a central laboratory.	To align the blood sample collection for PK analysis across the protocol.
Section 6.5. End of Study Treatment Section 17.1. Schedule of Events, Table 17.2	Clarified end of treatment (EOT) assessment timing must occur within 7 days from the date the Investigator decides to discontinue study treatment.	EOT assessments should occur within 7 days from the date the Investigator decides to discontinue study treatment.
Section 7.2. Appropriateness of Selected Efficacy Assessments	Clarified how the efficacy assessment of patient-reported outcome (PRO) index scores will be utilized.	To enumerate how the PRO index scores will be utilized.
Section 8.4 Immunogenicity	Updated to specify the analysis of the neutralizing antibody assay for samples confirmed anti-drug antibody (ADA) positive.	Modifications are for clarification.
Section 9.3. Adverse Events of Special Interest Section 9.3.2. Left Ventricular Ejection Fraction Decrease Section 9.3.2.1. Clinical Summary	Updated adverse events of special interest (AESI) language to remove QT prolongation and minor clarifications.	Review of QT data suggests that QT prolongation is not considered an important potential risk or AESI.

Section # and Title	Description of Change	Brief Rationale
Section 9.3.2.2 Management Guidance Section 9.5. Adverse Events and Adverse Event of Special Interest Reporting—Procedure for Investigators		
Section 9.3.1.3. Interstitial Lung Disease Adjudication Committee Section 9.5. Adverse Events and Adverse Event of Special Interest Reporting—Procedures For Investigators	Clarified the preferred terms that are submitted to the ILD Adjudication Committee.	Modifications are for clarification.
Section 9.3. Adverse Events of Special Interest Section 9.5. Adverse Events and Adverse Event of Special Interest Reporting—Procedure for Investigators	Removed infusion related reaction (IRR) text from the AESI section.	Review of IRR data suggests that IRRs are not considered important potential risks or AESI.
Section 9.4.6. Other Action Taken for Event	Updated the adverse event list of other actions taken for an event.	Per feedback from ILD advisory board meeting.
Section 9.5. Adverse Events Reporting—Procedure for Investigators	Added overdose reporting clarification	Modifications are for clarification.
Section 11.5.1. Adverse Event Analyses	Clarified the definition of a treatment-emergent adverse event (TEAE).	Modifications are for clarification.
Section 17.1. Schedule of Events, Table 17.1	Added a footnote to Table 17.1 to specify tissue screening informed consent must be signed before tumor tissue screening assessments and that the main informed consent form must be signed before initiating all other screening assessments. Clarified ophthalmologic assessment footnote.	Modifications are for clarification.