CLINICAL STUDY PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF TRASTUZUMAB DERUXTECAN (DS-8201A), AN ANTI-HER2-ANTIBODY DRUG CONJUGATE, VERSUS TREATMENT OF INVESTIGATOR'S CHOICE FOR HER2-POSITIVE, UNRESECTABLE AND/OR METASTATIC BREAST CANCER SUBJECTS PREVIOUSLY TREATED WITH T-DM1

(DESTINY-Breast02)

DS8201-A-U301

IND/EudraCT NUMBERS 127553/2018-000221-31

VERSION 8.0, 24 Apr 2023

Daiichi Sankyo Inc.

DOCUMENT HISTORY

Version Number	Version Date
8.0	24 Apr 2023
7.0	17 Mar 2022
6.0	05 Aug 2020
5.0	23 Apr 2020
4.0	26 Apr 2019
3.0	08 Mar 2019
2.0	20 Jun 2018
1.0	23 Mar 2018

INVESTIGATOR AGREEMENT

A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (DS-8201a), an anti-HER2-antibody drug conjugate, versus treatment of investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1

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 Council for 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 8.0 (dated 24 Apr 2023) vs. protocol Version 7.0 (dated 17 Mar 2022) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U301 clinical study protocol (Version 8.0) by section.

Amendment Rationale: The study concluded positively for the primary and secondary efficacy endpoints of the primary analysis, which was conducted 18 months after data cutoff for the last subject randomized. Since the study treatments are approved drugs, it is now justified to align a number of on-treatment or follow-up procedures with recommendations for routine practice for subjects who continue to receive protocol treatment and thereby reduce the burden on subjects and study site personnel. Key changes include updates to frequency of tumor assessments, removal of anti-drug antibody (ADA) and biomarker sample collection for on-treatment subjects, and updates to the adverse event management guidelines. At the same time, given the high relevance of the problem of developing drug resistance, it is justified to introduce into the protocol the possibility of obtaining an optional biopsy at the time of end of treatment with further central evaluation of the collected biopsy sample.

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
Protocol Synopsis (Study Duration) 3.1.3. Definition of the End of the Study	Provided the end of study definition.	To maintain internal consistency across the T-DXd program.
Table 17.2 Schedule of Events-Treatment and Follow-up Period	Added option to provide subjects the opportunity to transition to separate study	Allow subjects continued administration of T-DXd after study closure, if otherwise available.
3.1. Overall Design Table 5.2. Dose Modification for Trastuzumab Deruxtecan 5.4.1. Dose Reduction and Interruption Guidelines	Updated drug delay for adverse event management or medical intervention to 7 weeks from the last dose of investigator's choice drug and 18 weeks from the last T-DXd dose. Criteria involving CT/MRI scans before resuming drug were added.	To maintain internal consistency across the T-DXd program.

Section # and Title	Description of Change	Brief Rationale
Table 5.2. Dose Modification of Trastuzumab deruxtecan 9.3.1.2. Management Guidance	Added pulmonary function tests and blood tests. Updated pulmonary toxicity guidelines, including timeline of monitoring Grade 1 ILD/pneumonitis	To maintain internal consistency across the T-DXd program.
5.4.1. Dose Reduction and Interruption Guidelines 5.7.1. Discontinuation of Study Drug 6.2. Screening 6.5. End of Treatment	Updated modified RECIST (mRECIST) to RECIST	To maintain internal consistency across the T-DXd program.
5.6. Concomitant Medications (Drugs and Therapies)	Updated guidance in regard to prophylactic administration of anti-emetic medications for all subjects.	To maintain internal consistency across the T-DXd program.
6.4.1.1. Between -3 Days Through Immediately Before Infusion (All Cycles) 6.4.3. Every 4 Cycles (±7 d) after Cycle 1 6.5. End of Treatment 9.3. Adverse Events of Special Interest 9.3.2.1. Clinical Summary 9.3.2.2. Management Guidance 9.10. Electrocardiograms 17.1. Schedule of Events-Tissue Screening and Screening Period 17.2. Schedule of Events-Treatment and Follow-up	Updates made to cardiac function assessments, including ECGs and ECHO/MUGA	Based on a comprehensive review of the cumulative safety data for all cardiac events, risk for cardiac events is considered negligible. ECHO/MUGA and ECG assessments will take place at regular intervals during treatment as clinically indicated (and at end of treatment [EOT] for ECHO/MUGA). Please reference the IB for more information.
6.4.1.2 Day 1; Before Dosing (All Cycles, Unless Otherwise Noted) Table 17.2 Schedule of Events-Treatment and Follow-Up Period	Removed biomarker sampling for on-treatment assessment after Cycle 3 Day 1.	All subjects who remain on treatment have > 24 months of treatment duration; additional on-treatment samples beyond this time point are not needed.
6.4.1.2 Day 1; Before Dosing (All Cycles, Unless Otherwise Noted) 6.6.1. 40-day (+7 d) Follow-up Table 17.2 Schedule of Events-Treatment and Follow-Up Period	Removed ADA sampling for those with positive ADA at the follow-up visit and after protocol version 8 is implemented.	All subjects who remain on treatment have > 24 months of treatment duration and have provided immunogenicity samples, and results from the primary analysis indicate low prevalence of treatment-emergent ADAs with no impact on subject safety.

Section # and Title	Description of Change	Brief Rationale
6.4.1.2 Day 1; Before Dosing (All Cycles, Unless Otherwise Noted) Table 17.2 Schedule of Events-Treatment and Follow-Up Period	Removed exploratory biomarker sampling during treatment for subjects after protocol version 8 is approved.	All subjects who remain on treatment have > 24 months of treatment duration; additional on-treatment samples beyond this time point are not needed.
6.4.3. Every 6 weeks (12 weeks upon approval of version 8 ±7 d) 6.5 End of Treatment Table 17.2 Schedule of Events-Treatment & Follow-up Period 17.4.2.5. Frequency of Tumor Re-Evaluation	The following language was added to the tumor assessment schedule: "Tumor assessments, based on sites of disease identified at Screening and any additional newly suspected sites of progressive disease, will be conducted every 6 weeks (±7 days) from randomization, until protocol version 8 is approved by the site. After approval and implementation of this protocol version, tumor assessments will be conducted every 12 weeks (±7 days), independent of treatment cycle."	Scan frequency is updated to align with standard of care and to reduce patient burden.
6.5 End of Treatment 8.3 Biomarker Assessments Table 17.2 Schedule of Events-Treatment and Follow-Up Period	Added an optional newly obtained tumor tissue biopsy collection for the T-DXd group.	Collection of optional newly obtained biopsies at end of treatment was added for the purpose of biomarker analysis, including evaluation of mechanisms of resistance which may inform the clinical development of T-DXd.
6.5 End of Treatment 9.3.2.2 Management Guidance 9.8 Clinical Laboratory Evaluations Table 17.2 Schedule of Events-Treatment and Follow-Up Period	Removed blood sample troponin assessment at end of treatment	Based on a comprehensive review of the cumulative safety data for troponin levels, risk for increased troponin levels is considered negligible. Therefore, EOT troponin level assessments are no longer required and troponin level assessments should be performed only if clinically indicated. Please reference the IB for more information.
6.5 End of Treatment Table 17.2: Schedule of Events-Treatment and Follow-Up Period	Removed ophthalmologic assessment at end of treatment.	Based on a comprehensive review of the cumulative safety data for all ocular events, risk for ocular events is considered negligible. Therefore, EOT ophthalmologic assessments are no longer required and ophthalmologic assessments should be performed only if clinically indicated. Please reference the IB for more information.

Section # and Title	Description of Change	Brief Rationale
7.1.1. Primary Efficacy Endpoint	Added the language: "After the primary efficacy endpoint has been achieved, assessments by BICR (PFS, ORR, DoR, BOR, best percent change in the sum of the diameter of measurable tumors, and CBR) will be discontinued. Participants will continue with all other assessments as indicated in the SoE, including the assessment of tumor response and radiographic disease progression by investigators."	Scan frequency is updated to align with standard of care and to reduce patient burden.
8.1 Pharmacokinetic Assessments 17.2 Schedule of Events-Treatment & Follow-up Period 17.8 Instructions Related to Coronavirus Disease 2019 (COVID-19)	Removed PK assessments if chloroquine or hydroxychloroquine is administered	To maintain internal consistency across the T-DXd program.
9.2 Adverse Event Collection and Reporting	Updated instructions regarding the timepoint at which death is considered a serious adverse event	Clarification of instructions.
9.3.1.2 Management Guidance 17.2. Schedule of Events-Treatment & Follow-up Period	Added pulmonary function tests and blood tests	To maintain internal consistency across the T-DXd program.
9.5. Adverse Events Reporting-Procedure for Investigators	Added information regarding reporting of overdoses	Clarification
9.7 Exposure in Utero During Clinical Studies	Updated information regarding exposure during pregnancy for those subjects taking investigator choice drugs and the timeline for informing the Sponsor of pregnancy	Clarification of instructions regarding in utero exposure
10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45	Removed language regarding scoring	To maintain internal consistency across the T-DXd program.
Table 17.2 Schedule of Events-Treatment & Follow-up Period	Added the language: "After the primary efficacy endpoint has been achieved, the assessment of the scans by BICR is no longer required."	Scan frequency is updated to align with standard of care and to reduce patient burden.

Section # and Title	Description of Change	Brief Rationale
Table 17.2 Schedule of Events-Treatment & Follow-up Period	Moved arrow from coagulation row to concomitant medications row for Cycle 3 to EOT	Correction of an error
17.8 Instructions Related to Coronavirus Disease 2019 (COVID-19)	Updated dose modification of T-DXd for COVID-19 symptom grades, timeline of monitoring of symptoms, and method of confirmation of COVID-19	To maintain internal consistency across the T-DXd program.

PROTOCOL SYNOPSIS

EudraCT:	2018-000221-31
IND Number:	127553
NCT Number:	NCT03523585
Protocol Number:	DS8201-A-U301 (DESTINY-Breast02)
Investigational Product:	trastuzumab deruxtecan (DS-8201a)
Active Ingredients:	Trastuzumab deruxtecan 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 Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2-Antibody-Drug Conjugate, Versus Treatment of Investigator's Choice for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1 (DESTINY-Breast02)
Study Phase:	Phase 3
Indication Under Investigation:	Unresectable/metastatic breast cancer with human epidermal growth factor receptor 2 (HER2)-positive expression
Study Objectives:	Primary Objective: • To compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Key Secondary Objective: • To compare overall survival (OS) benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. Other Secondary Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice on: – Confirmed objective response rate (ORR); – Duration of response (DoR); • To further determine pharmacokinetics (PK) of trastuzumab deruxtecan. • To further evaluate safety of trastuzumab deruxtecan compared to investigator's choice. • To evaluate Health Economics and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to investigator's choice. Exploratory Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice by clinical benefit rate (CBR) and progression-free survival on the next-line of therapy (PFS2).

- To evaluate potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD]).
- To evaluate exposure-response relationships for efficacy and safety endpoints.

Study Design:

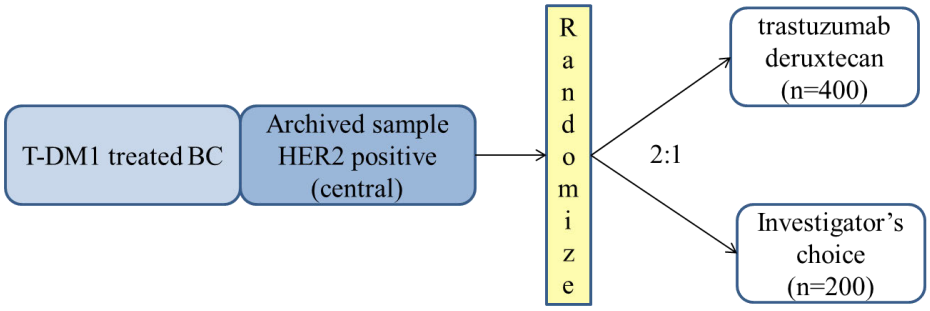
This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of trastuzumab deruxtecan versus the investigator's choice in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with standard of care HER2 therapies, including ado-trastuzumab emtansine (T-DM1). Approximately 600 subjects will be randomized 2:1 to trastuzumab deruxtecan versus the investigator's choice of

- Trastuzumab/capecitabine, or
- Lapatinib/capecitabine

Randomization will be stratified by:

- Hormone receptor status (positive, negative)
- Prior treatment with pertuzumab (yes, no)
- History of visceral disease (yes, no)

Study Design Schema of DS8201-A-U301



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 30 mo.

For each subject there will be a 40-Day (+7 d) 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 mo (± 14 d) from the date of 40-Day (+7 d) Follow-up, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

End of the Study:

Overall EOS will occur when any of the following conditions are met:

- The last subject's last visit has occurred.
- An alternative study becomes available for subjects continuing to derive benefit from treatment with T-DXd, where the study drug is offered to these subjects.
- The study is discontinued by the Sponsor for other reasons (eg, administrative or safety related).

	For clinical studies conducted in the European Union (EU) and under the EU clinical trial regulation (CTR), if the EOS in the last EU Member State occurs before the EOS in the last global country, the clinical study results summary will be submitted within 12 months after the EOS in the final global country (ie, in such a situation, the submission will not be based on the EOS in the last EU Member State). Holding the submission until the study is complete globally is justified, because in situations when the clinical study is still ongoing in other countries and data from these other countries are not available, the full statistical analysis planned for the study is not feasible, and incomplete results are uninterpretable.
Study Sites and Location:	Approximately 230 sites including, but not limited to, North and South America, Europe, and Asia.
Subject Eligibility Criteria:	Key Inclusion Criteria: • Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old.) • Pathologically documented breast cancer that: – is unresectable or metastatic. – has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines evaluated at a central laboratory. – was previously treated with T-DM1. • Documented radiologic progression (during or after most recent treatment or within 6 mo after completing adjuvant therapy). – Subjects must be HER2-positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, a fresh biopsy is required. • 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 7 mo after the last dose of trastuzumab deruxtecan, 6 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine. Male subjects must agree to inform all potential female partners that they are participating in a clinical trial of a drug that may cause birth defects. Male subjects must also agree to either avoid intercourse or that he and/or any female partner of reproductive/childbearing potential will use a highly effective form of contraception during and upon completion of the study and for at least 4.5 mo after the last dose of trastuzumab deruxtecan, 3 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine. • Adequate renal function, defined as: – Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation, • Adequate hepatic function, defined as:

- Total bilirubin ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and
- Aspartate transaminase/alanine transaminase ≤ 2.5 × ULN

Key Exclusion Criteria:

- Ineligible for the comparator arm treatment for reasons including but not limited to the following:
  - Prior treatment with capecitabine;
  - History of any contraindication included in the approved local label for capecitabine or for both trastuzumab and lapatinib;
  - Concurrent treatment with any medication prohibited in the applicable approved local label for capecitabine or for both trastuzumab and lapatinib.
- Prior participation in a study involving an antibody-drug conjugate produced by Daiichi Sankyo Inc
- Uncontrolled or significant cardiovascular disease, including any of the following:
  - History of myocardial infarction within 6 mo before randomization
  - History of symptomatic congestive heart failure (New York Heart Association Class II to IV)
  - Troponin levels consistent with myocardial infarction as defined according to the manufacturer within 28 d prior to randomization
  - Corrected QT interval prolongation to >470 ms (females) or >450 ms (male) based on average of screening triplicate 12 lead electrocardiogram (ECG)
  - Left ventricular ejection fraction (LVEF) < 50% within 28 d prior to randomization
- 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.
- Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or 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.

Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan for injection 100 mg: A trastuzumab deruxtecan lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. The starting dose of trastuzumab deruxtecan will be 5.4 mg/kg.

	The drug for intravenous (IV) infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight to a 100 mL or 250 mL infusion bag. The study treatment will be administered as an IV infusion every 21 d, initially for approximately 90 min, then, if there is no infusion related reaction, for a minimum of 30 min thereafter. Investigator's choice comparative therapy will be administered in accordance with the locally approved label in cycles of every 21 d. The choice needs to be pre-defined at time of randomization from the following options: • Trastuzumab/capecitabine • Lapatinib/capecitabine
Study Endpoints:	<u>Primary Efficacy Endpoint:</u> • PFS based on blinded independent central review (BICR) <u>Key Secondary Efficacy Endpoint</u> • OS <u>Other Secondary Efficacy Endpoints:</u> • ORR based on BICR and investigator assessment (confirmation of complete response [CR]/partial response [PR] is required) • DoR based on BICR • PFS based on investigator assessment <u>Exploratory Efficacy Endpoints:</u> • Time to response based on BICR • Best percent change in the sum of the diameter of measurable tumors based on BICR • CBR based on BICR • PFS2 based on investigator assessment <u>Health Economic and Outcomes Research Endpoints:</u> • 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 <u>Pharmacokinetic Endpoints:</u> • Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a <u>Biomarker Endpoints:</u> • Serum biomarkers (eg, HER2 extracellular domain [HER2ECD]) • Other potential biomarkers <u>Safety Endpoints:</u> • Serious adverse events (SAEs)

	• Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 • Adverse events of special interest (AESIs) • TEAEs associated with discontinuation of study treatment • Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS]) • Vital sign measurements • Standard clinical laboratory parameters • ECG parameters • Echocardiogram (ECHO)/multigated acquisition scan (MUGA) findings • Anti-drug antibodies (ADA)
Planned Sample Size:	The target sample size will be approximately 600 subjects, randomized in a 2:1 ratio into two treatment groups (trastuzumab deruxtecan versus investigator's choice).
Statistical Analyses:	The primary analysis for PFS will be performed when approximately 372 BICR-assessed PFS events are observed or 18 months from the last subject randomized, whichever comes first. <u>Efficacy Analyses</u> The primary efficacy analyses will be performed for the Full Analysis Set (FAS) that consists of all randomized subjects. The primary efficacy endpoint is PFS based on BICR. The primary efficacy analyses will compare PFS per BICR between the two treatment groups, using stratified log-rank test stratified by stratification factors per Interactive Web/Voice Response System (IXRS). PFS will be tested for statistical significance at an overall 2-sided alpha of 0.05. Kaplan-Meier estimates and survival curves will also be presented for each treatment group. 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 group. The hazard ratio (HR) and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by stratification factors per IXRS. The key secondary efficacy endpoint is OS, and other secondary efficacy endpoints are confirmed ORR (the proportion of subjects who achieved a best overall response of CR or PR) based on BICR and investigator assessment, DoR based on BICR, and PFS based on investigator assessment. Group sequential testing will be used to compare OS between the two treatment groups hierarchically, provided PFS is 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 group. In addition, Kaplan-Meier estimates at fixed time points along with their 2-sided 95% CIs will be provided for each treatment group. The HR and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by stratification factors per IXRS. Up to 3 analyses of OS could be performed:

- First interim analysis at the time of the final analysis for PFS (provided PFS is significant), at which point a total of approximately 240 OS events (55% information fraction) are expected.
- If the OS interim analysis is not significant, a second interim analysis for OS is planned when approximately 304 OS events (70% information fraction) are expected.
- If the second OS interim analysis is not significant, a final analysis for OS after approximately 434 OS events have been observed (expected 71 months from date of first subject to be randomized).

Cochran-Mantel-Haenszel tests stratified by stratification factors per IXRS will be used to compare ORR (based on BICR/investigator assessment) between the treatment groups. The estimates of ORR and the 2-sided 95% CIs will be provided using Clopper-Pearson method.

Duration of response (based on BICR) will be summarized with median DoR and its 2-sided 95% CI using Brookmeyer and Crowley method for each treatment group.

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 2-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (eg, 3, 6, 9, 12 months) and the 2-sided 95% CIs will be provided for each treatment group. The treatment effect HR and its 2-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 2-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.

Health Economic and Outcomes Research Analyses:

A detailed analysis plan of quality of life (QoL) endpoints, including control of type I error regarding QoL analyses, could be provided in the Statistical Analysis Plan.

Descriptive analyses of HEOR endpoints based on the following patient-reported outcome questionnaires will be summarized. For the European Organization for Research and Treatment of Cancer quality of life questionnaires (EORTC QLQ)-C30 and EORTC QLQ-BR45: changes from baseline over time on the global QoL scale, the functioning scales, symptom scales, and single-item scales of the EORTC QLQ-C30 and in each of the subscales of EORTC QLQ-BR45. For the EQ-5D-5L visual analogue scale, all 5 dimensions and associated utility scores; and for hospitalization-related endpoints: time to hospitalization as well as reason, discharge diagnosis, intensive care unit stay, and length of stay will be reported.

Time to definitive 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. The survival distributions will be estimated by Kaplan-Meier method and results will be presented graphically. The median time to definitive deterioration and the proportion of subjects without definitive deterioration at specific time points will be reported as well as the 2-sided 95% CIs for the medians. A stratified Cox regression model will be used to estimate the HR of time to definitive deterioration, along with 95% CI.

Pharmacokinetic Analyses

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

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

Samples collected for biomarker analyses, such as tissue and blood, may be used for exploratory biomarker assessments. Biomarker data may be summarized by treatment group using descriptive statistics.

Safety Analyses:

Safety endpoints will include SAEs, TEAEs, AESIs, DAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ADAs. TEAEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events 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(ies)
ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxic
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}21d}$	area under the concentration-time curve from time 0 to 21 days
AUC_{∞}	area under the concentration-time curve from 0 extrapolated to infinity
BI	before infusion/dosing
BICR	blinded independent central review
CBR	clinical benefit rate
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum plasma/serum concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
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
DAE	discontinuation due to adverse event
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid

ABBREVIATION	DEFINITION
DoR	duration of response
EC	Ethics Committee
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)
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol-5 dimensions-5 levels of severity
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
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	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	intensive care unit
ILD	interstitial lung disease
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	Interactive Web/Voice Response System

ABBREVIATION	DEFINITION
LV	left ventricular
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder
mAb	monoclonal antibody
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAIDs	nonsteroidal anti-inflammatory drugs
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival on the next-line of treatment
PK	pharmacokinetic
pop-PK	population pharmacokinetics
PO	oral(ly)
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
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event

ABBREVIATION	DEFINITION
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	stable disease
SID	subject identification
SMQ	Standardised MedDRA Query
SOC	system organ class
SOP	Standard Operating Procedure
SpO2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma/serum concentration (C_{max})
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 remains the most common cancer and the second leading cause of cancer mortality in women both in the United States (US) and globally. In 2015, there were 2.4 million new cancer cases leading to 523,000 deaths worldwide. Breast cancer was also the leading cause of morbidity in women, resulting in an estimated burden of 15.1 million disability-adjusted life years.[1]

In approximately 20% of breast cancer cases, overexpression of human epidermal growth factor receptor 2 (HER2) occurs.[2] These HER2-positive breast cancers have historically been associated with more aggressive disease and worse outcomes compared to HER2-negative breast cancers. Although anti-HER2 targeted therapies have improved outcomes, they are not curative in the metastatic setting. Treatment options for patients who have progressed after 2 lines of anti-HER2 therapy remain unclear and limited. Current options include: lapatinib + capecitabine, trastuzumab + capecitabine, trastuzumab + lapatinib, or trastuzumab + other agents.[3] Reported response rates for these regimens when given as second lines of anti-HER2 therapy range from 10% to 22%.[4,5,6] It is expected that these response rates would be lower when given in a later line of therapy.

The only study to report outcomes after 2 lines of anti-HER2 therapy was the TH3RESA study, which compared ado-trastuzumab emtansine (T-DM1) in the third-line setting to investigator's choice therapies. The two prior lines of anti-HER2 therapy in this case were regimens containing trastuzumab and lapatinib. In this setting, although 81% of investigator's choice treatments consisted of combining an anti-HER2 agent with chemotherapy, the objective response rate (ORR) for the investigator's choice treatment was only 9% and the median progression-free survival (PFS) was 3.3 mo.[6]

Treatment options for HER2-positive breast cancer, therefore, remain limited, with no targeted therapy specifically approved following trastuzumab, pertuzumab, and T-DM1 failure.[7] In this setting, recommended treatment options include continuation of an anti-HER2 therapy in combination with a standard chemotherapy agent. Due to the lack of clear superiority, no specific combination is currently endorsed by the National Comprehensive Cancer Network (NCCN) guidelines, and consideration of palliative care is recommended after 3 lines of targeted therapy.[3] Therefore, a high unmet medical need exists, and new treatment options need to be developed to improve outcomes for patients with disease progression following the failure of trastuzumab, pertuzumab, and T-DM1 regimens.

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody conjugated to a drug-linker carrying a topoisomerase I payload. Trastuzumab deruxtecan was studied in the Phase 1 DS8201-A-J101 study in HER2-expressing solid tumors and the Phase 2 DS8201-A-U201 study in HER2-positive metastatic breast cancer previously treated with T-DM1. Trastuzumab deruxtecan (Enhertu®) is approved as a treatment in multiple markets globally; please refer to the IB for additional information.

1.1.1. Investigational Product

1.1.1.1. Name

Trastuzumab deruxtecan (DS-8201a)

1.1.1.2. Description

Trastuzumab deruxtecan 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 (IgG1) monoclonal antibody (mAb) 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).[8,9,10] This ADC achieves a high drug-to-antibody ratio (approximately 8) with homogeneous conjugation with MAAA-1181a.[11] After binding to HER2 and internalization, trastuzumab deruxtecan 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 lyophilized powder (Lyo-DP) form of trastuzumab deruxtecan will be administered in this study.

The trastuzumab deruxtecan Phase 1 clinical study DS8201-A-J101 was initiated with the antibody component, MAAL-9001, produced using the Chinese hamster ovary (CHO)-O1 cell line (FL-DP1). To support new clinical studies, as well as commercial development, transition was made to MAAL-9001 production using a CHO-S cell line (FL-DP2). Analytic comparison of the two cell line products has shown comparability across a wide range of variables. Minor differences have been observed in glycan profile, charge variants, size variants, FcgRIIIA binding, FcRn binding, and antibody-dependent cellular cytotoxic (ADCC) activity. Following single intravenous (IV) administration of trastuzumab deruxtecan to cynomolgus monkeys, mean maximum plasma/serum concentration (C_{max}) of trastuzumab deruxtecan was similar while the area under the concentration-time curve (AUC) was about 22% lower for FL-DP2 material as compared to FL-DP1 material. However, in a xenograft study, no difference was seen in cytotoxicity between the two products.

1.1.1.3. Intended Use Under Investigation

This study will compare the activity of trastuzumab deruxtecan in subjects with HER2-positive, unresectable and/or metastatic breast cancer who are resistant or refractory to T-DM1 versus two potential investigator's choice options that are currently part of guideline recommendations for this line of therapy.

1.1.1.4. Comparators (Investigator's Choice)

The description of these can be found within their approved labels.

- Trastuzumab/capecitabine
- Lapatinib/capecitabine

1.1.1.5. Nonclinical Studies of Trastuzumab Deruxtecan

The pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of trastuzumab deruxtecan have been examined in nonclinical studies. For details of these experiments, please see the latest version of the Investigator's Brochure (IB).[12]

1.1.1.6. Clinical Experience

As of 08 Jun 2021, trastuzumab deruxtecan is being evaluated in 27 company-sponsored clinical studies (18 monotherapy studies and 9 combination therapy studies). An estimated total of 3462 subjects were treated with trastuzumab deruxtecan (alone or in combination with nivolumab or pembrolizumab) or were treated with a comparator.[12] Seven studies are complete (have finalized clinical study reports presenting the results for the study primary objective), and 20 studies are ongoing.[12] For updated results, please also see the latest version of the IB.[12]

The trastuzumab deruxtecan study, Protocol DS8201-A-U201, is a 2-part, open-label, single-group, multicenter, Phase 2 study in adults with pathologically documented HER2-positive metastatic breast cancer who had received previous treatment with trastuzumab emtansine. In the first part of the study, three different doses of trastuzumab deruxtecan were evaluated to establish a recommended dose and in the second part of the study, efficacy and safety were evaluated at the recommended dose of 5.4 mg/kg.

Results as of 01 August 2019 were reported in The New England Journal of Medicine.[13] Among the 184 subjects who received trastuzumab deruxtecan at the recommended dose of 5.4 mg/kg, the blinded independent central review (BICR) confirmed response rate was 60.9% (95% CI: 53.4, 68.0); of these subjects, 6.0% had a complete response (CR), and 54.9% had a partial response.[13] The disease control rate (DCR) was 97.3% (95% CI: 93.8, 99.1).[13] The median time to response was 1.6 months (95% CI: 1.4, 2.6), and the median duration of response (DoR) was 14.8 months (95% CI: 13.8, 16.9).[13] The median PFS was 16.4 months (95% CI: 12.7, not reached).[13] The estimated OS was 93.9% (95% CI: 89.3, 96.6) at 6 months and 86.2% (95% CI: 79.8, 90.7) at 12 months; the median overall survival was not reached.[13]

As of 01 August 2019, among 184 subjects who received 5.4 mg/kg trastuzumab deruxtecan, 99.5% had at least one adverse event (AE) and 57.1% had an AE of Grade 3 or higher.[13] The most common Grade 3 or higher AEs were neutrophil count decreased (20.7%), anemia (8.7%), nausea (7.6%), white blood cell count decreased (6.5%), lymphocyte count decreased (6.5%), and fatigue (6.0%).[13] AEs led to dose interruption in 35.3%, dose reduction in 23.4%, and dose discontinuation in 15.2% of subjects.[13] A total of 25 deaths were reported, including seven that occurred during treatment as a result of either disease progression (in three subjects) or AEs (hemorrhagic shock, general physical health deterioration, pneumonia, and acute organ failure in one subject each).[13] During survival follow-up (which was defined as 47 days after the end of treatment [EOT]), 18 of the 25 deaths occurred, two of which were caused by events associated with interstitial lung disease (ILD) that started during treatment; the remaining 16 deaths were considered by investigators to be unrelated to trastuzumab deruxtecan.[13]

For further details related to the efficacy and safety of trastuzumab deruxtecan reported from clinical studies, please see the latest version of the IB.[12]

1.1.1.7. Summary of Clinical Pharmacokinetics

Pharmacokinetics were evaluated in 24 subjects who received trastuzumab deruxtecan. 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 1.1. The C_{max} of trastuzumab deruxtecan 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 d ($AUC_{0\text{-}21d}$) at 6.4 mg/kg were 181 µg/mL and 901 µg•d/mL, respectively (Table 1.1). 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 ($t_{½}$) of trastuzumab deruxtecan was 7.33 d 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 trastuzumab deruxtecan (Table 1.2).

The C_{max} and AUC for the dosing interval ($AUC_{0\text{-}21d}$) 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 1.3). The $t_{½}$ of MAAA-1181a was similar to that of trastuzumab deruxtecan.

Table 1.1: Mean Pharmacokinetic Parameters of Trastuzumab Deruxtecan (± Standard Deviation)

Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h) median (range)	$AUC_{0\text{-}21d}$ (µg•d/mL)	AUC_{∞} (µg•d/mL)	$t_{½}$ (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
5.4 (N=6)	127 ± 17.2	1.92 (1.92, 2.16)	544 ± 165	590 ± 186	6.03 ± 0.603	10.1 ± 3.90	75.2 ± 24.2
6.4 (N=6)	181 ± 33.1	2.16 (1.44, 4.08)	901 ± 155	1030 ± 209	7.33 ± 1.64	6.41 ± 1.12	58.6 ± 11.0
8.0 (N=3)	216 ± 52.0	1.92 (1.92, 2.16)	914 ± 235	1020 ± 279	6.97 ± 0.357	8.17 ± 1.93	69.7 ± 13.1

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

Table 1.2: Mean Pharmacokinetic Parameters of Total Antibody (± Standard Deviation)

Trastuzumab Deruxtecan Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h) median (range)	$AUC_{0\text{-}21d}$ (µg•d/mL)	AUC_{∞} (µg•d/mL)	$t_{½}$ (d)
5.4 (N=6)	116 ± 13.9	1.92 (1.92, 6.96)	609 ± 151	682 ± 172	6.78 ± 2.39
6.4 (N=6)	146 ± 18.9	3.84 (2.16, 6.96)	878 ± 97.1	1050 ± 149	8.25 ± 2.16
8.0 (N=3)	178 ± 18.5	2.16 (1.92, 6.72)	1090 ± 213	1270 ± 296	7.35 ± 0.417

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

Table 1.3: Mean Pharmacokinetic Parameters of MAAA-1181a (± Standard Deviation)

Trastuzumab Deruxtecan Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h) median (range)	$AUC_{0\text{-}21\ d}$ (ng•d/mL)	AUC_{∞} (ng•d/mL)	$t_{½}$ (d)
5.4 (N=6)	10.8 ± 7.56	5.28 (3.84, 23.76)	40.6 ± 19.8	43.6 ± 21.2	6.11 ± 0.811
6.4 (N=6)	6.80 ± 1.72	6.72 (4.08, 7.20)	31.0 ± 5.11	34.2 ± 5.63	6.28 ± 1.17
8.0 (N=3)	9.25 ± 3.18	6.72 (6.72, 6.96)	39.4 ± 6.43	43.4 ± 9.16	6.36 ± 1.53

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

1.2. Study Rationale

A member of the HER superfamily, HER2 initiates signal transduction via the PI3K/Akt and RAS/MAPK pathways.[14,15] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and a variety of cultured tumor cell lines including breast cancer,[15,16] gastric cancer,[17,18] pancreatic cancer,[19] lung cancer,[20] colorectal cancer,[21] and ovarian cancer.[22] There are also many reports demonstrating an association between expression of HER2 protein and poor clinical prognosis. In normal human tissue, low expression of HER2 protein has been reported on cell membranes of epithelial cells in the gastrointestinal, respiratory, reproductive, and urinary tracts as well as in the skin, breast, and placenta.[23]

The current first line standard of care for HER2-positive metastatic breast cancer (mBC), with the addition of pertuzumab to trastuzumab and chemotherapy, was established based on results of the CLEOPATRA study. Like trastuzumab, pertuzumab is a humanized mAb that binds HER2 at a separate epitope in the extracellular domain. In addition to ADCC activity, pertuzumab adds a novel mechanism of action by inhibiting dimerization of HER2, a process thought to be important for HER2 activation. The CLEOPATRA study randomized subjects to receive trastuzumab plus docetaxel with or without the addition of pertuzumab as first line therapy for metastatic HER2-positive breast cancer. The addition of pertuzumab improved median PFS from 12.4 to 18.5 mo and median overall survival (OS) from 40.8 to 56.5 mo, leading to a new standard of care for patients with mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[24]

Additionally, the EMILIA study established T-DM1 as the standard for subsequent line of anti-HER2 therapy. T-DM1 is an ADC linking the trastuzumab antibody to emtansine, a tubulin inhibitor. In the EMILIA study, T-DM1 was compared with the combination of lapatinib and capecitabine for the treatment of subjects who had progressed after treatment with a trastuzumab and taxane combination. In this study, T-DM1 improved median PFS from 6.4 to 9.6 mo and median OS from 25.1 to 30.9 mo.[25]

The multitude of treatment options being used post-T-DM1 for HER2+ mBC reflect the unmet medical need in this setting and the absence of guideline specific recommendations. The NCCN has no recommendation, but offers lapatinib + capecitabine, trastuzumab + capecitabine, and trastuzumab + lapatinib as possibilities. The two most common regimens for HER2+ mBC

post-T-DM1 are trastuzumab + chemotherapy and lapatinib + chemotherapy, with capecitabine being the most common chemotherapy used in combination. Comparison of these regimens across studies, and in the limited data with direct comparisons, suggest that these two regimens were similar in terms of response rates and survival. This study therefore allows either trastuzumab + capecitabine or lapatinib + capecitabine to be chosen at the investigator's discretion as a comparator to trastuzumab deruxtecan in the post-T-DM1 setting.

Trastuzumab deruxtecan is a HER2-targeting ADC with a high drug-to-antibody ratio (7 to 8), and a novel topoisomerase I inhibitor as payload. Trastuzumab deruxtecan is expected to inhibit tumor growth on the basis of the following reasons: like trastuzumab, it induces ADCC activities and inhibits Akt phosphorylation when it binds to HER2; and the MAAA-1181a that is released from trastuzumab deruxtecan after the internalization induces apoptosis by inhibiting topoisomerase I. Nonclinical evidence demonstrates that the HER2 targeting of trastuzumab deruxtecan is highly specific. In nonclinical models, trastuzumab deruxtecan showed a much broader antitumor spectrum than T-DM1, including efficacy against T-DM1 resistant and HER2 low-expressing tumors. In vivo studies using a tumor-bearing mouse model suggest that administration of trastuzumab deruxtecan results in the regression of HER2-positive tumors.

Trastuzumab deruxtecan has a cytotoxic drug component with a different mechanism of action than that of T-DM1 and is expected to show activity in tubulin inhibitor insensitive tumors, so it is anticipated to be of benefit in the T-DM1-refractory patient population.

In the Phase 1 clinical study DS8201-A-J101, preliminary results from HER2-positive breast cancer subjects pretreated with T-DM1 showed that almost all subjects experienced tumor shrinkage with durable disease control. Subjects evaluable for confirmed responses (at least 2 post-baseline scans, total n = 33) showed ORR of 60.6% (20 of 33). The current Kaplan-Meier estimate for median PFS reached 10.4 mo (95% confidence interval [CI]: 32.1, not reached). In the combined Part 1 and Part 2 population of HER2-positive breast cancer subjects who received pertuzumab pretreatment (a subset of the T-DM1 treated population), an ORR of 60.0% (total of 18 responders out of 30 subjects in Part 1 and Part 2) and a DCR of 96.7% was observed. These results compare favorably to the historical results described above despite use of trastuzumab deruxtecan in a later line of therapy.

DS8201-A-U301 is designed to compare trastuzumab deruxtecan versus standard of care (investigator's choice) in subjects with unresectable and/or metastatic breast cancer previously treated with T-DM1.

1.3. Risks and Benefits for Study Subjects

Trastuzumab deruxtecan is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. The DS8201-A-U201 study was initiated based on preliminary clinical observations in the Phase 1 study (DS8201-A-J101) (see Section 1.1.1.6). In this study, trastuzumab deruxtecan demonstrates antitumor activity in HER2 expressing cancers including breast cancer and gastric cancer.

As of 01 Feb 2019, from the completed DS8201-A-J101 study, 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 BICR of 52.5%. Among the subjects with HER2-low breast cancer, confirmed ORR by BICR was 37.0%. The overall efficacy results in subjects with HER2-positive

gastric/gastroesophageal junction cancer at 5.4 mg/kg or 6.4 mg/kg demonstrated a confirmed ORR by BICR of 29.5%. The overall efficacy results in subjects with other cancers demonstrated a confirmed ORR by BICR of 29.5%.

Based on the cumulative review of nonclinical, clinical, and epidemiologic studies and the scientific literature on the safety profile of trastuzumab deruxtecan, ILD/pneumonitis and neutropenia (including febrile neutropenia) are classified as important identified risks as of 08 Jun 2021. Left ventricular (LV) dysfunction and embryo-fetal toxicity are classified as important potential risks.

In the trastuzumab deruxtecan 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/pneumonitis and neutropenia (including febrile neutropenia), important potential risks of LV dysfunction and embryo-fetal toxicity, and other risks.

ILD/pneumonitis and neutropenia are known adverse drug reactions (ADRs) of trastuzumab deruxtecan, and cases with fatal outcomes have been reported. Most events were Grade 1 or Grade 2 and were manageable by following clinical management guidelines, which included monitoring of signs/symptoms of ILD/pneumonitis (eg, cough, fever, and dyspnea) to identify potential ILD/pneumonitis and proactively managing events with appropriate intervention (including dose modification and treatment [eg, steroids]) and supportive care instituted in a timely fashion.

Other ADRs of trastuzumab deruxtecan were primarily gastrointestinal or hematologic in nature. These identified risks were generally manageable through dose modification and routine clinical treatment.

Trastuzumab deruxtecan has demonstrated a generally acceptable safety profile in the treated populations.

In conclusion, given the data available on the efficacy and safety of trastuzumab deruxtecan, the overall benefit/risk remains positive.

For current assessments of risks and benefits to subjects, please refer to the current IB[12] for trastuzumab deruxtecan.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to compare the PFS benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1.

2.1.2. Key Secondary Objective

The key secondary objective is to compare the OS benefit of trastuzumab deruxtecan to investigator's choice for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1.

2.1.3. Other Secondary Objectives

The secondary objectives are:

- To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice on:
  - Confirmed ORR;
  - DoR.
- To further determine PK of trastuzumab deruxtecan;
- To further evaluate safety of trastuzumab deruxtecan compared to investigator's choice;
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to investigator's choice.

2.1.4. Exploratory Objectives

The exploratory objectives are:

- To evaluate efficacy of trastuzumab deruxtecan compared to investigator's choice by clinical benefit rate (CBR) and progression-free survival on the next-line of therapy (PFS2).
- To evaluate potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD]).
- To evaluate exposure-response relationships for efficacy and safety endpoints.

2.2. Study Hypothesis

Trastuzumab deruxtecan confers a significant benefit in PFS compared to investigator's choice in HER2-positive breast cancer subjects previously treated with T-DM1.

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. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is OS.

2.3.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- ORR based on BICR and investigator assessment (confirmation of CR/partial response [PR] is required)
- DoR based on BICR
- PFS based on investigator assessment

2.3.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Time to response based on BICR
- Best percent change in the sum of the diameter of measurable tumors based on BICR
- CBR based on BICR
- PFS2 based on investigator assessment

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 questionnaire (QLQ)-C30
- EORTC QLQ-BR45
- EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L)
- Hospitalization-related endpoints (Section 10.3.1)

2.3.6. Pharmacokinetic/Biomarker Endpoints

2.3.6.1. Pharmacokinetic Endpoints

The PK endpoints include:

- Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a

2.3.6.2. Biomarker Endpoints

The biomarker endpoints include:

- Serum biomarkers (eg, HER2ECD)
- Other potential biomarkers

2.3.7. Safety Endpoints

The safety endpoints include:

- Serious adverse events (SAEs)
- TEAEs
- Adverse events of special interest (AESIs)
- TEAEs associated with discontinuations of study treatment
- Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
- Vital sign measurements
- Standard clinical laboratory parameters
- Electrocardiogram (ECG) parameters
- Echocardiogram (ECHO)/multigated acquisition scan (MUGA) findings
- Anti-drug antibodies (ADAs)

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, 2-arm, Phase 3, open-label, multicenter study designed to compare the safety and efficacy of trastuzumab deruxtecan versus investigator's choice in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1. Figure 3.1 shows the study design.

Trastuzumab deruxtecan for injection, 100 mg, will be administered IV at a starting dose of 5.4 mg/kg.

The comparator for this study is called investigator's choice with the options being 1 of the following:

- Trastuzumab/capecitabine
- Lapatinib/capecitabine

For subjects randomized to comparator, the treatment will be in cycles of every 21 d (± 2 d).

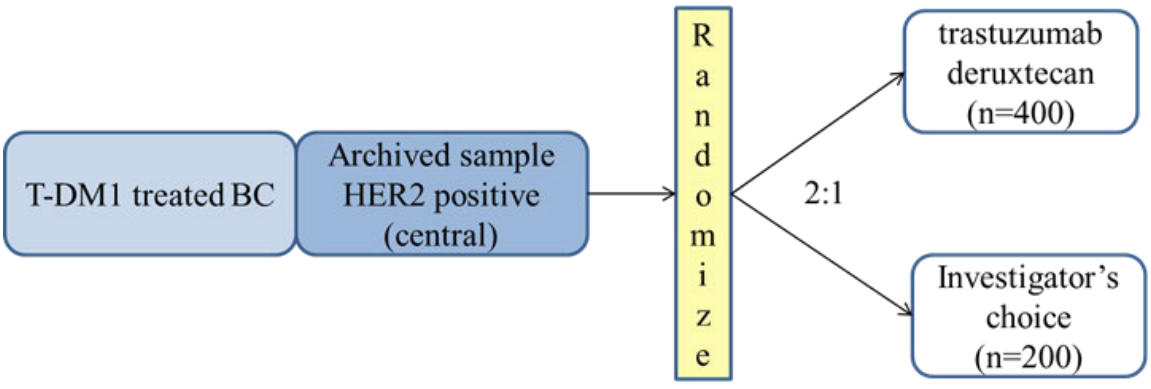
Randomization will be stratified by:

- Hormone receptor status (positive, negative)
- Prior treatment with pertuzumab (yes, no)
- History of visceral disease (yes, no)

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). If the study treatment is delayed more than 49 d (7 wks) for the investigator's choice group or 126 days (18 weeks) for the T-DXd group from the last infusion date, the subject will be withdrawn from the study treatment and will be followed for survival.

History of past treatment with pertuzumab will be collected for all study subjects.

Figure 3.1: Study Design Schema



BC = breast cancer; HER2 = human epidermal growth factor receptor 2; T-DM1 = ado-trastuzumab emtansine

3.1.1. Duration of the Study

Enrollment is planned to occur over approximately 30 mo.

The study team will monitor the number of PFS events. The study statistician will make projections of the data cutoff date for PFS analysis, first quarterly and then monthly. The projection 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. Progression-free survival 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. Similar projections on data cutoff date will be performed for the interim and final OS analyses (as needed), and data after the data cutoff date will be considered for OS analysis. Similar projections on data cutoff date will be performed for the OS analysis (as needed), and all data up to the data cutoff date will be used for OS analysis.

For each subject there will be a 40-Day (+7 d) 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 mo (± 14 d) from the date of 40-Day (+7 d) 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).

3.1.2. Duration of Subject Participation

The Screening period is up to 28 d. For trastuzumab deruxtecan, each cycle of treatment will be 21 d. The number of treatment cycles with trastuzumab deruxtecan is not fixed. Upon commencing study treatment, subjects may continue receiving study treatment until the occurrence of any of the events defined in Section 5.7.1.

For subjects randomized to investigators choice, treatment cycles will be on the same 21 d cycles.

After study treatment discontinuation, all subjects may be contacted every 3 mo 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).

3.1.3. Definition of the End of the Study

Overall end of study (EOS) will occur when any of the following conditions are met:

- The last subject's last visit has occurred.
- An alternative study becomes available for subjects continuing to derive benefit from treatment with T-DXd, where the study drug is offered to these subjects.
- The study is discontinued by the Sponsor for other reasons (eg, administrative or safety related).

For clinical studies conducted in the European Union (EU) and under the EU clinical trial regulation, if the EOS in the last EU Member State occurs before the EOS in the last global country, the clinical trial results summary will be submitted within 12 months after the EOS in the final global country (ie, in such a situation, the submission will not be based on the EOS in

the last EU Member State). Holding the submission until the study is complete globally is justified, because in situations when the clinical study is still ongoing in other countries and data from these other countries are not available, the full statistical analysis planned for the study is not feasible, and incomplete results are uninterpretable.

3.2. Discussion of Study Design

This study will be conducted in approximately 230 sites including, but not limited to, North and South America, Europe, and Asia.

The target sample size will be approximately 600 subjects, randomized in a 2:1 ratio into 2 treatment groups (trastuzumab deruxtecan versus investigator's choice).

4. STUDY POPULATION

Each subject will sign Study Informed Consent Form(s) (ICF) 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 Ethics Committee (EC) approved ICF before performance of any study-specific procedures or tests.
2. Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old.)
3. Pathologically documented breast cancer that:
    a. is unresectable or metastatic.
    b. has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines[26] evaluated at a central laboratory.
    c. was previously treated with T-DM1.
4. Documented radiologic progression (during or after most recent treatment or within 6 mo after completing adjuvant therapy).
5. Subjects must be HER2-positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, a fresh biopsy is required.
6. Presence of at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 (see Section 17.4).[27]
    - Brain lesions will be considered as non-target lesions only.
7. ECOG PS 0 or 1.
8. Adequate bone marrow function, within 14 d before randomization, defined as:

- Absolute neutrophil count ≥1.5 × 10^9/L (granulocyte colony-stimulating factor administration is not allowed within 1 wk prior to Screening assessment);
- Platelet count ≥100 × 10^9/L (Platelet transfusion is not allowed within 1 wk prior to Screening assessment);
- Hemoglobin level ≥9.0 g/dL (Red blood cell transfusion is not allowed within 1 wk prior to Screening assessment).

9. Adequate renal function within 14 d before randomization, defined as:
   - Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation ($\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ {× 0.85 for females}; Section 17.2).
10. Adequate hepatic function within 14 d before randomization, defined as:
    - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and
    - Aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 2.5 × ULN.
11. Adequate blood clotting function within 14 d before randomization, defined as:
    - International normalized ratio/prothrombin time: ≤ 1.5 × ULN and either partial thromboplastin or activated partial thromboplastin time ≤ 1.5 × ULN.
12. 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 7 mo after the last dose of trastuzumab deruxtecan, 6 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine. Male subjects must agree to inform all potential female partners that they are participating in a clinical trial of a drug that may cause birth defects. Male subjects must also agree to either avoid intercourse or that he and/or any female partner of reproductive/childbearing potential will use a highly effective form of contraception during and upon completion of the study and for at least 4.5 mo after the last dose of trastuzumab deruxtecan, 3 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine.

    Methods considered as highly effective methods of contraception include:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      - Oral (PO)
      - 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 7 mo for female subjects (4.5 mo for male subjects) after the last dose of trastuzumab deruxtecan, 6 mo after the last dose of lapatinib/capecitabine for female subjects (3 mo for male subjects), or 7 mo after the last dose of trastuzumab/capecitabine. True abstinence must be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception.

13. Non-childbearing potential is defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 mo 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 wk 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. Male subjects must not freeze or donate sperm throughout the study period beginning at Cycle 1 Day 1 and for at least 4.5 mo after the last dose of trastuzumab deruxtecan, 3 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine. Preservation of sperm should be considered prior to enrollment in this study.
14. Female subjects must not donate ova or retrieve them for their own use from the time of Screening and throughout the study treatment period, and for at least 7 mo after the last dose of trastuzumab deruxtecan, 6 mo after the last dose of lapatinib/capecitabine, or 7 mo after the last dose of trastuzumab/capecitabine.
15. 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:

1. Ineligible for the comparator arm treatment for reasons including but not limited to the following:
    a. Prior treatment with capecitabine;
    b. History of any contraindication included in the approved local label for capecitabine or for both trastuzumab and lapatinib;
    c. Concurrent treatment with any medication prohibited in the applicable approved local label for capecitabine or for both trastuzumab and lapatinib.
2. Prior participation in a study involving an ADC produced by Daiichi Sankyo.
3. Uncontrolled or significant cardiovascular disease, including any of the following:
    a. History of myocardial infarction within 6 mo before randomization;
    b. History of symptomatic congestive heart failure (New York Heart Association Class II to IV);
    c. Troponin levels consistent with myocardial infarction as defined according to the manufacturer within 28 d prior to randomization;
    d. Corrected QT interval (QTc) prolongation to > 470 ms (females) or >450 ms (male) based on average of Screening triplicate 12 lead ECG;
    e. Left ventricular ejection fraction (LVEF) < 50% within 28 d prior to randomization.
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. Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or 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 wk must have elapsed between the end of whole brain radiotherapy and study enrollment.
6. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
7. History of severe hypersensitivity reactions to other mAbs.
8. 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.

9. Social, familial, or geographical factors that would interfere with study participation or follow-up.
10. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
11. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Subjects positive for hepatitis C virus (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/EC.
12. Multiple primary malignancies within 3 y, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or contralateral breast cancer.
13. 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 wk before randomization or palliative stereotactic radiation therapy within 2 wk before randomization.
15. Systemic treatment with anticancer therapy (immunotherapy [non-antibody-based therapy], retinoid therapy, or hormonal therapy) within 3 wk before randomization; antibody-based-anticancer-therapy within 4 wk before randomization; or treatment with nitrosoureas or mitomycin C within 6 wk before randomization; or treatment with small-molecule targeted agents within 2 wk, or 5 half-lives before randomization, whichever is longer.
17. Participation in a therapeutic clinical study within 3 wk before randomization (for small-molecule targeted agents, this non-participation period is 2 wk or 5 half-lives, whichever is longer), or current participation in other investigational procedures.
18. Pregnant, breastfeeding, or planning to become pregnant.
19. Subject must not be an immediate family member of study site personnel working for the investigator or of Sponsor personnel.
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 3 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.

5. STUDY TREATMENTS

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Groups

There will be 2 treatment groups:

Trastuzumab deruxtecan and investigator's choice; within investigator's choice there are 2 options:

- Trastuzumab/capecitabine
- Lapatinib/capecitabine

The option chosen must be declared before randomization. Once assigned, subjects will remain on study in their treatment group and will not change groups. Within investigator's choice, the subject must remain on the declared option for their duration within the study.

5.1.2. Method of Treatment Allocation

Prior to randomization of a subject, all eligibility criteria must be met and a signed informed consent obtained.

Subjects will be randomized into 1 of the 2 treatment groups (trastuzumab deruxtecan versus investigator's choice) in a 2:1 ratio. The randomization will be stratified by hormone receptor status (positive, negative), prior treatment with pertuzumab (yes, no), and history of visceral disease (yes, no). 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 investigator'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 trastuzumab deruxtecan and investigator'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

5.2. Trastuzumab Deruxtecan

5.2.1. Description

Lyophilized powder (Lyo-DP)

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

5.2.2. Labeling and Packaging

Trastuzumab deruxtecan for injection 100 mg will be supplied by the Sponsor. Trastuzumab deruxtecan 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

Trastuzumab deruxtecan for IV infusion is prepared by dilution of the required volume of the study treatment calculated based on the subject's body weight to a 100 mL or 250 mL infusion bag. Prepared study treatment solutions should be used as directed in the pharmacy instructions. The preparation will be conducted in accordance with the pharmacy instructions provided by the Sponsor. 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

Trastuzumab deruxtecan will be administered initially as an IV infusion over 30 to 90 min every 21 d (± 2 d). The initial dose of trastuzumab deruxtecan will be infused for approximately 90 min. If there is no infusion related reaction, after the initial dose, the next doses of trastuzumab deruxtecan will be infused for a minimum of 30 min. The subject's weight at screening (baseline) will be used to calculate the initial dose. If during the course of treatment, the subject's weight changes by ≥±10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of trastuzumab deruxtecan.

Trastuzumab deruxtecan 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

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

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

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

For storage of the infusion solutions, see pharmacy instructions.

5.2.6. Drug Accountability

When a drug shipment is received from the Sponsor, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, check drug expiration date, and acknowledge receipt in IXRS. In addition, the investigator or designee shall 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 (trastuzumab deruxtecan/investigator'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),
- the initials of the dispenser.

At the study closure, as per local laws and/or directed by Sponsor, all unused study treatment will be returned to the supply depot or destroyed as per local laws or site policy and only after the study monitor has completed a final inventory. As applicable, the study site must file a copy of the appropriate institution policy within their investigator site file and provide a copy to the Sponsor. At study closure, a final study treatment reconciliation statement must be completed by the investigator or designee and provided to the Sponsor. See pharmacy instructions for details.

Unused drug supplies may be destroyed by the investigator when approved in writing by Sponsor and 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 which 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 (Investigator's Choice)

Subjects randomized to the investigator's choice will be treated according to 1 of the following regimens:

- Capecitabine in combination with trastuzumab for IV infusion:
  - Trastuzumab 8 mg/kg IV loading dose on the first day of treatment followed by 6 mg/kg every 21 d (± 2 d)
  - Capecitabine 1250 mg/m^2 administered PO twice daily approximately 12 h apart (equivalent to 2500 mg/m^2 total daily dose) on Days 1 to 14 of a 21-d (± 2 d) schedule

  - On the basis of the investigator's judgment, subjects may discontinue capecitabine and remain on trastuzumab alone, and subjects may also discontinue trastuzumab and remain on capecitabine alone. If both trastuzumab and capecitabine are delayed longer than 28 d from the planned date of administration, the subject will permanently discontinue study treatment and will be followed for survival (Section 5.4.1).

- Capecitabine in combination with lapatinib:
  - Lapatinib 1250 mg PO daily on Days 1 to 21 of a 21-d (± 2 d) schedule
  - Capecitabine 1000 mg/m^2 PO twice daily approximately 12 h apart (equivalent to 2000 mg/m^2 total daily dose) on Days 1 to 14 of a 21-d (± 2 d) schedule
  - On the basis of the investigator's judgment, subjects may discontinue capecitabine and remain on lapatinib alone, and subjects may also discontinue lapatinib and remain on capecitabine alone. If both lapatinib and capecitabine are delayed longer than 28 d from the planned date of administration, the subject will permanently discontinue study treatment and will be followed for survival (Section 5.4.1).

Accountability for the investigator's choice medications will follow the trastuzumab deruxtecan procedures (Section 5.2.6). Administration and storage for all medications must follow the locally approved label.

Trastuzumab IV is the only acceptable formulation for this study. Trastuzumab subcutaneous or biosimilar may not be used.

5.4. 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 below for trastuzumab deruxtecan. Dose adjustments for investigator's choice medications should be made in accordance with the locally approved label for that medication. All dose modifications should be based on the worst preceding toxicity (Common Toxicology 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 trastuzumab deruxtecan by the investigator(s), monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 d until the AE is determined to be resolving.

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

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. Dose Reduction and Interruption Guidelines

Trastuzumab deruxtecan:

NOTE: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 5.2.

The starting dose of the trastuzumab deruxtecan Lyo-DP formulation will be 5.4 mg/kg.

The trastuzumab deruxtecan dosage administered will be based upon the actual body weight calculated using the body surface area calculation method.

Two dose reductions will be permitted. The adjustment for reduced dosing of trastuzumab deruxtecan depending on the initial starting dose is as shown in Table 5.1.

Table 5.1: Dose Reduction Levels of Trastuzumab Deruxtecan

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

Once the dose of trastuzumab deruxtecan 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, then the subject will be withdrawn from study treatment. Trastuzumab deruxtecan dose increases are not allowed in the study.

Every effort should be made to limit study drug delay; however, in circumstances of AE management or medical intervention, the study drug can be held up to 18 weeks (126 days) from the last T-DXd dose. During this time, scheduled computed tomography (CT)/magnetic resonance imaging (MRI) scans should continue as per protocol, and subjects should fulfil all of the following criteria:

- Study drug may be resumed with confirmation of continued benefit per RECIST version 1.1. Scans should be performed at the frequency defined per protocol while the study drug is being held.
- At minimum, 1 restaging scan must be done within 6 weeks prior to restarting the study drug.
- Investigational product(s) is/are restarted within the guidance of the Toxicity Management Guidelines for T-DXd and any combination agents, if appropriate.
- No prohibited concomitant medications have been administered since the last dose of T-DXd.

If a subject is assessed as requiring a dose delay of longer than 126 days, the subject will be withdrawn from the study drug and followed for survival.

Treatment cycles for a subject for whom study treatment dosing was temporarily withheld for any reason may have future cycles scheduled based on the date of the last study treatment administration.

Investigators may contact the Sponsor Medical Monitor or designee to discuss questions regarding dose modification or discontinuation of study treatment.

5.4.1.1. Dose Modifications

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

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.

Dose adjustments guidelines for trastuzumab deruxtecan are shown in Table 5.2.

Table 5.2: Dose Modification for Trastuzumab Deruxtecan

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
No Toxicity	Maintain dose and schedule
Infusion related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h)	• Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of trastuzumab deruxtecan should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc, should be administered.

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
Troponin Increased	
Grade 1 (Levels above the ULN and below the level of myocardial infarction as defined by the manufacturer)	If troponin levels are above the upper limit of normal and below the level of myocardial infarction (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For new diagnosed Grade 1 detected on study, repeat troponin testing at 3 h ± 1 h after initial troponin test. • If repeat troponin level at 3 h ± 1 h rises significantly per institutional guidelines, – Perform ECG in triplicate – Repeat troponin testing at 6 h ± 1 h – Follow institutional guidelines for management of detectable troponin testing. • If repeat troponin level at 3 h ± 1 h does not rise significantly per institutional guidelines, – Repeat troponin testing 6 h ± 1 h or 24 h ± 2 h after initial troponin test Continue treatment with trastuzumab deruxtecan.
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	• Perform ECG in triplicate. • Repeat troponin testing at 6 h (± 1 h) and 12 h (± 1 h) 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 ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3 (Neutrophils: <1.0 to 0.5 × 10^9/L, WBCs: <2.0 to 1.0 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Neutrophils: <0.5 × 10^9/L, WBCs: <1.0 to 1.0 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2 • Reduce dose 1 level
Febrile Neutropenia (absolute neutrophil count < 1 × 10^9/L, fever > 38.3°C or a sustained temperature of ≥38°C for more than 1 h)	• Delay dose until resolved • Reduce dose by 1 level

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	• No dose modification
Grade 4 (< 0.2 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2: – If resolved in ≤ 14 d from day of onset, maintain dose – If resolved in > 14 d from day of onset, reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin [Hb] <8.0 g/dL); transfusion indicated	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Hb <8.0 g/dL) Life-threatening consequences; urgent intervention indicated	• Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (platelets <50 to 25 × 10^9/L)	• Delay dose until resolved to ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4 (platelets < 25 × 10^9/L)	• Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure	• Discontinue subject from study treatment
Decrease in LVEF 10-20% (absolute value), but LVEF > 45%	• Continue treatment with trastuzumab deruxtecan
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	• Continue treatment with trastuzumab deruxtecan • Repeat LVEF assessment within 3 wk
LVEF 40% to ≤ 45% and decrease is 10-20% (absolute value) from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 wk • 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) drop from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 wk • If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study treatment

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Electrocardiogram QT Prolonged	
Grade 3 (Average QTc > 500 ms or >60 ms change from baseline)	• Delay dose until resolved to ≤ Grade 1 (QTc ≤ 480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then – if attributed to trastuzumab deruxtecan, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Discontinue subject from study treatment
Troponin Increased	
Grade 1 (Levels above the ULN and below the level of myocardial infarction as defined by the manufacturer)	If troponin levels are above the upper limit of normal and below the level of myocardial infarction (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For new diagnosed Grade 1 detected on study, repeat troponin testing at 3 h ± 1 h after initial troponin test. • If repeat troponin level at 3 h ± 1 h rises significantly per institutional guidelines, – Perform ECG in triplicate – Repeat troponin testing at 6 h ± 1 h – Follow institutional guidelines for management of detectable troponin testing. • If repeat troponin level at 3 h ± 1 h does not rise significantly per institutional guidelines, – Repeat troponin testing 6 h ± 1 h or 24 h ± 2 h after initial troponin test – Continue treatment with trastuzumab deruxtecan.
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	• Perform ECG in triplicate. • Repeat troponin testing at 6 h (± 1 h) and 12 h (± 1 h) 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 ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Pulmonary Toxicity	If a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • High resolution CT • Pulmonologist consultation (infectious disease consultation as clinically indicated) • Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests (including forced vital capacity and carbon monoxide diffusing capacity) and pulse oximetry (SpO2) • Other clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, and C-reactive protein) • One blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered as needed (eg, COVID-19) If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
Grade 1	The administration of trastuzumab deruxtecan must be interrupted for any ILD event regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: – If resolved in ≤ 28 d from day of onset, maintain dose – If resolved in > 28 d from day of onset, reduce dose 1 level However, if the Grade 1 ILD/pneumonitis has not resolved within 18 weeks (126 days) from the last infusion, the study treatment should be discontinued. * If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given.
Grade 2	Permanently discontinue subject from study treatment. • Promptly start and treat with systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone). – Re-consider additional work-up for alternative etiologies as described above. • Escalate care as clinically indicated.

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
Grade 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required. • 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 followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, – Re-consider additional work-up for alternative etiologies as described above. • Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	• Delay dose until resolved to ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment
Blood Creatinine Increased	
Grade 3 (> 3.0 to 6.0 × ULN)	• Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (> 6.0 × ULN)	• Discontinue subject from study treatment
Hepatic Toxicity	
AST or ALT With Simultaneous Total Bilirubin Increased	
AST/ALT ≥3.0 × ULN with simultaneous total bilirubin ≥2.0 × ULN	• Delay study medication until drug-induced liver injury can be ruled out. • If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study treatment may occur after discussion between the investigator and Sponsor. • If drug-induced liver injury cannot be ruled out from diagnostic work-up, 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 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 × ULN	• Repeat testing within 3 d. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 × ULN, otherwise delay dose until resolved to ≤ baseline, then: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 3 (> 8.0 to 20.0 × ULN if baseline was normal; >8.0 to 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was > 3 × ULN	• Repeat testing within 3 d. Delay dose until resolved to ≤ baseline level, then: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4 (> 20 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	• Discontinue subject from study treatment
Total Bilirubin Increased	
Grade 2 (> 1.5 to 3.0 × ULN if baseline was normal; >1.5 to 3.0 × baseline if baseline was abnormal)	• If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level • If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (> 3.0 to 10.0 × ULN if baseline was normal; >3.0 to 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 d. Delay dose until resolved to ≤ Grade 1: – If resolved in ≤ 7 d from day of onset, reduce dose 1 level – If resolved in > 7 d from day of onset, discontinue trastuzumab deruxtecan If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 d. Delay dose until resolved to < Grade 2: – If resolved in ≤ 7 d from day of onset, reduce dose 1 level – If resolved in > 7 d from day of onset, discontinue trastuzumab deruxtecan
Grade 4 (> 10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	• Discontinue subject from study treatment

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Blood Alkaline Phosphatase Increased	
Grade 3(>5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × baseline if baseline was abnormal) or Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal))	• No modification unless determined by the investigator to be clinically significant or life-threatening
Gastrointestinal	
Nausea	
Grade 3	• Delay dose until resolved to ≤ Grade 1 – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	• Delay dose until resolved to ≤ Grade 1 – If resolved in ≤ 3 d from day of onset, maintain dose – If resolved in > 3 d from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment
Other Laboratory AEs	
Grade 3	• Delay dose until resolved to ≤ Grade 1 or baseline level: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment
Other Non-laboratory AEs	
Grade 3	• Delay dose until resolved to ≤ Grade 1 or baseline: – If resolved in ≤ 7 d from day of onset, maintain dose – If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	• Discontinue subject from study treatment

All dose modifications should be based on the worst preceding toxicity.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count;; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FVC = forced vital capacity; Hb = hemoglobin; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; QTc = corrected QT interval; SpO2 = peripheral oxygen saturation; ULN = upper limit of normal; WBC = white blood cell.

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.

Investigator's Choice:

Dose adjustments for investigator's choice medications should be made in accordance with the locally approved label for that medication. Changes in medication dosage, timing, etc will be documented in the eCRF. Investigator's choice medications can be interrupted for up to 28 d from the planned date of administration. If a subject requires a dose delay longer than 28 d (49 d 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

Trastuzumab deruxtecan and investigator's choice medication 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 study drug infusion (trastuzumab and trastuzumab deruxtecan) and amount of drug administered are to be recorded by clinical study personnel.

For lapatinib or capecitabine, treatment compliance will be reported by the subject or clinical study personnel.

5.6. Concomitant Medications (Drugs and Therapies)

Medications used from the time the subject signs the ICF to 40 d (+7 d) after the last administration of trastuzumab deruxtecan or control treatment will be recorded. Concomitant medications and therapies include all prescription, over-the-counter (OTC), 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 as per investigator's discretion and institutional guidelines.

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

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

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 HRT] is acceptable);
  - Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (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 PO) 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 local label for trastuzumab, lapatinib, or capecitabine 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 withdrawn from study treatment for the following reasons:

- PD per criteria set forth in RECIST version 1.1 (Section 17.4);
- Clinical progression (definitive clinical signs of PD), but a recent radiographic assessment did not meet the criteria for PD according to RECIST version 1.1;
- AE;
- Death;
- Pregnancy;
- Withdrawal of consent 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 withdrawn from study treatment should complete protocol-specified withdrawal procedures (Section 5.7.2) and follow-up procedures (Section 6.6). The investigator or sub-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 or sub-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 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 continue regular assessment of tumor response by investigator until disease progression. 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 below (Subject Withdrawal/Discontinuation from the Study) for definition of withdrawal by subject from the study (ie, withdrawal of consent).

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 or by any previously provided contact details
- 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 or sub-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 or sub-investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

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 due to 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 assessments (+7 d) and the 40-Day (+7 d) Follow-up assessments conducted after the last administration of study treatment (Section 6.5 and Section 6.6.1, respectively).

5.7.3. Subject Replacement

Randomized subjects will not be replaced.

5.7.4. 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).

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 is confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines[26] 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.
- Obtain adequate archived or recent tumor tissue sample for HER2 testing. Refer to 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 tissue is not available, collect 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 confirm HER2 status.
- Assign SID.

6.2. Screening

Obtain a signed and dated Main ICF before any study-related procedures or assessments are conducted.

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

- Unless required by local regulations or IRB/EC, an HIV antigen/antibody test is not required prior to randomization/enrollment.
- 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).
- 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.
- Additional slides for optional exploratory biomarker assessment are requested (see 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 study 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 RECIST version 1.1 (Section 17.4).

The following activities and/or assessments will be performed during the screening period **within 14 d before randomization** 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, previous cancer therapies (including prior radiation therapy) and oncology surgical history.
- Perform a complete physical examination (see Section 9.11) including weight and height.
- Assess functional status using the ECOG PS (Section 17.3).
- 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. ECGs will be taken in close succession while in a supine/semi-recumbent position (Section 9.10). ECG should be performed prior to blood draws.
  - 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)
  - Troponins (preferably high-sensitivity troponin-T); the test used to test troponin should remain the same throughout the course of a subject's time on study. In addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing.
  - Serum biomarkers (eg, HER2ECD [Section 8.3.2]; COVID-19 serology [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) 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 (trastuzumab deruxtecan versus investigator's choice, which has 2 available treatment paradigms).

Randomization will be stratified by hormone receptor status (positive, negative), prior treatment with pertuzumab (yes, no), and history of visceral disease (yes, no).

Investigators will choose 1 of the 2 control treatments for every subject before randomization.

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

6.4. Treatment Period

6.4.1. Cycle 1 to 4 and Subsequent Cycles

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 17.2 and further described below. Cycles for trastuzumab deruxtecan and investigator's choice are both 21 d in duration.

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

- The subject must complete the HEOR outcomes: EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or

procedures are done that day. Complete at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc).

- Perform 12-lead ECG at regular intervals and ECG, ECHO, or MUGA as clinically indicated.
- 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 Scale (Section 17.3)
- 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) and SpO2. 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
- For all female subjects of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test within 72 h 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, HEOR outcomes, and ECOG PS determination need not be repeated if they were performed within 3 d 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, Cycle 1 only, if the subject provides consent by signing the pharmacogenetics sample banking consent form. (This sample is not required for study participation.)
  - Serum biomarkers (eg, HER2ECD [Section 8.3.2] will be collected on Cycle 3 Day 1 and at EOT. After implementation of protocol version 8, serum biomarker samples will not be taken except at EOT.
  - COVID-19 serology [Section 17.8]) assessment will be collected on Cycle 3 Day 1. COVID-19 testing will be performed only on the serology samples from Cycle 5 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 17.8.

  - Only subjects randomized to trastuzumab deruxtecan:
    - PK assessment before dosing (within 8 h) on Day 1 of Cycles 1, 2, 3, 4, 6, and 8;
    - ADA at Cycles 1, 2, and 4, then every 4 cycles (Cycles 8, 12, 16, etc); EOT; and at the 40-day follow-up only for those subjects randomized to trastuzumab deruxtecan. After implementation of protocol version 8, ADA samples will not be taken except at EOT and 40-day follow-up.

- Obtain blood samples for exploratory biomarkers before treatment on Day 1 of Cycle 1 and every 3 cycles thereafter until protocol version 8 is approved and implemented. After approval and implementation of protocol version 8, collection of exploratory biomarkers will only occur at EOT.
- Record concomitant medications, AEs, and hospitalization-related records at every visit.

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

- Administer trastuzumab deruxtecan IV infusion approximately 90 min for the initial dose and, if no infusion related reaction after the initial dose, infuse subsequent doses over a minimum of 30 min.
  - Trastuzumab deruxtecan 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.
  - Trastuzumab deruxtecan arm only: during and following the first infusion (Cycle 1 Day 1), subjects will be observed for infusion related reaction until the PK collection time point, which is about 5 h (± 2 h) after the start of infusion of trastuzumab deruxtecan.
- Administration and monitoring of subjects randomized to the investigator's choice treatment should occur per the locally approved label. An ECG and blood samples for PK analyses are not required at the end of infusion (EOI)/treatment for investigator's choice treatment as part of this study protocol.
- Record start and stop times of any study treatment and amount of drug administered (trastuzumab and trastuzumab deruxtecan).
- Subjects randomized to investigator's choice treatments should be treated and monitored per the approved product label. Subjects randomized to trastuzumab/capecitabine will receive trastuzumab by IV once every 21 d (± 2 d) and capecitabine PO twice daily approximately 12 h apart on Days 1 through 14 of the 21 d (± 2 d) schedule. Subjects randomized to lapatinib/capecitabine will receive lapatinib PO daily on each day of a 21 d (± 2 d) schedule and capecitabine PO twice daily approximately 12 h apart on Days 1 through 14 of the 21 d (± 2 d) schedule."

- Obtain vital signs after each infusion of trastuzumab or trastuzumab deruxtecan (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Trastuzumab deruxtecan arm only: At Cycle 1, Day 1, perform ECG testing at 5 h after the start of drug administration (± 2 h).
  - If an abnormality is noted, perform triplicate ECG. ECGs will be taken in close succession while in a supine/semi-recumbent position. ECG should be performed prior to blood draws.
- Trastuzumab deruxtecan arm only: Collect blood samples for:
  - PK analysis samples on Day 1 of Cycles 1, 2, 3, 4, 6, and 8 should be collected as soon as possible after EOI and the actual time of sampling should be accurately recorded. In addition, for Cycle 1 Day 1 only, collect sample at 5 h after the start of drug administration (± 2 h).
- 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 5.2.

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

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2. 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 after Cycle 3

- The subject must complete the HEOR outcomes: EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day. Collect HEOR outcomes on Day 1 at Cycles 1, 2, and 3; thereafter, collect every 2 cycles (eg, Cycle 5, Cycle 7, Cycle 9, etc).

6.4.3. Every 6 Weeks (12 weeks upon approval of version 8 ±7 d)

- 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, until protocol version 8 is approved by the study site. After

approval and implementation of this protocol version, tumor assessments will be conducted every 12 weeks (±7 days), independent of treatment cycle. A CT and/or MRI (CT or MRI with ≤5 mm cuts) of the chest, abdomen, pelvis, and any other sites of disease 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 the 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 included with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.

Imaging results will be reviewed by an independent radiologic facility.

6.5. End of Treatment

The EOT is defined as the date the investigator decides to discontinue study treatment (+7 d). 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 d (±7 d) 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 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day.
- Perform a physical examination (Section 9.11), including weight.
- Assess functional status using the ECOG PS (Section 17.3).
- 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) and SpO2.
- Perform 12-lead ECG if clinically indicated.
- ECHO or MUGA (note: the same test at screening must be used for the subject at EOT).
- 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.
- Collect sample for ADA, only in subjects randomized to trastuzumab deruxtecan.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology;
  - Chemistry;

  - Serum biomarkers (eg, HER2ECD; Section 8.3.2, COVID-19 serology; Section 17.8);
  - Coagulation.
- Blood sample for exploratory biomarkers will be collected.
- Serum or urine sample for pregnancy testing in women of childbearing potential.
- 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 RECIST version 1.1 (Section 17.4). After approval and implementation of this protocol version, tumor assessments will be conducted every 12 weeks (±7 days), independent of treatment cycle. If the previous scan was within the last 12 wk (±7 d) 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, every attempt should be made to continue regular assessment of tumor response by the investigator until disease progression (see Section 5.7.1).
  - 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.
- An optional newly obtained tumor biopsy may be collected for those in the T-DXd group. See Section 8.3.3 for additional details.

6.6. Follow-up

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

Forty d (+7 d) 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 d (+7 d) after last treatment, then the EOT assessments can also function as the 40-Day (+7 d) Follow-up assessments.

- The subject must complete the HEOR outcomes: EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day.
- Perform a physical examination (Section 9.11), including weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Record concomitant medications, AEs, and hospitalization-related records.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology;
  - Chemistry;
  - Coagulation.

- Obtain blood samples for ADA, only for subjects randomized to trastuzumab deruxtecan.
- Serum or urine sample for pregnancy testing in women of childbearing potential.

6.6.2. Long-term/Survival Follow-up

After completion of the 40-Day (+7 d) Follow-up assessments, the Long-term/Survival Follow-up assessments will be performed every 3 mo (± 14 d), from the date of 40-Day (+7 d) 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 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day (only at the first 3 mo, which will be the last data collection point for these questionnaires);
- Record subsequent anticancer treatments, their outcomes, and survival;
- Further follow-up may be required for ongoing AEs (see Section 9.2).

If direct contacts are not possible due to 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.

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).

After the primary efficacy endpoint has been achieved, assessments by BICR (PFS, ORR, DoR, best overall response, best percent change in the sum of the diameter of measurable tumors, and CBR) will be discontinued. Subjects will continue with all other assessments as indicated in the Schedule of Events, including the assessment of tumor response and radiographic disease progression by investigators.

7.1.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is 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 or data cutoff date, whichever is earlier. Detailed censoring rules for OS will be specified in the SAP.

7.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be based on mRECIST version 1.1 (Section 17.4). Other secondary efficacy endpoints are:

- ORR, defined as the proportion of subjects who achieve a best overall response of CR or PR. Assessments based on BICR and based on investigator assessment will be analyzed. Confirmation of CR/PR is required for this study.
- 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. 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.
- PFS (based on investigator assessment), defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via investigator-assessed disease progression 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 secondary efficacy endpoints will be specified in the SAP.

7.1.4. Exploratory Efficacy Endpoints

- Time to response, 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.
- Best percent change in the sum of the diameter of measurable tumors, based on BICR.
- CBR, defined as the sum of CR rate, PR rate, and more than 6 mo SD rate based on BICR.
- 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; censoring date will be the last contact date in cases where there is no next-line therapy. In case a 2nd anticancer 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 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 wk. Progression-free survival has served as the basis of several recent approvals in the mBC setting including pertuzumab (CLEOPATRA study),[24] palbociclib (PALOMA studies),[28,29] ribociclib (MONALEESA-2),[30] and abemaciclib (MONARCH 2).[31] Sample size has been calculated to ensure the study is adequately powered to detect a clinically meaningful OS benefit.

Subjects with mBC 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 mBC 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 mBC 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.[32]

The index scores from the PROs will be used to show changes in overall health-related QoL 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 only from subjects randomized to trastuzumab deruxtecan 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 h) EOI[a] 5 h (± 2 h) after the start of drug administration
Cycles 2, 3, 4, 6, and 8	Day 1	BI (within 8 h) EOI[a]

BI = before infusion; EOI = end of infusion

[a] The sample should be collected as soon as possible after EOI and the actual time of sampling should be accurately recorded.

At each time point, blood will be collected for trastuzumab deruxtecan, 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 the central laboratory for PK samples will be provided in the Study Laboratory Manual.

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

8.2. Pharmacodynamic Assessment

Not applicable.

8.3. Biomarker Assessments

Samples for biomarker testing will be collected from all subjects at the time points specified in Table 17.2. In this study biomarker analyses will be used to investigate the effect of trastuzumab deruxtecan at the molecular and cellular level as well as to determine how changes in the markers may relate to 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 confirmation of HER2 status, if the subject agrees, additional slides for optional exploratory biomarker analysis are requested. 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 may be measured.

8.3.3. Optional Newly Obtained Tumor Tissue Biopsy

Additionally, an optional new tissue sample for exploratory biomarker analysis is requested after study treatment, if allowed by local laws and if consent is provided. This fresh biopsy sample can be obtained from subjects in the T-DXd group after the end of the study treatment, regardless of disease progression. Detailed instructions for the handling and shipping of tumor samples are included in the Study Laboratory Manual. It is recommended to obtain core needle biopsies. If a core needle biopsy is not feasible for safety reasons, a fine needle aspiration can be accepted. Bone biopsies will not be accepted for tissue samples.

8.3.4. 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 that may correlate with clinical benefit. Biosamples and data may be used to design or improve methods for analyzing development of diagnostic agents, characteristics of cancer, and research related to other diseases that may lead to new treatments. 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 y and further analyzed to address scientific questions related to trastuzumab deruxtecan and/or cancer.

8.3.5. 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 trastuzumab deruxtecan and at the time points specified in Table 17.2. A blood sample will be drawn at each time point. Serum concentrations of trastuzumab deruxtecan 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 analyzed by neutralizing antibody assay.

8.5. Pharmacogenetic Analysis

8.5.1. Pharmacogenetic Analysis

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

Pharmacogenetic samples may be analyzed for genes involved in the absorption, distribution, metabolism, elimination, and safety of trastuzumab deruxtecan. Additionally, samples may be analyzed for genes involved in trastuzumab deruxtecan-related signaling pathways or to examine diseases, physiologic processes, or safety related to trastuzumab deruxtecan, such as ILD. DNA samples will not be immortalized or sold to anyone. 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.

8.5.2. Banking of Specimens

If the subject agrees, the remaining samples (tumor, blood, or other specimen obtained in the study) may be stored for future research. The banked samples may be analyzed to design or improve methods for analyzing the development of diagnostic tests, for better understanding of the characteristics of cancer and, possibly, research-related other diseases that may lead to new treatments. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Additionally, banked samples from this study may be shared globally in the future by the Sponsor, Sponsor’s commercial partners, Sponsor’s authorized representatives, Sponsor’s research partners, and/or Sponsor’s collaborators or shared with third parties, including other commercial entities and drug companies.

8.5.2.1. Storage and Disposal of Specimens

If the subject agrees, banked samples will be stored for a maximum of 15 years, or longer if required per local regulations, after the finalization of the clinical study report for this protocol. During the storage period, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time, with written request to the investigator. However, the data will not be discarded if analysis has been completed before the subject withdraws consent.

8.5.2.2. Disclosure of the Results of Future Analysis

Because the nature and value of future analysis cannot be known at this time, any results obtained from research involving the banked samples will not be disclosed to the subject or investigators now or in the future.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoints

Safety endpoints will include SAEs, TEAEs, AESI, DAEs, physical examination findings (including ECOG PS), vital sign 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 d (+7 d) 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 d (+7 d) after last treatment will be recorded on the eCRF. Medical conditions (including 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 AESI are to be reported according to the procedures in Section 9.5.

All 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 sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study treatment 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 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 serious due to 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 preexisting 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/SAE. However, events associated with disease progression should be reported as an AE or an SAE. Death due to disease progression should be recorded on the Death eCRF.

Any AESI or SAE that occurs beyond 47 days after the last treatment (Safety Follow-up Period) that the investigator assesses as related to study treatment should be reported to the Sponsor (see Section 9.5).

9.3. Adverse Events of Special Interest

For the trastuzumab deruxtecan clinical program, based on the available pre-clinical data, review of the cumulative literature, reported toxicities for the same class of agents, and biological plausibility, ILD and LV dysfunction are considered to be AESIs.

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

Interstitial lung disease/pneumonitis is considered 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.[12]

9.3.1.2. Management Guidance

Interstitial lung disease/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD/pneumonitis 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 5.4.1.1).

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), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible, pulmonary function tests (including forced vital capacity [FVC] and carbon monoxide [CO] diffusing capacity) and pulse oximetry (SpO2), clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, and C-reactive protein), and one blood sample

collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed (eg, COVID-19 test).

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 5.2).

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 trastuzumab deruxtecan 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. These additional data collections will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for AEs reported for broad surveillance of ILD/pneumonitis based on a set of pre-defined preferred terms (PTs) eligible for adjudication as described in the Event Adjudication Site Manual. This list will be utilized for enhanced data collection.

9.3.2. Left Ventricular Dysfunction

9.3.2.1. Clinical Summary

LV dysfunction in association with trastuzumab deruxtecan 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.[12]

For broad surveillance of LV dysfunction, standard cardiac function testing (ECHO or MUGA scanning) should be performed to assess LVEF prior to initiation of T-DXd, as clinically indicated, and at EOT. Perform ECHO or MUGA if clinically indicated; if abnormal, follow institutional guidelines. 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.

9.3.2.2. Management Guidance

If clinically indicated, LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function. Troponin will be measured at Screening and as needed based on subject-reported cardiac signs and symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If ECG is abnormal, follow institutional guidelines. ECGs will be performed if clinically indicated, 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 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 Council on Harmonisation [ICH] E2A Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).[33]

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which 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 which 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).[33]

Medical and scientific judgment should be exercised in deciding whether 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 hospitalization for preexisting conditions that do not worsen in severity are not SAEs.
- Any AESI or SAE that occurs beyond 47 days after the last treatment (Safety Follow-up Period) that the investigator assesses as related to study treatment should be reported to the Sponsor (see Section 9.5).

9.4.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE version 5.0:

- 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 versus 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, 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 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 treatment 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 treatment 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 treatment 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 treatment 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 treatments

- Dose Not Changed
  - No change in study treatment dosage was made.
- Drug Withdrawn
  - The study treatment was permanently stopped.
- Dose Reduced
  - The dosage of study treatment was reduced.
- Drug Interrupted
  - The study treatment was temporarily stopped.
- Not Applicable
  - Subject died, study treatment had been permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of study treatment.

9.4.6. Other Action Taken for Event

- None
  - No treatment was required.
- Medication required
  - Prescription and/or OTC 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.
- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- 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 Reporting-Procedure for Investigators

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

Additional relevant information regarding the AESIs ILD/pneumonitis and LV dysfunction for the trastuzumab deruxtecan clinical program, regardless of seriousness, is to be collected through the targeted questionnaires built within the clinical study database.

For broad surveillance of LV dysfunction, 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 the trastuzumab deruxtecan arm, all targeted questionnaires are to be completed. For the comparator arm, only the ILD/pneumonitis targeted questionnaire is to be completed.

For broad surveillance of ILD/pneumonitis, a set of pre-defined list of PTs eligible for adjudication, as described in the Event Adjudication Site Manual, is utilized for enhanced data collection.

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 h of awareness:

- SAEs (see Section 9.4.2 for definition).
- All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) which meet the potential Hy’s Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated total bilirubin ≥2 × ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdose will be reported via Serious Adverse Event Report (SAVER)/overdose form or eCRF. 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 to be 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 trastuzumab deruxtecan dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the eCRF within the EDC.

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study treatment. 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 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 fatal/life-threatening cases, must be followed up and addressed promptly. The investigator will submit any important and updated SAE data, as noted above, to the Sponsor 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 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/Ethics Committee

Daiichi Sankyo and/or CRO will inform investigators, IRBs/ECs, and Regulatory Authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study sites or other studies of the study treatments, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study treatment, 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 ECs and Regulatory Authorities.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject or their female partner who becomes pregnant while receiving or within 7 mo of discontinuing the study treatment. For investigator's choice drugs, study sites should follow local or institutional guidelines.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the investigator should inform the Sponsor

within 24 hours of learning of the pregnancy. 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, including normal delivery and induced abortion. An adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. The investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous 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, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
2. Blood chemistry tests
    - Total protein, albumin, alkaline phosphatase, ALT, AST, TBL, blood urea nitrogen (BUN)/urea, calcium, chloride, serum creatinine, lactate dehydrogenase (LDH), magnesium, potassium, sodium.
    - A coagulation test will be performed (prothrombin time and either partial thromboplastin or activated partial thromboplastin time).
    - Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.2).
    - Troponin will be analyzed for each sample at Screening and as needed based on subject-reported signs or symptoms.
3. Urinalysis
    - Protein, glucose, blood, microscopy assessment (if indicated), and specific gravity.

In addition, the following parameters will be analyzed at the visits indicated in the Schedule of Events, Table 17.1 and Table 17.2.

- Pregnancy test (serum or urine) for all female subjects of childbearing potential must be performed during the Screening period, within 72 h prior to the beginning of dosing on Day 1 of each cycle, EOT, and at the 40-Day Follow-up assessments. 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

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

9.10. Electrocardiograms

Electrocardiograms will be taken in triplicate at Screening and if clinically indicated while on treatment. Singular ECGs will also be conducted at regular intervals during the study (see Table 17.2). If an abnormality is noted, follow institutional guidelines. Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by the 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). LV will be measured.

9.12.2. Pulmonary Assessments

The SpO2 will be measured at Screening, BI and EOI on Day 1 of each cycle, Days 8 and 15 of Cycle 1, EOT, and the 40-Day (+7 d) Follow-up assessments. For more details, please refer to Section 6 of the protocol.

An ILD AC will review all cases of (potential) ILD 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 EORTC 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 EORTC 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.

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 at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc) and at the EOT assessment. Data collection will continue at the 40-Day (+7 d) Follow-up assessments and the first Long-term/Survival Follow-up assessments 3 mo later, which will be the last data collection point for both questionnaires. Reporting will follow closely the Consolidated Standards of Reporting Trials (CONSORT) extension on reporting PROs.[34]

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 EORTC QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores and a decrease of 10 points or more for functional scale and global health status/QoL.[36]

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 (Section 17.7), a generic measure of standardized health status, before any other study procedures are performed at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc), and at the EOT assessments. Data collection will continue at the 40-Day (+7 d) Follow-up assessments and the first Long-term/Survival Follow-up assessments 3 mo later, which will be the last data collection point for both questionnaires.

The EQ-5D-5L is self-administered and consists of 2 parts, the EQ-5D-5L descriptive system, and the EQ 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: no problems, slight problems, moderate problems, severe problems, and extreme problems.[35] 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 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.

Reporting will follow closely the CONSORT extension on reporting PROs.[34]

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 for the health-related QoL 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 EORTC QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores and a decrease of 10 points or more for functional scale and global health status/QoL.[36]

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 UK value set
- Index score by disease state

10.3. Pharmacoeconomic Assessments

10.3.1. Hospitalization-Related Endpoints

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 analysis for PFS will be performed when approximately 372 BICR-assessed PFS events are observed or 18 months from the last subject randomized, whichever comes first.

Summary statistics will be presented by cohort/treatment group. 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.

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 Full Analysis Set (FAS). Some efficacy analyses such as PFS analysis will also be performed on the 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 FAS.

11.2. Analysis Sets

11.2.1. Full Analysis Set

The FAS will include all subjects randomized into the study. The FAS will be the primary analysis set for all efficacy analysis. Following the intent-to-treat principle, subjects will be analyzed according to the treatments and strata they were 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 from the FAS without any of the SAP-specified major protocol deviations and who received at least one dose of study treatment. Additional details will be specified in the SAP.

11.2.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects in the FAS who received at least 1 dose of trastuzumab deruxtecan and had any measurable post-dose serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a.

11.3. Study Population Data

Subject disposition will be summarized for subjects in the 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 FAS, and some baseline characteristics will also be summarized for PPS and Safety Analysis Set. Study treatment exposure and treatment duration will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

The primary efficacy endpoint, PFS, and the key secondary efficacy endpoint, OS, will be tested hierarchically to maintain an overall type I error rate of 0.05 (2-sided) or less.

11.4.1.1. Primary Efficacy Analyses

The primary efficacy analyses will be performed based on data from the FAS. The primary efficacy endpoint is PFS based on BICR.

PFS based on BICR will be compared between the treatment groups using stratified log-rank tests stratified by stratification factors per IXRS.

PFS will be tested for statistical significance at an overall 2-sided alpha of 0.05.

Kaplan-Meier estimates and survival curves will also be presented for each treatment group. The median survival time and 2-sided 95% CI for the median using Brookmeyer and Crowley methods will be provided for each treatment group. In addition, Kaplan-Meier estimates at fixed time points (eg, 3, 6, 9, 12 mo) along with their 2-sided 95% Cis will be provided for each treatment group. The hazard ratios (HRs) and their 2-sided 95% Cis will be estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors per IXRS.

11.4.1.2. Secondary Efficacy Analyses

The key secondary efficacy endpoint is OS, and other secondary efficacy endpoints include ORR based on BICR and investigator assessment, DoR based on BICR, and PFS based on investigator assessment. DoR will be measured for responding subjects (CR or PR) only.

Progression-free survival based on investigator assessment will be analyzed in the same manner as the analysis of PFS based on BICR. Detailed censoring rules for PFS based on investigator assessment will be specified in the SAP.

If the test of the primary endpoint, PFS based on BICR, is statistically significant, the key secondary endpoint, OS, will be tested.

Group sequential testing with 2 OS interim analyses are planned. The first OS interim analysis is planned at time of the PFS analysis, and the second OS interim analysis will be performed when approximately 304 OS events have been observed (70% of the planned 434 OS events).

Approximately 240 and 304 of the targeted 434 OS events will be documented (55% and 70% information fractions) by time of the first and second OS interim analyses, respectively. The

second OS interim analysis will occur after all subjects have been randomized. The final OS analysis will occur after approximately 434 OS events have been documented.

The OS interim analysis will allow the study to stop early for outstanding efficacy. Futility assessments will not be made at these interim analyses. Additional details of the interim analyses can be found in Section 11.5.

Overall survival will be compared between the 2 treatment groups, using stratified log-rank test stratified by stratification factors per IXRS. 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 group. In addition, Kaplan-Meier estimates at fixed time points along with their 2-sided 95% Cis will be provided for each treatment group. The HR and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by the stratification factors per IXRS.

Cochran-Mantel-Haenszel tests stratified by stratification factors per IXRS will be used to compare ORR (based on BICR and investigator assessment) between the treatment groups. ORR (based on BICR and investigator assessment) will be summarized by treatment group along with the 2-sided 95% Cis using Clopper-Pearson methods. In addition, ORR (based on BICR and investigator assessment) until fixed time points (eg, 3, 6, 9, 12 mo) along with the 2-sided 95% Cis will be provided by treatment group.

Duration of response (based on BICR) will be summarized with median DoR and its 2-sided 95% CI for the median using Brookmeyer and Crowley method for each treatment group. Detailed censoring rules for DoR will be specified in the SAP.

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 2-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (eg, 3, 6, 9, 12 months) and the 2-sided 95% Cis will be provided for each treatment group. The treatment effect HR and its 2-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 2 treatment groups will be compared at a 2-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.

11.4.1.3. Exploratory Efficacy Analyses

11.4.1.3.1. Subgroup Analyses

Subgroup analyses for PFS (based on BICR), OS, ORR (based on BICR), DoR (based on BICR), and CBR (based on BICR) will be performed for the FAS if the primary analysis is statistically significant. Subgroups will include:

- Hormone receptor status (positive, negative)
- ERs (positive, negative)
- Lines of prior systemic therapy not including hormone therapy (<3, ≥3)

- Prior treatment with pertuzumab (yes, no)
- Lines of therapy prior to pertuzumab treatment (<3 line, ≥3 line)
- Lines of therapy prior to T-DM1 treatment (<3 line, ≥3 line)
- 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)
- Best response to T-DM1 therapy (CR/PR/SD, PD)
- Clinically inactive CNS metastases (CNS metastases, no CNS metastases)
- Age (<65, ≥65 y)
- Race (Asian, Rest of World)
- Region (Asia, North American, Europe, RoW)
- ECOG PS (0, 1)

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 unstratified analysis and 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 and p-value will not be presented. Subgroup analyses of PFS will be performed only if at least 10 PFS events in each subgroup.

11.4.1.3.2. Analyses of Exploratory Efficacy Endpoints

Time to response based on BICR, best percent change in the sum of the diameter of measurable tumors based on BICR, CBR based on BICR, and PFS2 based on investigator assessment will be evaluated and considered as exploratory efficacy endpoints.

Descriptive statistics for percent change from baseline to the best (minimum) post-baseline sum of the diameter (based on BICR) and for time to response (based on BICR) will be provided by treatment group. A waterfall plot of the best percent change (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.

CBR (based on BICR) will be summarized by treatment group along with 2-sided 95% Cis using Clopper-Pearson method.

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 HR 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.

11.4.2. 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 group: 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, could be provided in the SAP. Some descriptive analysis will be performed as follows.

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

11.4.2.2. 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 and a decrease of 10 points or more for functional scale and global health status/QoL. The survival distributions will be estimated by Kaplan-Meier method and results will be presented graphically for each treatment. The median time to definitive deterioration and the proportion of subjects without definitive deterioration at specific time points will be reported along with the 2-sided 95% Cis for the medians. The treatment effect HR of time to definitive deterioration and its 95% Cis will be estimated using a stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

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

11.4.2.3. 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.

11.4.3. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

11.4.3.1. Pharmacokinetic Analyses

Descriptive statistics will be provided for all serum concentration data (trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a) at each time point. Descriptive statistics by region/country may also be provided for all serum concentration data at each time point.

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

11.4.3.2. Pharmacodynamic Analyses

Not applicable

11.4.3.3. Biomarker Analyses

Samples collected for biomarker analyses, such as tissue and blood, may be used for exploratory biomarker assessments. Biomarker data may be summarized by treatment group using descriptive statistics.

11.4.4. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set for each cohort 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.

11.4.4.1. 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 (SOC), PT, relationship to the study treatment, and the worst CTCAE grade. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by treatment group, 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, SOC, 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 group for the subgroups described in the SAP.

11.4.4.2. Clinical Laboratory Evaluation Analyses

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.

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 deemed of clinical significance or of Grade 3 or 4 will be listed.

11.4.4.3. Vital Sign Analyses

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

11.4.4.4. Electrocardiogram Analyses

Descriptive statistics will be provided by treatment group 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 ECG interval values meeting the criteria will be tabulated (eg, QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms). The QT intervals will be corrected for heart rate by Fridericia's formula (QTcF; $QTcF = QT/[RR]^{1/3}$). ECG data will also be listed.

11.4.4.5. Physical Examination Analyses

Physical examination findings will be listed.

11.4.4.6. Concomitant Medication Analyses

Concomitant medications will be coded using the World Health Organization drug dictionary. Number and percentage of subjects taking concomitant medications will be summarized. Concomitant medications will also be listed.

11.4.4.7. Immunogenicity (Anti-Drug Antibody) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. A summary table by scheduled visit will be provided for incidence of ADA. The raw values for ADA titers for ADA positive subjects will be listed and summarized using descriptive statistics by scheduled visit.

The number and percentage of the treatment-emerging ADA incidence will be calculated. Treatment-emergent ADA positive subject will be defined as subjects who are ADA negative at baseline and become ADA positive post-treatment, or 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 post-treatment. The number and percentage of subjects positive for neutralizing anti-drug antibody (NAB) of trastuzumab

deruxtecan, if analyzed, will also be determined. A listing of all ADA/NAB assessments will be provided. Further details will be provided in the SAP.

11.4.4.8. Other Safety Analyses

All other safety endpoints (eg, physical examination findings including ECOG PS and ECHO/MUGA) will be listed.

11.5. Interim Analyses

There is no planned interim analysis of the primary endpoint PFS. The primary PFS analysis will be performed when approximately 372 PFS events are observed or 18 months from the last subject randomized, whichever comes first.

Overall survival endpoint will be tested only if the test of the primary efficacy endpoint PFS is statistically significant. Group sequential testing with 2 OS interim analyses are planned. The first OS interim analysis is planned at the time of the PFS analysis (approximately 240 OS events are anticipated), and the second OS interim analysis is planned when approximately 304 OS events (70% information fraction) have been observed.

The OS interim analysis will allow the study to stop early for outstanding efficacy. Futility assessments will not be made at these interim analyses.

A group sequential design utilizing 3-look Lan DeMets implementation of O'Brien-Fleming alpha spending function will be used to construct the efficacy stopping boundaries (significance levels) with an overall 2-sided type I error 0.05.[37]

If the interim and final analyses are carried out with exactly 240, 304, and 434 OS events respectively, the efficacy boundaries expressed in 2-sided p-value scale (HR scale) at the interim and final analyses are presented in Table 11.1 below. The efficacy boundaries will be recalculated based on the actual number of observed events using the pre-specified alpha spending function if different from the specified number below.

The final OS analysis will occur after approximately 434 OS events have been documented.

See Table 11.1 for stopping boundaries for OS.

Table 11.1: Efficacy Stopping Boundaries for OS

Endpoint	**Median OS: 20 m for the T-DXd Arm, 15 m for the Investigator's Choice Arm; HR = 0.75**			
OS	**Number of OS Events**	**IF (%)**	**Boundary**	
			2-sided p-value	**HR**
1st IA	240	55%	0.0052	0.682
2nd IA	304	70%	0.0132	0.740
Final	434	100%	0.0452	0.816

IA = interim analysis; HR = hazard ratio; IF = information fraction; OS = overall survival.

11.6. Sample Size Determination

This is a prospectively randomized open-label study comparing the primary endpoint of PFS and the key secondary endpoint of OS between the 2 treatment groups, trastuzumab deruxtecan and investigator's choice, with a randomization ratio of 2:1.

The hypothesized median PFS in the trastuzumab deruxtecan arm and the control arm were 4.7 and 3.3 months (HR=0.7), respectively. If the true hazard ratio is 0.7 (under alternative hypothesis), a total of 372 PFS events are required to have 90% power at a 2-sided overall 5% level of significance to reject the null hypothesis (HR=1) using a log-rank test. PFS analysis will be performed when approximately 372 PFS events are observed or 18 months from the last subject randomized, whichever comes first.

OS will be compared between the 2 treatment groups, provided that the test of the primary endpoint PFS is statistically significant. Based on available data from the TH3RESA study, the median OS in the investigator's choice arm is expected to be 15 months.[7] It is hypothesized that treatment with trastuzumab deruxtecan will result in a 25% reduction in the hazard rate of death (corresponding to an increase in median OS from 15 to 20 months under the exponential model assumption). If the true HR is 0.75 (under alternative hypothesis), a total of 434 OS events are needed to have 80% power at an overall 2-sided overall 5% level of significance to reject the null hypotheses (HR=1) using a log-rank test and a 3-look group sequential design. For details of the planned OS analyses, see Section 11.5.

Approximately 600 subjects will be randomized (400 subjects to trastuzumab deruxtecan and 200 subjects to investigator's choice) in 30 months.

The sample size computation is performed using EAST v6.4.

11.7. Statistical Analysis Process

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 treatment exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized before half enrollment.

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

The investigator/investigational site will permit study-related monitoring, audits, IRB/EC 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 Practices (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 will be 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 shall 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 labs 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 treatment, regulatory documents (eg, protocol and amendments, IRB/EC 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/EC and the Sponsor.
- Records related to the study treatment(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 y after the last approval of a marketing authorization in an ICH region and until there are no pending or contemplated marketing authorizations in an ICH region or at least 2 y 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 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 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 shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION, PUBLIC DISCLOSURE POLICY, AND DATA SHARING

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, EU, 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.

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.

The data from this study may be shared with or used by third parties, including commercial partners.

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:

- Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 Apr 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC and/or
- 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.

For EU study sites, the Sponsor will observe the rules laid down in the General Data Protection Regulation 2016/679/EU on the protection of individuals with regard to the processing of personal data and the free movement of such data.

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/EC 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 EC/IRB 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 EC 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 EC or IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the EC 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 which 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 that the investigator becomes aware of.

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 treatment, data should be collected for safety purposes.

If applicable, the investigator should notify the IRB/EC 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, IRBs/ECs, 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 the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/EC. 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/EC 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 wellbeing of subjects who will be participating in this study by monitoring the progress and results. The DMC will comprise qualified physicians and scientists who are not investigators in the study and not otherwise directly associated with the Sponsor.

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

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

15.10. Address List

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

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17. APPENDICES

17.1. Schedule of Events

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

Visit/Cycle	Tissue Screening	Screening	
Window (Day)		**-28 to -1**	**-14 to -1**
Procedures			
Tissue Screening Informed Consent[a]	X		
Tumor Sample for HER2 Status	X[b]		
Main Informed Consent[a]		X	
Optional Biomarker		X[c]	
Eligibility Assessment			X
Demographics			X
Medical and Surgical History (including target disease)			X
Physical Examination			X
Weight			X
Height			X
ECOG PS			X
Adverse Events	X[d]		X[e]
Concomitant Medications			X[e]
Hospitalization-related Records			X[e]
Vital Signs			X
SpO2			X
12-lead ECG in Triplicate[f]			X
ECHO or MUGA (LVEF)[g]		X	
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease)		X	
CT/MRI of the Brain		X	
Ophthalmologic Assessments[h]		X	

Visit/Cycle	Tissue Screening	Screening	
Window (Day)		**-28 to -1**	**-14 to -1**
Hematology, Coagulation, Chemistry			X
Urinalysis[i]			X
Troponin[j]			X
Serum Biomarkers (eg, HER2ECD, COVID-19 serology) Sample			X
HIV Antibody Test (as required by local regulations or IRBs/ECs)		X	
Hepatitis B/C Serology		X	
Pregnancy Test (urine or serum)[k]			X
Assign SID	X		
Randomization			X
Declaration of Investigator's Choice Paradigm			X

COVID-19 = coronavirus disease 2019; CT = computed tomography; d = days; 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; ICF = informed consent form; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); SAE = serious adverse event; SID = subject identification; 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 before initiating all other screening assessments.

[b] Archived tissue appropriate for central laboratory HER2 testing. If archived tissue is not available, fresh biopsy is required.

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

[d] For subjects who sign only the Tissue Screening Informed Consent Form, report only SAEs directly related to tissue screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other adverse events is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

[e] Collected after the Main ICF is signed.

[f] ECG will be taken in triplicate at Screening.

[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.

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

[i] Urinalysis test to be performed at baseline and as clinically indicated.

[j] In addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing.

[k] For female subjects of childbearing potential. 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.

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

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Q6W	EOT[a]	Follow-up	
Study Day	1		8	15	1 ± 2		1 ±2		1 ± 2				40-day[b]	LT/S[c]
Window (Day)	BI[d]	EOI[e]	± 1	± 1	BI	EOI	BI	EOI	BI	EOI	±7		+7	± 14
Procedures														
HEOR outcomes: EORTC QLQ-C30 & EORTC QLQ-BR45, EQ-5D-5L[f]	X[h]				X[h]		X[h]		X[h]			X	X	X[g]
Physical Examination	X[h]				X[h]		X[h]		X[h]			X	X	
Weight[i]	X[h]				X[h]		X[h]		X[h]			X	X	
ECOG PS	X[h]				X[h]		X[h]		X[h]			X	X	
Adverse Events	←												→	
Concomitant Medications	←												→	
Hospitalization-related records	←												→	
Vital Signs	X[h]	X	X	X	X[h]	X	X[h]	X	X[h]	X		X	X	
SpO2	X[h]	X	X	X	X[h]	X	X[h]	X	X[h]	X		X	X	
12-lead ECG[j]	X[h]	X			X[h]		X[h]							
ECHO or MUGA (LVEF)[j]												X		
Pregnancy Test (urine or serum)[k]	X[h]				X[h]		X[h]		X[h]			X	X	
Hematology, Chemistry	X[h]		X	X	X[h]		X[h]		X[h]			X	X	
Coagulation[l]												X	X	

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

Visit/Cycle	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and Subsequent Cycles		Q6W	EOT[a]	Follow-up	
Study Day	**1**		**8**	**15**	**1 ± 2**		**1 ±2**		**1 ± 2**				**40-day[b]**	**LT/S[c]**
Window (Day)	**BI[d]**	**EOI[e]**	**± 1**	**± 1**	**BI**	**EOI**	**BI**	**EOI**	**BI**	**EOI**	**±7**		**+7**	**± 14**
PK Blood (Serum) Sample	X[m]	X[n,o]			X[m]	X[n]	X[m]	X[n]	X[m]	X[n]				
ADA Blood Sample	X[p]				X[p]				X[p]			X[p]	X[p]	
Serum biomarkers (eg, HER2ECD, COVID-19 serology) Sample							X[q]					X		
Exploratory Biomarker Blood Samples[r]	X[r]								X[r]			X[r]		
Pharmacogenetics Blood Sample	X[s]													
Administer Study Treatment as appropriate[t]	X				X		X		X					
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease)[u]											X[v,w]	X[v,w]		
CT/MRI of the Brain[x]											X[w]	X[w]		
Newly obtained tumor tissue sample												X[y]		
Survival Follow-up														X

ADA = anti-drug antibody; BI = before infusion/dosing; BICR = blinded independent central review; CO = carbon monoxide; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; d = days; ECG = electrocardiogram; ECHO = echocardiogram; 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; FVC = forced vital capacity; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; HCQ = hydroxychloroquine; LT/S = Long-term/Survival; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PK = pharmacokinetic; Q6W = every 6 wk; SpO2 = peripheral oxygen saturation.

[a] All assessments required as part of EOT must occur within 7 days from the date the investigator decides to discontinue study treatment. If the EOT assessments have been performed within 30 d (±7 d) of subject's last treatment, there is no need to repeat them.

[b] 40 d (+7 d) after the last study treatment administration or before starting new anticancer treatment, whichever comes first. If EOT assessments occur > 40 d (+7 d) after last treatment, then the EOT assessments can also function as the 40-Day (+7 d) Follow-up assessments.

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

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

[e] EOI assessments are not required for subjects on lapatinib/capecitabine.

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

[g] Performed only 3 mo after the 40-Day (+7 d) Follow-up.

[h] Within 3 d BI.
[i] Body surface area should be calculated for subjects treated with capecitabine.
[j] At Cycle 1 Day 1 for trastuzumab deruxtecan subjects only, record ECG 5 hr (± 2 h) after start of drug administration. Perform ECG at regular intervals and ECG, ECHO, or MUGA if clinically indicated; if abnormal, follow institutional guidelines.
[k] For female subjects of childbearing potential. During treatment, a positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative result within 72 hours prior to drug administration.
[l] Coagulation tests to be performed at EOT, at 40-Day (+7 d) Follow-up, and as clinically indicated.
[m] PK samples should be obtained within 8 h BI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8 for trastuzumab deruxtecan subjects only. ECGs should be performed before PK blood draws.
[n] The sample should be collected as soon as possible after EOI and the actual time of sampling should be accurately recorded on Day 1 of Cycles 1, 2, 3, 4, 6 and 8, for trastuzumab deruxtecan subjects only.
[o] 5 h (± 2 h) after the start of drug administration, for trastuzumab deruxtecan subjects only.
[p] Obtained at Cycles 1, 2, and 4 then every 4 cycles; EOT; and at the 40-day follow-up only for subjects randomized to trastuzumab deruxtecan. After implementation of protocol version 8, ADA samples during treatment will not be taken except at EOT and 40-day follow-up.
[q] Before administration at Cycle 3 Day 1for non-COVID-19 biomarkers. . After implementation of protocol version 8, these samples will not be taken except at EOT.
[r] Collected at Cycle 1 and every 3 cycles until protocol version 8 is approved. After approval and implementation of this protocol version , collection of these samples will only occur at EOT.
[s] Participation is optional for all subjects.
[t] Trastuzumab deruxtecan should only be initiated by a physician or healthcare professional experienced in the administration of cytotoxic chemotherapy. For trastuzumab deruxtecan only. During and following the first infusion (Cycle 1 Day 1), subjects will be observed for infusion related reaction until the PK collection time point, which is about 5 h (± 2 h) after the start of infusion of trastuzumab deruxtecan. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use. Treatment administration and monitoring of subjects randomized to the investigator's choice treatment should occur per the locally approved label.
[u] CT/MRI should be used unless another modality of disease assessment is necessary for the lesions. If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to continue regular assessment of tumor response by investigator until disease progression. See Section 5.7.1.
[v] This assessment frequency will be conducted every 6 weeks (±7 days) from randomization, until protocol version 8 is approved by the study site. After approval and implementation of this protocol version, tumor assessments will be conducted every 12 weeks (±7 days), independent of treatment cycle.
[w] After the primary efficacy endpoint has been achieved, the assessment of the scans by BICR is no longer required.
[x] CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. After protocol version 8 is approved and implemented, CT/MRI scans will occur every 12 weeks. Additional brain scans for all other subjects can be done if clinically indicated.
[y] At the end of the study treatment, an optional newly obtained tumor tissue biopsy may be collected for those in the T-DXd group.

Note: After study closure end date, subjects still benefiting from the study drug may be offered the opportunity to transition to a separate study to continue receiving trastuzumab deruxtecan, depending on country regulation.

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

Evaluations should include the following:

- High resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO2)
- Clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential white blood cell count, and C-reactive protein)
- One blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed (eg, COVID-19 test)

17.2. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; 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 (SI) – serum creatinine in µmol/L:

Male:

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

Female:

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

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

17.3. Eastern Cooperative Oncology Group Performance Status

Table 17.3: Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	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;5:649-55

17.4. Response Evaluation Criteria in Solid Tumors, Version 1.1

17.4.1. Measurability of Tumor at Baseline

17.4.1.1. Definitions

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

17.4.1.1.1. 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 CT/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 (ie, Screening for this study) and in follow-up (ie, all on-study measurements), only the short axis will be followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.4.1.1.2. 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 exam that is not measurable by reproducible imaging techniques.

17.4.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.4.1.1.3.1. Bone Lesions

- Bone scan, positron emission tomography (PET) 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.

17.4.1.1.3.2. 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 noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.4.1.1.3.3. 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.

17.4.1.2. Specifications by Methods of Measurements

17.4.1.2.1. 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 28 d before randomization

17.4.1.2.2. 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 performed 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. MRI is also acceptable in certain situations (eg, for body scans).

17.4.2. Tumor Response Evaluation

17.4.2.1. 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.

17.4.2.2. Baseline Documentation of "Target" and "Non-target" Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to 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 which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which 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 which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Up to 2 nodal target lesions can be recorded. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded.

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

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

17.4.2.3. Response Criteria

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

17.4.2.3.1. 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 1 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 diameters while on study).

17.4.2.3.2. 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 which 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 likely 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 retroperitoneum; 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."

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

Progressive disease (PD): Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of 1 or more new lesions is also considered progression).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s).

17.4.2.3.4. 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.

17.4.2.3.5. 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 preexisting 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 brain ordered which 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.

17.4.2.4. 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.

Confirmation of CR/PR is required for this study.

17.4.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.4 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, see Table 17.4.

Table 17.4: 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

Target Lesions	Non-target Lesions	New Lesions	Time Point Response[a]
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 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.

[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.

17.4.2.4.2. Missing Assessments and Non-evaluable Designation

When no imaging/measurement is performed 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.

17.4.2.4.3. Best Overall Response: All Time Points

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

17.4.2.4.4. 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 may 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.

17.4.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 wk (±7 d) while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up. This assessment frequency will be conducted every 6 weeks (±7 days) from randomization, until protocol version 8 is approved by the study site. After approval and implementation of this protocol version, tumor assessments will be conducted every 12 weeks (±7 days), independent of treatment cycle. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 28 d 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.

17.5. New York Heart Association Functional Classification

Table 17.5: 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. O**bjective evidence of severe cardiovascular disease.

Source: American Heart Association, Inc. 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

17.6. 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)

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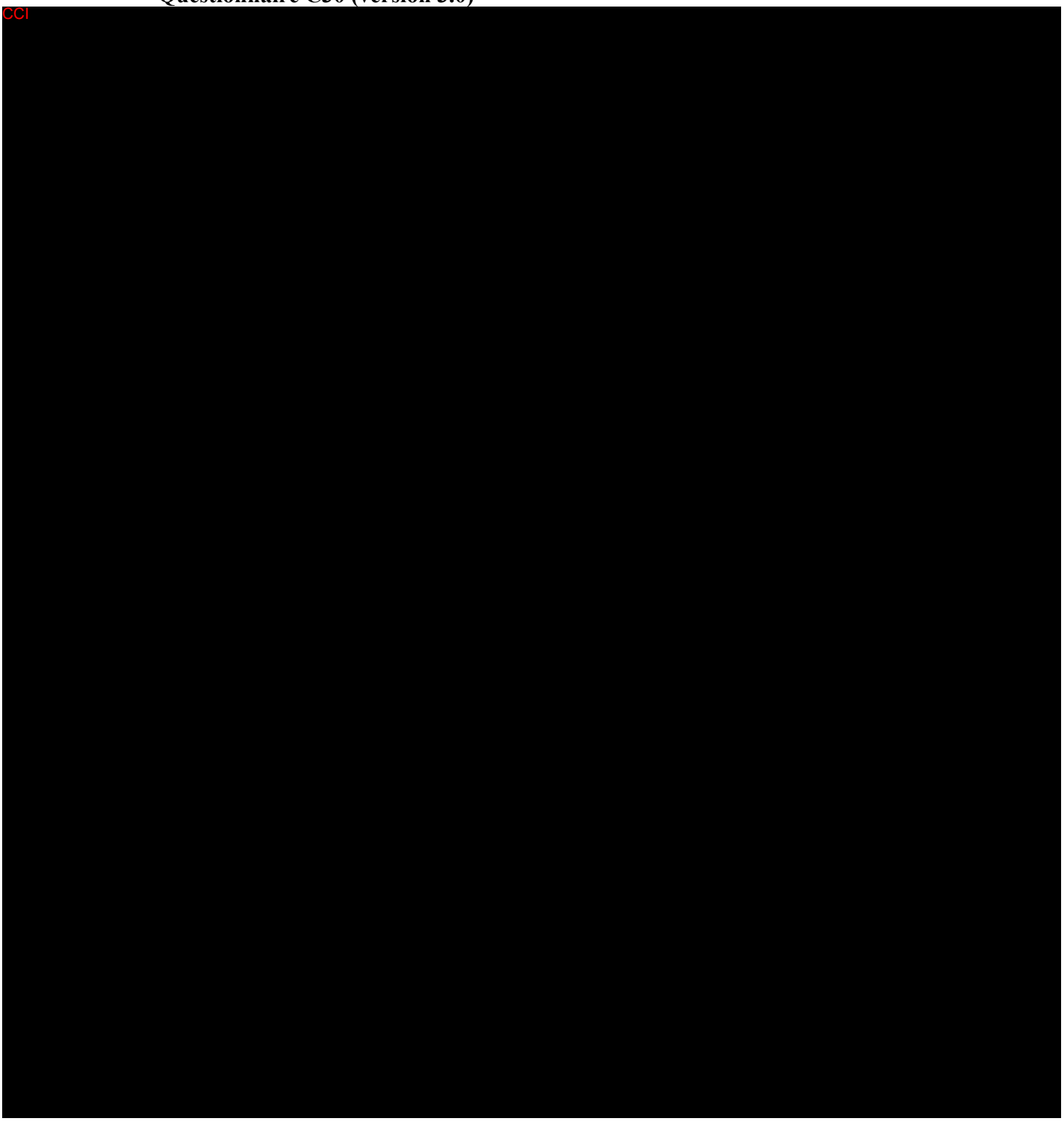

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17.6.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire BR45

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17.7. EuroQoL Five Dimensions Five Levels

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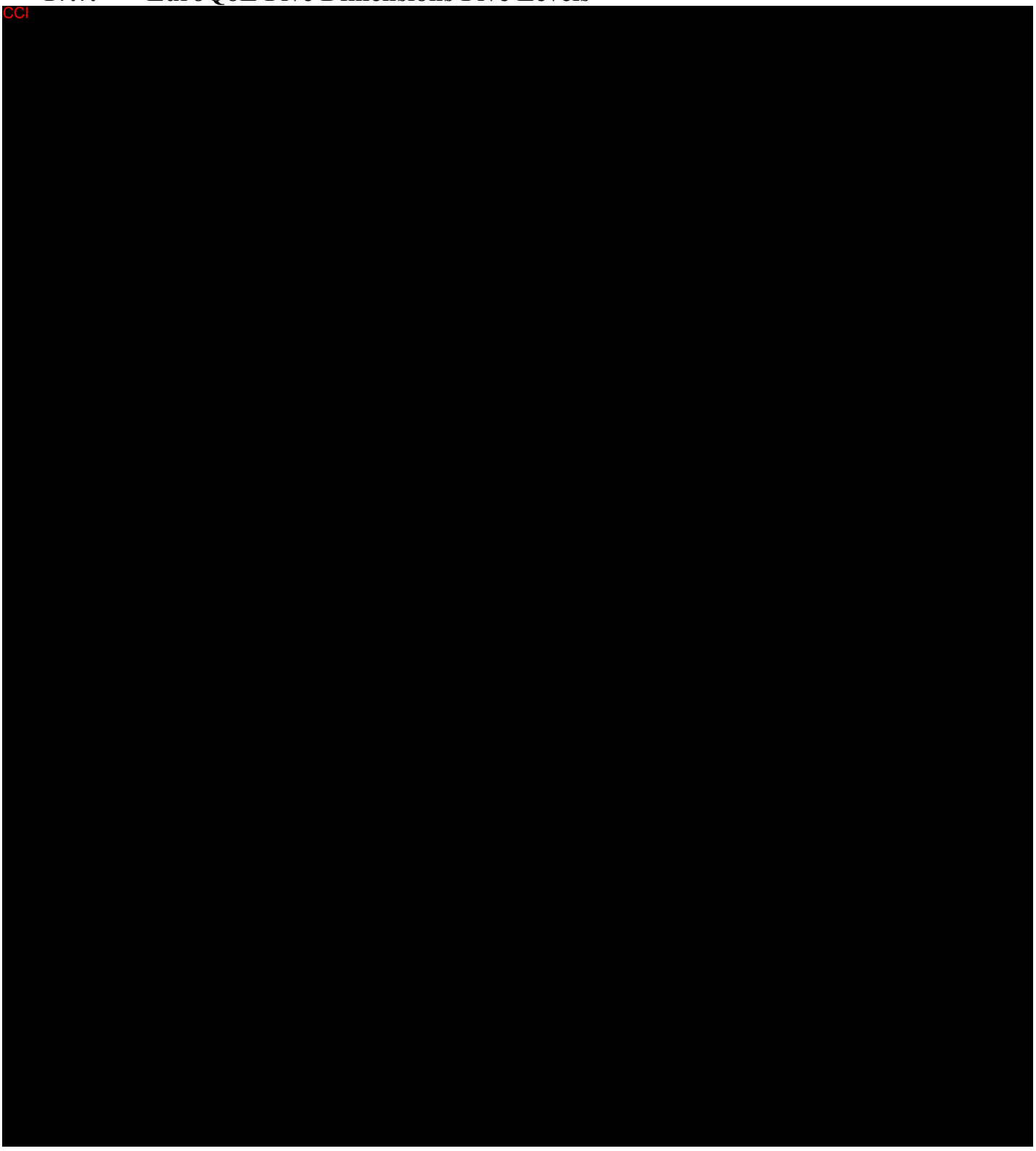

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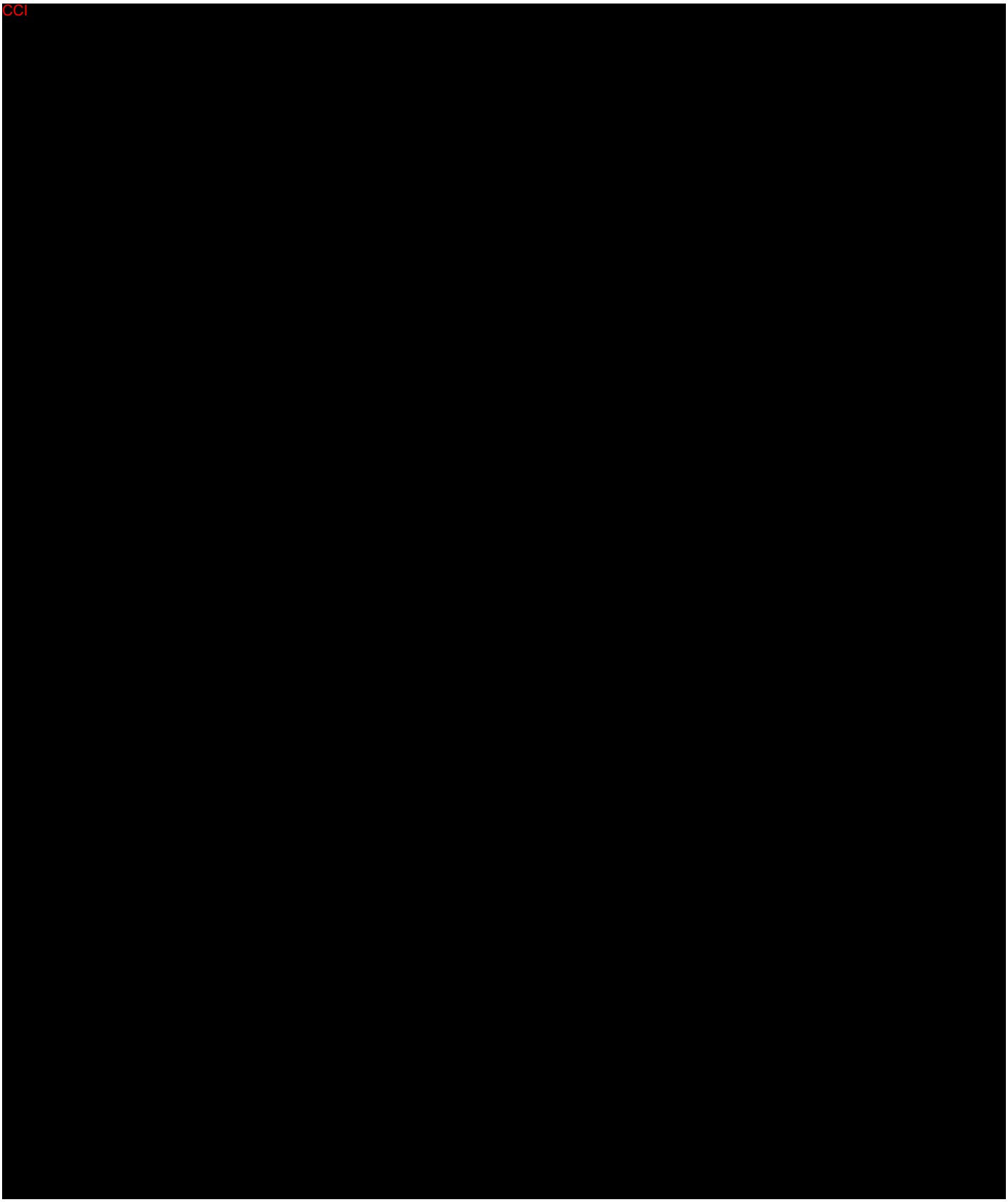

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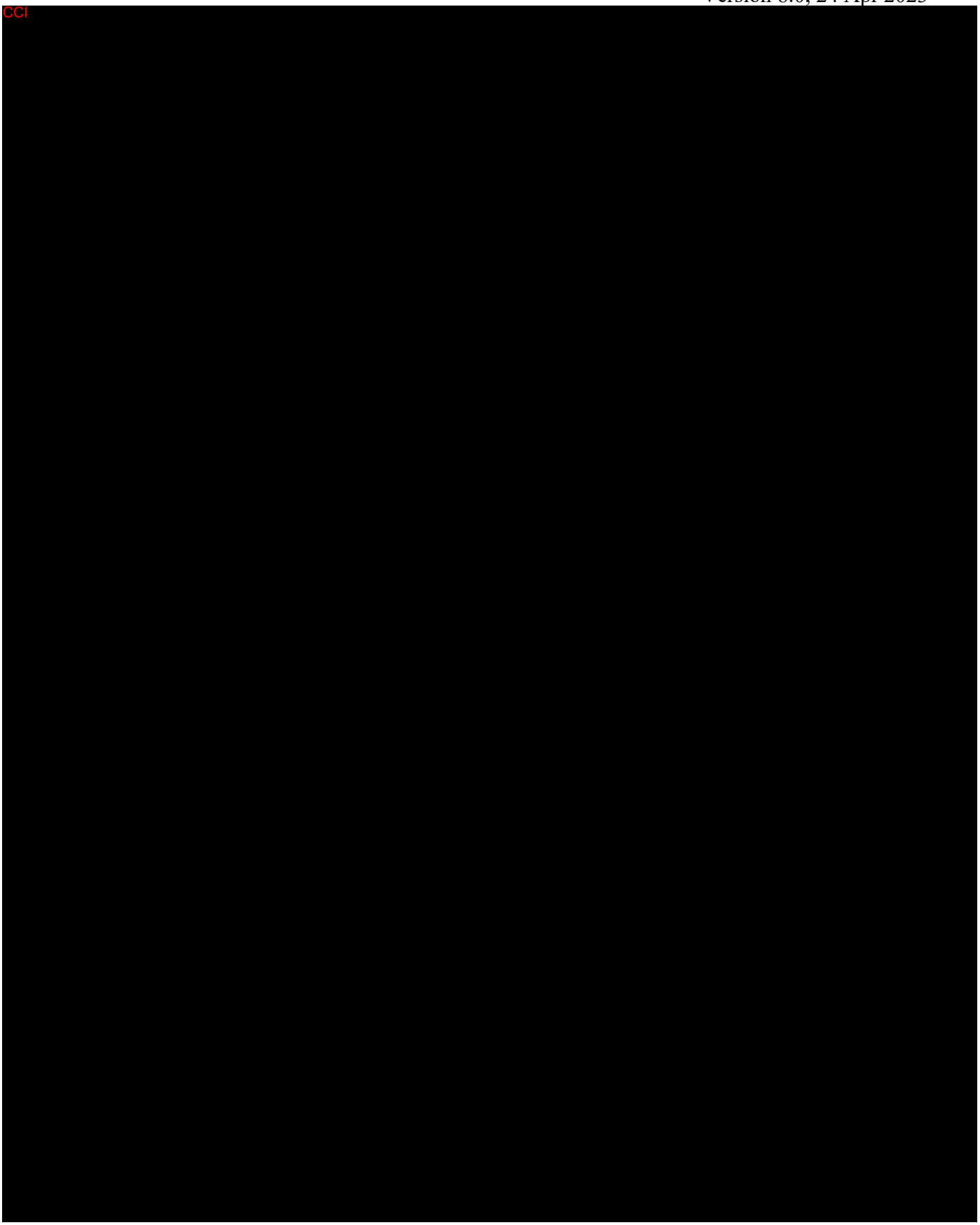

17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)

Dose modification criteria for suspected or confirmed Severe Acute Respiratory Syndrome Coronavirus 2 infection

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Dose modifications will be based on the worst CTCAE grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. **Please use CTCAE v5.0 general grading criteria to evaluate COVID-19.**

Dose modification criteria

If symptomatic or asymptomatic COVID-19 is suspected, interrupt trastuzumab deruxtecan and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 5.2.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, follow dose modification as outlined below and manage COVID-19 per local guidance until recovery from COVID-19. COVID-19 recovery is defined as no respiratory signs/symptoms and completely or nearly resolved chest CT findings,* which are equivalent to CT Severity Score of 1 (CT Severity Score of 1 = Subtle Ground Glass Opacities) and very few findings. Then follow below dose modifications:
  - If Grade 1, after recovery, resume trastuzumab deruxtecan at the same dose.
  - If Grade 2, after recovery,
    - Maintain same dose if chest CT findings are completely resolved;
    - Reduce by 1 dose level if chest CT findings are nearly resolved (equivalent to CT Severity Score of 1).
  - If Grade 3, after recovery,
    - Reduce by 1 dose level if chest CT findings are completely resolved;
    - Discontinue study drug if chest CT findings are not completely resolved.
  - If Grade 4, discontinue study treatment.

Closely monitor signs/symptoms after restarting trastuzumab deruxtecan, with a weekly phone call or site visit for 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 drug-related ILD, manage per protocol ILD management guideline. *Resolved or nearly resolved chest CT findings assume that COVID-19-associated findings were detected at the time of COVID-19 diagnosis or during the course of infection.

Severe Acute Respiratory Syndrome Coronavirus 2 Infection Assessment(s)

All confirmed or suspected COVID-19 events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, infection should be confirmed via nucleic acid amplification test (such as real-time polymerase chain reaction) or rapid antigen

testing. Severe acute respiratory syndrome coronavirus 2 antigen testing can be used to confirm infection but not rule it out.

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

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 SAP.

17.9. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative form the Sponsor.

For product complaints, refer to the Pharmacy Manual for instructions and details.

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DS8201-A-U301: A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled

Approval with eSign	PPD g 27-Apr-2023 23:13:17 GMT+0000

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