CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, RANDOMIZED STUDY OF TRASTUZUMAB DERUXTECAN IN SUBJECTS WITH HER2-OVEREXPRESSING LOCALLY ADVANCED, UNRESECTABLE OR METASTATIC COLORECTAL CANCER (DESTINY-CRC02)

PROTOCOL NUMBER: DS8201-A-U207

IND NUMBER 136179

EudraCT NUMBER 2020-004782-39

VERSION 1.0, 29 Oct 2020

DAIICHI SANKYO, INC

211 MOUNT AIRY ROAD

BASKING RIDGE, NEW JERSEY 07920

INVESTIGATOR AGREEMENT

A Phase 2, Multicenter, Randomized Study of Trastuzumab Deruxtecan in Subjects with HER2-overexpressing Locally Advanced, Unresectable or Metastatic Colorectal Cancer (DESTINY-CRC02)

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Medical Monitor	30 Oct 2020
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, 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)**

DOCUMENT HISTORY

Version Number	Version Date
1.0	29 Oct 2020

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
A Phase 2, Multicenter, Randomized, Study of Trastuzumab Deruxtecan in Subjects with HER2-overexpressing Locally Advanced, Unresectable or Metastatic Colorectal Cancer (DESTINY-CRC02)
Protocol Short Title
Trastuzumab deruxtecan for subjects with HER2-overexpressing advanced or metastatic CRC
Protocol Number
DS8201-A-U207
Sponsor/Collaborators
Daiichi Sankyo, Inc./AstraZeneca and Syneos Health
Registry Identification(s)
EudraCT Number: 2020-004782-39
IND Number
136179
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites, and Location
Global study at approximately 70 study sites, including but not limited to the Americas, Asia-Pacific, and Europe.
Study Population
Subjects with human epidermal growth factor 2 (HER2)-overexpressing locally advanced, unresectable, or metastatic colorectal cancer (mCRC).
Study Objectives/Outcome Measures and Endpoints

The table below lists primary and secondary study objectives and endpoints which have outcome measures.

Objectives	Outcome Measures	Endpoints	Category
Primary			
To assess the efficacy of trastuzumab deruxtecan (T-DXd), as measured by the confirmed ORR by BICR in HER2-overexpressing (defined as IHC 3+ or IHC 2+/ISH+) mCRC subjects treated at the 5.4 mg/kg and 6.4 mg/kg doses	**Title:** Confirmed ORR **Description:** CR and PR as assessed by blinded data review and based on RECIST version 1.1 **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with CR or PR, assessed by BICR based on RECIST version 1.1	Efficacy

Secondary			
To evaluate the clinical efficacy of T-DXd by confirmed ORR by Investigator assessment	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by confirmed ORR by Investigator assessment **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	Confirmed ORR as indicated above assessed by Investigator assessment based on RECIST version 1.1	Efficacy
To evaluate the clinical efficacy of T-DXd by DoR	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by DoR **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	DoR, defined as time from the initial response (CR or PR) by BICR and Investigator assessment until documented tumor progression or death from any cause	Efficacy
To further evaluate the clinical efficacy of T-DXd by DCR, CBR, PFS, and OS	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by DCR, CBR, PFS, and OS **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA (DCR, PFS) and 6 months after the last subject is registered for the primary analysis (DCR, CBR, PFS, OS)	Based on BICR and Investigator assessment according to RECIST version 1.1 (unless otherwise specified): • DCR, defined as the proportion of subjects who achieved CR, PR, or SD for a minimum of 6 weeks during study treatment; DCR based on BICR and DCR based on Investigator assessments will both be determined • CBR, defined as proportion of subjects who achieved CR, PR, or SD for at least 6 months; CBR based on BICR and CBR based on Investigator assessments will both be determined • PFS, defined as the time from date of randomization/ registration until first objective radiographic	Efficacy

		tumor progression or death from any cause, based on BICR and Investigator assessment • OS, defined as the time from date of randomization/ registration until death from any cause	
To further evaluate the safety and tolerability of T-DXd	**Title:** TEAEs and other safety parameters during the study **Description:** Descriptive statistics of safety endpoints **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	Safety endpoints will include, incidence and severity of (according to the NCI-CTCAE version 5.0): • TEAEs (including SAEs and AESIs) • TEAEs associated with death • Incidence of dose interruptions, dose modifications, and discontinuations due to AEs • ECOG PS • Vital sign measurements • Clinical laboratory parameters (hematologic and non-hematologic) • ECG parameters • ECHO/MUGA • Ophthalmologic assessments	Safety
To evaluate HEOR endpoints including patient-reported HRQoL, symptoms, and physical functioning	**Title:** PROs during the study **Description:** EORTC QLQ-C30 and EORTC QLQ-CR29, EQ-5D-5L, PGI-TT, PGIS, and PGIC **Time frame:** 6 months after the last subject is registered or later	PROs include: • Change from baseline in EORTC QLQ-C30 and EORTC QLQ-CR29 scale scores • EQ-5D-5L health state utility index • Patient-reported treatment tolerability with PGI-TT • Proportion of subjects with overall PGIS and PGIC	HEOR
To evaluate healthcare resource utilization for both treatment arms	**Title:** Healthcare resource use during the study **Description:** Healthcare resource use	Healthcare resource use will be captured/collected, including inpatient admissions, intensive care unit admissions, and length of stay in hospital	Healthcare resource use

	Time frame: 6 months after the last subject is registered or later		
To evaluate PK of T-DXd	**Title:** PK profile **Description:** Serum concentrations **Time frame:** 6 months after the last subject is registered or later	The PK endpoints include serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181a	PK
To evaluate immunogenicity of T-DXd	**Title:** Immunogenicity profile **Description:** Incidence of ADA and NAb **Time frame:** 6 months after the last subject is registered or later	The immunogenicity endpoint includes incidence of ADA and NAb	Immuno-genicity
Exploratory			
To further evaluate the clinical efficacy of T-DXd by TTR, best percent change in the SoD for all target lesions, and TTD in ECOG PS	**Title:** Clinical efficacy **Description:** Further evaluation of the clinical efficacy of T-DXd at 5.4 and 6.4 mg/kg doses by TTR, SoD, and TTD in ECOG PS **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	• TTR, defined as the time from the date of randomization/registration to the date of first documented objective response (CR or PR), based on BICR and Investigator assessment • Best percentage change from baseline in the SoD for all target lesions, based on BICR and Investigator assessment • TTD in ECOG PS, defined as the time from the date of randomization/registration to the date when ECOG PS score of ≥2 is observed for the first time	Efficacy
To assess the relationship between changes in tumor markers (CEA and CA19-9) and radiographic response to T-DXd treatment	Not applicable	Changes in CEA and CA19-9	PD
To evaluate ERBB2 copy number detected in cfDNA and cfRNA at baseline as an exploratory predictive biomarker of response	Not applicable	ERBB2 copy number at baseline and its association with clinical outcomes	Biomarker
To evaluate other potential biomarkers of resistance or	Not applicable	• Liquid biomarkers (eg, cfRNA) at baseline and	Biomarker

clinical benefit to study treatment		its association with clinical outcomes • Potential DNA, RNA, and protein-based biomarkers evaluated by different methodologies (eg, cfDNA, NGS based analysis of DNA and RNA, protein-based analysis, IHC digital pathology analysis etc. of tumor samples)	
To explore an exposure/response relationship	Not applicable	• T-DXd PK concentration versus selected safety and efficacy endpoints	PK, Safety, and Efficacy

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; BICR = blinded independent central review; CA19-9 = carbohydrate antigen 19-9; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; cfDNA = cell-free deoxyribonucleic acid; cfRNA = cell-free ribonucleic acid; CR = complete response; DCR = disease control rate; DNA = deoxyribonucleic acid; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQol-5 dimensions-5 levels of severity; ERBB2 = erb-b2 receptor tyrosine kinase 2; HEOR = Health Economics and Outcomes Research; HER2=Human epidermal growth factor receptor 2; HRQoL = health-related quality of life; IA = interim analysis; IHC = immunohistochemistry; ISH = in situ hybridization; MAAA-1181a (DXd) = released drug; mCRC = metastatic colorectal cancer; MUGA = multigated acquisition; NAb = neutralizing antibodies; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NGS = next-generation sequencing; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PGIC = Patient Global Impression-Change; PGIS = Patient Global Impression-Severity; PGI-TT = Patient Global Impression-Treatment Tolerability; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; PS = performance status; QLQ = Quality of Life Questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; SD = stable disease; SOC = standard of care; SoD = sum of diameters; TEAE = treatment-emergent adverse event; TTD = time to deterioration; TTR = time to response.

Study Design

The Tissue Pre-Screening Period will start on the day of obtaining a signed and dated written Tissue Pre-Screening informed consent form (ICF) from the subject prior to collecting tissue from a recent tumor biopsy (preferred) or archival tissue to confirm HER2 status. A tissue sample is considered a recent sample if it is collected from a biopsy performed after the subject's discontinuation of the last treatment regimen (and most recent disease progression). For subjects who sign this ICF, only serious adverse events (SAEs) directly related to the tissue pre-screening procedure (ie, tumor biopsy) should be reported via the SAVER Form. Unless documentation of other adverse events (AEs) are required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue pre-screening. The tissue pre-screening may occur any time before the Screening Period.

The Screening Period will start on the day a subject signs the Main ICF and will comprise a maximum duration of 28 days. Rescreening is permitted once during this phase if the subject fails initial Screening. During the 28-day Screening Period, subjects' eligibility will be confirmed. The activities and/or assessments will be performed within 28 days before randomization/registration during the Screening Period and are listed in the Schedule of Events. Within 14 days before randomization/registration, the subjects will undergo medical history evaluation, vital signs determination, physical examination, pulse oximetry, height and weight measurements, functional status confirmation using the Eastern Cooperative Oncology Group (ECOG)

performance status (PS), laboratory testing (including blood tests for safety), and electrocardiogram (ECG). Eligible subjects will be randomized/registered and enter the Treatment Period.

The Treatment Period starts on Day 1 of Cycle 1. Eligible subjects will be randomized to 1 of 2 treatment arms in **Stage 1**:

- Arm 1: T-DXd for injection will be administered intravenously (IV) at a dose of 5.4 mg/kg every 3 weeks (Q3W)
- Arm 2: T-DXd for injection will be administered IV at a dose of 6.4 mg/kg Q3W

After Stage 1 enrollment is complete (N=80), eligible subjects will all be registered to T-DXd administered IV at a dose of 5.4 mg/kg Q3W in **Stage 2** (N=40). Subjects will receive the assigned dose of T-DXd (5.4 mg/kg Q3W or 6.4 mg/kg Q3W) until progression of disease or the subject meets one of the discontinuation criteria. Combining both stages of the study, a maximum of 30 subjects per subgroup will be registered onto each of the HER2 IHC 2+/ISH+ and *RAS*-mutant subgroups. A minimum of 20 subjects with *RAS*-mutant status will be enrolled in the study. Once the maximum number of 30 subjects is reached, all subsequent subjects enrolled in the study should have HER2 IHC 3+ or *RAS* wild-type tumor.

The **End of Treatment** (EOT) is defined as the date the Investigator decides to discontinue study treatment. Subjects who permanently discontinue the study treatment should be scheduled for an EOT visit within +7 days following the date study treatment is permanently discontinued. If the decision to discontinue the subject occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the subject return for an additional visit.

The Follow-up Period will start upon permanent discontinuation of T-DXd. Subjects will be followed 40 days (+7 days) after the last study treatment administration or before starting new anticancer treatment, whichever comes first. Subjects who discontinue study drug for any reason other than progressive disease (PD), death, or loss to follow-up will be followed every 6 weeks (Q6W) until radiological disease progression or start of new anticancer treatment. If EOT is >40 days after last treatment, then the EOT assessments may take the place of the 40-day Follow-up Visit assessments. Long-term disease follow-up to monitor survival will be documented every 3 months (±14 days) for up to 2 years, every 6 months from 3 to 5 years, and annually from 6 to 10 years. Survival follow-up contact (either scheduled visit or telephone call) will be performed every 3 months (±14 days) from the date of the 40-day Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

The **primary completion date** is the date when the last enrolled subject has completed 6 months of follow-up treatment or when all subjects have been discontinued from the study and completed the 40-day Follow-up Visit, whichever is earlier. This date is used as the cut-off date for the analysis of the primary efficacy endpoint(s) of the study. All subjects still on treatment and continuing to derive benefit from study drug at the primary completion date will continue to follow the study Schedule of Events until the overall End of Study (EOS) is reached.

Overall EOS will occur when:

- the last subject last visit has occurred or
- the study is discontinued by the Sponsor for other reasons (administrative, program-level, or class-related)

The subject's EOS is the date of their last study visit/contact.

Study Duration

The study start date is the date when the first subject has signed the Main ICF. A subject is eligible to be enrolled into the interventional phase of the study when the Investigator or designee has obtained written ICF (both Tissue Pre-Screening and Main), has confirmed all eligibility criteria have been met by the subject, and all Screening procedures have been completed.

Anticipated total duration of the study is approximately 30 months.

- Projected enrollment duration of approximately 18 months

- Treatment and follow-up duration: 12 months

The EOS is defined as the date of completion of the last visit or procedure shown in the Schedule of Events in the trial globally, or the study is ended by the Sponsor.

Key Eligibility Criteria

Key Inclusion Criteria:

Subjects eligible for inclusion in this study have to meet all inclusion criteria for this study. Below is a list limited to the key inclusion criteria:

- Sign and date the Tissue Pre-Screening and Main ICFs, prior to the start of any respective study-specific qualification procedures.
- Adults aged ≥20 years in Japan, Taiwan, and Korea, or those aged ≥18 years in other countries, at the time the ICFs are signed. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years).
- Pathologically-documented, unresectable, recurrent, or metastatic colorectal adenocarcinoma. Subject must have *BRAF* wild-type cancer and *RAS* status identified in primary or metastatic site, tested by a Clinical Laboratory Improvement Act (CLIA), ISO15189, or equivalent-certified laboratory.
- The following therapies should be included in prior lines of therapy:
  - Fluoropyrimidine, oxaliplatin, and irinotecan, unless contraindicated
  - Anti-epidermal growth factor receptor (EGFR) treatment, if *RAS* wild-type and if clinically indicated
  - Anti-vascular endothelial growth factor (VEGF) treatment, if clinically indicated
  - Anti-programmed death-ligand 1 (PD-[L]-1) therapy, if tumor is microsatellite instable (MSI)-high/deficient mismatch repair (dMMR), or tumor mutational burden (TMB)-high, if clinically indicated
- Is willing and able to provide an adequate tumor sample for tissue pre-screening to confirm HER2 status by central laboratory (most recent tumor tissue preferred).
- Confirmed HER2-overexpressing status assessed by central laboratory and defined as IHC 3+ or IHC 2+/ISH+.
- Presence of at least one measurable lesion assessed by the Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Lesions situated in a previously-irradiated area are considered measurable if progression has been demonstrated in such lesions after the end of radiotherapy.
- ECOG PS of 0 or 1.
- Has left ventricular ejection fraction (LVEF) ≥50% within 28 days before randomization/registration.
- Has adequate organ function within 14 days before randomization/registration, defined as:

Parameter	Laboratory value
Adequate bone marrow function	
Platelet count	≥100,000/mm3 (Platelet transfusion is not allowed within 1 week prior to Screening assessment)
Hemoglobin	≥9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to Screening assessment)
Absolute neutrophil count (ANC)	≥1500/mm3 (granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to Screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation

Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤5 × upper limit of normal (ULN)
Total bilirubin	≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Serum Albumin	≥2.5 g/dL
Adequate blood clotting function	
International normalized ratio (INR)/Prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)	≤1.5 × ULN

- Has adequate treatment washout period before randomization/registration, defined as:

Treatment	Washout Period
Major surgery	≥4 weeks
Radiation therapy, including palliative stereotactic radiation to chest	≥4 weeks (palliative stereotactic radiation therapy to other areas ≥2 weeks)
Anticancer chemotherapy (immunotherapy [non-antibody-based therapy]), retinoid therapy	≥3 weeks (≥2 weeks or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥6 weeks for nitrosoureas or mitomycin C)
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/hydroxychloroquine	>14 days

Key Exclusion Criteria:

Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key exclusion criteria:

- Medical history of myocardial infarction (MI) within 6 months before randomization/registration, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV). Subjects with troponin levels above ULN at Screening (as defined by the manufacturer), and without any MI-related symptoms, should have a cardiologic consultation before randomization/registration to rule out MI.
- Has a corrected QT interval (QTcF) prolongation to >470 msec (female subjects) or >450 msec (male subjects) based on the average of the Screening triplicate 12-lead ECGs.
- Has a history of (non-infectious) 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.
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of the randomization/registration, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion, etc.).
- Any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, etc.) where there is documented, or a suspicion of, pulmonary involvement at the time of Screening. Full details of the disorder should be recorded in the eCRF for subjects who are included in the study.
- Prior pneumonectomy.
- Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids

or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and randomization/registration.

- Subjects with leptomeningeal carcinomatosis.
- Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated.
- Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
- Has a history of severe hypersensitivity reactions to other monoclonal antibodies.
- Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals.
- Has substance abuse or any other medical conditions such as clinically significant cardiac 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.
- Has known human immunodeficiency virus (HIV) infection. Unless required by local regulations or institutional review board (IRB)/ethics committee (EC), an HIV antigen/antibody test is not required prior to randomization/enrollment.
- Active hepatitis B and/or hepatitis C infection, such as those with serologic evidence of viral infection within 28 days before study randomization/registration. Subjects with past or resolved hepatitis B virus (HBV) infection are eligible if hepatitis B surface antigen (HBsAg) negative (-) and antibody to hepatitis B core antigen (anti-HBc) positive (+). Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible at the discretion of the Investigator and approval of the Sponsor.
- Previous treatment with a DXd-containing antibody-drug conjugate (ADC).
- Evidence of ongoing uncontrolled systemic bacterial, fungal, or viral infection. Note: Subjects with localized fungal infections of skin or nails are eligible.
- Female subject who is pregnant, breastfeeding, or intends to become pregnant during the study.

Investigational Medicinal Product, Dose, and Mode of Administration

T-DXd is an investigational agent. The T-DXd drug product containing 100 mg of T-DXd is provided as a sterile lyophilized powder in a glass vial (Lyo-DP). Each glass vial should be reconstituted with 5 mL water for injection to a concentration of 20 mg/mL (ie, 100 mg/5 mL). T-DXd will be administered with 5% dextrose as an IV infusion. Each vial is designed for single-use only and is not to be used to treat more than one subject.

The drug for IV infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight in an infusion bag, by the study site pharmacist. The study treatment will be administered as an IV infusion every 3 weeks, initially for approximately 90 minutes, then, if there is no infusion-related reaction, for a minimum of 30 minutes thereafter.

If dose reduction is required, dosing should be reduced by 1 dose level at a time. Up to 2 dose reductions will be permitted for subjects. Once the dose of study drug is reduced, no dose re-escalation will be permitted.

Table 1.1: Dose Reduction Levels of Study Treatment

Treatment Arm	Starting Dose	Dose Level -1	Dose Level -2
1	5.4 mg/kg	4.4 mg/kg	3.2 mg/kg
2	6.4 mg/kg	5.4 mg/kg	4.4 mg/kg

T-DXd dose interruption, re-initiation, dose reduction, and/or discontinuation will follow Sponsor dose modification guidance in the protocol body.

Active Ingredient(s)/INN
Trastuzumab deruxtecan (T-DXd; DS-8201a) is an ADC, that consists of an anti-HER2 antibody, MAAL-9001, covalently linked to approximately 8 molecules of MAAA-1162a (GGFG tetra-peptide cleavable linker and a topoisomerase I inhibitor [MAAA-1181a]).
Planned Sample Size
Approximately 120 subjects will be enrolled in this study. In Stage 1, the first 80 subjects will be randomized in a 1:1 ratio to receive T-DXd at either the 5.4 mg/kg or 6.4 mg/kg dose level. Then in Stage 2, an additional 40 subjects will be registered at the 5.4 mg/kg dose to further inform on the efficacy and safety of this dose in mCRC. In Stage 1, with 40 subjects in each treatment arm, the probability to exclude the objective response rate (ORR) benchmark of 20.0% is at least 80% when the true ORR is 41%. At the end of Stage 2, assuming 80 total subjects in the 5.4 mg/kg, the probability to exclude the ORR benchmark of 20.0% is at least 80% when the true ORR is 34%. With 80 subjects at the 5.4 mg/kg dose level and 40 subjects at the 6.4 mg/kg dose level, if the higher dose true ORR is at least 13.75% higher than that of the lower dose, the probability of observing the ORR difference between dose levels being 5% or more is at least 80%. Assuming 80 subjects at the 5.4 mg/kg dose level and 40 subjects at the 6.4 mg/kg dose level, the 95% confidence interval of the ORR difference between dose levels is expected to extend approximately 0.18 from the observed difference in proportions to either confidence limit.
Statistical Analyses
• Efficacy Analyses The primary efficacy endpoint of ORR per blinded independent central review (BICR) will be calculated at an interim and a final analysis. The interim analysis (IA) will be performed when approximately 80 subjects have been randomized and had at least 12 weeks of follow-up after randomization or have discontinued treatment. The purpose of this IA is to look at preliminary efficacy and safety signals for both the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd in HER2-overexpressing mCRC subjects. The primary analysis will be performed after all 120 subjects have been randomized/registered into the study and had at least 6 months of follow-up after initiation of therapy. The primary efficacy analyses will be performed for the Full Analysis Set (FAS), according to the treatment and the strata they are randomized/registered. The ORR for each dose level will be estimated along with two-sided exact 95% confidence intervals using the Clopper and Peterson method. The ORR difference between dose levels will be presented along with 95% confidence interval of the difference, using a stratified analysis, adjusting for the randomization stratification factors. Analyses of secondary efficacy endpoints are specified in the Statistical Analysis Plan (SAP). • Health Economic and Outcomes Research Analyses Health economic and outcomes research (HEOR) endpoints based on the hospitalization-related data collection form and the following PRO questionnaires will be summarized by treatment group: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, EORTC QLQ-CR29, EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L), Patient Global Impression-Severity (PGIS), Patient Global Impression-Change (PGIC), and Patient Global Impression-Treatment Tolerability (PGI-TT). The global health status/quality of life (QoL) scale of the EORTC QLQ-C30 questionnaire is the HEOR measurement. A score of the global health status/QoL at each assessment will be calculated per "EORTC QLQ-C30 Scoring Manual." Descriptive statistics will be calculated to summarize change from the baseline in symptoms, physical functioning, and general health-related QoL (HRQoL) scales in the C30 and CR29 study questionnaires at each scheduled assessment time point by dose level. The number of subjects completing each patient questionnaire and the number of missing or incomplete assessments will be provided for each scheduled assessment time point by dose level. • Pharmacokinetic Analyses

Pharmacokinetics (PK) analyses will be performed using the PK Analysis Set. Serum concentrations for T-DXd, total anti-HER2 antibody and MAAA-1181a (DXd) will be listed and summarized using descriptive statistics at each time point. Additional analyses are specified in the protocol.

- Biomarker Analyses

Biomarker analysis will be performed using the FAS.

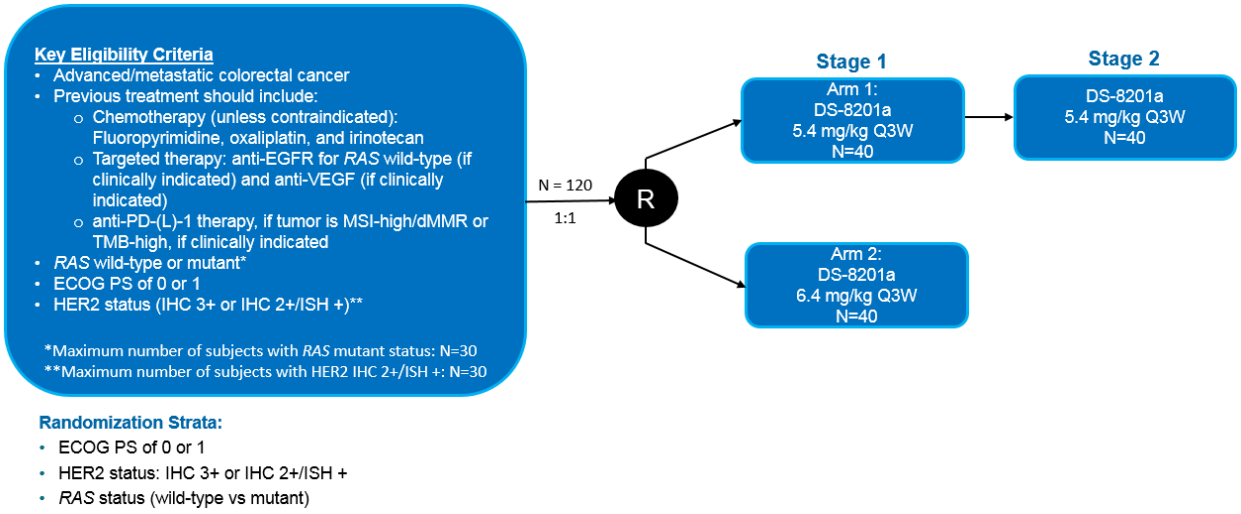
Descriptive statistics including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be computed by evaluation time for biomarkers as specified in the protocol. If possible, change from baseline and percent change from baseline will also be summarized.

- Safety Analyses

Safety endpoints will include SAEs, TEAEs, AEs of special interest (AESIs), discontinuations due to AEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, echocardiogram (ECHO)/multigated acquisition (MUGA) findings, and anti-drug antibodies (ADAs). TEAEs will be graded according to the NCI-CTCAE version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



dMMR = deficient mismatch repair; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; MSI = microsatellite instable; PD = progressive disease; PD-(L)-1 = programmed death-ligand 1; Q3W = every 3 weeks; RAS = rat sarcoma viral oncogenes homologue; TMB = tumor mutational burden; VEGF = vascular endothelial growth factor.

1.3. Schedule of Events

Table 1.2: Schedule of Events – Tissue Pre-Screening and Screening

Visit	Tissue Pre-Screening	Screening		CSP Section(s)	Comment(s)
Window (Day) Procedures	Any time before Screening	-28 to -1	-14 to -1 (or as noted)		
Tissue Pre-Screening ICF	X			8.1.1; 8.1.2; 10.1.2	A signed and dated Tissue Pre-Screening ICF must be obtained before tumor tissue pre-screening assessments. The Tissue Pre-Screening ICF can be obtained any time before Screening (ie, during previous therapy).
Tumor Sample for Tissue Pre-Screening	X*	X**		8.1.2; 8.1.4; 10.1.2	Central laboratory testing. *At tissue pre-screening, subjects must provide a tumor sample: archival tissue (most recent preferred), recent tumor tissue, or a new tumor biopsy (if archival tissue is not available). A tissue sample is considered a recent sample if it is collected from a biopsy performed after the subject's discontinuation of the last treatment regimen and most recent disease progression. **If slides are sent in place of a paraffin embedded tissue block at Pre-Screening, then additional slides will be required at Screening. Refer to the Study Laboratory Manual for preparation, number of slides required, storage, and shipment procedures.
Assign SID from IRT	X			8.1.2	One SID will be assigned at tissue pre-screening.
Main ICF		X		8.1.1; 10.1.2	A signed and dated Main ICF must be obtained before initiating all other study-specific procedures or assessments.
Optional PGx ICF		X		8.7.2	A signed and dated PGx ICF must be obtained before sample collection.
Eligibility Assessment		X		8.1	Review all inclusion/exclusion criteria to determine eligibility.
Demographics			X	8.1.6	Demographic data will include age, sex, country, and self-reported race/ethnicity where allowed per local regulations.
Medical History			X	8.1.3; 8.1.5	Including CRC history.

Visit	Tissue Pre-Screening	Screening		CSP Section(s)	Comment(s)
Window (Day) Procedures	Any time before Screening	-28 to -1	-14 to -1 (or as noted)		
Vital Signs			X	8.4.4.2	Blood pressure, pulse rate, respiratory rate, and temperature should be taken approximately 5 minutes or more after the subject has rested in a recumbent position and prior to laboratory blood draws and ECG measurements.
Height			X	8.4.4.2	Assessment(s) to be performed within 14 days before Cycle 1 Day 1.
Weight			X	8.4.4.2	
SpO2			X	8.4.4.2	SpO2 will be assessed via pulse oximetry.
ECOG PS			X	8.4.4.3	
Physical Examination			X	8.4.4.1	
Ophthalmologic Assessments		X		8.4.4.7	Ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy will be performed at Screening.
ECHO/MUGA		X		8.4.4.5	ECHO or MUGA assessments to be performed at Screening. Use the same test for a subject throughout the study.
12-lead ECG (in triplicate)			X	8.4.4.4	
Hematology and Chemistry			X	8.4.3; 10.2	Hematology tests to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute ± differential (%) WBC count: basophils, eosinophils, lymphocytes, monocytes, neutrophils. Blood chemistry tests to include albumin, ALT, ALP, AST, bilirubin (total), BUN/urea, Ca, Cl, creatinine (serum), LDH, Mg, K, protein (total), Na, and FSH and estradiol (if applicable) to confirm menopausal status.
Coagulation			X	8.4.3; 10.2	Coagulation tests will include PT/INR and PTT/aPTT.
Troponin (preferably high-sensitivity troponin-T)			X	8.4.3; 10.2	Collect blood samples for local and central troponin (preferably high-sensitivity troponin-T and troponin I or troponin-T).

Visit	Tissue Pre-Screening	Screening		CSP Section(s)	Comment(s)
Window (Day) Procedures	Any time before Screening	-28 to -1	-14 to -1 (or as noted)		
Urinalysis (abbreviated)			X	8.4.3; 10.2	Urinalysis tests to include glucose, microscopy assessments (if indicated), occult blood, protein, specific gravity.
Pregnancy test			X	5.1; 8.4.2.1	Urine pregnancy test to be done within 72 hours before randomization/registration for all female subjects of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test.
HIV Ab Test		X		8.1.7	Unless required by local regulations or independent IRB/EC, an HIV antigen/Ab test is not required prior to randomization/enrollment.
HBsAg, HC Ab		X		5.2; 8.1.8	Active HBV and/or HCV infection, such as those with serologic evidence of viral infection within 28 days before study randomization/registration. Subjects with past or resolved HBV infection are eligible if HBsAg negative (-) and anti-HBc positive (+). Patients positive for HCV Ab are eligible only if polymerase chain reaction is negative for HCV RNA.
Optional Tumor Biopsy Sample for Exploratory Biomarkers		X		8.7.1.1.1	Biopsies are optional (strongly recommended). The detailed procedures for collection, handling, and shipping tumor tissue samples will be provided in the Study Laboratory Manual.
Blood Sample for HER2ECD			X	8.7.1	
Blood Sample for Tumor Markers (CEA and CA19-9)			X	10.4	
Radiographic Tumor Assessment		X		8.3.4; 8.4.1.9.1	Baseline tumor assessment will include the chest, abdomen, and pelvis as well as any other sites of disease are required. Baseline CT of chest will serve to monitor for ILD/pneumonitis required for all subjects.

Visit	Tissue Pre-Screening	Screening		CSP Section(s)	Comment(s)
Window (Day) **Procedures**	**Any time before Screening**	**-28 to -1**	**-14 to -1 (or as noted)**		
CT/MRI of the Brain		X		8.3.4	At baseline, a CT or MRI of the brain is required ONLY if the subject has a history of brain metastases and/or symptoms suggestive of brain metastases. If there are no brain metastases at the time of Screening, a brain CT or MRI should only be performed during the study treatment if symptoms associated with brain metastases appear during the study period. If no clinical symptoms are observed, a CT or MRI of the brain is not mandatory at Screening.
Randomization/Registration			X	8.2	Cycle 1 Day 1 of treatment *should* occur within 7 days (Days 0-7) after randomization/registration. However, it is permissible for a subject to receive the first dose of T-DXd on the same day as randomization/registration, if applicable.
AEs		X		8.4.1	
Concomitant Medications		X		6.6	

Ab = antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = calcium; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; cfDNA = cell-free deoxyribonucleic acid; Cl = chloride; CRC = colorectal cancer; CSP = clinical study protocol; CT = computed tomography; EC = Ethics Committee; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; HBcAg = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2ECD = human epidermal growth factor receptor-2 extracellular domain; HIV = human immunodeficiency virus; ICF = informed consent form; ILD = interstitial lung disease; INR = international normalized ratio; IRB = institutional review board; IRT = interactive response technology; K = potassium; LDH = lactate dehydrogenase; Mg = magnesium; MRI = magnetic resonance imaging; MUGA = multigated acquisition; Na = sodium; PGx = pharmacogenomic; PS = performance status; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNA = ribonucleic acid; SID = subject identification; SpO2 = peripheral oxygen saturation; WBC = white blood cell

Table 1.3: Schedule of Events – Treatment and Follow-up

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
Vital Signs	X[d]	X	X	X	X[d]	X	X[d]	X	X[d]		X	X		8.4.4.2	Blood pressure, pulse rate, respiratory rate, and temperature should be taken approximately 5 minutes after the subject has rested in a recumbent position and prior to ECG measurements and laboratory blood draws. [d] Assessment(s) to be performed within 3 days before study drug administration.
Weight	X[d]				X[d]		X[d]		X[d]		X	X		8.4.4.2	[d] Assessment(s) to be performed within 3 days before study drug administration.
SpO2	X[d]	X	X	X	X[d]	X	X[d]	X	X[d]		X	X		8.4.4.2	
Physical Examination	X[d]				X[d]		X[d]		X[d]		X	X		8.4.4.1	
Ophthalmologic Assessments	(if clinically indicated)										X			8.4.4.7	
ECOG PS	X[d]				X[d]		X[d]		X[d]		X	X		8.4.4.3; 10.3.3	[d] Assessment(s) to be performed within 3 days before study drug administration.

Procedure	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
ECHO/MUGA									X		X			8.4.4.5	Use the same test for a subject throughout the study. ECHO or MUGA assessments to be performed BI on Day 1 of Cycle 5, and then every 4 cycles (±7 days) thereafter (ie, Cycles 9, 13, etc.), at EOT, and as clinically indicated.
12-lead ECG	X[d]								X[d]		X			8.4.4.3	After Cycle 1, single ECGs will be taken at every fourth cycle (ie, Cycles 4, 8, 12, etc), unless an abnormality is noted, then subsequent ECGs will be performed in triplicate in close succession (approximately 3 minutes apart). ECGs will be performed prior to blood draws and while the subject is in a supine/semi-recumbent position.

Procedure / Day	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															[d] Within 3 days before study drug administration.
Hematology and Chemistry	X[d]		X	X	X[d]		X[d]		X[d]		X	X		8.4.3; 10.2	[d] Assessment(s) to be performed within 3 days before study drug administration. If hematology and chemistry were done within 3 days of Cycle 1 Day 1 at Screening, then these can replace the Cycle 1 Day 1 assessments.
Coagulation											X			8.4.3; 10.2	Coagulation tests will include PT/INR and PTT/aPTT.
Troponin (preferably high-sensitivity troponin-T)	(if clinically indicated)										X			8.4.3; 10.2	Collect blood samples for local and central troponin (preferably high-sensitivity troponin-T) at EOT and if, at any time a subject reports signs or symptoms suggesting CHF, MI, or other causes of myocyte necrosis.
Pregnancy Test	X				X		X		X		X	X		5.1; 8.4.2.1	Perform repeat pregnancy tests

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															(urine or serum test per institutional guideline) on women of childbearing potential 72 hours BI of each cycle, at EOT, and at the 40-day FU visit.
Optional SARS-CoV-2 Sample	X								X[e]		X			10.6	If subject provides consent, samples should be collected prior to study drug infusion. [e] Starting at Cycle 5 Day 1 and every 4 cycles thereafter. For subjects with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Appendix 7 (Section 10.6).
Optional PK Sampling for CQ/HCQ Administration	If CQ or HCQ is administered for SARS-CoV-2, additional PK blood samples should be collected at the following visits: Prior to the first CQ or HCQ dose (Day 1) Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4 hours) Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4 hours)													8.6; 10.6	If subject provides consent, samples should be collected. [f] A washout period of more than 14 days is required before restarting T-DXd

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
	The day of T-DXd resumption, after the CQ/HCQ washout period, (within 8 hours BI of T-DXd).[f]														
Optional Tumor Biopsy Sample for Exploratory Biomarkers							X				X			8.7.1.1	During study treatment, biopsies are optional (strongly recommended). The detailed procedures for collection, handling, and shipping tumor tissue samples will be provided in the Study Laboratory Manual.
Blood Sample for cfRNA	X													8.7.1	Pretreatment sample will be collected within 3 days before study drug administration.
Blood Samples for cfDNA	X[d]				X[d]		X[d]		X[d,g]		X			8.7.1	[d] Assessment(s) to be performed within 3 days before study drug administration [g] cfDNA samples will be collected BI on Day 1 of Cycles 1, 2, 3, 4, 7, then every 4 cycles, and at EOT (+7 days).
Optional PGx Blood Sample	X													8.7.2	Participation in the PGx part of the study

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															is optional for all subjects.
PK Blood Sample	X[h]	X[i,j]	X	X	X[h]	X[i]	X[h]	X[i]	X[h]	X[i]				8.6	Central laboratory testing. [h] Specified PK samples within 8 hours BI on Day 1 of Cycles 1, 2, 3, 4, and 6. [i] Specified PK samples within 15 minutes of EOI on Day 1 of Cycles 1, 2, 3, and 4. [j] Specified PK samples to be collected 5 hours (±15 minutes) after the start of administration on Day 1 of Cycle 1.
Immunogenicity Blood Sample (ADA and NAb)[p]	X[k]				X[k]				X[k]		X	X	X[l]	8.7.3	[k] Immunogenicity samples to be collected within 8 hours BI on Day 1 of Cycles 1, 2 and 4, and then every 4 cycles. [l] For subjects with positive ADA at the FU visit, additional serum ADA samples

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															may be collected during long-term follow-up that is, every 3 months (±14 days) up to 1 year after the last dose of the study drug, or until the immunogenicity result becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
Blood Sample for Tumor markers (CEA and CA19-9)							X[m]		X[m]					10.4	[m] Sample to be collected every 2 cycles beginning on Day 1 of Cycle 3 (ie, Day 1 of Cycles 3, 5, 7, 9, etc), These samples should be collected only if these biomarkers are informative (abnormal), as

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															assessed by the Investigator.
CT/MRI of the Brain	X (The first on-study imaging assessment should be performed at 6 weeks [42 days (+7) days] from Cycle 1 Day 1.)													8.3.4	At baseline, a CT or MRI of the brain is required ONLY if the subject has a history of brain metastases and/or symptoms suggestive of brain metastases. When the subject has brain metastases identified at baseline, a CT or MRI of the brain is required throughout the study (at tumor assessment time points) and EOT.
Radiographic Tumor Assessment	X^n										X^n			8.3.4	[n] Tumor imaging should be performed every 6 weeks (±7 days) from Day 1 of Cycle 1 or more frequently if clinically indicated. The first on-study imaging assessment should be performed at 6 weeks (42 days [+7] days) from Cycle 1 Day 1. After 12 months (365 days [±7] days), subjects

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															who remain on treatment will have imaging performed every 12 weeks (±14 days) until disease progression or start of new anticancer treatment. Regarding the EOT tumor assessment: If the previous scan was within the last 6 weeks (within 12 weeks if the subject completed the first year of tumor assessments), the tumor assessment at the EOT Visit does not need to be performed. If the Investigator makes a clinical diagnosis that there has been progression, imaging examinations should be performed as promptly as possible, and efforts should be made to obtain an image-based assessment of PD. Imaging timing should follow

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															calendar days. (For suspected ILD/pneumonitis, see Section 6.5.2.)
Allocate ePRO Device and ePRO Subject Training	X													8.5.1.6	The ePRO device must be charged and fully functional prior to the subject's arrival at the site for Cycle 1 Day 1 (-3 days) to ensure that the ePROs can be completed at the start of the visit. The subject should be trained on the use of the device, including the importance of completing the ePRO questionnaires throughout the study in accordance with the completion schedule.
EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L, PGIS	X[d]				X[d]		X[d]		X[d]		X	X	X	8.5.1	[d] Assessment(s) to be performed within 3 days before study drug administration. EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L, and PGIS to be completed at Day 1

Procedure / Day / Window	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															of Cycles 1, 2, 3, and then every 2 cycles (ie, Cycle 5, 7, 9, etc.), EOT, 40-day FU visit (+7 days) and at approximately 6 months and 12 months (±14 days) after the 40-day FU visit. Subjects should complete the questionnaires before any other assessments or procedures are done.
PGIC					X[d]		X[d]		X[d]		X	X	X	8.5.1	[d] Assessment(s) to be performed within 3 days before study drug administration.
PGI-TT					X[d]		X[d]		X[d]		X			8.5.1	[d] Assessment(s) to be performed within 3 days before study drug administration.
Administer Study Drug (T-DXd)	X				X		X		X					6.2.2	Administer Q3W (±2 days) unless discontinuation criteria are met.
Healthcare Resource Use	At each scheduled visit, the site should review clinical notes for any non-study-related hospital admissions and visits that have occurred.													8.5.2	If a subject discontinues study treatment for reasons

	Treatment										Follow-up			CSP Section(s)	Comment(s)
	Cycle 1				Cycle 2		Cycle 3		Cycle 4 – Cycle x		EOT[a]	40D FU[b]	LTFU[c]		
Day	1		8	15	1		1		1						
Window / Procedure	BI	EOI	±1D	±1D	±2D		±2D		±2D		±1D	+7D	±14D		
					BI	EOI	BI	EOI	BI	EOI					
															other than RECIST (version 1.1) progression, the HOSPAD eCRF module form should continue to be administered until progression has been confirmed.
AEs	X													8.4.1	
Concomitant Medications	X													6.6	
Survival Follow-up													X	8.3.7	

ADA = anti-drug antibody; AE = adverse event; BI = before infusion; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; cfDNA = cell-free deoxyribonucleic acid; cfRNA = cell-free ribonucleic acid; CHF = congestive heart failure; CQ = chloroquine; CSP = clinical study protocol; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; EC = Ethics Committee; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FU = follow-up; HCQ = hydroxychloroquine; HOSPAD = Hospital Admission (eCRF module); ILD = interstitial lung disease; LTFU = long-term follow-up; MI = myocardial infarction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NAb = neutralizing antibody; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGI-TT = Patient Global Impression of Treatment Tolerability; PGx = pharmacogenomic; PK = pharmacokinetic; PRO = patient-reported outcome; PS = performance status; Q3W = once every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2 = peripheral oxygen saturation.

[a] EOT is the date when the Investigator decides to discontinue study treatment (+7 days).

[b] FU is 40 days (+7 days) after the last T-DXd administration or before starting new anticancer treatment, whichever comes first. If EOT is >40 days (+7 days) of subject's last treatment, then the EOT assessments may take the place of the 40-day FU Visit assessments.

[c] Long-term follow-up will occur every 3 months (±14 days).

2. INTRODUCTION

2.1. Background

Colorectal cancer (CRC) is the third most common cancer worldwide. There were approximately 1.85 million new cases diagnosed and 880,000 associated deaths worldwide in 2018.[1] Several standard therapies for advanced or metastatic CRC (mCRC) are listed in the guidelines.[2,3,4] However, many patients with mCRC eventually progress on current standard of care treatments. The treatment benefit of third-line or subsequent therapy is also limited in patients who maintain a good performance status (PS) after receiving available treatments.

Approximately 2% of all CRCs are human epidermal growth factor receptor 2 (HER2)-positive and approximately 2% of Kirsten rat sarcoma viral oncogene homologue (*KRAS*) wild-type CRC are HER2 positive.[5] Most HER2 amplifications are found in rat sarcoma viral oncogenes homologue (*RAS*)/*BRAF* wild-type CRCs.[6,7] HER2 gene amplification/overexpression is considered to be associated with resistance to anti-epidermal growth factor receptor (EGFR)-targeted therapy,[8,9,10] and HER2 amplification/overexpression is a predictive marker of shorter progression-free survival (PFS) after anti-EGFR antibody cetuximab treatment in patients with mCRC harboring *RAS* wild-type and v-raf murine sarcoma viral oncogene homologue B1 (*BRAF*) wild-type. There is a high concordance between HER2 overexpression staining and HER2 gene amplification in colorectal adenocarcinomas.[11,12]

However, the reported frequency of HER2 amplification and overexpression in CRC varies between studies because of differences in examination methods and objective criteria.[13] The HER2 Amplification for Colorectal Cancer Enhanced Stratification (HERACLES) study assessed the antitumor activity of trastuzumab and lapatinib in patients with HER2-positive CRC, and found 5% of patients had HER2-positive tumors in human *KRAS* wild-type CRC.[14] In reported analyses of 3256 patients enrolled in the Quantitative Assessment of Swallowing after Radiation (QUASAR), Fluorouracil, Oxaliplatin, and Irinotecan: Use and Sequencing (FOCUS), and Panitumumab, Irinotecan, and Cyclosporin in Colorectal Cancer (PICCOLO) studies, HER2 overexpression in *KRAS*/*BRAF* mutated colorectal cancer tumor was 1.0%.[1]

Trastuzumab deruxtecan (T-DXd; DS-8201a) is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody conjugated to a drug-linker carrying a topoisomerase I payload. In the Phase 1 clinical study, DS8201-A-J101, in subjects with advanced HER2-expressing solid tumors, T-DXd was well tolerated at repeated doses of up to 8.0 mg/kg intravenously (IV) once every 3 weeks (Q3W). Preliminary data from DS8201-A-J101 and the Phase 2 clinical study DS8201-A-J203 (DESTINY-CRC01), in subjects with advanced HER2-expressing CRC studies have shown promising preliminary clinical efficacy in this patient population.[15]

T-DXd was also studied in the DS8201-A-U201 (DESTINY-Breast01) study in HER2-positive metastatic breast cancer previously treated with T-DM1.[16,17]

Based on data from DESTINY-Gastric01, T-DXd was granted orphan drug designation in the United States for the treatment of patients with GC/gastro-esophageal junction (GEJ) adenocarcinoma and Breakthrough Therapy Designation for the treatment of patients with

HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma who have received 2 or more prior regimens including trastuzumab based on data from DESTINY-Gastric01.[18]

Based on the results of these studies, T-DXd (ENHERTU®) obtained accelerated approval in the United States on 20 December 2019 for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who received 2 or more prior anti-HER2-based regimens in the metastatic setting.[19] On 25 March 2020, T-DXd obtained approval under the conditional early approval system in Japan for the treatment of patients with HER2-positive unresectable or recurrent breast cancer after prior chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments).

2.1.1. Investigational Product Trastuzumab Deruxtecan (T-DXd; DS-8201a)

T-DXd is a novel anti-HER2 ADC, that consists of an anti-HER2 antibody, MAAL-9001, covalently linked to approximately 8 molecules of MAAA-1162a (GGFG tetra-peptide cleavable linker and a topoisomerase I inhibitor [MAAA-1181a]). The drug MAAA-1181a (DXd), a derivative of exatecan, is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I. MAAL-9001 shares amino acid sequences with 2 currently approved anti-HER2 agents, trastuzumab and the antibody part of T-DM1, and thus T-DXd similarly targets HER2 expressing tumors.

Due to incorporation of a novel linker, T-DXd achieves a higher drug-to-antibody ratio (DAR) of approximately 8 with homogeneous conjugation of DXd compared with all currently approved ADCs composed of a DAR of 3 to 4. Despite the high DAR in T-DXd, the cleavable linker in T-DXd is more stable in plasma than T-DM1 to confer a favorable safety profile as observed in the nonclinical toxicology rat and monkey studies.

After binding to HER2 and internalization, T-DXd is cleaved by lysosomal enzymes preferentially expressed in tumor cells and releases the drug DXd in the cytoplasm. DXd is an exatecan derivative with greater potency than SN-38, the active metabolite of irinotecan. T-DXd is expected to exhibit antitumor activity through MAAA-1181a induced apoptosis and the antibody-dependent cellular cytotoxic (ADCC) activity of MAAL-9001 which leads to the inhibition of Akt phosphorylation.

As further differentiation from T-DM1, the released cytotoxic drug, MAAA-1181a, is cell membrane permeable after it is cleaved from the linker and exhibits a bystander effect.[20,21] This could allow potent activity even against tumors with HER2 heterogeneity.

2.2. Study Rationale

HER2 gene amplification is considered to be associated with resistance to EGFR-targeted therapy[22] and HER2 amplification is a predictive marker of shorter PFS after anti-EGFR antibody cetuximab treatment in patients with mCRC.[23] Therefore, HER2 is considered to be an important target for mCRC, although anti-HER2 combinations are recommended in National Comprehensive Cancer Network (NCCN) guidelines for HER2-amplified/*KRAS* wild-type CRC patients, no approved HER2-targeted therapies exist for CRC. In the third or later-line setting, therapies including Stivarga® and Lonsurf® are approved, but with modest efficacy: objective response rate (ORR) of Lonsurf® and Stivarga® are up to 1.6%, and PFS is 1.9 to 2.0 months.

Although HER2 amplification can be found in *RAS*/*BRAF* mutant CRC tumors, the clinical significance of this and how to effectively target it are unknown. New treatment options are needed for the HER2 positive/*RAS*-mutant or -wild-type (mt/wt) population.

In the MyPathway study which evaluated the combination of pertuzumab and trastuzumab in HER2 amplified mCRC subjects, 13 *RAS*-mutant subjects were enrolled and the ORR was 8% (95% CI: 0.2, 36), median PFS was 1.4 months (95% CI: 1.2, 2.8).[24] An unmet medical need exists for patients with *RAS*-mutant mCRC. Given the current evidence on the potential role of the HER2 pathway in mCRC, anti-HER2 treatment approaches are considered for further investigation.

Both 5.4 and 6.4 mg/kg doses of T-DXd have shown clinical efficacy in multiple cancer indications. However, the 5.4 mg/kg dose has not yet been tested in HER2 positive mCRC subjects. This Phase 2, randomized study to evaluate 5.4 mg/kg and 6.4 mg/kg doses in HER2-overexpressing mCRC subjects will further characterize the benefit-risk profile of T-DXd in this population.

2.3. Benefit and Risk Assessment

T-DXd has been developed for the treatment of HER2-expressing malignant tumors and has demonstrated substantial antitumor activity at a dose of 5.4 mg/kg in studies DS8201-A-J101 and DS8201-A-U201 (DESTINY-Breast01). As of 01 August 2019, the confirmed ORRs by independent central review (ICR) were 51.0% (95% CI: 36.6, 65.2) in DS8201-A-J101 and 60.9% (95% CI: 53.4, 68.0) in DS8201-A-U201 with a sustained duration of response (DoR) (median DoR for confirmed responses of 10.8 months [95% CI: 6.7, not evaluable (NE)] in DS8201-A-J101 and 14.8 months [95% CI: 13.8, 16.9] in DS8201-A-U201) and a prolonged PFS (median PFS by ICR of 13.7 months [95% CI: 8.5, 19.6] in DS8201-A-J101 and 16.4 months [95% CI: 12.7, NE] in DS8201-A-U201), all of which represent a clinically meaningful improvement over available therapies based on historical and real-world experience.

Preliminary clinical evidence for T-DXd in HER2-overexpressing mCRC comes from DS8201-A-J203. As of 09 August 2019, in DS8201-A-J203 study, mCRC subjects were enrolled in 3 cohorts (A: IHC 3+ and IHC 2+/ ISH+; B: IHC 2+/ ISH-; C: IHC 1+). All subjects were *RAS* wild-type. Patients were treated at 6.4 mg/kg every 3 weeks (Q3W).[25] A total of 53 subjects were enrolled in Cohort A. The confirmed ORR was 45.3% (95% CI: 31.6, 59.6), median PFS was 6.9 months (95% CI: 4.1, NE), and median DoR was not yet observed (95% CI: 4.2, NE) based on ICR. In the subgroup analysis in Cohort A: 40 subjects had IHC 3+ and 13 subjects had IHC 2+/ ISH+. The confirmed ORR in these subgroups were 57.5% (23/40) and 7.7% (1/13), respectively. However, there were no objective responses observed in subjects enrolled in Cohorts B (N=7) and C (N=18).[25]

Based on the cumulative review of the safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished) and taking into consideration biological plausibility, interstitial lung disease (ILD)/pneumonitis, anaemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease are classified as important identified risks. Left ventricular (LV) dysfunction is classified as an important potential risk.

ILD/pneumonitis is an important serious risk of T-DXd and cases with fatal outcomes have been reported. Most ILD/pneumonitis events in the above studies were Grade 1 or Grade 2, were manageable by dose modification and by following clinical treatment guidelines for drug-induced ILD/pneumonitis. In DS8201-A-J203, a total of 5 patients (6.4%) experienced ILD as adjudicated by an independent committee (two Grade 2; one Grade 2; and two Grade 5).[25] ILD/pneumonitis requires proper monitoring including early identification, and management instituted in a timely fashion.

T-DXd has demonstrated an overall acceptable safety profile in the treated populations to date.

In conclusion, the data available on the efficacy and safety of T-DXd supports the overall benefit-risk profile remaining favorable for clinical development.

For current assessments of risks and benefits to subjects, refer to the most current Investigator's Brochure (IB) for T-DXd.[26]

2.3.1. Benefit/Risk in Regard to SARS-CoV-2

With the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comes an increased safety risk for all subjects. Due to the potential impact of SARS-CoV-2 on the lung, the Sponsor has developed a monitoring plan to limit and manage the potential risk of SARS-CoV-2 to T-DXd study subjects. For any subjects with suspected or confirmed SARS-CoV-2, study treatment will be interrupted until they fully recover for treatment resumption (as outlined in the dose modification guidance; Section 10.6). All clinical study protocols have been updated to include language on dose modification for SARS-CoV-2.

As the subjects included in this study are at high risk of recurrence, and improved therapies are still needed for this population, the Sponsor considers the potential benefit of T-DXd for subjects in this study outweighs any potential risks associated with SARS-CoV-2.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives, definitions of associated endpoints as well as applicable outcome measures are described in Table 3.1. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 9.5.1, Section 9.5.2, Section 9.5.3, and Section 9.5.4.

Table 3.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measures	Endpoints	Category
Primary			
To assess the efficacy of T-DXd, as measured by the confirmed ORR by BICR in HER2-overexpressing (defined as IHC 3+ or IHC 2+/ISH+) mCRC subjects treated at the 5.4 mg/kg and 6.4 mg/kg doses	**Title:** Confirmed ORR **Description:** CR and PR as assessed by blinded data review and based on RECIST version 1.1 **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with CR or PR, assessed by BICR based on RECIST version 1.1	Efficacy
Secondary			
To evaluate the clinical efficacy of T-DXd by confirmed ORR by Investigator assessment	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by confirmed ORR by Investigator assessment **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	Confirmed ORR as indicated above assessed by Investigator assessment based on RECIST version 1.1	Efficacy
To evaluate the clinical efficacy of T-DXd by DoR	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by DoR **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	DoR, defined as time from the initial response (CR or PR) by BICR and Investigator assessment until documented tumor progression or death from any cause	Efficacy

Objectives	Outcome Measures	Endpoints	Category
To further evaluate the clinical efficacy of T-DXd by DCR, CBR, PFS and OS	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by DCR, CBR, PFS, and OS **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA (DCR, PFS) and 6 months after the last subject is registered for the primary analysis (DCR, CBR, PFS, OS)	Based on BICR and Investigator assessment according to RECIST version 1.1 (unless otherwise specified): • DCR, defined as the proportion of subjects who achieved CR, PR, or SD for a minimum of 6 weeks during study treatment; DCR based on BICR and DCR based on Investigator assessments will both be determined • CBR, defined as proportion of subjects who achieved CR, PR, or SD for at least 6 months; CBR based on BICR and CBR based on Investigator assessments will both be determined • PFS, defined as the time from date of randomization/registration until first objective radiographic tumor progression or death from any cause, based on BICR and Investigator assessment • OS, defined as the time from date of randomization/registration until death from any cause	Efficacy

Objectives	Outcome Measures	Endpoints	Category
To further evaluate the safety and tolerability of T-DXd	**Title:** TEAEs and other safety parameters during the study **Description:** Descriptive statistics of safety endpoints **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	Safety endpoints will include, incidence and severity of (according to the NCI-CTCAE version 5.0): • TEAEs (including SAEs and AESIs) • TEAEs associated with death • Incidence of dose interruptions, dose modifications, and discontinuations due to AEs • ECOG PS • Vital sign measurements • Clinical laboratory parameters (hematologic and non-hematologic) • ECG parameters • ECHO/ MUGA • Ophthalmologic assessments	Safety
To evaluate HEOR endpoints including patient-reported HRQoL, symptoms, and physical functioning	**Title:** PROs during the study **Description:** EORTC QLQ-C30 and EORTC QLQ-CR29, EQ-5D-5L, PGI-TT, PGIS, and PGIC **Time frame:** 6 months after the last subject is registered or later	PROs include: • Change from baseline in EORTC QLQ-C30 and EORTC QLQ-CR29 scale scores • EQ-5D-5L health state utility index • Patient-reported treatment tolerability with PGI-TT • Proportion of subjects with overall PGIS and PGIC	HEOR
To evaluate healthcare resource utilization for both treatment arms	**Title:** Healthcare resource use during the study **Description:** Healthcare resource use **Time frame:** 6 months after the last subject is registered or later	Healthcare resource use will be captured/collected, including inpatient admissions, intensive care unit admissions, and length of stay in hospital	Healthcare resource use
To evaluate PK of T-DXd	**Title:** PK profile **Description:** Serum concentrations **Time frame:** 6 months after the last subject is registered or later	• The PK endpoints include serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181a	PK

Objectives	Outcome Measures	Endpoints	Category
To evaluate immunogenicity of T-DXd	**Title:** Immunogenicity profile **Description:** Incidence of ADA and NAb **Time frame:** 6 months after the last subject is registered or later	• The immunogenicity endpoint includes incidence of ADA and NAb	Immunogenicity
Exploratory			
To further evaluate the clinical efficacy of T-DXd by TTR, best percent change in the SoD for all target lesions, and TTD in ECOG PS	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of T-DXd at 5.4 mg/kg and 6.4 mg/kg doses by TTR, SoD, and TTD in ECOG PS **Time frame:** 12 weeks after the first 80 subjects are randomized for the IA and 6 months after the last subject is registered for the primary analysis	• TTR, defined as the time from the date of randomization/registration to the date of first documented objective response (CR or PR), based on BICR and Investigator assessment • Best percentage change from baseline in the SoD for all target lesions, based on BICR and Investigator assessment • TTD in ECOG PS, defined as the time from the date of randomization/registration to the date when ECOG PS score of ≥2 is observed for the first time	Efficacy
To assess the relationship between changes in tumor markers (CEA and CA19-9) and radiographic response to T-DXd treatment	Not applicable	Changes in CEA and CA19-9	PD
To evaluate ERBB2 copy number detected in cfDNA at baseline as an exploratory predictive biomarker of response	Not applicable	ERBB2 copy number at baseline and its association with clinical outcomes	Biomarker

Objectives	Outcome Measures	Endpoints	Category
To evaluate other potential biomarkers of resistance or clinical benefit to study treatment	Not applicable	• Liquid biomarkers (eg, cfRNA and cfDNA) and its association with clinical outcomes • Potential DNA, RNA, and protein-based biomarkers evaluated by different methodologies (eg, cfDNA, NGS based analysis of DNA and RNA, protein-based analysis, IHC digital pathology analysis etc. of tumor and blood samples)	Biomarker
To explore an exposure/response relationship	Not applicable	• T-DXd PK concentration versus selected safety and efficacy endpoints	PK, Safety, and Efficacy

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; BICR = blinded independent central review; CA19-9 = carbohydrate antigen 19-9; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; cfDNA = cell-free deoxyribonucleic acid; cfRNA = cell-free ribonucleic acid; CR = complete response; DCR = disease control rate; DNA = deoxyribonucleic acid; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQol-5 dimensions-5 levels of severity; ERBB2 = erb-b2 receptor tyrosine kinase 2; HEOR = Health Economics and Outcomes Research; HER2=Human epidermal growth factor receptor 2; HRQoL = health-related quality of life; IA = interim analysis; IHC = immunohistochemistry; ISH = in situ hybridization; MAAA-1181a = released drug; mCRC = metastatic colorectal cancer; MUGA = multigated acquisition; NAb = neutralizing antibodies; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NGS = next-generation sequencing; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIC = Patient Global Impression-Change; PGIS = Patient Global Impression-Severity; PGI-TT = Patient Global Impression-Treatment Tolerability; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; PS = performance status; QLQ = Quality of Life Questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; SD = stable disease; SOC = standard of care; SoD = sum of diameters; TEAE = treatment-emergent adverse event; TTD = time to deterioration; TTR = time to response.

3.1. Rationale for Selection of Primary and Secondary Endpoints

The primary and key secondary efficacy endpoints selected will evaluate evidence of drug anti-tumor activity. ORR is defined as the proportion of subjects with complete or partial response (PR) as defined by RECIST version 1.1 in this study. ORR is a direct measure of drug antitumor activity, which can be evaluated in the current study. Because ORR is directly attributable to drug effect, it is an appropriate measure of efficacy.[27]

DoR in subjects with confirmed response is an important secondary endpoint of the study. A durable response is clinically meaningful in cancer patients and is an important measure to supplement ORR.

PFS represents the time interval from randomization/registration to disease progression or death, and provides a direct evidence of the activity of an investigational treatment in delaying tumor growth.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, randomized, 2-arm, parallel, Phase 2 study to evaluate 2 doses of T-DXd (5.4 mg/kg Q3W or 6.4 mg/kg Q3W) in subjects with locally advanced, unresectable, or metastatic HER2-overexpressing CRC (IHC 3+ or IHC 2+/ISH+) in 2 stages. The treatment assignment will remain unknown to the study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers, and the ILD Adjudication Committee (AC). The Sponsor and the contract research organization (CRO) are not blinded to the treatment assignment of the subjects. This study is planned to be conducted in approximately 70 study sites, including but not limited to the Americas, Asia-Pacific, and Europe. The subject population is described in Section 5.

The study start date is the date when the first subject has signed the main informed consent form (ICF). A subject is eligible to be enrolled into the interventional portion of the study when the Investigator or designee has obtained written (main) consent, has confirmed all eligibility criteria have been met by the subject, and all Screening procedures have been completed.

Randomization/registration is defined as the time point at which the Investigator has obtained the subject's randomization/registration code through the interactive response technology (IRT) system and study drug dose has been assigned (5.4 mg/kg Q3W or 6.4 mg/kg Q3W).

4.1.1. Design Overview

Approximately 850 subjects will be pre-screened for tumor tissue via a central laboratory to enroll approximately 120 subjects with HER2-overexpressing CRC of *BRAF* wild-type and either *RAS* wild-type or mutant tumor type, previously treated with standard therapy.

Eighty subjects will be randomized in a 1:1 ratio through the IRT to 5.4 mg/kg Q3W or 6.4 mg/kg Q3W of T-DXd at Stage 1. Randomization will be stratified by the following factors:

1. Eastern Cooperative Oncology Group (ECOG) PS (0 or 1)
2. HER2 status (IHC 3+ or IHC 2+/ISH+)
3. *RAS* status (wild-type or mutant)

The treatment assignment will remain unknown to the study subjects, Investigators, study site personnel (except the unblinded pharmacist), central imaging readers, and the ILD AC. The Sponsor and the CRO are not blinded to the treatment assignment of the subjects.

After enrollment is completed in Stage 1, forty subjects will be registered to the 5.4 mg/kg arm at Stage 2. An interim analysis (IA) is planned when at least 80 subjects have been randomized in Stage 1 of the study and have been followed for at least 12 weeks or have discontinued from the study.

The study will be divided into the following periods: Tissue Pre-Screening Period, Screening Period, Treatment Period, End of Treatment (EOT), and Follow-up Period.

- **The Tissue Pre-Screening Period** will start on the day of obtaining a signed and dated written Tissue Pre-Screening ICF from the subject prior to collecting tissue from a recent tumor biopsy (preferred) or archival tissue to confirm HER2 status. A tissue sample is considered a recent sample if it is collected from a biopsy performed after the subject's discontinuation of the last treatment regimen (and most recent disease progression). For subjects who sign this ICF, only serious adverse events (SAEs) directly related to the tissue pre-screening procedure (ie, tumor biopsy) should be reported via the SAVER Form. Unless documentation of other adverse events (AEs) are required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue pre-screening. The tissue pre-screening may occur any time before the Screening Period.
- **The Screening Period** will start on the day a subject signs the Main ICF and will comprise a maximum duration of 28 days. Rescreening is permitted once during this phase if the subject fails initial Screening. During the 28-day Screening Period, subjects' eligibility will be confirmed. The activities and/or assessments will be performed within 28 days before randomization/registration during the Screening Period are listed in Table 1.2. Within 14 days before randomization/registration, the subjects will undergo medical history evaluation, vital signs determination, physical examination, pulse oximetry (peripheral oxygen saturation [SpO2]), height and weight measurements, functional status confirmation using the ECOG PS, laboratory testing (including blood tests for safety), and 12-lead electrocardiograms (ECG) in triplicate. Eligible subjects will be randomized/registered and enter the Treatment Period.
- **The Treatment Period** starts on Day 1 of Cycle 1. Eligible subjects will be randomized to 1 of 2 treatment arms in **Stage 1**:
  - Arm 1: T-DXd for injection will be administered IV at a dose of 5.4 mg/kg Q3W
  - Arm 2: T-DXd for injection will be administered IV at a dose of 6.4 mg/kg Q3W
- After Stage 1 enrollment is complete (N=80), eligible subjects will be registered to T-DXd administered IV at a dose of 5.4 mg/kg Q3W in **Stage 2** (N=40). Subjects will receive the assigned dose of T-DXd (5.4 mg/kg Q3W or 6.4 mg/kg Q3W) until progression of disease or the subject meets one of the discontinuation criteria (Section 7.1). Combining both stages of the study, a maximum of 30 subjects per subgroup will be registered onto each of the HER2 IHC 2+/ISH+ and *RAS*-mutant subgroups. A minimum of 20 subjects with *RAS*-mutant status will be enrolled in the study. Once the maximum number of 30 subjects is reached, all subsequent subjects enrolled in the study should have HER2 IHC 3+ or *RAS* wild-type tumor.
- The **EOT** is defined as the date the Investigator decides to discontinue study treatment. Subjects who permanently discontinue the study treatment should be scheduled for an EOT visit within +7 days following the date study treatment is permanently discontinued. If the decision to discontinue the subject occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the subject return for an additional visit.

- **The Follow-up Period** will start upon permanent discontinuation of T-DXd. Subjects will be followed 40 days (+7 days) after the last study treatment administration or before starting new anticancer treatment, whichever comes first. Subjects who discontinue study drug for any reason other than PD, death, or loss to follow-up will be followed every 6 weeks (Q6W) until radiological disease progression or start of new anticancer treatment. If EOT is >40 days after last treatment, then the EOT assessments may take the place of the 40-day Follow-up Visit assessments. Long-term disease follow-up to monitor survival will be documented every 3 months (±14 days) for up to 2 years, every 6 months from 3 to 5 years, and annually from 6 to 10 years. Survival follow-up contact (either scheduled visit or telephone call) will be performed every 3 months (±14 days) from the date of the 40-day Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

The subject population is described in Section 5. A flow diagram of study activities is presented in Figure 1.1.

4.1.2. End of Study

The **primary completion date** is the date when the last enrolled subject has completed 6 months of follow-up treatment or when all subjects have been discontinued from the study and completed the 40-day Follow-up Visit, whichever is earlier. This date is used as the cut-off date for the analysis of the primary efficacy endpoint(s) of the study. All subjects still on treatment and continuing to derive benefit from study drug at the primary completion date will continue to follow the study schedule of assessments (Table 1.2) until the **overall End of Study (EOS)** is reached.

Overall EOS will occur when the last subject last visit has occurred or the study is discontinued by the Sponsor for other reasons (administrative, program-level, or class-related).

The subject's EOS is the date of their last study visit/contact.

4.1.3. Dose Regimen

Eligible subjects will be randomized to 1 of 2 treatment arms in Stage 1:

- Arm 1: T-DXd for injection will be administered IV at a dose of 5.4 mg/kg Q3W
- Arm 2: T-DXd for injection will be administered IV at a dose of 6.4 mg/kg Q3W

After Stage 1 enrollment is complete, eligible subjects will be registered to the arm that T-DXd for injection will be administered IV at a dose of 5.4 mg/kg Q3W in Stage 2.

Subjects will continue to receive T-DXd if they experience clinical benefit or until unacceptable toxicity/symptomatic deterioration attributed to PD (ie, pain secondary to disease or unmanageable ascites, etc.), after an integrated assessment of both radiographic data and clinical status by the Investigator. See Table 6.1 for complete details on dose regimen.

4.1.4. Duration

Duration of Treatment and Subject Participation

Subjects will receive T-DXd until discontinuation criteria are met (see Section 7.1) or in the absence of disease progression as assessed by Investigators, death, pregnancy, withdrawal of subject consent, loss to follow-up, study closure, physician decision, AE, protocol deviation, or other reasons (see details in Section 7.2).

Overall Study Duration

Enrollment is planned to occur over approximately 18 months. The anticipated total duration of the study is expected to be 30 months.

See Section 4.1 for the definition of study start and Section 4.1.2 for the definition of the overall EOS.

Study Drug Continuation After the End of Study

Not applicable.

4.2. Rationale for Study Design

This Phase 2 study design is based on Study DS8201-A-J203 which demonstrated the clinical efficacy of T-DXd in HER2 overexpressing mCRC subjects at the 6.4 mg/kg dose. Both 5.4 mg/kg and 6.4 mg/kg doses of T-DXd have shown clinical efficacy in multiple cancer indications. However, the 5.4 mg/kg dose has not been tested in HER2 overexpressing mCRC. Therefore, it is important to further characterize the benefit-risk profile for both doses in this study.

The study design of Stage 1 will implement both blinding (with respect to study subjects and Investigators) and randomization to minimize bias in the trial conduct and to allow unbiased assessment of 5.4 mg/kg and 6.4 mg/kg doses. Moreover, randomization will be stratified by important and potential prognostic/predictive factors which include ECOG PS (0 or 1), HER2 status (IHC 3+ or IHC 2+/ISH+), *RAS* status (wild-type or mutant), in order to reduce the risk of prognostic imbalance between treatment groups.

4.3. Justification for Dose

The dose selection of 5.4 mg/kg and 6.4 mg/kg in this study was based on the efficacy, safety, tolerability, and PK data of T-DXd from prior clinical studies in subjects with breast cancer, colorectal cancer, and other solid tumors.

The T-DXd dose of 5.4 mg/kg has been evaluated in the DS8201-A-J101 study and a Phase 2 study (DS8201-A-U201) in subjects with HER2-positive, unresectable, and/or metastatic breast cancer. The dose of 5.4 mg/kg has shown robust efficacy with confirmed ORR of 58.3% (137/235; 95% CI: 51.7% 64.7%) in subjects with metastatic breast cancer. From a safety perspective, a numeric trend for better safety profile was observed at the 5.4 mg/kg dose compared with higher doses (≥6.4 mg/kg) in subjects with breast cancer. The T-DXd dosing regimen of 5.4 mg/kg Q3W has also received approval in the United States and Japan for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer and is

also being evaluated in ongoing global Phase 3 studies in subjects with metastatic HER2-positive breast cancer and also in subjects with HER2 expressing non-small cell lung cancer (NSCLC) in an ongoing study (DS8201-A-U204).

The systemic exposure (area under the concentration-time curve [AUC] in the dosing cycle during Cycle 1 or at steady state) of intact T-DXd and DXd at 6.4 mg/kg dose in colorectal cancer patients were comparable to values observed in metastatic breast cancer patients at 5.4 mg/kg (for intact T-DXd) and 6.4 mg/kg (for DXd) doses, respectively. In subjects with breast cancer, DXd exposures were correlated with incidence of the safety endpoints, such as AE-related dose reduction or drug interruption, AEs Grade ≥3, SAE, anaemia, neutropenia, or thrombocytopenia. In these analyses, approximately 2% to 7% higher incidence of these safety endpoints was estimated at DXd exposures associated with 6.4 mg/kg dose compared with 5.4 mg/kg dose in subjects with breast cancer. These data suggest potentially lower incidence of these safety events expected at DXd exposures predicted at 5.4 mg/kg dose of T-DXd in subjects with colorectal cancer. In addition, the exposure-response analysis for ORR in subjects with colorectal cancer predicted about 5% lower ORR rate at 5.4 mg/kg dose compared with the 6.4 mg/kg dose.

In the dose escalation portion (Part 1) of the first-in-human Study DS8201-A-J101, no dose-limiting toxicities were observed, and the maximum tolerated dose (MTD) was not reached in the evaluated dose range of 0.8 to 8.0 mg/kg. Based on the efficacy and safety data in Part 1, the 5.4 mg/kg and 6.4 mg/kg doses exhibited clinical activity with a qualitatively similar safety profile, and therefore were selected for the dose expansion portion (Part 2) of Study DS8201-A-J101 in subjects with breast cancer, colorectal cancer, and other solid tumors; subjects with colorectal cancer (N =20) received only 6.4 mg/kg dose of T-DXd. T-DXd dose of 6.4 mg/kg has shown activity in HER2-expressing colorectal cancer subjects with confirmed ORR of 5% (1/20) and median DoR of 13 months and median (95% CI) PFS of 4 (2.7, 5.6) months following a median treatment duration of 8.1 months (range: 0.7 to 29 months) at the time of data cut (data cut-off date: 01 Feb 2019).

The T-DXd dose of 6.4 mg/kg is also being evaluated in the ongoing Phase 2 Study DS8201-A-J203 in subjects with HER2-expressing advanced colorectal cancer. Promising efficacy was also observed based on the data (data cut-off date: 9 Aug 2019) from this ongoing study with median treatment duration of 4.8 months (median; range: 3.9 to 5.8 months) at the time of data cut. In subjects with HER2-expressing advanced colorectal cancer (IHC 3+ or IHC 2+/ISH+) following treatment with T-DXd dose of 6.4 mg/kg, confirmed ORR by ICR was 45.3% (24/53; 95% CI: 31.6% - 59.6%) with median DoR not reached (95% CI: 4.2 months to NE) and the median PFS was 6.9 months (95% CI: 4.1 months to NE).

These findings along with the observed efficacy and safety data in subjects with HER2 expressing colorectal cancer in the Studies DS8201-A-J101 and DS8201-A-J203 support the selection of 5.4 mg/kg and 6.4 mg/kg doses to further characterize the benefit-risk profile of T-DXd in HER2 overexpressing CRC subjects.

5. STUDY POPULATION

Adult subjects with a diagnosis of locally advanced, unresectable, or metastatic HER2 overexpressing colorectal cancer with *BRAF* wild-type status.

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for randomization/registration into the study:

1. Sign and date the Tissue Pre-Screening and Main ICFs, prior to the start of any respective study-specific qualification procedures.
2. Adults aged ≥20 years in Japan, Taiwan, and Korea, or those aged ≥18 years in other countries, at the time the ICFs are signed. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years).
3. Pathologically-documented, unresectable, recurrent, or metastatic colorectal adenocarcinoma. Subject must have *BRAF* wild-type cancer and *RAS* status identified in primary or metastatic site, tested by a Clinical Laboratory Improvement Act (CLIA), ISO15189, or equivalent-certified laboratory.
4. The following therapies should be included in prior lines of therapy:
    a. Fluoropyrimidine, oxaliplatin, and irinotecan, unless contraindicated
    b. Anti-EGFR treatment, if *RAS* wild-type and if clinically indicated
    c. Anti-VEGF treatment, if clinically indicated
    d. Anti-PD-(L)-1 therapy, if tumor is MSI-high/deficient mismatch repair (dMMR), or tumor mutational burden (TMB)-high, if clinically indicated
5. Is willing and able to provide an adequate tumor sample for tissue pre-screening to confirm HER2 status by central laboratory (most recent tumor tissue preferred).
6. Confirmed HER2-overexpressing status assessed by central laboratory and defined as IHC 3+ or IHC 2+/ISH+.
7. Presence of at least one measurable lesion assessed by the Investigator per RECIST version 1.1. Lesions situated in a previously-irradiated area are considered measurable if progression has been demonstrated in such lesions after the end of radiotherapy.
8. ECOG PS of 0 or 1.
9. Has LVEF ≥50% within 28 days before randomization/registration.
10. Has adequate organ function within 14 days before randomization/registration, defined as:

Parameter	**Laboratory value**
Adequate bone marrow function	
Platelet count	≥100,000/mm3 (Platelet transfusion is not allowed within 1 week prior to Screening assessment)

Parameter	Laboratory value
Hemoglobin	≥9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to Screening assessment)
Absolute neutrophil count (ANC)	≥1500/mm^3 (Granulocyte-colony stimulation factor [G-CSF] administration is not allowed within 1 week prior to Screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation (Section 10.3.1)
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤5 × upper limit of normal (ULN)
Total bilirubin	≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Serum Albumin	≥2.5 g/dL
Adequate blood clotting function	
International normalized ratio (INR)/Prothrombin time (PT) and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)	≤1.5 × ULN

11. Has adequate treatment washout period before randomization/registration, defined as:

Treatment	Washout Period
Major surgery	≥4 weeks
Radiation therapy, including palliative stereotactic radiation to chest	≥4 weeks (palliative stereotactic radiation therapy to other areas ≥2 weeks)
Anticancer chemotherapy (immunotherapy [non-antibody-based therapy]), retinoid therapy	≥3 weeks (≥2 weeks or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥6 weeks for nitrosoureas or mitomycin C)

Treatment	Washout Period
Antibody-based anticancer therapy	≥4 weeks
Chloroquine/hydroxychloroquine	>14 days

12. If the subject is a woman of childbearing potential, she must have a negative urine pregnancy test within 72 hours before randomization/registration; a positive urine pregnancy test result must immediately be confirmed using a serum test. The subject must also be willing to use highly effective birth control, as detailed in Section 10.3.4, upon randomization/registration, during the Treatment Period, and for 7 months, following the last dose of study drug. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
    a. Non-childbearing potential is defined as premenopausal female subjects with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory). Female subjects on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one 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 randomization/registration. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.
13. If male, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.4) upon randomization/registration, during the Treatment Period, and for 4 months following the last dose of study drug.
14. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to randomization/registration in this study.
15. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study Treatment Period, and for at least 7 months after the final study drug administration.
16. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
17. Life expectancy is ≥3 months.

5.2. Exclusion Criteria

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

1. Medical history of myocardial infarction (MI) within 6 months before randomization/registration, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV). Subjects with troponin levels above ULN at Screening (as defined by the manufacturer), and without any MI-related symptoms, should have a cardiologic consultation before randomization/registration to rule out MI.
2. Has a corrected QT interval (QTcF) prolongation to >470 msec (female subjects) or >450 msec (male subjects) based on the average of the Screening triplicate 12-lead ECGs.
3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
4. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of the randomization/registration, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion, etc.).
5. Any autoimmune, connective tissue, or inflammatory disorders (eg, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, etc.) where there is documented, or a suspicion of, pulmonary involvement at the time of Screening. Full details of the disorder should be recorded in the electronic case report form (eCRF) for subjects who are included in the study.
6. Prior pneumonectomy.
7. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and randomization/registration.
8. Subjects with leptomeningeal carcinomatosis.
9. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumors curatively treated.
10. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
11. Has a history of severe hypersensitivity reactions to other monoclonal antibodies.
12. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
13. Has substance abuse or any other medical conditions such as clinically significant cardiac 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.

14. Has known human immunodeficiency virus (HIV) infection. Unless required by local regulations or institutional review board (IRB)/ethics committee (EC), an HIV antigen/antibody test is not required prior to randomization/enrollment.
15. Active hepatitis B and/or hepatitis C infection, such as those with serologic evidence of viral infection within 28 days before study randomization/registration. Subjects with past or resolved hepatitis B virus (HBV) infection are eligible if hepatitis B surface antigen (HBsAg) negative (-) and antibody to hepatitis B core antigen (anti-HBc) positive (+). Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible at the discretion of the Investigator and approval of the Sponsor.
17. Previous treatment with a DXd-containing ADC.
18. Evidence of ongoing uncontrolled systemic bacterial, fungal, or viral infection. Note: Subjects with localized fungal infections of skin or nails are eligible.
19. Female subject who is pregnant, breastfeeding, or intends to become pregnant during the study.
20. Psychological, social, familial, or geographical factors that would prevent regular follow-up.
21. Otherwise considered inappropriate for the study by the Investigator.

5.3. Screening Failures, Rescreening, and Subject Replacement

Rescreening is permitted once for any subject who fails to meet reversible or transient eligibility criteria upon initial screening. The rescreening must be performed within the Screening Period. The subject identifier (SID) number must remain the same at the time of rescreening. The initial Screening information and the reason why the subject was ineligible for the initial evaluation will be recorded on the Screening Log.

For subjects that had an initial tumor sample sent but where the central laboratory reports that there was an analytical failure (ie, quality control samples fail, tissue with quality issues [including no staining, no tumor, or equivocal cases]) then the site can send additional tissue, archival or by performing a new tumor biopsy. NOTE: This is not a second attempt at prescreening, this is part of the initial/same prescreening procedure.

Randomized/registered subjects will not be replaced.

6. STUDY TREATMENT

See Figure 1.1 for treatment sequence.

6.1. Study Drug Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of T-DXd.

Table 6.1: Study Drug Dosing Information

Study Drug Name	**Trastuzumab deruxtecan (T-DXd; DS-8201a)**
Dosage Formulation	T-DXd for injection 100 mg will be provided as a lyophilized powder containing 100 mg of T-DXd in a single-use glass vial.[27]
Dosage Level(s)	5.4 mg/kg or 6.4 mg/kg
Route of Administration	Intravenous (IV)
Dosing Regimen	One IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day (±2 days) cycle
Duration	Intermittent dosing, 21 days per cycle
Packaging	T-DXd for injection 100 mg will be labeled and packaged in compliance with regulatory requirements
Labeling	The packaging will clearly display the name of the study drug, the lot number, storage condition, and other required information in accordance with local regulations

6.2. Preparation, Handling, Storage, and Accountability for Study Drug

6.2.1. Preparation, Handling, and Disposal

T-DXd for IV infusion is prepared by dilution of the required volume of the study treatment calculated based on the subject's body weight. The preparation of study drug will be conducted in accordance with the Pharmacy Instruction provided by the Sponsor.

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures (SOP) of the site.

6.2.2. Administration

The initial dose of study treatment will be infused for approximately 90 minutes. If there is no infusion-related reaction, after the initial dose, the next doses of study treatment will be infused for a minimum of 30 minutes (approximately ±5 minutes). Following which, the study treatment may be administered as an IV infusion over 30 to 90 minutes every 21 days (±2 days). 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. For weight changes <10%,

dose-calculation adjustments should follow local guidelines. Refer to the pharmacy instructions for detailed information about administration of study treatment.

T-DXd should only be administered 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.

6.2.3. Storage

T-DXd must be stored in a secure, limited access storage area under the recommended storage conditions noted on the label. If storage conditions are not maintained per specified requirements, the Sponsor or CRO should be contacted.

T-DXd for injection 100 mg must be stored at 2°C to 8°C (protected from light) for lyophilized powder.

See the Pharmacy Manual and Pharmacy Instruction for storage conditions of the infusion solution.

6.2.4. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug against the shipping documentation, check for appropriate local language in the label, check drug expiration date, and acknowledge receipt in the IRT system.

In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment. The original shipment documentation will be retained at the study site.

The Investigator is responsible for study drug accountability, reconciliation and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

A Drug Accountability Record will be provided for study treatment. The record must be kept current and should contain all of 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 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 the study closure, a final study treatment reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. See the Pharmacy Manual 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.

6.3. Measure to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Allocation

6.3.1.1. Stage 1

Randomization to either 5.4 mg/kg Q3W or 6.4 mg/kg Q3W will occur in Stage 1 of the study.

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

Subjects will be randomized into 1 of the 2 treatment arms (T-DXd at 5.4 mg/kg Q3W or 6.4 mg/kg Q3W) in a 1:1 ratio. The randomization will be stratified by the following 3 stratification factors:

- ECOG PS (0 or 1)
- HER2 status (IHC 3+ or IHC 2+/ISH+)
- *RAS* status (wild-type or mutant)

Randomization will be managed through the IRT for subjects meeting all eligibility criteria. The directions on how to use the system will be provided in the IRT Reference Manual.

The system will assign a unique SID number and treatment arm for that subject (ie, Arm 1 vs Arm 2). Cycle 1 Day 1 of treatment should occur within 7 days (Days 0-7) after randomization/registration. However, it is permissible for a subject to receive the first dose of T-DXd on the same day as randomization/registration, if applicable.

The assignment of the subjects is blinded to the site through the roles and permissions document in the IRT. The randomization schedule will be developed by a third party vendor.

6.3.1.2. Stage 2

For Stage 2, subjects will be registered onto the 5.4 mg/kg Q3W treatment arm only.

Combining both stages of the study, a maximum of 30 subjects per subgroup will be registered onto each of the HER2 IHC 2+/ISH+ and *RAS*-mutant subgroups.

6.3.2. Blinding

The treatment assignment will remain unknown to the study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers, and the ILD AC. The Sponsor is not blinded to the treatment assignment of the subjects, nor the CRO except central imaging vendor.

The randomization schedule will be kept securely.

6.3.3. Emergency Unblinding Procedure

In the case of a rare emergency where, in the opinion of the Investigator, discontinuation of study drug is not sufficient and study treatment must be unblinded to evaluate a further course of medical treatment, the following procedures will apply:

This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment dose assignment. The occurrence of an SAE should not precipitate the immediate unblinding of the investigational product dose. The Investigator must contact the Sponsor prior to unblinding a subject's treatment assignment. However, to prevent delays to the Investigator or medical personnel responding to a potentially emergent situation, unblinding of the study treatment will not be dependent upon the Investigator receiving approval from the Sponsor (ie, the Investigator will be able to obtain the code break information independent of the Sponsor). If a subject's treatment assignment is unblinded, the Sponsor must be notified immediately.

In the event of emergency unblinding, the subject will be informed about their treatment assignment. Information about the treatment assignment must be restricted to designated study site staff/personnel who are providing immediate care to the subject. Any documentation of the treatment assignment must be maintained separately (ie, a secured file). When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the Investigator and selected Daiichi Sankyo study personnel from the IRT vendor. The notification will not contain any unblinding information. This will trigger the follow-up process to document the unblinding by completing the Emergency Unblinding by Investigator Form (to be provided to the Sponsor by study personnel upon receipt of IRT notification) and submission to Daiichi Sankyo Clinical Safety and Pharmacovigilance; please refer to the form for completion instructions. Once the study treatment has been unblinded for a specific subject, the study treatment should be discontinued for the subject, and the subject should exit the study treatment phase. The EOT and follow-up assessments for the subjects will be performed as defined in the protocol.

6.4. Treatment Compliance

T-DXd will be administered by IV only to subjects participating in the study and under the supervision of clinical study personnel at the site. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for administration of the study drug. Start and stop date/times of injection and amount of drug administered must be recorded in the eCRF.

6.5. Guidelines for Dose Modification

The Investigator will evaluate which toxicities are attributable to T-DXd and adjust the dose as recommended below. All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity (NCI-CTCAE version 5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of T-DXd are listed in Table 6.3, which is applicable only to treatment-emergent AEs (TEAEs) that are assessed as related to use of T-DXd by the Investigator(s) unless otherwise instructed. 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 the initiating the study drug until 47 days after last dose of the study drug. For non-drug-related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

All dose interruptions or modifications must be recorded in the eCRF. If study drug is interrupted, missed doses will not be made up.

In the event of a dose interruption occurring prior to completion of a PK/immunogenicity blood sampling in the study, Investigators should contact the Sponsor's Medical Monitor for guidance regarding scheduling of these procedures.

Prophylactic or supportive treatment for expected toxicities, including management of study drug-induced AEs will be as per the Investigator's discretion and institutional guidelines.

For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 days until the AE is determined to be resolving or subject is discontinued at the EOT.

Note: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 6.3.

6.5.1. Dose Reduction Guidelines

If dose reduction is required, dosing should be reduced by 1 dose level at a time. Up to 2 dose reductions will be permitted for subjects (Table 6.2). If toxicity continues after the permitted dose reductions, the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Once the dose of T-DXd has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. Once the dose of T-DXd is reduced, no escalation is permitted.

Table 6.2: Dose Reduction Levels of T-DXd

Treatment Arm	Starting Dose	Dose Level −1	Dose Level −2
1	5.4 mg/kg	4.4 mg/kg	3.2 mg/kg
2	6.4 mg/kg	5.4 mg/kg	4.4 mg/kg

If toxicity continues after 2 dose reductions, the subject will be withdrawn from the study treatment. T-DXd dose increases are not allowed in the study.

6.5.2. Dose Interruption and Modification / Toxicity Management Guidelines for T-DXd

Specific criteria for T-DXd dose interruption, re-initiation, dose reduction, and/or discontinuation in case of TEAEs that are considered related to the use of T-DXd by the Investigator are presented in Table 6.3, which is applicable only to TEAEs that are assessed as related to use of T-DXd by the Investigator(s). 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 the study drug until 47 days after last dose of the study drug. For non-drug-related TEAEs or if nothing is noted in Table 6.3, standard practice guidelines for management of AEs should be followed. Appropriate experts should be consulted as deemed necessary. The Investigator may consider dose interruptions or T-DXd discontinuation based on other events not listed in Table 6.3 according to the subject's condition.

There will be no dose modifications for Grade 1 or Grade 2 TEAEs unless specified in Table 6.3. For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed frequently and at an interval no greater than 7 days.

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

A subject for whom T-DXd dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last study drug dose.

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. Please refer to Section 10.6 for additional information on dose modification related to SARS-CoV-2.

Table 6.3: Dose Modification Guidelines for T-DXd

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
No toxicity	Maintain dose and schedule
Infusion-Related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion-related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hrs)	• Administration of T DXd should be interrupted and symptomatic treatment started (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids). • If the event resolves or improves to Grade 1, infusion can be re started at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of T DXd should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc., should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2, • Reduce dose 1 level

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
Febrile Neutropenia (absolute neutrophil count <1 × 109/L, fever >38.3°C or a sustained temperature of ≥38°C for more than one hour)	Delay dose until resolved, • Reduce dose by 1 level
Lymphocyte Count Decreased[a]	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (<0.2 × 109/L)	Delay dose until resolved to ≤ Grade 2: • If resolved in ≤14 days from day of onset, maintain dose • If resolved in >14 days from day of onset, reduce dose 1 level
Anaemia	
Grade 3 (Hemoglobin [Hb] <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life-threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (platelets <50 - 25 × 109/L)	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (platelets <25 × 109/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure (CHF)	Discontinue subject from study treatment
Decrease in left ventricle ejection fraction (LVEF) 10 20% (absolute value), but LVEF >45%	Continue treatment with T DXd
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	• Continue treatment with T DXd • Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤45% and decrease is 10-20% (absolute value) from baseline	• Interrupt T DXd dosing • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment • If LVEF recovers to within 10% from baseline, resume treatment with study drug
LVEF <40% or >20% (absolute value) drop from baseline	• Interrupt T DXd dosing • Repeat LVEF assessment within 3 weeks • If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
Electrocardiogram QT prolonged	
Grade 3 (Average QTc> 500 ms or >60 ms change from baseline)	Delay dose until resolved to ≤ Grade 1 (corrected QT ≤480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then if attributed to T DXd, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment
Pulmonary Toxicity	If a subject develops radiographic changes potentially consistent with interstitial lung disease (ILD)/pneumonitis 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 adverse event (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 computed tomography (CT) • Pulmonologist consultation (Infectious Disease consultation as clinically indicated) • Blood culture and complete blood count (CBC). Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests and pulse oximetry (SpO2) • Arterial blood gases if clinically indicated • One blood sample collection for pharmacokinetic (PK) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of T DXd must be interrupted for any ILD/pneumonitis events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry.

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
	• Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade 1 events, T DXd can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤28 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose 1 level However, if the event Grade 1 ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given.
Grade 2	Permanently discontinue subject from study treatment. • Promptly start and treat with systemic steroids (eg, at least 1.0 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days: o Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone). o Reconsider additional work-up for alternative etiologies as described above. o Escalate care as clinically indicated.
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 or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days:

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
	○ Reconsider additional work-up for alternative etiologies as described above. ○ Consider other immunosuppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Blood creatinine increased	
Grade 3 (>3.0 to 6.0 × upper limit of normal [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	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous total bilirubin (TBL)	
AST/ALT >3.0 × ULN with simultaneous TBL >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 drug 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 TBL twice weekly until resolution or return to baseline.
Aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT)	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 × ULN, otherwise delay dose until resolved to ≤ baseline, then: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 3: (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was >3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level

Worst Toxicity National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (unless otherwise specified)	**Management Guidelines for T DXd**
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Total Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline at baseline, continue study treatment
Grade 3 (>3.0 - 10.0 × ULN if baseline was normal; >3.0 - 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, reduce dose 1 level • If resolved in >7 days from day of onset, discontinue T DXd If documented Gilbert's syndrome or liver metastases at baseline at baseline, repeat testing within 3 days. Delay dose until resolved to < Grade 2: • If resolved in ≤7 days from day of onset, reduce dose 1 level • If resolved in >7 days from day of onset, discontinue T DXd
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) or Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1 • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Diarrhoea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 • If resolved in ≤3 days from day of onset, maintain dose • If resolved in >3 days from day of onset, reduce dose 1 level

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

[a] There will be no dose modifications for Grade 1 to Grade 3 lymphopenia.
Note: All dose modifications should be based on the worst preceding toxicity.

In addition, Investigators may consider dose reductions or discontinuations of T-DXd according to the subject's condition and after discussion with the Sponsor's Medical Monitor or designee.

6.6. Prior and Concomitant Medications

Therapies used from the time the subject signs the Main ICF for study participation to the 40-day Follow-up Visit (+7 days) after the last administration of T-DXd will be recorded in the eCRF. Prophylactic therapies (including any required premedications), prior therapies, and all concomitant therapies will be recorded in the eCRF.

All therapies received by subjects within 28 days prior to randomization will be recorded as prior therapies. Concomitant therapies include all prescription, over-the-counter, and herbal remedies. In addition, details of prior neoadjuvant therapy and radiotherapy (if applicable) will be recorded in the eCRF.

6.6.1. Prohibited Therapies/Products

The following medications/ treatment and procedures will be prohibited during the Treatment Period. 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).
- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response and it does not interrupt treatment for more than the maximum time specified in the dose modification section).

- Radiotherapy to the thorax.
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs (inhaled steroids or intra-articular steroid injections are permitted in this study).
  - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Section 10.6 for further details.

6.6.2. Permitted Therapies/Products

The following therapies/products are permitted during study treatment.

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator.
- Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
- Prophylactic or supportive treatment of study drug induced-AEs will be otherwise as per Investigator's discretion and institutional guidelines.
- Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NK1) receptor antagonists and/or steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

6.6.3. Restricted Products

- Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of T-DXd treatment administration must be recorded. Reasons for treatment discontinuation include:

- Death
- AE
- Progressive disease (PD) per RECIST version 1.1 assessed by the Investigator
- Clinical progression (definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for PD according to RECIST version 1.1)
- Withdrawal of consent by subject (**to discontinue study drug**); NOTE: In this section this is only withdrawal for treatment with study drug and 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).
- Physician decision
- Lost to follow-up (see Section 7.3 for details on when a subject is considered lost to follow-up)
- Pregnancy
- Protocol deviation
- Study termination by Sponsor
- Emergency unblinding
- Other

After study drug is permanently discontinued for any reason other than death or lost to follow-up, the subject will be treated as clinically indicated by the Investigator or referring physician. 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 except for the following cases:

Discontinuation due to drug-related TEAE which required 49 days dose delay from the last infusion date

- Discontinuation due to more than 2 dose reductions required

The Investigator must discuss with the subject that their decision to permanently discontinue the study drug means the subject still agrees to continue into the Follow-up Period for onsite or

modified follow-up visits. Subjects will be followed for disease progression, if applicable, and survival at regularly scheduled intervals (see Table 1.2).

7.1.1. Procedures for Discontinuation from Study Drug

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF;
- Due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized;
- An EOT evaluation should be performed as described in the Schedule of Events (SoE) (Table 1.3);
- A safety follow-up evaluation should be performed approximately 40 (+7) days after the last dose of study drug as described in the SoE (Table 1.3);
- If subject has not discontinued for "PD," continue tumor assessments until progression or start of new therapy, if applicable, and survival as described in the SoE (Table 1.3);
- Long-term follow-up evaluations will be performed to assess survival as described in the SoE (Table 1.3).

The Investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose. All procedures and tumor assessments specified for the EOT visit will be conducted. See Table 1.2 for specific EOT procedures.

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.

7.1.2. 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 (may be quarterly, bi-annually, annually, or only at EOS)
- 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 from alternative sources (eg, doctor's notes, hospital records)

Dates of the modified follow-up contact(s) should be recorded. See Section 7.2 for definition of withdrawal by subject from the study (ie, withdrawal of consent).

7.2. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- Death
- 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
- Lost to Follow-up (see Section 7.3 for details on when a subject is considered Lost to Follow-up)
- Study Termination by Sponsor
- Other

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are PD or AE. If reason of death is unknown every effort should be made to obtain the primary cause of death. Only one AE will be recognized as the primary cause of death.

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

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel contacting an alternative person
- Study personnel accessing and reviewing the subject's medical information from alternative sources

If the subject refuses all of the above methods of follow-up, the Investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

7.2.1. Withdrawal Procedures

If a subject is withdrawn from both the interventional and follow-up portions of 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 dose, date of last contact, and the reason for withdrawal;
- And disclosure of future information is also withdrawn, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent;
- The subject may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records;
- Study site personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status.

See SoE (Table 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

Subjects will be considered lost to follow-up if he/she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff. Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

If direct contact with the subject is not possible the site must make every effort to collect survival status from public records (eg, obituaries, death certificates, etc) in accordance with local laws.

8. STUDY PROCEDURES

See the SoEs in Table 1.2 and Table 1.3 for Tissue Pre-Screening, Screening, Treatment, EOT, and follow-up study procedures.

8.1. Eligibility Assessment

Review the subject's demographics, medical and CRC disease history, vital signs, and results of tests (eg, physical examination, ECHO/multigated acquisition [MUGA], ECG, ECOG PS, laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2). See Section 5.3 for rescreening.

8.1.1. 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 drugs are administered. Subjects should be given the opportunity to ask questions and receive responses 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. See Section 10.1.2 for additional details.

8.1.2. Qualifying Tumor Tissue Specimen

To determine eligibility, subjects must have CRC that has confirmed HER2 overexpression as determined according to the gastric American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guideline scoring algorithm[28] evaluated at a central laboratory.

Note: Subjects may continue on prior therapy (if applicable) while HER2 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 Pre-Screening ICF from the subject prior to collecting tissue.
- Obtain adequate archival, recent tumor tissue sample, or new tumor biopsy for HER2 testing.
- If slides are sent in place of a paraffin embedded tissue block at Pre-Screening, then additional slides will be required at Screening.
- Refer to Study Laboratory Manual for preparation, number of slides required, storage, and shipment procedures.
- Send the samples to the central laboratory to confirm HER2 status.
- Assign SID from IRT.

8.1.3. Colorectal Cancer History

Subject's CRC history will be obtained by the Investigator or a qualified designee. *RAS* status in primary or metastatic site(s) must be tested by a CLIA, ISO15189, or equivalent certified laboratory. Subjects are required to have at least *KRAS* and *BRAF* status determined locally.

8.1.4. HER2-overexpression Status

Subjects must have HER2 overexpressing status confirmed by a central laboratory to be enrolled in the study. HER2 expression will be determined by investigational IHC and ISH assays and test results will be determined by trained pathologists. HER2 overexpressing status will be based on pre-screening results and defined as an IHC score of 3+ or 2+ and positive by ISH (defined as a ratio of ≥2.0 for the number of HER2 gene copies to the number of signals for CEP17) confirmed by a central laboratory prior to study enrollment. If sufficient material from the archival tissue, recent tumor tissue, or new tumor biopsy is not available for submission, central HER2 determination for eligibility may be performed on residual tumor tissue from the time of definitive surgery. See also Section 8.1.2.

8.1.5. General Medical History and Baseline Conditions

Subject's medical history will be obtained by the Investigator or a qualified designee.

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of CRC/vital signs that are out of range) that were diagnosed or known to exist prior to the main consent date will be recorded on the General Medical History and Baseline Conditions eCRF, not the AE eCRF. Record the start date of any medical occurrence that started after the Main ICF was signed and is ongoing at the time of the first dose of T-DXd on the General Medical History and Baseline Conditions eCRF.

8.1.6. Demographics

Review the subject's demographics against the eligibility criteria. Demographic data will include age, sex, country, and self-reported race/ethnicity where allowed per local regulations.

8.1.7. Human Immunodeficiency Virus Antibody Test

As required by local regulations or independent IRB/EC, perform an HIV antigen/antibody test prior to randomization/enrollment.

8.1.8. Hepatitis Screening

Perform hepatitis B/C serology. Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

8.2. Randomization/Registration

For Stage 1, after all Screening procedures are performed, results of Screening tests are available, and subjects are confirmed to continue to meet all eligibility criteria, eligible subjects will be randomized in a 1:1 ratio into 1 of 2 treatment groups (T-DXd 5.4 mg/kg Q3W versus T-DXd 6.4 mg/kg Q3W).

Randomization will be stratified by following factors:

- ECOG PS of 0 or 1
- HER2 status: IHC 3+ or IHC 2+/ISH+
- *RAS* status (wild-type versus mutant)

For Stage 2, after all Screening procedures are performed, results of Screening tests are available, and subjects are confirmed to continue to meet all eligibility criteria, eligible subjects will be registered into the T-DXd 5.4 mg/kg Q3W treatment group.

Combining both stages of the study, a maximum of 30 subjects (per subgroup) will be registered onto each of the IHC 2+/ISH+ and *RAS*-mutant subgroups. A minimum of 20 subjects with *RAS*-mutant status will be enrolled in the study.

Cycle 1 Day 1 of treatment *should* occur within 7 days (Days 0-7) after randomization/registration. However, it is permissible for a subject to receive the first dose of T-DXd on the same day as randomization/registration, if applicable.

8.3. Efficacy Assessments

8.3.1. Primary Efficacy Endpoint

Efficacy assessments will be based on tumor assessments to be performed at Screening and every 6 weeks while the subject remains on study drug. The primary efficacy endpoint is ORR, defined as the proportion of subjects with a best overall response (BOR) of confirmed CR or confirmed PR, assessed by blinded independent central review (BICR) based on RECIST version 1.1. Refer to Section 8.3.4 and Section 10.4 for details regarding RECIST for radiological tumor assessments.

8.3.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Confirmed ORR assessed by the Investigator based on RECIST version 1.1
- DoR, defined as time from the initial response (complete response [CR] or PR) until document tumor progression based on RECIST version 1.1 or death from any cause
- Disease control rate (DCR), defined as the proportion of subjects who achieved CR, PR, or stable disease (SD) for a minimum of 6 weeks during study treatment
- Clinical benefit rate (CBR), defined as proportion of subjects achieved CR, PR, or SD for at least 6 months
- PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause
- OS defined as the time from date of randomization until death from any cause

8.3.3. Exploratory Efficacy Endpoints (Including QoL and Biomarker)

Exploratory efficacy endpoints include the following:

- Time to response (TTR); defined as time from the date of randomization/registration to the date of first documented objective response (CR or PR) based on BICR and Investigator assessment
- Best percentage change from baseline in sum of diameters (SoD) for all target lesions based on BICR and Investigator assessment
- Time to deterioration (TTD) in ECOG PS
- Change from baseline in EORTC QLQ-C30 and EORTC QLQ-CR29 scale scores
- EQ-5D-5L health state utility index
- Patient-reported treatment tolerability with PGI-TT
- Proportion of patients with overall PGIS and PGIC
- Healthcare resource use will be captured/collected, including inpatient admissions, intensive care unit admissions, and length of stay in hospital
- Changes in carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)
- ERBB2 copy number at baseline and its association with clinical outcomes
- Other potential biomarkers of resistance or clinical benefit to study treatment

8.3.4. Radiographic Tumor Assessments

At baseline, a computed tomography (CT) or MRI of the brain is required ONLY if the subject has a history of brain metastases and/or symptoms suggestive of brain metastases. If there are no brain metastases at the time of Screening, a brain CT or MRI during the study treatment should only be performed if symptoms associated with brain metastases appear during the study period.

If no clinical symptoms are observed, a CT or MRI of the brain is not mandatory at Screening or during the study period. A CT or MRI of the brain is required throughout the study (at tumor assessment time points) and EOT when the subject has brain metastases identified at baseline.

Radiographic tumor assessments will include all known or suspected disease sites. Scans of the chest, abdomen, pelvis, and any other sites of disease are required and may be performed at any time, as clinically indicated, and according to the Investigator and details recorded in the eCRF.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons, follow the local label/package insert/SMPC or institutional guidelines for allergic reactions to contrast agents.

Computed tomography and/or MRI (spiral CT or MRI with ≤5 mm cuts) of chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. The same assessment modality should be used throughout the study for all assessments for each subject, unless prior approval is obtained from Sponsor or its designee. Unscheduled tumor assessments may be performed if disease progression is suspected.

Baseline tumor assessment should be performed within 28 days of randomization/registration. The first on-study imaging assessment should be performed at 6 weeks (42 days [+7] days) from Cycle 1 Day 1.

Subsequently, antitumor activity will be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 in the first 12 months. After 12 months (365 days [±7] days), subjects who remain on treatment will have imaging performed every 12 weeks (±14 days) until disease progression or start of new anticancer treatment.

Imaging should continue to be performed until disease progression is identified by the Investigator or notification by the Sponsor, whichever occurs first.

Regarding the EOT tumor assessment: If the previous scan was within the last 6 weeks (within 12 weeks if the subject completed the first year of tumor assessments), the tumor assessment at the EOT Visit does not need to be performed. If the Investigator makes a clinical diagnosis that there has been progression, imaging examinations should be performed as promptly as possible, and efforts should be made to obtain an image-based assessment of PD.

All supplemental imaging must be submitted to the central imaging vendor.

Imaging timing should follow calendar days.

Imaging time points will be projected from the previous examination date and should not be adjusted for delays in cycle starts. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 4 weeks).

Tumor measurements are performed as per RECIST version 1.1 (Section 10.4). See also Table 1.2 for the SoE.

8.3.5. Response Assessment

Assess the subject based upon the local laboratory results using the Response Criteria (Section 10.4).

8.3.6. Subsequent Anticancer Treatments

Subsequent anticancer treatments taken since the EOT and their outcomes must be monitored and recorded in the eCRF until the end of the study.

8.3.7. Survival Follow-up

All subjects should be followed for survival at least every 3 months (±14 days) after discontinuing study drug. Survival monitoring will continue until the end of the study.

8.4. Safety Assessments

8.4.1. Adverse Event

8.4.1.1. Method to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.5. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) 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. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue T-DXd.

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

Additional relevant information regarding the AEs of special interest (AESIs) ILD and LV dysfunction for the T-DXd clinical program, regardless of seriousness is to be collected through the targeted questionnaires within the clinical study database.

For broad surveillance of LV dysfunction, relevant AEs under the MedDRA SMQs of Cardiac Failure is included for enhanced data collection; additional data for these AEs are collected via TQs of heart failure.

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

8.4.1.2. Time Period for Collecting Adverse Events, Including AESIs and Serious Adverse Events

All SAEs occurring after the subject signs the Main ICF and up to 40 (+7) days after the last dose of study medication (ie, the Follow-up Period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

All non-serious AEs occurring after the subject has signed the Main ICF until up to 40 (+7) days after the last dose of study medication will be recorded on the AE eCRF.

Exacerbation of a pre-existing medical condition and symptom after the first dose of T-DXd including increase in severity of the symptom will be recorded as an AE on the AE eCRF, unless it is a condition of CRC.

8.4.1.3. Reporting Procedure for Investigators

All AEs (including AESIs and SAEs) will be reported in the AE eCRF. All AEs (serious and non-serious) must be reported with the Investigator's assessment of seriousness, severity, and causality to T-DXd.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom 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, report them as individual entries of AE or SAE.

8.4.1.4. Disease-Specific AEs and SAEs

Disease progression/worsening of CRC will **not** be recorded as an AE on the AE eCRF. However, events associated with disease progression may be recorded as AEs.

Death due to disease progression should be recorded on the Death eCRF.

8.4.1.5. Treatment-Emergent Adverse Events

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 the initiating the study drug until 47 days after last dose of the study drug. SAEs with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

8.4.1.6. Serious Adverse Events Reporting

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

- SAEs (Section 10.5.2)
- Hepatic events (both serious and non-serious) meeting the laboratory criteria of a potential Hy's Law criteria (as defined in Section 8.4.1.7).
- 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 described by the Event Adjudication Site Manual).
- Overdose defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the subject.
  - Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including T-DXd dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the Case Report Form (CRF) within EDC

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should 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.

For subjects who sign the Tissue Pre-Screening ICF, only SAEs directly related to tissue pre-screening procedure (ie, tumor biopsy) should be reported via the SAVER Form since EDC is not available at this timing.

If using EDC for SAE reporting: Complete the eCRF within 24 hours of awareness. In the event that the eCRF is unavailable, report SAEs by faxing or emailing the SAVER Form to Sponsor/CRO using the provided fax transmittal form and the appropriate fax number provided for your country or e-mail address. Once EDC becomes available, please enter SAEs reported on the SAVER Form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

Contact your study monitor for any questions on SAE reporting. See Section 8.4.1 for details on the time period for collecting SAEs.

8.4.1.6.1. Reporting Requirement to Sites and Regulatory Authorities

Sponsor and/or CRO will inform Investigators and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of T-DXd, as appropriate per institutional and/or local reporting requirements.

Sponsor and/or CRO will comply with any additional local safety reporting requirements. The Investigator will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB.[26]

8.4.1.6.2. Follow-up for AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

Urgent safety queries must be followed up and addressed promptly. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. 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 report.

8.4.1.7. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be

reported to (CRO or Sponsor) within 24 hours of awareness. Overdose involving a subject will be reported via 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 as clinically relevant, ie, poses an actual or potential risk to the subject.

Occupational exposures must be reported via the SAVER Form.

8.4.1.8. Combined Elevations of Aminotransferases and Bilirubin

Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) ≥3 × ULN and an elevated TBL >2 × ULN, regardless if it is due to disease progression per Investigator assessment, that may occur at different time points during the study conduct, should always be reported to the Sponsor.[29] These events must be reported either by eCRF, with the Investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of Investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 10.2 in order to determine the nature and severity of the potential liver injury.

8.4.1.9. Adverse Events of Special Interest

For the T-DXd 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.

8.4.1.9.1. Interstitial Lung Disease/Pneumonitis

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.

Management Guidance

ILD/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 (Table 6.3).

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

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of the study protocol (Table 6.3).

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

Independent ILD Adjudication Committee (AC)

An independent ILD AC for the T-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collection 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 based on a set of predefined list of PTs eligible for adjudication as defined in the Event Adjudication Site Manual.

8.4.1.9.2. Left Ventricular Dysfunction

Clinical Summary

Left ventricular dysfunction in association with T-DXd is considered to be important potential risk based on the available pre-clinical data, literature, and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical trial data.

Management Guidance

Left ventricular ejection fraction will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.

Troponin will be measured at Screening, EOT, and as needed based on subject-reported cardiac signs or symptoms suggesting CHF, MI, or other causes of cardiac myocyte necrosis. If an ECG is abnormal, follow institutional guidelines.

Electrocardiograms will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not the ECG measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

8.4.2. Pregnancy

Sponsor must be notified of any female subject or partner of a male subject who becomes pregnant while receiving or within 7 months (or 4 months for a female partner of a male subject) of discontinuing the T-DXd.

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 or partner of a male subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the female subject or partner of a male subject (upon obtaining written consent from partner) until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs.

8.4.2.1. Pregnancy Test

For women of childbearing potential (as defined in Section 5.1): document the results of a negative urine or serum (per institutional guidelines) pregnancy test.

For eligibility, if not performed as a part of routine care within 72 hours of randomization/registration, a pregnancy test must be performed with the results available prior to randomization/registration (see Table 1.2).

Thereafter, repeat pregnancy test (urine or serum per institutional guidelines) must be performed 72 hours before infusion at each cycle, at EOT visit, and at the 40-day Follow-up Visit.

A positive urine pregnancy test must immediately be confirmed using a serum test.

8.4.3. Clinical Laboratory Evaluations

The clinical laboratory tests including hematology, coagulation, blood chemistry, and urinalysis will be performed. Blood samples for troponin, preferably high-sensitivity troponin-T, will be collected at Screening, EOT, and as clinically indicated. Refer to Section 10.2 for the complete list of laboratory parameters. 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, the SAE should be reported in the CRF and other relevant procedures must be followed (see Section 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 relevant. New or worsened clinically relevant abnormalities should be recorded as AEs on the AE eCRF.

8.4.4. Other Safety

8.4.4.1. Physical Examinations

Physical examinations will be performed for each subject according to the SoE (Table 1.2 and Table 1.3). A complete physical examination should include a height (obtained once during Screening) and weight measurement, and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs on the AE eCRF.

8.4.4.2. Vital Signs

Vital signs will be measured and recorded for every subject according to the SoE (Table 1.2 and Table 1.3). Vital signs will include the measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures, and temperature.

Vital signs will be measured after the subject has rested in a recumbent position for 5 minutes or more and prior to laboratory blood draws and ECG measurements.

8.4.4.3. ECOG Performance Status

Assess and record the subject's ECOG PS (see Section 10.3.3) according to the SoE (Table 1.2 and Table 1.3). Further, TTD on ECOG PS will be assessed. Deterioration is defined as a decrease of 1 score in ECOG PS.

8.4.4.4. Electrocardiograms

Standard supine/semi-recumbent 12-lead ECGs will be taken before blood draws and will be performed at the time points described in the SoE (Table 1.2 and Table 1.3). The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more.

If an abnormality is noted, ECGs should then be performed in triplicate. When taken in triplicate, ECGs should be taken in close succession (approximately 3 minutes apart). The full set of triplicates should be completed in less than 15 minutes.

Standard ECG parameters will be measured, including heart rate, RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by the Investigator or delegated physician for the presence of abnormalities.

QTc intervals will be calculated at each time point according to Fridericia's formula.

8.4.4.5. Multigated Acquisition Scan or Echocardiogram

Multigated acquisition/ECHO scan must be performed according to the SoE (Table 1.2 and Table 1.3) and as clinically indicated. The same test must be used for the subject throughout the study.

Subjects must have a LVEF ≥50% within 28 days before randomization/registration to be eligible for the study.

8.4.4.6. Pulmonary Assessments

Pulmonary assessments, including CT and additional assessments (as outlined in the SoE), ILD management algorithm, and pulse oximetry (SpO2), will be performed as described in the SoE (Table 1.2 and Table 1.3).

8.4.4.6.1. Monitoring for ILD/Pneumonitis

To further understand the risk of ILD/pneumonitis in the CRC population treated with T-DXd, close monitoring of the underlying potential risk of ILD/pneumonitis is needed (see Section 8.4.1.9.1).

All potential cases of ILD will be adjudicated by the independent ILD AC (blinded review). The Sponsor will continue to closely monitor the enrolled subjects and the enrollment will continue as planned (Section 8.4.1.9.1).

8.4.4.7. Ophthalmological Examinations

Ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy will be performed as per the SoE (Table 1.2 and Table 1.3) and as clinically indicated.

8.5. Health Economics and Outcomes Research

8.5.1. Patient-Reported Outcomes

Patient-reported outcome measures will be used to examine the impact of treatment on symptoms, functioning, health-related quality of life (HRQoL) and overall health status, patient-perceived treatment tolerability, and benefit/risk from the patients' perspective. PROs have become increasingly important in evaluating the efficacy and tolerability of study treatments in clinical studies as part of the overall benefit/risk evaluation.[30] The PROs included in this study are as follows and will be administered in this order:

- EORTC QLQ-C30
- EORTC QLQ-CR29
- EQ-5D-5L
- Patient Global Impression-Treatment Tolerability (PGI-TT)
- Patient Global Impression-Severity (PGIS)
- Patient Global Impression-Change (PGIC)

The following questionnaires will be administered as per the SoE (Table 1.3) to evaluate the health economic and outcomes research (HEOR) endpoints:

8.5.1.1. EORTC QLQ-C30 and EORTC QLQ-CR29

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

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

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

Due to limitations inherent in its generic focus, the EORTC QLQ-C30 is supplemented by disease-specific modules such as the EORTC QLQ-CR29, which are designed to be administered in addition to the core questionnaire. The EORTC QLQ-CR29 is a specific questionnaire for CRC.

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, diarrhoea, and financial impact) of the EORTC QLQ-C30 and in each of the subscales (urinary frequency, blood and mucus in stool, stool frequency, and body image) of the EORTC QLQ-CR29.

Further details on the scoring of these scales, including missing items, will be provided in the statistical analysis plan (SAP).

8.5.1.2. EuroQol-5 Dimensions-5 Levels of Severity

Study subjects will be asked to complete the EQ-5D-5L questionnaire as per the SoE (Table 1.3).

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.[31] 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.

8.5.1.3. Patient Global Impression-Treatment Tolerability

The PGI-TT item is included to assess how a patient perceives the overall tolerability of the study treatment over the past 7 days. This is a single-item questionnaire, and patients will rate the bother associated with any treatment-related symptoms using response options ranging from "Not at all" to "Very much".

8.5.1.4. Patient Global Impression-Severity

The PGIS item is included to assess how a patient perceives the overall severity of cancer symptoms over the past 7 days. This is a single-item questionnaire, and patients will choose the response that best describes the severity of their overall cancer symptoms with options ranging from "No Symptoms" to "Very Severe".

8.5.1.5. Patient Global Impression-Change

The PGIC item is included to assess how a patient perceives their overall change in health status since the start of study treatment. This is a single-item questionnaire, and patients will choose from response options ranging from "Much Better" to "Much Worse".

8.5.1.6. Administration of Patient-Reported Outcome Measures

The PRO measures will be self-administered by subjects using an electronic (ePRO) device provided at the site in accordance with the SoE (Table 1.3). PROs will be provided in the language of the country in which it will be administered. It will take approximately 20 to 30 minutes for subjects to complete the questionnaires.

The following instructions should be followed when collecting PRO data via an electronic (ePRO) device:

- The research nurse or appointed site staff must explain to subjects the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is not routinely shared with study staff. Therefore, if subjects have any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.
- It is vital that the PRO-reporting is initiated at the baseline visit (Cycle 1 Day 1), as specified in the SoE (Table 1.3) to capture the effect of study treatment. The tablet must be charged and fully functional prior to the subject's arrival at the site for Cycle 1 Day 1 (-3 days) to ensure that the PROs can be completed at the start of the visit.
- The subject should be trained on the use of the device, including the importance of completing the ePRO questionnaires throughout the study in accordance with the completion schedule.
- All questionnaires must be completed using an electronic device; paper questionnaires are not allowed in this study. It is therefore very important to set up the device in advance of the subject's first treatment visit, ideally at least the day before, to ensure the device is functioning properly and to identify and address any technical issues prior to the visit.

- PRO questionnaires must be completed before treatment administration and ideally before any discussions of health status to avoid biasing the subject's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.
- PRO questionnaires must be completed by the subject in a quiet and private location and the subject given enough time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff must remind subjects that there are no right or wrong answers and avoid introducing bias by not interpreting or clarifying items.
- The subject should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a subject uses visual aids (eg, glasses or contact lenses) for reading and does not have them when he or she visits the site, the subject will be exempted from completing the PROs at the visit.
- Site staff must not read or complete the PRO questionnaires on behalf of the subject. If the subject is unable to read the questionnaire (eg, is blind, illiterate or not fluent in the available language), that subject should be exempted from completing PRO questionnaires but may still participate in the study. Subjects exempted in this regard should be flagged appropriately by the site staff in the source documents and the Review of PRO/Questionnaire/Diary eCRF.
- Site staff must administer questionnaires available in the language that the subject speaks and understands. For example, questions should not be read in the available language and then translated into another language for the subject.

Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a subject could not complete assessments in the eCRF. The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of study success.

8.5.2. Hospitalization-Related Endpoints (Healthcare Resource Use)

The impact of treatment and disease on healthcare resource use (including inpatient admissions, intensive care unit admissions, and length of stay in hospital) will be captured/collected in this study on an event-driven basis. The Hospital Admission (HOSPAD) module in eCRF will be used to collect information on key healthcare resource use that a subject receives that is not part of the study. The data may be used to support health technology assessments and payer-related submissions.

At each scheduled visit, the site should review clinical notes for any non-study-related hospital admissions and visits that have occurred. Where any visits have occurred, the site should complete the HOSPAD. If a subject discontinues study treatment for reasons other than RECIST version 1.1 progression, the HOSPAD form should continue to be administered until progression has been confirmed.

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

8.6. Pharmacokinetic (PK) Assessment(s)

Blood samples for PK analyses will be obtained at the time points specified in the SoE (Table 1.3) and in Table 8.4. 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 8.4: Blood Sampling for Pharmacokinetic Analysis

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (-8 to 0 hours) EOI: Within 15 minutes after EOI 5 hours after the start of drug administration (±15 minutes)
	Day 8	7 days after the start of drug administration (±1 day)
	Day 15	14 days after the start of drug administration (±1 day)
	(Day 22)	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of drug administration (±2 days). If the next schedule is not delayed, sampling at this point is not necessary
Cycles 2, 3, and 4	Day 1	BI (-8 to 0 hours) EOI: Within 15 minutes after EOI
Cycle 6	Day 1	BI (-8 to 0 hours)

BI = before infusion; EOI = end of infusion

In case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection, additional PK serum samples should be collected at the following time points for T-DXd treated subjects (Table 8.5).

Table 8.5: Schedule of PK Sample Collection in Case of Chloroquine or Hydroxychloroquine Treatment

Day of Chloroquine or Hydroxychloroquine Administration	Sampling Time Point
Day 1	Prior to chloroquine or hydroxychloroquine dose
Day 2 or 3	Prior to chloroquine or hydroxychloroquine dose (within 4 hours)
End of treatment	Prior to chloroquine or hydroxychloroquine dose (within 4 hours)
Prior to re-initiation of T-DXd	BI (within 8 hours)

BI = before infusion

At each time point, blood will be collected for T-DXd, total anti-HER2 antibody, and DXd PK analysis. The actual time of study drug administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF, including for samples collected in case of chloroquine or hydroxychloroquine administration. The date and time of chloroquine or hydroxychloroquine administration should also be recorded in case of their administration to study subjects.

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

Serum concentrations of T-DXd, total anti-HER2 antibody, and DXd will be measured using validated assays at the bioanalytical laboratory. Serum concentrations of T-DXd and/or total anti-HER2 antibody may be measured using the same samples for purpose immunogenicity assessment.

8.7. Pharmacodynamic Assessment(s)

In this study, biomarker analyses will be used to investigate the effect of the T-DXd at the molecular and cellular level and to determine how changes in the markers may relate to exposure and clinical outcomes. The sample collection information 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.

8.7.1. Pharmacodynamic Assessments in Blood Samples and Tumor Specimens

Pharmacodynamic biomarkers will be analyzed with the intent of monitoring the anti-tumor impact of treatment with T-DXd.

A pretreatment blood sample will be collected for cell-free RNA (cfRNA) analysis within 3 days before study drug administration.

The peripheral pharmacodynamic biomarker is cell-free DNA (cfDNA). Blood samples will be collected for cfDNA analysis in the plasma for HER2 amplification and mutations at the time points specified in Table 8.6.

Table 8.6: Cell-Free Deoxyribonucleic Acid Sampling Time Points

Cycle	Sampling Time Point (Acceptable Range)
Day 1 of Cycles 1, 2, 3, 4, and 7	Within 3 days before administration
Every 4 cycles from Cycle 7 (eg, Cycle 11, 15, 19, 23, 27, etc.)	Within 3 days before administration
End of Treatment	The date when the Investigator decides on discontinuation of the study treatment (+7 days)

8.7.1.1. Optional Tumor Biopsy Sample

Collection of tumor specimens is critical to assess the pharmacodynamic effect of T-DXd. The tumor biopsy (optional) collected at baseline, on treatment and EOT as per Table 1.2 will be used to assess the HER2 status using IHC and/or ISH, mRNA expression profile, and DNA analysis using NGS technology and/or other methods.

8.7.1.1.1. Exploratory Translational Biomarker Analysis

Samples for biomarker testing will be collected from subjects at the time points specified in Table 1.2 and Table 1.3. In this study biomarker analyses of tumor and blood samples collected from subjects will be used to investigate the effect of T-DXd at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes.

Both tumor and blood-based biomarker samples will be used to analyze DNA, RNA, and/or protein measurement to identify predictors of sensitivity or resistance to T-DXd and evaluate biomarker changes upon treatment. Samples will be analyzed using appropriate technologies including, but not limited to: RNA seq, exome or targeted DNA sequencing, IHC, and/or mass spectrometry. Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Study Laboratory Manual.

The remaining samples (tumor tissues, blood, and plasma) may be stored for up to 15 years.

8.7.2. Optional Pharmacogenomic (Inherited Genetic) Analysis

An optional single blood sample for pharmacogenomics analysis will be collected from each subject, who consented to this test, on Day 1 of Cycle 1, and where allowed per local regulations. Participation in this part of the study is optional for all subjects.

Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of T-DXd. Additionally, samples may be analyzed for genes involved in T-DXd related signaling pathways, or to examine diseases or physiologic processes related to T-DXd, such as ILD/pneumonitis.

Genetic analyses will not be performed on blood samples collected for PK or safety assessments. Subject confidentiality will be maintained.

If subjects agree to the test, the remaining DNA will be stored, as outlined in Section 8.7.2.1 for performing future pharmacogenetic analysis. Otherwise, all remaining DNA samples will be destroyed.

Detailed instructions for the collection, handling, and shipping of samples are outlined in the Study Laboratory Manual.

8.7.2.1. Optional Banking of Specimens for Inherited Genetic Analysis

Procedures for the long-term preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject that consented are described in the Study Laboratory Manual.

The banked samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of T-DXd. Additionally, samples may be analyzed for genes involved in T-DXd related signaling pathways, or to examine diseases or physiologic processes related to T-DXd. 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 drug, as well as helping in the development of new drugs or improvement of existing drugs.

Storage and Disposal of Specimens

Banked DNA samples will be stored for a maximum of 15 years after the finalization of the clinical study report (CSR) for this protocol. These specimens will be kept for pharmacogenetic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic) to T-DXd, or in case serious adverse drug reactions are noted in a clinical study and pharmacogenetic analysis is to be conducted for investigation into the cause.

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

Disclosure of the Results of Future Pharmacogenetic Analysis

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

8.7.3. Immunogenicity

Blood samples for immunogenicity (anti-drug antibody [ADA] and NAb) assessments will be collected at the time points specified in the SoE (Table 1.2). A blood sample will be drawn at each time point. Serum concentrations of T-DXd and/or total anti-HER2 antibody may be measured using the same samples as for the purpose of immunogenicity assessment.

For subjects with positive ADA at the FU visit, additional serum ADA samples may be collected during long-term follow-up that is, every 3 months (±14 days) up to 1 year after the last dose of the study drug, or until the immunogenicity result becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

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 NAb assay.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

The data cut-off date for the primary analysis will occur at least 6 months after the last subject has been enrolled or when all subjects have discontinued from the study, whichever is earlier. All data collected up to the data cut-off date will be included in the primary analyses. Data from all sites will be pooled for analyses.

The final analysis of the study will occur after all subjects have discontinued from the study and have completed the 40-day Follow-up Visit. Data collected beyond the primary analysis data cut-off will be presented as appropriate in a CSR addendum if deemed necessary.

Descriptive statistics on continuous variables will include the number of observations, mean, standard deviation, median, and minimum and maximum values (as well as geometric mean and geometric coefficient of variation for PK variables, if applicable). Categorical variables will be summarized using frequency counts and percentages. Graphical representation of data will be employed when appropriate.

An IA of efficacy and safety for both the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd will be performed when all subjects in Stage 1 (ie, the randomized portion of the trial) have been randomized and had at least 12 weeks of follow-up after initiation of therapy or have discontinued treatment. No formal direct comparison will be made between both treatment arms. The purpose of this IA is to look at preliminary efficacy and safety signals within the IHC 2+/ISH+ and *RAS*-mutant subgroups. It is not the intent to modify the study design based on the IA results.

In general, the baseline value for an efficacy variable is the last non-missing value before randomization. The baseline value for a safety variable is the last non-missing value before the first dose of study treatment. Summary for change from baseline and percent change from baseline will include only subjects with both baseline and post-baseline assessments. Missing data will not be imputed for data analysis, unless specifically noted otherwise.

9.2. Statistical Hypothesis

The primary objective of this study is to evaluate confirmed ORR of T-DXd in HER2 overexpressing mCRC subjects treated at 5.4 mg/kg and 6.4 mg/kg doses. The evaluation of the study results will be based primarily on the estimation.

9.3. Sample Size Determination

The sample size in this study is determined on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeds and excludes the ORR benchmark of 20.0%. This benchmark is the lower bound of the 95% CI (ORR 32.0; 95% CI: 20.0 to 45.0) in pertuzumab plus trastuzumab arm in the MyPathway phase 2a open-label trial, that was investigated for patients with HER2-amplified metastatic colorectal cancer.[24]

Approximately 120 subjects will be enrolled in this study. In Stage 1, the first 80 subjects will be randomized in a 1:1 ratio to receive T-DXd at either 5.4 mg/kg or 6.4 mg/kg dose level.

Then, in Stage 2, an additional 40 subjects will be registered at the 5.4 mg/kg dose to further inform on the efficacy and safety of this dose in mCRC.

In Stage 1, with 40 subjects in each treatment arm, the probability to exclude the ORR benchmark of 20.0% is at least 80% when the true ORR is 41%. At the end of Stage 2, assuming 80 total subjects in the 5.4 mg/kg, the probability to exclude the ORR benchmark of 20.0% is at least 80% when the true ORR is 34%. Details of the probability evaluation under different true ORR values are shown in Table 9.1.

The resulting 95% CIs using exact (Clopper-Pearson) method under several scenarios of observed ORR are provided in Table 9.2, indicating that with 80 subjects at 5.4 mg/kg and 30% observed ORR, the 95% CI excludes the benchmark of 20.0% ORR. With 40 subjects at 6.4 mg/kg and 35% observed ORR, the 95% CI excludes the benchmark of 20.0% ORR.

With 80 subjects at the 5.4 mg/kg dose level and 40 subjects at the 6.4 mg/kg dose level, if the higher dose true ORR is at least 13.75% higher than that of the lower dose, the probability of observing the ORR difference between dose levels being 5% or more is at least 80%.

Assuming 80 subjects at the 5.4 mg/kg dose level and 40 subjects at the 6.4 mg/kg dose level, the 95% confidence interval of the ORR difference between dose levels is expected to extend approximately 0.18 from the observed difference in proportions to either confidence limit.

Table 9.1: The Probability that the Resulting Clopper-Pearson 95% CI will Exclude the Benchmark of 20.0% ORR

True ORR (%)	Probability evaluated for N=80 (%)	Probability evaluated for N=40 (%)
30	54.2	29.7
31	61.8	34.7
32	68.9	39.9
33	75.2	45.2
34	80.8	50.6
40	97.6	78.9
41	98.4	82.4
50	99.9	98.1

Table 9.2: Confidence Interval with 40 and 80 Subjects Under Scenarios of Observed Objective Response Rate

Sample size at a dose level	Dose level	Observed ORR (%)	95% CI using exact method (%)
80	5.4 mg/kg	30	(20.3, 41.3)
		35	(24.7, 46.5)
		40	(29.2, 51.6)
		45	(33.8, 56.5)
		50	(38.6, 61.4)
		55	(43.5, 66.2)
		60	(48.4, 70.8)
40	6.4 mg/kg	30	(16.6, 46.5)
		35	(20.6, 51.7)
		40	(24.9, 56.7)
		45	(29.3, 61.5)
		50	(33.8, 66.2)
		55	(38.5, 70.7)
		60	(43.3, 75.1)

CI = confidence interval; ORR = objective response rate
Calculations were made using R package of binom

9.4. Population for Analysis Sets

Analysis Sets

- The **Full Analysis Set (FAS)** will include all subjects for whom study treatment has been assigned by randomization. Following the Intent-to-Treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization process.
- The **Safety Analysis Set** will include all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is the randomized/assigned study drug if the subject took at least one dose of the randomized/assigned study drug; otherwise the first treatment received will be used.
- The **Response Evaluable Set** (RES) will include all subjects in FAS who received at least one dose of study treatment and had measurable target lesions as assessed by BICR at baseline.
- The **PK Analysis Set** will include all enrolled subjects who received at least one dose of study drug and had measurable serum concentrations of T-DXd.

9.5. Statistical Analysis

The SAP will be developed and finalized before IA database finalization and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Efficacy Analyses

Table 3.1 lists the primary and secondary endpoints and their corresponding definitions of all endpoints. Additional details for the analysis and censoring rules are noted in the following sections. Detailed censoring rules for the applicable secondary efficacy endpoints will be specified in the SAP.

Efficacy analyses will be performed for FAS and RES. Point estimates will be accompanied with 2-sided 95% CIs, unless specified otherwise.

9.5.1.1. Primary Efficacy Analyses

The primary efficacy endpoint is confirmed ORR, defined as the sum of CR and PR rate, assessed by the BICR based on RECIST version 1.1.

The primary analysis of ORR will be performed for FAS. The ORR for each dose level will be estimated along with the two-sided 95% confidence intervals (Clopper-Pearson). In addition, the ORR difference between dose levels will be estimated using a stratified analysis, where the strata-adjusted ORR difference is computed, and each stratum is weighted according to the inverse of variance. The 95% confidence interval will also be computed.

9.5.1.2. Secondary Efficacy Analyses

The secondary endpoint of confirmed ORR by Investigator assessment based on RECIST version 1.1 will be analyzed using the same method as for the primary efficacy endpoint.

Duration of Response, defined as time from the initial response (CR or PR), until documented tumor progression or death from any cause, will be summarized using Kaplan-Meier approach for each dose level.

Disease Control Rate is defined as the proportion of subjects who achieve CR, PR, or SD during study treatment. Disease Control Rate based on BICR and DCR based on Investigator assessments will both be determined.

Clinical Benefit Rate is defined as the proportion of subjects who achieved CR or PR or had SD for at least 6 months per RECIST version 1.1. Clinical Benefit Rate based on BICR and DCR based on Investigator assessments will both be determined. Disease Control Rate and CBR will be analyzed in the same approach as ORR.

Progression-free Survival, defined as the time from date of randomization/registration until first objective radiographic tumor progression or death from any cause based on BICR and Investigator assessments, will be analyzed using the Kaplan-Meier approach.

Likewise, OS, defined as the time from date of randomization/registration until death from any cause, will also be similarly analyzed. The censoring rules for PFS and OS will be detailed in the SAP.

9.5.1.3. Exploratory Analyses

Time to Response, defined as the time from the date of randomization/registration to the date of the first documentation of objective response (CR or PR), will be summarized using descriptive statistics, for each dose level.

Best percent change from baseline in the sum of the diameters for all target lesions will be summarized with descriptive statistics by dose level.

Time to Deterioration in ECOG PS is defined as the time from the date of randomization/registration to the date when ECOG PS score of ≥2 is observed for the first time, with censoring occurring at the date of the last ECOG PS assessment if no deterioration is observed. Time To Deterioration in ECOG PS will be summarized using Kaplan-Meier approach for each dose level.

For the following subgroups, analyses using the same methods as for the FAS will be performed, provided that a minimum number (10) subjects in at least one treatment arm are available:

- Lines of prior systemic therapy for advanced disease (2, 3, ≥4)
- Age (<65, ≥65 yrs.)
- Sex (female, male)
- ECOG PS (0 or 1)
- HER2 status (IHC 3+ or IHC 2+/ISH+)
- *RAS* status (wild-type or mutant)
- Region: United States, European Union, Asia-Pacific
- Primary tumor site (right, left/rectum)
- Number of metastatic sites (<2, ≥2)
- Prior treatment with irinotecan or other topoisomerase I inhibitors (Yes or No)
- Prior treatment with HER2 targeted regimen
- Prior treatment with any anti EGFR antibody
- Prior treatment with any VEGF antibody
- Prior treatment with regorafenib or TAS-102 (Yes or No)
- Prior treatment with anti-PD-(L)-1 inhibitor
- Presence of liver metastases at baseline (Yes or No)
- Renal impairment at baseline (within normal range, and mild/moderate impairment)

9.5.1.4. Multiplicity Adjustment

The evaluation of the study results will be based primarily on the estimation. Multiplicity adjustment is not applicable.

9.5.2. Safety Analyses

Safety analyses involving safety data (ie, extent of exposure, TEAEs, clinical laboratory results, ECG, vital signs and physical examinations) will be performed on the Safety Analysis Set according to the actual treatment received by subjects. No inferential statistical analysis is planned for safety data, unless otherwise specified. Descriptive statistics will be calculated for quantitative safety data and frequency counts and percentages will be compiled for classification of qualitative safety data. All percentages will be calculated based on the number of subjects in the Safety Analysis Set, unless otherwise indicated. If the number of subjects with available data does not allow for the reliable estimation of variability at a scheduled time point, no summary statistics will be presented for that time point, unless otherwise indicated. Unless otherwise noted, baseline values will be the last non-missing assessment collected prior to first dose of study treatment.

Safety analyses, primarily summaries by description statistics of safety variables, will be performed by dose level.

Adverse Events

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 the initiating the study drug until 47 days after last dose of the study drug. SAEs with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

Adverse events will be coded using MedDRA and graded using NCI-CTCAE version 5.0. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class, preferred term, relationship to the study drug, and the worst NCI-CTCAE grade and dose level. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by dose level, as well as TEAEs leading to discontinuation of the study treatment.

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 drug will be provided. Deaths, other SAEs, AESIs, and other significant AEs, including those leading to discontinuation of the study treatment, will be listed.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by dose level at each scheduled time of evaluation. In addition, mean change from baseline will be presented by dose level for the maximum and minimum post-treatment values and the values at the EOT visit.

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.

A listing of abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be provided.

ECG

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. 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). Maximum change from baseline will be tabulated (≤30 ms, >30 to ≤60 ms, >60 ms). The QT intervals will be corrected for heart rate by Fridericia's formula (ie, QTcF).

A listing of ECG data will be provided.

Vital Signs

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation and by dose level, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. A listing of vital sign data will be provided.

Other

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

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

9.5.3. HEOR Analysis

To assess patient HRQoL, the following PROs questionnaires will be administered:

- A cancer specific PRO (EORTC QLQ-C30) along with tumor-specific modules (EORTC QLQ-CR29) to assess patient-reported tolerability and clinical benefit.
- A generic health status questionnaire, the EQ-5D-5L module including EQ-VAS to assess patient-reported health utility for health economic evaluations.
- Three global anchors (PGIS, PGIC, and PGI-TT) will be included to estimate meaningful change thresholds for EORTC QLQ-C30 and EORTC QLQ-CR29.

Descriptive statistics will be calculated to summarize change from baseline in symptoms, physical functioning, and general HRQoL scales in the EORTC QLQ-C30 and EORTC QLQ-CR29 study questionnaires at each scheduled assessment time point by dose level. The number of subjects completing each patient questionnaire and the number of missing or incomplete assessments will be provided for each scheduled assessment time point by dose level.

9.5.4. Other Analyses

The following other analyses are planned in this study.

Pharmacokinetics

Pharmacokinetics analyses will be performed using the PK Analysis Set.

Descriptive statistics will be provided for serum concentration data of T-DXd, DXd, and total anti-HER2 antibody at each time point for each dose level of T-DXd. PK parameters (Cmax, Tmax, AUC, [AUClast (area under the concentration time-curve from time 0 to the last measurable concentration)], and AUC0-21d [area under the concentration time-curve from time 0 to 21 days]) of T-DXd, total anti-HER2 antibody and DXd may also be determined using non-compartmental analysis after the first dose and summarized using descriptive statistics by dose level if data allows.

Serum concentration data of T-DXd, and DXd from this study may be analyzed using population PK modeling approach. In addition, exposure-response relationships between serum exposures of T-DXd, and/or DXd with key efficacy and safety endpoints may also be evaluated. For the population PK and exposure-response analyses, data from this study may be combined with other T-DXd studies and results reported separately from the CSR.

Immunogenicity Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. The number and percentage of subjects positive for ADA at baseline (prior to the first administration of T-DXd) and during the study after start of administration of T-DXd will be determined. The ADA titer values will be summarized by time point and dose level using descriptive statistics. The treatment-emerging ADA incidence will be calculated by dose level. 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 NAb of T-DXd by dose level will also be determined.

Biomarker

Biomarker analysis will be performed using the FAS.

Descriptive statistics including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be computed by evaluation time for biomarkers listed in Section 8.7.1.1.1. If possible, change from baseline and percent change from baseline will also be summarized. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.6. Interim Analysis

Efficacy and safety IA for both the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd will be performed when all subjects in Stage 1 (40 subjects for each dose) have been randomized and had at least 12 weeks of follow-up after initiation of therapy or have discontinued treatment. It is not the intent to modify the study design based on the IA results. During the study, individual subject

data will be reviewed on an ongoing basis and aggregate safety data will be monitored by the study team across the duration of the trial. The data review and analysis will be based on the available Investigator reported data in the clinical database at the respective time on a monthly basis.

In addition, pharmacokinetic and exposure-response analyses may also be performed at the time of the IA.

For each dose, the primary efficacy endpoint of ORR will be summarized using descriptive statistics including 2-sided exact 95% confidence interval (Clopper-Pearson). Other efficacy endpoints based on response rates will be summarized by dose using the same methodology as the primary efficacy endpoint. For time to event endpoint such as PFS, Kaplan-Meier estimates of median and their corresponding 95% CIs using Brookmeyer and Crowley method will be provided. Safety data related to AEs will be summarized using descriptive statistics.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the Investigator Brochure, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the independent IRB or EC 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. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB or EC.

The Investigator should notify the IRB or EC 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.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing the final CSR and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least one subject. However, where an Investigator has special knowledge of the field or of the study, the Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

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 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 (27 Mar 1997) and/or;

- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 (25 Nov 2014);
- Other applicable local regulations.

In addition, the Investigator will inform the Sponsor in writing within 24 hours 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 non-compliance that the Investigator becomes aware of.

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, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the EC/IRB. 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 Main ICF.

10.1.2. Informed Consent

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 ICFs 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 ICFs 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 ICFs should be retained in accordance with institutional policy, and a copy of the signed ICFs should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICFs after the subject has consented to their participation. By signing the ICFs, the witness attests that the information in the ICFs and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

Suggested model text for the ICFs for the study and any applicable subparts (PK, pharmacodynamic, etc) is provided in the Sponsor's ICF templates for the Investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

10.1.3. 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 European Union (EU) study sites, the Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC 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 SID 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(s), and the independent 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.

10.1.4. Data Integrity and Quality Assurance

Monitoring and Inspections

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

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

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

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

In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any Screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the Investigator via the EDC system's electronic signature. This signature will indicate that the Investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

Data Management

Each subject will be identified in the database by a unique SID.

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

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

All AEs will be coded using MedDRA. Serious AEs in the clinical database will be reconciled with the safety database.

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

Data that may potentially unblind the treatment assignment (ie, study drug serum concentrations and study drug 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.

10.1.5. Committees

An independent ILD AC for the T-DXd program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collection 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 based on a set of predefined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual.

10.1.6. 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 obtain informed consent and make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited information of the subjects, date, and outcome of the Screening process.

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 code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

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

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, EC/IRB 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 (site specific 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 local laws or regulations 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 provide further instruction.

Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (site specific 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 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 independent IRB/EC and the Sponsor.
- Records related to the study drug 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 essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable laws or 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.

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

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

10.1.7. Finances

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

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.

10.1.8. Publication, Public Disclosure Policy, and Data Sharing

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor 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. The Sponsor will 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 (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE 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 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.

10.1.9. Protocol Deviations

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

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.

The Sponsor must be notified in writing of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) within 24 hours and in accordance with the clinical study agreement between the parties.

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 one administration of study drug, data should be collected for safety purposes.

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

10.1.10. Study and Site Closure

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

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

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

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

10.1.11. 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.

10.2. Appendix 2: Central and/or Local Laboratory

The clinical laboratory tests listed in Table 10.1 are to be performed in this study.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry	albumin alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bilirubin (total) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine (serum)	lactate dehydrogenase (LDH) magnesium (Mg) potassium (K) protein (total) sodium (Na) FSH and estradiol during Screening (if applicable) to confirm menopausal status
Troponin	high-sensitivity troponin-T (central or local laboratory) troponin I or troponin-T (local laboratory)	
Hematology	hemoglobin hematocrit platelet count red blood cell (RBC) count white blood cell (WBC) count	absolute ± differential (%) WBC count: basophils eosinophils lymphocytes monocytes neutrophils
Coagulation	prothrombin time (PT)- international normalized ratio (INR) partial thromboplastin time (PTT) activated partial thromboplastin time (aPTT)	

Test	Analytes	
Urinalysis (abbreviated)	glucose microscopy assessments, if indicated occult blood protein	specific gravity

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds):[32]

Conventional – serum creatinine in mg/dL:

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

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

$$\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times 0.0113 \times \text{serum creatinine (µmol/L)}} \quad \{\times 0.85 \text{ for females}\}$$

10.3.2. New York Heart Association (NYHA)

The NYHA classifications are summarized below.[33]

Table 10.2: New York Heart Association Classifications

Class	Functional Capacity	Objective Assessment
I	Subjects 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.
II	Subjects 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.
III	Subjects 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.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994. https://professional.heart.org/en/guidelines-and-statements/classification

10.3.3. Eastern Cooperative Oncology Group Performance Status

The ECOG PS scale scores are summarized below.[34]

Table 10.3: Eastern Cooperative Oncology Group Performance Status

Score	Performance Status
0	Fully active, able to carry on all pre-disease 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 housework, 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.

10.3.4. Highly Effective Contraception

Methods considered to be highly effective contraception include:[35]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse when it is in line with the preferred and usual lifestyle of the subject. Study subjects should refrain from heterosexual intercourse during and upon completion of the study and for at least 7 months for female subjects and 4 months for male subjects after the last dose of study drug. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to the study drug, and withdrawal are not acceptable methods of contraception.

10.4. Appendix 4: Response Criteria

Response Evaluation Criteria in Solid Tumors (Version 1.1)

Assessment of tumor responses will be performed according to revised RECIST version 1.1.[36] Some of these definitions and criteria are highlighted below.

Measurability of Tumor at Baseline Definitions

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

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT 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 the short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

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. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

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

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.

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.

Lesions with prior local treatment:

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

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks (or 28 days) before randomization/registration.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by 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).

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

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

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

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one 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. 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. 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 or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum 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 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 record form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

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 SoD of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the SoD 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 must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.)

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

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 unlikely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro-peritoneum.) 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.

If the radiologist is able to provide an actual measurement, 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'.

Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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 one 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 extremely rare.

New Lesions

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

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of the brain 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 that indicated its presence.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR or PR is [not] required in this study. The subject's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 10.4 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

All post-baseline scans must be anchored against the baseline scan.

Table 10.4: Time Point Response: Subjects With Target (+/–Non-Target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Missing Assessments and In-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is NE at that time point. If only a subset of lesion measurements is 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.

Best Overall Response: All Time Points

The BOR is determined once all the data for the subject are known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline (within 4 weeks prior to the first dose of study drug), 7 weeks, in the case of scan intervals of 8 weeks (or “5 weeks”, in the case of scan intervals of 6 weeks.) 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 NE.

Table 10.5: Best Overall Response When Confirmation of CR and PR Required

Overall response		Overall response
First time point	**Subsequent time point**	**Best**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
NE	NE	NE

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

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Table 3. Euro J of Can. 2009:45;228-47

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR might not have a total sum of '0' on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of T-DXd without objective evidence of disease progression at that time should be reported as 'clinical progression.' Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study drug. The objective response status of such subjects is to be determined by evaluation of target and non-target disease. If a radiographic tumor assessment has not been performed within 4 weeks of the time of clinical progression, then

another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

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.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at Screening, and then at the intervals specified, or sooner if clinically indicated. The interval between scans is based on the last scan visit. Tumor measurement will be performed during the EOT visit if it was not done within the previous 6 weeks or the previous assessment demonstrated disease progression.

Baseline tumor assessments must be performed within 4 weeks prior to the first dose of study drug.

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 the chest, abdomen, and pelvis. Any additional suspected sites of disease 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.

10.5. Appendix 6: General Information - Adverse Events

10.5.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[37]

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.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events NOT Meeting the AE Definition

- Any clinically relevant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.5.2. Serious Adverse Event

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

- Results in death
- Is life-threatening
  - 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
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline or for administration of anticancer therapy after discontinuation of study drug is not considered an AE.
- Results in persistent or significant disability/incapacity

  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is an important medical event
- Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Events Exempted from SAE Reporting

Serious events that are also efficacy endpoints and/or safety endpoints will be exempted from SAE processing and expedited reporting.[37] 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.

10.5.3. Grade Assessment

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

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

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Difference Between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe MI); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.5.4. Causality Assessment

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

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

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

10.5.5. Action Taken Regarding Study Drug

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study drug completed/permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of treatment
- Unknown: Subject is lost to follow-up

10.5.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.

  - Prescription and/or over-the-counter medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

10.5.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no sequelae observed.
- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE
- Unknown

10.6. Appendix 7: Instructions Related to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Due to the potential impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected SARS-CoV-2 while being treated with T-DXd. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate SARS-CoV-2.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria for Suspected or Confirmed SARS-CoV-2

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. Dose modifications will be based on the worst CTCAE grade. All interruptions or modifications must be recorded on the AE and drug administration eCRFs. **Please use CTCAE v5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria

If SARS-CoV-2 infection is suspected, interrupt T-DXd and rule out SARS-CoV-2 per local guidance.

- If SARS-CoV-2 is ruled out, follow dose modification and management guidance as outlined in Table 6.3.
- If SARS-CoV-2 is confirmed or diagnosis is still suspected after evaluation follow dose modification as outlined in Table 10.6 below and manage SARS-CoV-2 per local guidance until recovery of SARS-CoV-2. SARS-CoV-2 recovery is defined as no signs/symptoms of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.
  - If PCR testing is not available (locally/at the site), the subject must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging to be considered recovered from SARS-CoV-2.

Table 10.6: SARS-CoV-2 Dose Modification Criteria

SARS-CoV-2 Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	**Schedule Modification for T-DXd**
Grade 1	Resume study drug at the same dose
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CT = computed tomography

In addition to the recommendations outlined in Table 10.6, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 6.3).

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 6.6.1).
  - If treatment (with chloroquine or hydroxychloroquine) is absolutely required for SARS-CoV-2 T-DXd must be interrupted.
  - If administered, then a washout period of no less than 14 days is required before restarting T-DXd.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected from each subject who provides consent, if chloroquine or hydroxychloroquine is administered for SARS-CoV-2 infection, at the time points specified in the SoE (Table 1.2 and Table 1.3).

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

COVID-19 (SARS-CoV-2) Assessment(s)

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

Serum samples will be used for SARS-CoV-2 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, at the time points specified in the SoE (Table 1.3), shipped to a central laboratory, and stored there until the tests become available.

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

Serum, nasopharyngeal swab/saliva, and PK sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of COVID-19 (SARS-CoV-2)

If deemed appropriate, analyses will be performed to explore the impact of SARS-CoV-2 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of SARS-CoV-2 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the SAP.

10.7. Appendix 8: Patient-Reported Outcomes

10.7.1. EORTC QLQ-CR29

ENGLISH

EORTC QLQ – CR29

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

ENGLISH

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

10.7.2. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

10.7.3. EQ-5D-5L

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

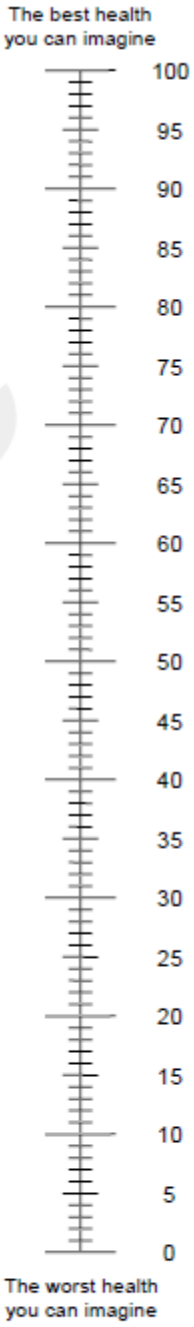
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



10.7.4. PGI-TT

PATIENT GLOBAL IMPRESSION OF TREATMENT TOLERABILITY (PGI-TT)

In the last 7 days, how bothered were you by the side effects of your cancer treatment?	
☐	Not at all
☐	A little bit
☐	Somewhat
☐	Quite a bit
☐	Very much

10.7.5. PGIS

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS)

Please choose the response below that best describes the severity of your overall cancer symptoms over the past 7 days.	
☐	No Symptoms
☐	Very Mild
☐	Mild
☐	Moderate
☐	Severe
☐	Very Severe

10.7.6. PGIC

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Overall, how would you rate the change in your health status since starting this Study? Please tick (✓) one box only:	
☐	Much Better
☐	Moderately Better
☐	A Little Better
☐	About the Same
☐	A Little Worse
☐	Moderately Worse
☐	Much Worse

11. REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol. 2018;23:1–34.
3. NCCN Clinical Practice Guidelines in Oncology, Colon Cancer, Rectal Cancer Version 2. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
4. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27:1386–422.
5. Siena S, Sartore-Bianchi A, Marsoni S, et al. Targeting the human epidermal growth factor receptor 2 (HER2) oncogene in colorectal cancer. Ann Oncol. 2018;29:1108–19.
6. Nam SK, Yun S, Koh J, et al. BRAF, PIK3CA, and HER2 oncogenic alterations according to KRAS mutation status in advanced colorectal cancers with distant metastasis. PLoS One. 2016;11:e0151865.
7. Sawada K, Nakamura Y, Yamanaka T, et al. Prognostic and predictive value of HER2 amplification in patients with metastatic colorectal cancer. Clin Colorectal Cancer. 2018;17:198–205.
8. Bertotti A, Papp E, Jones S et al. The genomic landscape of response to EGFR blockade in colorectal cancer. Nature 2015; 526: 263–7.
9. Leto SM, Trusolino L. Primary and acquired resistance to EGFR-targeted therapies in colorectal cancer: impact on future treatment strategies. J Mol Med (Berl). 2014; 92: 709–22.
10. Yonesaka K, Zejnullahu K, Okamoto I, et al. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. Sci Transl Med. 2011; 3: 99ra86.
11. Wang XY, Zheng ZX, Sun Y, et al. Significance of HER2 protein expression and HER2 gene amplification in colorectal adenocarcinomas. World J Gastrointest Oncol. 2019;11:335-47.
12. Richman SD, Southward K, Chambers P, et al. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. J Pathol. 2016;238:562–70.
13. Takegawa N, Yonesaka K. HER2 as an Emerging Oncotarget for Colorectal Cancer Treatment After Failure of Anti-Epidermal Growth Factor Receptor Therapy. Clin Colorectal Cancer. 2017;16:247–51.

14. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17(6):738–46.

15. A Phase 1, Two-part, Multicenter, Non-randomized, Open-label, Multiple-dose, First-in-human Study of DS-8201a, in Subjects with Advanced Solid Malignant Tumors. Daiichi Sankyo. Clinical Study Report. 17 Jul 2019; Study No.: DS8201-A-J101.

16. A Phase 2 Multicenter, Open-label Study of DS-8201a, an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1. Daiichi Sankyo. Clinical Study Report. 18 Jul 2019; Study No.: DS8201-A-U201.

17. USPI for Kadcyla (T-DM1). 2019 May [cited on 2019 May 03]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf

18. Shitara K, Iwata H, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol 2019;20:827–36.

19. USPI for ENHERTU® (fam-trastuzumab deruxtecan-nxki), accessed on 20 Dec 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf

20. Ogitani Y, Hagihara K, Oitate M, et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci. 2016;107:1039–46.

21. Takegawa N, Tsurutani J, Kawakami H, et al. fam- Trastuzumab deruxtecan, antitumor activity is dependent on HER2 expression level rather than on HER2 amplification. Int J Cancer. 2019;145:3414–24.

22. Martin V, Landi L, Molinari F, et al. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients. Br J Cancer. 2013;108:668–75.

23. Jeong JH, Kim J, Hong YS, et al. HER2 Amplification and Cetuximab Efficacy in Patients With Metastatic Colorectal Cancer Harboring Wild-type RAS and BRAF. Clin Colorectal Cancer. 2017;S1533-0028(17)3003213.

24. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20:518–30. doi:10.1016/S1470-2045(18)30904-5.

25. Salvatore S, Di Bartolomeo M, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. Journal of Clinical Oncology. 2020; 38. 4000-4000. 10.1200/JCO.2020.38.15_suppl.4000.

26. Trastuzumab deruxtecan (DS-8201a) Investigator's Brochure. Version 7.0. 31 Aug 2020.

27. FDA. Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. December 2018. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

28. Bartley, AN, Washington, MK, Ventura, CB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med. 2016;140(12):1345-63.

29. Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. July, 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072278.pdf

30. Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol. 2018;19:e267–74.

31. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–6.

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

33. American heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994. Available from: https://professional.heart.org/en/guidelines-and-statements/classification

34. 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.

35. Heads of Medicines Agencies. Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 2014. Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

36. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Euro J Cancer. 2009:45;228–47.

37. ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

12. LIST OF ABBREVIATIONS

Abbreviation	Definition
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxic
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BI	before infusion
BICR	blinded independent central review
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homologue B1
CA19-9	carbohydrate antigen 19-9
CAP	College of American Pathologists
CBC	complete blood count
CBR	clinical benefit rate
CEA	carcinoembryonic antigen
cfDNA	cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
cfRNA	cell-free ribonucleic acid
CHF	congestive heart failure
Cmax	maximum concentration
CLIA	Clinical Laboratory Improvement Act
COPD	chronic obstructive pulmonary disease
CQ	chloroquine
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form

Abbreviation	Definition
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DAR	drug-to-antibody ratio
DCR	disease control rate
DoR	duration of response
dMMR	deficient mismatch repair
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EIU	exposure in utero
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
ePRO	electronic patient-reported outcome
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	Follow-up
GCP	good clinical practice
GEJ	gastro-esophageal junction
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HEOR	health economic and outcomes research
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HIV	human immunodeficiency virus
HOSPAD	Hospital Admission
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
ICR	independent central review
ICU	intensive care unit
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
JSCCR	Japanese Society for Cancer of the Colon and Rectum
KRAS	Kirsten rat sarcoma viral oncogene homologue
LV	left ventricular
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable

Abbreviation	Definition
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-(L)-1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression-Change
PGIS	Patient Global Impression-Severity
PK	pharmacokinetic
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q3M	every 3 months
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	quality of life
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RAS	rat sarcoma viral oncogenes homologue
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
RES	Response Evaluable Set
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SID	subject identifier
SMQ	Standardized MedDRA Query

Abbreviation	Definition
SOC	standard of care
SoD	sum of diameters
SoE	schedule of events
SOP	standard operating procedures
SpO2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum plasma concentration
TMB	tumor mutational burden
TTD	time to deterioration
TTP	time to progression
TTR	time to response
t1/2	half life
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organization
WHODrug	World Health Organization drug dictionary