CLINICAL STUDY PROTOCOL

A PHASE 1B, MULTICENTER, TWO-PART, OPEN-LABEL STUDY OF TRASTUZUMAB DERUXTECAN, AN ANTI-HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 (HER2)-ANTIBODY DRUG CONJUGATE (ADC), IN COMBINATION WITH NIVOLUMAB, AN ANTI-PD-1 ANTIBODY, FOR SUBJECTS WITH HER2-EXPRESSING ADVANCED BREAST AND UROTHELIAL CANCER

DS8201-A-U105

IND NUMBER 127553/EudraCT 2018-000371-32

VERSION 6.0, 15 JUNE 2020

DAIICHI SANKYO, INC.

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INVESTIGATOR AGREEMENT

A PHASE 1B, MULTICENTER, TWO-PART, OPEN-LABEL STUDY OF TRASTUZUMAB DERUXTECAN, AN ANTI-HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 (HER2)-ANTIBODY DRUG CONJUGATE (ADC), IN COMBINATION WITH NIVOLUMAB, AN ANTI-PD-1 ANTIBODY, FOR SUBJECTS WITH HER2-EXPRESSING ADVANCED BREAST AND UROTHELIAL CANCER

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

PPD	PPD
Print Name	**Signature**
Clinical Study Lead	16 Jun 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 the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

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

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

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

DOCUMENT HISTORY

Version Number	Version Date
6.0	15 June 2020
5.0	18 Nov 2019
4.0	30 April 2019
3.0	04 Jan 2019
2.0	01 July 2018
1.0	09 Feb 2018

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 6.0 (dated 15 June 2020) vs. protocol Version 5.0 (dated 18 Nov 2019) for actual changes in text. The summary of changes below is a top-line summary of main changes in the current DS8201-A-U105 clinical study protocol (Version 6.0) by section.

Amendment Rationale:

This amendment is primarily driven by the inclusion of an interim analysis for subjects that were enrolled in the breast cohorts in Part 1 and Part 2 that achieved at least 12 weeks of follow-up or have discontinued study treatment. The objective of the interim analysis is to obtain preliminary efficacy and safety data of the study treatment that could inform further clinical development.

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of subjects nor the scientific value of the study.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

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

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

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis 2.3.5 Pharmacokinetic/Pharmacodynamic /Biomarker Endpoint(s)	The pharmacokinetic (PK) and biomarker endpoints were updated	To provide clarification
Protocol Synopsis 4.1. Inclusion Criteria	Presentation of the Cockcroft-Gault equation in criterion #8 was updated. Use of Chloroquine/Hydroxychloroquine was added to criterion #11.	To align with the latest safety information

Protocol Synopsis 4.1. Inclusion Criteria 9.7. Exposure in Utero during Clinical Studies	The contraception periods for males and females were updated to 7 months each.	To align with the latest safety information
5.2.4.1. Maximum Duration of Treatment with Nivolumab	This section was updated to include the maximum number of cycles treatment with nivolumab will be administered in the absence of disease progression or unacceptable toxicity.	To provide clarification
5.5.1. Guidelines for Delay, Reduction and/or Discontinuation for Trastuzumab Deruxtecan and Nivolumab	The following sentence was added: All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. Please refer to Appendix 17.8 for additional information on dose modification.	To include management guidelines for SARS-CoV-2 infection (ie, COVID-19)
Table 5.1 Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab	The table was updated	To align with the latest safety information
5.7. Prior and Concomitant Medications	Nivolumab was added to this section because Investigators are required to record concomitant treatment up to 40 days (+7 days) after the last dose of trastuzumab deruxtecan or nivolumab	To provide clarification
Table 5.1 Management Guidelines	Guidelines for managing cardiac, pulmonary and hepatic toxicities were updated	To align with the latest safety information
Table 6.1 End of Combination Treatment (EOCT) Assessments	The table was updated	To provide clarification
6.1.2 Screening	Troponin testing was removed from the list of assessments to be performed when a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis.	To align with the latest safety information

6.6 Additional PK assessments due to SARS-CoV-2 infection Table 8.2 Schedule of PK Sample Collections in case of Chloroquine and Hydroxychloroquine Treatment	The section and table were added.	To monitor potential drug-drug interactions between investigational/study drug treatment and SARS-CoV-2 infection (ie, COVID-19) specific treatment
8.3. Immunogenicity	This section was updated.	To align with the latest changes to anti-drug antibody analyses
9.2. Adverse Event Collection and Reporting	This section was updated	To provide clarification and to align with the latest safety information
9.3.1.3. Interstitial Lung Disease Adjudication Committee	This section was updated	To align with the latest safety information
9.4. Adverse Events	This section was updated	To provide clarification
9.5. Serious Adverse Events and Adverse Event of Special Interest Reporting–Procedure For Investigators	This section was updated	To align with the latest safety information
9.8. Clinical Laboratory Evaluations	The description of Troponin testing was updated and testing by local laboratory deleted	To align with the latest safety information
11.1. General Statistical Considerations	This section was updated	To introduce an interim analysis
11.2 Analysis Sets	The definition of Full Analysis Set (FAS) was updated Safety Analysis Set (SAF) was added	To introduce an interim analysis
11.4 Efficacy Analyses	This section and its subsections were updated	To introduce an interim analysis
11.6 Interim Analysis	This section was added	To introduce an interim analysis

Table 17.1 Schedule of Events	The table was updated	To provide clarification To align with the latest safety information
17.8 Instructions related to SARS-CoV-2 infection	This section was added.	To provide management guidelines for SARS-CoV-2 infection (ie, COVID-19)
Throughout the protocol	The phrase, “interstitial lung disease (ILD)” was replaced by “interstitial lung disease (ILD)/pneumonitis”	To align with the latest safety information

PROTOCOL SYNOPSIS

EudraCT:	2018-000371-32
IND Number:	127553
Protocol Number:	DS8201-A-U105
Investigational Product:	Trastuzumab deruxtecan and nivolumab
Active Ingredient(s)/International Non-proprietary Name:	Trastuzumab deruxtecan consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a. Nivolumab is a human monoclonal antibody directed against the programmed death 1 (PD-1) receptor.
Study Title:	A Phase 1b, Multicenter, Two-Part, Open-Label Study of trastuzumab deruxtecan, an Anti-Human Epidermal Growth Factor Receptor-2 (HER2)-Antibody Drug Conjugate (ADC), in Combination with Nivolumab, an Anti-PD-1 Antibody, for Subjects with HER2-Expressing Advanced Breast and Urothelial Cancer
Study Phase:	Phase 1b
Indication Under Investigation:	Combination therapy with trastuzumab deruxtecan and nivolumab will be evaluated in subjects with HER2-expressing advanced/metastatic solid tumors. This study will enroll HER2-expressing breast or urothelial cancer subjects that are refractory to standard therapies or for which no standard therapy is available. Part 1 enrollment will start first. Part 2 will start enrolling after completion of Part 1 and determination of recommended expansion dose (RDE)/maximum tolerated dose (MTD).
Study Objectives:	<u>Primary Objectives</u>: • To determine the MTD or the RDE of trastuzumab deruxtecan when used in combination with nivolumab (Part 1). • To evaluate the efficacy of combination treatment with trastuzumab deruxtecan and nivolumab in HER2-expressing advanced breast cancer as well as HER2-expressing advanced urothelial cancer (Part 2).

	Secondary Objectives: • To assess the safety and tolerability of the combination of trastuzumab deruxtecan and nivolumab. • To determine the pharmacokinetics (PK) of trastuzumab deruxtecan when dosed concomitantly with nivolumab. • To further evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab. Exploratory Objectives: • To evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab by using the immune Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines as assessed by the study investigator (Part 2) • To further evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab in terms of clinical benefit rate (CBR) in breast cancer cohorts. • To perform biomarker analyses related to the combination to understand the mechanism of action and resistance based on pretreatment, post-treatment, and on-treatment biopsies. • To evaluate the immunogenicity of trastuzumab deruxtecan and nivolumab (if analyzed)
Study Design:	This is a Phase 1b, open-label, 2-part, multicenter, non-randomized, multiple-dose study of trastuzumab deruxtecan in combination with nivolumab. The study will include both a dose escalation part, to identify the RDE/MTD of trastuzumab deruxtecan in combination with nivolumab and a dose expansion part, to evaluate efficacy, safety, and tolerability. **Part 1 (Dose Escalation)** Part 1 will enroll subjects meeting the eligibility criteria set up for any of the 4 cohorts of Part 2 specified below using a 3 + 3 + 3 design. As noted in the table below, escalating doses of trastuzumab deruxtecan in combination with nivolumab

will be assessed. Trastuzumab deruxtecan and nivolumab will be administered on Day 1 of each 21-day cycle.

Dose Escalation of Trastuzumab deruxtecan

Dose Level	Trastuzumab deruxtecan	Nivolumab
1	3.2 mg/kg Q3W	360 mg
2	5.4 mg/kg Q3W	360 mg

Enrollment starts at 3.2 mg/kg trastuzumab deruxtecan and 360 mg nivolumab combination. Escalation/de-escalation to the next dose will be based on an acceptable safety signal from the earlier dose cohort. Escalations from the start dose of either trastuzumab deruxtecan or nivolumab for individual subjects are not allowed. Additionally, dose reduction for nivolumab is not permitted.

The dose-limiting toxicity (DLT) observation period will be 2 cycles (6 weeks). Upon completion of the DLT observation period, subjects may continue to receive study treatments in subsequent cycles as previously described, until unacceptable toxicity, progressive disease (PD), or withdrawal of consent. Subjects may continue to receive nivolumab beyond disease progression if the investigator believes this will provide clinical benefit to the subject.

Nivolumab treatment can continue for a maximum of 24 months (approximately 35 cycles).

Part 2 (Dose Expansion)

Upon completion of dose escalation (Part 1) with determination of RDE, the dose expansion part will begin.

Part 2 will consist of 4 cohorts as follows:

Cohort 1 (n=30): Pathologically documented advanced/metastatic breast cancer that has centrally-determined HER2-positive expression (IHC 1+ or IHC 2+/ISH-) as per ASCO-CAP guidelines. Subjects who have received prior trastuzumab emtansine (T-DM1) with documented progression.

Cohort 2 (n=15): Pathologically documented advanced/metastatic breast cancer that has centrally-determined low HER2 expression (IHC 1+ or IHC 2+/ISH-). Subjects who have exhausted treatments that can confer any clinically meaningful benefit (e.g., other therapies such as hormonal therapy for subjects who are hormone receptor positive).

	Cohort 3 (n=30): Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 2+ or 3+. Subjects who received prior platinum-based therapy with documented progression. **Cohort 4** (n=15): Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 1+. Subjects who have received prior platinum-based therapy with documented progression.
Study Duration:	The screening period is up to 28 days. Upon commencing study drug, subjects may continue receiving study drug until the occurrence of unacceptable toxicity, PD, or withdrawal of consent. Enrollment for both Part 1 and Part 2 combined is planned to occur over approximately 18 months. Anticipated total duration of the study is approximately 24 months. The primary database lock will occur 6 months from the last subject enrolled in the study or when 80% of the subjects have experienced disease progression or discontinued study treatment, whichever occurs first. The end of study is defined as the date of completion of the last visit or procedure shown in the Schedule of Events in the trial globally. There will be a 40-Day Follow-up Visit (+7 days) and a 100-Day Safety Follow-up, followed by Long Term Follow-up Visits. Subjects who discontinue study treatment for any reason other than disease progression will be followed every 6 weeks (± 7 days) for tumor assessment during the first year and every 12 weeks (± 14 days) thereafter until disease progression or start of new anticancer therapy. Subjects who discontinue study treatment due to disease progression will be followed 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. When the subject discontinues 1 study drug due to any reason(s), they may continue on the other study drug at investigator discretion until they meet a discontinuation criterion applicable to the remaining study drug.
Study Sites and Location:	Approximately 5 sites for Part 1 and 25 sites for Part 2 in the United States and Europe

Subject Eligibility Criteria:

Key Inclusion Criteria:

1. Adults ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old.)
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
3. Pathologically documented HER2-expressing locally advanced/metastatic breast cancer or urothelial cancer that is unresectable, and refractory to or intolerant of existing therapy(ies) known to provide clinical benefit and as specified in each study cohort.

   Note: Subjects with urothelial cancer eligible to receive anti PD-1/PD-L1 treatment as per the approved local label may be considered eligible for the study.
4. Subjects must have an adequate archival tumor sample available for determination of HER2 status by the central laboratory (most recent tumor tissue preferred). Subjects are eligible to participate if they meet HER2 status criteria based on results from the central laboratory.
5. Presence of at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
6. Has adequate cardiac function, as defined by LVEF ≥50% within 28 days before enrollment.
7. Adequate bone marrow function, defined as:
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L (Granulocyte colony-stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment.)
   - White blood cell >2000/mm^3
   - Platelet count $\geq 100 \times 10^9$/L (Platelet transfusion is not allowed within 1 week prior to screening assessment.)
   - Hemoglobin level ≥9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment.)
8. Adequate renal function, defined as:

- Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation:

  CLcr (mL/min) =

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

  (Section 17.4).

9. Adequate hepatic function, including mild to moderate hepatic impairment defined as the following:
   - Total bilirubin ≤1.5 × upper limit of normal (ULN; except subjects with documented Gilbert's syndrome or liver metastases at baseline who must have a total bilirubin level of ≤2.0 × ULN).
   - Aspartate aminotransferase/alanine aminotransferase values ≤2.5 × ULN (≤5 × ULN in subjects with liver metastases or other etiologies).
10. Adequate blood clotting function, defined as: international normalized ratio (INR) and prothrombin time (PT)/activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) ≤1.5 × ULN, unless the subject is receiving an anticoagulant therapy, in which case INR and PT/aPTT or PTT must be within therapeutic range of intended use of anticoagulant.
11. Adequate treatment washout period before enrollment, defined as:
    - Major surgery: ≥4 weeks
    - Radiation therapy: ≥4 weeks (if palliative stereotactic radiation therapy, >2 weeks)
    - Systemic anticancer therapy [including immunotherapy (non-antibody-based therapy)], retinoid therapy, hormonal therapy [metastatic breast cancer indication]): ≥3 weeks
    - Small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel: ≥2 weeks or 5 half-lives, whichever is longer
    - Nitrosoureas or mitomycin C: ≥6 weeks
    - Antibody-based anti-cancer therapy: ≥4 weeks.
    - Chloroquine/Hydroxychloroquine: >14 days

12. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months after the last dose of study drug. Methods considered as highly effective methods of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Complete sexual abstinence, defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months (females) or 7 months (males) after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.
13. Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 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 study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.

14. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 7 months after the last dose of study drug. Preservation of sperm should be considered prior to enrollment in this study.
15. Female subjects must not donate or retrieve ova for their own use, from the time of Screening and throughout the study treatment period, and for at least 7 months after the last dose of study drug.
16. Life expectancy of at least 3 months.

Inclusion Criteria Specific to Part 1

1. Subjects meeting the eligibility criteria set up for any of the 4 cohorts in Part 2 would be eligible to enroll in Part 1.

Inclusion Criteria Specific to Part 2

For Cohort 1:

1. Pathologically documented advanced/metastatic breast cancer that has centrally-determined HER2-positive expression as per ASCO-CAP guidelines
2. Prior T-DM1 therapy with documented progression.

For Cohort 2:

1. Pathologically documented advanced/metastatic breast cancer that has centrally-determined low HER2 expression (IHC 1+ or IHC 2+/ISH-).

2. Subject must have exhausted treatments that can confer any clinically meaningful benefit (e.g., other therapies such as hormonal therapy for subjects who are hormone receptor positive).

For Cohort 3:

1. Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 2+ or 3+.
2. Prior treatment with platinum-based combination chemotherapy regimen with documented progression.

For Cohort 4:

1. Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 1+.
2. Prior treatment with platinum-based combination chemotherapy regimen with documented progression.

Key Exclusion Criteria:

1. Has received prior treatment with nivolumab or trastuzumab deruxtecan.
2. Medical history of myocardial infarction (MI) within 6 months before enrollment, symptomatic congestive heart failure (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 enrollment to rule out MI.
3. Has a corrected QT interval by Fredericia (QTcF) prolongation to >470 ms (females) or >450 ms (males) based on an average of the screening triplicate 12-lead electrocardiogram.
4. Has a history of interstitial lung disease (ILD) /pneumonitis (non-infectious) that required steroids, has current ILD/pneumonitis, or where suspected ILD /pneumonitis cannot be ruled out by imaging at screening.
5. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. 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 do not require 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 being symptomatic or requiring therapy with corticosteroids or between the end of whole brain radiotherapy and study enrollment.

7. Known carcinomatous meningitis.
8. Has received a live vaccine within 30 days prior to the first dose of study drug.
9. Subjects with an active, known or suspected autoimmune disease. Subjects with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. Uncontrolled adrenal insufficiency.
11. Has had prior anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
12. Prior anti-HER2 therapy is not permitted except for subjects with HER2-positive breast cancer as per ASCO-CAP guidelines.
13. Note: Subjects with HER2 negative residual disease treated with adjuvant anti HER2 therapy as per standard practice may be eligible. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer (metastatic breast cancer indication).
14. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e. pulmonary emboli within three months of the study enrollment, severe asthma, severe COPD, restrictive lung

disease, pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e. Rheumatoid arthritis, Sjogren's, sarcoidosis etc.), or prior pneumonectomy.

15. Has history of severe hypersensitivity reactions to other monoclonal antibodies and/or to either the drug substances or inactive ingredients in the drug product.
16. Has known psychiatric, substance abuse, or any other medical conditions that would increase the safety risk to the subject or interfere with participation of the subject or evaluation of the clinical study in the opinion of the investigator.
17. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to enrollment if required by local regulations or Institutional Review Board (IRB)/Ethics Committee (EC).
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
19. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Medical Monitor or designee (e.g., Grade 2 chemotherapy-induced neuropathy).
20. Is pregnant, breastfeeding, or planning to become pregnant.
21. History of previous organ transplantation, including stem cell allograft.
22. Has an uncontrolled infection requiring intravenous (IV) antibiotics, anti-virals, or anti-fungals. Uncontrolled infection is inclusive of active tuberculosis.
23. Otherwise considered inappropriate for the study by the investigator.

	24. Subject must not be a family member of study site personnel working for the investigator or of Sponsor personnel.
Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan as a lyophilized powder for reconstitution (trastuzumab deruxtecan for injection 100 mg) to be administered at doses of 3.2 mg/kg or 5.4 mg/kg IV for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1. Nivolumab as an aqueous solution formulated at 10 mg/mL, to be administered at a flat dose of 360 mg IV over 30 minutes. Trastuzumab deruxtecan and nivolumab will be administered on Day 1 of each 21-day cycle.
Study Endpoints:	<u>Primary Endpoint:</u> • DLT to assess MTD or RDE (Part1) • Objective response rate (ORR) as assessed by the Independent Central Review (ICR) Committee based on RECIST Version 1.1 (Part 2) <u>Secondary Endpoints:</u> • Key safety endpoints will include assessment of serious adverse events (SAEs), treatment emergent adverse events (TEAEs): TEAEs leading to discontinuation, and adverse events of special interest and immune-mediated AEs. • Other safety endpoints include: hematology and chemistry laboratory parameters, physical examination, vital signs, left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)/multigated acquisition/(MUGA) scan. • PK and biomarker endpoints including serum concentrations of trastuzumab deruxtecan, MAAA-118a and total anti-HER2 antibody and nivolumab (if analyzed) • Duration of response (DOR), Disease control rate (DCR), progression-free survival (PFS), time to response (TTR) based on ICR Committee • ORR as assessed by the investigator based on RECIST Version 1.1 (Part 2) • Overall survival (OS)

	Exploratory endpoints: • ORR by immune Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines as assessed by the investigator (Part 2) • Clinical benefit rate (CBR) in breast cancer cohorts, defined as proportion of subjects who achieved complete response (CR), or partial response (PR), or had stable disease (SD) for at least 6 months per RECIST Version 1.1 • Biomarker analyses related to the combination (i.e. PD-L1, microsatellite instability status, tumor mutation burden) to understand the mechanism of action and resistance based on pretreatment, post-treatment, and on-treatment new biopsies • Evaluation of serum concentration of trastuzumab deruxtecan and nivolumab (if analyzed) anti-drug antibodies (ADAs)
Planned Sample Size:	The estimated total number of subjects planned is between 99 to 108 subjects.
Statistical Analyses:	The primary database lock will occur 6 months after the last subject's first visit or when 80% of subjects experience disease progression or discontinue study treatment, whichever occurs first. An interim analysis is planned to be initiated for all breast cancer subjects in the study, including those from Part 1. Efficacy and safety interim analyses will be performed when all subjects enrolled into Cohorts 1 and 2 in Part 2 had at least 12 weeks of follow up after initiation of study treatment or have discontinued study treatment. For each cohort, the analyses for efficacy outcomes will be repeated adding the corresponding subject populations from Part 1 of the study. The estimate of DCR and ORR assessed by the ICR Committee based on RECIST Version 1.1 and their 2-sided 95% exact confidence interval will be provided. DOR, PFS, and OS will be summarized with median event times using Kaplan Meier method and their 2-sided 95% confidence intervals using Brookmeyer and Crowley method. Safety analysis will be performed using the Full Analysis Set (FAS). (The Safety Analysis Set is the same as the FAS). Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary

	statistics. Listings of safety data will be provided and details will be specified in the Statistical Analysis Plan. Descriptive statistics will be provided for serum concentration data at each time point for each dose level for trastuzumab deruxtecan and nivolumab (if analyzed).

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADA	Anti-drug Antibody
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BI	Before Infusion
BSA	Body Surface Area
CAP	College of American Pathologists
CART	Cell-free and Concentrated Ascites Reinfusion Therapy
Cavgss	Concentration Average at Steady State
CBR	Clinical Benefit Rate
cfDNA	Cell-free DNA
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CrCl	Creatinine Clearance Rate
CRF	Case Report Form
CRO	Contract Research Organization
CSPV	Clinical Safety and Pharmacovigilance
CT	Computed Tomography
Ctx	Platinum-based chemotherapy
DCR	Disease Control Rate
DILI	Drug-induced Liver Injury
DOR	Duration of Response
DLT	Dose-limiting Toxicity
DSI	Daiichi Sankyo Inc.
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram

ABBREVIATION	DEFINITION
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIU	Exposure in Utero
EOCT	End of Combination Treatment
EOI	End of Infusion
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FFPE	Formalin-fixed Paraffin-Embedded
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HER2	Human Epidermal Growth Factor 2
HER2ECD	HER2 Extracellular Domain
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICR	Independent Central Review
ICH	International Council for Harmonisation
ICMJE	International Council of Medical Journal Editors
ID	Infectious Disease
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
I-O	Immuno-oncology
irAEs	Immune related Adverse Events
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV	Intravenous

ABBREVIATION	DEFINITION
IXRS	Interactive Web/Voice Response System
LFT	Liver Function Test
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MAAA-1181a	The drug component of trastuzumab deruxtecan – a derivative of exatecan, a topoisomerase I inhibitor, free form
MAAA-1181c	Additive form of MAAA-1181a(3/10MeCN. 2/5MeOH.3/10 H20)
MAAL-9001	The antibody component of trastuzumab deruxtecan – a recombinant humanized anti-HER2 IgG1 monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-free Survival
PK	Pharmacokinetic
PR	Partial Response
Q3M	Every 3 Months
Q6W	Every 6 Weeks
QTc	Corrected QT Interval
QTcF	Corrected QT Interval by Fredericia
RDE	Recommended Expansion Dose
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Response Evaluable Set
SAE	Serious Adverse Event

ABBREVIATION	DEFINITION
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAVER	Serious Adverse Event Report
SD	Stable Disease
SE	Standard Error
SID	Subject Identifier
SJS	Stevens-Johnson Syndrome
SMT	Safety Management Team
SpO2	Peripheral Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T-DM1	Trastuzumab Emtansine
TEAE	Treatment-emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
Tx	Treatment
ULN	Upper Limit of Normal
US	United States

1. INTRODUCTION

1.1. Background

Breast cancer remains the most common cancer and the second leading cause of cancer mortality in women in developed countries and the first cause of death in developing countries. In 2015, there were 2.4 million new cancer cases leading to 523,000 deaths worldwide. Breast cancer was also the leading cause of morbidity in women, resulting in an estimated burden of 15.1 million disability-adjusted life years.[1]

In approximately 20% of breast cancer cases, overexpression of human epidermal growth factor receptor 2 (HER2) is considered the molecular oncologic alteration resulting in a historically aggressive disease with poor outcomes. Although HER2-targeted drugs have been developed as individualized molecularly targeted therapies, locally advanced and metastatic tumors invariably relapse with time.[1]

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

The only trial to report outcomes after 2 lines of anti-HER2 therapy was the THERESA trial, which compared trastuzumab emtansine (T-DM1) in the third-line setting to physician's choice therapies. The 2 prior lines of anti-HER2 therapy in this case were regimens containing trastuzumab and lapatinib. In this setting, although 81% of physician's choice treatments consisted of combining an anti-HER2 agent with chemotherapy, the objective response rate (ORR) for the physician's choice treatment was only 9%, and the median progression-free survival (PFS) was 3.3 months.[6] Treatment options for HER2-positive breast cancer, therefore, remain limited, with no targeted therapy specifically approved following trastuzumab, pertuzumab, and T-DM1 failure.[6] In this setting, recommended treatment options include continuation of an anti-HER2 therapy in combination with a standard chemotherapy agent. Due to the lack of clear superiority, no specific combination is currently endorsed in established guidelines, and consideration of palliative care is recommended after 3 lines of targeted therapy. Therefore, a high unmet medical need exists, and new treatment options need to be developed to improve outcomes for patients with disease progression following the failure of trastuzumab, pertuzumab, and T-DM1 regimens.

Urothelial bladder cancer is the ninth most common malignancy in the world.[7] In the United States, approximately 79,000 new cases and 17,000 deaths occur each year due to bladder cancer.[8] In Europe, there were an estimated 118,000 cases and 52,000 deaths in 2012.[9] In developed regions such as North America and Europe, bladder cancer is predominantly urothelial.

At the time of diagnosis, approximately 80% of urothelial bladder carcinomas are superficial and 20% of them will become invasive. The treatment of locally advanced or metastatic disease is currently based on the M-VAC regimen (methotrexate, vinblastine, doxorubicin, cisplatin), or gemcitabine and cisplatin.[10] Approximately half of patients with bladder cancer do not respond to their initial, or first-line therapy, and only 10% to 15% of those patients respond to second-line chemotherapy. Recently, programmed death 1 (PD-1)/PD-L1 antibodies have been approved for the treatment of patients with locally advanced or metastatic bladder cancer whose disease has progressed during or after first-line, adjuvant, or neoadjuvant therapy with platinum-containing chemotherapy.[11]

The HER2 is known to contribute to physiologic mechanisms of cell proliferation by an intrinsic tyrosine kinase activity. The assessment of HER2 status is a crucial in breast cancer patient management.[12] In invasive urothelial bladder carcinomas, HER2 overexpression was also found. However, the true incidence of HER2 overexpression remains uncertain ranging from 12% to 80% for overexpression.[10]

Unlike breast cancer, where the role of HER2-targeting agents has been well established in both metastatic and adjuvant settings, the experimental use of HER2-targeting agents has only emerged recently in bladder cancer clinical research. A possible involvement of the HER2 receptor in the proliferation of invasive urothelial bladder cancer has led to initiate HER2-targeted therapy trials in locally advanced or metastatic disease.[10]

Earlier trials of HER2 targeted therapies (monotherapy or in combination with chemotherapy) in HER2 overexpressing urothelial cancer have failed to show evidence of efficacy.[11] National Comprehensive Cancer Network guidelines recommends participation in clinical trials for new agents in patients that failed first line therapy indicating a high unmet medical need and a need to develop new treatment options for patients with this disease.[12]

1.2. Study Rationale

Trastuzumab deruxtecan is an anti-HER2 antibody drug conjugate incorporating a novel linker with a target number of 7 to 8 drug linker to 1 antibody molecule using a novel topoisomerase I inhibitor warhead different from currently approved tubulin inhibitors. In preclinical models as well as preliminary results from Phase 1 trials performed in the salvage line setting, trastuzumab deruxtecan has shown efficacy across a broad array of tumor types as well as in both HER2 high and low expressing models and tumors.

Preliminary evidence of clinical efficacy of trastuzumab deruxtecans monotherapy was seen in several tumor types at various levels of HER2 expression in the J101 study.[13]

The immune checkpoints prevent autoimmunity by down-regulating T-cell activation or effector function. By engaging immune checkpoints, tumors evade the immune system.

Programmed death 1 plays a key role in regulating and maintaining the balance between T-cell activation and immune tolerance. The PD-1 receptor, which is expressed on activated T-cells, is engaged by ligands PD-L1 and PD-L2, which are expressed by tumor cells and infiltrating immune cells. Tumor PD-L1 expression is prevalent in many tumor cells, and the interaction of PD-1 with the PD-L1 and PD-L2 ligands inhibits T-cell activation and promotes tumor immune

escape (i.e., the mechanism by which tumor cells escape recognition and elimination by the immune system).[14]

Nivolumab is a fully human IgG4 PD-1 immune-checkpoint–inhibitor antibody that disrupts PD-1–mediated signaling and restores antitumor immunity.[11,12,14] In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM).[15]

Nivolumab is currently approved for use in several solid tumors including urothelial cancer.

Immune checkpoint inhibitor efficacy depends on expression levels of major histocompatibility (MHC)-class I on tumor cell. The MHC-class I recovery approaches might synergize with complementary forms of immunotherapy. Trastuzumab deruxtecan causes cancer cell death and release of antigen and drug molecule (DX-8951 derivative), leading to MHC-class I up-regulation (bystander effect). The dendritic cell activation and increased MHC-class I expression on cancer cell in turn increases T-cell recognition of cancer cell.

In preclinical studies trastuzumab deruxtecan showed antitumor effect in an immunocompetent mouse model with human HER2-expressing CT26.WT cells (syngeneic mouse model) and formation of immunological memory. Combination of trastuzumab deruxtecan with an anti-PD-1 antibody exhibited significantly better survival prolongation compared with each single treatment in preclinical testing due to activating dendritic cell and MHC-class I markers and up-regulating PD-L1.[16]

Therefore, trastuzumab deruxtecan has potential synergistic effect with anti-PD-1therapy.

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure (IB).[13]

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are discussed further in Section 9.2 and Section 17.7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (HRT; (endocrinopathies) as instructed in these algorithms. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

The observed preclinical data and clinical data from the monotherapy trials of trastuzumab deruxtecan and nivolumab and the mechanisms of action of the 2 drugs provide scientific rationale for a clinical trial with this combination. The efficacy of trastuzumab deruxtecan at dose levels ranging from 0.8 to 8.0 g/kg of trastuzumab deruxtecan was observed in J101. Nivolumab 360 mg every 3 weeks is currently under investigation in monotherapy and combination oncology studies. The less frequent dosing regimens are designed to afford more convenience to the target patient populations and allow combination of nivolumab with other agents using alternative dosing regimens versus every 2 weeks. This nivolumab dose was selected using PK and exposure-response analyses modeling and simulation approaches such that it is predicted to provide approximately equivalent exposures (Cavgss) following administration

of nivolumab 3 mg/kg every 2 weeks.[17] In addition, to mitigate the safety risk of the combination in study subjects, the U105 trial design starts with a lower dose of trastuzumab deruxtecan (3.2 mg/kg). This design allows early assessment of safety risk of the combination prior to escalating to a recommended expansion dose (RDE) of trastuzumab deruxtecan as a combination or prior to enrolling a higher number of subjects in dose expansion cohorts.

1.2.1. Part 1 Safety Data (with a data-cutoff date of 22 July 2019) and Rationale to Support the RDE for Part 2

A total of 7 subjects were enrolled in Part 1 (4 subjects in cohort 1 and 3 subjects in cohort 2). No DLTs were declared among the DLT evaluable subjects (3 in each cohort). Therefore, based on the safety data of Part 1, the recommended dose for expansion [RDE] (phase 2) was declared at: trastuzumab deruxtecan 5.4 mg/kg and nivolumab 360 mg every three weeks. The data will be further detailed in the final Clinical Study Report (CSR).

2. STUDY OBJECTIVES, HYPOTHESIS, AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To determine the MTD or the RDE of trastuzumab deruxtecan when used in combination with nivolumab (Part 1).
- To evaluate the efficacy of combination treatment of trastuzumab deruxtecan and nivolumab in HER2-expressing advanced breast cancer as well as HER2-expressing advanced urothelial cancer (Part 2).

2.1.2. Secondary Objectives

- To assess the safety and tolerability of the combination of trastuzumab deruxtecan and nivolumab.
- To determine the pharmacokinetics (PK) of trastuzumab deruxtecan when dosed concomitantly with nivolumab. To further evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab.

2.1.3. Exploratory Objectives

- To evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab by by using the immune Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines as assessed by the study investigator (Part 2)
- To further evaluate the efficacy of the combination of trastuzumab deruxtecan and nivolumab in terms of clinical benefit rate (CBR) in breast cancer cohorts
- To perform biomarker analyses related to the combination to understand the mechanism of action and resistance based on pretreatment, post-treatment, and on-treatment biopsies
- To evaluate the immunogenicity of trastuzumab deruxtecan and nivolulmab (if analyzed).

2.2. Study Hypotheses

Trastuzumab deruxtecan plus nivolumab at the tolerated dose level will confer significant clinical benefit as reported by ORR and other efficacy endpoints.

2.3. Study Endpoints

2.3.1. Primary Endpoints

- DLT to assess MTD or RDE (Part1)
- ORR as assessed by the ICR Committee based on RECIST Version 1.1 (Part 2)

2.3.2. Secondary Endpoint(s)

- Key safety endpoints will include assessment of SAEs, TEAEs: TEAEs leading to discontinuation, adverse events of special interest, and immune-mediated AEs.
- Other safety endpoints include: hematology and chemistry laboratory parameters, physical examination, vital signs, left ventricular ejection fraction (LVEF) by echocardiogram (ECHO)/multigated acquisition/(MUGA) scan.
- PK and biomarker endpoints including serum concentrations of trastuzumab deruxtecan, MAAA- 118a and total anti-HER2 antibody and nivolumab (if analyzed).
- Duration of response (DOR), disease control rate (DCR), PFS, time to response (TTR) based on ICR Committee
- ORR as assessed by the investigator based on RECIST Version 1.1 (Part 2)
- Overall survival (OS).

2.3.3. Exploratory Endpoints

- ORR by iRECIST guidelines as assessed by the investigator (Part 2)
- CBR in breast cancer cohorts, defined as proportion of subjects who achieved CR, or PR, or had SD for at least 6 months per RECIST Version 1.1
- Biomarker analyses related to the combination (i.e. PD-L1, microsatellite instability status, tumor mutation burden) to understand the mechanism of action and resistance based on pretreatment, post-treatment, and on-treatment new biopsies.
- Evaluation of serum concentration of trastuzumab deruxtecan and nivolumab (if analyzed) anti-drug antibodies (ADAs)

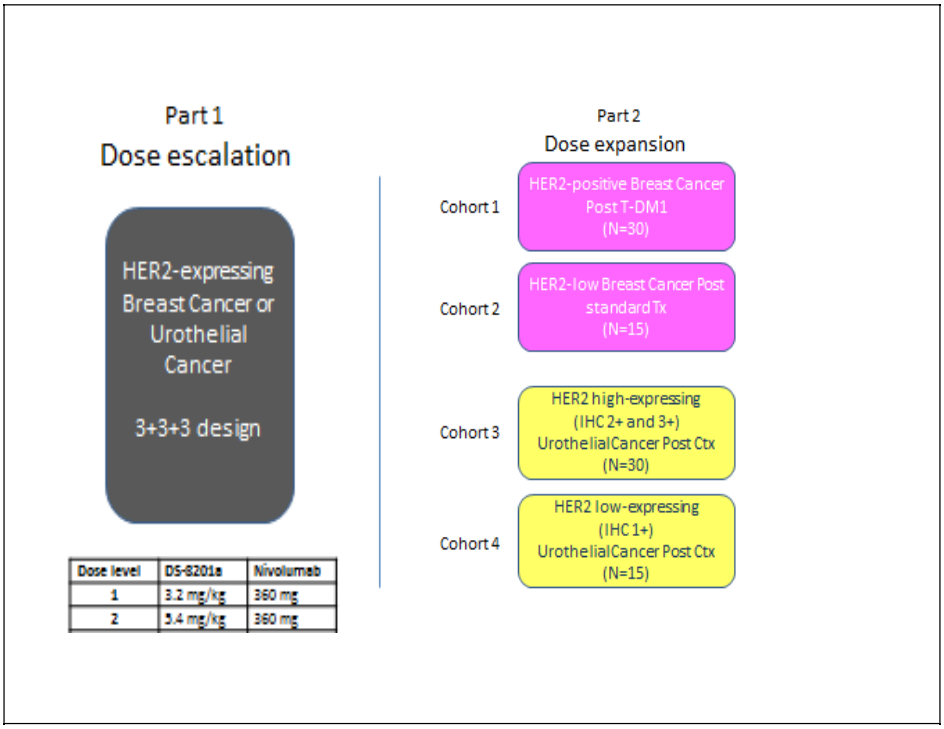
3. STUDY DESIGN

3.1. Overall Design

This is a Phase 1b, open-label, 2-part, multicenter, non-randomized, multiple-dose, study of trastuzumab deruxtecan in combination with nivolumab. This 2-part study will include both a dose escalation part, to identify the RDE of trastuzumab deruxtecan in combination with a fixed dose of nivolumab, and a dose expansion part, to evaluate efficacy, safety, and tolerability.

A schema of the study design is provided in Figure 3.1.

Figure 3.1: Study Design Schema



Ctx = platinum-based chemotherapy; HER2 = human epidermal growth factor 2; IHC = immunohistochemistry; T-DM1 = trastuzumab emtansine; Tx = treatment

3.2. Discussion of Study Design

Part 1 is a dose escalation phase for trastuzumab deruxtecan to determine RDE for Part 2 and Part 2 is a dose expansion phase as discussed in Section 3.1. Nivolumab will be infused over approximately 30 minutes on Day 1 of each cycle prior to the administration of trastuzumab deruxtecan with no less than a 30-minute gap between the 2 infusions. The initial dose of trastuzumab deruxtecan will be infused intravenously into each subject for approximately 90 minutes on Day 1 of Cycle 1. If no infusion reaction is observed, infusion may occur over 30 minutes on subsequent cycles.

Part 1 (Dose Escalation)

Part 1 will enroll subjects meeting the eligibility criteria set up for any of the 4 cohorts of Part 2 using a 3 + 3 + 3 design. Escalating doses of trastuzumab deruxtecan (Table 3.1) in combination with nivolumab will be assessed. Trastuzumab deruxtecan and nivolumab will be administered on Day 1 of each 21-day cycle.

Table 3.1: Trastuzumab Deruxtecan Dose Escalation

Dose Level	Trastuzumab Deruxtecan	Nivolumab
1	3.2 mg/kg Q3W	360 mg Q3W
2	5.4 mg/kg Q3W	360 mg Q3W

The starting dose of trastuzumab deruxtecan will be 3.2 mg/kg and a fixed dose of 360 mg for nivolumab combination given every 3 weeks. Escalation/de-escalation to the next dose will be based on acceptable safety signal from the earlier dose cohort. Intrasubject dose escalations are not allowed. Note: If the maximum dose of 5.4 mg/kg for trastuzumab deruxtecan is lower than MTD, the RDE of 5.4 mg/kg will be taken as RDE.

The DLT observation period will be the first 2 cycles (6 weeks). Upon completion of the DLT observation period, subjects may continue to receive study treatment in subsequent cycles as previously described, until the occurrence of unacceptable toxicity, progressive disease (PD), or withdrawal of consent. Subjects may continue to receive nivolumab beyond progression if the investigator believes this will provide clinical benefit to the subject (See Section 3.2.3 for specification of DLT).

Part 2 (Dose Expansion)

Upon completion of dose escalation (Part 1) with determination of RDE, the dose expansion part will begin.

Part 2 will consist of 4 cohorts as follows:

Cohort 1 (n=30):

Pathologically documented advanced/metastatic breast cancer that has centrally-determined HER2-positive expression as per ASCO-CAP guidelines. Subjects who have received prior trastuzumab emtansine (T-DM1) with documented progression.

Cohort 2 (n=15):

Pathologically documented advanced/metastatic breast cancer that has centrally-determined low HER2 expression (IHC 1+ or IHC 2+/ISH-). Subjects who have exhausted treatments that can confer any clinically meaningful benefit (e.g., other therapies such as hormonal therapy for subjects who are hormone receptor positive).

Cohort 3 (n=30):

Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 2+ or 3+. Subjects who received prior platinum-based therapy with documented progression.

Cohort 4 (n=15):

Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 1+. Subjects who have received prior platinum-based therapy with documented progression.

The estimated total number of subjects planned is between 99 to 108 subjects.

Approximately 5 sites are planned for Part 1 and 25 sites for Part 2 in the United States (US) and Europe.

3.2.1. Duration of the Study

Enrollment for both Part 1 and Part 2 combined is planned to occur over approximately 18 months. An efficacy and safety interim analysis will be performed when all subjects enrolled into Cohorts 1 and 2 in Part 2 have had at least 12 weeks of follow-up after initiation of study treatment or have discontinued study treatment. Anticipated total duration of the study is approximately 24 months. The primary database lock will occur 6 months from the last subject enrolled in the study or when 80% of the subjects have experienced disease progression or discontinued study treatment, whichever occurs first.

The end of the study is defined as the date of completion of the last visit or procedure shown in the Schedule of Events in the trial globally.

There will be a 40-Day Follow-up Visit (± 7 days), and a 100-Day safety follow up, followed by Long-term Follow-up Visits. Subjects who discontinue study treatment for any other reason than disease progression will be followed as described in Section 6.3 for tumor assessment until disease progression or start of new anticancer therapy. Subjects who discontinue study treatment due to disease progression will be followed every 3 months (±14 days) from the date of 40-Day Follow-up Visit until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

Safety and survival information will be collected via a 100-Day Telephone Follow-up.

Subjects will continue trastuzumab deruxtecan and nivolumab until they have disease progression or meet any other criteria for treatment discontinuation. Nivolumab treatment beyond progression is allowed only if the potential benefits of treatment outweigh the risks in the opinion of the investigator. A maximum of 35 cycles/2 years of nivolumab can be administered to a subject. Trastuzumab deruxtecan may be administered until occurrence of disease progression as per RECIST 1.1.

Sponsor may terminate the study at any time due to administrative reason or at request from competent regulatory authorities.

3.2.2. Duration of Study Participation

The screening period is up to 28 days. Upon commencing, subjects may continue receiving study drug until the occurrence of unacceptable toxicity, PD, or withdrawal of consent. Each treatment cycle will be 21 days.

Subjects who discontinued both study treatments due to any reason other than disease progression will continue Long-term Follow-up for tumor assessment until disease progression

or start of additional anticancer treatment as described in Section 6.3 and every 3 months (±14 days) thereafter, from the date of 40-Day Follow-up Visit/last tumor assessment until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs later. Subjects who discontinued study treatments due to disease progression would be followed every 3 months (±14 days), to obtain information about subsequent treatment(s) and survival status from the date of 40-Day Follow-up Visit until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs later.

3.2.2.1. Nivolumab Treatment Beyond Progression

Accumulating evidence indicates that a minority of patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients will be permitted to continue on nivolumab treatment beyond initial RECIST Version 1.1-defined PD for up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Continues to tolerate study drug.
- Patient has stable ECOG performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases).

The assessment of clinical benefit should take into account whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor, and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records.

For patients who stay on nivolumab treatment beyond RECIST Version 1.1-defined PD, all study procedures (Section 6, Study Procedures) should be performed continuously, including radiographic assessment by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) as described in Section 6.3. Patients will be discontinued from the treatment upon further evidence of disease progression, as per iRECIST criteria. If a subject has confirmed radiographic progression (iCPD) as defined by iRECIST, nivolumab should be discontinued. Treatment with nivolumab can only be administered for 24 months regardless of tumor progression.

3.2.3. Dose-Limiting Toxicity Definition

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the DLT evaluation period (2 complete cycles during Part 1) and is Grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The list of potential DLTs and exceptions are defined below:

For hematological toxicities, a potential DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days
- Grade ≥3 febrile neutropenia
- Grade 4 anemia
- Grade 4 platelet count decreased
- Grade ≥3 platelet count decreased lasting >7 days
- Grade ≥3 platelet count decreased with clinically significant hemorrhage
- Grade 4 lymphocyte count decreased lasting ≥14 days

For hepatic organ toxicities, a DLT is defined as follows:

- Grade ≥3 total bilirubin increased
- Subject without baseline liver metastases: Grade 3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased
- Subject with liver metastases: AST or ALT >5 × upper limit of normal (ULN) if the baseline level was ≤3 × ULN or AST or ALT >8 × ULN if the baseline level was >3 × ULN
- AST or ALT >3 × ULN (in subjects with baseline liver metastases, AST or ALT >5 × ULN) if accompanied by Grade ≥2 blood bilirubin increased

For non-hematological, non-hepatic major organ toxicities, a potential DLT is defined as follows:

- Symptomatic congestive heart failure
- LVEF decline to <40% or >20% drop from baseline
- Grade ≥2 interstitial lung disease (ILD)
- Any Grade ≥2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Other Grade ≥3 non-hematological, non-hepatic major organ toxicities

The following TEAEs are NOT considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤2 within 3 days
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline
- Grade 3 lymphocyte count decreased

Sponsor will collaborate with investigator/principal investigator to determine whether a specific toxicity observed during DLT period would qualify as a DLT taking into account the criteria above as well as other circumstances around the toxicity observed such as evidence of disease progression.

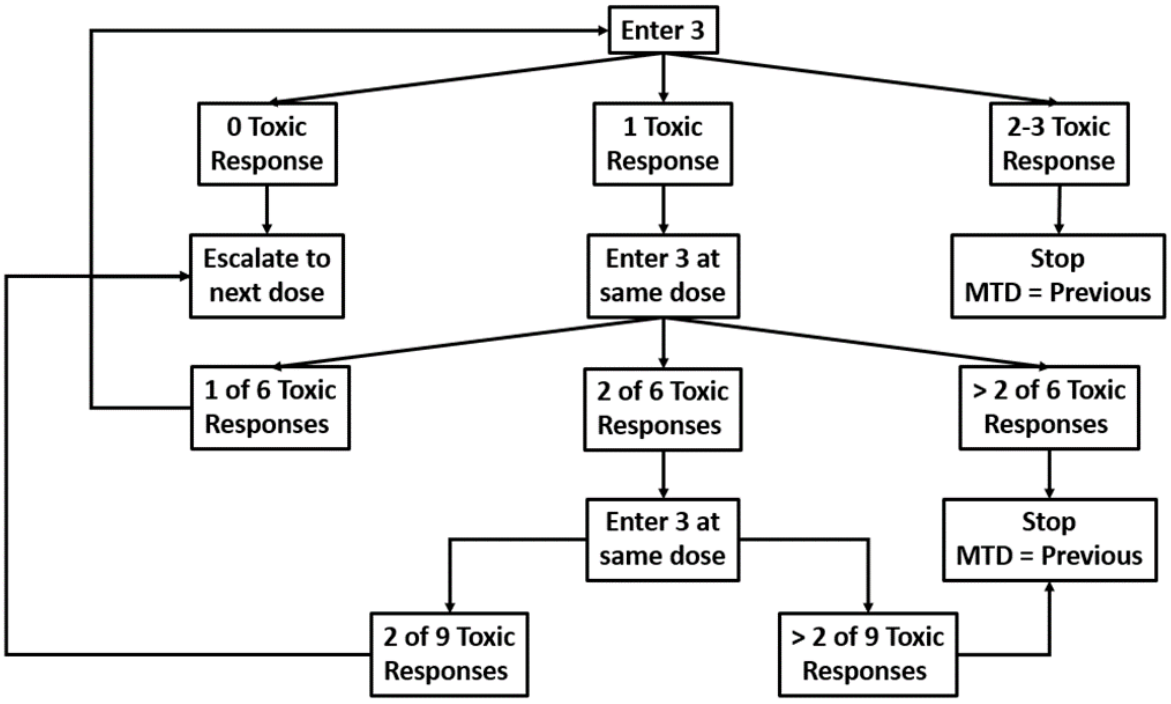
3.2.4. Maximum Tolerated Dose and Recommended Expansion Dose Definition

The MTD or RDE is determined in Part 1. The RDE may be either the MTD/RDE determined in Part 1, or an alternative dose, pending discussions between the Sponsor and the investigator(s). Once the RDE has been determined, enrollment to Part 2 will begin.

3.2.5. Dose Escalation to MTD

The 3 + 3 + 3 design uses the dose escalation/de-escalation rules as shown in Figure 3.2 below.

Figure 3.2: 3+3+3 Clinical Study Design



MTD: Maximum tolerated dose

The MTD is determined as follows:

- At a trastuzumab deruxtecan dose, if 2 DLTs out of 3 subjects, or ≥3 DLTs out of 6 subjects or 9 subjects, then the previous dose is the MTD unless the current dose is 3.2 mg/kg, which means that 3.2 mg/kg of trastuzumab deruxtecan is above the MTD. The Sponsor will determine the next step in consultation with the investigator.
- At 5.4 mg/kg trastuzumab deruxtecan dose, if 0 DLTs out of 3 subjects, or ≤1 DLT out of 6 subjects, or ≤2 DLTs out of 9 subjects, then 5.4 mg/kg is the RDE, although MTD has not been reached.

4. STUDY POPULATION

4.1. Inclusion Criteria

Prior to the start of any study-specific qualification procedures, all subjects must sign and date the informed consent form (ICF), which will be provided to them by the study site.

Subjects must satisfy all of the following criteria to be included in the study:

4.1.1. Key Inclusion Criteria

1. Adults ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old.)
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (Section 17.2).
3. Pathologically documented HER2-expressing locally advanced/metastatic breast cancer or urothelial cancer that is unresectable, and refractory to or intolerant of existing therapy(ies) known to provide clinical benefit and as specified in each study cohort.

   Note: Subjects with urothelial cancer eligible to receive anti PD-1/PD-L1 treatment as per the approved local label may be considered eligible for the study.
4. Subjects must have an adequate archival tumor sample available for determination of HER2 status by the central laboratory (most recent tumor tissue preferred). Subjects are eligible to participate if they meet HER2 status criteria based on results from the central laboratory.
5. Presence of at least 1 measurable lesion per RECIST Version 1.1. as assessed by the Investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions (Section 1.1).
6. Has adequate cardiac function, as defined by LVEF ≥50% within 28 days before enrollment.
7. Adequate bone marrow function, defined as:
   - Absolute neutrophil count ≥1.5 × 10^9/L (Granulocyte colony-stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment.)
   - White blood cell >2000/mm^3
   - Platelet count ≥100 × 109/L (Platelet transfusion is not allowed within 1 week prior to screening assessment.)
   - Hemoglobin level ≥9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment.)
8. Adequate renal function, defined as:
   - Creatinine clearance ≥30 mL/min, as calculated using the Cockcroft-Gault equation CLcr (mL/min) = [140 - age (years)] × weight (kg) /72 × serum creatinine (mg/dL) {× 0.85 for females} (Section 17.4).

9. Adequate hepatic function, including mild to moderate hepatic impairment defined as the following:
   - Total bilirubin ≤1.5 × ULN (except subjects with documented Gilbert's syndrome or liver metastases at baseline who must have a total bilirubin level of ≤2.0 × ULN).
   - AST/ALT values ≤2.5 × ULN (≤5 × ULN in subjects with liver metastases or other etiologies).
10. Adequate blood clotting function, defined as: international normalized ratio (INR) and prothrombin time (PT)/activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) ≤1.5 × ULN unless the subject is receiving anticoagulant therapy, in which case INR and PT/aPTT or PTT must be within therapeutic range of intended use of anticoagulant.
11. Adequate treatment washout period before enrollment, defined as:
    - Major surgery: ≥4 weeks
    - Radiation therapy including palliative stereotactic radiation to chest: ≥4 weeks (palliative stereotactic radiation therapy to other areas, ≥2 weeks)
    - Systemic anticancer therapy including immunotherapy (non-antibody-based therapy), retinoid therapy, hormonal therapy (metastatic breast cancer indication): ≥3 weeks
    - Small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel: ≥2 weeks or 5 half-lives, whichever is longer
    - Nitrosoureas or mitomycin C:>6 weeks)
    - Antibody-based anti-cancer therapy: ≥4 weeks.
    - Chloroquine/Hydroxychloroquine: >14 days
12. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months after the last dose of study drug. Methods considered as highly effective methods of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      a. Oral
      b. Intravaginal
      c. Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
      a. Oral
      b. Injectable
      c. Implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence, defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months (males and females) after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

13. Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >40 mIU/mL and estradiol <40 pg/mL [<147 pmol/L] is confirmatory). Females on HRT and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.
14. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 7 months after the final study drug administration. Preservation of sperm should be considered prior to enrollment in this study.
15. Female subjects must not donate or retrieve ova for their own use from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.
16. Life expectancy of at least 3 months.

4.1.2. Inclusion Criteria Specific to Part 1

Subjects meeting the eligibility criteria set up for any of the 4 cohorts in Part 2 would be eligible to enroll in Part 1.

4.1.3. Inclusion Criteria Specific to Part 2

<u>For Cohort 1</u>:

1. Pathologically documented advanced/metastatic breast cancer that has centrally-determined HER2-positive expression as per ASCO-CAP guidelines.
2. Prior T-DM1 therapy with documented progression.

<u>For Cohort 2:</u>

1. Pathologically documented advanced/metastatic breast cancer that has centrally-determined low HER2 expression (IHC 1+ or IHC 2+/ISH-).

2. Subject must have exhausted treatments that can confer any clinically meaningful benefit (e.g., other therapies such as hormonal therapy for patients who are hormone receptor positive).

For Cohort 3:

1. Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 2+ or 3+.
2. Prior treatment with a platinum-based combination chemotherapy regimen with documented progression.

For Cohort 4:

1. Pathologically documented advanced/metastatic urothelial carcinoma that has centrally-determined HER2 expression of IHC 1+.
2. Prior treatment with a platinum-based combination chemotherapy regimen with documented progression.

4.2. Exclusion Criteria

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

1. Has received prior treatment with nivolumab or trastuzumab deruxtecan.
2. Medical history of myocardial infarction within 6 months before enrollment, symptomatic congestive heart failure (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 enrollment to rule out MI.
3. Has a QTcF prolongation to >470 ms (females) or >450 ms (males) based on an average of the screening triplicate12-lead electrocardiograms ECGs.
4. Has a history of ILD/pneumonitis (non-infectious) that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
5. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. 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 do not require 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 being

symptomatic or requiring therapy with corticosteroids or between the end of whole brain radiotherapy and study enrollment.

7. Known carcinomatous meningitis.
8. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
9. Subjects with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. Uncontrolled adrenal insufficiency.
11. Has had prior anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
12. Prior anti-HER2 therapy is not permitted except for subjects with HER2-positive breast cancer as per ASCO-CAP guidelines. Note: Subjects with HER2 negative residual disease treated with adjuvant anti HER2 therapy as per standard practice may be eligible.
13. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer (metastatic breast cancer indication).
14. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e. pulmonary emboli within three months of the study enrollment, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e. Rheumatoid arthritis, Sjogren's, sarcoidosis etc.), or prior pneumonectomy.
15. Has history of severe hypersensitivity reactions to other monoclonal antibodies and/or to either the drug substances or inactive ingredients in the drug product.
16. Has known psychiatric, 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.
17. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to enrollment if required by local regulations or Institutional Review Board (IRB)/Ethics Committee (EC).

18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
19. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Medical Monitor or designee (e.g., Grade 2 chemotherapy-induced neuropathy).
20. Is pregnant, breastfeeding, or planning to become pregnant.
21. History of previous organ transplantation, including stem cell allograft.
22. Has an uncontrolled infection requiring intravenous (IV) antibiotics, anti-virals, or anti-fungals. Uncontrolled infection is inclusive of active tuberculosis.
23. Otherwise considered inappropriate for the study by the investigator.
24. Subject must not be a family member of study site personnel working for the investigator or of Sponsor personnel.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequences

This study consists of 2 dose levels of trastuzumab deruxtecan with a flat dose of nivolumab for dose escalation (Part 1) and 4 expansion cohorts (Part 2). All subjects will be receiving nivolumab and trastuzumab deruxtecan. Nivolumab will be administered prior to trastuzumab deruxtecan. Part 2 enrollment will start after Part 1 is completed and an RDE has been established.

5.1.2. Method of Treatment Allocation

For Part 1, treatment allocation is based on available dose combination following the 3 + 3 + 3 design. Details of dose escalation are provided in Section 3.2.5. For Part 2, subjects of all 4 expansion cohorts will be treated with RDE of trastuzumab deruxtecan plus nivolumab.

5.1.3. Blinding

Not applicable due to single-arm study design (no comparator arm).

5.1.4. Emergency Unblinding Procedure

Not applicable due to single-arm study design (no comparator arm).

5.2. Study Drug(s)

5.2.1. Description

The trastuzumab deruxtecan drug product will be provided as a lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. Each glass vial should be reconstituted with sterile water to a concentration of 20.0 mg/mL. Each vial is designed for single use only and is not to be used to treat more than 1 subject.

Nivolumab injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. It is supplied in 10-mL Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. Each vial is designed for single use only and is not to be used to treat more than 1 subject.

5.2.2. Labeling and Packaging

Trastuzumab deruxtecan and nivolumab will be supplied by the Sponsor. Both drugs will be labeled in compliance with regulatory requirements and packaged. 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.

5.2.3. Preparation

The study drug (DS-8201) for IV infusion is prepared by the study site pharmacist by reconstitution with sterile water for injection and dilution of the required volume of the study drug calculated based on the subject's body weight in a volume of 100 mL. Prepared study drug solutions should be used as directed in the Pharmacy Manual. The preparation will be conducted in accordance with the Pharmacy Manual provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures of the study site.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection are provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with glass bottles and polyvinyl chloride or polyolefin containers and infusion sets.

5.2.4. Administration

Nivolumab will be infused over approximately 30 minutes on Day 1 of each cycle prior to the administration of trastuzumab deruxtecan with no less than a 30-minute gap between the infusions of the 2 study drugs. Do not co-administer the 2 drugs through the same IV line. Flush the IV line after infusion of each drug. Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE version 5.

The study drug (trastuzumab deruxtecan) will be administered initially as an IV infusion over 30 or 90 minutes every 3 weeks. The initial dose of trastuzumab deruxtecan will be infused over approximately 90 minutes. If there is no infusion-related reaction, after the initial dose, the next dose of trastuzumab deruxtecan will be infused for approximately 30 minutes. The prophylactic premedication can be administered as per investigator's discretion and as per institutional guidelines for subjects who have experienced potential Grades 1-2 infusion-related reactions during the previous infusion. The subject's weight at screening (baseline) will be used to calculate the initial dose. During the course of treatment, if the subject's weight changes by ± 10% of the baseline weight, then recalculate the trastuzumab deruxtecan dose based on the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of study drug.

It is recommended that study sites provide basic life support and advanced life support with necessary equipment and appropriate and available emergency medications to manage any

potential hypersensitivity/infusion-related reactions in/or close proximity to the infusion area. At least an oxygen tank, nasal prongs, and an oxygen mask must be available to manage respiratory symptoms. Access to other respiratory equipment is also critical in all settings of care and would include an ambu bag, oral airway, and suction apparatus in case a subject becomes unconscious. Large-gauge IV catheters are recommended to enable administration of normal saline and emergency medications. A cardiopulmonary resuscitation board is not necessary as long as the treatment chairs are low enough for a subject to be eased to the floor if necessary.

5.2.4.1. Maximum Duration of Treatment with Nivolumab

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary.

Accumulating evidence from different clinical trials in different tumor types with nivolumab, or nivolumab combined to ipilimumab, indicates that most of the responses are generally occurring early, with a median TTR of 2 to 4 months, including in patients with NSCLC,[18,19] and a recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[20]

For these reasons, in study DS8201-A-U105, treatment with nivolumab will be administered for up to 35 cycles/approximately 24 months in the absence of disease progression or unacceptable toxicity. Trastuzumab deruxtecan will be given as per the study dosing schedule (Table 17.1). Treatment with nivolumab could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year.

5.2.5. Storage

Drug supplies must be stored in a secure, limited-access storage area under the recommended storage conditions.

Trastuzumab Deruxtecan

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

Nivolumab

- Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

If storage conditions are not maintained per specified requirements, the Sponsor or Clinical Research Organization (CRO) should be contacted.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C [36°F to 46°F]) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C [68°F to 77°F]) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

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

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, check the drug expiration date, and sign the Receipt of Shipment Form provided.

The Receipt of Shipment Form should be faxed as instructed on the form unless receipt is controlled by an Interactive Web/Voice Response System. The original will be retained at the study site.

In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drugs, active drugs, and diluents or products of regulatory concern. The record must be kept current and should contain;

- The dates and quantities of study drug received,
- Subject's identification number and/or initials or supply number, as applicable, (for whom the study drug was dispensed).
- The date and quantity of study drug dispensed and remaining.
- The initials of the dispenser.

At the end of the study, a final study drug reconciliation statement must be completed by the investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the investigator when approved in writing by the Sponsor and the Sponsor has received copies of the study site's drug handling and disposition standard operating procedures and it is ensured that the Sponsor will receive copies of the certificate of destruction that is traceable to the study drug.

All study drug inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors.

5.3. Control Treatment

Not applicable due to single-arm study design.

5.4. Dose-Limiting Toxicity or Maximum Tolerated Dose

See Section 3.2.3, Section 3.2.4, and Section 3.2.5.

5.5. Dose Modification (Delay, Reduction, and/or Discontinuation) for Trastuzumab Deruxtecan and Nivolumab

5.5.1. Guidelines for Delay, Reduction and/or Discontinuation for Trastuzumab Deruxtecan and Nivolumab

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity (CTCAE version 5.0) as shown in Table 5.1 Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in the table below, which is applicable only to TEAEs that are assessed as related to use of

trastuzumab deruxtecan by the investigator. For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

Dose increases are not permitted for trastuzumab deruxtecan. In the event that a dose reduction of trastuzumab deruxtecan is required, only 2 dose reductions are allowed: dose level -1: 4.4mg/kg, and dose level -2: 3.2mg/kg. Dose reductions below 3.2 mg/kg are strictly prohibited. Once the dose of trastuzumab deruxtecan has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. ***If toxicity continues after 2 dose reductions, the subject will be withdrawn from the study treatment.***

Dose reductions or increases for nivolumab are not permitted.

All interruptions or modifications must be recorded on the case report form (CRF). Appropriate clinical experts should be consulted as deemed necessary.

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 AE is determined to be resolving or back to baseline. Monitoring of Grade 3 or 4 AEs will also be performed for subjects who discontinued study treatment (s).

Prophylactic or supportive treatment for expected toxicities will be as per the treating physician's discretion and institutional guidelines.

If a specific toxicity can be attributed to only 1 of the study treatments, then the management guidelines for that specific treatment should be followed as listed in Table 5.1 below.

However, if a specific toxicity cannot be attributed to only 1 of the study treatments, the management guidelines for each of the study treatments should be followed as listed in Table 5.1 below.

In cases of diarrhea/colitis and pulmonary toxicities, management guidelines for each of the study treatments should be followed, regardless of the causality assessment.

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

Dose reduction for trastuzumab deruxtecan in Part 2 will be applicable and will be based on the RDE dose and available lower dose level(s). The study treatment (either or both drugs) can be delayed up to 7 weeks from the previous dose received beyond which the subject will be withdrawn from the study drug. If the subject will restart/continue on both the study drugs, then it is recommended that both drugs are given on the same day whenever possible.

Future cycles schedule should be based on the date of the last study treatment received.

All confirmed or suspected Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection events must be recorded in the eCRF. Please refer to Section 1.1 for additional information on dose modification.

5.5.2. Toxicity Management for Immune-Related Adverse Events Associated With Nivolumab

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related AEs. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

Adverse events associated with nivolumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of nivolumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of nivolumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy and endoscopy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue nivolumab and administer corticosteroids. Dose modification and toxicity management guidelines for immune-mediated AEs associated with nivolumab are provided in Appendix 17.7.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
Infusion Reaction	Grade 1 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 1 Infusion interruption not indicated. Intervention not indicated. Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations
	Grade 2 Interrupt the infusion. Symptomatic treatment started (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous [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. Use of prophylactic premedication is recommended as per investigator's discretion and as per institutional guidelines for subjects who had Grade 2 (or above) infusion-related reactions during the previous infusion.	Grade 2 Stop the infusion. Begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen). Remain at bedside and monitor subject until resolution of symptoms. When symptoms resolve, restart at 50% of the original infusion rate. If no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit. For future infusions, the following prophylactic pre-medications are recommended: Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
	Grade 3-4 Discontinue immediately and permanently. Urgent intervention needed**.**	**Grade 3-4** Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms. In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
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.	**Grade 1-2** No dose modification. **Grade 3** First occurrence: withhold dose - resume treatment when improves to Grade 0 or 1 Recurrence of same Grade 3: permanently discontinue **Grade 4** Permanently Discontinue
Febrile Neutropenia	Delay dose until resolved; reduce dose 1 level.	**Grade 3** First occurrence: withhold dose – resume treatment when it improves to grade 0. Recurrence of same grade 3: permanently discontinue **Grade 4:** Permanently discontinue
Lymphocyte Count Decreased	**Grade 1-3** No dose modification. **Grade 4** 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.	**Grade 1-2** No dose modification. **Grade 3** First occurrence: withhold dose - resume treatment when improves to Grade 0 or 1 Recurrence of same Grade 3: permanently discontinue **Grade 4** Permanently discontinue.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
Anaemia	**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.	**Grade 1-2** No dose modification. **Grade 3** First occurrence: withhold dose - resume treatment when improves to Grade 0 or 1 **Recurrence of same Grade 3:** permanently discontinue **Grade 4** Permanently discontinue.
Platelet Count Decreased	**Grade 1-2** No dose modification. **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** Delay dose until resolved to ≤Grade 1, then reduce dose 1 level.	**Grade 1-2** No dose modification. **Grade 3** First occurrence: withhold dose - resume treatment when improves to Grade 0 or 1 **Recurrence of same Grade 3:** permanently discontinue **Grade 4** Permanently discontinue.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
Renal Toxicity		
Blood Creatinine Increased	**Grade 3 (>3.0 to 6.0 × ULN)** Delay dose until resolved to ≤Grade 2 or baseline. Reduce dose 1 level. **Grade 4 (>6.0 × ULN)** Discontinue subject from study treatment.	**Grade 2 and 3** Delay dose. Resume treatment when it improves to Grade 0 or 1. **Grade 4** Discontinue.
Hepatic Toxicity		
AST/ALT ≥3.0 × ULN with Simultaneous Total Bilirubin >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.	Discontinue if: Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
AST/ALT	**Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)** No action **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 x 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. **Grade 4(>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)** Discontinue subject from study treatment.	**For subjects <u>without</u> baseline liver metastases:** **Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal):** Delay dose. Resume treatment when it improves to Grade 0 or 1. **Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) or higher:** Permanently discontinue Note: In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the Sponsor Medical Monitor/designee must occur. **For subjects <u>with</u> baseline liver metastases** **Grade 2 & 3 (up to 10 times the ULN):** Withhold dose. Resume treatment when it improves to Grade 0 or 1 **Grade 3 (from 10 - 20 times the ULN) and grade 4 AST or ALT:** Permanently discontinue

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
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.	Grade 2 – 4 Withhold if clinically significant or life-threatening determined by the investigator. Resume treatment when it improves to Grade 0 or 1

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
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, 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 trastuzumab deruxtecan If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤Grade 2: If resolved in ≤ 7 days from day of onset, reduce dose 1 level If resolved in > 7 days from day of onset, discontinue trastuzumab deruxtecan **Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal**) Discontinue subject from study treatment.	**Grade 2** Withhold. Resume treatment when it improves to Grade 0 or 1. **Grade ≥ 3 Total Bilirubin** Permanently discontinue.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
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.	Refer to "Other Non-laboratory Adverse Events" for Nivolumab.
Diarrhea/Colitis	*Regardless of the causality assessment, also follow the diarrhea/colitis treatment guidelines for nivolumab.* **Grade 3** Delay dose until resolved to Grade 1. If resolved in ≤3 days from day of onset, maintain dose. If resolved in >3 days from day of onset, reduce dose 1 level. **Grade 4** Discontinue subject from study treatment.	*Regardless of the causality assessment, also follow the diarrhea/colitis treatment guidelines for trastuzumab deruxtecan.* **Grade 2 & 3** Withhold dose. Resume treatment when it improves to Grade 0 or 1. **Grade 4** Permanently discontinue.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
Pulmonary Toxicity	*Regardless of the causality assessment, also follow the pulmonary toxicity treatment guidelines for nivolumab.* 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, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: High resolution CT Pulmonologist consultation (Infectious Disease consultation as clinically indicated) Blood culture and CBC. Other BLOOD tests could be considered as needed Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible Pulmonary function tests and pulse oximetry (SpO2) Arterial blood gases if clinically indicated One blood sample collection for PK (central) 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.	*Regardless of the causality assessment, also follow the pulmonary toxicity treatment guidelines for trastuzumab deruxtecan.* **Grade 1 (radiological changes only)** Consider dose delay. Monitor symptoms every 2-3 days. Consider pulmonary and infectious disease consults. Re-image as clinically indicated. **Grade 2 (mild to moderate new symptoms)** Delay dose. Pulmonary and infectious disease consults. Monitor symptoms daily; consider hospitalization. Systemic corticosteroids. Consider lung biopsy, bronchoscopy. Re-image as clinically indicated. **Grade 3-4** Permanently discontinue study therapy. Pulmonary and infectious disease consults. Systemic corticosteroids. Consider lung biopsy, bronchoscopy. Add prophylactic antibiotics. If worsening: add additional immunosuppression.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
Pulmonary Toxicity (Cont'd)	All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation. **Confirmed study drug-induced ILD** **Grade 1** The administration of trastuzumab deruxtecan must be interrupted for any ILD/pneumonitis events regardless of grad Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry Consider follow-up imaging in 1-2 weeks (or as clinically indicated). Consider starting systemic steroids (e.g. 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.* ** If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given* For Grade 1 events, trastuzumab deruxtecan 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	

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
	Grade 2 **Permanently discontinue subject from study treatment.** Promptly start and treat with systemic steroids (e.g., at least 1mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. Monitor symptoms closely. Re-image as clinically indicated. If worsening or no improvement in clinical or diagnostic observations in 5 days, Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone). Re-consider additional work-up for alternative etiologies as described above. Escalate care as clinically indicated. **Grade 3 and 4** **Permanently discontinue subject from study treatment.** Hospitalization required. Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. Re-image as clinically indicated. If still no improvement within 3 to 5 days, Re-consider additional work-up for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.	

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
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	**Grade 2** Withhold. Resume treatment when it improves to Grade 0 or 1. **Grade 3-4:** Permanently discontinue
Cardiac Toxicity		
Symptomatic congestive heart failure	Discontinue subject from study treatment.	

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose or Schedule Modification For Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (Unless Otherwise Specified): Dose Or Schedule Modification For Nivolumab
Left Ventricular Ejection Fraction (LVEF)	**LVEF >45% and decrease in LVEF by 10% to 20% (absolute value)** Continue treatment with trastuzumab deruxtecan. **LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline** Continue treatment with trastuzumab deruxtecan. Repeat LVEF assessment within 3 weeks. **LVEF 40% to ≤45% and decrease is 10-20% (absolute value) from baseline** Interrupt trastuzumab deruxtecan dosing. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment. If LVEF recovers to within 10% from baseline, resume study drug treatment **LVEF <40% or >20% (absolute value) drop from baseline** Interrupt trastuzumab deruxtecan dosing. Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment.	**Grade 3 & 4** Permanently discontinue.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for trastuzumab deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
Electrocardiogram QTcF Prolonged	**Grade 3 (QTc >500 ms on 2 separate ECGs, or >60 ms change from baseline)** Delay dose until resolved to ≤Grade 1 (QTc ≤480 ms). Determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected . If attributed to trastuzumab deruxtecan, reduce dose 1 level. **Grade 4 (Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia)** Discontinue subject from study treatment.	Refer to "Other Non-laboratory Adverse Events" for Nivolumab.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
Endocrinopathy	**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** Permanently discontinue subject from study treatment.	**Hypophysitis:** Withhold (Grade 2* or 3*). Permanently discontinue (Grade 4). **Adrenal Insufficiency:** Withhold (Grade 2*). Permanently Discontinue (Grade 3 or 4). **Type 1 Diabetes Mellitus:** Withhold (Grade 3*). Permanently discontinue (Grade 4). **Hypothyroidism/Hyperthyroidism:** Withhold (Symptomatic Grade 2* or 3*). Permanently Discontinue (Grade 4). *Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Resume treatment when adverse reaction improves to Grade 0 or 1 Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
Skin Adverse Event	**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.	**Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)** Withhold dose. Resume treatment when adverse reaction improves to Grade 0 or 1. **Grade 4 rash or confirmed SJS or TEN:** Permanently discontinue.
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** Permanently discontinue subject from study treatment.	**Grades 1-2:** No modification required **Grade 3:** First occurrence – withhold treatment. Resume treatment once recovered to Grade 0 or 1. **Recurrence of same grade 3:** Permanently discontinue **Grade 4** Permanently discontinue subject from study treatment except for the following events which do not require discontinuation: Grade 4 asymptomatic amylase or lipase. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

Table 5.1: Criteria for Dose Modification for Trastuzumab Deruxtecan and Nivolumab (Continued)

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Trastuzumab Deruxtecan	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Nivolumab
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** Permanently discontinue subject from study treatment.	**Encephalitis:** Withhold dose for new-onset moderate or severe neurologic signs or symptoms. Resume treatment when adverse reaction improves to Grade 0 or 1. Permanently discontinue for immune-mediated encephalitis. **Myocarditis:** **Grade 2:** Withhold dose. Follow adverse event management in appendix 17.7 **Grade ≥ 3**: Permanently discontinue. **Other Non-laboratory Adverse Events:** **Grade 1-2** No modification required **Grade 3** Withhold (first occurrence). Resume treatment when it improves to Grade 0 or 1. **Grade 4 or recurrent Grade 3** Permanently Discontinue. **<u>Discontinue Nivolumab:</u>** If require 10 mg per day or greater prednisone or equivalent for more than 12 weeks. If persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; DILI = drug-induced liver injury, ECG = electrocardiogram; ILD = interstitial lung disease; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

5.5.2.1. Criteria to Resume Nivolumab Treatment

If nivolumab dosing has been delayed due to an AE, the subject may resume treatment when the drug-related AE resolves to Grade ≤1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 5.5.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Medical Monitor.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor.

5.5.2.2. Pregnancy

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary, for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

5.6. Method of Assessing Treatment Compliance

Trastuzumab deruxtecan and nivolumab will be administered IV only to subjects participating in the study and under the supervision of clinical study personnel at the study site. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for administration of the study treatment. Start and stop date/time of injection, amount of drug administered, and reason for change or interruption (if applicable) must be recorded in medical record by clinical study personnel. These data will be recorded in the electronic CRF (eCRF).

5.7. Prior and Concomitant Medications

Medications used from the time the subject signs the ICF for study participation to the Follow-up 40 Day Visit (+ 7 days) after the last administration of trastuzumab deruxtecan or nivolumab will be recorded. Prophylactic treatment for the study treatment and all concomitant medications will be recorded in the eCRF. Concomitant medications will be collected 40 days after both study drugs discontinued.

Prohibited Therapies/Products

The following medications and products 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 (other than study drug nivolumab), antibody, retinoid, or anticancer hormonal treatment. Concurrent use of hormones for noncancer-related conditions (e.g. insulin for diabetes and hormone replacement therapy) is acceptable.

  Live vaccines must be avoided during the course of the study and for a period of 3 months after the last dose of study drug(s).

- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification Section 5.5. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.
- 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.)
- Chloroquine or hydroxychloroquine:
  - if treatment with chloroquine or hydroxychloroquine is required for SARS-CoV-2 infection (ie, COVID-19), trastuzumab deruxtecan must be interrupted and a wash-out period of >14 days is required before restarting trastuzumab deruxtecan.

Permitted Products:

- Subjects are permitted to use topical, intraocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone or equivalent.
- A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy, chemotherapy induced nausea) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
- 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 AE will be as per investigator's discretion and the institutional guidelines unless specified in this protocol.
- Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic anti-emetic agents prior to infusion of trastuzumab deruxtecan and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NK1) receptor antagonists and/or steroids (e.g. dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Restricted Products:

- Use of e-cigarettes and vaping is strongly discouraged but not prohibited

Subjects who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF including all prescriptions, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 40 days after the last dose of study treatment should be recorded. Concomitant medications administered 40 days after the last dose of study treatment should be recorded for SAEs and AESIs as defined in Section 9.4.2.

5.8. Subject Withdrawal/Discontinuation

Any subject who is withdrawn from the study treatment or from the study for any reason will have their reasons for withdrawal recorded.

5.8.1. Reasons for Withdrawal

5.8.1.1. Reasons for Withdrawal of Study Drug

Any subject who is withdrawn from the study treatment for any reason will have their reasons for withdrawal recorded. Subject may withdraw from both study drugs at the same time or 1 study drug at a time.

Some examples include:

- PD per RECIST Version 1.1 (Section 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);

- AE;
- Death;
- Pregnancy;
- Withdrawal by subject;
- Lost to follow-up;
- Physician decision;
- Study terminated by Sponsor;
- Protocol deviation
- Other, specify.

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

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedures (Section 5.8.2) and follow-up procedures (Section 6.5). Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (e.g., death certificates) as allowed by local laws.

5.8.1.2. Reasons for Discontinuation of Study Participation

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

- Death;
- Study terminated by Sponsor;
- Withdrawal by subject;
- Lost to follow-up;
- Other, specify (for e.g., If subject becomes a prisoner during the study, the subject should be withdrawn from the study).

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

5.8.2. Withdrawal Procedures

If a subject is withdrawn from the study treatment, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal. Investigator should make all efforts to retain subject in the study for survival follow-up after withdrawal from study treatment.

If the subject is withdrawn from the study treatment due to an AE, the investigator will follow the subject until the AE has resolved or stabilized and perform the study procedures as per Section 6.5.2.

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be conducted during the End of Treatment (EOT) Visit (+ 7 days) and the 40-Day Follow-up Visit (+ 7 days) [Section 6 and Table 17.1].

5.8.3. Subject Replacement

Subjects will be replaced in Part 1 at the same dose level if they discontinued study treatment due to any other reason than DLT prior to the completion of the DLT period. Subjects enrolled and administered study medication in Part 2 will not be replaced. However, it is allowable to replace a subject that was screen-failed but not administered any study medication.

5.8.4. Subject Re-prescreening Procedures

Re-prescreening is permitted for any subject that had initial tumor sample sent for analysis to central lab and the report states that the subject is ineligible (i.e. IHC score 0). The limit of re-prescreening is 1. At re-prescreening, sites can send newer additional archival tissue or perform a new tumor biopsy. Subjects that perform re-prescreening would need to sign a new prescreening ICF.

Subjects that had initial tumor sample sent but central lab reports that there was an analytical failure (i.e. quality control samples fail, tissue with quality issues (including no staining, no tumor, or equivocal cases)) then site can send additional tissue, archival or by performing a new tumor biopsy. NOTE: this is not a re-prescreening, this is part of the same prescreening procedure.

5.8.5. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet the eligibility criteria in the initial screening. The limit of re-screening is 1 time. The site subject identifier must remain the same at the time of re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded in the Screening Log.

6. STUDY PROCEDURES

Study procedures as described below are presented in schematic form in Table 17.1.

6.1. Screening

6.1.1. Central Laboratory HER2 (Pre-Screening)

To determine eligibility, subjects must meet tumor biomarker criteria.

Note: If an archival tissue sample is provided at pre-screening, subjects may continue on prior therapy while tissue testing takes place.

Please refer to the Laboratory Manual for required tumor sample shipping instructions.

The following procedures will be conducted:

- Obtain a signed and dated written consent from the subject to collect tissue and/or perform a biopsy as needed. This may be done 14 days prior to tissue collection.
- The sample must be a formalin-fixed paraffin embedded (FFPE) block and not stored slides cut previously from such a FFPE block.
- If an archived tumor tissue sample is not available or is inadequate, new tumor biopsy is required for HER2 screening.
- Prepare and send the tissue samples to the Central Laboratory.
- The central laboratory will assess the HER2 status and provide results to Investigators and Daiichi Sankyo Inc (DSI).
- If a tumor biopsy is performed, report any SAEs directly related to tissue screening procedure (i.e., tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.
- Additional slides for exploratory biomarker assessment are requested.

6.1.2. Screening

The duration of the screening/baseline period is up to 28 days (+7 days). Informed consent will be obtained from the subject before any study-specific procedures are initiated.

The following activities and/or assessments will be performed within 28 days (+ 7 days) before enrollment during the screening period:

- Obtain written (i.e., signed and dated) informed consent.
- Assign subject identifier.
- Obtain ophthalmologic assessments: visual acuity testing, slit lamp examination, and fundoscopy.
- Obtain HIV antibody test (as required by local regulations).
- Obtain Hepatitis B surface antigen/hepatitis C antibody.

Perform Baseline tumor measurement per RECIST Version 1.1 (spiral CT or MRI with ≤5 mm cuts). Existing radiographic scans can be used as baseline if scan was performed within 4 weeks prior to the first scheduled day of treatment. The baseline scan will include the chest, abdomen, and pelvis. Brain MRI/CT is required if the subject has a history of brain metastases and/or symptoms suggestive of brain metastases at baseline. Any existing brain metastases must have been effectively treated and shown to be stable at the baseline scan over an interval of at least 4 weeks. The method of tumor assessment used must remain consistent at each assessment. MRI is the strongly preferred modality for imaging the brain. If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. For the purposes of assessing tumor imaging, the term "Investigator" refers to the local Investigator at the site and/or the radiological reviewer located at the site or at an offsite facility. The method of tumor assessment used must remain consistent at each assessment.

Any supplemental imaging done such as plain X-rays that may be acquired for correlation, should be submitted to the central imaging vendor.

- Record prior and concomitant medications.
- Assess the subject for AEs.
- Record hospitalization-related records
- If the subject is a screen failure, deactivate the subject in the interactive response technology.

Unless otherwise noted, the following activities and/or assessments will be performed at/during Screening and within 14 days (except as indicated) before starting study treatment:

- Review inclusion and exclusion criteria and confirm subject's eligibility when the results of all screening procedures have been obtained.
- Collect blood samples for the other biomarker analyses (only if new tissue sample is collected at screening).
- Details regarding shipping instructions to the central laboratory will be provided in the Laboratory Manual.
- Record demographic and history information.
- Perform a complete physical examination.
- Obtain vital sign measurements (e.g., systolic and diastolic blood pressure, heart rate, and body temperature).
- Height and weight.

- Obtain peripheral oxygen saturation (SpO2).
- Assess functional status using the ECOG Performance Status.
- Obtain a blood sample for hematology.
- Obtain two blood samples (one for local lab test and one for central lab test) for troponin (preferably high-sensitivity troponin-T). Eligibility assessment will be based on the local lab result. If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis:
  - Perform ECG in triplicate.
  - If ECG is abnormal, follow institutional guidelines.
- Obtain a blood sample for serum chemistry and coagulation.
- Obtain a urine sample for urinalysis.
- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential within 72 hours before enrollment. Test must be confirmed negative within 72 hours prior to drug administration. A positive urine pregnancy test result must immediately be confirmed using a serum test.
- Obtain an ECHO or MUGA scan for LVEF.
- Obtain a 12-lead ECG in triplicate. ECGs to be taken ≤3 minutes apart, with the subject in a supine/semi-recumbent position.
- After eligibility is confirmed, register subject to Interactive Web/Voice Response System (IXRS) as eligible or ineligible.

6.2. Enrollment

This is a single-arm open-label trial consisting of 2 parts: Part 1 (Dose Escalation) and Part 2 (Dose Expansion). Part 2 includes 4 different cohorts. Part 1 will enroll before Part 2. First eligible subjects will be directly registered in Part 1 at the lowest dose level. The first group of 3 subjects can be registered simultaneously or sequentially. Enrollment of the next 3 subjects will occur after the first 3 subjects have completed the DLT observation period and safety data have been reviewed by the Sponsor team and investigator(s). Based on their recommendations, the next 3 eligible subjects will be registered at the same or next dose level. Up to 9 subjects will be registered at a dose level until an MTD is reached or subjects have been registered and have successfully completed the DLT observation period at both dose levels. At each dose level, subjects will be considered DLT evaluable if they were able to complete 2 cycles of treatment of both study drugs (trastuzumab deruxtecan and nivolumab) and had completed DLT assessment or discontinued from study due to a DLT. A subject will be replaced if discontinued from the study during the DLT period due to any other reason than DLT (refer to Section 5.8.3).

No subject shall receive study drug until approved by the Sponsor or designee. The Sponsor or designee will notify the other sites of the inclusion of a new subject and will inform study sites about the next possible enrollment date. Subjects must be registered in IXRS prior to the beginning of treatment as IXRS is used to manage dispensing of material.

6.3. Treatment Period

Study procedures as described below are presented in schematic form in Table 17.1.

Subjects must be registered in IXRS prior to the beginning of treatment as IXRS is used to manage dispensing of material.

The first on-study imaging assessment should be performed per RECIST Version 1.1 (spiral CT or MRI with ≤5 mm cuts) at 6 weeks (42 days ±7 days) from Cycle 1, Day 1. Subsequent tumor imaging should be performed every 6 weeks (±7 days) from Day 1 of Cycle 1 or more frequently if clinically indicated. After 52 weeks (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 timing should follow calendar days. Imaging time points should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor. Tumor assessment at 40 days follow up is no longer required, because subjects who discontinue study treatment due to progression, should not have any additional tumor assessment performed. However, subjects that discontinue due to reasons other than disease progression, will continue assessment as per initial schedule until start of new anticancer therapy. In cases where EOT and 40-Day Follow-up Visit fall within 7 days, then both of these visits' requirements can be completed during the same visit.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Response does not typically need to be verified in real time by the central imaging vendor.

Per iRECIST, disease progression should be confirmed by the site 4 to 8 weeks after the site assessed first radiologic evidence of PD in a clinically stable subject. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 17.5.2 Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Subjects who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment.

Tumor measurement per RECIST version 1.1 (spiral CT or MRI with ≤5 mm cuts) is to be performed every 6 weeks (±7 days) in the first year after Day 1 of Cycle 1 and thereafter every 12 weeks (±14 days) until disease progression or start of new anticancer treatment. CT or MRI (spiral CT or MRI with ≤5 mm cuts) of brain, chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions at screening period. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time of screening, brain CT or MRI should only be done if symptoms associated with brain metastasis appear during the study period. If no clinical symptoms are observed, brain CT or MRI is not

mandatory during the study period. Treatment decision will be based on the investigator-based assessment. If the investigator decides to continue the treatment post-progression, the study site should continue to scan the subject after initial progression has been identified to continue tumor assessment by iRECIST.

All scans, scheduled or unscheduled, should be submitted to the central imaging vendor for review as soon as possible.

Concomitant medication, AEs, and hospitalization (except hospitalization for study drug infusion) should be recorded at each visit.

Thyroid function testing is required every 6 weeks while on nivolumab treatment. Thyroid panel should include:

- Triiodothyronine (T3) or free triiodothyronine (FT3)
- Free thyroxine (FT4)
- TSH

If TSH <0.5 × lower limit of normal (LLN) or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.

6.3.1. Cycle 1

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 17.1 and further described below. Procedures are to be performed within -3 days of the Day 1 visit of each cycle unless otherwise specified.

6.3.1.1. Cycle 1, Day 1

Before Dosing: Between -3 Days through immediately Before Infusion (note: if these assessments are done -3 Days through immediately Before Infusion for screening purposes, then these may not be repeated at Day 1 of Cycle 1):

- Record ECOG performance status.
- Record triplicate 12-lead ECG.
- Record concomitant medications and AEs.
- Record physical examination.
- Record vital signs and weight.
- Obtain SpO2.
- Collect blood samples for hematology.
- Collect blood samples for chemistry.
- Collect blood samples for coagulation.
- Urinalysis test is to be performed at screening and as clinically indicated throughout the study.

- Collect blood samples for serum amylase and lipase testing.
- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential within 72 hours prior to study drug infusion. A positive urine pregnancy test result must immediately be confirmed using a serum test.
- Collect blood sample for pharmacogenomic analysis (if the subject has consented to provide a pharmacogenomic sample).
- Collect a blood sample for biomarker analysis and/or banking

Day 1 Before Infusion

- Record triplicate 12-lead ECG (if not done within 3 days before Day 1).
- Collect blood sample for pharmacogenomics and biomarker analysis and/or banking (if the subject has consented to provide a pharmacogenomic sample).
- Collect blood samples for
  - PK assessments (Table 8.1).
  - Anti-drug antibodies (ADAs). Section 8.3.
  - Thyroid function tests: While on nivolumab, the subject must have thyroid panel including TSH testing every 6 weeks. If TSH <0.5 × LLN or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.
- Collect serum samples for SARS-CoV-2 testing. For subjects with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Section 17.8 Record concomitant medications and AEs.

Study Drug Administration (refer to Section 5.2.4)

- Nivolumab will be infused over approximately 30 minutes on Day 1 of each cycle prior to the administration of trastuzumab deruxtecan with no less than a 30-minute gap between the infusions of 2 study drugs.
- Collect blood samples for PK assessment (Table 8.1). Samples should be collected according to the schedule in Table 8.1. At the time of PK sampling, record PK sampling times).
- Allow 30 minutes between the end of nivolumab infusion and start of trastuzumab deruxtecan infusion.
- Administer trastuzumab deruxtecan IV infusion: approximately 90 minutes for the initial dose and, if no infusion-related reaction after the initial dose, infuse subsequent doses over approximately 30 minutes. Record start and stop times of any study drug. trastuzumab deruxtecan is to be administered every 3 weeks ± 2 days. Nivolumab will be administered in cycles of every 3 weeks ± 2 days.

- Record each study drug's start and end time for infusion. Record any infusion interruptions.
- Record concomitant medications and AEs.

After Infusion

- Assess vital signs within 30 minutes of completing the infusion of each study drug. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- For Part 1 subjects only: Assess DLTs.
- Record concomitant medications and AEs.
- Obtain SpO2.
- Collect blood samples for troponin 2 to 3 hours after end of infusion (EOI) of trastuzumab deruxtecan to be submitted for central laboratory testing only. Local troponin testing should be performed only if clinically indicated.
- Collect blood samples for post dose PK analysis. Samples should be collected according to the schedule in Table 8.1. At the time of PK sampling, record the PK sampling time.

6.3.1.2. Cycle 1, Days 8 and 15 (± 1 Day)

- Record vital signs.
- Record SpO2.
- Collect blood for hematology.
- Collect blood for chemistry.
- For Part 1 subjects only: Assess DLTs.
- Record concomitant medications and AEs.
- Record hospitalization-related records.
- Collect samples for urinalysis and coagulation only if clinically indicated.
- Collect blood samples for PK analysis. Samples should be collected according to the schedule in Table 8.1. At the time of PK sampling, record the PK sampling time.

6.3.2. Cycle 2, Day 1

Treatment and procedures performed on Day 1 of Cycle 2 and beyond are specified in Table 17.1 and further described below. Procedures are to be performed within -3 days of the Day 1 visit of each cycle unless otherwise specified.

Before Treatment

- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential within 72 hours prior to study drug infusion. A

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

- For Part 1 subjects only: Assess DLTs.
- Record ECOG performance status.
- Record triplicate 12-lead ECG.
- Record concomitant medications and AEs.
- Record hospitalization-related records
- Record physical examination.
- Record vital signs and weight.
- Record SpO2.
- Collect blood samples for PK analysis. Samples should be collected according to the schedule in Table 8.1. At the time of PK sampling, record the PK sampling time.
- Collect blood samples for hematology.
- Collect blood samples for chemistry.
- Collect samples for urinalysis and coagulation only if clinically indicated.
- Collect blood sample for ADAs.
- Collect blood samples for serum amylase and lipase testing.

Study Drug Administration

- Administer second doses of study drugs at the study site as in Section 6.3.1.1. Record the study drug administration time.
- Record concomitant medications and AEs.

After Infusion

- Assess vital signs as in Section 6.3.1.1.
- Collect blood sample for central lab troponin testing as in Section 6.3.1.1. Local troponin testing should be performed only if clinically indicated.
- Collect blood samples for PK analysis. Samples should be collected according to the schedule in Table 8.1.
- Record concomitant medications and AEs.
- Obtain SpO2.

6.3.3. Cycle 3, Day 1

Before Treatment

- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential within 72 hours prior to study drug infusion. A

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

- Tumor assessment at 6 weeks (± 7 days) from Cycle 1, Day 1.
- For Part 1 subjects only: Assess DLTs.
- Record ECOG performance status.
- Record triplicate 12-lead ECG.
- Record concomitant medications and AEs.
- Record hospitalization-related records
- Record physical examination.
- Record vital signs and weight.
- Obtain SpO2.
- Collect blood samples for hematology.
- Collect blood samples for chemistry.
- Collect samples for urinalysis and coagulation only if clinically indicated.
- Collect blood sample for ADAs (Section 8.3).
- Thyroid function tests: While on nivolumab, the subject must have thyroid panel including TSH testing every 6 weeks. If TSH <0.5 × LLN or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.
- Collect blood samples for serum amylase and lipase testing.
- Collect blood samples for PK analysis (Table 8.1). At the time of PK sampling, record PK sampling times.
- Collect blood samples for biomarker analysis (Table 8.3) and every 4 cycles starting on Cycle 3 (e.g., Cycle 3, 7, 11...).
- Collect on-treatment tissue sample (optional new biopsy).

Study Drug Administration

- Administer third doses of study drugs at the study site. Record the study drug administration time.

After Infusion

- Record vital signs.
- Collect blood samples for central lab troponin testing as in Section 6.3.1.1. Local troponin testing should be performed only if clinically indicated

- Record concomitant medications and AEs as in Section 6.3.1.1.
- Obtain SpO2.

6.3.4. Cycle 4 and Subsequent Cycles, Day 1

Before Treatment

- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential within 72 hours prior to study drug infusion. A positive urine pregnancy test result must immediately be confirmed using a serum test.
- Tumor assessment every 6 weeks (± 7 days) in the first year after Day 1 of Cycle 1 and thereafter every 12 weeks (± 14 days).
- Record ECOG performance status.
- Record triplicate 12-lead ECG.
- Record concomitant medications and AEs.
- Record hospitalization-related records
- Record physical examination.
- Record vital signs and weight.
- Record SpO2.
- Collect blood samples for hematology.
- Collect blood samples for chemistry.
- Collect samples for urinalysis and coagulation only if clinically indicated.
- Collect serum samples for SARS-CoV-2 testing on Day 1 of Cycle 5 and every 4 cycles thereafter (i.e C5D1, C9D1 etc). For subjects with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Section 17.8
- Collect blood sample for ADAs (Section 8.3) ADA samples will be obtained prior to study treatment on Day 1 of Cycles, 1, 2, and 3 and thereafter every 4 cycles and at the 40 Day Follow-Up visit. Additional serum ADA samples may be collected at the Long-term Follow-Up visits as follows:
  - Every 3 months (± 14 days) up to 1 year after the last dose of the study drug, or until the ADA becomes negative, or until the ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another anti-cancer therapy or withdraws consent from the study, whichever occurs first.
- Thyroid function tests: While on nivolumab, the subject must have thyroid panel including TSH testing every 6 weeks. If TSH <0.5 × LLN or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested

at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.

- Collect blood samples for serum amylase and lipase testing on the first day of each treatment cycle.
- Obtain ECHO or MUGA scan for LVEF. This assessment will be performed at screening and before infusion on Day 1 of Cycle 5 and then every 4 cycles (± 7 days [e.g., Cycles 5, 9, 13, etc]). The same test must be used for a given subject throughout the study.

After Infusion

- Record vital signs.
- Collect blood samples for central lab troponin testing as in Section 6.3.1.1. Local troponin testing should be performed only if clinically indicated.
- Obtain SpO2.

Study Drug Administration

- Administer scheduled doses of study drugs at the study site as in Section 6.3.1.1. Record the study drug administration time.
- Record concomitant medications and AEs.

After Infusion

- Record vital signs as in Section 6.3.1.1.
- Collect blood sample for troponin as in Section 6.3.1.1.
- Record concomitant medications and AEs.
- Obtain SpO2.

6.3.5. End of Combination Treatment (See Section 6.4): Optional Biopsy and Biomarker Blood Samples

End of Combination Treatment (EOCT) is defined as the date of discontinuation of one of the study drugs.

- Obtain an optional new tumor specimen at discontinuation of any 1 of the study drugs, either trastuzumab deruxtecan or nivolumab, if amenable. Tumor tissue will be sent to the central laboratory for an exploratory biomarker analysis.
- Collect blood samples for biomarker analysis according to the schedule in Table 8.3.

Table 6.1: End of Combination Treatment (EOCT) Assessments

EOCT Assessments where trastuzumab deruxtecan or nivolumab is discontinued	EOT Assessments where trastuzumab deruxtecan or nivolumab has been discontinued previously and the remaining study drug is completed	EOT Assessments where trastuzumab deruxtecan **and** Nivolumab are discontinued concurrently
Collect Blood Samples for: Optional Tumor Sample Exploratory Biomarkers HER2ECD cfDNA	All EOT assessments found in the Schedule of Events Table (See Table 17.1) with the exception of the biomarkers that were previously collected when trastuzumab deruxtecan or nivolumab was discontinued	All EOT assessments found in the Schedule of Events table (See Table 17.1)

6.4. End of Treatment

End of Treatment (EOT) on a subject level is defined as the date investigator decides to discontinue study treatment (+7 days). Subjects who permanently discontinue the study treatment should be scheduled for an EOT visit within approximately +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. At EOT visit, all the following assessments will be performed:

Record ECOG performance status (Section 17.2).

- Record triplicate 12-lead ECG.
- Record physical exam.
- Record vital signs and weight.
- Obtain SpO2.
- Collect blood samples for hematology.
- Collect blood samples for chemistry.
- Collect blood samples for coagulation
- Collect samples for urinalysis if clinically indicated.
- Obtain two blood samples (one for local lab test and one for central lab test) for troponin (preferably high-sensitivity troponin-T).
- Collect blood samples for serum amylase and lipase testing.
- Obtain blood samples for exploratory biomarkers (Table 8.3).

- Obtain a blood or urine sample to perform a serum or urine pregnancy test for female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test.
- Tumor assessments should include all sites of disease identified at screening and any other locations if PD is suspected (e.g., MRI of the brain if brain metastases are suspected) should also be imaged, per RECIST Version 1.1 (Section 1.1). If the previous scan was within the last 6 weeks (within 12 weeks if the subject completed 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 effort should be made to obtain an image-based assessment of PD.
- An MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need brain scan for tumor assessment unless clinically indicated.
- Ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy.
- Obtain ECHO or MUGA scan for LVEF. The same test must be used for a given subject throughout the study.
- Obtain an optional new tumor biopsy after discontinuation of combination treatment (i.e., at discontinuation of either trastuzumab deruxtecan or nivolumab). Tumor tissue will be sent to the central laboratory for exploratory biomarker analyses.
- Record concomitant medications and AEs. Grade 3 or Grade 4 AEs ongoing at the discontinuation of study drug(s) will be monitored (including local laboratory tests when appropriate) at intervals no greater than 7 days until the AE is determined to be resolving or back to baseline.
- Record hospitalization-related records.

6.5. Follow-up

6.5.1. 40-Day Follow-up (+7 Days)

Forty days (+7 days) after the last study drug administration (when both study drugs are either discontinued together) or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in the Schedule of Events. If EOT is >40 days (+7 days) after last treatment, then the EOT assessments can also function as the Follow-up Visit.

- Perform and record complete physical examination.
- Record ECOG performance status.
- Record vital signs (sitting systolic and diastolic blood pressure, heart rate, and body temperature) and weight.
- Obtain SpO2.

- Take blood samples for hematology and chemistry.
- Take blood samples for ADAs. For subjects with positive ADA at the 40-Day Follow-up Visit, additional serum ADA samples may be collected every 3 months (± 14 days) up to 1 year after the last dose of the study drug, or until the ADA becomes negative, or until the ADA titer becomes less than 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 later.
- Record AEs and treatments (drug and non-drug) given for AEs, and hospitalization-related records. Grade 3 or Grade 4 AEs ongoing at the discontinuation of study drug(s) will be monitored (including local laboratory tests when appropriate) at intervals no greater than 7 days until the AE is determined to be resolving or back to baseline.
- Record concomitant medications, including subsequent anticancer treatment.
- In cases where EOT and 40-Day Follow-up Visit fall within 7 days, then both of these visits' requirements can be completed during the same visit.

6.5.2. Long-term Follow-up (±7/±14 Days)

- Subjects who discontinued both study treatments due to any other reason than disease progression will continue Long-term Follow-up for tumor assessment as per scan schedule (i.e., every 6 weeks ± 7 days in the first year and every 12 weeks ± 14 days thereafter) by radiological imaging to monitor disease status until PD or start of new anticancer treatment.

  Once subject progresses or starts additional anticancer treatment, survival follow-up is performed every 12 weeks (± 14 days) by telephone to assess for survival status until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.
- Subjects who discontinued study treatments due to disease progression will be followed every 3 months (± 14 days) from the date of 40-Day Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

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

- Tumor assessments only during Long-term Follow-up (if discontinued study treatment due to any other reason than disease progression).
- Record subsequent anticancer treatments and their outcomes, and survival.
- Further follow-up may be required for ongoing AEs.
- Record concomitant medications and AEs.
- Survival status.

- Subjects with positive ADAs at 40-Day Follow-up Visit, additional serum samples may be collected at Long-term Follow-up visits as follows: Every 3 months (± 14 days) up to 1 year after the last dose of the study drug, until the ADA becomes negative, until the ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another anticancer therapy or withdraws consent from the study.

If direct contacts are not possible due to withdrawal of consent or because the subject becomes lost to follow-up, the study site must make every effort to collect survival status from public records (e.g., death certificates) in accordance with local laws.

6.5.3. 100-Day Follow-up

The 100-Day Follow-up Visit will occur at 100 days from the last study treatment of nivolumab. The following activities will take place during 100-Day Follow-up by telephone contact:

- Record subsequent anticancer treatments and their outcomes, and survival.
- Further follow-up may be required for ongoing AEs.
- Record concomitant medications and AEs.
- Survival status.

If direct contacts are not possible due to withdrawal of consent or because the subject becomes lost to follow-up, the study site must make every effort to collect survival status from public records (e.g., death certificates) in accordance with local laws.

6.5.4. Assessment of Disease

6.5.4.1. RECIST Version 1.1 Assessment of Disease

RECIST version 1.1 (Section 1.1) will be used by independent central imaging review as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). RECIST version 1.1 references a maximum of 5 target lesions in total and 2 per organ.

6.5.4.2. iRECIST Assessment of Disease

iRECIST (Section 17.5) is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Section 17.5.4. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective independent review.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iRECIST-confirmed progressive disease [iCPD]) as defined in Section 17.5, study treatment should be discontinued; however, if the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 17.5 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Section 17.5, with additional details in the iRECIST publication. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6.2.

Table 6.2: Imaging and Treatment with Nivolumab After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST version 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST-confirmed progressive disease; iCR = iRECIST-confirmed complete response; iPR = partial response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST-confirmed stable disease; iUPD = iRECIST-unconfirmed progressive disease; PD = progressive disease; RECIST version 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1

6.6. Additional PK assessments due to SARS-CoV-2 infection

In case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection (ie, COVID-19), additional PK serum samples should be collected at the following time points (See Table 8.2)

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

The clinical activity of trastuzumab deruxtecan and nivolumab combination treatment will be assessed by evaluating tumor response. Tumor response will be evaluated using RECIST Version 1.1 (Section 1.1). Efficacy assessments will be based on tumor assessments (to be performed at screening and every 6 weeks (± 7 days) in the first year after Day 1 of Cycle 1 and thereafter every 12 weeks (±14 days) until disease progression or initiation of additional anticancer therapy) and survival (See Section 6.5.2). CT or MRI (spiral CT or MRI with ≤5 mm cuts) of brain, chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions at screening period. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastases at the time of screening, CT or MRI should only be done when symptoms associated with brain metastases appear during the study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during the study period. Subjects that are treated with nivolumab beyond RECIST 1.1 PD will continue tumor assessments until confirmed PD as per iRECIST.

The following primary efficacy endpoints will be assessed.

Primary Efficacy Endpoint:

- ORR (the sum of CR rate and PR rate) assessed by ICR Committee based on RECIST Version 1.1 for Part 2.

Secondary Efficacy Endpoint:

Secondary endpoint will be assessed based on ICR Committee unless specified otherwise.

- DCR (the sum of CR, PR, and SD rates).
- DOR.
- TTR.
- PFS.
- Percent change in target lesion.
- ORR (the sum of CR rate and PR rate) assessed by investigator based on RECIST Version 1.1 for Part 2.

Exploratory endpoints:

- ORR by iRECIST guidelines by study investigator (part 2).
- CBR for breast cancer cohorts, defined as proportion of subjects achieved CR, or PR, or had SD for at least 6 months per RECIST Version1.1.

7.2. Appropriateness of Selected Efficacy Assessment(s)

All selected efficacy endpoints provide evidence of drug activity. ORR is defined as the proportion of subjects with CR and PR as defined by RECIST Version 1.1 in this trial. ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study. Because ORR is directly attributable to study drug effect, it is an appropriate measure of efficacy in single-arm trials.

In addition, PFS is not confounded by subsequent therapies compared to OS, and OS is considered the "gold standard" for demonstrating clinical benefit.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessment(s)

Blood samples for trastuzumab deruxtecan and nivolumab PK analyses will be obtained at the time points specified in the Schedule of Events (Table 17.1)

Table 8.1: Sampling Times for Pharmacokinetic Assessments

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 1	Day 1	**BI:** (-8 hours) • Both samples (one for each study drug) taken at the same time before nivolumab infusion **EOI:** • Within 15 minutes after EOI of nivolumab • Within 15 minutes after EOI of trastuzumab deruxtecan • 5 hours from start of trastuzumab deruxtecan infusion (± 2 hours)
	Day 8 and Day 15	Draw sample on Day 8 (± 1 day) and Day 15 (± 1 day)
Cycle 2	Day 1	**BI:** (-8 hours) • Both samples (one for each study drug) taken at the same time before nivolumab infusion **EOI:** • Within 15 minutes after EOI of nivolumab • Within 15 minutes after EOI of trastuzumab deruxtecan • 5 hours from start of trastuzumab deruxtecan infusion (± 2 hours)
Cycle 3	Day 1	**BI:** (Within 30 minutes) • Both samples (one for each study drug) taken at the same time before nivolumab infusion

BI = before infusion; EOI = end of infusion.
Note: Obtain one blood sample collection for PK as soon as ILD is suspected, if feasible

In case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection (ie, COVID-19), additional PK samples should be collected at the following time points

Table 8.2: 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 3 or 4	Prior to chloroquine or hydroxychloroquine dose (within 4 h)
EOT with chloroquine or hydroxychloroquine	Prior to chloroquine or hydroxychloroquine dose (within 4 h)
Prior to re-initiation of trastuzumab deruxtecan	BI (within 8 hours)

BI = Before Infusion; EOT = End of Treatment

At each time point, blood will be collected for nivolumab and trastuzumab deruxtecan analysis. The actual times of study drug administrations and the exact time of blood sampling for trastuzumab deruxtecan and nivolumab PK analysis must be recorded on the eCRF, including those samples collected in case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection (ie, COVID-19). For the samples to be taken before infusion at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1, both samples (one for each study drug) should be taken at the same time before nivolumab infusion, within the acceptable time ranges as per Table 8.1.

Instructions for the handling of blood samples and shipping of serum samples for trastuzumab deruxtecan and nivolumab PK analyses are included in a separate document (i.e., Laboratory Manual). The trastuzumab deruxtecan and nivolumab PK samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory. Note that separate EOI draw times will be required for trastuzumab deruxtecan and nivolumab to maintain the proper time windows. Samples for nivolumab PK will be retained and analyzed if necessary.

Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, MAAA-1181a and nivolumab will be measured using validated assays at bioanalytical laboratories. The serum PK parameters (listed in Section 2.3.2) for trastuzumab deruxtecan, total anti-HER2 antibody, MAAA-1181a and nivolumab for each subject will be estimated using standard noncompartmental method.

Data will be analyzed using a population PK modeling approach and may be reported separately from the clinical study report.

8.2. Biomarker Assessment(s)

Exploratory blood biomarkers will be analyzed with the intent of monitoring the anti-tumor impact of treatment with trastuzumab deruxtecan. Blood samples will be collected for HER2ECD and cfDNA analysis at the time points specified in Table 8.3.

Biomarker samples will be shipped to a central laboratory.

Table 8.3: Biomarker Blood Sampling Time Points (HER2ECD, cfDNA)

Cycle	Sampling Time Point (Acceptable Range)
Cycle 1, Day 1	Within 3 days before administration
Every 4 cycles starting on Cycle 3 (e.g., Cycle 3, 7, 11...)	Within 3 days before administration
End of Combination Treatment (EOCT)	The date when the investigator decides on discontinuing **one** of the study treatments
End of Treatment (EOT)	End of Treatment (EOT) on a subject level is defined as the date investigator decides to discontinue study treatment (+7 days).

cfDNA = cell-free DNA; HER2ECD = human epidermal growth factor 2 extracellular domain

Tumor specimens will be used to assess HER2 and PD-L1 expression using IHC and/or ISH and possibly, but not limited to, mRNA expression profile, mutation burden, using next-generation sequencing technology or other methods. Pharmacodynamic biomarkers are planned with intent of monitoring the antitumor impact of treatment with trastuzumab deruxtecan.

8.2.1. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, additional exploratory biomarker research may be conducted on tissue and/or liquid biopsy samples. This additional research is intended to expand the translational research and development capability at DSI, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right subjects. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

The Sponsor will not collect the samples for additional biomarker assessments but will conduct the additional research using the remaining samples of biomarker assessments described in Section 8.2.

The remaining biomarker samples (tumor tissue, blood or other specimen obtained in the study) may be stored for up to 15 years and further analyzed to address scientific questions related to trastuzumab deruxtecan, nivolumab, and/or cancer.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the Sponsor's senior leaders in research and development to ensure the research supports appropriate and well-defined scientific research activities.

8.3. Immunogenicity

Blood samples for ADA analyses will be collected prior to study treatment on Day 1 of Cycles 1, 2, and 3 and thereafter every 4 cycles, and 40-Day Follow-up (Table 17.1). A blood sample will be drawn at each time point. Instructions for the handling and shipping of ADA serum samples

are included in the Laboratory Manual. The ADA samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory.

For subjects with positive ADAs at the 40-Day Follow-up Visit, additional serum samples may be collected at the Long-term Follow-up visits as follows:

- Every 3 months (± 14 days) up to 1 year after the last dose of the study drug, until the ADA becomes negative, until the ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another anticancer therapy or withdraws consent from the study.

The immunogenicity testing will be performed using validated ADA assay following tiered assay steps including screening, confirmatory as well as titer determination. . In addition to the trastuzumab deruxtecan ADA analyses, these blood samples may be used to perform nivolumab ADA analyses. Samples confirmed ADA positive maybe analyzed with neutralizing anti-drug antibody (NAB) assay. Serum concentrations of trastuzumab deruxtecan, or total anti-HER2 antibody, may be measured using the same ADA samples as part of ADA assessment.

8.4. Pharmacogenomic Analysis

8.4.1. Genomic or Genetic Banking and Analysis

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

In the event that pharmacogenomics analysis will be carried out in the future, the Sponsor will prepare a plan for conducting pharmacogenomics analysis, and it will be deliberated at the review committee. This review committee also participates as a member who has no interest in the Sponsor, and scientific and ethical deliberations will be held on the plan for conducting pharmacogenomics analysis.

The following procedures will be used for the long-term preservation (banking) of DNA specimens extracted from subjects' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of trastuzumab deruxtecan. Additionally, samples may be analyzed for genes involved in trastuzumab deruxtecan-related signaling pathways, or to examine diseases or physiologic processes related to trastuzumab deruxtecan. 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.

Specimen shipping and handling details will be included in the Laboratory Manual.

8.4.1.1. Disclosure of the Results of Genomic or Genetic Analysis

See ICF for the details on disclosure.

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

Samples will be retained until the genetic material has been exhausted or until Sponsor directs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the genetic samples will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

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

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Key safety endpoints will include assessment of DLTs, SAEs, TEAEs, TEAEs leading to discontinuation, and AESIs.

9.2. Adverse Event Collection and Reporting

In Part 1 (dose escalation), the (DLT) observation period will be 2 cycles (6 weeks). DLT is defined in Section 3.2.3.

All clinical non serious AEs and AESI (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and a minimum of 47 days after study treatment ends, and should continue to be collected until 100 days after the last dose of study medication (i.e., the follow-up period), or start of a new anti-cancer therapy, whichever is earlier, whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF page. Grade 3 or Grade 4 AEs ongoing at the discontinuation of study drug(s) will be monitored (including local laboratory tests when appropriate) at intervals no greater than 7 days until the AE is determined to be resolving or back to baseline. All SAEs occurring after subject signs the main ICF and up to 100 days after the last dose of nivolumab or trastuzumab deruxtecan, must also be reported by the Investigator.

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

Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to signing the informed consent will be recorded as part of medical history. 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 (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The investigator's assessment must be clearly documented in the study site's source documentation with the investigator's signature.

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.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF)

procedures or treatments requiring hospitalization for preexisting conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Disease progression/worsening of breast cancer/urothelial cancer will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression (i.e. thrombocytopenia), may be recorded as AEs. Death due to disease progression should be recorded on the Death eCRF.

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

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the eCRF. General guidelines for safety management of immune-mediated AEs are provided in Appendix 17.7 (Safety Management Algorithms).

9.3. Adverse Events of Special Interest

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

Relevant information regarding the AESIs ILD, and LVEF decrease for the trastuzumab deruxtecan clinical program, regardless of seriousness, is to be collected through the targeted questionnaires (TQ) within the applicable eCRFs in the clinical study database.

9.3.1. Interstitial Lung Disease

9.3.1.1. Clinical Summary

Interstitial lung disease 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 cases reviewed by the independent ILD Adjudication Committee, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB[13] for a summary of preliminary clinical study data.

9.3.1.2. Management Guidance

Interstitial lung disease/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated “Other Non-laboratory Adverse Events” dose modification section of this study protocol (Section 5.5.1).

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

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of this study protocol (Section 5.5.1).

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

9.3.1.3. Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for the trastuzumab deruxtecan program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collections will cover a more in-depth relevant medical history (e.g., smoking, radiation, chronic obstructive pulmonary disease and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for adverse events reported using selected 42 Preferred Terms [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

9.3.2. LVEF Decrease

9.3.2.1. Clinical Summary

LVEF decrease in association with trastuzumab deruxtecan 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.

9.3.2.2. Management Guidance

LVEF will be measured at screening, Day 1 of Cycle 5, then every 4 cycles from Cycle 5 and at EOT by either ECHO or MUGA scan. All ECHOs/MUGA scans will be evaluated by the investigator or delegated physician for cardiac function monitoring.

Troponin will be measured centrally as well at screening and EoT. While the subject is receiving trastuzumab deruxtecan, troponin will also be measured on day 1 of each cycle 2-3 hours post infusion of trastuzumab deruxtecan for retrospective central analysis. Subjects may also have local troponin testing as clinically indicated during the treatment phase based on subject reported cardiac symptoms. An additional sample will be submitted for central lab troponin-T testing, and ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines.

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

9.4. Adverse Events

All non-serious AEs and AESI should be collected continuously during the treatment period and for a minimum of 47days after the last dose (for non-serious adverse events), and should continue to be collected until 100 days following discontinuation of last study treatment or start of new anticancer therapy, whichever is earlier, whether related or not to study treatment. Grade 3 or Grade 4 AEs ongoing at the discontinuation of study drug(s) will be monitored (including local laboratory tests when appropriate) at intervals no greater than 7 days until the AE is determined to be resolving or back to baseline. All SAEs from the time of obtaining a signed ICF and up to 100 days after the last dose of nivolumab or trastuzumab deruxtecan, must also be reported by the Investigator.

For subjects enrolled but never treated with study drug, SAEs should be collected for 30 days from the date of enrollment.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected.

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[21] It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings that should be considered AEs.

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. 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.

9.4.2. Serious Adverse Event

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,

- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.[21]

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

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.
- Disease progression is a study endpoint and consequently should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate cause, disease progression should be reported as an SAE.

9.4.3. Severity Assessment

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

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

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

9.4.4. Causality Assessment

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

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

9.4.5. Action Taken Regarding Study Drug(s)

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

9.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

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

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

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

Additional relevant information regarding the AESIs ILD and LVEF, for the trastuzumab deruxtecan clinical program regardless of seriousness is to be collected through the targeted questionnaires built within the applicable eCRFs in the clinical study database.

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

For broad surveillance of ILD/pneumonitis, selected 42 Preferred Terms [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure are included for enhanced data collections. The following types of events should be reported by the investigator in electronic data capture within 24 hours of awareness. **This data entry of an SAE in the eCRF is the expedited way of reporting of SAEs to the sponsor.**

- SAEs (see Section 9.4.2 for definition).
- All potential ILD/pneumonitis cases should be reported within 24 hours, including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur either at different time points or simultaneously

during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.

- Overdose, for trastuzumab deruxtecan and/or nivolumab, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the Investigator as clinically relevant, i.e. poses an actual or potential risk to the subject.
    - Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including trastuzumab deruxtecan and/or nivolumab dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within eDC.

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

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up. In the event that the eCRF is unavailable, report SAEs by faxing the paper Serious Adverse Event Report (SAVER) Form to the CRO using the provided fax cover sheet and the appropriate fax number provided for your country. Once the eCRF 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.

See the Study Site Manual for contact information for SAE reporting. Please call the local SAE Hotline (see the Study Site Manual) or your Medical Monitor for any questions on SAE reporting.

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

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

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

In the European Economic Area states, it is the Sponsor's responsibility to report SUSARs to all ECs.

9.7. Exposure in Utero during Clinical Studies

DSI must be notified of any subject who becomes pregnant while receiving study treatment or within 7 months of end of study treatment for female participants and 7 months for partners of male participants discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject or a male subject's female partner using the Exposure in Utero (EIU) Reporting Form. Please contact your study Medical Monitor to receive the EIU Reporting Form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or 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 (i.e., 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 outlined in Section 9.5.

For reports of pregnancy in the female partner of a male subject, the EIU Reporting Form (or SAE Form if associated with an adverse outcome) should be completed with the subject's identification number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

9.8. Clinical Laboratory Evaluations

The following items will be measured. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used.

Information will be collected on whether or not measured, date of measurement, and measurement results for the following items.

Blood samples for laboratory tests (hematology and blood chemistry, as follows) will be obtained at screening (-14 days), and on Day 1 (-3 days), Days 8 and 15 of Cycle 1(± 1 day). On subsequent cycles blood samples for hematology and chemistry will be obtained on Day 1 (-3 days) of each cycle. Samples will also be obtained at EOT and Follow-Up.

1. Pregnancy test will be performed within 72 hours before enrollment and at each cycle before study drug infusion for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test.
2. HIV antibody test: (as required by local laws, hepatitis B surface antigen/hepatitis C antibody will be done at screening.

3. Hematology tests:
    - Red blood cell count, hemoglobin, hematocrit, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils to be recorded as absolute ± percentage differential values), and platelet count.
4. Blood chemistry tests:
    - Total protein, albumin, total bilirubin (direct/indirect), AST, ALT, alkaline phosphatase, lactate dehydrogenase, creatinine kinase, blood urea nitrogen/urea, glucose, serum creatinine, uric acid, sodium, potassium, chloride, calcium, and magnesium.
    - Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.4).
    - A coagulation test will be performed (prothrombin time, activated partial thromboplastin time or partial thromboplastin time, and international normalized ratio).
    - Troponin will be analyzed at the local level at Screening and EOT. During the treatment period, (while the subject is receiving trastuzumab deruxtecan), troponin will be analyzed at the central laboratory retrospectively. Local lab values will be used to assess eligibility, and the central lab values will be stored within the central database. Collect blood samples for troponin testing by local lab, if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. Whenever a local troponin testing is performed (during the study treatment period), an additional sample will be submitted for central lab troponin-T testing and ECG performed in triplicate. If ECG is abnormal, follow institutional guidelines.
5. ADA samples will be obtained within 8 hours before infusion on Day 1 of Cycles 1, 2, 3, and 4, then every 4 cycles and 40-Day Follow-up (Section 8.3 for details). For subjects with positive ADA at the 40-Day F/U Visit, additional serum ADA samples may be collected at the Long-term F/U visits as follows:
    - Every 3 months (± 14 days) up to 1 year after the last dose of the study drug, or until the ADA becomes negative, or until the ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another anti-cancer therapy or withdraws consent from the study, whichever occurs first.
6. Urinalysis: Urinary glucose, urinary protein, urinary occult blood, urinary ketone bodies, urinary bilirubin, urinary urobilinogen, urine pH, and urine sediments (red blood cells, white blood cells, and urinary casts) will be obtained at screening and if clinically indicated at subsequent visits.
7. Thyroid function tests: While on nivolumab, the subject must have thyroid panel including TSH testing every 6 weeks. If TSH $<0.5 \times$ LLN or TSH $>2 \times$ ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.

8. Amylase and lipase testing before infusion on the first day of each treatment cycle and at EOT.

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

9.9. Electrocardiograms

Triplicate 12-lead ECGs, in close succession, will be taken with the subject in a supine/semi-recumbent position at screening and before infusion, on Day 1 of all cycles and at EOT.

The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more. Whether or not measurement is performed, date performed, results, and findings for the following parameters will be recorded in the CRF:

Heart rate, PR interval, RR interval, QRS amplitude, and QT interval (QTc).

9.10. Physical Examinations

Physical exam, SpO2, weight, and ECOG performance status will be performed at screening, Day 1 of each cycle before infusion and EOT and 40-Day Follow-up Visit. Vital signs will be performed at every visit (before infusion and EOI on Day 1 of each cycle).

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

Information will be entered in the CRF on whether or not measured, date of measurement, and measurement results for the following items: systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, pulse oximetry, height (at screening), and body weight.

9.11. Other Examinations

ECHO or MUGA scan (the same test must be used for the subject throughout the study) will be performed at screening and before infusion on Day 1 of Cycle 5 and then every 4 cycles (± 7 days) (e.g., Cycle 5, 9,13…) as well as at EOT.

Ophthalmologic assessments including visual acuity testing, slit lamp examination and fundoscopy will be performed at screening and at EOT only.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary database lock will occur 6 months after the last subject's first visit or when 80% of subjects experience disease progression or discontinue study treatment, whichever occurs first. Summary statistics will be presented by cohort. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

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

The DLT analysis will be summarized in the DLT Evaluable Analysis Set for assessment of the MTD or RDE. Efficacy analyses will be performed on the Full Analysis Set (FAS) and Response Evaluable Set (RES). Safety analyses will be performed on the Safety Analysis Set (SAF). Analysis of PK parameters will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the FAS.

An interim analysis is planned (Section 11.6) to be initiated for all Breast Cancer subjects in the study, including those from Part 1. Efficacy and safety interim analysis will be performed when all subjects enrolled into Cohorts 1 and 2 in Part 2 had at least 12 weeks of follow up after initiation of study treatment or have discontinued study treatment. The purpose of this interim analysis is to look at preliminary efficacy and safety signals for breast cancer subjects in the study. The results from this interim analysis will not be used to change the conduct of the study.

11.2. Analysis Sets

DLT Evaluable Analysis Set will include all subjects who were able to complete two cycles of treatment of both study drugs (trastuzumab deruxtecan and nivolumab) or have discontinued from study due to a DLT.

FAS will include all subjects who signed the main ICF and were enrolled in the study.

SAF will include all enrolled subjects who have received at least one dose of any of the study drugs.

RES will include all enrolled subjects who received at least 1 dose of both study drugs and had measurable disease at baseline per independent ICR Committee.

PK Analysis Set will include all subjects who received at least one dose of trastuzumab deruxtecan plus nivolumab and had measurable serum concentrations.

11.3. Study Population Data

Subject disposition will be summarized for subjects in the FAS. The total number of subjects for each defined analysis set will also be tabulated. The demographic and baseline characteristics

will be summarized descriptively for the FAS and RES. Study drug exposure and treatment duration will be summarized using descriptive statistics for the FAS.

11.4. Efficacy Analyses

The primary efficacy analysis will be performed for the FAS. All efficacy analyses will be performed for the FAS and RES. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

11.4.1. Primary Efficacy Analyses

The primary efficacy endpoint for Part 2 is ORR, as assessed by Independent ICR Committee and defined as the proportion of subjects who achieved a confirmed response (CR or PR) during study treatment (from first dose to start of new anticancer treatment) based on specified analysis set FAS.

ORR will be summarized by cohort for FAS (primary analysis). The 2-sided 95% exact confidence interval will be provided.

11.4.2. Secondary Efficacy Analyses

- The secondary efficacy endpoints based on RECIST version 1.1 are: DoR, DCR, PFS, and TTR, all based on ICR Committee and investigator assessment, as well as ORR based on investigator assessment, and OS. DOR, defined as time from first documented objective response (CR or PR) to disease progression as per RECIST 1.1. DOR will be measured for responding subjects (CR or PR) only. Detailed censoring rules for DOR analysis will be specified in the Statistical Analysis Plan (SAP).
- DCR, defined as proportion of subjects achieved CR, PR, or SD.
- PFS, defined as time from the date of first dose to the date of objective disease progression as per RECIST 1.1 or death (if no progression) due to any cause. Detailed censoring rules for PFS analysis will be specified in the SAP.
- OS, defined as time from the date of first dose to the date of death due to any cause. Subjects alive will be censored at date of last known to be alive.
- TTR, defined as time from the date of first dose to the date of first documented objective response (CR or PR). TTR will be measured for responding subjects only.
- ORR, as assessed by investigator and defined as the proportion of subjects who achieved a confirmed response (CR or PR) during study treatment (from first dose until the first documented disease progression as per RECIST v1.1).

ORR and DCR will be summarized by cohort for FAS and RES, and their 95% exact confidence intervals will be provided.

Summary statistics (n, mean, standard deviation, median, minimum, maximum) will be provided for TTR by cohort.

For time to event endpoints (DOR, PFS, OS), Kaplan-Meier estimates of medians and 95% confidence intervals for medians using Brookmeyer and Crowley method will be provided by cohort. Kaplan-Meier estimates of survival curves will be plotted.

These analyses will be repeated for pooled Part 1 and Part 2 subjects by cancer type (breast cancer and urothelial cancer) and HER2 status.

11.4.3. Other Secondary Efficacy Analyses

11.4.4. Exploratory Efficacy Analyses

Exploratory efficacy endpoints include:

- ORR by iRECIST guidelines by study investigator (part 2)
- CBR for breast cohorts, defined as proportion of subjects achieved CR, PR, or SD for at least 6 months per RECIST Version 1.1.

11.4.5. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

PK and biomarker endpoints include:

- Pharmacokinetics: Serum concentrations of trastuzumab deruxtecan, MAAA-118a, total anti-HER2 antibody and nivolumab. Nivolumab samples may not be analyzed.
- Exploratory biomarkers related to understand the mechanism of response and resistance
- Immune biomarkers such as PD-L1, tumor mutation burden, and microsatellite instability (MSI).

11.4.5.1. Pharmacokinetic Analyses

Descriptive statistics will be provided for serum concentration data of trastuzumab deruxtecan, MAAA-1181a, total anti-HER2 antibody and nivolumab (if analyzed) at each time point for each dose level of trastuzumab deruxtecan. Serum concentration data of trastuzumab deruxtecan, MAAA-1181a and nivolumab (if necessary and analyzed) from this study may be analyzed using population PK modeling and results reported separately from the clinical study report. For the population PK modeling, data from this study may be combined with other trastuzumab deruxtecan studies. Additional analyses maybe done if appropriate and useful for the interpretation of data.

11.4.5.2. Pharmacodynamic Analyses

Pharmacodynamic analyses will be described in a separate SAP.

11.4.5.3. Biomarker Analyses

Biomarkers (HER2 IHC, PD-L1 IHC, TMB, and MSI) will be summarized by cohort using descriptive statistics. 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.

11.4.5.4. Pharmacogenomic Analyses

Pharmacogenomic analyses will be described in a separate SAP.

11.4.5.5. Immunogenicity (Anti-Drug Antibody) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. The number and percentage of subjects will be calculated for the presence or absence of development of ADA after the start of administration, defining subjects who are negative for ADA at all time points as negative and subjects who are positive for ADA at least 1 time point after drug treatment as positive. The ADA titer values and change from baseline for ADA titers will be summarized by time point and by cohort using descriptive statistics. The treatment-emerging ADA incidence will be calculated. Treatment-emergent ADA positive subject will be defined as subjects who are ADA negative at baseline and become ADA positive post-treatment, or who are ADA positive at baseline and post-treatment, but have an increase in ADA titer from baseline to post-treatment, or those who have missing ADA data at baseline but become ADA positive post-treatment. The number and percentage of subjects positive for NAB of trastuzumab deruxtecan, if analyzed, will also be determined.

11.5. Safety Analyses

DLT data will be summarized for DLT evaluable subjects enrolled in Part 1. The subjects will be considered DLT evaluable if they were able to complete 2 cycles of treatment of both study drugs (trastuzumab deruxtecan and nivolumab) or have discontinued from study due to a DLT. A subject will be replaced if discontinued from the study during the DLT period due to any other reason than DLT (refer to Section 5.8.4).

Safety analysis for subjects enrolled in each part will be performed using the Safety Analysis Set.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. Listings of safety data will be provided and details will be specified in the SAP.

11.5.1. Adverse Event Analyses

AEs (Section 9.4.1) will be coded using Medical Dictionary for Regulatory Activities (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 individual study drug and to any study drug, the worst NCI-CTCAE grade, and cohort. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by cohort, as well as TEAEs leading to discontinuation of the study drugs.

The AE (including TEAE) data listing including but not limited to the verbatim terms, system organ class, preferred term, 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 drugs, will be listed.

Non-serious AEs or non-related SAEs occurring 48 days or more after the last dose will not be included in the analysis of TEAE but will be summarized separately.

11.5.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by cohort at each scheduled time of evaluation.

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

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

11.5.3. Vital Sign Analyses

Descriptive statistics will be provided by cohort for vital sign measurements and changes from baseline by scheduled time of evaluation. All vital sign data will also be listed. The baseline value is defined as the last non-missing value before the initial administration of study treatment.

11.5.4. Electrocardiogram Analyses

Descriptive statistics will be provided by cohort for ECG parameters and changes from baseline by scheduled time of evaluation. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (QTcF ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms). QTcF change from baseline will be tabulated (≤30 ms, >30 to ≤60 ms, >60 ms) where QTcF intervals are the QT corrected for heart rate by Fredericia's formula. ECG data will also be listed.

11.5.5. Physical Examination Analysis

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

11.5.6. Exploratory Safety Analyses

Not applicable.

11.5.7. Other Endpoint Analysis

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

All other safety endpoints (e.g., physical examination findings including ECOG performance status, ECHO/MUGA scan, and ophthalmologic findings) will be listed.

11.6. Interim Analysis

Efficacy and safety interim analysis will be performed when all subjects enrolled into Cohorts 1 and 2 in Part 2 have had at least 12 weeks of follow up after initiation of study treatment or have discontinued study treatment.

Subjects enrolled in Part 1 will be pooled according to their trastuzumab deruxtecan dose and HER2 expressing levels (HER2 positive or HER2 low). For example, subjects who were dosed at 5.4 mg/kg of trastuzumab deruxtecan and have HER2-positive expression Breast Cancer (IHC score 3+ or IHC score 2+/ISH+) in Part 1 will be pooled with the same subjects from Part 2 (in this case, subjects enrolled in Cohort 1).

For each dose and HER2 expressing level combination, 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 cohort using the same methodology as the primary efficacy endpoint. For time to event endpoints PFS, Kaplan-Meier estimates of medians and their corresponding 95% CIs using Brookmeyer and Crowley method will be provided by each dose and HER2 expressing level combination. Safety data related to adverse events will be summarized with descriptive statistics for each dose and HER2 expressing level combination.

11.7. The results from this interim analysis will not be used to change the conduct of the study. Data Monitoring Committee

An external Data Monitoring Committee is not planned for this study. DSI has in place a multi-layered process for ensuring subject safety through close collaboration of study site investigators, the DSI study team, and the DSI Clinical Safety and Pharmacovigilance (CSPV)-led Safety Management Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of DSI CSPV, who operate independently from the clinical team and monitor safety across all DSI protocols. Adverse events are monitored continuously by DSI CSPV. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the DSI CSPV safety physician (chairman of the SMT) and DSI CSPV single case review physician, the study Medical Monitor(s), the study biostatistician, and epidemiologist. The SMT monitors actual or potential issues related to subject safety that could result in a significant change in the medical risk-benefit balance associated with the use of study drugs. Furthermore, investigators will be kept updated of important safety information by Sponsor. If appropriate, select safety issues may be escalated to a senior level, multidisciplinary, DSI-wide Global Safety Board for further evaluation and action.

To support safety oversight, DSI has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the DSI Medical Monitor and the investigators will have access to all data necessary for safety evaluation.

All participants in this study represent individuals with high unmet medical need as the prognosis for advanced/metastatic solid tumors is generally very poor.

DSI has elected not to use a Data Monitoring Committee for this study. In addition to the comprehensive safety monitoring plan outlined above, the following key points were considered for this decision:

- This is an open-label study.
- Subjects will be observed frequently for clinical evaluation and blood counts during dose escalation.
- The eligibility criteria exclude subjects with disease characteristics that could predispose to higher risk of morbidity, including: subjects with pre-existing cardiac and lung and autoimmune diseases as specified.
- Well-defined discontinuation criteria are established in the protocol for individual subjects for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

In summary, DSI has determined that, given the study design and the points listed above, an independent Data Monitoring Committee is not required for this study.

11.8. Sample Size Determination

At most, 18 evaluable subjects will be registered for Part 1 following 3+3+3 design (Dose Escalation).

Preliminary results from the dose expansion part of the Phase 1 study of trastuzumab deruxtecan monotherapy in a subgroup analysis of HER2-expressing metastatic breast cancer subjects pre-treated with trastuzumab emtansine (T-DM1) and pertuzumab demonstrated a 46.7% overall response rate (14 of 30 patients).[22] Assume that 30 subjects were treated in Cohort 1 and observed ORR = 63.3% (19 responders out of 30 subjects), the 80% confidence interval would be (50.0%, 75.2%).

The results of a Phase 2 clinical trial of nivolumab with 270 bladder cancer patients demonstrated a 19.6% overall response rate (53 of 270 patients).[17,23] Assume that 30 patients were treated in Cohort 3 and observed ORR = 30% (9 responders out of 30 subjects), the 80% confidence interval would be (19.0%, 43.2%).

Cohorts 2 and 4 are exploratory cohorts and approximately 15 subjects will be registered into Cohorts 2 and 4, respectively.

All confidence intervals are based on Clopper-Pearson (Exact) approach (SAS 9.4).

11.9. Statistical Analysis Process

The clinical study data will be analyzed by the designated CRO.

The detailed statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications will be specified in the study SAP.

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The CRO Monitor, Sponsor, 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 (e.g., CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The Monitor is responsible for inspecting the CRFs 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 CRFs. Detailed information is provided in the monitoring plan.

The Monitor will communicate deviations from the protocol, standard operating procedures, 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 site may be selected for audit by representatives from the Sponsor. Audit of study site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

DS or a designee will supply eCRFs. 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 the EDC software's "audit trail."

Completion of the eCRF should be kept current to enable the Medical Monitor to review the subject's status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed and signed off or e-signed by the investigator. The investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator inspected or reviewed the data on the eCRF, the data queries, and the study site notifications, and agrees with the content.

12.3. Data Management

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

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

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

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

All AEs will be coded using MedDRA. Concomitant medications, prior and additional anticancer therapy will be coded using World Health Organization Drug Reference (WHODRUG) List.

12.4. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs 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 screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects registered 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 CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, CT and MRI scans, and correspondence.

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

policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

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

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

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

All study-related essential documentation will be retained by the investigator until at least 3 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 3 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (1996, § 42, paragraph 1, clause 1), the ICH consolidated Guideline E6 for 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 GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March 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 of 25 November 2014;
- Other applicable local regulations.

15.2. Subject Confidentiality

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

The investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (e.g., 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 IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

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

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

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

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) are provided in the Sponsor's ICF template 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). Also, a separate special consent will be required for pharmacogenomic testing for this protocol.

15.4. Regulatory Compliance

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

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

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing and approving the final clinical study report 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 registered and treated at least 1 subject. However, where an investigator has special knowledge of the field or of the trial, 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.

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

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to

the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required. Please note that in EU, minor changes to the protocol do not need to be submitted and in some cases even cannot be submitted to health authorities. Instead these changes need to be notified with any substantial amendment submitted.

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

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

15.5. Protocol Deviations

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

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

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

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

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

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

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

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

If the subject information is revised, it must be re-approved by the IRB/EC. The investigator should obtain written informed consent to continue participation with the revised written

information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by DSI or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

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

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

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities (*please note that this is not applicable in the EU; non-substantial protocol amendments may be implemented without IRB/EC and regulatory approval)* where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

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

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

A list of key study personnel (including personnel at the Sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and regularly updated as necessary. The addresses are also included in the Study Site Manual.

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17. APPENDICES

17.1. Appendix 1: Schedule of Events

Table 17.1: Schedule of Events

Visit/Cycle	**Tissue Screen**	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4 and Subsequent Cycles**		**Q6W**	**EOCT[a]**	**EOT[a]**	**Follow-up**		
Study Day			**1**		**8**	**15**	**1**		**1**		**1**					**40-day[b]**	**LTFU[p] (Q6W/Q3M)**	**100-Day**
Window (d)		**-14 to -1**	**BI**	**EOI**	**-3**	**-3**	**BI**	**EOI**	**BI**	**EOI**	**BI**	**EOI**	**± 7**			**+ 7**	**± 7/± 14**	
Procedures																		
Informed Consent	X	X[m]																
Assign SID		X																
Administer Study Drug[c]			X				X		X		X							
Tumor Biopsy[d] Exploratory Biomarkers[d]	X	X							X					X	X			
Medical History, including Target Disease		X																
Demographic		X																
Physical Examination[e]		X	X				X		X		X				X	X		
Weight[e]		X	X				X		X		X				X	X		
Height		X																
ECOG Performance Status		X	X				X		X		X				X	X		
Vital Signs[e]		X	X	X[n]	X	X	X	X[n]	X	X[n]	X	X[n]			X	X		
SpO2[e]		X	X	X	X	X	X	X	X	X	X	X			X	X		
Hematology, Coagulation, & Chemistry, Urinalysis[e]		X	X		X	X	X		X		X				X	X		

Visit/Cycle	**Tissue Screen**	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4 and Subsequent Cycles**		**Q6W**	**EOCT[a]**	**EOT[a]**	**Follow-up**		
Study Day			**1**		**8**	**15**	**1**		**1**		**1**					**40-day[b]**	**LTFU[p] (Q6W/Q3M)**	**100-Day**
Window (d)		**-14 to -1**	**BI**	**EOI**	**-3**	**-3**	**BI**	**EOI**	**BI**	**EOI**	**BI**	**EOI**	**± 7**			**+ 7**	**± 7/± 14**	
Procedures																		
ECHO or MUGA scan (LVEF)[f]		X									X				X			
Ophthalmologic Assessments[g]		X[m]													X			
Tumor Assessment (CT/MRI of the chest, abdomen, pelvis, and any other sites of disease)		X[m]							X				X		X		X	
Troponin[h]		X		X				X		X		X			X			
Pregnancy Test (Urine or Serum)[i]		X	X				X		X		X				X			
PK Blood (Serum) Sample[j]			X	X	X	X	X	X	X									
PK Sampling in case of for CQ/HCQ Administration			If CQ or HCQ is administered for SARS-CoV-2 infection, additional PK blood samples should be collected at the following visits: • Prior to the first CQ or HCQ dose (Day 1) • Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) • Last day of the CQ/HCQ treatment prior to CQ/HCQ dose (within 4h) The day of trastuzumab deruxtecan resumption, after the CQ/HCQ washout period[w], (within 8h BI of trastuzumab deruxtecan)															
ADA Blood Sample[k]			X				X		X		X					X	X	
HER2ECD Biomarker Blood (serum) Sample[l]			X						X*					X	X			
cfDNA Biomarker Blood (plasma) Samples[l]			X						X*					X	X			
Pharmacogenomics Blood Sample			X															

Visit/Cycle	**Tissue Screen**	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4 and Subsequent Cycles**		**Q6W**	**EOCT[a]**	**EOT[a]**	**Follow-up**		
Study Day			**1**		**8**	**15**	**1**		**1**		**1**					**40-day[b]**	**LTFU[p] (Q6W/Q3M)**	**100-Day**
Window (d)		**-14 to -1**	**BI**	**EOI**	**-3**	**-3**	**BI**	**EOI**	**BI**	**EOI**	**BI**	**EOI**	**± 7**			**+ 7**	**± 7/± 14**	
Procedures																		
HIV Antibody Test (as required by local regulations)[m]		X																
Hepatitis B/C Serology [m]		X																
SARS-CoV-2 infection sample[u]			X								X[v]				X			
AEs[o]	X ←								X									X
Prior/Concomitant Medications/Additional Anticancer Treatment		←							X									X
Hospitalization-related Records		←							X									X
CT/MRI of the Brain (as needed clinically)[q]		X											X		X			
Thyroid panel (T3 or FT3, FT4, TSH)[r]			X						X				X					
Serum Amylase and Lipase[s]			X				X		X		X				X			
12-lead ECG [t]		X	X				X		X		X				X			
Survival Follow-up (every 3 months)																	X	X

Schedule of Events – Legend

ADA = anti-drug antibody; AE = adverse event; BI = before infusion, cfDNA = cell-free DNA; CQ = chloroquine; CT = computed tomography; d = days; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = End of Treatment; HBsAg = hepatitis B surface antigen; HCQ = hydroxychloroquine; HER2 = human epidermal growth factor receptor 2; HER2ECD = HER2 extracellular domain; HIV = human immunodeficiency virus; LTFU = Long-term Follow-up; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; Q3M = every 3 months; Q6W = every 6 weeks; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SID = subject identifier; SpO2 = peripheral oxygen saturation.

[a] End of Treatment (EOT) on a subject level is defined as the date investigator decides to discontinue study treatment (+7 days). End of Combination Treatment (EOCT) is the date the investigator decides to discontinue **one** of the study drugs. In the event combination treatment is discontinued, optional tumor biopsy and biomarker blood samples assessments should be collected.

[b] 40 days (+ 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. In cases where EOT and 40-Day follow-up Visit fall within 7 days then both of these visit requirements can be completed during the same visit.

[c] Trastuzumab deruxtecan and nivolumab to be administered every 3 weeks ± 2 days unless discontinued or delayed per protocol (Section 5.5.1, Section 5.8.1). Nivolumab will be administered prior to trastuzumab deruxtecan.

[d] At tissue pre-screening (Section 6.1.1), collect adequate, archived tumor tissue sample for central laboratory HER2 testing. If an archived tissue sample is not available or is inadequate, a new tumor biopsy is required for HER2 screening. The sample must be a formalin-fixed paraffin embedded (FFPE) block and not stored slides cut previously from such an FFPE block.
Collection of a new tumor biopsy is optional at Screening (Section 6.1.2), Cycle 3, Day 1, and at the end of combination treatment, (i.e the discontinuation of trastuzumab deruxtecan or nivolumab). Additional exploratory biomarker testing may be conducted on tissue and/or liquid biopsy samples collected during the study.

[e] Within 3 days before administration. Urinalysis test is to be performed at screening and as clinically indicated throughout the study. Coagulation tests are to be performed at baseline, Cycle l, Day 1, EOT, and as clinically indicated.
Total bilirubin testing also includes direct bilirubin and indirect bilirubin.

[f] ECHO/MUGA scan will be performed at screening and before infusion on Day 1 of Cycle 5 and then every 4 cycles (± 7 days [eg, Cycles 5, 9, 13, etc)]. The same test must be used for a given subject throughout the study.

[g] Ophthalmologic assessments including visual acuity testing, slit lamp examination, and fundoscopy at screening and EOT only and as clinically indicated.

[h] Collect blood samples for troponin testing (preferably high-sensitivity troponin-T) by **local** (for eligibility) AND **central** labs at screening and EOT. During the study, local troponin testing should only be performed if clinically indicated (i.e. a subject reports signs or symptoms suggestive of congestive heart failure, myocardial infarction, or other causes of myocyte necrosis). Whenever a local troponin testing is performed (during the study treatment period), an additional sample will be submitted for central lab troponin-T testing, and ECG performed in triplicate. If ECG is abnormal, follow institutional guidelines. Blood samples will also be collected on Day 1 of each cycle, 2-3 hours post infusion for retrospective central lab analysis of troponin.

[i] Within 72 hours before enrollment for all female subjects of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours before infusion of each cycle and at EOT.

[j] Timing of blood samples for PK analysis is shown in Table 8.1.

[k] ADA samples will be obtained prior to study treatment on Day 1 of Cycles, 1, 2, and 3 and thereafter every 4 cycles, and 40-Day Follow-up (Section 8.3. For subjects with positive ADA at the 40-Day F/U Visit, additional serum ADA samples may be collected at the Long-term F/U visits as follows:

- Every 3 months (± 14 days) up to 1 year after the last dose of the study drug, or until the ADA becomes negative, or until the ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another anti-cancer therapy or withdraws consent from the study, whichever occurs first.

[l] Biomarker sampling time points are shown in Table 8.3. * Every 4 cycles starting on Cycle 3 (eg, Cycle 3, 7, 11...).

[m] Within 28 days (+7 days) before enrollment.

[n] Within 30 minutes of completing infusion of each study drug.

[o] Part I subjects should be assessed for dose-limiting toxicities on Cycles 1 and 2 (through Cycle 3, Day 1). Grade 3 or Grade 4 AEs ongoing at the discontinuation of study drug(s) will be monitored (including local laboratory tests when appropriate) at intervals no greater than 7 days until the AE is determined to be resolving or back to baseline. Refer to Section 9.2.

[p] Subjects who discontinue study treatment for any reason other than disease progression will be followed every 6 weeks (± 7 days) during first year and every 12 weeks (± 14 days) the year after for tumor assessment until disease progression or start of new anticancer therapy. Subjects who discontinue study treatment

due to disease progression will be followed 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.

[q] At baseline, brain MRI/CT is required if the subject has a history of brain metastases and/or symptoms suggestive of brain metastases. If there is no brain metastases at the time of screening, 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, brain CT or MRI is not mandatory at screening or during the study period. At EOT, brain MRI/CT is required when subject has stable baseline brain metastases.

[r] Thyroid function tests: While on nivolumab, the subject must have a thyroid panel including TSH testing every 6 weeks.
Thyroid panel should include:

- Triiodothyronine (T3) or free triiodothyronine (FT3)
- Free thyroxine (FT4)
- Thyroid stimulating hormone (TSH)

If TSH <0.5 × LLN or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements: FT4 is required to be tested at subsequent cycles as clinically indicated, and an endocrinology consult should be considered.

[s] Serum amylase and lipase testing every 3 weeks (sampling before treatment). Amylase and lipase testing before infusion on the first day of each treatment cycle and at EOT.

[t] ECG will be taken in triplicate at screening. Subsequent ECGs will be performed in triplicate, in close succession if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position.

[u] If subject provides consent, samples should be collected prior to study drug infusion. See Section 9.11. For subjects with suspected or confirmed SARS-CoV-2 infections (ie, COVID-19), follow the dose modifications in Section 17.8

[v] Starting at Cycle 5, Day 1 and every 4 cycles thereafter.

[w] a washout period of no less than14 d since last dose of CQ/HCQ is required before restarting trastuzumab deruxtecan. See Table 8.2

For suspected interstitial lung disease (ILD)/pneumonitis, treatment with study drug should be interrupted pending evaluation.
Evaluations should include:

- high resolution CT
- pulmonologist consultation (Infectious Disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- pulmonary function tests and pulse oximetry (SpO2)
- arterial blood gases if clinically indicated
- one blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible.

17.2. Appendix 2: Eastern Cooperative Oncology Group Performance Status (ECOG Performance Status)

Table 17.2: Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking h
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking h
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(6):649-55

17.3. Appendix 3: Response Evaluation Criteria in Solid Tumors Version 1.1

17.3.1. Measurability of Tumor at Baseline

17.3.1.1. Definitions

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

17.3.1.1.1. 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)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (i.e., screening for this study) and in follow-up (i.e., all measurements past screening for this study), only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.3.1.1.2. Non-Measurable

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

17.3.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.3.1.1.3.1. Bone Lesions

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

17.3.1.1.3.2. Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.3.1.1.3.3. Lesions with Prior Local Treatment

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

17.3.1.2. Specifications by Methods of Measurements

17.3.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 28 days before enrollment.

17.3.1.2.2. Method of Assessment

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

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

17.3.2. Tumor Response Evaluation

17.3.2.1. Assessment of Overall Tumor Burden and Measurable Disease

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

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

17.3.2.2. 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 five lesions total (representative of all involved organs) should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four 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 two 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").

17.3.2.3. Response Criteria

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

17.3.2.3.1. Evaluation of Target Lesions

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

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

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

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

17.3.2.3.2. Special Notes on the Assessment of Target Lesions

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

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

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

17.3.2.3.3. Evaluation of Non-target Lesions

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

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

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

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

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

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

17.3.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the

identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

17.3.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug until the EOT.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

17.3.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.3 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, see Table 17.3.

Table 17.3: Overall 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
SD	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; NE = in-evaluable; PD = progressive disease; PR = partial response; SD = stable disease

17.3.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular timepoint, the subject is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, 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 three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

17.3.2.4.3. Best Overall Response: All Time Points

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

Best response is defined as the lesser of the two best responses across two consecutive scans (eg, a subject who has PR at first assessment, SD at second assessment, and PD on last assessment; this would report as a best overall response of SD). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks (± 7 days). 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 inevaluable.

17.3.2.4.4. Special Notes on Response Assessment

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." 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 therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

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

17.3.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 week (± 7 days) while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

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

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from Cycle 1, Day 1. Subsequent tumor imaging should be performed every 6 weeks (±7 days) or more frequently if clinically indicated. After 52 weeks (365 days ±7 days), subjects who remain on treatment will have imaging performed every 12 weeks (±14 days). Imaging timing should follow calendar days. Imaging time points should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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

The radiographic evaluation must include CT or MRI scanning of chest, abdomen, and pelvis at screening period. An MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. Follow-up evaluations should include all sites of disease identified at screening and any other locations if PD is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

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

17.4. Appendix 4: Cockcroft-Gault Equation

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

Conventional – serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

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

Female:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31-41.

17.5. Appendix 5: Description of the iRECIST Process for Assessment of Disease Progression

17.5.1. Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

17.5.2. Assessment and Decision at RECIST 1.1 Progression

For subjects who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a subject on study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table 6.2). This decision by the Investigator should be based on the subject's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective ICR Committee.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions - Non-target.

17.5.3. Assessment at the Confirmatory Imaging

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

17.5.4. Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

17.5.5. Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

17.5.6. Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

17.5.7. Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Table 6.2 and submitted to the central imaging vendor.

17.5.8. Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time

- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.

17.6. Appendix 6: New York Heart Association Functional Classification

Table 17.4: New York Heart Association Functional Classification

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

Source: American Heart Association, Inc. Classification of Functional Capacity and Objective Assessment. 1994 [cited 2017 Oct 12]. Available from: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp