CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, RANDOMIZED STUDY OF TRASTUZUMAB DERUXTECAN IN SUBJECTS WITH HER2-MUTATED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

[DESTINY-LUNG02]

(Trastuzumab deruxtecan for subjects with HER2-mutated metastatic NSCLC)

PROTOCOL NUMBER: DS8201-A-U206

IND NUMBER 137009

VERSION 4.0, 09 November 2022

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INVESTIGATOR AGREEMENT

A Phase 2, multicenter, randomized study of trastuzumab deruxtecan in subjects with HER2-mutated metastatic Non-Small Cell Lung Cancer (NSCLC)

[DESTINY-Lung02]

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

PPD

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

Investigator's Signature:

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

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

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

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

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

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

DOCUMENT HISTORY

Version Number	Version Date
4.0	09 Nov 2022
3.0	01 Dec 2021
2.0	22 Oct 2020
1.0	02 Jun 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 4.0 (dated 09 Nov 2022) vs. protocol Version 3.0 (dated 01 Dec 2021) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U206 clinical study protocol (Version 4.0) by section.

Amendment Rationale:

Based on available data from the DS8201-A-U204 (DESTINY-Lung01) study, trastuzumab deruxtecan has shown the potential for responses in subjects to occur late, (beyond 9 months from enrollment). The final analysis in this study is therefore being adjusted to allow for adequate follow-up of subjects treated with trastuzumab deruxtecan that were responders. Thus, the primary scope of this protocol amendment is to update the timing of the final analysis until after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in 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	Description of Change	Brief Rationale
Synopsis, Study Objectives Table 3.1, Description of Objectives, Outcome Measures and Endpoints	Removed “approximately 31 months” where this refers to timing of final analysis. Study duration (also “approximately 31 months”) remains unchanged	To align with the timing for the final analysis.
Synopsis, Secondary Objectives Table 3.1, Description of Objectives, Outcome Measures and Endpoints	Added “definitive” to deterioration in EORTC QLQ-C30	To align with statistical analysis plan.
Table 1.1 Schedule of Events	Ophthalmologic assessments removed at EOT	To align with the latest safety information.
Table 1.1 Schedule of Events Section 8.4.1.2 Adverse Events of Special Interest (AESIs) Section 8.7.4 Immunogenicity	Deleted ADA at Long Term Follow-up Visit Deleted troponin at EOT	Currently, based on the totality of data collected from T-DXd clinical studies, immunogenicity profile of T-DXd has been well established. No further collection of blood samples for ADA analyses to understand immunogenicity is needed.

Section	Description of Change	Brief Rationale
Table 1.1 Schedule of Events Section 7.1 Discontinuation of Study Drug	Added if EOT is > 40 days after last treatment, then the EOT assessments can also account for the 40-Day Follow-up visit	Clarification and consistency with other studies in this program.
Section 1.3 Schedule of Events Table 6.6 Management Guidelines for Other Non-Hematologic Toxicity Section 8.4.1.2 Adverse Events of Special Interest (AESIs), Management Guidance	Modified management guidelines for suspected ILD/pneumonitis	To align with the latest safety information by adding details regarding pulmonary function tests (including FVC and CO diffusing capacity), clinical laboratory tests including blood cell count, differential white blood cell count, C-reactive protein and reformatting the presentation of evaluations. In addition, the duration of drug interruption for Grade 1 ILD/pneumonitis has been updated from up to 49 days to up to 18 weeks (126 days).
Section 2.1.5 Clinical Experience	Removed whether study was completed or ongoing in each header	Clarification.
Section 6.5 Guidelines for Dose Modification	Modified dose delay text	To align with the latest safety information.
Section 6.5 Guidelines for Dose Modification	Changed dose delay requiring withdrawal from 49 to 126 days	To align with the latest safety information, which could be up to 18 weeks.
Table 6.6 Management Guidelines for Other Non-Hematologic Toxicity	For Grade 1 ILD/pneumonitis, changed timing for resolution from within 49 days to within 18 weeks (126 days) from the last infusion	To align with the latest safety information, which could be up to 18 weeks.
Section 6.6 Prior and Concomitant Medications, subsection Prohibited Therapies/Products	Added: 7. Receipt of live, attenuated vaccine (mRNA and replication deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first exposure to study intervention. Note: Participants, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of study intervention.	To align with the latest safety information to reflect the safety concerns for live, attenuated vaccine.
Section 6.6 Prior and Concomitant Medications, subsection Permitted products	Deleted previous text and changed #4 as follows: Trastuzumab deruxtecan is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of trastuzumab deruxtecan, subjects should be premedicated with a combination regimen of two or three medicinal products (eg, dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for	To align with the latest safety information to reflect the need of prophylaxis of nausea and vomiting.

Section	Description of Change	Brief Rationale
	prevention of chemotherapy-induced nausea and vomiting.	
Section 7.1 Discontinuation of Study Drug	Added: If there is evidence the subject is receiving benefit from treatment even though the subject has met criterion for discontinuation, the subject may remain on study treatment after discussion with approval from the Sponsor Medical Monitor or designee.	Clarification and consistency with other studies in this program.
Section 9.1 General Statistical Considerations	Modified when the final analysis of the study will occur from when all subjects have discontinued to after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first)	Trastuzumab deruxtecan has shown the potential for responses in subjects to occur late, (beyond 9 months from enrollment). The final analysis in this study is therefore being adjusted to allow for adequate follow-up of subjects treated with trastuzumab deruxtecan.
Section 10.6, Appendix 6 Instructions Related to Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Modified text as follows: Due to the potential impact of SARS-CoV-2 infection, ie COVID-19, on subject safety, ~~the Sponsor recommends~~ the following **SARS-Cov-2 infection assessment and** dose modification and management plan for subjects with confirmed or suspected SARS-CoV-2 infection while being treated with trastuzumab deruxtecan **should be followed**. Changed SARS-CoV-2 infection to COVID-19, where appropriate, throughout this section and in Table 10.7 Added if COVID-19 diagnosed as well as confirmed to follow dose modification in Table 10.7 Deleted the bullet regarding PCR testing Modified Table 10. 7	To align with the latest safety information to reflect the updated instructions related to COVID-19.
Section 12 List of Abbreviations	The list was updated.	As required

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
A Phase 2, multicenter, randomized study of trastuzumab deruxtecan in subjects with HER2-mutated metastatic Non-Small Cell Lung Cancer (NSCLC) [DESTINY-Lung02]
Protocol Short Title
Trastuzumab deruxtecan for subjects with HER2-mutated metastatic NSCLC
Protocol Number
DS8201-A-U206
Sponsor/Collaborators
Daiichi Sankyo Inc.(DSI)/AstraZeneca
Registry Identification(s)
• NCT Number: NCT04644237 • EudraCT Number: 2017-004781-94
IND Number
IND Number 137009.
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites and Location
The number of sites is approximately 45, including but not limited to, North America, Europe, and Asia-Pacific.
Study Population
Adult subjects with HER2-mutated metastatic NSCLC who had at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy drug.
Study Objectives/Outcome Measures and Endpoints

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

Objectives	Outcome Measure	Endpoints	Category
Primary			
To evaluate confirmed ORR of trastuzumab deruxtecan in human epidermal growth factor receptor 2-(HER2-) mutated NSCLC subjects treated at 5.4 and 6.4 mg/kg doses.	**Title:** Confirmed ORR **Description:** Complete response (CR) and partial response (PR) as assessed by blinded data review and based on Response Evaluation Criteria in	The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with CR or PR, assessed by the blinded independent central review (BICR) based on RECIST version 1.1	Efficacy

	Solid Tumors (RECIST) version 1.1 **Time frame:** At least 9 months after the last subject is randomized			
Secondary				
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by confirmed ORR by investigator assessment	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by confirmed ORR by investigator assessment. **Time frame:** At least 9 months after the last subject is randomized	•	Confirmed ORR as indicated above assessed by investigator assessment based on RECIST v.1.1.	Efficacy
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by duration of response (DoR).	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DoR **Time frame:** At least 9 months after the last subject is randomized	•	DoR, defined as time from the initial response (CR or PR) by BICR and investigator assessment until documented tumor progression or death from any cause.	Efficacy
To evaluate further the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by disease control rate (DCR), progression-free survival (PFS) and Overall survival (OS)	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DCR, PFS and OS	•	DCR, defined as the proportion of subjects who achieve CR, PR, or stable disease (SD) during study treatment. DCR based on BICR and DCR based on investigator assessments will both be determined.	Efficacy

	Time frame: At least 9 months after the last subject is randomized Note: PFS and OS will be updated at the final database lock.	• PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, based on BICR and investigator assessment • OS, defined as the time from date of randomization until death from any cause.	
To evaluate safety of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title:** Safety **Description:** The number and percentage of treatment-emergent adverse events (TEAEs) collected between first dose and database lock points **Time frame**: At least 9 months after the last subject is randomized Note: Safety will be updated at the final database lock	• Adverse Events (AEs) including TEAEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) that will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 • Physical examination findings that may include Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, electrocardiogram (ECG) parameters, echocardiogram (ECHO)/multi-gated acquisition (MUGA) findings, and radiologic findings.	Safety
To evaluate pharmacokinetics (PK) and immunogenicity of trastuzumab deruxtecan at 5.4	**Title:** Evaluation of PK and immunogenicity **Description:**	• The PK endpoints include serum concentrations of trastuzumab deruxtecan, total anti-	Clinical Pharmacology

and 6.4 mg/kg doses.	Evaluation of PK of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA 1181a Determine the incidence of anti-drug antibodies (ADAs). **Time frame:** At least 9 months after the last subject is randomized Note: PK and immunogenicity will be updated at the final database lock	HER2 antibody, and MAAA 1181a. • The immunogenicity endpoint includes incidence of ADA.		
To assess symptoms, functioning and Health-related Quality of life (HRQoL) in subjects treated with trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title**: HRQoL **Description**: Assessment of symptom functioning and HRQoL in subjects treated with trastuzumab deruxtecan. **Time frame**: 9 months after the last subject is randomized Note: HRQoL will be updated at the final database lock	The (patient-reported outcomes) PROs include: • Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and EORTC quality of life questionnaire for lung cancer trials (QLQ-LC13) scale scores • Time to definitive deterioration in EORTC QLQ-C30 scores	Health economics and outcomes research (HEOR)	

Exploratory			
To evaluate time to response (TTR) and best percent change in the sum of the diameters for all target lesions	Not applicable	• TTR, defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), based on BICR and investigator assessment. • Best percent change from baseline to the sum of the diameters for all target lesions based on BICR and investigator assessment.	Efficacy
To assess associations between biomarker status and efficacy and/or safety	Not applicable	• Biomarker endpoints may include blood samples for pharmacogenetics and circulating tumor DNA (ctDNA), and additional exploratory analyses in remaining tumor samples (eg, RNAseq, whole exome sequencing [WES], mass spectrometry [MS] analysis, digital pathology analysis etc)	Biomarkers
• To explore symptoms functioning and HRQoL with newly recommended NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ) • To explore the impact of treatment and disease state on health utility using the 5-level EQ-5D	**Title:** Utility, patient-reported impression of change & healthcare resource utilization **Description:** To assess symptoms, functioning and HRQoL in subjects treated with trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses. **Time frame:**	The PROs include: – Change from baseline in NSCLC-SAQ scale scores – EQ-5D-5L health state utility index – Patient-reported treatment tolerability with Patient Global Impression of Treatment Tolerability (PGI-TT) questionnaire – Proportion of patients with overall Patient Global	HEOR

version (EQ-5D-5L) • To assess patient-reported treatment tolerability • To assess the subject's overall impression of the severity of their cancer symptoms, change in condition since starting the study • To explore the impact of treatment and disease on health care resource use	At least 9 months after the last subject is randomized Note: These HEOR assessments will be updated at the final database lock	Impression of Severity) PGIS, and (Patient Global Impression of Change) PGIC – Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital.		

Study Design

This is a randomized, 2 arm, Phase 2, multicenter study to evaluate the safety and efficacy of trastuzumab deruxtecan at 5.4 or 6.4 mg/kg in HER2-mutated NSCLC subjects who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (second-line or later, 2L+) that must have contained a platinum-based chemotherapy drug. The study is designed to randomize approximately 150 subjects to one of the following two arms in a 2:1 ratio to receive trastuzumab deruxtecan at a dose of 5.4 mg/kg every 3 weeks (Q3W) or 6.4 mg/kg Q3W, respectively. Randomization will be stratified by subjects who (i) received prior anti-programmed cell death receptor-1 (PD-1) and/or anti-programmed cell death ligand 1 (PD-L1) treatment and (ii) those who received neither.

The treatment assignment will remain blinded to study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers and Interstitial Lung Disease (ILD) Adjudication Committee. The Sponsor and the Contract Research Organization (CRO) are not blinded to the treatment assignment of subjects. The study start date is the date when the first subject has signed informed consent form (ICF). A subject is randomized when the Investigator or designee has obtained written consent, has confirmed all eligibility criteria have been met and all screening procedures have been completed.

Participation of a subject in the study will be divided into three periods: Screening, Treatment, and Follow-up (which includes the 40-day Follow-up [40-D FUP] and the Long-Term Survival Follow-Up [LTSFU]). The Screening Period will be a maximum of 28 days (d) after the ICF is signed. Subjects will be randomized once considered eligible and will then enter the Treatment Period. A maximum of 7 days are allowed between randomization and first dose of the treatment in the study. Subjects will undergo radiographic assessment of the disease status every 6 weeks (Q6W) ± 1 week from the first dose of study treatment until disease progression or start of new therapy. The Follow-up Period begins upon discontinuation from study drug, regardless of reason. After completion of the 40-D FUP visit, subsequent LTSFU visits will occur at the following frequencies to assess survival and collect information on anticancer treatments.

See Figure 1.1 for the study flow diagram.

Study Duration

Enrollment is planned to occur over approximately 16 months. The study start date is the date when the first subject has signed informed consent (ICF). A subject is randomized when the Investigator or designee has written ICF, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed.

Anticipated total duration of the study is approximately 31 months:

- Projected enrollment duration of approximately 16 months
- Treatment and 40-D FUP duration of 15 months in total
- Target dates for milestones:
  - Site activation: Fourth quarter of 2020 (4Q 2020)
  - Enrollment completion: 2Q 2022
- The end of study (EOS) is defined as the date of completion of the last visit or procedure shown in the Schedule of Events (SoE) in the trial globally
- Planned number of sites and countries:
  - The number of sites is approximately 45, including but not limited to, North America, Europe, and Asia-Pacific.

Eligibility Criteria

Inclusion Criteria:

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

1. Must have provided informed consent for study participation (see Section 10.1.2) before performance of any study-specific procedure or test.
2. Men or women ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old).
3. Pathologically documented metastatic NSCLC with a known activating HER2 mutation (please refer to the list of HER2 mutations, see Table 10.2). The HER2 mutation must be documented from an archival or fresh tumor tissue sample analyzed by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent laboratory performing testing to Good Laboratory Practice (GLP) standard.

   Note: HER2 mutation documented only from a liquid biopsy sample cannot be used for enrollment.
4. Subjects who had previous treatment including platinum therapy in the metastatic/locally advanced setting and not amenable to curative surgery or radiation. The subject must have progressed during or after the last treatment regimen or discontinued because of unacceptable toxicity.
5. Presence of at least 1 measurable lesion confirmed by BICR based on RECIST version 1.1.
6. Is willing and able to provide an adequate archival tumor tissue sample. A fresh biopsy is required if an archival tumor tissue sample cannot be supplied. Resection and core needle biopsy are acceptable. Other tissue samples, eg, fine needle aspirates or cell block are not acceptable. For detailed instruction on tissue submission, please refer to the laboratory manual.
7. Has ECOG PS of 0 to 1.
8. Has left ventricular ejection fraction (LVEF) ≥ 50% within 28 days before randomization.
9. Has adequate organ function within 14 days before randomization, defined as:

Parameter	Laboratory value
Adequate bone marrow function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm^3 (Granulocyte-colony stimulating factor [G-CSF]) administration is not allowed within 1 week prior to screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation*
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤ 5 × upper limit of normal (ULN)
Total bilirubin	≤ 1.5 x ULN if no liver metastases or < 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
Serum Albumin	≥ 2.5 g/dL
Adequate blood clotting function	
International normalized ratio (INR) / activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

*Cockcroft-Gault equation:

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

10. Has adequate treatment washout period before randomization defined as:

Treatment	Washout Period
Major surgery	≥ 4 weeks
Radiation therapy including palliative stereotactic radiation to chest	≥ 4 weeks
Palliative stereotactic radiation therapy to other anatomic areas	≥ 2 weeks
Anticancer chemotherapy (Immunotherapy [non-antibody-based therapy]), retinoid therapy	≥ 3 weeks
Targeted agents and small molecules (eg, 5-fluorouracil-based agents, paclitaxel)	≥ 2 weeks or 5 half-lives, whichever is longer
Nitrosureas or mitomycin C	≥ 6 weeks

Tyrosine kinase inhibitors (TKIs) approved for the treatment of non-small cell lung cancer (NSCLC)-baseline computerized tomography (CT) scan must be completed after discontinuation of TKI	≥ 1 week
Antibody-based anticancer therapy	≥ 4 weeks
Chloroquine /Hydroxychloroquine	> 14 days
Cell-free and concentrated ascites reinfusion therapy peritoneal shunt or drainage of pleural effusion, ascites, or pericardial effusion.	≥ 2 weeks prior to screening assessment

11. 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 for females and 4 months for males, after the last dose of study drug. Methods considered as highly effective methods of contraception are described in Section 5.1.
12. Male subjects must not freeze or donate sperm starting at randomization and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to randomization in this study.
13. Female subjects must not donate, or retrieve for their own use, ova from the time of randomization and throughout the study treatment period, and for at least 7 months after the final study drug administration. Female subjects must refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.
14. Life expectancy of 3 months or more.

Exclusion Criteria:

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

1. Has a known driver mutation in the epidermal growth factor receptor (EGFR), BRAF, or MET exon 14 gene or a known anaplastic lymphoma kinase (ALK), ROS1, RET, or NTRK fusion.
2. Medical history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV. Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any MI related symptoms should have a cardiologic consultation before randomization to rule out MI.
3. Has a corrected QT interval (QTcF) prolongation > 470 msec (females) or >450 msec (males) based on average of triplicate12-lead ECG at screening.
4. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
5. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of brain radiotherapy and study randomization.
6. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
7. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
8. Has a history of severe hypersensitivity reactions to other monoclonal antibodies.

9. Has an uncontrolled infection requiring intravenous (IV) antibiotics, antivirals, or antifungals.
10. Has substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
11. Known human immunodeficiency virus (HIV) infection. Subjects should be tested for HIV prior to randomization if required by local regulations or institutional review board (IRB)/ independent ethics committee (IEC).
12. Known active clinically relevant liver disease (eg, active hepatitis B, or active hepatitis C), such as those with serologic evidence of viral infection within 28 days of Cycle 1, Day 1. Subjects with past or resolved hepatitis B virus (HBV) infection are eligible, if negative for hepatitis B surface antigen (HBsAg[-]) and positive for hepatitis B core antibody (anti-HBc[+]). Subjects positive for hepatitis C (HCV) antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.
13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Note: Subjects may be enrolled with chronic Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to randomization and managed with standard of care treatment) which the investigator deems related to previous anticancer therapy, such as:
    a. Chemotherapy-induced neuropathy
    b. Fatigue
    c. Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:
        - Hypothyroidism/ hyperthyroidism
        - Type I diabetes
        - Hyperglycemia
        - Adrenal insufficiency
        - Adrenalitis
        - Skin hypopigmentation (vitiligo)
14. Is pregnant, breastfeeding, or planning to become pregnant.
15. Otherwise considered inappropriate for the study by the investigator.
16. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg. pulmonary emboli within three months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc.).
17. Any autoimmune, connective tissue or inflammatory disorders (eg, Rheumatoid arthritis, Sjögren's, sarcoidosis etc.) where there is documented, or a suspicion of pulmonary involvement at the time of screening. Full details of the disorder should be recorded in the eCRF for patients who are included in the study.
18. Prior complete pneumonectomy.
19. Had prior treatment with any agent, including an antibody drug conjugate (ADC), containing a chemotherapeutic agent targeting topoisomerase I.

Investigational Medicinal Product, Dose and Mode of Administration

Trastuzumab deruxtecan is an investigational agent.

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

Trastuzumab deruxtecan will be administered on Day 1 of a 3-week cycle Q3W at a dose of either 5.4 or 6.4 mg/kg IV.		
Active Ingredient(s)/ international non-proprietary name (INN)		
Trastuzumab deruxtecan		
Statistical Methodology		
Efficacy Analyses	Primary	Efficacy analyses will be performed on the full analysis set (FAS), which will include all subjects for whom study treatment has been assigned by randomization. The primary endpoint, ORR, is defined as the proportion of subjects with a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 criteria. ORR will be calculated on the FAS based on the BICR review of tumor scan data. The ORR for each dose level will be estimated along with the two-sided 95% confidence intervals (CIs). In addition, if the lower limit of the 95% confidence interval (CI) in a dose level is greater than 26.4%, the ORR in the dose level will be concluded to exceed 26.4%. The ORR difference between dose levels will be estimated using a stratified analysis, where the strata-adjusted ORR difference is computed, and each stratum is weighted according to the inverse of variance. The 95% confidence interval will also be computed.
	Key Secondary	ORR, based on the investigator assessment, will be analyzed using the same approach for the primary efficacy endpoint of the ORR based on BICR. DoR will be summarized by dose level. DoR is the duration from the first time a response is documented to the first subsequent progression or death. Median DoR will be reported based on the Kaplan-Meier method.
	Other Secondary	DCR by dose level will be estimated, as well as DCR difference between dose levels, using similar approach of the ORR analysis. PFS and OS, for each dose level, will be summarized using Kaplan-Meier method, with median and the two-sided 95% CI reported.
Safety Analyses		Safety analyses involving safety data (extent of exposure, TEAEs, clinical laboratory results, ECG, vital signs and physical exam) will be performed on the Safety Analysis Set, which comprises all subjects who received at least one dose of study treatment. No inferential statistical analysis is planned for safety data, unless otherwise specified. Descriptive statistics will be calculated for quantitative safety data and frequency counts and percentages will be compiled for classification of qualitative safety data. All percentages will be calculated based on the number of subjects in the Safety Analysis Set, unless otherwise indicated. If the number of subjects with available data does not allow for the reliable estimation of variability at a scheduled time point, no summary statistics will be presented for that time point, unless otherwise indicated. Unless otherwise noted, baseline values will be the last non-missing assessment collected prior to first dose of study treatment. Safety analyses, primarily summaries by description statistics of safety variables, will be performed by dose level.
Pharmacokinetic Analyses		Serum concentrations for trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a will be listed and summarized using descriptive statistics at each time point by dose level. PK parameters (Cmax, Tmax, AUC (ie, AUClast [area under the concentration time-curve from time 0 to the last measurable concentration] and AUC0-21d [area under the concentration time-curve from time 0 to 21 d]) of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a may also be determined using non-compartmental analysis after the first dose and summarized using descriptive statistics by dose level.

	Population PK analysis may also be conducted by combining data from this study with other clinical studies of trastuzumab deruxtecan. In addition, exposure-response (ER) analysis for key efficacy and safety endpoints may be conducted. The results of population PK and ER analyses will be provided in a separate report outside the clinical study report (CSR) for this study. Immunogenicity will be assessed through characterization of incidence and titer of the ADA. The number and percentage of subjects will be reported for the presence or absence of development of ADA after the start of administration of study treatment, defining subjects who are negative for ADA at all-time points as negative and subjects who are positive for ADA at least one time point post-study drug treatment as positive. The ADA titer values will be summarized by time point and dose level 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 posttreatment, or who are ADA positive at baseline and posttreatment, but have an increase in ADA titer from baseline to posttreatment, 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 may also be determined.
Health Economic & Outcomes Research Analyses (optional)	Descriptive statistics will be calculated to summarize change from the baseline in symptoms, physical functioning and general HRQoL scales in the C30 and LC13 study questionnaires at each scheduled assessment time point by dose level. The number of subjects completing each patient questionnaire and the number of missing or incomplete assessments will be provided for each scheduled assessment time point by dose level.
Analysis Population	• Full Analysis Set The Full Analysis Set will include all subjects for whom study treatment has been assigned by randomization. • Response Evaluable Set (RES) The Response Evaluable Set (RES) will include all subjects in FAS who received at least one dose of study treatment and had measurable target lesions as assessed by BICR at baseline. • Safety Analysis Set The Safety Analysis Set will include all subjects who received at least one dose of study treatment. • PK Analysis Set The PK Analysis Set will include all randomized subjects who received at least one dose of study drug and had measurable serum concentrations of trastuzumab deruxtecan.
Data Cut-off	The primary analysis data cut-off (DCO) will occur when all subjects completed at least 9 months of follow-up after the last subject has been randomized or has discontinued treatment.
Adjustments for Multiplicity	Not applicable.
Interim Analyses (IA)	Two interim analyses (IAs) are planned for this study. If the planned DCO of the second IA is anticipated to fall within 3 months of the primary analysis DCO, when the data are sufficiently mature, then the second IA may not be performed. The first IA will occur when a total of at least 75 subjects have been randomized to receive a dose of trastuzumab deruxtecan (5.4 mg/kg or 6.4 mg/kg) and have had

	at least 4.5 months of follow-up before the DCO or have discontinued treatment. The DCO of the second IA will be approximately 6 months after the DCO of the first IA. If the planned DCO of the second IA is anticipated to fall within 3 months of the primary analysis DCO, when the data are sufficiently mature, then the second IA may not be performed.

Planned Sample Size

One hundred and fifty subjects will be randomized in a 2:1 ratio to receive trastuzumab deruxtecan at 5.4 mg/kg or 6.4 mg/kg dose level, respectively.

For each single arm, the probability that the resulting Clopper-Pearson 95% CI will exceed and exclude the benchmark of 26.4% ORR was computed. This benchmark is the upper bound of the 95% CI (ORR 22.9%; 95% CI: 19.7% to 26.4%) in ramucirumab plus docetaxel arm in the REVEL trial, that was investigated as a second-line treatment for patients with stage IV NSCLC after platinum-based therapy.[28]

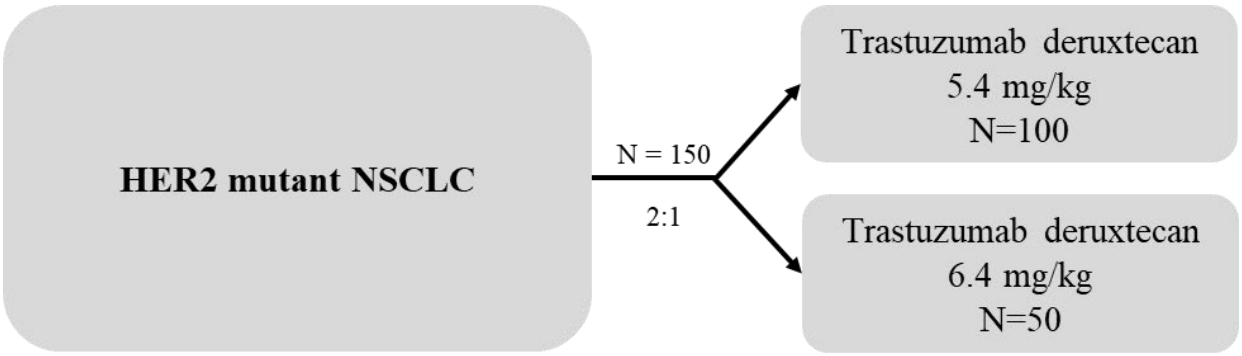
With 100 subjects in the treatment arm at the 5.4 mg/kg dose level, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 40%. On the other hand, with 50 subjects in the 6.4 mg/kg concurrent arm in this randomized study, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 45%.

1.2. Study Schema

This is a randomized, 2 arm, Phase 2, multicenter study to evaluate the safety and efficacy of trastuzumab deruxtecan at 5.4 or 6.4 mg/kg in HER2-mutated non-small cell lung cancer (NSCLC) subjects who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (second-line or later, 2L+) that must have contained a platinum-based chemotherapy drug.

A total of 150 subjects will be randomized in a 2:1 ratio to receive trastuzumab deruxtecan at the 5.4 mg/kg or 6.4 mg/kg dose cohort, respectively.

Figure 1.1: Study Level Flow Diagram



Randomization will be stratified by subjects who (i) received prior anti-PD-1 and/or anti-PD-L1 treatment and (ii) those who received neither.

HER2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death receptor-1; PD-L1 = programmed cell death ligand 1

1.3. Schedule of Events

Table 1.1: Schedule of Events

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
Informed Consent		X																	Obtain prior to performing any study procedures See Section 8.1 and Section 10.1.2
Tumor tissue specimen		X																	For the 2 study arms, archival tumor sample or fresh biopsy sample must be obtained. It is not required to perform a fresh tumor biopsy if the subject already has an adequate archived tumor tissue sample that is available to be submitted. Resection and core needle biopsy are acceptable. Other tissue samples, eg, fine needle aspirates or cell block are not acceptable. The detailed procedures for preparing and submitting tumor tissue samples will be provided in the laboratory manual. See Section 8.1

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
Pre-treatment tumor biopsy		X[d]	X[e]																[d] A fresh tumor biopsy is optional if the subject already has an adequate archived tumor tissue sample. Fine needle aspirates are not acceptable. The detailed procedures for preparing and submitting tumor tissue samples will be provided in the laboratory manual. [e]An optional fresh on-treatment biopsy will be taken during the treatment period, after Day 43 from Cycle 1 Day 1 (±7 d) and at the end of treatment (EOT) if a subject agrees. Section 8.1
Administer trastuzumab deruxtecan			X					X			X			X					See Section 6

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	**-28**	**1**		**8**	**15**	**22**	**1**		**22**	**1**		**22**	**1**					
	Window		**BI**	**EOI**	**±1 D**	**±1D**	**±2D**	**BI**	**EOI**	**±1D**	**BI**	**EOI**	**±1D**	**BI**	**EOI**	**+7D**	**+7D**	**±14D**	
Demo-graphics		X[f]																	[f] Within 14 days before randomization See Section 8.1
General Medical History and Baseline Conditions	Medical history (including NSCLC)	X[f]																	
	Smoking history	X[f]																	
Vitals	Vital Signs	X[f]	X	X	X	X		X	X		X	X		X	X	X	X		[f] Within 14 days before randomization [g] Within 72 hours (h) of infusion. If performed within 3 days before each dosing, the assessment does not need to be repeated. See Section 8.4.4
	Weight	X[f]	X[g]					X[g]			X[g]			X[g]		X	X		
	SpO_2	X[f]	X	X	X	X		X	X		X	X		X	X	X	X		
	Height	X[f]																	
Safety	Physical Examination	X[f]	X[g]	X	X	X		X[g]			X[g]			X[g]		X	X		[f] Within 14 days before randomization [g] Within 72 h of infusion. If performed within 3 days before each dosing,

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	ECOG PS	X[f]	X[g]		X	X		X[g]			X[g]			X[g]		X	X		physical examination and ECOG PS assessment do not need to be repeated. See Section 8.4.4
	Ophthalmo-logic Assessments	X[h,i]																	[h] Within 28 days before randomization [i] Ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy at Screening and as clinically indicated. See Section 8.4.4

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	ECHO or MUGA (LVEF)	X[h,j]												X[j]		X[j]			[h] Within 28 days before randomization [j] ECHO or MUGA scan assessments (note that the same assessment must be used for the subject throughout the study) will be performed at Screening and every 4 cycles (±7 d) starting with Cycle 5 (ie, Cycle 5, 9, 13…) and EOT. See Section 8.4.4

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	12-lead ECG	X[f]	X											X[k]		X			[f] Within 14 days before randomization ECG will be taken in triplicate at screening. ECGs will be taken approximately 3 minutes apart, while the subject is in a supine/semi-recumbent position. If an abnormality is noted, follow institutional guidelines. ECGs should be performed before PK blood draws. [k] ECGs will be taken at every 4 cycles starting with Cycle 5 (ie., Cycle 5, 9, 13) . See Section 8.4.4
	Pulmonary Function Test	X[l]									X[l]								[l]Pulmonary function testing will be performed within 28 days before randomization, or at C1D1 before infusion and if ILD/pneumonitis is suspected. See Section 8.4.4 for details.

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
AEs	SAEs	X								X								X[m]	[m]SAEs should be reported when assessed as related to study drug by investigator See Section 8.4.1, and Section 10.5
	Non SAEs									X									
Prior/Concomitant Therapies	Prior and Concomitant Non-Drug Therapies, and Radiotherapy									X									See Section 6.6

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
Laboratory Assessments[n]	Hematology	X[f]	X[g]		X	X		X[g]			X[g]			X[g]		X	X		[f] Within 14 days before randomization [g] Within 72 h of infusion. If performed within 3 days before each dosing, clinical laboratory tests do not need to be repeated. See Section 8.4.3 and Table 10.1
	Chemistry	X[f]	X[g]		X	X		X[g]			X[g]			X[g]		X	X		[f] Within 14 days before randomization [g] Within 72 h of infusion. If performed within 3 days before each dosing, clinical laboratory tests do not need to be repeated. See Section 8.4.3 and Section 10.2
	Coagulation	X[f]																	[f] Within 14 days before randomization See Section 8.4.3 Section 10.2

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	Troponin[o]	X[f]																	[f] Within 14 days before randomization See Table 6.3, See Section 8.4.1.2 and Section 10.2
	Urinalysis	X[f]																	[f] Within 14 days before randomization. See Section 8.4.3 and Section 10.2
	Pregnancy Test	X[p]	X[p]					X[p]			X[p]			X[p]		X	X		[p] Within 72 h before randomization 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 h before infusion of each cycle and at EOT. See Section 8.4.2
	HIV Ab Test (as required by local regulations)	X[h]																	[h] Within 28 days before randomization See Section 8.1
	Hepatitis B/C Serology	X[h]																	

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	SARS-CoV-2 Sample		X											X[q]		X			If subject provides consent, samples should be collected prior to study drug infusion. [q] Starting at C5, D1 and every 4 cycles thereafter. For subjects with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Section 10.6

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	PK Sample		X[r]	X[s,t]	X	X	X[u]	X[r]	X[s]		X[r]	X[s]		X[r]					[r] Within -8 h BI on Day 1 of each cycle until Cycle 4 and then at Cycle 6 (ie, Cycle 1, 2, 3, 4, 6). [s] Within 15 min after EOI on Day 1 of each cycle until Cycle 3 (eg, Cycle 1, 2 and, 3). [t] Cycle 1 Day 1 only, 5 h (±2 h) after the start of drug administration. [u] If treatment of next cycle is delayed for 3 days or more, or subject is discontinued, collect PK blood on C1D22 (±2 days). See Section 8.6
	PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for SARS-CoV-2, additional PK blood samples should be collected at the following visits: • Prior to the first CQ or HCQ dose (Day 1) • Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 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[v], (within 8h BI of trastuzumab deruxtecan)																If subject provides consent, samples should be collected. [v] A washout period of no less than 14 days is required before restarting trastuzumab deruxtecan. See Table 8.2

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	Exploratory blood samples (eg, ctDNA)		X					X			X			X		X			Blood plasma samples will be collected for ctDNA analysis BI on Day 1 of cycles 1 to 4 and then starting from Cycle 7, every 4 cycles, and at EOT. See Section 8.7.1
	Immuno-genicity		X[w]					X[w]						X[w]			X		[w] Within -8 h BI on Day 1 in Cycles 1, 2 and 4, and then every 4 cycles. See Section 8.7.4
	Pharmacogenomics (Inherited Genetic Analysis) Sample (optional)		X																See Section 8.7.2

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
Treatment response/ disease assessments	CT/MRI of the Brain	X[h]	X																A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Q6W (±7 d) until PD or start of new therapy regardless of Posttreatment Follow-up period. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated. [h] Within 28 days before Cycle 1 Day 1 See Section 8.1
	Tumor Assessment	X[h]	X																[h] Within 28 days before Cycle 1 Day 1
	Pulmonary Imaging	X[h]	X																Q6W (±7 d) until PD or start of new therapy regardless of Posttreatment Follow-up period See Section 8.3.3 and Section 10.4

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	Bone Scan	X	X																Bone scan (bone scintigraphy) or 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT is required within 28 days before Cycle 1 Day 1 and if bone metastases are present at baseline, and Q12W (± 7d) from Cycle 1 Day 1. See Section 8.3.2
OS	Survival FU																	X	
HEOR assessments	Healthcare resource use[x]		At each scheduled visit, the site should review clinical notes for any non-study-related hospital admissions and visits that have occurred.																See Section 8.5
	Allocate ePRO device[y]		X																
	ePRO subject training[z]		X																
	EORTC QLQ-C30, EORTC QLQ-LC13, NSCLC-SAQ, EQ-5D-5L, PGIS		X					X			X			X		X	X		To be completed before any other assessments or procedures. EORTC QLQ-C30, EORTC QLQ-LC13, NSCLC-SAQ, EQ-5D-
	PGIC							X			X			X		X	X		

Assessments		SCR	C1					C2			C3			C4 - Cx		EOT[a] (+7 D)	40-D FUP [b]	LTSFU Q3M[c]	Comment
	Procedure																		
	Day	-28	1		8	15	22	1		22	1		22	1					
	Window		BI	EOI	±1 D	±1D	±2D	BI	EOI	±1D	BI	EOI	±1D	BI	EOI	+7D	+7D	±14D	
	PGI-TT							X			X			X		X			5L, PGIS, PGIC, PGI-TT: • On Day 1 of every Cycle (±3 days) • At EOT and 40D FU visits • PGIC: As above except no assessment on Cycle 1 Day 1. • PGI-TT: as above except assessments start at Cycle 2 and there is no assessment after EOT

ADA = anti-drug antibody; BI = before infusion; C = cycle; CQ = chloroquine; ctDNA = circulating tumor DNA; CT = computerized tomography; D = day; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (Core); EORTC QLQ-LC13= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire LC13 (Lung Cancer); EQ-5D-5L = EuroQol 5 Dimension 5 Levels; HEOR = Health Economics and Outcomes Research; HIV Ab = human immunodeficiency virus antibody; HCQ = hydroxychloroquine; LTSFU = long-term survival follow-up; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NSCLCS-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OS = overall survival; PGIS = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change; PGI-TT = Patient Global Impression of Treatment Tolerability; EOT = End of Treatment; FU = follow-up; PD = progressive disease; PK = pharmacokinetic; Q6W = every 6 weeks; Q3M = every 3 months; RECIST = response evaluation criteria in solid tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = screening

[a] The date Investigator decides to discontinue study treatment (within + 7 d). If EOT is > 40 days after last treatment, then the EOT assessments can also function as the 40-Day Follow-up visit.

[b] 40 days (+7 d) after the last study drug administration or before starting new anticancer treatment, whichever comes first.

[c] Every 3 months from EOT

[n] For laboratory tests see Appendix 2: Local Laboratory. Coagulation tests performed only at screening include PT/INR and PTT/aPTT.

[o] Collect blood samples for troponin (preferably high-sensitivity troponin-T) at screening and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. If ECG is abnormal, follow institutional guidelines.

[x] If a patient discontinues study treatment for reasons other than RECIST 1.1 progression, the Hospital Admission (HOSPAD) form should continue to be administered until progression has been confirmed.
[y] The electronic patient-reported outcome (ePRO) device should be charged and fully functional prior to the patient's arrival at the site for Cycle 1 Day 1 (-3 d) to ensure that the PROs can be completed at the start of the visit.
[z] The patient should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the completion schedule.

Notes "d" to "m" and "p" to "w" are located in the "Comment" column of the SoE.

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

- High resolution computed tomography (CT)
- Pulmonologist consultation (Infectious Disease consultation as clinically indicated)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2)
- Clinical laboratory tests
    - Arterial blood gases if clinically indicated
    - Blood culture, blood cell count, differential white blood cell count, C-reactive protein
- One blood sample collection for pharmacokinetic (PK) as soon as ILD/pneumonitis is suspected, if feasible.

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

2. INTRODUCTION

2.1. Background

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide; accounting for approximately 18% of all cancer deaths.[1] For years, platinum-based chemotherapy has been the cornerstone of treatment for NSCLC in the first line. However, the 5-year survival with conventional chemotherapy regimens is around only 5%.[2]

In recent years, several targeted therapies have been approved and recommended for use in patients with advanced/metastatic NSCLC. In particular, the advent of targeted therapies for specific driver mutations such as epidermal growth factor receptor (EGFR) as well as immune checkpoint inhibitors have significantly changed the outlook for this disease. Despite recent advances, however, a significant number of advanced/metastatic NSCLC patients eventually progress on these treatments, and hence an unmet medical need exists for these patients.

Human epidermal growth factor receptor 2 (HER2) activating mutations have been reported in approximately 2% to 3% of all NSCLC adenocarcinoma patients.[3, 4,5,6,7,8] Whilst in an afatinib Phase 3 trial, 4.9% (12 of 245) of the squamous NSCLC patients also had the HER2 mutation.[9] Results from clinical studies suggest a potential role of an HER2-targeting antibody-drug conjugate (ADC) in NSCLC. A trastuzumab emtansine (T-DM1) study reported an objective response rate (ORR) of 44% in patients with HER2-mutated NSCLC.[10] HER2 mutation is also considered a distinct molecular target, however, no HER2-targeted therapies are approved in NSCLC.

2.1.1. Description of Trastuzumab Deruxtecan

Trastuzumab deruxtecan is an ADC targeting HER2. It consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component, MAAA-1181a. MAAL-9001 is an in-house humanized immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab. MAAA-1181a, an exatecan derivative, is a topoisomerase I inhibitor that is cell membrane permeable, and more potent than SN-38 (active metabolite of irinotecan).[4] This ADC achieves a high drug-to-antibody ratio (DAR) (7 - 8:1) with homogeneous conjugation with MAAA-1181a. Trastuzumab deruxtecan is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm after it binds to the HER2 receptor, which gets internalized in tumor cells.

The Lyo-DP form will be administered in this trial. For details of other forms of trastuzumab deruxtecan, refer to the latest version of the Investigator's Brochure (IB).[11]

2.1.2. Intended Use Under Investigation

This study will investigate the safety and efficacy of trastuzumab deruxtecan in HER2-mutated NSCLC subjects.

2.1.3. Nonclinical Studies of Trastuzumab Deruxtecan

In nonclinical studies for MAAA-1181a (free form), MAAA 1181c (additive form [3/10 MeCN·2/5 MeOH·3/10 H2O]) or MAAA-1181d (monohydrate) were used. The doses and concentrations of MAAA-1181c and MAAA-1181d are expressed as those of MAAA-1181a, the free form.

2.1.4. Nonclinical Studies

2.1.4.1. Pharmacology

In studies on the mechanism of action of trastuzumab deruxtecan, trastuzumab deruxtecan was confirmed to have an HER2-mediated Akt phosphorylation inhibition and an antibody-dependent cellular cytotoxicity (ADCC) activity, and has also been confirmed to cause DNA damage and induce apoptosis, effects that are assumed to be the result of MAAA-1181c, which has topoisomerase I inhibitory activity.

Therefore, trastuzumab deruxtecan is considered to exhibit HER2-specific cell growth inhibition and antitumor activity via a novel mechanism of action that combined the pharmacological activities of MAAL-9001, the antibody component, with those of MAAA-1181a, the drug component.

2.1.4.2. Safety Pharmacology

In a safety pharmacology study in monkeys treated with single IV doses of trastuzumab deruxtecan, no effects on the cardiovascular system, the respiratory system, or the central nervous system were observed under the study condition. In addition, in human ether- a-go-go-related gene (hERG) studies of MAAA-1181a, MAAA-1181a did not inhibit the hERG channel current.

2.1.4.3. Pharmacokinetics and Drug Metabolism

In vitro release rates of MAAA-1181a from trastuzumab deruxtecan in mouse, rat, monkey, and human plasma up to 3 weeks were 3.9% or less. Cytochrome P450 (CYP) 3A4 was the primary CYP enzyme involved in the metabolism of MAAA-1181a[12]. No human-specific metabolites were detected in vitro; the plasma protein binding of MAAA-1181a is approximately 97% in humans.

In monkeys, excretion of radioactivity from administered 14C-trastuzumab deruxtecan into feces was predominant. In rats, excretion of radioactivity from administered 14C-labeled MAAA 1181a (14C-MAAA-1181a) into feces via bile was predominant.

MAAA-1181d did not show any inhibition potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (concentration producing 50% inhibition [IC50] >50 μmol/L). MAAA-1181d did not show any induction potential for CYP3A4, CYP1A2, and CYP2B6 up to 30 μmol/L. MAAA-1181d did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion- transporting polypeptide (OATB) 1B3, multidrug and toxin extrusion (MATE) 1, MATE2-K, P-glycoprotein, breast cancer resistance protein, and bile salt export pump (IC50 >30 μmol/L). MAAA-1181d inhibited OAT1 and OATP1B1 with the IC50 values of 12.7 μmol/L and 14.4 μmol/L, respectively; however, the values were much

higher than the maximum concentration (Cmax) of MAAA-1181a in humans (9.25 ng/mL [0.019 µmol/L] at 8.0 mg/kg of trastuzumab deruxtecan). In addition, OATPs were considered to contribute to the human hepatic uptake of MAAA-1181a. A summary of clinical pharmacokinetic (PK) data following administration of trastuzumab deruxtecan is provided in Section 2.1.6.

2.1.4.4. Toxicology

In a study of intermittent IV dosing of trastuzumab deruxtecan in rats (every 3 weeks, Q3W × 2), no deaths or moribund animals were found at dose levels up to 197 mg/kg, the maximum dose. The major observed findings included testicular and intestinal toxicity at dose levels of 20 mg/kg and greater, and lymphatic/hematopoietic, skin, incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater. Except for the testicular and incisor tooth changes, these changes were all found to recover.

In an intermittent IV dosing study of trastuzumab deruxtecan in cynomolgus monkeys (Q3W × 2), one female was sacrificed moribund at 78.8 mg/kg, the highest dose level. The major toxicity findings in this moribund animal were observed in the intestine, hematopoietic system, skin, and kidney. The cause of the moribundity appeared to be the deteriorated condition of the animal from decreased body weight and food consumption, as well as bone marrow toxicity and intestinal toxicity. The major findings of toxicity in the surviving animals were observed in the intestine at dose levels of 10 mg/kg and greater, and in the lung, testes, and skin at dose levels of 30 mg/kg and greater. In addition, hematopoietic system toxicity, renal toxicity, and electrocardiogram (ECG) abnormalities (shortened PR interval and corrected QT interval [QTc] prolongation) were found at 78.8 mg/kg. Except for the pulmonary and skin toxicity (pigmentation), these findings tended to recover.

Thus, as described above, the severely toxic dose in 10% of the animals in a rat intermittent IV dosing study of trastuzumab deruxtecan was found to be greater than 197 mg/kg. In the monkey study, due to observed moribundity at 78.8 mg/kg and evidence of critical pulmonary toxicity (eg, interstitial inflammation and/or alveolar edema) in the surviving animals, it was concluded that the highest non-severely toxic dose is 30 mg/kg.

In an intermittent IV dose toxicity study of MAAA-1181a (morning dosing for 4 weeks), findings in the lymphatic/hematopoietic system, intestinal tract, and the cornea of the eye were observed at 3 mg/kg and greater in rats and there was no death or moribundity at up to 30 mg/kg. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of 1 mg/kg and greater. In addition, one female monkey died and one male monkey was sacrificed moribund at 12 mg/kg. Although effects on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male along with the above-mentioned toxicities, there were no abnormal heart findings in the female that died, even though both animals exhibited worsening clinical conditions associated with sustained decreases in food consumption, bone marrow toxicity, and intestinal toxicity. These changes were considered to be the cause of the death and moribundity. The common adverse findings in both trastuzumab deruxtecan and MAAA 1181a studies were intestinal and lymphatic/hematopoietic system toxicities. For trastuzumab deruxtecan treatment, pulmonary, testicular, skin, and renal toxicities were observed while heart, liver, and corneal toxicities were found only when MAAA-1181a was administered.

In a human cross-reactivity study of trastuzumab deruxtecan with a panel of human tissues, trastuzumab deruxtecan-related cell membrane staining was found only in the placenta. In a cross-reactivity study of trastuzumab deruxtecan with selected cynomolgus monkey tissues (eg, brain, liver, kidney, lung, heart, intestines, lymphoid organs, testes, and skin), neither membranous nor cytoplasmic staining was noted in any tissues.

In an in vitro 3T3 NRU phototoxicity study, MAAA-1181a was found to be phototoxic to Balb/c 3T3 mouse fibroblasts. However, in an in vivo single dose phototoxicity study of MAAA-1181d in pigmented rats, no phototoxic reaction was noted at 3 mg/kg, the highest dose tested. For additional nonclinical data supporting trastuzumab deruxtecan use in nonclinical studies, please refer to the Investigator's Brochure (IB).

2.1.5. Clinical Experience

As of 08 Jun 2019, trastuzumab deruxtecan has been evaluated in 12 company-sponsored clinical studies (11 monotherapy studies and 1 combination therapy study) in multiple oncology indications, with an estimated 1036 subjects exposed to at least 1 dose.

Study DS8201-A-J101 is a first-in-human, open-label, dose finding study to assess the safety and tolerability of trastuzumab deruxtecan in subjects with advanced solid tumors. Part 1 (dose escalation) enrolled subjects with either advanced breast cancer or gastric/gastroesophageal junction adenocarcinoma. Part 2 is the expansion phase and focuses on HER2-expressing breast and gastric/gastroesophageal junction adenocarcinoma, HER2-low-expressing breast cancer, as well as other HER2-expressing or -mutated solid cancers including NSCLC.

2.1.5.1. Efficacy: DS8201-A-J101

Efficacy results[11] as of 01 Feb 2019 showed confirmed ORR by blinded independent central review (BICR) of 52.5% (95% confidence interval [CI]: 43.1 to 61.8) among the 118 subjects with HER2-positive breast cancer, with confirmed ORR of 51.0% (95% CI: 36.6 to 65.2) for the 51 subjects in the 5.4 mg/kg dose group and confirmed ORR of 53.7% (95% CI: 41.1 to 66.0) for the 67 subjects in the 6.4 mg/kg dose group. The median confirmed duration of response (DoR) by BICR was 13.3 months, 12.7 months, and 13.6 months for the pooled, 5.4 mg/kg, and 6.4 mg/kg dose groups, respectively. The median progression-free survival (PFS) by BICR was 13.7 months, 13.7 months, and 14.1 months for the pooled, 5.4 mg/kg, and 6.4-mg/kg dose groups, respectively. Median overall survival (OS) was not reached as of the data cut-off (DCO).

As of the DCO date of 01 Feb 2019, efficacy results for all subjects with NSCLC in the Study DS8201-A-J101 study are summarized in Table 2.1. All NSCLC subjects received a 6.4 mg/kg dose of trastuzumab deruxtecan.

In the Enrolled Analysis Set, a confirmed ORR was observed in 55.6% (95% CI: 30.8 to 78.5) of NSCLC subjects (N = 18) and 73% among HER-2 mutant NSCLC subjects (N =11). The median confirmed DoR (calculated using the Kaplan-Meier method) was 10.7 months and the median PFS was 11.3 months (95% CI: 7.2 to 14.3) in NSCLC subjects.

Table 2.1: Efficacy Results in NSCLC Cancers in Study DS8201-A-J101 (Enrolled Analysis Set)

Efficacy Variable	**NSCLC (N = 18)**
Confirmed ORR, n (%) (95% CI[a]) See Table 5.14 IB)	
ORR by BICR	10 (55.6) (30.8, 78.5)
ORR by investigator	10 (55.6) (30.8, 78.5)
ORR by BICR in response evaluable set (RES), n/N	10/17 (58.8) (32.9, 81.6)
- CR	0
- PR	10 (55.6)
- Stable disease	5 (27.8)
- PD	2 (11.1)
- NE	1 (5.6)
Confirmed best overall response by investigator, n (%)	
CR	0
PR	10 (55.6)
Stable disease	4 (22.2)
PD	3 (16.7)
Non-Evaluable (NE)	1 (5.6)
Confirmed DoR, median (95% CI) (months)	
DoR by BICR	10.7 (6.9, 11.5)
DoR by investigator	9.9 (6.9, 11.5)
Confirmed DCR,[c] n (%) (95% CI[a])	
DCR by BICR	15 (83.3) (58.6, 96.4)
DCR by investigator	14 (77.8) (52.4, 93.6)
Time to confirmed response by BICR, median[b] (95% CI) (months)	1.4 (1.2, 2.8)
Duration of confirmed stable disease by BICR, median[b] (95% CI) (months)	- (2.1, -)
PFS by BICR	

Efficacy Variable	**NSCLC (N = 18)**
Events, n (%)	9 (50.0)
Median[b] (95% CI) (months)	11.3 (7.2, 14.3)
PFS by investigator	
Events, n (%)	11 (61.1)
Median[b] (95% CI) (months)	11.3 (5.5, 14.1)
Events, n (%)	4 (22.2)
Median[b] (95% CI) (months)	Not reached (17.3, -)
Survival at 6 months, % (95% CI[d])	88.9 (62.4, 97.1)
Survival at 12 months, % (95% CI[d])	83.3 (56.8, 94.3)
Survival at 18 months, % (95% CI[d])	66.7 (26.2, 88.4)
Survival at 24 months, % (95% CI[d])	- (-, -)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DoR = duration of response; HER2 = human epidermal growth factor receptor 2; IB = Investigator's Brochure; NE = non-evaluable; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response

[a] 95% exact binomial CI.

[b] Median was from Kaplan-Meier estimate. CI for median as computed using the Brookmeyer-Crowley method.

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

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

Dashes (-) represent data that are not estimable

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

Part 2 subjects are included.

Data cut-off date: 01 Feb 2019. Source: Trastuzumab deruxtecan IB, 09 Sep 2019.

2.1.5.2. Efficacy: DS8201-A-U204

A DCO was performed on 25 November 2019 to undertake an analysis of the initial 42 HER2 mutant NSCLC subjects enrolled in Cohort 2, prior to the expansion of this cohort. As of 25 Nov 2019, the median duration of follow-up was 8.0 months (range: 1.4-14.2). Treatment in 19 subjects (45.2%) was ongoing at the time of data cut-off (DCO). The median treatment duration was 7.75 months (range: 0.7-14.3).

Of the 42 subjects, the median age was 63.0 years (range: 34-83), 64.3% were female, 45.2% had central nervous system (CNS) metastases, and Eastern Cooperative Oncology Group (ECOG)

performance status (PS) was 0 in 23.8% and 1 in 76.2% of subjects. HER2 mutations were predominantly in the kinase domain (90.5%).

Forty-one (97.6%) of the 42 subjects reported at least one prior systemic cancer therapy, and the median number of prior systemic cancer therapies was 2 [range: 1 to 6]. Thirty-eight subjects (90.5%) received prior platinum-based therapy, 20 (47.6%) and 6 (14.3%) received prior anti-programmed cell death receptor-1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) treatment, respectively.

Confirmed ORR by independent committee review (ICR) among the 42 subjects was 61.9% (95% CI: 45.6 to 76.4). Median DoR was not reached; 16 of 26 responders remained on treatment at DCO. Table 2.2 provides the efficacy results from the analysis by ICR.

Table 2.2: Efficacy Results for DS8201-A-U204 Cohort 2 by ICR

Efficacy variable	**HER2-mutant NSCLC Cohort 2 (N=42)**
Best Overall Response (Confirmed)	n (%)
Complete Response (CR)	1 (2.4)
Partial Response (PR)	25 (59.5)
Stable Disease (SD)	12 (28.6)
Progressive Disease (PD)	2 (4.8)
Non-Evaluable (NE)	2 (4.8)
Confirmed ORR 95% CI[a]	26 (61.9) (45.6, 76.4)
DoR, median (months) (95% CI)[b]	NE (5.3, NE)
PFS, median (months) (95% CI)[b]	14.0 (6.4, 14.0)

DoR = duration of response; NE = not estimable; ORR = overall response rate; PFS = progression-free survival.
Overall Response is determined by independent central review assessment based on RECIST criteria, Version 1.1.
[a] The 2-sided 95% confidence intervals are based on the exact (Clopper-Pearson) binomial distribution.
[b] 95% CI for median is computed using the Brookmeyer-Crowley method.

2.1.5.3. Safety: DS8201-A-J101

As of 01 Feb 2019, a total of 288 (99.7%) subjects experienced at least 1 treatment-emergent adverse event (TEAE), with most of the common TEAEs being gastrointestinal or hematological in nature.

No dose-limiting toxicities (DLTs) were reported, and the maximum tolerated dose (MTD) was not reached in the Dose Escalation Phase.

- Gastrointestinal: Nausea was most frequently reported, was predominantly Grade 1 or Grade 2, occurred early in the treatment (the majority occurring in the first 1 to 3 cycles), and was manageable under routine clinical practice.

- Hematological: Events were predominantly Grade 1 or Grade 2, occurred early in treatment (the majority occurring in the first 1 to 3 cycles), and were manageable under routine clinical practice. Platelet count decrease (grouped term for preferred terms [PTs] platelet count decreased and thrombocytopenia) was commonly seen.

Treatment-emergent adverse events reported in ≥20% of total subjects (N = 289) by PT and grouped term, tumor type, and dose are provided in Table 2.3.

The TEAEs of Grade ≥3 were reported in 168 (58.1%) subjects. The most frequently (≥5% of subjects) reported TEAEs of Grade ≥3 in any tumor type and dose by PT were anaemia (60 [20.8%] subjects), neutrophil count decreased (53 [18.3%] subjects), white blood cell (WBC) count decreased (37 [12.8%] subjects), platelet count decreased (33 [11.4%] subjects), and hypokalaemia (18 [6.2%] subjects).

Across all tumor types, a numerically higher proportion of subjects in the 6.4-mg/kg dose group than in the 5.4-mg/kg group experienced AEs of Grade ≥3 (overall and causally related), serious adverse events (SAEs) (including causally related), AEs leading to drug withdrawal (overall and causally related), and AEs leading to dose reduction (overall and causally related).

Table 2.3: Summary of Treatment-Emergent Adverse Events (≥20% of Subjects) in Study DS8201-A-J101

MedDRA Preferred Term	Number (%) of Subjects[a]									
	HER2-Positive Breast Cancer		HER2-Low Breast Cancer		HER2-Positive Gastric/GEJ Cancer		Other Cancers[b]	Total (N = 274)		Total (N = 289)
	5.4 mg/kg (N = 50)	6.4 mg/kg (N = 66)	5.4 mg/kg (N = 21)	6.4 mg/kg (N = 33)	5.4mg/kg (N = 19)	6.4 mg/kg (N = 25)	6.4 mg/kg (N = 59)	5.4 mg/kg (N = 91)	6.4 mg/kg (N = 183)	All Doses
Subjects with any TEAEs	50 (100.0)	66 (100.0)	20 (95.2)	33 (100.0)	19 (100.0)	25 (100.0)	59 (100.0)	90 (98.9)	183 (100.0)	288 (99.7)
Nausea	43 (86.0)	52 (78.8)	15 (71.4)	26 (78.8)	12 (63.2)	19 (76.0)	44 (74.6)	71 (78.0)	141 (77.0)	222 (76.8)
Decreased appetite	23 (46.0)	47 (71.2)	7 (33.3)	20 (60.6)	8 (42.1)	22 (88.0)	35 (59.3)	38 (41.8)	124 (67.8)	168 (58.1)
Vomiting	28 (56.0)	35 (53.0)	10 (47.6)	14 (42.4)	3 (15.8)	8 (32.0)	31 (52.5)	41 (45.1)	88 (48.1)	133 (46.0)
Alopecia	19 (38.0)	45 (68.2)	6 (28.6)	18 (54.5)	4 (21.1)	4 (16.0)	20 (33.9)	29 (31.9)	87 (47.5)	120 (41.5)
Anaemia[c]	24 (48.0)	30 (45.5)	7 (33.3)	14 (42.4)	4 (21.1)	14 (56.0)	23 (39.0)	35 (38.5)	81 (44.3)	118 (40.8)
Fatigue	24 (48.0)	32 (48.5)	11 (52.4)	9 (27.3)	4 (21.1)	3 (12.0)	21 (35.6)	39 (42.9)	65 (35.5)	111 (38.4)
Diarrhoea	18 (36.0)	28 (42.4)	9 (42.9)	16 (48.5)	3 (15.8)	5 (20.0)	19 (32.2)	30 (33.0)	68 (37.2)	102 (35.3)
Constipation	18 (36.0)	30 (45.5)	7 (33.3)	14 (42.4)	5 (26.3)	7 (28.0)	16 (27.1)	31 (34.1)	67 (36.6)	100 (34.6)
Platelet count decrease[d]	15 (30.0)	24 (36.4)	3 (14.3)	14 (42.4)	5 (26.3)	12 (48.0)	22 (37.3)	24 (26.4)	72 (39.3)	100 (34.6)
Neutrophil count decrease[e]	12 (24.0)	25 (37.9)	3 (14.3)	13 (39.4)	2 (10.5)	12 (48.0)	21 (35.6)	18 (19.8)	71 (38.8)	91 (31.5)
White blood cell count decrease[f]	9 (18.0)	22 (33.3)	4 (19.0)	13 (39.4)	3 (15.8)	11 (44.0)	17 (28.8)	17 (18.7)	63 (34.4)	82 (28.4)
Aspartate aminotransferase increased	9 (18.0)	23 (34.8)	3 (14.3)	10 (30.3)	1 (5.3)	3 (12.0)	12 (20.3)	13 (14.3)	48 (26.2)	63 (21.8)
Malaise	6 (12.0)	19 (28.8)	2 (9.5)	13 (39.4)	3 (15.8)	5 (20.0)	13 (22.0)	11 (12.1)	50 (27.3)	62 (21.5)
Pyrexia	10 (20.0)	18 (27.3)	1 (4.8)	9 (27.3)	3 (15.8)	8 (32.0)	9 (15.3)	14 (15.4)	44 (24.0)	60 (20.8)
Stomatitis[g]	7 (14.0)	18 (27.3)	4 (19.0)	13 (39.4)	1 (5.3)	4 (16.0)	10 (16.9)	12 (13.2)	45 (24.6)	58 (20.1)

GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event

[a] Part 1 and Part 2 subjects are included. Percentage was calculated using the number of subjects in the column heading as the denominator.

[b] Does not include 1 subject with HER2-low gastric cancer who received trastuzumab deruxtecan at 5.4 mg/kg.

[c] Grouped term that includes PTs anaemia, hemoglobin count decreased, and red blood cell count decreased.

[d] Grouped term that includes PTs platelet count decreased and thrombocytopenia.

[e] Grouped term that includes PTs neutrophil count decreased and neutropenia.

[f] Grouped term that includes PTs white blood count decreased and leukopenia.

[g] Grouped term that includes PTs stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

Adverse events were coded using MedDRA Version 20.1.

Table is presented by decreasing order of preferred terms within the Total (N = 289) All Doses column. Numbers of subjects with TEAEs are expressed as n (%)

Data cut-off date: 01 Feb 2019.

Source: DS8201-A-J101 CSR, Table 10.6.

2.1.5.4. Safety: DS8201-A-U204

As of 25 Nov 2019, 42 subjects received at least one dose of trastuzumab deruxtecan in Cohort 2. The median treatment duration was 7.75 months (range: 0.7-14.3). Of the 42 HER2 mutated NSCLC subjects (all dosed at 6.4 mg/kg), treatment was ongoing in 19 (45.2%) subjects at the time of DCO.

All subjects experienced a TEAE in Cohort 2. A summary of TEAEs (>10% based on Cohort 2) of any Grades for Cohort 2 is shown in Table 2.4. In descending order of frequency, TEAEs with a frequency of at least 30% in Cohort 2 were nausea, alopecia, anaemia, decreased appetite, neutrophil count decreased, vomiting, diarrhoea, and weight decreased.

Table 2.4: Summary of Treatment-Emergent Adverse Events (TEAEs) (>10 % [Based on Cohort 2 by Descending Order]) from DS8201-A-U204, Cohort 2 and Overall

Preferred Term	HER2-mutant NSCLC Cohort 2 (N=42) n (%)	Overall (HER2-expressing and HER2-mutant NSCLC)* Cohort 1 and Cohort 2 (N=84)[a] n (%)
Subjects with Any TEAE	42 (100.0)	83 (98.8)
Nausea	32 (76.2)	53 (63.1)
Alopecia	20 (47.6)	26 (31.0)
Anaemia	18 (42.9)	28 (33.3)
Decreased Appetite	18 (42.9)	31 (36.9)
Neutrophil Count Decreased	18 (42.9)	25 (29.8)
Vomiting	17 (40.5)	27 (32.1)
Diarrhoea	15 (35.7)	24 (28.6)
Weight Decreased	13 (31.0)	21 (25.0)
Constipation	11 (26.2)	22 (26.2)
Fatigue	11 (26.2)	25 (29.8)
White Blood Cell Count Decreased	11 (26.2)	14 (16.7)
Aspartate Aminotransferase Increased	9 (21.4)	11 (13.1)
Malaise	8 (19.0)	13 (15.5)
Lung Infection	7 (16.7)	8 (9.5)
Pyrexia	7 (16.7)	7 (8.3)
Asthenia	6 (14.3)	11 (13.1)
Urinary Tract Infection	6 (14.3)	8 (9.5)
Alanine Aminotransferase Increased	5 (11.9)	7 (8.3)
Dry Skin	5 (11.9)	6 (7.1)
Dyspnoea	5 (11.9)	14 (16.7)
Pneumonitis	5 (11.9)	10 (11.9)

*Due to the dynamic nature of the safety dataset, the numbers might be subject to change.
[a] N=84 comes from Cohort 1 N=42 and Cohort 2 N=42 as of 25 Nov 2019 data cut-off.

Of the 42 subjects in Cohort 2, 27 (64.3%) subjects experienced at least one Grade ≥ 3 TEAE. A summary of Grade ≥ 3 TEAEs (>5% based on Cohort 2) is shown in Table 2.5. In descending order of frequency, Grade ≥ 3 TEAEs with a frequency of at least 5% in Cohort 2 were neutrophil count decreased, anaemia, fatigue, and nausea.

Table 2.5: Summary of Grade ≥ 3 TEAEs (>5% - [Based on Cohort 2 by Descending Order]) from DS8201-A-U204 Cohort 2 and Overall

Preferred Term	Cohort 2 (N=42) n (%)	Overall* Cohort 1 and Cohort 2 (N=84)[a] n (%)
Subjects with Any Grade ≥ 3 TEAE	27 (64.3)	54 (64.3)
Neutrophil Count Decreased	11 (26.2)	18 (21.4)
Anaemia	7 (16.7)	12 (14.3)
Fatigue	3 (7.1)	7(8.3)
Nausea	3 (7.1)	5 (6.0)

*Due to the dynamic nature of the safety dataset, the numbers might be subject to change.
[a] N=84 comes from Cohort 1 N=42 and Cohort 2 N=42 as of 25 Nov 2019 data cut-off.

Of the 42 subjects in Cohort 2:

- 9 (21.4%) subjects had a TEAE associated with death. The TEAE associated with death reported in more than one subject was disease progression (5).
- 25 (59.5%) subjects had a dose interruption due to TEAEs. The TEAEs leading to dose interruption reported in more than one subject included neutrophil count decreased (8), lung infection (3), keratitis (2), and malaise (2).
- 16 (38.1%) subjects had dose reductions due to TEAEs. The TEAEs leading to dose reduction reported in more than one subject included fatigue (5), nausea (4), febrile neutropenia (2), and malaise (2).
- 10 (23.8%) discontinued study treatment due to TEAEs. The TEAE leading to treatment discontinuation reported in more than one subject was pneumonitis (4).

Adverse events of special interest (AESIs) include interstitial lung disease (ILD)/pneumonitis and left ventricular ejection fraction (LVEF) decrease. An independent ILD adjudication committee has been established to adjudicate all potential ILD/pneumonitis cases on an ongoing basis. A set of pre-defined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual, will be utilized for enhanced data collection. As of 25 Nov 2019, in Cohort 2, 5 subjects experienced drug-related Grade 2 ILD as adjudicated by the independent ILD AC; there was no Grade 5 ILD observed. As per protocol, all these subjects discontinued study therapy due to the diagnosis of ILD. In Cohort 1, 4 subjects experienced drug-related ILD (2 Grade 1, 1 Grade 2, and 1 Grade 5).

As of 25 November 2019, 1 subject had two events of ejection fraction decreased (Grade 2). Of the 2 events, 1 event was reported as recovered and 1 event is recovering. Dose was interrupted for 1 event and drug discontinued for 1 event.

2.1.6. Summary of Clinical Pharmacokinetics

Following a single IV administration of trastuzumab deruxtecan, the systemic exposure of trastuzumab deruxtecan increased approximately proportional to dose across the dose range of 0.8 to 8.0 mg/kg. The mean terminal elimination half-life (t1/2) of trastuzumab deruxtecan was approximately 6.0 to 7.0 days. The t1/2 of MAAA-1181a was similar to that of trastuzumab deruxtecan. The PK parameters of total antibody were close to that of trastuzumab deruxtecan.

The trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a PK parameters at 6.4 mg/kg dose in Cycle 1 in NSCLC subjects are shown in Table 2.6.

The Cmax of trastuzumab deruxtecan was achieved with a median time to Cmax (Tmax) approximately 2.5 h. The Cmax and area under the curve (AUC) from time 0 to 21 days (AUC0-21 days), at 6.4 mg/kg were 162 µg/mL and 675 µg•d/mL, respectively. The Cmax and AUC of MAAA-1181a for the dosing interval were quite low compared to the corresponding values for trastuzumab deruxtecan.

Table 2.6: Mean Pharmacokinetic Parameters of Trastuzumab Deruxtecan, Total Anti-HER2 Antibody and MAAA-1181a Following Cycle 1 (± Standard Deviation) in subjects with NSCLC at 6.4 mg/kg dose

	Cmax (µg/mL)[a] or (ng/mL)[b]	Tmax (h) Median (range)	$AUC_{0\text{-}21d}$ (µg•d/mL)[a] or (ng•d/mL)[b]
Trastuzumab deruxtecan	162.1± 36.1	2.57 (1.50, 6.83)	675.0 ± 212.20
Total Anti-HER2 Antibody	147.7 ± 33.8	2.41 (1.50, 6.83)	772.5 ± 293.2
MAAA-1181a	11.5 ± 3.7	6.75 (3.83, 7.08)	40.38 ±12.8

AUC = area under the concentration time curve; AUC0-21d = AUC from the time 0 to 21 d; Cmax = maximum serum concentration; d = day, N = number of evaluable subjects; Tmax = time to Cmax
[a] Trastuzumab deruxtecan or total anti-HER2 antibody
[b] MAAA-1181a

2.2. Study Rationale

Targeted therapies (eg, EGFR, anaplastic lymphoma kinase [ALK], proto-oncogene 1 [ROS1] tyrosine kinase inhibitor [TKI]) are recommended as systemic treatment for a subset of NSCLC patients who have those driver mutations/rearrangements. HER2 mutation is also considered a distinct molecular target, however, no HER2-targeted therapies are approved in NSCLC. Several pan-class HER family TKIs were investigated in HER2-mutated NSCLC; however, clinical activity of those treatments was very limited, with ORR range of 0 to 19%.[13,14,15,16] Platinum- or taxane-based chemotherapy or immune checkpoint inhibitor remain the treatment options for no known mutation or after disease progression against molecular targeted therapy.

Results from clinical studies suggest a potential role of HER2-targeting ADC in NSCLC. A single-center, investigator-sponsored, phase II basket trial of T-DM1 study reported an ORR of 44% (n=8/18; 95% CI: 22 to 69) in patients with HER2-mutant NSCLC.[10] While there are no

direct HER2-targeted therapies approved for NSCLC, further investigation of HER2 targeting strategies are warranted in this patient population.

Trastuzumab deruxtecan is a HER2-targeting ADC with a high DAR, and a novel topoisomerase I inhibitor. Trastuzumab deruxtecan is expected to inhibit tumor growth on the basis of the following reasons: it exhibits ADCC activities and Akt phosphorylation inhibition similar to those of trastuzumab when it binds to HER2; and the MAAA-1181a that is released from trastuzumab deruxtecan after the internalization induces apoptosis by inhibiting topoisomerase I. Nonclinical evidence demonstrates that the HER2 targeting of trastuzumab deruxtecan is highly specific.

In Part 1 of Study DS8201-A-J101, there have been no reported DLTs, the MTD was not reached in the 0.8 to 8.0 mg/kg Q3W, and 5.4 mg/kg or 6.4 mg/kg were considered as the recommended Phase 2 doses. Efficacy results as of 01 Feb 2019 showed confirmed ORR by BICR of 52.5% (95% CI: 43.1 to 61.8) among the 118 subjects with HER2-positive breast cancer, with confirmed ORR of 51.0% (95% CI: 36.6 to 65.2) for the 51 subjects in the 5.4 mg/kg dose group and confirmed ORR of 53.7% (95% CI: 41.1 to 66.0) for the 67 subjects in the 6.4 mg/kg dose group. Trastuzumab deruxtecan dose of 6.4 mg/kg has shown promising efficacy in HER2-expressing and HER2-mutant NSCLC subjects in the Study DS8201-A-J101. The confirmed ORR was 55.6% across all NSCLC subjects (N =18) and 73% among HER2 mutant NSCLC subjects (N =11). See Section 2.1.5.1. Moreover, as of the DCO date, 25 Nov 2019, a data snapshot for Study DS8201-A-U204 (ORR: 61.9% [n=26/42]; 95% CI: 26.8 to 69.4) has shown clinical efficacy in HER2-mutated NSCLC subjects at the 6.4 mg/kg dose. Preliminary evidence suggests that the response rate with trastuzumab deruxtecan is substantially higher than the standards of care for second-line or later, namely nivolumab, docetaxel, or docetaxel and ramucirumab.

Both 5.4 and 6.4 mg/kg doses of trastuzumab deruxtecan have shown clinical efficacy in multiple cancer indications. However, the 5.4 mg/kg dose was not tested in HER2 mutated NSCLC subjects but is being tested in HER2-expressing NSCLC subjects.

This Phase 2, randomized study will evaluate the efficacy and safety of the 5.4 mg/kg dose in HER2-mutated NSCLC subjects for the first time. It will also be used to confirm the efficacy of the 6.4 mg/kg dose thereby fully characterizing the benefit-risk profile of trastuzumab deruxtecan in this population.

2.3. Benefit and Risk Assessment

Preliminary clinical evidence for trastuzumab deruxtecan in HER2-mutated NSCLC comes from Study DS8201-A-U204 and is supported by the results from Study DS8201-A-J101. In Study DS8201-A-U204, confirmed ORR (DCO date: 25 Nov 2019) was 61.9% (95% CI: 45.6 to 76.4) and the median DoR was not reached (95% CI: 6.2 months to NE) in HER2-mutated NSCLC subjects.

As of 08 Jun 2020, based on the cumulative review of the safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished) and taking into consideration biological plausibility, ILD/pneumonitis and neutropenia including febrile neutropenia are classified as important identified risks. Left ventricular (LV) dysfunction and embryo-fetal toxicity are classified as important potential risks.

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

Other identified risks of trastuzumab deruxtecan were generally manageable through dose modification and routine clinical practice.

In the trastuzumab deruxtecan clinical program, the inclusion/exclusion criteria and monitoring/management guidelines are currently in place in all protocols to mitigate the important identified risks of ILD/pneumonitis and neutropenia, including febrile neutropenia, important potential risks of LV dysfunction and embryo-fetal toxicity, and other risks.

Trastuzumab deruxtecan has demonstrated an overall acceptable safety profile in the treated populations to date.

In conclusion, given the data available on the efficacy and safety of trastuzumab deruxtecan, the overall benefit-risk profile remains favorable for clinical development.

For current details on safety and tolerability profile of trastuzumab deruxtecan and assessments of risks and benefits to subjects, please refer to the current IB.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

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

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

Objectives	Outcome Measure	Endpoints	Category
Primary			
To evaluate confirmed ORR of trastuzumab deruxtecan in HER2-mutated NSCLC subjects treated at 5.4 and 6.4 mg/kg doses.	**Title:** Confirmed ORR **Description:** Complete response (CR) and partial response (PR) rate as assessed by blinded data review and based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 **Time frame:** At least 9 months after the last subject is randomized	The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with CR or PR, assessed by BICR based on RECIST version 1.1	Efficacy
Secondary			
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by confirmed ORR by investigator assessment	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 64 mg/kg doses by confirmed ORR by investigator assessment **Time frame:** At least 9 months after the last subject is randomized	• Confirmed ORR as indicated above assessed by investigator assessment based on RECIST v.1.1.	Efficacy
To evaluate the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DoR.	**Title:** Clinical Efficacy **Description:** Evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DoR **Time frame:** At least 9 months after the last subject is randomized	• DoR, defined as time from the initial response (CR or PR) by BICR and investigator assessment until documented tumor progression or death from any cause.	Efficacy

Objectives	Outcome Measure	Endpoints	Category
To evaluate further the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DCR, Progression-free survival (PFS) and Overall survival (OS)	**Title:** Clinical Efficacy **Description:** Further evaluation of the clinical efficacy of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses by DCR, PFS and OS **Time frame:** At least 9 months after the last subject is randomized Note: PFS and OS will be updated at the final database lock.	• DCR, defined as the proportion of subjects who achieve CR, PR, or SD during study treatment. DCR based on BICR and DCR based on investigator assessments will both be determined. • PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, based on BICR and investigator assessment. • OS, defined as the time from date of randomization until death from any cause.	Efficacy
To evaluate safety of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title:** Safety **Description:** The number and percentage of any TEAEs collected between first dose and database lock points **Time frame:** At least 9 months after the last subject is randomized Note: Safety will be updated at the final database lock.	• AEs including TEAEs, SAEs, and AESIs that will be graded according to the CTCAE Version 5.0 • Physical examination findings that may include ECOG PS, vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, echocardiogram (ECHO)/MUGA findings, and radiologic findings.	Safety

Objectives	Outcome Measure	Endpoints	Category
To evaluate pharmacokinetics (PK) and immunogenicity of trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title:** Evaluation of PK and immunogenicity **Description:** Evaluation of PK of trastuzumab deruxtecan total anti-HER2 antibody, and MAAA 1181a Determine the incidence of ADAs **Time frame:** At least 9 months after the last subject is randomized Note: PK and immunogenicity will be updated at the final database lock	• The PK endpoints include serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA 1181a. • The immunogenicity endpoint includes incidence of ADA.	PK, immunogenicity
To assess symptoms, functioning and Health-related Quality of life (HRQoL) in subjects treated with trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses.	**Title:** HRQoL **Description:** Assessment of symptom functioning and HRQoL in subjects treated with trastuzumab deruxtecan. **Time frame**: At least 9 months after the last subject is randomized Note: HRQoL will be updated at the final database lock	The (patient-reported outcomes) PROs include: • Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and EORTC quality of life questionnaire for lung cancer trials (QLQ-LC13) scale scores • Time to definitive deterioration in EORTC QLQ-C30 scores	HEOR
Exploratory			
To evaluate time to response (TTR) and best percent change in the sum of the diameters for all target lesions	Not applicable	• TTR, defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), based on BICR and investigator assessment. • Best percent change from baseline to the sum of the diameters for all target lesions based on BICR and investigator assessment.	Efficacy

Objectives	Outcome Measure	Endpoints	Category
To assess associations between biomarker status and efficacy and/or safety	Not applicable	• Biomarker endpoints may include blood samples for pharmacogenetics and ctDNA, and additional exploratory analyses in remaining tumor samples (eg RNAseq, whole exome sequencing [WES], MS analysis, digital pathology analysis etc)	Biomarkers
• To explore symptoms functioning and HRQoL with newly recommended NSCLC-SAQ • To explore the impact of treatment and disease state on health utility using the EQ-5D-5L • To assess patient-reported treatment tolerability • To assess the subject's overall impression of the severity of their cancer symptoms, change in condition since starting the study • To explore the impact of treatment and disease on health care resource use	**Title:** Utility, patient-reported impression of change & healthcare resource utilization **Description:** To assess symptoms, functioning and HRQoL in subjects treated with trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses. **Time frame:** At least 9 months after the last subject is randomized Note: These HEOR assessments will be updated at the final database lock	The PROs include: • Change from baseline in NSCLC-SAQ scale scores • EQ-5D-5L health state utility index • Patient-reported treatment tolerability with PGI-TT • Proportion of patients with overall PGIS, and PGIC • Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital.	HEOR

3.1. Rationale for Selection of Primary and Secondary Endpoints

The primary and secondary efficacy endpoints are selected to evaluate evidence of drug activity. ORR is defined as the proportion of subjects with CR or PR as defined by RECIST version 1.1 in this study. ORR is based on objective and quantitative assessment, and is a direct measure of the treatment's antitumor activity.[17] It is a suitable primary endpoint in this study that evaluates the two dose levels of trastuzumab deruxtecan.

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, 2 arm, Phase 2, multicenter global study to evaluate the safety and efficacy of trastuzumab deruxtecan at 5.4 or 6.4 mg/kg in HER2-mutated NSCLC subjects who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (2L+) in the metastatic/locally advanced setting, including platinum therapy.

The number of the sites is approximately 45, including but not limited to, North America, Europe, and Asia-Pacific. The subject population is described in Section 5.

4.1.1. Design Overview

This study will enroll approximately 150 NSCLC subjects with documented HER2 mutant status who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (2L+), including platinum therapy. Randomization will be stratified by (i) subjects who received prior anti-PD-1 and/or anti-PD-L1 treatment and (ii) those who received neither, in a 2:1 ratio to receive trastuzumab deruxtecan at a dose of 5.4 mg/kg or 6.4 mg/kg, respectively. See Section 2.3.

- Two dose arms:
  - 5.4 mg/kg Q3W (N = 100)
  - 6.4 mg/kg Q3W (N = 50)

The treatment assignment will remain blinded to study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers and ILD Adjudication Committee. The Sponsor and the Contract Research Organization (CRO) are not blinded to the treatment assignment of the subjects. The study start date is the date when the first subject has signed ICF. A subject is randomized when the Investigator or designee has obtained written consent, has confirmed all eligibility criteria have been met and all screening procedures have been completed.

During the Treatment Period, subjects will receive the assigned dose of study drug Q3W until progression of disease or until the subject meets one of the discontinuation criteria (Section 7.1). Subjects who discontinue study drug for any reason other than PD, death or loss to follow-up will be followed every 6 weeks (Q6W) until radiological disease progression or start of new therapy.

After study treatment is discontinued, subjects will be followed for 40 days for safety. Subjects will then enter long-term follow-up for collection of information on subsequent anticancer treatment and survival including the cause and date of death.

Two interim analyses (IAs) are planned for this study. The first IA will be performed when a total of at least 75 subjects have been randomized to receive a dose and had at least 4.5 months of follow-up before the DCO or have discontinued treatment. The DCO of the second IA will be approximately 6 months after the DCO of the first IA. If the planned DCO of the second IA is anticipated to fall within 3 months of the primary analysis DCO, when the data are sufficiently

mature, then the second IA may not be performed. The main purpose of these IAs is to evaluate the safety and efficacy of each dose without the intent to modify the study design and study conduct. There is no plan for stopping the trial for efficacy. The evaluation of the study results will be based primarily on point estimation and 95% CI. Hence, futility and efficacy stopping boundaries are not defined for both IAs. A PK assessment will also be performed. Additionally, exposure-response analyses for key efficacy and safety endpoints may be performed at the time of these IAs.

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

4.1.2. End of Study

The **primary completion date** is the date when the last randomized subject has completed at least 9 months of follow-up treatment or when all subjects have been discontinued from the study, whichever is earlier. This date is used as the cut-off date for the analysis of the primary efficacy endpoint. All subjects still on treatment and continuing to derive benefit from trastuzumab deruxtecan at the primary completion date will continue to follow the study schedule of events (SoE) (Table 1.1) until the **overall EOS** is reached.

EOS will occur when the last subject's last visit has occurred, all subjects have discontinued from the study or have died, an alternative study has become available where trastuzumab deruxtecan is offered to subjects continuing to derive benefit from such treatment, or the study is discontinued by the Sponsor for other reasons.

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

4.1.3. Dose Regimen

Trastuzumab deruxtecan will be administered at doses of either 5.4 mg/kg or 6.4 mg/kg respectively, as an IV infusion over 90 min (± 10 min) Q3W ±2 d.

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

4.1.4. Duration

Study duration is inclusive of 3 periods: Screening Period, Treatment Period and Follow-up Period (which includes the long-term survival follow-up) as shown in the SoE, Table 1.1.

Duration of Treatment and Subject Participation

Each subject is expected to receive approximately 14 months of treatment with trastuzumab deruxtecan. It is expected that a subject's total duration of participation in the study will be approximately 16 months: 4 weeks in the Screening Period, 14 months in the Treatment Period, and 40 days of Follow-up. All subjects who discontinue study drug will be followed for survival assessment every 3 months.

Overall Study Duration

Enrollment is planned to occur over approximately 16 months. The anticipated total duration of the study is expected to be 31 months. See Section 4.1 for the definition of study start and Section 4.1.2 for the definition of the overall EOS.

Study Drug Continuation After the End of Study

Not applicable.

4.2. Rationale for Study Design

This Phase 2 study design is based on data from the Study DS8201-A-J101 and the preliminary data from the Study DS8201-A-U204 demonstrating the clinical efficacy of trastuzumab deruxtecan in HER2-mutated NSCLC subjects at the 6.4 mg/kg dose.

Both 5.4 and 6.4 mg/kg doses of trastuzumab deruxtecan have shown clinical efficacy in multiple cancer indications. However, the 5.4 mg/kg dose has not been tested in HER2-mutated subjects although it is being tested in HER2 expressing subjects. It is important to more fully characterize the benefit-risk profile for the two doses in this study.

The study design will implement both blinding (with respect to study subjects and investigators) and randomization to minimize bias in the trial conduct and to allow unbiased assessment of 5.4 and 6.4 mg/kg doses. Moreover, randomization will be stratified by important and potential prognostic/predictive factor of whether the subject had prior therapy of anti-PD-1 or anti-PD-L1 antibody, in order to reduce the risk of prognostic imbalance between treatment groups.

4.3. Justification for Dose

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

In the dose escalation portion (Part 1) of the first-in-human Study DS8201-A-J101, no DLTs were observed, and the MTD was not reached in the evaluated dose range of 0.8 to 8.0 mg/kg. Based on the efficacy and safety data in Part 1, the 5.4 mg/kg and 6.4 mg/kg doses exhibited clinical activity with a qualitatively similar safety profile, and therefore were selected for the dose expansion portion (Part 2) of Study DS8201-A-J101 in subjects with NSCLC and other solid tumors; subjects with NSCLC received only 6.4 mg/kg dose of trastuzumab deruxtecan. Trastuzumab deruxtecan dose of 6.4 mg/kg is also being evaluated in Cohort 2 of the ongoing Phase 2 Study DS8201-A-U204.

Trastuzumab deruxtecan dose of 6.4 mg/kg has shown promising efficacy in HER2-expressing and HER2-mutant NSCLC subjects in Study DS8201-A-J101. The confirmed ORR was 55.6% across all NSCLC subjects (N =18) and 73% among HER-2 mutant NSCLC subjects (N =11). See Section 2.1.5.1.

A trastuzumab deruxtecan dose of 6.4 mg/kg is also being evaluated in the ongoing Phase 2 Study DS8201-A-U204 in subjects with HER2-mutated NSCLC and the 5.4 mg/kg and 6.4 mg/kg doses in subjects with HER2-expressing NSCLC. Promising efficacy was also observed based on analysis (DCO date: 25 Nov 2019) using data from the ongoing Study DS8201-A-U204

(Section 2.1.5.2). In subjects with HER2-mutated NSCLC following treatment with trastuzumab deruxtecan dose of 6.4 mg/kg, confirmed ORR by ICR was 61.9% (26/42; 95% CI: 45.6 to 76.4) with median DoR not reached (95% CI: 5.3 months to NE) and the median PFS was 14.0 months (95% CI: 6.4 months to 14.0 months). From a safety perspective, trastuzumab deruxtecan dose of 6.4 mg/kg was generally tolerated with an acceptable and manageable safety profile consistent with the safety profile observed in other solid tumors. These results support evaluation of a trastuzumab deruxtecan dose of 6.4 mg/kg in subjects with HER2-mutated NSCLC in Study DS8201-A-U206.

A trastuzumab deruxtecan dose of 5.4 mg/kg has been evaluated in the DS8201-A-J101 study and a Phase 2 study (DS8201-A-U201) in subjects with HER2-positive, unresectable and/or metastatic breast cancer. The dose of 5.4 mg/kg has shown robust efficacy with confirmed ORR of 60.9% (111/184; 95% CI: 53.4 to 68.0). From a safety perspective, a numeric trend for better safety profile was seen at the 5.4 mg/kg dose compared to higher doses (≥ 6.4 mg/kg) in subjects with breast cancer. The trastuzumab deruxtecan dose of 5.4 mg/kg is currently being evaluated in the ongoing Phase 3 studies in subjects with metastatic breast cancer and also in subjects with HER2 expressing NSCLC in the ongoing Study DS8201-A-U204.

From the PK perspective, the systemic exposures parameters (Cmax, AUC0-21d [AUC over 21 days of dosing cycle] and Ctrough in Cycle 1) of intact trastuzumab deruxtecan and MAAA-1181a were comparable across subjects with metastatic breast cancer and HER2-expressing or -mutated NSCLC at the 6.4 mg/kg dose. Based on the exposure-response (ER) analyses for efficacy, the mean (90% CI) probability of ORR in subjects with metastatic breast cancer was predicted to be 63% (55%- 70%) and 68% (58% - 77%) for the 5.4 mg/kg and 6.4 mg/kg dose groups, respectively. Hence, the ER analyses support clinically meaningful efficacy for trastuzumab deruxtecan at both the 5.4 mg/kg and 6.4 mg/kg doses and a small improvement in ORR at 6.4 mg/kg compared to the 5.4 mg/kg dose level in subjects with metastatic breast cancer.

The ER analyses for safety estimated a numerically higher incidence (approximately 1% to 7%) of the safety endpoints (AE related discontinuation, dose reduction or drug interruption), AEs ≥ Grade 3, SAE, anaemia, neutropenia or thrombocytopenia and ILD (any grade and ≥ Grade 3), and decreased LVEF (≥ Grade 2) at 6.4 mg/kg dose compared to 5.4 mg/kg dose. The details of these analyses were provided in a separate report (DS8201-PMx003), submitted to the Agency under BLA 761139 (SN. 0002) for the breast cancer indication. Overall, these ER results for efficacy and safety indicate that while both 5.4 and 6.4 mg/kg doses showed a positive benefit-risk profile, the 6.4 mg/kg dose showed a numerical trend for an increase in the ORR as well as a numerical increase in the incidence of AEs compared to the 5.4 mg/kg dose. These findings along with the observed efficacy and safety data in subjects with NSCLC in the Studies, DS8201-A-J101 and DS8201-A-U204 support the selection of 6.4 and 5.4 mg/kg doses in subjects with HER2-mutated NSCLC in the current study.

Based on the efficacy, tolerability and PK profile of trastuzumab deruxtecan, the doses of 5.4 mg/kg and 6.4 mg/kg were selected for evaluation in the Study DS8201-A-U206 to more fully characterize the benefit-risk profile in subjects with HER2-mutated NSCLC.

5. STUDY POPULATION

Adult subjects with HER2-mutated metastatic NSCLC.

5.1. Inclusion Criteria

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

1. Must have provided informed consent for study participation (see Section 10.1.2) before performance of any study-specific procedure or test.
2. Men or women ≥18 years old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old).
3. Pathologically documented metastatic NSCLC with a known activating HER2 mutation (please refer to the list of HER2 mutations, Table 10.2). The HER2 mutation must be documented from an archival or fresh tumor tissue sample analyzed by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent laboratory performing testing to Good Laboratory Practice (GLP) standard.

   Note: HER2 mutation documented only from a liquid biopsy sample cannot be used for enrollment.
4. Subjects who had previous treatment including platinum therapy in the metastatic/locally advanced setting and not amenable to curative surgery or radiation. The subject must have progressed during or after the last treatment regimen or discontinued because of unacceptable toxicity.
5. Presence of at least 1 measurable lesion confirmed by BICR based on RECIST version 1.1.
6. Is willing and able to provide an adequate archival tumor tissue sample. A fresh biopsy is required if an archival tumor tissue sample cannot be supplied. Resection and core needle biopsy are acceptable. Other tissue samples, eg, fine needle aspirates or cell block are not acceptable. For detailed instruction on tissue submission, please refer to the laboratory manual.
7. Has ECOG PS of 0 to 1.
8. Has LVEF ≥ 50% within 28 days before randomization.
9. Has adequate organ function within 14 days before randomization, defined as:

Parameter	**Laboratory value**
Adequate bone marrow function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm^3

Parameter	Laboratory value
	(granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation*
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤ 5 × ULN
Total bilirubin	≤ 1.5 x ULN if no liver metastases or < 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
Serum Albumin	≥ 2.5 g/dL
Adequate blood clotting function	
International normalized ratio (INR) / activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

*Cockcroft-Gault equation:

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

10. Has adequate treatment washout period before randomization, defined as:

Treatment	Washout Period
Major surgery	≥ 4 weeks
Radiation therapy including palliative stereotactic radiation to chest	≥ 4 weeks
Palliative stereotactic radiation therapy to other anatomic areas	≥ 2 weeks
Anticancer chemotherapy (Immunotherapy [non-antibody-based therapy]), retinoid therapy	≥ 3 weeks
Targeted agents and small molecules (eg, 5-fluorouracil-based agents, paclitaxel)	≥ 2 weeks or 5 half-lives, whichever is longer
Nitrosureas or mitomycin C	≥ 6 weeks
Tyrosine kinase inhibitors (TKIs) approved for the treatment of non-small cell lung cancer (NSCLC) - baseline computerized tomography (CT) scan must be completed after discontinuation of TKI	≥ 1 week
Antibody-based anticancer therapy	≥ 4 weeks
Chloroquine/Hydroxychloroquine	>14 days

Treatment	Washout Period
Cell-free and concentrated ascites reinfusion therapy peritoneal shunt or drainage of pleural effusion, ascites, or pericardial effusion	≥ 2 weeks prior to screening assessment

11. 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 for females and for 4 months for males after the last dose of study drug. Methods considered as highly effective methods of contraception are listed below.

    - 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 for females and 4 months for males after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

    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 [FSH] > 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 randomization. For most forms of HRT, at least 2-4 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.

12. Male subjects must not freeze or donate sperm starting at randomization and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to randomization in this study.
13. Female subjects must not donate, or retrieve for their own use, ova from the time of randomization and throughout the study treatment period, and for at least 7 months after the final study drug administration. Female subjects must refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.
14. Life expectancy of 3 months or more.

5.2. Exclusion Criteria

1. Has a known driver mutation in the EGFR, BRAF, or MET exon 14 gene or a known ALK, ROS1, RET, or NTRK fusion.
2. Medical history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any MI related symptoms should have a cardiologic consultation before randomization to rule out MI.
3. Has a corrected QT interval (QTcF) prolongation > 470 msec (females) or >450 msec (males) based on average of the triplicate12-lead ECG at screening.
4. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
5. Has spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of brain radiotherapy and study randomization.
6. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
7. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
8. Has a history of severe hypersensitivity reactions to other monoclonal antibodies.

9. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
10. Has substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
11. Known human immunodeficiency virus (HIV) infection. Subjects should be tested for HIV prior to randomization if required by local regulations or institutional review board (IRB)/independent ethics committee (IEC).
12. Known active clinically relevant liver disease (eg, active hepatitis B, or active hepatitis C), such as those with serologic evidence of viral infection within 28 days of Cycle 1, Day 1. Subjects with past or resolved hepatitis B virus (HBV) infection are eligible, if negative for hepatitis B surface antigen (HBsAg[-]) and positive for hepatitis B core antibody (anti-HBc[+]). Subjects positive for hepatitis C (HCV) antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.
13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Note: Subjects may be enrolled with chronic Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to randomization and managed with standard of care treatment) which the investigator deems related to previous anticancer therapy, such as:
    a. Chemotherapy-induced neuropathy
    b. Fatigue
    c. Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:
        - Hypothyroidism/ hyperthyroidism
        - Type I diabetes
        - Hyperglycemia
        - Adrenal insufficiency
        - Adrenalitis
        - Skin hypopigmentation (vitiligo)
14. Is pregnant, breastfeeding, or planning to become pregnant.
15. Otherwise considered inappropriate for the study by the investigator.
16. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg. pulmonary emboli within three months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc.).
17. Any autoimmune, connective tissue or inflammatory disorders (eg, Rheumatoid arthritis, Sjögren's, sarcoidosis etc.) where there is documented, or a suspicion of pulmonary involvement at the time of screening. Full details of the disorder should be recorded in the eCRF for patients who are included in the study.

18. Prior complete pneumonectomy.
19. Had prior treatment with any agent, including an ADC, containing a chemotherapeutic agent targeting topoisomerase I.

5.3. Screening Failures, Re-screening, and Subject Replacement

For subjects who do not meet the criteria for participation in the study, the reason for screening failure must be recorded in the Screening Log.

Subjects who have dropped out will not be replaced.

Re-screening is permitted one time for any subject who failed to meet reversible or transient eligibility criteria upon initial screening. The screening period for subjects who are re-screened is 28 d. The subject identification number must remain the same at the time of re-screening.

6. STUDY TREATMENT(S)

See Table 1.1 for treatment sequence.

6.1. Study Drug(s) Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of trastuzumab deruxtecan for the 2 study arms: 5.4 mg/kg and 6.4 mg/kg.

Table 6.1: Study Drug Dosing Information

Study Drug Name	Trastuzumab Deruxtecan
Dosage Formulation	Trastuzumab deruxtecan for injection 100 mg will be provided as a sterile lyophilized powder containing 100 mg of Trastuzumab deruxtecan in a glass vial (Lyo-DP). Each glass vial should be reconstituted with 5 mL water for injection to a concentration of 20 mg/mL (ie, 100 mg/5 mL).
Dosage Level(s)	5.4 mg/kg 6.4 mg/kg
Route of Administration	Trastuzumab deruxtecan will be administered with 5% dextrose as an IV infusion.
Dosing [Instructions/Regimen]	Each vial is designed for single use only and is not to be used to treat more than one subject. Refer to Pharmacy Instructions.
Duration	The study drug will be administered as an IV infusion over 90 min (± 10 min) Q3W ± 2 days.
Packaging	Trastuzumab deruxtecan for injection 100 mg will be labeled in compliance with regulatory requirements and packaged.
Labeling	The packaging will clearly display the name of the study drug, the lot number, storage condition, and other required information in accordance with local regulations.

min = minutes; PO = oral

Trastuzumab deruxtecan will be supplied to the clinical site by Daiichi Sankyo Inc. (DSI), unless this is prohibited by country or institutional regulations.

Refer to Table 6.1 above for description on administration.

6.2. Preparation, Handling, Storage, and Accountability for Study Drug(s)

Preparation, Handling, and Disposal

The study drug for IV infusion is prepared by dilution of the required volume of the study drug calculated based on the subject's body weight, by the study site pharmacist. Prepared study drug solutions should be used as directed in the pharmacy instructions provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site.

The preparation of study drug will be conducted in accordance with the Pharmacy Manual provided by the Sponsor.

Administration

The study drug will be administered as an IV infusion 90 min (± 10 min) Q3W ± 2 d. If there is no infusion-related reaction (IRR), after the initial dose, the subsequent doses of trastuzumab deruxtecan will be infused over 30 ± 10 min. The subject's weight (at screening or Cycle 1 Day 1 before infusion) will be used to calculate the initial dose. If a subject experiences IRR, follow management guidelines for adverse events in Table 6.6 of this document.

If during the course of treatment, the subject's weight changes by ≥10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of study drug.

Storage

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

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

If storage conditions are not maintained per specified requirements, the Sponsor or CRO should be contacted.

See pharmacy instructions for storage conditions of the infusion solution.

Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, drug expiration date, and acknowledge receipt in interactive response technology (IRT). In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for study drug (trastuzumab deruxtecan). The record must be kept current and should contain the following:

- Dates and quantities of drug received,
- Subject Identification (SID) and/or initials or supply number (as applicable),
- The date and quantity of study drug dispensed and remaining (if from individual subject drug units),
- The initials or seal of the dispenser.

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

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 SOPs and it is assured that the sponsor will receive copies of the certificate of destruction which is traceable to the study drug.

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

6.3. Measure to Minimize Bias: Randomization and Blinding

Method of Treatment Allocation

Once all screening procedures have been completed and study eligibility has been confirmed, subjects will be enrolled in the study and centrally randomized in a 2:1 ratio to receive trastuzumab deruxtecan 5.4 mg/kg or 6.4 mg/kg, respectively. Randomization will be stratified by subjects who (i) received prior anti-PD-1 and/or anti-PD-L1 treatment and (ii) those who received neither. The randomization schedule will be developed by a third-party vendor.

After randomization, the first dose of study treatment should occur as soon as possible and no more than 7 days after the randomization date.

Blinding

The treatment assignment will remain blinded to study subjects, Investigators, study site personnel (except the unblinded pharmacist and other unblinded staff members as deemed necessary for site operations to maintain the blind), central imaging readers and the ILD Adjudication Committee. The Sponsor and the CRO are not blinded to the treatment assignment of subjects.

The randomization schedule will be kept securely.

6.4. Treatment Compliance

Trastuzumab deruxtecan 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 the medical record by clinical study personnel. These data will be recorded in the electronic case report form (eCRF).

6.5. Guidelines for Dose Modification

The investigator will evaluate which toxicities are attributed to the study drug and adjust the dose of the drug as recommended below for study drug. All dose modifications should be based on the worst preceding toxicity (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in table below, which is applicable only to TEAEs that are assessed as related to use of trastuzumab deruxtecan by the investigator(s). For non drug-related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

If there is no toxicity, dose and schedule should be maintained.

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. More than 2 dose reductions are not allowed and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs. The adjustments for reduced dosing of trastuzumab deruxtecan depending on the initial starting dose are shown in Table 6.2.

Table 6.2: Sample Dose Reduction Levels of Trastuzumab Deruxtecan

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

Every effort should be made to limit study drug delay, however, in circumstances of adverse event management or medical intervention, the study drug can be held up to 18 weeks (126 days) from the last trastuzumab deruxtecan dose. During this time, scheduled CT/MRI scans should continue as per protocol, and subjects should fulfil all of the following criteria:

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

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

Treatment cycles for a subject for whom trastuzumab deruxtecan dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last trastuzumab deruxtecan dose. 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 10.6 for additional information on dose modification.

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

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 subject is discontinued at EOT.

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

6.5.1. Dose Modifications

6.5.1.1. Cardiac Toxicities

Table 6.3: Management Guidelines for Cardiac Toxicities

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Cardiac Toxicities	
Symptomatic CHF	Discontinue subject from study drug
Decrease in LVEF 10 to 20% (absolute value), but LVEF > 45%	Continue treatment with study drug
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with study drug Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤ 45% and decrease is 10-20% (absolute value) from baseline	Interrupt study drug dosing Repeat LVEF assessment within 3 weeks If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study drug If LVEF recovers to within 10% from baseline, resume treatment with study drug
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt study drug dosing Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study drug
ECG QT prolonged	
Grade 3 (average QTc>500 ms or >60 ms change from baseline)	Delay dose until resolved to ≤ Grade 1 (QTc ≤ 480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. Then if attributed to study drug, reduce by one dose level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study drug

AMI = acute myocardial infarction; CHF = congestive heart failure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; NCI = National Cancer Institute; QTc = corrected QT interval; ULN = upper limit of normal

6.5.1.2. Hematologic Toxicity

Table 6.4: Management Guidelines for Hematologic Toxicities

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
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 by one dose level
Febrile Neutropenia (absolute neutrophil count < 1 × 10^9/L, fever > 38.3°C or a sustained temperature of ≥ 38°C for more than one h)	Delay dose until resolved, Reduce by one dose level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (< 0.2 × 10^9/L)	Delay dose until resolved to ≤ Grade 2: If resolved in ≤ 14 d from day of onset, maintain dose If resolved in > 14 d from day of onset, reduce dose one level
Anaemia	
Grade 3 (Hemoglobin <8.0 g/dL); transfusion indicated	Transfuse. Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Hemoglobin <8.0 g/dL) Life-threatening consequences; urgent intervention indicated	Transfuse. Delay dose until resolved to ≤ Grade 2, then reduce dose one level
Platelet Count Decreased	
Grade 3 (<50 to 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose one level
Grade 4 (< 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose one level

CTCAE = Common Terminology Criteria for Adverse Events

6.5.1.3. Non-Hematologic/non-cardiac Toxicity

6.5.1.3.1. Hepatic Toxicity

Dose and schedule modifications for hepatic toxicities in subjects with normal hepatic function and mild/moderate hepatic impairment at baseline (ie, the last measurement prior to study drug administration on Cycle 1 Day 1) should be followed as outlined in Table 6.5.

Table 6.5: Management Guidelines for Hepatic Toxicities

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) with Simultaneous Total Bilirubin (TBL)	
AST/ALT ≥3.0 × ULN with simultaneous TBL ≥2.0 × ULN	Delay study medication until drug-induced liver injury (DILI) can be ruled out. If DILI is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If DILI cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
AST or ALT	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal). In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 × ULN	Repeat testing within 3 d. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, then: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 3: (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 x baseline if baseline was abnormal). In subjects with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 d. Delay dose until resolved to ≤ baseline level, then: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4 (>20.0 x ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Total Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
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 d. Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, reduce dose 1 level If resolved in > 7 d from day of onset, discontinue trastuzumab deruxtecan If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 d. Delay dose until resolved to < Grade 2: If resolved in ≤ 7 d from day of onset, reduce dose 1 level If resolved in > 7 d from day of onset, discontinue trastuzumab deruxtecan
Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
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.

CTCAE = Common Terminology Criteria for Adverse Events; d = days; SAE = serious adverse event; ULN = upper limit of normal

6.5.1.4. Other Non-Hematologic/Cardiac Toxicity

Table 6.6: Management Guidelines for Other Non-Hematologic Toxicity

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Infusion-Related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion-related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 h)	Administration of study drug should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	Administration of study drug should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc., should be administered.
Pulmonary Toxicity	
	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 AEs" in the dose modification section of the study protocol. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluation. Evaluations should include: • High resolution CT • Pulmonologist consultation (Infectious Disease consultation as clinically indicated) • Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2) • Clinical laboratory tests – Arterial blood gases if clinically indicated – Blood culture, blood cell count, differential white blood cell count, C-reactive protein • One blood sample collection for PK analyses as soon as ILD/pneumonitis is suspected, if feasible.

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
	Other tests could be considered, as needed (eg, COVID-19 test). If the AE is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of trastuzumab deruxtecan must be interrupted for any ILD/pneumonitis events regardless of grade. • Monitor and closely follow-up in 2 to 7 d for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines. * For Grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤ 28 days from day of onset, maintain dose • If resolved in > 28 days from day of onset, reduce dose 1 level However, if the event grade 1 ILD/pneumonitis has not resolved within 18 weeks (126 days) from the last infusion, the study drug should be discontinued. * If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given
Grade 2	Permanently discontinue subject from study treatment. • Promptly start and treat with systemic steroids (eg, at least 1mg/kg/day prednisone or equivalent) for at least 14 d then followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (IV) (eg, methylprednisolone). Re-consider additional workup for alternative etiologies as described above. Escalate care as clinically indicated.

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Grades 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 d), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 d followed by a gradual taper over at least 4 weeks • Re-image as clinically indicated. • If still no improvement within 3 to 5 d, re-consider additional workup for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Blood creatinine increased	
Grade 3 (> 3.0 to 6.0 × ULN)	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose one level
Grade 4 (> 6.0 × ULN)	Discontinue subject from study drug
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose one level
Diarrhoea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤ 3 d from day of onset, maintain dose If resolved in > 3 d from day of onset, reduce dose one level
Grade 4	Discontinue subject from study drug
Other Laboratory AEs	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other Non-Laboratory AEs	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

AEs = adverse events; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; d = days; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; SAE = serious adverse event; ULN = upper limit of normal

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

6.6. Prior and Concomitant Medications

Medications used from the time the subject signs the ICF for study participation to the 40-D FUP (+7 d) visit after the last administration of trastuzumab deruxtecan will be recorded. Prophylactic treatment for the study treatment and all concomitant medications will be recorded in the eCRF.

All therapies received by subjects within 28 days prior to randomization will be recorded. Concomitant therapies include all prescription, over-the-counter, and herbal remedies.

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.

1. Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and HRT] is acceptable).
2. Other investigational therapeutic agents.
3. 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).
4. Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs (topical steroids, inhaled steroids, physiologic dose of steroids to prevent or treat adrenal insufficiency, or intra articular steroid injections are permitted in this study).
    - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
5. Radiotherapy to the thorax.
6. Chloroquine or hydroxychloroquine
    - If treatment with chloroquine or hydroxychloroquine is required, trastuzumab deruxtecan must be interrupted and a washout period of >14 days is required before restarting trastuzumab deruxtecan.
7. Receipt of live, attenuated vaccine (mRNA and replication deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first exposure to study intervention. Note: Participants, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of study intervention.

Permitted products:

1. Hematopoietic growth factor may be used for prophylaxis or treatment based on the clinical judgment of the investigator.
2. Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
3. Prophylactic or supportive treatment of study drug-induced AE will be otherwise permitted as per investigator's discretion and the institutional guidelines.
4. Trastuzumab deruxtecan is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of trastuzumab deruxtecan, subjects should be premedicated with a combination regimen of two or three medicinal products (eg, dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Restricted products

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

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of trastuzumab deruxtecan treatment administration must be recorded. Reasons for treatment discontinuation include:

- Death
- Adverse Event
- Progressive Disease
- Clinical Progression
- Withdrawal by Subject (**to discontinue study drug**) NOTE: in this section this is only withdrawal for treatment with study drug and is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including survival follow-up).
- Physician Decision
- Lost to Follow-up (see Section 7.3 for details on when a subject is considered Lost to Follow-up)
- Pregnancy
- Protocol Deviation
- Study Termination by Sponsor
- Other

If there is evidence the subject is receiving benefit from treatment even though the subject has met criterion for discontinuation, the subject may remain on study treatment after discussion with approval from the Sponsor Medical Monitor or designee.

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

The Investigator must discuss with the subject that their decision to permanently discontinue the study drug means the subject still agrees to continue into the Follow-up Period for onsite or modified follow-up visits. Subjects will be followed for disease progression, if applicable, and survival at regularly scheduled intervals (see Table 1.1).

Procedures for Discontinuation from Study Drug

The subject should be instructed to contact the Investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF;
- Due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized;
- An end of treatment (EOT) evaluation should be performed as described in the SoE (Table 1.1);
- A safety follow-up evaluation should be performed approximately 40 days after the last dose of study drug as described in the SoE (Table 1.1) (If EOT is > 40 days after last treatment, then the EOT assessments can also function as the 40-Day Follow-up visit);
- If subject has not discontinued for "Progressive Disease," continue disease progression assessments until progression or start of new therapy, if applicable, and survival as described in the SoE (Table 1.1);
- Long-term follow-up evaluations will be performed to assess survival as described in the SoE (Table 1.1).

The Investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose. All procedures and tumor assessments specified for the EOT visit will be conducted. See Table 1.1 for specific EOT procedures.

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

Modified Follow-up Options

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

- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at EOS)
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records)

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

7.2. Subject Withdrawal/Discontinuation from the Study

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

- Death
- Withdrawal by Subject (**from the study**) NOTE: this indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival

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

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

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

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

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

Withdrawal Procedures

If a subject is withdrawn from both the interventional and follow-up portions of the study:

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

See SoE (Table 1.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

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

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

8. STUDY PROCEDURES

See SoE, Table 1.1 for study procedures during the Screening period, Treatment, EOT, and Follow-up study procedures.

8.1. Eligibility Assessment

Review the subject's demographics, medical and target disease history, vitals, and results of tests (eg, physical examination, ECHO/multi-gated acquisition [MUGA], ECG, ECOG PS, ophthalmologic assessments, laboratory assessments, CT/MRI of the brain, tumor assessment and pulmonary imaging) and compare against the eligibility criteria (Section 5.1 and Section 5.2). See Section 5.3 for information on re-screening. For screening procedures, see SoE, Table 1.1.

Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population. See Section 10.1.2 for additional details.

Tumor Tissue Specimen

For the 2 study arms, archival tumor sample or fresh biopsy sample must be obtained. It is not required to perform a pre-treatment biopsy if the subject already has an adequate archived tumor tissue sample that is available to be submitted. Resection and core needle biopsy are acceptable. Other tissue samples, eg, fine needle aspirates or cell block are not acceptable. For detailed instruction on tissue submission, please refer to the laboratory manual.

Assessment of HER2 Mutation Status

Archival tumor sample and fresh biopsy sample will be analyzed for HER2 mutant status as well as exploratory biomarkers.

General Medical History and Baseline Conditions

The subject's medical history will be obtained by the Investigator or a qualified designee and will include his/her NSCLC history (eg, prior biomarker history) and smoking history.

Untoward medical occurrences (including clinically relevant laboratory values that are not symptoms of NSCLC vital signs that are out of range) that were diagnosed or known to exist prior to the first dose of study medication/consent date will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF. Record the start date of any medical occurrence that started after the ICF was signed and is ongoing at the time of the first dose of trastuzumab deruxtecan on the General Medical History and Baseline Conditions eCRF.

Demographics

Review the subject's demographics against the eligibility criteria.

Human Immunodeficiency Virus (HIV) Antibody Test

Perform an HIV antibody test as required by local regulations or independent IRBs/ECs.

Hepatitis Screening

Perform hepatitis B and C screening (HBsAg, anti-HBc, anti-hepatitis B surface antigen [anti-HBS] and anti-HCV antibody).

8.2. Randomization in a 2:1 Ratio

After all screening procedures are performed, results of screening tests are available (ie, between the Screening visit and the Cycle 1 Day 1 visit), and subjects are confirmed to continue to meet all eligibility criteria, eligible subjects will be randomized to receive trastuzumab deruxtecan in 1 of the 2 following treatment groups:

- 5.4 mg/kg Q3W (N = 100)
- 6.4 mg/kg Q3W (N = 50)

The subject will be randomized in IRT to one of the dose levels listed above and an unblinded pharmacist will prepare the assigned dose. Randomization will be stratified by subjects who (i) received prior anti-PD-1 and/or anti-PD-L1 treatment and (ii) those who received neither.

If a subject does not meet the eligibility criteria on the scheduled day of randomization, Investigators must discuss with the Sponsor (Clinical Leader/Scientist).

Subjects can receive trastuzumab deruxtecan on the same day as randomization.

8.3. Efficacy Assessments

8.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is confirmed ORR, defined as the sum of CR and PR rates, assessed by BICR based on RECIST version 1.1. Efficacy assessments will be based on tumor assessments to be performed at screening and Q6W until PD or start of new therapy regardless of the posttreatment Follow-up period.

8.3.2. Secondary Efficacy Endpoints

Tumor assessments, based on sites of disease identified at Screening and any additional newly suspected sites of PD, will be conducted Q6W (±7 d) from Cycle 1 Day 1, independent of treatment cycle. A CT and/or MRI (spiral CT or MRI with ≤ 5 mm cuts) of chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. The same assessment modality should be used throughout the study for all assessments for each subject unless prior approval is obtained from the Sponsor or its designee. Unscheduled tumor assessments may be performed if progression is suspected.

A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.

Bone scan (bone scintigraphy) or 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT is required at baseline and if bone metastases are present within 28 days before Cycle 1 Day 1, and Q12W (±7 d) from Cycle 1 Day 1. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of response for subjects who have bone metastases.

Other secondary efficacy endpoints are DCR (the sum of CR, PR, and SD rates), PFS, and OS. These endpoints will be assessed by the investigator and/or BICR review will be based on RECIST version 1.1. (except OS) and include:

- DoR, defined as time from the initial response (CR or PR) until documented tumor progression or death from any cause. DoR is only defined for subjects who achieved confirmed CR or PR. DCR is defined as the proportion of subjects who achieve CR, PR, or SD during study treatment.
- PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, based on BICR and investigator assessment. Detailed censoring rules will be provided in statistical analysis plan (SAP).
- ORR, defined above, based on investigator assessment
- OS, defined as the time from date of randomization until death from any cause (based on records in clinical database and public records where it is allowed by law). Subjects last known to be alive are censored at the date of last contact.

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

8.3.3. Exploratory Efficacy Endpoints (ORR and QoL)

Exploratory efficacy endpoints include:

- Best percent change from baseline in the sum of the diameters for all target lesions based on BICR and investigator assessment
- Explore symptoms functioning and HRQoL with newly recommended NSCLC-SAQ
- To explore the impact of treatment and disease state on health utility using the EQ-5D-5L
- To assess patient-reported treatment tolerability
- To assess the patient's overall impression of the severity of their cancer symptoms, change in condition since starting the study
- To explore the impact of treatment and disease on health care resource use

Radiographic Tumor Assessments

Radiographic tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan at baseline (screening) for all subjects.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons, follow the local label/package insert/SMPC or institutional guidelines for allergic reactions to contrast agents. Baseline tumor assessment should be performed within 28 days of expected Cycle 1 Day 1 (tumor assessment performed for the assessment of disease progression on the prior therapy will be acceptable as baseline if performed within 28 days of Cycle 1 Day 1). A complete set of the scans is required in this study. Perform radiographic tumor assessments using spiral CT or MRI with ≤5 mm cuts unless another modality of disease assessment is necessary for the lesions.

Antitumor activity will be assessed at baseline (screening), at Q6W (±7 d) from Cycle 1 Day 1 independent of treatment cycle until documented PD or start of new therapy, or death, or loss to follow-up, or withdrawal of consent (Table 1.1). Subjects who discontinue study treatment for other reasons than PD will continue to undergo tumor assessments Q6W during the Follow-up period until documented PD or start of new therapy. Imaging timing should follow calendar days. Imaging time points will be projected from Cycle 1 Day 1 date and should not be adjusted for delays in cycle starts. In addition, radiographic tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 6 weeks). Tumor measurements are performed as per RECIST version 1.1 criteria (Section 10.4). See Table 1.1.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Bone scan (bone scintigraphy) or 18F-FDG-PET/CT is required within 28 days before Cycle 1 Day 1 and if bone metastases are present at baseline, Q12W (±7 d) from Cycle 1 Day 1. Otherwise bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of response for subjects who have bone metastases.

When tumor assessments at a visit are performed over multiple days, the date of response (CR, PR, SD, or not evaluable [NE]) should be recorded as the date of the last radiographic evaluation included in the series for that assessment and the date of PD should be recorded as the date of the earliest date of the scan which has documented progression if scans span multiple days.

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

Assessment of response will be made using RECIST version 1.1.

Response Assessment

Assess the subject based upon the local laboratory results using the Response Criteria[22] (Section 10.4).

Subsequent Anticancer Treatments

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

Disease Progression

The date of disease progression on subsequent therapies will be recorded in the eCRF regardless of subsequent anticancer treatments.

Survival Follow-up

All subjects should be followed for survival at least every 3 months from EOT. Survival monitoring will continue until the end of the study.

8.4. Safety Assessments

Safety endpoints will include:

- AEs including TEAEs, SAEs and AESIs will be graded according to the CTCAE Version 5.0.
- Physical examination findings (including ECOG PS), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, and ECHO/MUGA findings.

8.4.1. Adverse Event

Method to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.5. Adverse Events may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue trastuzumab deruxtecan.

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

Time Period for Collecting Adverse Events, including Adverse Events of Special Interest and Serious Adverse Events

All SAEs occurring after the subject signs the ICF and up to 40 (+7) days after the last dose of study medication (ie, the Follow-up Period), whether observed by the Investigator or reported by

the subject, will be recorded on the Adverse Event eCRF. SAEs with an onset or worsening subsequent to the Follow-up Period, if considered related to the study treatment by the Investigator, are also TEAEs. They will also be recorded on the Adverse Event eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

After the 40-day Safety Follow-up Visit, only SAEs considered to be related to study drug by the investigators should be reported.

All non-serious AEs occurring after the subject has taken the first dose of trastuzumab deruxtecan until 40 days after the last dose of trastuzumab deruxtecan will be recorded on the Adverse Event eCRF.

Exacerbation of a pre-existing medical condition and symptom after the first dose of trastuzumab deruxtecan including increase in severity of the symptom will be recorded as an AE on the Adverse Event eCRF, unless it is a condition of NSCLC.

Reporting Procedure for Investigators

All AEs (including AESIs and SAEs) will be reported in the Adverse Event eCRF. All AEs (serious and non-serious) must be reported with the Investigator's assessment of seriousness, severity, and causality to trastuzumab deruxtecan.

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.

Disease-Specific AEs and SAEs

Disease progression/worsening of NSCLC will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as bronchitis, Pneumocystis jirovecci pneumonia, may be recorded as AEs.

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

8.4.1.1. Serious Adverse Events Reporting

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

- SAEs
- All potential ILD/pneumonitis cases should be reported within 24 h; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD is described by the Event Adjudication Site Manual).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) $\geq$ 3 x ULN and an elevated TBL $\geq$ 2 x ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.

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

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

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

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

See Section 8.4.1 for details on the time period for collecting SAEs.

Reporting Requirement to Sites and Regulatory Authorities

Daiichi Sankyo Inc., and/or CRO will inform Investigators and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of trastuzumab deruxtecan, as appropriate per institutional and/or local reporting requirements.

DS and/or CRO will comply with any additional local safety reporting requirements. The Investigator will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB.[11]

Follow-up for AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or

investigations, histopathological examinations, or consultation with other health care professionals.

Urgent safety queries and follow-up information, such as those upgraded to fatal/life-threatening cases, must be followed up and addressed promptly. The investigator will submit any updated SAE data to the safety database within 24 hours of receipt of the information. Other follow-up information and responses to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.4.1.2. Adverse Events of Special Interest (AESIs)

The AESIs include LV dysfunction and ILD/pneumonitis. Additional relevant information regarding the AESIs, ie, LV dysfunction and ILD/pneumonitis regardless of seriousness is to be collected through the targeted questionnaires (TQs) within the clinical study database.

- For broad surveillance of LV dysfunction, relevant AEs under the MedDRA SMQs of Cardiac Failure are included for enhanced data collection; additional data for these AEs are collected via TQs of heart failure.
- For broad surveillance of ILD/pneumonitis, a set of pre-defined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual, is utilized for enhanced data collection.

Left Ventricular (LV) Dysfunction:

Clinical Summary:

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

Management Guidance:

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

Troponin will be measured locally at screening, and as needed based on subject reported cardiac signs or symptoms suggesting CHF, myocardial infarction, or other causes of cardiac myocyte necrosis. If ECG is abnormal, follow institutional guidelines.

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

Interstitial Lung Disease/Pneumonitis:

Clinical Summary:

ILD/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee, available data from recent epidemiology/literature, biological plausibility, and safety

information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.

ILD/pneumonitis Monitoring:

Non-symptomatic grade 1 ILD/pneumonitis has been detected in clinical studies of trastuzumab deruxtecan in metastatic NSCLC during the regularly scheduled chest CT imaging performed Q3W as part of tumor assessment.

Management Guidance:

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

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation (infectious disease consultation as clinically indicated), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2), clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential White Blood Cell count, C-reactive protein), and one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed (eg, COVID-19 test).

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

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

Interstitial Lung Disease Adjudication Committee

An independent ILD AC for the trastuzumab deruxtecan program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth and relevant medical history (eg, smoking, radiation, chronic obstructive pulmonary disease, and other chronic lung conditions), diagnostic evaluation, treatment, and outcome of the event. This data collection will be based on a set of pre-defined list of PTs eligible for adjudication as described in the Event Adjudication Site Manual.

Combined Elevations of Aminotransferases and Bilirubin

Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) ≥3 × ULN and an elevated TBL ≥2 × ULN, regardless if it is due to disease progression per Investigator assessment, that may occur at different time points during the study conduct, should always be reported to the Sponsor.[18] These events must be reported either by eCRF, with the Investigator's assessment of seriousness, severity, causality,

and a detailed narrative. These events should be reported within 24 hours of Investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 8.4.3 in order to determine the nature and severity of the potential liver injury.

8.4.2. Pregnancy

Sponsor must be notified of any female subject who becomes pregnant while receiving or within 7 months of discontinuing the trastuzumab deruxtecan. Similarly, the Sponsor must also be notified if a female partner of a male subject becomes pregnant while receiving or within 4 months of discontinuing trastuzumab deruxtecan.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 h of learning of the pregnancy.

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

Infants born to female subjects or partners of male subjects who were exposed to trastuzumab deruxtecan should have follow-up safety information collected 40 (+7) days after the birth for immediate safety follow-up, focusing especially on any presumable congenital birth defect.

Any presumable congenital birth defects, regardless of the time of the diagnosis, should also be reported to the Sponsor.

Pregnancy Test

For women of childbearing potential (as defined in Section 5.1), document the results of a negative serum or urine pregnancy test. A positive urine pregnancy test must immediately be confirmed using a serum test. Repeat pregnancy test (urine or serum per institutional guidelines) must be performed 72 h before infusion at each cycle and at EOT visit (see SoE, Table 1.1).

8.4.3. Clinical Laboratory Evaluations

The clinical laboratory tests including hematology, blood chemistry, and pregnancy will be performed as per the SoE by the local laboratory (Table 1.1). Coagulation testing and urinalysis

will be performed at screening only. Refer to Section 10.2 for the complete list of laboratory parameters.

All laboratory values must be appraised by the investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, the SAE should be reported in the CRF and other relevant procedures must be followed (See Section 8.4.1.1).

Abnormal laboratory values (CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically relevant. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.4.4. Other Safety

Physical Examinations

Physical examinations should be performed as per the SoE (Table 1.1). A complete physical examination should include a weight measurement and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Vital Signs

Vital signs will be measured and recorded as per the SoE (Table 1.1). They include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, temperature, pulse oximetry, SpO_2, height (obtained once, prior to dosing) and body weight. Blood pressure and pulse rate will be measured after the subject has rested for 5 minutes or more and prior to laboratory draws, if both are done sequentially. The same procedure for measuring the subject's blood pressure and pulse rate should be used throughout the study.

Electrocardiograms

Twelve lead-ECGs will be performed and recorded for every subject (SoE, Table 1.1). The ECG will be measured after the subject has rested in a supine/recumbent position for 5 minutes or more. The baseline ECG must be performed within 14 days prior to randomization. Triplicate ECGs are required at screening or if an abnormality is detected. The three individual ECG tracings should be obtained as closely as possible in succession, approximately 3 minutes apart. ECGs should be performed before PK blood draws. At any visit during which a subject exhibits a heart rate ≤50 bpm or other clinical indications for ECG, the ECG will be repeated. Abnormal, clinically relevant findings occurring postbaseline will be reported as AEs. Regardless of whether the measurement is performed, the date on which the standard ECG parameters were

scheduled to be measured (including RR, PR, QT intervals, and QRS duration and results), will be recorded in the eCRF.

Multi-gated Acquisition Scan or Echocardiogram

MUGA/ECHO must be performed as per the SoE (Table 1.1) and within 28 days of randomization. Subjects must have LVEF ≥50% to be eligible for the study. If the planned date of study drug administration is delayed after examination of ECHO or MUGA, and there are no abnormal findings on the examination, it is up to the Investigator's judgment as to whether ECHO or MUGA need to be repeated.

ECOG Performance Status

Assess and record the subject's ECOG PS (Table 1.1).

Ophthalmologic Assessments

The ophthalmologic assessment must be performed as per the SoE (Table 1.1) and must include a visual acuity testing, slit lamp examination, and fundoscopy. If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether ophthalmologic assessments need to be repeated.

Pulmonary Assessments

Computed tomography or MRI of the chest will be performed per the SoE (Table 1.1). Additionally, SpO2 will be measured as part of Vital Signs as mentioned above.

An ILD AC will review all cases of (potential) ILD on an ongoing basis. Description of the ILD AC is available in Section 8.4.1.2.

Pulmonary Function Test

Pulmonary function will be performed as per the SoE (Table 1.1), and should include basic spirometry with optional additional components as follows:

Required spirometry components	Optional components
Forced vital capacity (FVC) (L)	Peak expiratory flow (PEF)
FVC % predicted	Diffusion capacity of the lungs for carbon monoxide (DLCO)
Forced expiratory volume – 1 second (FEV1) (L)	(Forced expiratory volume – 6 seconds) FEV6
FEV1 % predicted	Total lung capacity (TLC)
FEV1/FVC	

See Table 6.6 for tests required if ILD/pneumonitis is suspected.

8.5. Health Economics and Outcomes Research

Patient-Reported Outcomes

PROs provide an understanding of the impact a treatment has on a subject. The EORTC QLQ-C30 is a validated and reliable self-report measure and has been widely used in assessing quality of life (QoL) in subjects with NSCLC.[7,8,9] The core instrument assesses global health

status/QoL, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms. It consists of 30 questions assessing global health−related QoL, five aspects of subject functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), and six single-items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.

The EQ-5D-(5L) is a generic preference-based HRQoL questionnaire that provides a single index value for health status (see Section 9.5.3) and is used to inform pharmacoeconomic evaluations. The EQ-5D-(5L) consists of two parts; the first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. From these five items, a utility measure is obtained for each subject. The second part, consisting of a visual analog scale, will not be used in this study.

A paper instrument or electronic patient-reported outcome (ePRO) data collection modality may be employed. The PRO questionnaires, translated as required in the local language, will be distributed by the Investigator's staff and completed in their entirety by the subject. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of trastuzumab deruxtecan. Study personnel should review all questionnaires for completeness before the subject leaves the study site. Hard copy originals of the questionnaires must be maintained as part of the subject's medical record at the site for source data verification. These originals should have the subject's initials on each page in compliance with good clinical practices (GCP).

The PRO questionnaires (EORTC QLQ-C30 and EQ-5D-[5L]) will be completed as per the SoE Table 1.1.

Healthcare Resource Utilization

The following variables will be collected and recorded to assess healthcare resource utilization during the Treatment Period:

- Hospitalizations
- Emergency room visits
- Skilled nursing facility care
- Unscheduled clinic visits
- Hospice care
- Concomitant medications and procedures.

8.6. Pharmacokinetic (PK) Assessment

The PK endpoints include serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA 1181a. PK parameters will include AUC, Cmax and Ctrough.

Blood samples for PK analyses will be obtained at the time points shown in Table 8.1. ECGs should be performed before PK blood draws.

Table 8.1: Schedule of PK Sample Collection

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI 5 h after the start of drug administration (±2 h)
Cycle 1	Day 8	7 d after the start of drug administration (±1 d)
Cycle 1	Day 15	14 d after the start of drug administration (±1 d)
Cycle 1	Day 22	If treatment of next cycle is delayed by 3 days or more, or subject is discontinued, collect PK blood sample on C1, D22 (±2 days).
Cycle 2	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI
Cycle 3	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI
Cycle 4	Day 1	BI (– 8 to 0 h)
Cycle 6	Day 1	BI (– 8 to 0 h)

BI = before infusion; C = cycle; d = day; EOI = end of infusion; h = hour; min = minutes
Note: Obtain one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible

In case of chloroquine or hydroxychloroquine administration, additional PK samples should be collected at the following time points (Table 8.2).

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 h)

BI = before infusion; EOT = end of treatment; h = hours

At each time point, blood will be collected for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a PK analysis. The actual time of study drug administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF, including those samples collected in case of chloroquine or hydroxychloroquine administration.

Details for blood sampling, processing, storage, and shipment for PK samples will be provided in the study laboratory manual. Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a will be measured using validated assays at the bioanalytical laboratory.

8.7. Pharmacodynamic Assessment(s)

8.7.1. Pharmacodynamic Biomarker Analysis

Biomarker analyses will be used to investigate the effect of trastuzumab deruxtecan at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. Blood plasma samples will be collected for circulating tumor DNA analysis BI on Day 1 of Cycles 1 to 4 and then starting from Cycle 7, every 4 cycles, and at EOT. See the SoE (Table 1.1).

8.7.2. Pharmacogenomic (Inherited Genetic) Analysis (Optional)

A single blood sample for pharmacogenomic analysis will be collected from each subject who provides consent, where allowed per local regulations. This optional pharmacogenomic blood sample will be scheduled for Cycle 1 Day 1 predose. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Study Laboratory Manual.

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 physiological pathways or safety related to trastuzumab deruxtecan, such as ILD.

Genetic analyses will not be performed on blood samples collected for PK or safety assessments. Subject confidentiality will be maintained. If subjects agree, the remaining DNA will be stored, as outlined in Section 8.7.3, for performing future pharmacogenomic analysis. Otherwise, all remaining DNA samples will be destroyed.

8.7.3. Storage and Disposal of Specimens for Genomic or Genetic Banking and Analysis

Samples will be retained for a maximum of 15 years after the finalization of the clinical study report for this study.

These specimens will be kept for pharmacogenomic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic) to trastuzumab deruxtecan, or in case serious adverse drug reactions are noted in a clinical study and pharmacogenomic analysis is to be conducted for investigation into the cause.

During the period of storage, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if the analysis has been completed before the subject withdraws consent.

Disclosure of the Results of Future Pharmacogenetic Analysis

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

8.7.4. Immunogenicity

Blood samples for ADA analyses will be collected prior to dosing in Cycles 1, 2, 4, and thereafter every 4 cycles, and 40-D FUP (+7 d) visit.

Immunogenicity will be assessed through characterization of incidence and titer of ADA. Details for ADA serum sampling, processing, storage, and shipment for immunogenicity samples will be provided in the Study Laboratory Manual. Serum concentrations of trastuzumab deruxtecan and/or total anti-HER2 antibody may be measured using the same immunogenicity samples as used for ADA assessment.

The ADA testing will be performed using validated ADA assay following tiered assay steps including screening, confirmatory as well as titer determination. Only samples confirmed positive for ADA may be analyzed for the presence of neutralizing ADA.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

The DCO date for the primary analysis will occur when all subjects have completed at least 9 months of follow-up after the last subject has been randomized or have discontinued treatment. All data collected up to the DCO date will be included in the primary analyses. Data from all sites will be pooled for analyses.

The final analysis of the study will occur after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first). Data collected beyond the primary analysis DCO will be presented as appropriate in a clinical study report (CSR) addendum if deemed necessary.

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

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

9.2. Statistical Hypothesis

The primary objective of this study is to evaluate confirmed ORR of trastuzumab deruxtecan in HER2-mutated NSCLC subjects treated at 5.4 and 6.4 mg/kg doses. For each single arm, the evaluation of the study results will be based primarily on point estimation and 95% CI. For both IAs described in Section 9.6, no statistical hypothesis testing is planned. However, for the primary analysis referenced in Section 9.1, statistical hypothesis against the null of 26.4% will be performed by comparing the lower bound of the 95% Clopper-Pearson CI of confirmed ORR with the benchmark value of 26.4%.

9.3. Sample Size Determination

The sample size in this study is determined on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeds and excludes the ORR benchmark of 26.4%.

Consistent with the primary objective, for each of the two single arm treatment groups, the probability that the resulting Clopper-Pearson 95% CI will exclude the ORR benchmark of 26.4% will be evaluated. This benchmark is the upper bound of the 95% CI (ORR 22.9; 95% CI: 19.7 to 26.4) in ramucirumab plus docetaxel arm in the REVEL trial that was investigated as a second-line treatment for patients with stage IV NSCLC after platinum-based therapy.[28]

One hundred and fifty subjects will be randomized in a 2:1 ratio to receive trastuzumab deruxtecan at the 5.4 mg/kg or 6.4 mg/kg dose level, respectively.

With 100 subjects to receive trastuzumab deruxtecan at 5.4 mg/kg, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 40%. Assuming 50 subjects

will be randomized in the 6.4 mg/kg concurrent arm, the probability to exclude the ORR benchmark of 26.4% is at least 80% when the true ORR is 45%. Details of the probability evaluation under different true ORR values are shown in Table 9.1.

The resulting 95% CIs using exact (Clopper-Pearson) method under several scenarios of observed ORR are provided in Table 9.2, indicating that with 50 subjects and 42% observed ORR, the 95% CI excludes the benchmark of 26.4% ORR. With 100 subjects and 36% observed ORR, the 95% CI excludes the benchmark of 26.4% ORR.

With 100 subjects at 5.4 mg/kg and 50 subjects at the 6.4 mg/kg dose level, if the higher dose true ORR is at least 12.3% higher than that of the lower dose, the probability of observing the ORR difference between dose levels being 5% or more is at least 80%.

Assuming 100 subjects at 5.4 mg/kg and 50 subjects at the 6.4 mg/kg dose level, the 95% CI of the ORR difference between dose levels is expected to extend approximately 16% from the observed difference in proportions to either confidence limit.

Table 9.1: The Probability That the Resulting Clopper-Pearson 95% Confidence Interval (CI) Will Exclude the Benchmark of 26.4% ORR

True ORR (%)	Probability evaluated for N=100 (%)	Probability evaluated for N=50 (%)
36	53.8	32.6
37	61.9	38.1
38	69.4	43.8
39	76.2	49.6
40	82.1	55.4
45	97.3	80.3
50	99.8	94.1
55	99.9	98.8

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

Table 9.2: Confidence Interval with 50 and 100 Subjects Under Scenarios of Observed ORR

N=100		N=50	
Observed ORR (%)	95% CI using exact method (%)	Observed ORR (%)	95% CI using exact method (%)
35	(25.7, 45.2)	36	(22.9, 50.8)
36	(26.6, 46.2)	42	(28.2, 56.8)
45	(35.0, 55.3)	44	(30.0, 58.7)
50	(39.8, 60.2)	54	(39.3, 68.2)
55	(44.7, 64.9)	58	(43.2, 71.8)
60	(49.7, 69.7)	60	(45.2, 73.6)
65	(54.8, 74.3)	64	(49.2, 77.1)

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

9.4. Population for Analysis Sets

Analysis Sets

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

9.5. Statistical Analysis

The SAP will be developed and finalized before database lock and will describe the details of the planned statistical analyses. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Efficacy Analyses

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

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

9.5.1.1. Primary Efficacy Analyses

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

The primary analysis of ORR will be performed for FAS. The ORR for each dose level will be estimated along with the two-sided Clopper-Pearson 95% CIs. In addition, if the lower limit of the 95% CI in a dose level is greater than 26.4%, the ORR in the dose level will be concluded to have exceeded 26.4%.

In addition, the ORR difference between dose levels will be estimated using a stratified analysis, where the strata-adjusted ORR difference is computed, and each stratum is weighted according to the inverse of variance. The 95% confidence interval will also be computed.

9.5.1.2. Secondary Efficacy Analyses

The secondary endpoint of confirmed ORR by investigator assessment based on RECIST version 1.1 will be analyzed using the same method as for the primary efficacy endpoint. DoR, defined as time from the initial response (CR or PR), until documented tumor progression or death from any cause, will be summarized using Kaplan-Meier approach for each dose level.

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

PFS, defined as the time from date of randomization until first objective radiographic tumor progression or death from any cause, will be analyzed using the Kaplan-Meier approach. Likewise, OS, defined as the time from date of randomization until death from any cause, will also be similarly analyzed. The censoring rules for PFS and OS will be detailed in the SAP.

9.5.1.3. Exploratory Analyses

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

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

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

- Region: US, European Union (EU), Asia-Pacific
- Prior therapy: subjects who (i) received prior anti-PD-1 and/or anti-PD-L1 treatment and (ii) those who received neither.

9.5.1.4. Multiplicity Adjustment

The evaluation of the study results at DCOs for both IAs and primary analysis will be based primarily on point estimation and 95% CI. For both IAs, there is no plan to stop the trial in response to the efficacy results. Hence, multiplicity adjustment is not applicable.

9.5.2. Safety Analyses

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

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

Adverse Events

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug.

Adverse Events will be coded using MedDRA version 24.0 and graded using CTCAE version 5.0. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC), preferred term (PT), relationship to the study drug, the worst CTCAE grade and dose level. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by dose level, as well as TEAEs leading to discontinuation of the study treatment.

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

Clinical Laboratory Evaluation

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

Abnormal clinical laboratory results will be graded according to 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 posttreatment value according to CTCAE grade, will be provided for clinical laboratory tests.

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

ECG

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms). Maximum change from baseline will be tabulated ($\leq$30 ms, >30 to $\leq$60 ms, >60 ms). The QT intervals will be corrected for heart rate by Fridericia's formula (QTcF).

A listing of ECG data will be provided.

Vital Signs

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

Other

Concomitant medications will be coded using the World Health Organization drug dictionary (WHODD) (June 2007). Number and percentage of subjects taking concomitant medications will be summarized. Concomitant medications will also be listed.

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

9.5.3. HEOR Analysis

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

- A cancer specific PRO (EORTC QLQ-C30) along with tumor-specific modules (EORTC QLQ-LC13 & NSCLC-SAQ) to assess patient-reported tolerability and clinical benefit.
- A generic health status questionnaire, the EQ-5D-5L module including EQ-VAS to assess patient-reported health utility for health economic evaluations.
- Three global anchors (PGIS, PGIC, PGI-TT) included to estimate meaningful change thresholds for EORTC QLQ-C30 / LC13

Descriptive statistics will be calculated to summarize change from the baseline in symptoms, physical functioning and general HRQoL scales in the C30 and LC13 study questionnaires at each scheduled assessment time point by dose level. The number of subjects completing each patient questionnaire and the number of missing or incomplete assessments will be provided for each scheduled assessment time point by dose level.

9.5.4. Other Analyses

The following other analyses are planned in this study.

Pharmacokinetics

Pharmacokinetics (PK) analyses will be performed using the PK Analysis Set. Serum concentrations for trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a will be listed and summarized using descriptive statistics at each time point by dose level. PK parameters (Cmax, Tmax, AUC (AUClast [area under the concentration time-curve from time 0 to the last measurable concentration] and AUC0-21d [area under the concentration time-curve from time 0 to 21 d]) of trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a may also be determined using non-compartmental analysis after the first dose and summarized using descriptive statistics by dose level.

Population PK analysis may also be conducted by combining data from this study with other clinical studies of trastuzumab deruxtecan. In addition, ER analysis for key efficacy and safety endpoints may be conducted. The results of population PK and ER analyses will be provided in a separate report outside the CSR for this study.

Immunogenicity Analyses

Immunogenicity will be assessed through characterization of incidence and titer of the ADA. The number and percentage of subjects will be reported for the presence or absence of

development of ADA after the start of administration of study treatment, defining subjects who are negative for ADA at all-time points as negative and subjects who are positive for ADA at least one time point post-study drug treatment as positive. The ADA titer values will be summarized by time point and dose level 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 posttreatment, or who are ADA positive at baseline and posttreatment, but have an increase in ADA titer from baseline to posttreatment, 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 may also be determined.

Biomarker

Biomarker analysis will be performed using the FAS.

Descriptive statistics including mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum will be computed by evaluation time for biomarkers listed in Section 8.7. If possible, change from baseline and percent change from baseline will also be summarized. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

Statistical Analysis - Assessment of the Impact of SARS-CoV-2 Infection

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

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

9.6. Interim Analyses

Two IAs are planned for this study. The first IA will be performed when a total of at least 75 subjects have been randomized to receive a dose of trastuzumab deruxtecan (5.4 mg/kg or 6.4 mg/kg) and have had at least 4.5 months of follow-up before the DCO or have discontinued treatment. The DCO of the second IA will be approximately 6 months after the DCO of the first IA. If the planned DCO of the second IA is anticipated to fall within 3 months of the primary analysis DCO, when the data are sufficiently mature, then the second IA may not be performed. The main purpose of these IAs is to evaluate the safety and efficacy of each dose without the intent to modify the study design and study conduct. There is no plan for stopping the trial for efficacy. The evaluation of the study results will be based primarily on point estimation and 95% CI. Hence, futility and efficacy stopping boundaries are not defined for both IAs. A PK assessment will also be performed. Additionally, exposure-response analyses for key efficacy and safety endpoints may be performed at the time of these IAs.

For each dose, the primary efficacy endpoint of confirmed ORR by BICR will be summarized using descriptive statistics including 2-sided exact 95% CI (Clopper-Pearson). Other efficacy endpoints based on response rates will be summarized by dose level using the same methodology as the primary efficacy endpoint. For time-to-event endpoints such as DoR, Kaplan-Meier

estimates of median and their corresponding 95% CIs using Brookmeyer and Crowley method will be provided. Safety data related to AEs will be summarized using descriptive statistics.

For the first IA, in addition to analyzing and presenting the FAS for efficacy and SAS for safety with respect to both DCO dates, data from the subset of subjects who were randomized at least 4.5 months before the DCO will also be analyzed and presented to allow for a more robust assessment of the efficacy and safety data from this pre-defined subset.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

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

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB or EC.

The Investigator should notify the IRB or EC of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (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 (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 (27 Mar 1997) and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 (25 Nov 2014);
- Other applicable local regulations.

In addition, the Investigator will inform the Sponsor in writing within 24 h of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

Supply of New Information Affecting the Conduct of the Study

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

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

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

10.1.2. Informed Consent

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

The subject's written ICF 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 ICF should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP Guideline, Section 10.1.2, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

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

Suggested model text for the ICF for the study and any applicable subparts (PK, pharmacodynamic, etc) is 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).

10.1.3. Subject Confidentiality

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

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

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

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

10.1.4. Data Integrity and Quality Assurance

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

Monitoring and Inspections

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

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

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

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

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

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

Data Collection

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

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. The information should be entered into the eCRF within 5 days of the visit and should be completed, reviewed, and signed off by the investigator within 2 weeks of the last subject visit. Query resolution should be completed within 48 h.

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

Data Management

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

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

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

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

All concomitant medications and prior cancer therapies will be coded using the WHODD.

10.1.5. Study Documentation and Storage

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

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

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

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

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

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

Record Keeping

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

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

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

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

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

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

10.1.6. Finances

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

Reimbursement, Indemnity, and Insurance

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

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

10.1.7. Publication, Public Disclosure Policy, and Data Sharing

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

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

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

10.1.8. Protocol Deviations

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

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

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

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

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

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

10.1.9. Study and Site Closure

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

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

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

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

10.1.10. Product Complaints

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

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

10.2. Appendix 2: Local Laboratory

Table 10.1: Clinical Laboratory Tests

Test	Analytes
Blood Chemistry	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin (total) Bilirubin (direct) Blood urea nitrogen/urea Calcium Chloride Serum creatinine Creatinine clearance Lactate dehydrogenase Potassium Sodium Magnesium Total protein
Troponin	High-sensitivity troponin T (preferred) or Troponin-I
Hematology	Red blood cell count Hemoglobin Hematocrit White blood cell (WBC) count Differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Platelet count
Coagulation	Prothrombin time- international normalized ratio Activated partial thromboplastin time or partial thromboplastin time
Urinalysis (abbreviated)	Protein Glucose Blood Microscopy assessment (if indicated) Specific gravity

Table 10.2: List of HER2 (ERBB2) Mutations

HER2 mutations
Exon 20 insertion (any)
Tyr772_Ala775dup (Ala771_Tyr772insTyrValMetAla, Glu770_Ala771insAlaTyrValMet Ala775_Gly776insTyrValMetAla)
Ala775_Gly776insVal
Ala775_Gly776insThrValMetAla (Tyr772_Val773insValMetAlaThr)
Gly776delinsLeuCys
Gly776delinsValCys
Gly776_Val777insLeu
Gly778_Ser779insCysValGly (Gly776_Val777insValGlyCys)
Val777_Gly778insCysGly (Gly776_Val777delinsCysValCysGly),
Val777_Ser779dup (Gly776_Val777insValGlySer , Ser779_Pro780insValGlySer)
Gly778_Ser779insLeuProSer
Gly778dup (Val777_Gly778insGly)
Gly778_Pro780dup (Val777_Gly778insGlySerPro, Pro780_Tyr781insGlySerPro)
Ser310Phe
Ser310Tyr
Arg678Gln
Thr733Ile
Leu755Ala
Leu755Met
Leu755Pro
Leu755Ser
Leu755Trp
Ile767Met
Asp769Asn
Asp769His
Asp769Tyr
Gly776Cys
Gly776Ser
Gly776Val
Val777Leu
Val777Met
Val842Ile
Thr862Ile
Leu869Arg
Arg896Cys
Arg896His
Gly778_Ser779insCysProGly (Val777_Gly778insGlyCysPro)
Leu755_Glu757delinsSer
Leu755_Thr759del
Val777_Gly778insCysVal
Ile767Phe
Thr798Ile

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds)[19]:

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:

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

Female:

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

10.3.2. Corrected Calcium Formula for Eligibility

To correct calcium for serum albumin in case of hypoalbuminemia for eligibility, as referenced in inclusion criterion , please use one of the following formulas[20]:

In mg/dL:

Corrected Calcium [mg/dL] = (0.8 × (Normal Albumin - Albumin) + Calcium

In mmol/L:

Corrected Calcium [mmol/L] = (0.02 × (Normal Albumin - Albumin) + Calcium

10.3.3. New York Heart Association (NYHA)

The NYHA classifications are summarized below.[21]

Table 10.3: New York Heart Association Classifications

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

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994.
http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

10.3.4. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status scale scores are summarized below.[22]

Table 10.4: Eastern Cooperative Oncology Group Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649 55.

10.3.5. Highly Effective Contraception

Methods considered to be highly effective contraception include:[23]

- 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

10.3.6. Calculation of Body Surface Area

Body surface area as calculated using the Mosteller equation:[24]

$$BSA = \sqrt{\frac{height \times weight}{3600}}$$

Source: Mosteller RD. Simplified Calculation of Body Surface Area. N Engl J Med. 1987;317(17):1098 (letter)

10.4. Appendix 4: Response Criteria

Response Evaluation Criteria in Solid Tumors (Version 1.1)

Assessment of tumor responses will be performed according to revised RECIST guidelines, Version 1.1.[25] Some of these definitions and criteria are highlighted below.

Measurability of Tumor at Baseline Definitions

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

Measurable

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

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

Non-measurable

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

Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of Assessment

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

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

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

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

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

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

When more than one measurable lesion is present at baseline all lesions up to a total of two lesions per organ and 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').

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 one or more new lesions is also considered progression).

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

Special Notes on the Assessment of Target Lesions

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

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

If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

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

Evaluation of Non-Target Lesions

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).

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

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

Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for

unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

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

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

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

Evaluation of Best Overall Response

The 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 d). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 10.5 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

All postbaseline scans must be anchored against the scan.

Table 10.5: Time Point Response: Subjects With Target (±Non-Target) Disease

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

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

Missing Assessments and In-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 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.

Best Overall Response: All-Time Points

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

Table 10.6: Best Overall Response When Confirmation of CR and PR Required

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

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

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

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

Special Notes on Response Assessment

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

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

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

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

Frequency of Tumor Re-evaluation

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

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

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

The radiographic evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the SOC for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

10.5. Appendix 5: General Information - Adverse Events

10.5.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[26]

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

Events Meeting the Adverse Event Definition

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

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

Events NOT Meeting the Adverse Event Definition

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

Serious Adverse Event

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

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

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

Events Exempted from SAE Reporting

Serious events that are also efficacy endpoints (eg, PD) and/or safety endpoints will be exempted from SAE processing and expedited reporting[27]. Disease progression should not be reported as an AE/SAE (Section 8.4.1).

10.5.2. Grade Assessment

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

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

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

Difference between Severity and Seriousness

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

10.5.3. Causality Assessment

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

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

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

10.5.4. 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 drug completed/permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of treatment
- Unknown: Subject is lost to follow-up

10.5.5. Other Action Taken for Event

- None.
  - No treatment was required.

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

10.5.6. Adverse Event Outcome

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

10.6. Appendix 6: Instructions Related to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Due to the potential impact of SARS-CoV-2 infection, ie COVID-19, on subject safety, the following SARS-Cov-2 infection assessment and dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with trastuzumab deruxtecan should be followed. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose modification criteria for suspected or confirmed SARS-CoV-2 infection

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

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Section 6.5.
- If COVID-19 is confirmed or diagnosis is suspected after evaluation, follow dose modification as outlined in Table 10.7, below, and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no

respiratory signs/symptoms of COVID-19 and completely or nearly resolved chest CT findings, which are equivalent to CT Severity Score of 1 (CT Severity Score of 1 = Subtle Ground Glass Opacities and very few findings), then follow below dose modifications (Table 10.7).

Table 10.7: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI-CTCAE Version 5.0 Grade (Unless Otherwise Specified)	Schedule Modification for Trastuzumab Deruxtecan
Grade 1	After recovery, resume study treatment(s) at the same dose
Grade 2	After recovery, resume study treatment(s) at the same dose if chest CT findings are completely resolved Reduce by 1 dose level if chest CT findings are nearly resolved (equivalent to CT Severity Score of 1)
Grade 3	After recovery, reduce by 1 dose level if chest CT findings are completely resolved Discontinue drug if chest CT findings are not completely resolved
Grade 4	Discontinue study drug

COVID-19 = coronavirus disease 2019; CT = computed tomography; CT Severity Score of 1 = Subtle Ground Glass Opacities and very few findings; NCI-CTCAE = National Cancer Institute- Common Terminology Criteria for Adverse Events

Closely monitor subjects for signs/symptoms after resuming trastuzumab deruxtecan with a weekly phone call or a site visit, for a total of 6 weeks.

In addition to the recommendations outlined in Table 10.7, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 6.6) signs/symptoms.

SARS-CoV-2 Infection Assessment(s)

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of SARS-CoV-2 infection should be confirmed via NAAT (nucleic acid amplification test such as RT-PCR) or rapid antigen testing. SARS-CoV-2 antigen testing can be used to confirm infection, but not to rule it out. .

Serum samples will be collected and may be used for SARS-CoV-2 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion (Table 1.1), shipped to a central laboratory and stored there until the testing is required.

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

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

Statistical Analysis - Assessment of the Impact of SARS-CoV-2 Infection

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

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

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first line
2L+	second-line or later
40-D FUP	40-day follow-up
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BI	before infusion
BICR	blinded independent central review
CBC	complete blood count
CFR	code of federal regulations
CHF	congestive heart failure
CI	confidence interval
Cmax	maximum serum concentration
CO	carbon monoxide
COVID-19	coronavirus 2019
CR	complete response
CrCl	creatinine clearance
CRO	Contract Research Organization
CT	computed tomography
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCO	data cutoff
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity

Abbreviation	Definition
DoR	duration of response
DSI	Daiichi Sankyo, Inc.
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EIU	exposure in utero
EOI	end of infusion
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (Core)
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire LC13 (Lung Cancer)
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 Dimension 5 Levels
ER	Exposure-Response
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GLP	good laboratory practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEOR	health economics and outcomes research
HER2	human epidermal growth factor receptor 2
hERG	Human ether-a-go-go-related gene
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator’s Brochure

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
ICR	Independent committee review
IEC	independent ethics committee
ILD	interstitial lung disease
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous
LTSFU	long-term survival follow-up
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose/regimen
MUGA	multi-gated acquisition
NE	not evaluable
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death receptor-1
PDL-1	programmed cell death ligand 1
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGI-TT	Patient Global Impression of Treatment Tolerability
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcomes

Abbreviation	Definition
PS	performance status
PT	prothrombin time
Q3M	every 3 months
Q3W	every 3 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RECIST	response evaluation criteria in solid tumors version 1.1
RES	response evaluable set
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SID	subject identifier
SMQ	Standardised MedDRA Queries
SOC	standard of care
SoE	Schedule of Events
SpO_2	peripheral oxygen saturation
t1/2	terminal elimination half-life
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
Tmax	time to reach maximum concentration
TTR	time to response
ULN	upper limit of normal
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary
wk	week

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A Phase 2, multicenter, randomized study of trastuzumab deruxtecan in subjects w

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