CLINICAL STUDY PROTOCOL

HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects with Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)

(Patritumab Deruxtecan in Subjects with Metastatic or Locally Advanced EGFR-mutated NSCLC)

PROTOCOL NUMBER: U31402-A-U201

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DAIICHI SANKYO, INC

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INVESTIGATOR AGREEMENT

HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects with Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
PPD, Global Oncology Research and Development	31 Mar 2021
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

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

DOCUMENT HISTORY

Version Number	Version Date
3.0	31 Mar 2021
2.0	20 Nov 2020
1.0	26 Jun 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 3.0 (dated 31 Mar 2021) vs. protocol Version 2.0 (dated 20 Nov 2020) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current U31402-A-U201 clinical study protocol (Version 3.0) by section.

Amendment Rationale:

The primary purpose of this amendment is CCI [redacted] 1) to ensure that at least 80% of the total randomized/enrolled subjects have received prior osimertinib treatment CCI [redacted] for consistency with current standard of care in the US and 2) to ensure that subjects enrolled in South Korea known to harbor a clinically actionable genomic alteration in addition to epidermal growth factor receptor (EGFR) mutation have received at least 1 approved genotype-directed therapy per local standard of care CCI [redacted].

The identified risks for patritumab deruxtecan were updated to include hypokalemia, febrile neutropenia, and epistaxis. The amendment includes revised specifications regarding pregnancy assessments and urinalysis.

Other minor editorial changes were made to enhance clarity.

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

Section # and Title	Description of Change	Brief Rationale
1.1. Protocol Synopsis Figure 1.1 Study Level Flow Diagram 5.1. Inclusion Criteria	Starting after local approval of this amendment, prior osimertinib treatment is required for eligibility.	To address recommendation from the US Food and Drug Administration and for consistency with current standard of care in the US.
1.1. Protocol Summary 5.1. Inclusion Criteria	The following text was added to inclusion criterion: Subjects known to harbor a clinically actionable genomic alteration in addition to EGFR mutation (eg, anaplastic lymphoma kinase [ALK] or ROS protocol-oncogene 1 [ROS1] fusion) for which treatment is available must have also received prior treatment with at least 1 approved genotype-directed therapy, unless unable (ie, if contraindicated). No new testing for these genomic alterations	To ensure that subjects in South Korea known to harbor a clinically actionable genomic alteration in addition to EGFR mutation have received at least 1 approved genotype-directed therapy per local standard of care.

Section # and Title	Description of Change	Brief Rationale
	(eg, ALK or ROS1 fusion) is required for Screening.	
1.3 Schedule of Events Table 1.1	The time frame for the urinalysis Screening assessment was changed from 72 hours prior to Cycle 1 Day 1 to 28 days prior to Cycle 1 Day 1.	To clarify the schedule of urinalysis assessment.
1.3 Schedule of Events, Table 1.1	The following text was deleted~~: HIV antibody test is optional unless required by local regulations or IRB/ECs.~~ The following text was revised: If required **by local regulations**, perform within 28 days prior to Cycle 1 Day 1,	To clarify the requirement of HIV antibody testing.
1.3. Schedule of Events Table 1.1 8.4.2. Pregnancy	Specified serum pregnancy testing at Screening should be performed within 28 days prior to Cycle 1 Day 1; a urine or serum pregnancy test per institutional guidelines should be performed within 72 hours prior to infusion of each cycle (including prior to Cycle 1 Day 1) for all female subjects of childbearing potential. If a urine pregnancy test result is positive, it must immediately be confirmed using a serum pregnancy test. Results are required prior to administration of study treatment. Cycle 1 Day 1 assessment does not need to be repeated if Screening assessment was performed within 72 hours prior to Cycle 1 Day 1 infusion.	To clarify the schedule of pregnancy testing.
2.3. Benefit and Risk Assessment	Revised text to align with Investigator's Brochure (IB) Version 8.0. Specifically, identified risks were updated to include hypokalemia, febrile neutropenia, and epistaxis.	To align with IB Version 8.0.
10.3.4. Highly Effective Contraception 11. References	Revised the following text regarding abstinence from "Complete sexual abstinence" to "True abstinence: when this is in line with the preferred and usual lifestyle of the subject" and updated reference for Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical studies to the most current version.	To align with current recommendation on true abstinence based on CTFG. Recommendations related to contraception and pregnancy testing in clinical studies to the most current version.
10.5.2. Serious Adverse Event	Specified that disease progression is also an efficacy endpoint and should not be reported as an adverse event/serious adverse event (SAE). However, when a death occurs due to disease progression with no other immediate cause, then disease progression should be reported as an SAE and should be recorded in the	To clarify the events that are exempt from SAE processing and expedited reporting.

Section # and Title	Description of Change	Brief Rationale
	designated electronic case report form; in this circumstance, the SAE will be processed and reported as per local regulatory requirements and institutions, as applicable.	
10.7. Instructions Related to Coronavirus Disease 2019 (COVID-19)	Revised text pertaining to the management of subjects with suspected or confirmed COVID-19 infection.	To clarify the management of subjects with suspected or confirmed COVID-19 infection.

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects with Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)
Protocol Short Title
Patritumab Deruxtecan in Subjects with Metastatic or Locally Advanced EGFR-mutated NSCLC
Protocol Number
U31402-A-U201
Sponsor/Collaborators
Sponsor: Daiichi Sankyo, Inc.
Registry Identification(s)
EudraCT Number: 2020-000730-17
IND Number
IND Number 133343
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites and Location
Global study at approximately 135 study sites located in North America, the European Union, and Asia Pacific region including Japan
Study Population
Subjects with metastatic or locally advanced NSCLC with an activating epidermal growth factor receptor [EGFR] mutation (exon 19 deletion or L858R) and who progressed during/after systemic treatment with at least 1 platinum-based chemotherapy regimen and at least 1 EGFR-tyrosine kinase inhibitor (TKI)
Study Objectives/Outcome Measures and Endpoints

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

Objectives	Outcome Measure	Endpoints	Category
Primary			
To investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** ORR **Description:** ORR as assessed by BICR per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up,	ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.	Efficacy

	or withdrawal by the subject.		
Secondary			
To investigate the durability of patritumab deruxtecan antitumor activity in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** DoR **Description:** DoR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	DoR is defined as the time from the first documented response (confirmed CR or confirmed PR) to the date of progression or death due to any cause.	Efficacy
To further investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** PFS **Description:** PFS as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject. Death date is collected until the subject discontinues the study.	PFS is defined as the time from the start of study treatment to the earlier of the dates of the first documentation of objective PD or death due to any cause.	Efficacy
	Title: ORR **Description:** ORR as assessed by Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression, death, lost to follow-up, or withdrawal by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.	Efficacy

	Title: DCR **Description:** DCR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	DCR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or SD.	Efficacy
	Title: TTR **Description:** TTR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	TTR is defined as the time from the start of study treatment to the date of the first documentation of response (confirmed CR or confirmed PR).	Efficacy
	Title: Best percentage change in the SoD of measurable tumors **Description:** SoD as assessed by BICR and by Investigator per RECIST V1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	The best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.	Efficacy
	Title: OS **Description:** OS **Time frame:** Death date is collected until the subject discontinues the study.	OS is defined as the time from the start of study treatment to the date of death due to any cause.	Efficacy

To assess the safety and tolerability of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** Safety parameters during the study* **Description:** Descriptive statistics of safety endpoints **Time frame:** From the time the subject signs the main study ICF and up to 40 (+ 7) days after the last dose of study drug (ie, 5 half-lives of the ADC/the follow-up period) *Although this is a secondary objective, this is a primary outcome measure.	Incidence of TEAEs, SAEs, AESIs (ILD and elevation of aminotransferases and TBL), ECOG PS, vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), ECG parameters, ECHO/MUGA scan findings, and ophthalmologic findings. AEs and laboratory test results will be coded using the most recent version of MedDRA and will be graded using NCI-CTCAE v5.0.	Safety
To evaluate HER3 protein expression in tumor tissue and its relationship with efficacy	**Title:** Correlation between HER3 protein expression (as determined by HER3 IHC assay) and efficacy **Description:** Descriptive summary of HER3 status, and a correlative analysis between HER3 protein expression level and efficacy **Time frame:** Efficacy data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject. HER3 data are collected at baseline (biopsy).	HER3 protein expression in tumor tissue (as determined by IHC) and correlation with ORR, DoR, and PFS	Efficacy/Biomarker
To assess the immunogenicity incidence against patritumab deruxtecan	**Title:** Immunogenicity **Description:** ADA prevalence, incidence	ADA prevalence: the proportion of all subjects having a confirmed positive	Immunogenicity

	and titer for patritumab deruxtecan. **Time frame:** Data are collected from the start of study treatment until documented disease progression. Additional time points are specified in Table 1.1 and Table 1.2.	ADA sample at any point in time. ADA incidence: the proportion of subjects having treatment-emergent ADA. ADA titer will be determined for confirmed ADA positive samples. Neutralizing antibodies: when neutralizing assay became available confirmed ADA positive samples may be analyzed for neutralizing activity.	

ADA = anti-drug antibody; ADC = antibody drug conjugate; AE = adverse event; AESI = adverse event of special interest; BICR = blinded independent central review; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EOT = End of Treatment; HER3 = human epidermal growth factor receptor 3; ICF = informed consent form; IHC = immunohistochemistry; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; mRNA = messenger ribonucleic acid; MUGA = multigated acquisition; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; SoD = sum of diameters; TBL = total bilirubin; TEAE = treatment-emergent adverse event; TTR = time to response; v = version.

Study Design

This is a global, multicenter, open-label, Phase 2 study of subjects with metastatic or locally advanced NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) who have received and progressed on or after at least 1 EGFR TKI and 1 platinum-based chemotherapy-containing regimen. This study will initially randomize subjects to one of 2 arms in a 1:1 ratio, for dose selection, to receive either a 5.6 mg/kg fixed dose regimen (Arm 1) or an up-titration dose regimen (Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg; Arm 2) of patritumab deruxtecan (HER3-DXd; U3-1402) on Day 1 of each 21-day cycle.

In the ongoing U31402-A-U102 study, the same population is being studied in multiple expansion cohorts: Cohort 3a and 3b (with 45 subjects planned to be randomized to each dose regimen, 5.6 mg/kg every 3 weeks [Q3W] or up-titration) and Cohort 1 (45 subjects dosed with 5.6 mg/kg Q3W). If, during the conduct of the current study (U31402-A-U201), analyses from the U31402-A-U102 study indicate that one dose regimen provides clear advantages over the other in terms of benefit/risk, further enrollment into one arm may be discontinued.

- If a single dose regimen (Arm 1 or Arm 2) is selected to continue enrollment, subjects enrolled after the decision point will be assigned to the selected dose regimen. Subjects enrolled before the decision point will continue their originally assigned dose regimen without crossover.
- If there is no significant difference in efficacy and/or safety from the U31402-A-U102 NSCLC study, both dose regimens/arms in this study (U31402-A-U201) will continue to enroll to study completion.

The study will be divided into 3 periods: the Screening Period, Treatment Period, and Follow-up Period.

- The Screening Period will start on the day of signing the main informed consent form (ICF) and will have a maximum duration of 35 days. The study will allow rescreening once for any subject who failed to meet eligibility criteria upon initial Screening or whose Screening window has elapsed.
- Eligible subjects will be enrolled and enter the Treatment Period. The Treatment Period starts on the day of enrollment (ie, Cycle 1 Day 1) and continues until a subject permanently discontinues patritumab deruxtecan. To minimize the possibility of developing tumor flare with discontinuation of EGFR TKI, subjects who fulfill eligibility criteria and are receiving an EGFR TKI at the time of informed consent should be instructed to continue their current EGFR TKI until 5 days prior to Cycle 1 Day 1. Radiographic assessment of tumor response will be performed based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter, independent of treatment cycle, until documented disease progression by blinded independent central review (BICR per RECIST v1.1), death, lost to follow-up, or withdrawal of consent.
  Subjects will continue to receive patritumab deruxtecan until documented disease progression per RECIST v1.1, clinical progression, unacceptable toxicity, withdrawal of consent by the subject, physician's decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons. If progressive disease is suspected by Investigator tumor assessment, imaging must be submitted to BICR for expedited confirmation of disease progression. The decision to discontinue patritumab deruxtecan is according to Investigator judgement and should consider BICR assessment.
- The Follow-up Period will start upon permanent discontinuation of patritumab deruxtecan. After completion of the 40-day (+7 days) safety Follow-up Visit, subjects will be followed every 3 months for survival.

The **primary completion date** will occur when all subjects have either a minimum of 9 months follow-up or have discontinued from the study earlier. This date is used as the data cut-off (DCO) date for the primary analysis of the study. All subjects still on treatment and continuing to derive benefit from patritumab deruxtecan at the primary completion date will continue to follow the study Schedule of Events (SoE) (Table 1.2) until the **overall End of Study (EOS)** is reached. The overall EOS will occur after the last subject last visit has occurred, when all subjects have discontinued treatment and discontinued long-term survival follow-up or have died, an alternative study becomes available for subjects continuing to derive benefit from treatment with patritumab deruxtecan where the study drug is offered to these subjects, or the study is discontinued by the Sponsor for other reasons (administrative, program-level or class-related).

See Figure 1.1 for the study flow diagram.

Study Duration

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

Anticipated total duration of the study is expected to be 26 months consisting of approximately 12 months for enrollment and 14 months on treatment. The study will continue until the overall EOS is reached.

Key Eligibility Criteria

Key Inclusion Criteria:

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

- Histologically or cytologically documented locally advanced or metastatic NSCLC not amenable to curative surgery or radiation.
- Documentation of radiological disease progression while on/after receiving most recent treatment regimen for locally advanced or metastatic disease. Subjects must have received both of the following:

- Prior treatment with osimertinib. Subjects receiving an EGFR TKI at the time of signing informed consent should continue to take the EGFR TKI until 5 days prior to Cycle 1 Day 1.

Subjects in South Korea known to harbor a clinically actionable genomic alteration in addition to EGFR mutation (eg, anaplastic lymphoma kinase [ALK] or ROS1 protocol oncogene 1 [ROS1] fusion) for which treatment is available must have also received prior treatment with at least 1 approved genotype-directed therapy, unless unable (eg, if contraindicated). No new testing for these genomic alterations (eg, ALK or ROS1 fusion) is required for Screening.

- Systemic therapy with at least 1 platinum-based chemotherapy regimen.

- Documentation of an EGFR-activating mutation detected from tumor tissue or blood sample: exon 19 deletion or L858R.
- At least 1 measurable lesion confirmed by BICR as per RECIST v1.1 (see Section 10.4)
- Consented and willing to provide required tumor tissue of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by hematoxylin and eosin [H&E] staining at the central laboratory). Required tumor tissue can be provided as either:
  - Pretreatment tumor biopsy from at least 1 lesion not previously irradiated and amenable to core biopsy OR
  - Archival tumor tissue collected from a biopsy performed within 3 months prior to signing of the tissue consent and since progression while on or after treatment with the most recent cancer therapy regimen.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at Screening (see Section 10.3.3).
- Has adequate bone marrow reserve and organ function based on local laboratory data within 14 days prior to Cycle 1 Day 1:

Laboratory Test	**Laboratory Value**
Platelet count	≥100 000/mm^3 or ≥100 × 10^9/L (platelet transfusions are not allowed up to 14 days prior to Cycle 1 Day 1 to meet eligibility)
Hemoglobin	≥9.0 g/dL (transfusion and/or growth factor support is allowed)
Absolute neutrophil count	≥1500/mm^3 or ≥1.5 × 10^9/L
Serum creatinine OR creatinine clearance	SCr ≤1.5 × ULN, OR CrCl ≥30 mL/min as calculated using the Cockcroft-Gault equation or measured CrCl
Aspartate aminotransferase/ Alanine aminotransferase	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN if no liver metastases (<3 × ULN in the presence of documented Gilbert's syndrome [unconjugated hyperbilirubinemia] or liver metastases)
Serum albumin	≥2.5 g/dL
PT or PT-INR and aPTT/PTT	≤1.5 × ULN, except for subjects on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-INR within therapeutic range as deemed appropriate by the Investigator

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; SCr = serum creatinine; ULN = upper limit of normal.

Key Exclusion Criteria:

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

- Any previous histologic or cytologic evidence of small cell OR combined small cell/non-small cell disease in the archival tumor tissue or pretreatment tumor biopsy.
- Any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current interstitial lung disease (ILD), or is suspected to have such disease by imaging during Screening.
- Clinically severe respiratory compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
  - Any underlying pulmonary disorder (eg, pulmonary emboli within 3 months prior to the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD]), restrictive lung disease, pleural effusion);
  - Any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (eg, rheumatoid arthritis, Sjogren's syndrome, sarcoidosis);

  OR prior complete pneumonectomy.
- Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory or any form of immunosuppressive therapy prior to enrollment. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
- Evidence of any leptomeningeal disease.
- Evidence of clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive or treated brain metastases who are asymptomatic (ie, without neurologic signs or symptoms and not requiring treatment with corticosteroids or anticonvulsants) may be included in the study. Subjects must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1.
- Inadequate washout period prior to Cycle 1 Day 1, defined as:
  - Whole brain radiation therapy <14 days or stereotactic brain radiation therapy <7 days;
  - Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), <14 days or 5 half-lives, whichever is longer;
  - Monoclonal antibodies, other than immune checkpoint inhibitors, such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFR) <28 days;
  - Immune checkpoint inhibitor therapy <21 days;
  - Major surgery (excluding placement of vascular access) <28 days;
  - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <14 days; or
  - Chloroquine or hydroxychloroquine <14 days.
- Prior treatment with an anti-human epidermal growth factor receptor 3 (HER3) antibody or single-agent topoisomerase I inhibitor.
- Prior treatment with an antibody drug conjugate (ADC) that consists of any topoisomerase I inhibitor.
- Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, Grade ≤1 or baseline. Subjects with chronic Grade 2

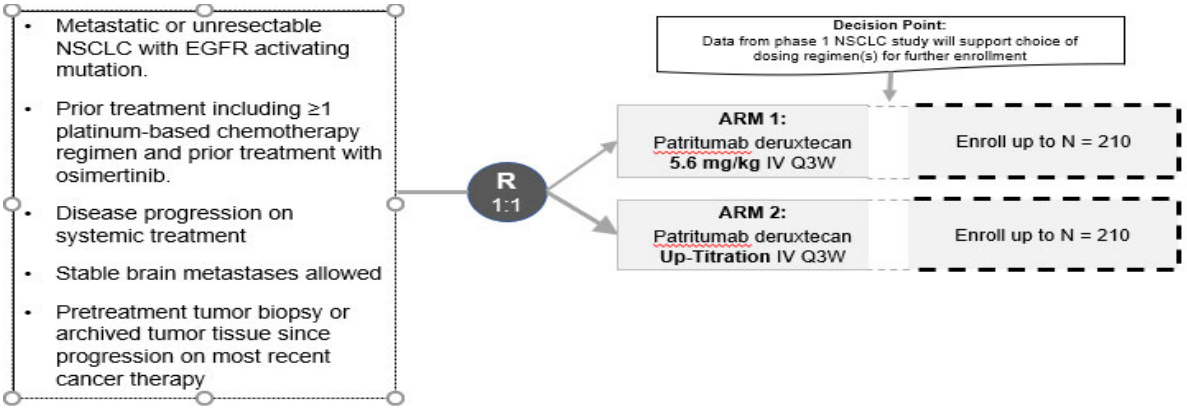
toxicities may be eligible at the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee.

- Has history of other active malignancy within 3 years prior to enrollment, except:
  - Adequately treated non-melanoma skin cancer;
  - Superficial bladder tumors (Ta, Tis, T1);
  - Adequately treated intraepithelial carcinoma of the cervix uteri;
  - Low risk non-metastatic prostate cancer (with Gleason score <7, and following local treatment or ongoing active surveillance);
  - Any other curatively treated in situ disease.
- Uncontrolled or significant cardiovascular disease prior to Cycle 1 Day 1, including:
  - QT interval corrected with Fridericia's formula (QTcF) prolongation interval of >470 ms for females and >450 ms for males;
  - Left ventricular ejection fraction (LVEF) <50% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan;
  - Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg;
  - Myocardial infarction within 6 months;
  - New York Heart Association (NYHA) Classes 2 to 4 congestive heart failure (See Section 10.3.2);
  - Uncontrolled angina pectoris within 6 months;
  - Cardiac arrhythmia requiring antiarrhythmic treatment.
- Active hepatitis B and/or hepatitis C infection, 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:
    - Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody [anti-HBc] positive; **OR**
    - HBsAg positive and HBV deoxyribonucleic acid (DNA) viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation with normal transaminases values (in the absence of liver metastasis); **OR**
    - HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL, in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation for subjects with liver metastasis and abnormal transaminases with a result of AST/ALT <3 × ULN.
  - Subjects with a history of hepatitis C infection will be eligible for enrollment only if the viral load according to local standards of detection is documented to be below the level of detection in the absence of anti-viral therapy during the previous 12 weeks (ie, sustained viral response according to the local product label but no less than 12 weeks, whichever is longer).
- Subject with any human immunodeficiency virus (HIV) infection.
- Any evidence of severe or uncontrolled diseases including active bleeding diatheses, active infection, psychiatric illness/social situations, geographical factors, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.

Investigational Medicinal Product, Dose and Mode of Administration
Patritumab deruxtecan drug product will be provided as a sterile lyophilized-drug product (Lyo-DP) consisting of 100 mg of lyophilized powder in a single-use amber glass vial to be reconstituted with 5 mL water for injection to 20 mg/mL. Patritumab deruxtecan will be administered as an intravenous (IV) solution Q3W on Day 1 of each 21-day cycle as 1 of 2 dose regimens: 5.6 mg/kg or up-titration (Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg). The dose can be delayed for up to 28 days from the planned date of administration (ie, 49 days from the last infusion date). If a subject is assessed as requiring a dose delay longer than 28 days, the subject should be discontinued from the study treatment, unless there is following discussion and agreement between the Investigator and the Sponsor to resume study treatment at a later date.
Active Ingredient(s)/INN
U3-1402/Patritumab Deruxtecan Patritumab deruxtecan is an ADC comprising a recombinant fully human anti-HER3 IgG1 monoclonal antibody (patritumab, U3-1287) covalently linked to MAAA-1162a (glycine-glycine-phenylalanine-glycine) tetrapeptide linker containing a topoisomerase I inhibitor [MAAA-1181a]). MAAA-1181a is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I.
Planned Sample Size
The primary efficacy endpoint of objective response rate (ORR) is used for sample size determination. From the REVEL trial, ORR of 23% from ramucirumab plus docetaxel arm was observed (upper bound of the exact 95% confidence interval (CI) = 26.4%. Clinically meaningful ORR of 37% is expected from patritumab deruxtecan. The one-sample exact binomial test for single proportion with a nominal 2-sided significance level of 5% will have approximately 91% power to detect the difference between a null hypothesis (H_0) of ORR = 26.4%and an alternative hypothesis (H_1) of ORR = 37% when the sample size is 210. Up to approximately 420 subjects will be randomized/enrolled depending on whether one dose arm is dropped or not during the study. The sample size computation is performed using exact test for single proportion in nQuery v8.5.2. No formal comparison between the two arms is planned, and sample size is calculated for each arm individually.
Statistical Analyses
The primary analysis data cut-off will occur when all enrolled subjects have either a minimum of 9 months of follow-up or have discontinued from the study earlier. The primary analysis will be included in the clinical study report (CSR). The primary efficacy endpoint is ORR, defined as the proportion of subjects who achieved a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as assessed by BICR per RECIST v1.1. Secondary efficacy endpoints include disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS). Response endpoints (ORR and DCR) will be summarized with the exact 95% CI using the Clopper-Pearson method in the Efficacy Analysis Set. Distribution of time to event endpoints (DoR, PFS, and OS) will be estimated using the Kaplan-Meier method and results presented graphically. Median event time with a 2-sided 95% CI will be calculated using Brookmeyer and Crowley methods. TTR will be summarized using descriptive statistics. Data will be summarized by treatment arm. No formal comparison between the 2 arms is planned. Safety analyses in general will be descriptive using the Safety Analysis Set. Serum concentrations for patritumab deruxtecan, total anti-HER3 antibody, and free payload MAAA-1181a will be listed, plotted, and summarized at each time point in the Pharmacokinetic (PK) Analysis Set. PK parameters will be listed and summarized by arm using descriptive statistics.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



IV = intravenous; NSCLC = non-small cell lung cancer; Q3W = every 3 weeks.

Dose Regimens
Fixed dose regimen (Arm 1) Q3W: • 5.6 mg/kg **Up-titration dose regimen (Arm 2) IV Q3W**: • Cycle 1: 3.2 mg/kg; • Cycle 2: 4.8 mg/kg; • Cycle 3 and subsequent cycles: 6.4 mg/kg

IV= intravenous; Q3W = every 3 weeks.

1.3. Schedule of Events

Table 1.1: Schedule of Events for Screening and Cycles 1 through 3 of the Treatment Period

	Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
			Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
				Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window		-35D				±1D	±1D		±1D		±1D	
Informed Consent	X	X										Obtain signed tissue ICF and signed main ICF prior to performing any study procedures. See Section 8.1 and Section 10.1.2.
Eligibility Assessment	X	X										See Section 5.1, Section 5.2 and Section 8.1.
Pretreatment Tumor Biopsy	X											Pretreatment or archival tumor tissue is required to be of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by H&E staining at the central laboratory). Pretreatment tumor biopsy is required for all subjects. Subjects may be exempted from the requirement to provide a pretreatment tumor biopsy if the archival tumor tissue was collected within 3 months prior to signing of the tissue consent and since progression while on or after the most recent cancer therapy regimen. See Sections 8.1 and 8.7.2.
Archived Tumor Biopsy	X											
Demographics		X										Includes: birth date, age at Screening, sex, race, ethnicity, country. See Section 8.1.
Medical History		X										See Section 8.1.
Prior Cancer History		X										See Section 8.1.
Prior Cancer Medical Therapy		X										See Section 8.1.
EGFR Mutation History		X										See Section 8.1.

	Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
			Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
				Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window		**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
HIV Ab Test		X										If required by local regulations, perform within 28 days prior to Cycle 1 Day 1. See Section 8.1.
HBsAg, HCV Ab, HCV RNA		X										Perform required hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) test within 28 days prior to Cycle 1 Day 1. Subjects with past or resolved HBV infection are eligible if: • HBsAg negative and hepatitis B core antibody [anti-HBc] positive; **OR** • HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation with normal transaminases values (in the absence of liver metastasis); **OR** • HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation for subjects with liver metastasis and abnormal transaminases with a result of AST/ALT <3 x ULN. Subjects with a history of hepatitis C infection will be eligible for enrollment only if the viral load according to local standards of detection is documented to be below the level of detection in the absence of anti-viral therapy during the previous 12 weeks (ie, sustained viral response according to the local product label but no less than 12 weeks, whichever is longer). See Section 8.1.

		Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
				Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
					Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window			**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
Final Dose of EGFR TKI				X									Subjects who are currently receiving an EGFR TKI at the time of informed consent should be instructed to take the final dose of their EGFR TKI 5 days prior to the start of Cycle 1, Day 1.
Randomization [a] / Enrollment					X								[a] Dosing must occur within 3 days of randomization. Every effort should be made to minimize the time between randomization and study drug administration. See Section 8.2.
Patritumab Deruxtecan Administration					X			X		X			Subjects must receive study drug within 3 days of randomization/enrollment. The subject's weight at baseline (defined as the last measurement on or prior to Cycle 1 Day 1) will be used to calculate the initial dose. The subject's weight will be determined at the beginning of each cycle. If during Cycle 1 Day 1 or throughout the course of treatment, the subject's weight changes ≥10% from the baseline weight, the dose will be recalculated using this new weight and will be considered the new baseline for all subsequent dosing calculations. Patritumab deruxtecan will be administered as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after the initial dose, subsequent doses of patritumab deruxtecan will be infused over approximately 30 minutes on Day 1 of each subsequent cycle Q3W. Refer to Table 6.4 for additional information on drug administration following infusion-related reactions. Refer to Pharmacy Manual and Section 6 for information on storage and preparation of patritumab deruxtecan.
Physical /Vitals	Height		X										Within 28 days prior to Cycle 1 Day 1. See Section 8.4.4.

		Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
				Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
					Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window			**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
	Weight		X [b]		X			X		X			[b] Within 28 days prior to Cycle 1 Day 1. See Sections 8.2 and 8.4.4.
	Physical Exam including ECOG PS		X [b]		X			X		X			[b] Within 28 days prior to Cycle 1 Day 1. See Sections 8.4.4 and 10.3.3.
	Vital Signs including SpO_2		X [b]		X	X	X	X	X	X	X		Includes systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation (SpO_2). Blood pressure and pulse rate should be measured after the subject has rested in a supine/semi-recumbent position for 5 minutes. [b] Within 28 days prior to Cycle 1 Day 1. See Section 8.4.4.
Safety	Hematology/ Chemistry Tests		X [c]		X[d]		X	X[d]		X[d]		X	[c] Within 14 days prior to Cycle 1 Day 1. [d] Should be performed within 72 hours of scheduled visit. Results are required prior to study treatment. See Sections 8.4.3 and 10.2.
	Coagulation		X										Within 14 days prior to Cycle 1 Day 1. Subjects taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio. See Sections 8.4.3 and 10.2.
	Urinalysis		X										Screening assessment should be performed within 28 days prior to Cycle 1 Day 1. Assessments may be repeated as clinically indicated as part of a scheduled or unscheduled visit and should include microscopic evaluation as indicated. See Sections 8.4.3 and 10.2.

		Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
				Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
					Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window			**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
	Pregnancy Test		X[a]		X[b]			X[b]		X[b]			[a] For all female subjects of childbearing potential, a serum pregnancy test at Screening should be performed within 28 days prior to Cycle 1 Day 1 [b] A pregnancy test (urine or serum test per institutional guidelines) should be performed within 72 hours prior to infusion of each cycle (including prior to Cycle 1 Day 1) for all female subjects of childbearing potential; a positive urine pregnancy test result must immediately be confirmed using a serum pregnancy test. Results are required prior to administration of study treatment. Cycle 1 Day 1 assessment does not need to be repeated if Screening assessment was performed within 72 hours of Cycle 1 Day 1 infusion. See Section 8.4.2
	12-lead ECG		X										Within 28 days prior to Cycle 1 Day 1. Subjects should rest supine/semi-recumbent for at least 10 minutes prior to the assessment. The same test must be used for Screening, EOT, and as clinically indicated. See Section 8.4.4.
	ECHO/ MUGA		X										Within 28 days prior to Cycle 1 Day 1. The same test must be used for Screening, EOT, and for as clinically indicated testing. See Section 8.4.4.
	COVID-19 Sample				X								If subject provides consent, samples should be collected prior to study drug infusion. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Section 10.7.
	Ophthalmo-logic Assessments		X										Has to occur within 7 days prior to Cycle 1 Day 1 and includes a visual acuity test (ETDRS, Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry. Assessments may be repeated as clinically indicated as part of a scheduled or unscheduled visit. See Section 8.4.4.

		Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
				Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
					Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window			**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
BM	BM Blood Sample				X[e]			X[f]		X[f]			[e] For Cycle 1 Day 1, a minimum of 34 mL of blood is required to be drawn. This includes 20 mL for cfDNA, 10 mL for cfRNA, and 4 mL for HER3 ECD. [f] A minimum 24 mL of blood is required to be drawn. This includes 10 mL for cfDNA, 10 mL for cfRNA, and 4 mL for HER3 ECD. See Section 8.7.1.
	PGx Blood Sample					X							If subject provides consent, a single blood sample for PGx analysis should be collected on Cycle 1 Day 1 post-infusion. Alternatively, a blood sample may be collected at any time after Cycle 1 Day 1. See Section 8.8.
	ADA Blood Sample				X		X	X					See Section 8.5.1.
Pharmacokinetics Sample					X	X[g]	X	X	X[g]	X	X[g]	X	[g] Within 15 minutes of end of infusion then 4 hours (±15 minutes) after the end of infusion. See Section 8.5.
PK Sampling for CQ/HCQ Administration					If CQ or HCQ is administered for COVID-19, 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 patritumab deruxtecan resumption, after the CQ/HCQ washout period [h], (within 8h BI of patritumab deruxtecan).							If subject provides consent, samples should be collected. [h] A washout period of more than 14 days is required before restarting patritumab deruxtecan. See Section 10.7.

	Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
			Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
				Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window		**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
Tumor Assessments[i]		X[j,k]		X[k] Every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter, independent of treatment cycle, until documented disease progression by BICR per RECIST v1.1, death, lost to follow-up, or withdrawal of consent								[i] The same methodology (CT or MRI) and scan acquisition techniques (including nonuse and use of IV contrast unless medically infeasible, ie, newly developed AE or allergy to contrast agent) as were used for the Screening assessments should be used throughout the study for each body region across all assessments for each subject unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1 Day 1. Tumor assessments should be performed per RECIST v1.1 (Section 10.4) and submitted for BICR. SpO_2 should be conducted with CT/MRI per Investigator discretion. [j] Within 28 days prior to Cycle 1 Day 1. [k] Perform radiographic tumor assessments (CT/MRI) of the chest, abdomen, pelvis, brain, and for all sites of disease identified at screening, and for any newly suspected disease sites, as per RECIST v1.1 (Section 10.4). Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). See Section 8.3.

	Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
			Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
				Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window		**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
Bone Scan		X[l]		X[m] Every 24 weeks (±7 days) from Cycle 1 Day 1								[l] A bone scan (^{99m}technetium polyphosphonate scintigraphy, whole body bone MRI, ^{18}F- NaF PET/CT or ^{18}F-FDG PET/CT) to assess bone metastases should be performed within 6 weeks prior to Cycle 1 Day 1 (historical scans are acceptable). [m] A bone scan (^{99m}technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF PET/CT or ^{18}F-FDG PET/CT) to assess bone metastases should be performed every 24 weeks (±7 days) from Cycle 1 Day 1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan is required at confirmation of CR to exclude new bone metastases. Lesions detected on bone scans must be followed with cross-sectional imaging. See Section 8.3.
Prior/Concomitant Medications		X										See Section 6.6.

		Tissue Requirement	Screening	Cycle 1				Cycle 2		Cycle 3			Comments
				Day -5	Day 1		Day 8	Day 1		Day 1		Day 8	
					Pre-I	Post-I		Pre-I	Post-I	Pre-I	Post-I		
Visit Window			**-35D**				**±1D**	**±1D**		**±1D**		**±1D**	
AE	SAEs	X											Any SAEs after signing the appropriate ICF should be reported until 40 days (+7 days) after the last dose of the study drug. Any SAEs directly related to a tumor biopsy procedure performed after signing the appropriate Tissue Screening ICF or Tissue Collection ICF should be reported according to the Adverse Event Reporting Requirements section. Any serious, untoward event that may occur subsequent to the 40-day (+ 7 days) follow-up reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE. 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 patritumab deruxtecan on the General Medical History and Baseline Conditions eCRF. See Section 8.4.1.
	Non-SAEs		X										Any AEs from first dose until 40 days (+7 days) after the last dose of the study drug should be followed until resolution or stabilized. See Section 8.4.1.

ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; BM = biomarker; cfDNA = cell-free deoxyribonucleic acid; cfRNA = cell-free RNA; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CR = complete response; CT = computed tomography; D = day; DNA = deoxyribonucleic acid; EC = Ethics Committee; ECD = extracellular domain; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; EOT = end of treatment; ETDRS = Early Treatment Diabetic Retinopathy Study; FDG = fluorodeoxyglucose; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCQ = hydroxychloroquine; HCV Ab = hepatitis C virus antibody; H&E = hematoxylin and eosin; HER3 = human epidermal growth factor receptor 3; HIV Ab = human immunodeficiency virus antibody; ICF = informed consent form; IHC = immunohistochemistry; IRB = Institutional Review Board; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NGS = next generation sequencing; PET = positron emission tomography; PGx = pharmacogenetics; PK = pharmacokinetic(s); Post-I = Post-infusion; Pre-I = Pre-infusion; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RNA = ribonucleic acid; SAE = serious adverse event; SpO_2 = peripheral oxygen saturation; TKI = tyrosine kinase inhibitor.

Table 1.2: Schedule of Events for Cycle 4 and Subsequent Cycles of the Treatment Period, End of Treatment, and Follow-up Period

		Cycle 4 and Subsequent Cycles Day 1		EOT[a]	40-Day Follow-up[b]	Long-Term Follow-up (Every 3 Months)	Comments
		Pre-I	Post-I				
Visit Window		**±1D**			**+7D**	**±14 D**	
End-of-Treatment Tumor Biopsy				X			An optional EOT tumor biopsy will also be performed at the time of progression or discontinuation from study treatment. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy should be obtained from primary tumor or metastatic site, preferably from a site of recent radiographic progression, within 40 days of the last dose of patritumab deruxtecan, and prior to starting any new anticancer treatment. See Section 8.7.2.
Patritumab Deruxtecan Administration		X					The subject's weight at baseline (defined as the last measurement on or prior to Cycle 1 Day 1) will be used to calculate the initial dose. The subject's weight will be determined at the beginning of each cycle. If during Cycle 1 Day 1 or throughout the course of treatment, the subject's weight changes by ≥10% from the baseline weight, the dose will be recalculated using this new weight and will be considered the new baseline for all subsequent dosing calculations. Patritumab deruxtecan will be administered as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after the initial dose, subsequent doses of patritumab deruxtecan will be infused over approximately 30 minutes on Day 1 of each subsequent cycle Q3W. Refer to Table 6.4 for additional information on drug administration following infusion-related reactions. Refer to Pharmacy Manual and Section 6 for information on storage and preparation of patritumab deruxtecan.
Physical /Vitals	Weight	X		X	X		See Section 8.2 and Section 8.4.4.
	Physical Exam including ECOG PS	X		X	X		See Section 8.4.4 and Section 10.3.3.

		Cycle 4 and Subsequent Cycles Day 1		EOT[a]	40-Day Follow-up[b]	Long-Term Follow-up (Every 3 Months)	Comments
		Pre-I	Post-I				
Visit Window		**±1D**			**+7D**	**±14 D**	
	Vital Signs including SpO_2	X	X	X	X		Includes systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation (SpO_2). Blood pressure and pulse rate should be measured after the subject has rested in a supine/semi-recumbent position for 5 minutes. See Section 8.4.4.
Safety	Hematology/ Chemistry Tests	X[c]		X	X		[c] Should be performed within 72 hours of scheduled visit. Results are required prior to study treatment. See Sections 8.4.3 and 10.2.
	Urinalysis			X			Assessments may be repeated as clinically indicated as part of a scheduled or unscheduled visit and should include microscopic evaluation as indicated. See Sections 8.4.3 and 10.2.
	Pregnancy Test	X		X	X		Perform pregnancy tests (urine or serum test per institutional guidelines) 72 hours before infusion of each cycle and at the end of treatment. See Section 8.4.2.
	12-lead ECG			X			Subjects should rest supine/semi-recumbent for at least 10 minutes prior to the assessment. The same test must be used for Screening, EOT, and as clinically indicated. Assessment for EOT Visit may be performed with a window up to 7 days. See Section 8.4.4.
	ECHO/MUGA			X			The same test must be used for Screening, EOT, and as clinically indicated. Assessment for EOT Visit may be performed with a window up to 7 days. See Section 8.4.4.
	COVID-19 Sample	X Starting at Cycle 5, Day 1 and every 4 cycles thereafter		X			If subject provides consent, samples should be collected prior to study drug infusion. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Section 10.7.

		Cycle 4 and Subsequent Cycles Day 1		EOT[a]	40-Day Follow-up[b]	Long-Term Follow-up (Every 3 Months)	Comments
		Pre-I	Post-I				
Visit Window		**±1D**			**+7D**	**±14 D**	
	Ophthalmologic Assessments			X[d]			Includes a visual acuity test (ETDRS, Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry. Assessments may be repeated as clinically indicated as part of a scheduled or unscheduled visit. [d] A 40 (+7) Day F/U assessment is required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality. See Section 8.4.4.
BM	BM Blood Sample	X		X			A minimum of 24 mL of blood is required to be drawn. This includes 10 mL for cfDNA, 10 mL for cfRNA, and 4 mL for HER3 ECD. See Section 8.7.1.
	ADA Blood Sample	X [e] Cycle 4, Day 1 and every 2 cycles thereafter		X [e]		X [e, f]	[e] PK assay can be performed on the ADA sample collected. [f] For subjects with positive ADA, additional serum ADA samples should be collected every 3 months (± 14 days) for up to 1 year after the last dose of patritumab deruxtecan, unless one or more of the following occurs sooner: the ADA becomes negative; the ADA titer falls below baseline if ADA was measurable prior to Cycle 1 Day 1; the subject starts another therapy for cancer, or the subject withdraws consent from the study, whichever occurs first. See Section 8.5.1.
Pharmacokinetics Sample		X Cycle 4, 6, 8					Pre-infusion and within 15 minutes of end of infusion. See Section 8.5.

	Cycle 4 and Subsequent Cycles Day 1		EOT[a]	40-Day Follow-up[b]	Long-Term Follow-up (Every 3 Months)	Comments
	Pre-I	Post-I				
Visit Window	±1D			+7D	±14 D	
PK Sampling for CQ/HCQ Administration	If CQ or HCQ is administered for COVID-19, 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 patritumab deruxtecan resumption, after the CQ/HCQ washout period [g], (within 8h BI of patritumab deruxtecan).					If subject provides consent, samples should be collected. [g] A washout period of more than 14 days is required before restarting patritumab deruxtecan. See Section 10.7.
Tumor Assessments[h]	X[i] Every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter, independent of treatment cycle, until documented disease progression by BICR per RECIST v1.1, death, lost to follow-up, or withdrawal of consent					[h] The same methodology (CT or MRI) and scan acquisition techniques (including nonuse and use of IV contrast unless medically infeasible, ie, newly developed AE or allergy to contrast agent) as were used for the Screening assessments should be used throughout the study for each body region across all assessments for each subject unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1 Day 1. Tumor assessments should be performed per RECIST v1.1 (Section 10.4) and submitted for BICR. SpO_2 should be conducted with CT/MRI per Investigator discretion. [i] Perform radiographic tumor assessments (CT/MRI) of the chest, abdomen, pelvis, brain, and for all sites of disease identified at Screening, and for any newly suspected disease sites, as per RECIST v1.1 (Section 10.4) . Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). See Section 8.3.

		Cycle 4 and Subsequent Cycles Day 1		EOT[a]	40-Day Follow-up[b]	Long-Term Follow-up (Every 3 Months)	Comments
		Pre-I	Post-I				
Visit Window		**±1D**			**+7D**	**±14 D**	
Bone Scan		X Every 24 weeks (±7 days) from Cycle 1 Day 1					A bone scan (^{99m}technetium polyphosphonate scintigraphy, whole body bone MRI, ^{18}F-NaF PET/CT or ^{18}F- FDG PET/CT) to assess bone metastases should be performed every 24 weeks (±7 days) from Cycle 1 Day 1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan is required at confirmation of CR to exclude new bone metastases. Lesions detected on bone scans must be followed with cross-sectional imaging. See Section 8.3.
Prior/Concomitant Medications		X					See Section 6.6.
AE	SAEs	X					Any SAEs after signing the appropriate ICF should be reported until 40 days (+7 days) after the last dose of the study drug. Any SAEs directly related to a tumor biopsy procedure performed after signing the appropriate the Tissue Screening ICF or Tissue Collection ICF should be reported according to the Adverse Event Reporting Requirements section. Any serious, untoward event that may occur subsequent to the 40-day (+ 7 days) follow-up reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE. See Section 8.4.1.
	Non-SAEs	X					Any AEs from first dose until 40 days (+7 days) after the last dose of the study drug should be followed until resolution or stabilized. 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 patritumab deruxtecan on the General Medical History and Baseline Conditions eCRF. See Section 8.4.1.
OS	New Cancer Tx					X	
	Survival F/U					X	See Section 7.1.

ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; BM = biomarker; cfDNA – cell-free deoxyribonucleic acid; cfRNA = cell-free ribonucleic acid; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CR = complete response; CT = computed tomography; D = day; EC = Ethics Committee; ECD = extracellular domain; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; EOT = end of treatment; ETDRS = Early Treatment Diabetic Retinopathy Study; FDG = fluorodeoxyglucose; F/U = follow-up; HCQ = hydroxychloroquine; ICF = informed consent form; IRB = Institutional Review Board; IV = intravenous; MRI = magnetic resonance imaging;

MUGA = multigated acquisition; OS = overall survival; PET = positron emission tomography; PK = pharmacokinetic(s); Post-I = Post-infusion; Pre-I = Pre-infusion; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SpO_2 = peripheral oxygen saturation; TKI = tyrosine kinase inhibitor; TR= tumor requirement; Tx = treatment.

[a] This visit occurs within 7 days after the final dose of study treatment, or before starting new anticancer treatment, whichever comes first. If the decision to discontinue patritumab deruxtecan occurs >7 days after the final dose of patritumab deruxtecan, then this visit will occur within 7 days after the decision to discontinue patritumab deruxtecan or before the start of new anticancer treatment; whichever comes first If the EOT Visit occurs ≥40 days after the final dose of patritumab deruxtecan, the 40-Day F/U Visit does not need to be conducted.

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

2. INTRODUCTION

2.1. Background

Non-small Cell Lung Cancer Background

Lung cancer is the most common cancer and the leading cause of cancer-related mortality worldwide, with an estimated 2.1 million new cases in 2018 (11.6% of all new cases) and 1.8 million deaths (18.4% of all cancer deaths) globally based on GLOBOCAN data.[1] In the United States alone, 228,820 newly diagnosed cases (12.7% of all new cases) and 135,720 deaths (22.4% of all cancer deaths) associated with cancers of the lung and bronchus are estimated to occur in 2020.[2] In Japan, lung cancer is the leading cause of cancer related deaths in males (52,505 deaths) and the second leading cause of cancer-related death in females (20,891 deaths).[3] Advances in early detection of lung cancer have been slow, and more than half of lung cancers are still diagnosed at an advanced stage.[4] Only 19.4% of all patients with lung cancer are alive 5 years or more after diagnosis.[5] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[6]

In epidermal growth factor receptor (EGFR)-mutated NSCLC, it has been well established through multiple large Phase 3 studies that EGFR tyrosine kinase inhibitors (TKIs) represent the first-line treatment of choice.[7,8,9,10,11,12,13] Among EGFR TKIs, the greatest clinical benefit as measured by progression-free survival (PFS) and overall survival (OS) has been demonstrated with osimertinib in the Phase 3 FLAURA study, which compared osimertinib versus erlotinib or gefitinib in patients with untreated advanced EGFR-mutated (EGFRm) NSCLC. In this study, first-line osimertinib demonstrated superiority to erlotinib or gefitinib as measured by PFS (18.9 months vs. 10.2 months; hazard ratio: 0.46; 95% confidence interval [CI]: 0.37 to 0.57; $P<0.001$).[14] At the final OS analysis, the median OS was 38.6 months (95% CI: 34.5, 41.8) in the osimertinib arm vs. 31.8 months (95% CI: 26.6, 36.0) in the comparator arm with a hazard ratio of 0.80 (95% CI: 0.64, 1.00); $P=0.046$.[15] Despite a higher duration of exposure of 20.7 months in the osimertinib arm and 11.5 months in the comparator arm; the incidence of Grade 3 or higher adverse events was 42% and 47%, respectively.[15] Osimertinib has also demonstrated benefit in the second-line setting in patients who develop resistance to first- or second- generation TKIs and harbor the T790M mutation.[16,17]

Although osimertinib confers benefit (median PFS of 18.9 months and median OS of 38.6 months) in previously untreated patients, development of resistance with disease progression is typical. In order to further investigate osimertinib resistance mechanisms, circulating tumor deoxyribonucleic acid (DNA) from patient plasma samples who had progressed and/or discontinued from the Phase 3 FLAURA and AURA3 studies were analyzed utilizing next generation sequencing (NGS). In the first-line setting, 91/113 evaluable plasma samples were analyzed in patients with untreated EGFRm (exon 19 deletion or L858R) NSCLC and as part of the FLAURA study. The most common acquired resistance mechanisms identified were MET amplification and C797S detected in 14/91 (15%) and 6/91 (7%) patients, respectively. Other mechanisms included PIK3CA 6/91 (7%), human epidermal growth factor receptor 2 (HER2) amplification 2/91 (2%), and RAS mutation 3/91 (3%).[18] In the second-line setting, plasma samples were analyzed in EGFRm T790M advanced NSCLC patients as part of

the AURA3 study. Of the 73/83 evaluable plasma samples, 11/73 (15%) acquired secondary mutation in C797 (C797S n=1; C797G n=1) and amplification of MET, HER2, and PIK3CA in 14/73 (19%), 4/73 (5%), and 3/73 (4%) respectively.[19]

Following progression on EGFR TKIs, platinum-based chemotherapy remains the standard treatment; however, these responses are generally not durable.[20] In patients with EGFRm NSCLC, immune checkpoint inhibitors have also yet to demonstrate clear benefit compared to platinum-based chemotherapy.[21] For patients who develop resistance to platinum-based chemotherapy in the NSCLC setting, standard of care options have limited efficacy and are associated with a high toxicity profile.[22] One such option, ramucirumab plus docetaxel, has demonstrated modest benefit in OS over docetaxel in patients with squamous or non-squamous NSCLC who had progressed during or after a first-line platinum-based chemotherapy regimen. In that study, median OS was 10.5 months for the ramucirumab plus docetaxel group and 9.1 months for the placebo plus docetaxel group (hazard ratio: 0.86; 95% CI: 0.75 to 0.98; *P*=0.023). Therefore, NSCLC patients who have experienced progression on platinum-based chemotherapy and who require subsequent systemic treatment because of symptoms or tumor growth represent an important unmet medical need.

Patritumab Deruxtecan

Patritumab deruxtecan (U3-1402) is an antibody drug conjugate (ADC) comprising a recombinant fully human anti- human epidermal growth factor receptor 3 (HER3) immunoglobulin G1 (IgG1) monoclonal antibody (patritumab, U3-1287) covalently linked to MAAA-1162a (glycine-glycine-phenylalanine-glycine [GGFG]) tetrapeptide linker containing a topoisomerase I inhibitor [MAAA-1181a]). MAAA-1181a, a derivative of exatecan (DX-8951f),[23,24,25] is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I.

2.2. Study Rationale

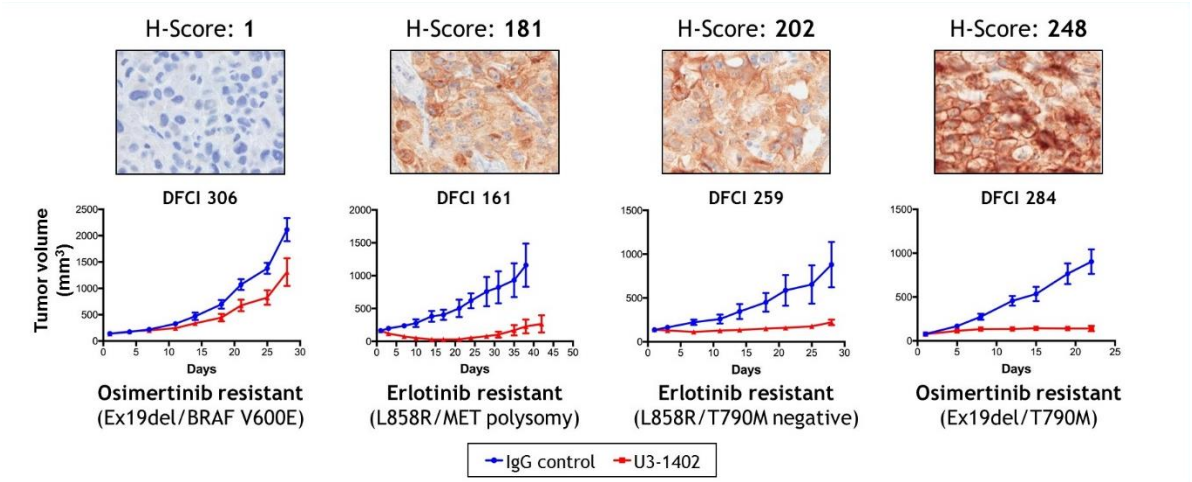
In NSCLC, HER3 overexpression has been demonstrated to be one of the mechanisms of acquired resistance to gefitinib treatment of EGFRm tumors and is an important mechanism of resistance in tumors such as those with amplification of c-MET.[26] The Erb-B2 receptor tyrosine kinase 3 (ERBB3)/HER3 is overexpressed in many cancers including breast,[27] ovarian,[28] prostate,[29] head and neck,[30] gastric,[31] and lung.[32] In addition, higher expression of HER3 correlates with poorer outcomes.[33] Published retrospective prevalence studies show that HER3 is expressed in a substantial number of NSCLC patient tumors. A large series (n = 443) of NSCLC patient tumors were analyzed for HER3 expression using immunohistochemistry (IHC), and 68% of these patient tumors demonstrated the presence of HER3 expression.[34] In a study of 192 NSCLC patients, ERBB3 messenger ribonucleic acid (mRNA) expression was measured by quantitative polymerase chain reaction. Comparison of EGFRm-positive patients to EGFRm-negative patients demonstrated that the ERBB3 level was significantly higher in patients with an EGFR mutation (24.610 ± 34.626) than in those without EGFR mutation (13.868 ± 24.034; *P*=0.0124).[35] Furthermore, HER3 expression is increased in human tumor cell lines after treatment with gefitinib in vitro.[36,37]

Exatecan (DX-8951f), the parent component of the topoisomerase I inhibitor payload component (MAAA-1181a) of patritumab deruxtecan, has activity in NSCLC subjects and a wide range of advanced solid tumors.[24,25,38,39]

Patritumab deruxtecan at 5 mg/kg showed significant antitumor activity in an osimertinib-resistant xenograft model of human EGFRm NSCLC using the PC9AZDR7 cell line. In vivo studies indicate that patritumab deruxtecan exhibits HER3 expression-dependent cell growth inhibition activity.

Antitumor activity of patritumab deruxtecan was also evaluated in vivo using four patient-derived xenograft (PDX) models derived from EGFR-mutant NSCLC.[40] These models were obtained from two patients who developed resistance to osimertinib (Dana-Farber Cancer Institute [DFCI] 306 and DFCI 284) and two patients who developed resistance to erlotinib (DFCI 161 and DFCI 259). As shown in Figure 2.1, a subset of patients from whom the xenograft tumors were derived had known specific resistance mechanisms identified and immunohistochemical evaluation of membrane HER3 (using H-score) demonstrated moderate to high expression in three models (DFCI 161, DFCI 259, DFCI 284) and low/negative expression in one model (DFCI 306). NSG mice with subcutaneous tumors (150-200 mm^3) were treated with either immunoglobulin G1 (IgG1) control or a single dose of patritumab deruxtecan, administered at 10 mg/kg, and tumor growth was assessed twice weekly with digital calipers. Tumor growth inhibition by patritumab deruxtecan compared to control was observed in the 3 models with moderate to high expression of HER3.

Figure 2.1: Patritumab Deruxtecan Inhibits Tumor Growth in HER3-expressing EGFR-mutant EGFR TKI-resistant PDX Models



EGFR = epidermal growth factor receptor; HER3 = human epidermal growth factor receptor 3; IgG = immunoglobulin G; PDX = patient-derived xenograft; TKI = tyrosine kinase inhibitor.
Source: Jänne PA, Yu HA, Johnson ML, et al. Safety and preliminary antitumor activity of U3-1402, a HER3-targeted antibody drug conjugate in EGFR TKI-resistant, EGFRm NSCLC. J Clin Oncol. 2019;37 (15 suppl):9010.

In addition to the evidence for the activity of patritumab deruxtecan in non-clinical models, early clinical evidence, specifically in the U31402-A-U102 study, suggests that patritumab deruxtecan is adequately tolerated in patients with NSCLC and has evidence of clinical activity, particularly in patients with NSCLC harboring an EGFR-activation mutation.

The U31402-A-U102 study is an ongoing multicenter, open-label, Phase 1 study of patritumab deruxtecan in subjects with metastatic or unresectable NSCLC. This study includes Dose Escalation in which subjects receive intravenous (IV) patritumab deruxtecan in 21-day cycles with a starting dose of 3.2 mg/kg, and Dose Expansion in which subjects receive patritumab deruxtecan at the recommended dose for expansion (RDE) determined in Dose Escalation or an up-titration dose regimen.

As of the 03 May 2019 data cut off, 30 EGFRm TKI-resistant NSCLC subjects were evaluated for safety and efficacy. Of the 30 subjects enrolled, the most frequent treatment-emergent adverse events (TEAEs) reported in >20% of subjects, all grades, regardless of causality and in decreasing order of frequency were nausea, fatigue, vomiting, thrombocytopenia, alopecia, decreased appetite, constipation, and diarrhea. Dose-limiting toxicities observed included one (1) grade 3 febrile neutropenia and one (1) grade 4 platelet count decreased in the 5.6 mg/kg cohort, three (3) grade 4 platelet count decreased in the 6.4 mg/kg cohort and no dose limiting toxicities in the 3.2 mg/kg and 4.8 mg/kg cohorts.[41] Of 26 efficacy-evaluable subjects, 23 subjects had at least 1 post-baseline tumor assessment and confirmed responses were observed in 6 subjects (2 partial responses each at 4.8, 5.6, and 6.4 mg/kg), including 3 subjects with an EGFR C797S resistance mutation and 1 subject with a MET amplification.[41] This preliminary safety and efficacy data indicates that patritumab deruxtecan administered as a single agent may provide clinical benefit in subjects with metastatic or locally advanced NSCLC, particularly in patients with NSCLC harboring an EGFR-activating mutation with diverse mechanisms of TKI resistance and previously treated with osimertinib.

As of the data cut-off date of 05 Aug 2019, all (100.0%) of the 36 enrolled subjects in the U31402-A-U102 study had received at least one dose of patritumab deruxtecan. Subjects had a median duration of treatment of 4.5 months (range 0.7 to13.8 months). All (100%) subjects had at least one TEAE. The most frequent TEAEs reported in >20% of subjects, all grades, regardless of causality and in decreasing order of frequency are presented in Table 2.1.

Table 2.1: Treatment-emergent Adverse Events Occurring in Greater than 20% of Subjects in Ongoing Study U31402-A-U102

Preferred Term	Number of Subjects (N = 36): n (%)	
	All Grades	Grade ≥3[a]
Subjects with any TEAE	36 (100)	16 (44.4)
Nausea	23 (63.9)	1 (2.8)
Vomiting	15 (41.7)	0
Fatigue	14 (38.9)	1 (2.8)
Platelet count decreased	11 (30.6)	7 (19.4)
Constipation	10 (27.8)	0
Alopecia	9 (25.0)	NA
Decreased appetite	9 (25.0)	0

MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; TEAE = treatment-emergent adverse event.
[a] None of the reported TEAEs with preferred terms listed in this table were Grade 5.
Note: Coded with MedDRA version 21.0.
Source: Data cutoff of 05 Aug 2019.

TEAEs of Grade 3 or higher were reported in 16 (44.4%) subjects as of 05 Aug 2019. The most common Grade ≥3 TEAEs in more than 5% of subjects included platelet count decreased (7 [19.4%] subjects), troponin increased (3 [8.3%] subjects), and anaemia and hypoxia (2 [5.6%] subjects each).

Seven (19.4%) subjects experienced TEAEs that were associated with a dose interruption; the Investigator considered these TEAEs as related to study drug in 5 (13.9%) subjects. There were 8 (22.2%) subjects who underwent a dose reduction and 3 (8.3%) subjects who discontinued study drug due to TEAEs (all considered drug-related by the Investigator) as of the data cut-off date. One (2.8%) subject experienced an adverse event of special interest (AESI) of pneumonitis (Grade 2) considered by the Investigator as related to patritumab deruxtecan. No subject met the potential Hy's Law criteria as of the data cut-off date. No subject had a TEAE that was associated with a fatal outcome. This clinical experience indicates that patritumab deruxtecan can be administered safely to subjects with previously treated NSCLC.

With consideration to this clinical experience, a dose of 5.6 mg/kg was identified for further clinical investigation in subjects with NSCLC with an EGFR-activating mutation. Moreover, preliminary evidence for the tolerability of an "up-titration" regimen with initial dose escalation of patritumab deruxtecan was identified, and this regimen was selected also for further clinical evaluation.

See Section 4.3 for dose justification.

2.3. Benefit and Risk Assessment

In subjects with EGFRm NSCLC who have progressed after TKI and platinum doublet therapy, standard therapy (eg, with ramucirumab plus docetaxel) is associated with a median OS of approximately 10 months. Thus, there is a considerable unmet medical need for such subjects.

Based on the preliminary clinical safety data from the ongoing patritumab deruxtecan studies, nausea, decreased appetite, vomiting, diarrhea, platelet count decreased/thrombocytopenia, white blood cell count decreased/leukopenia, neutrophil count decreased/neutropenia, febrile neutropenia, anemia, fatigue, malaise, stomatitis, constipation, hypokalemia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, epistaxis, and alopecia are identified risks.[42] The dose regimens comprising a fixed dose of 5.6 mg/kg or the up-titration regimen have each demonstrated tolerability in study subjects (see Section 4.3).

Preliminary data as of 03 May 2019 from the ongoing study U31402-A-U102 are as follows: of the 23 efficacy-evaluable patients, 6 had confirmed partial responses (2 each at 4.8, 5.6, and 6.4 mg/kg). Thus, preliminary evidence of efficacy has been demonstrated in patients with EGFR mutated NSCLC (see Section 2.2).[41] Therefore, the collective information from both clinical as well as preclinical evaluations indicates that the benefit/risk ratio of patritumab deruxtecan investigation therapy is favorable in subjects with EGFRm NSCLC.

Please refer to the most recent version of the Investigator's Brochure (IB) for more information.

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 investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** ORR **Description:** ORR as assessed by BICR per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.	Efficacy
Secondary			
To investigate the durability of patritumab deruxtecan antitumor activity in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** DoR **Description:** DoR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	DoR is defined as the time from the first documented response (confirmed CR or PR) to the date of progression or death due to any cause.	Efficacy
To further investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR	**Title:** PFS **Description:** PFS as assessed by BICR and Investigator per RECIST v1.1	PFS is defined as the time from the start of study treatment to the earlier of the dates of the first documentation of objective PD or death due to any cause.	

Objectives	Outcome Measure	Endpoints	Category
mutation (exon 19 deletion or L858R)	**Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject. Death date is collected until the subject discontinues the study.		
	Title: ORR **Description:** ORR as assessed by Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression, death, lost to follow-up, or withdrawal by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR.	Efficacy
	Title: DCR **Description:** DCR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	DCR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or SD.	Efficacy
	Title: TTR **Description:** TTR as assessed by BICR and Investigator per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	TTR is defined as the time from the start of study treatment to the date of the first documentation of response (confirmed CR or PR).	Efficacy

Objectives	Outcome Measure	Endpoints	Category
	Title: Best percentage change in the SoD of measurable tumors **Description:** SoD as assessed by BICR and by Investigator per RECIST V1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject.	The best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.	Efficacy
	Title: OS **Description:** OS **Time frame:** Death date is collected until the subject discontinues the study.	OS is defined as the time from the start of study treatment to the date of death due to any cause.	Efficacy
To assess the safety and tolerability of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	**Title:** Safety during the study* **Description:** Descriptive statistics of safety endpoints **Time frame:** From the time the subject signs the main study ICF and up to 40 (+ 7) days after the last dose of study drug (ie, 5 half-lives of the ADC/the follow-up period). *Although this is a secondary objective, this is a primary outcome measure.	Incidence of TEAEs, SAEs, AESIs (ILD and elevation of aminotransferases and TBL), ECOG PS, vital sign measurements, standard clinical laboratory parameters (hematology, serum chemistry, and urinalysis), ECG parameters, ECHO/MUGA scan findings, and ophthalmologic findings. AEs and laboratory test results will be coded using the most recent version of MedDRA and will be graded using NCI-CTCAE v5.0.	Safety
To evaluate HER3 protein expression in tumor tissue and its relationship with efficacy	**Title:** Correlation between HER3 protein expression (as determined by HER3 IHC assay) and efficacy **Description:** Descriptive summary of HER3 status, and a correlative analysis between HER3 protein expression level (as	HER3 protein expression in tumor tissue (as determined by IHC) and correlation with ORR, DoR, and PFS	Efficacy/Biomarker

Objectives	Outcome Measure	Endpoints	Category
	determined by HER3 IHC assay) and efficacy **Time frame:** Efficacy data are collected at baseline, then from the start of study treatment until documented disease progression by BICR, death, lost to follow-up, or withdrawal by the subject. HER3 data are collected at baseline (biopsy).		
To assess the immunogenicity incidence against patritumab deruxtecan	**Title:** Immunogenicity **Description:** ADA prevalence, incidence and titer for patritumab deruxtecan. **Time frame:** Data are collected from the start of study treatment until EOT. Additional time points are specified in Table 1.1 and Table 1.2.	ADA prevalence: the proportion of all subjects having a confirmed positive ADA sample at any point in time. ADA incidence: the proportion of subjects having treatment-emergent ADA. ADA titer will be determined for confirmed ADA positive samples. Neutralizing antibodies: when neutralizing assay became available confirmed ADA positive samples may be analyzed for neutralizing activity.	Immunogenicity
Exploratory			
To explore changes in HER3 expression levels (mRNA in tissue and blood-based measurement) and HER3 dynamics	Not applicable	HER3 expression level (mRNA in tissue and blood-based measurement) and HER3 dynamics (mRNA and protein level) will be assessed in correlation with ORR, DoR, and PFS (confirmed by BICR).	Biomarker
To explore biomarkers that may identify subjects that will derive optimal therapeutic benefit from patritumab deruxtecan	Not applicable	Potential biomarkers (gene expression, genomic alteration, gene signatures) will be assessed in association with patritumab deruxtecan sensitivity/resistance	Biomarker

Objectives	Outcome Measure	Endpoints	Category
To characterize the pharmacokinetics (PK) of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)	Not applicable	Serum concentration of patritumab deruxtecan (ADC, total anti-HER3 antibody, and MAAA-1181a) Population PK (PopPK) analysis	Pharmacokinetic
To evaluate the Exposure-Response for efficacy and safety endpoints	Not applicable	Exposure-Response for efficacy and safety parameters	Efficacy/Safety

ADA = anti-drug antibody; ADC = antibody drug conjugate; AE = adverse event; AESI = adverse event of special interest; BICR = blinded independent central review; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EOT = end of treatment; HER3 = human epidermal growth factor receptor 3; ICF = informed consent form; IHC = immunohistochemistry; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; mRNA = messenger ribonucleic acid; MUGA = multigated acquisition; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; SoD = sum of diameters; TBL = total bilirubin; TEAE = treatment-emergent adverse event; TTR = time to response; v = version.

3.1. Rationale for Selection of Primary and Key Secondary Endpoints

The primary and key efficacy endpoints selected will evaluate evidence of drug activity. ORR is defined as the proportion of subjects with complete or partial response as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 in this study. ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study. Because ORR is directly attributable to drug effect, it is an appropriate measure of efficacy in single-arm studies.[43]

Duration of response in subjects with confirmed response of complete response (CR) or partial response (PR) is an important secondary endpoint of the study. A durable response is clinically meaningful in subjects with locally advanced or metastatic NSCLC who have received at least 1 regimen of platinum-based chemotherapy with or without immunotherapy in which there remains an unmet medical need.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, open-label, Phase 2 study of subjects with metastatic or locally advanced NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) who have received and progressed on or after at least 1 EGFR TKI and 1 platinum-based chemotherapy-containing regimen. This study will initially randomize subjects to one of 2 arms in a 1:1 ratio, for dose selection, to receive either a 5.6 mg/kg fixed dose regimen (Arm 1) or an up-titration dose regimen (Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg every 3 weeks [Q3W]; Arm 2) of patritumab deruxtecan on Day 1 of each 21-day cycle.

In the ongoing U31402-A-U102 study the same population is being studied in multiple expansion cohorts: Cohorts 3a and 3b (with 45 subjects planned to be randomized to each dose regimen, 5.6 mg/kg Q3W or up-titration) and Cohort 1 (45 subjects dosed with 5.6 mg/kg Q3W). If, during the conduct of the current study (U31402-A-U201), analyses from the U31402-A-U102 study indicate that one dose regimen provides clear advantages over the other in terms of benefit/risk, further enrollment into one arm may be discontinued:

- If a single dose regimen (Arm 1 or Arm 2) is selected to continue enrollment, subjects enrolled after the decision point will be assigned to the selected dose regimen. Subjects enrolled before the decision point will continue their originally assigned dose regimen without crossover.
- If there is no significant difference in efficacy and/or safety from the U31402-A--U102 NSCLC study, both dose regimens/arms in this study (U31402-A-U201) will continue to enroll to study completion.

The subject population is described in Section 5.

The study will be conducted at approximately 135 study sites located in North America, the European Union (EU), and the Asia Pacific region including Japan.

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

4.1.1. Design Overview

This study will initially randomize subjects to one of 2 arms in a 1:1 ratio, for dose selection, to receive either a 5.6 mg/kg fixed dose regimen (Arm 1) or an up-titration dose regimen (Arm 2) of patritumab deruxtecan on Day 1 of each 21-day cycle.

Based on the accumulated data collected in the ongoing Phase 1 U31402-A-U102 study, a decision to continue enrollment in Arm 1, Arm 2, or both arms of this study (U31402-A-U201) will be made. The total number of subjects will be dependent on the following scenarios:

- **Scenario 1 (continue enrollment in the 5.6 mg/kg fixed dose regimen arm only)** - will enroll approximately 210 subjects in the 5.6 mg/kg fixed dose regimen arm only

and enrollment in the up-titration dose regimen arm will be halted at the time of the decision point. Subjects enrolled in the up-titration dose regimen arm will continue with their assigned treatment and will NOT cross over to the 5.6 mg/kg fixed dose regimen arm. Sample size in the up-titration dose regimen arm cannot be determined a priori, since it depends on enrollment speed and the timing of the decision from the Phase 1 (U31402-A-U102) data.

- **Scenario 2 (continue enrollment in the up-titration dose regimen arm only)** - analogous considerations to scenario 1.
- **Scenario 3 (continue enrollment in both arms)** - The 5.6 mg/kg fixed dose regimen arm and the up-titration dose regimen arm will enroll approximately 210 subjects in each arm for a total of up to approximately 420 subjects.

The Schedule of Events (SoE) is presented in Table 1.1 (Screening and Cycles 1 through 3 of Treatment Period) and Table 1.2 (Cycle 4 onwards, End of Treatment [EOT], and Follow-up).

The study will be divided into 3 periods: a Screening Period, Treatment Period, and Follow-up Period.

- The Screening Period will start on the day of signing the main informed consent form (ICF) and will have a maximum duration of 35 days. During the 35-day Screening Period, the subject's eligibility will be determined. The subject will undergo a medical history evaluation, hepatitis B and C testing, a physical examination, measurement of vital signs, standard clinical laboratory tests, an electrocardiogram (ECG) recording, an echocardiogram (ECHO) or multigated acquisition (MUGA) scan, and an ophthalmologic assessment. Baseline tumor imaging must be performed within 28 days prior to Cycle 1 Day 1. A pretreatment tumor biopsy can be performed or archival tumor tissue can be provided prior to enrollment during the Screening Period. Pretreatment or archival tumor tissue must be of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by hematoxylin and eosin [H&E] staining at the central laboratory). Archival tumor tissue must have been collected from a biopsy within 3 months prior to signing of the tissue consent and since progression on the most recent cancer therapy. Subjects must have documentation of an EGFR-activating mutation detected from tumor tissue: exon 19 deletion or L858R. If test results for an EGFR-activating mutation are not available, subjects are required to undergo testing for these genomic alterations using assays approved in their country of testing (see Section 8.1).
- Eligible subjects will be enrolled and enter the Treatment Period. The Treatment Period starts on the day of enrollment (ie, Cycle 1 Day 1) and continues until a subject permanently discontinues patritumab deruxtecan. To minimize the possibility of developing tumor flare with discontinuation of EGFR TKI, subjects who fulfill eligibility criteria and are receiving an EGFR TKI at the time of informed consent should be advised to continue their current EGFR TKI until 5 days prior to Cycle 1 Day 1. See the washout period for prior treatments in Sections 5.2 and 6.6. Subjects will undergo radiographic assessment of tumor response based on RECIST v1.1 every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days), independent of treatment cycle, until documented disease progression by

blinded independent central review (BICR), death, lost to follow-up, or withdrawal of consent.
Subjects will continue to receive patritumab deruxtecan until documented disease progression per RECIST v1.1, clinical progression, unacceptable toxicity, withdrawal of consent by the subject, physician's decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons. If progressive disease is suspected by Investigator tumor assessment, imaging must be submitted to BICR for expedited confirmation of disease progression. The decision to discontinue patritumab deruxtecan is according to Investigator judgement and should consider BICR assessment.

- The Follow-up Period will start upon permanent discontinuation of patritumab deruxtecan. After completion of the 40-day (+7 days) safety follow-up visit, subjects will be followed every 3 months for survival. Subjects who discontinue study treatment for any reason other than documented disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject will continue to undergo tumor assessments at the same frequency of every 6 weeks (±7 days) from Cycle 1, Day 1 for the first 24 weeks then every 12 weeks (±7 days) during the Follow-up Period.

The primary analysis of ORR as assessed by BICR will be conducted after all enrolled subjects have either a minimum of 9 months of follow-up or have discontinued from the study earlier. The final analysis will occur after all subjects have discontinued from the study (see definition of overall End of Study [EOS] in Section 4.1.2).

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 all enrolled subjects have either a minimum of 9 months of follow up or have discontinued from the study earlier. This date will be used as the data cut-off (DCO) date for the primary analysis of the study. All subjects still on treatment and continuing to derive benefit from patritumab deruxtecan at the primary completion date will continue to follow the study SoE (Table 1.2) until the **overall End of Study (EOS)** is reached.

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

Overall EOS will occur when:

- after the last subject last visit;
- all subjects have discontinued treatment and discontinued long-term survival follow-up or have died;
- an alternative study becomes available, for subjects continuing to derive benefit from treatment with patritumab deruxtecan, where the study drug is offered to these subjects;
- the study is discontinued by the Sponsor for other reasons (administrative, program-level or class-related). In the event the end of study is reached prior to last

subject last dose, the Sponsor will provide notification and rationale according to local regulatory requirements.

At the time of study closure, any subjects who are continuing treatment with patritumab deruxtecan and who are judged by the Investigator to have ongoing benefit may continue to receive treatment with patritumab deruxtecan through a rollover protocol or another mechanism consistent with local requirements.

4.1.3. Dose Regimen(s)

Patritumab deruxtecan will be administered as an IV infusion Q3W on Day 1 of each 21-day cycle as a fixed dose regimen of 5.6 mg/kg Q3W or an up-titration dose regimen at a dose of 3.2 mg/kg at Cycle 1, 4.8 mg/kg at Cycle 2, and 6.4 mg/kg at Cycle 3 Q3W and subsequent cycles (depending on the assigned dose group) on Day 1 of each 21-day cycle. The study will use the intended patritumab deruxtecan lyophilized-drug product (Lyo-DP).

See Table 6.1 for complete details on dose regimen.

4.1.4. Duration

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

Duration of Treatment and Subject Participation

The duration of study treatment will continue until progressive disease, clinical progression, unacceptable toxicity, withdrawal of consent by the subject, physician's decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons, whichever occurs first. The total duration of subject participation will include a 40 (+7) day safety follow-up and every 3-month survival follow-up, or until withdrawal of consent by the subject, lost to follow-up, study termination by the Sponsor, death, or other reasons.

Overall Study Duration

Anticipated total duration of the study is expected to be 26 months consisting of approximately 12 months for enrollment and 14 months on treatment. 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 is designed to investigate the antitumor activity of patritumab deruxtecan using the primary endpoint of ORR (as assessed by BICR per RECIST v1.1) and key secondary endpoint of duration of response (DoR) (as assessed by BICR per RECIST v1.1). Two dose regimens will be investigated in this study: a 5.6 mg/kg fixed dose regimen and an up-titration dose regimen. Each dose regimen has demonstrated preliminary efficacy and acceptable safety based on a program-wide analysis conducted in the U31402-A-U102 and U31402-A-J101

studies (see Section 4.3). Both regimens are also being further explored in the U31402-A-U102 Phase 1 study (Section 4.1).

This study will be based on the assumption that treatment with patritumab deruxtecan will result in a clinically meaningful confirmed ORR of 37% (alternative hypothesis) that is durable compared to an ORR of 26.4% (null hypothesis) that is based on the upper bound of the 95% CI of a historic ORR of 23% of the ramucirumab plus docetaxel arm from the REVEL trial.[22] These assumptions will be utilized to help determine the potential clinical benefit of patritumab deruxtecan.

To enroll subjects into each arm with similar subject demographic and baseline, randomization is being implemented but there will be no direct comparison between the study arms. However, accumulated efficacy, safety, and pharmacokinetic (PK)/pharmacodynamic (PD) data from U31402-A-U102 will support the Sponsor's decision to continue enrollment in Arm 1, Arm 2, or both arms of this study (U31402-A-U201). This decision will be made in order to select the most optimal dose regimen with the most favorable benefit/risk profile in subjects with NSCLC harboring activating EGFR mutations (exon 19 deletion or L858R).

Until this decision is made, both the 5.6 mg/kg fixed dose regimen (Arm 1) and the up-titration dose regimen (Arm 2) will continue to be explored in this study (U31402-A-U201).

The rationale for selection of the primary and key secondary efficacy endpoints is presented in Section 3.1.

4.3. Justification for Dose Regimen(s)

Two dose regimens are being evaluated for safety and efficacy in this study (U31402-A-U201):

- Fixed dose regimen (Arm 1): 5.6 mg/kg IV Q3W
- Up-titration dose regimen (Arm 2): Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg IV Q3W

The 2 dose regimens are currently being evaluated in studies U31402-A-U102 and U31402-A-J101. See Table 4.1 for details.

Table 4.1: Subjects Treated and Planned by Dose Regimen

	Fixed Dose Regimen			Up-titration Dose Regimen	
Dosing	**5.6 mg/kg IV Q3W**			**Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg IV Q3W cycles**	
Study	**Cohort**	**Treated**	**Planned**	**Treated**	**Planned**
U31402-A-U102	**Dose Escalation** (NSCLC with EGFR-activating mutations)	12	12	--	--
	Dose Expansion Cohort 1 (NSCLC with EGFR-activating mutations)	45	45	--	--
	Dose Expansion Cohort 2 (NSCLC without EGFR-activating mutations)	19	45	--	--
	Dose Expansion Cohort 3a (NSCLC with EGFR-activating mutations)	1	45	--	--
	Dose Expansion Cohort 3b (NSCLC with EGFR-activating mutations)	--	--	1	45
U31402-A-J101	**Dose Finding** (HER3-positive metastatic breast cancer)	--	--	12	12

EGFR= epidermal growth factor receptor; HER3 = human epidermal growth factor receptor 3; IV = intravenous; NSCLC= Non-small cell lung cancer; Q3W = every 3 weeks.
Source: Preliminary data as of 30 Apr 2020 for study U31402-A-U102 and as of 11 Mar 2020 for study U31402-A-J101

The **5.6 mg/kg fixed dose regimen** was selected based on preliminary analysis of PK, safety, and efficacy from 30 subjects in U31402-A-U102 (DCO 03 May 2019)[41] and 130 subjects in U31402-A-J101 (DCO 29 Mar 2019) studies. Together with exposure-response modeling of efficacy and safety parameters, these analyses supported 5.6 mg/kg as the RDE. For further details, see Section 2.2.

The **up-titration dose regimen** was additionally chosen for study based on data collected in the U31402-A-J101 study that demonstrated preliminary evidence of a favorable safety profile at this dose regimen. During the U31402-A-J101 dose escalation, Grade 3 or 4 thrombocytopenia was observed most often in Cycle 1 followed by a reactive thrombocytosis over Cycle 2 and Cycle 3 resulting in a pre-infusion Cycle 3 platelet count equal to or greater than baseline (Screening). The incidences of both ≥Grade 3 thrombocytopenia and (≥Grade 3 neutropenia increased with respect to administered dose, and exposure-response analyses showed that probability of either of these events correlated with the Cmax of the drug payload (MAAA-1181a). Furthermore, the payload Cmax was noted to be higher in Cycle 1 versus Cycle 3. Based on these preliminary observations, an up-titration dose regimen was chosen for study in the U31402-A-J101 study, whereby 3.2 mg/kg is administered in Cycle 1, 4.8 mg/kg in Cycle 2, and 6.4 mg/kg in Cycle 3 and beyond, in 3-week cycles. This is based on the hypothesis that starting with a lower dose in Cycle 1 would be associated with a lower payload

Cmax and hence a lower risk of ≥Grade 3 thrombocytopenia or neutropenia during Cycle 1, and that reactive thrombocytosis and decreases in payload Cmax over Cycles 2 and 3 might present a lower risk of ≥Grade 3 thrombocytopenia or neutropenia in later cycles.

As of 05 Aug 2019, the up-titration dose regimen in the U31402-A-J101 study has shown an incidence of ≥Grade 3 thrombocytopenia in 16.7% of subjects; whereas, the 4.8 mg/kg or 6.4 mg/kg fixed dose regimens was 24.4% and 53.5%, respectively (Table 4.2). In addition, ≥Grade 3 neutropenia was observed in 50.0% of subjects treated with the up-titration dose regimen compared to 22.2% and 48.8%, respectively, in the 4.8 mg/kg or 6.4 mg/kg fixed dose regimens.

Based on this preliminary evidence, both a fixed dose regimen and an up-titration dose regimen are being evaluated in the present study to provide a deeper understanding of the safety and efficacy of both regimens.

Table 4.2: Preliminary Data by Dose Regimen in Subjects with HER3-positive Breast Cancer in Study U31402-A-J101

	Fixed Dose Regimen		**Up-Titration Regimen**
Dosing	**4.8 mg/kg IV Q3W**	**6.4 mg/kg IV Q3W**	**Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg IV Q3W cycles**
Efficacy Analysis Set (n)	37	36	12
Confirmed ORR (by Investigator Assessments), n (%)	8 (21.6)	11 (30.6)	5 (41.7)
Safety Analysis Set (n)	45	43	12
Serious TEAEs	12 (26.7)	18 (41.9)	3 (25.0)
Grade ≥3 Thrombocytopenia (%)	11 (24.4)	23 (53.5)	2 (16.7)
Grade ≥3 Neutropenia (%)	10 (22.2)	21 (48.8)	6 (50.0)
Grade ≥3 Anemia (%)	9 (20.0)	11 (25.6)	1 (8.3)

HER3 = human epidermal growth factor receptor 3; IV = intravenous; ORR = objective response rate; Q3W = every 3 weeks; TEAE = treatment-emergent adverse event.
As of the 05 Aug 2019 data cut-off date

5. STUDY POPULATION

Adult subjects (aged ≥18 years in the United States [US]; ≥20 years old in Japan and South Korea; for other countries, guidelines on the legal age to consent[44] should be followed) with a diagnosis of metastatic or locally advanced NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) after progression with systemic therapy who have received at least one prior line of TKI and 1 platinum-based chemotherapy containing regimen in the metastatic or locally advanced setting.

5.1. Inclusion Criteria

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

1. Sign and date the tissue ICF and the main ICF, prior to the start of any study-specific qualification procedures.
2. Male or female subjects aged ≥18 years (follow local regulatory requirements if the legal age of consent[44] for study participation is >18 years old).
3. Histologically or cytologically documented locally advanced or metastatic NSCLC not amenable to curative surgery or radiation.
4. Documentation of radiological disease progression while on/after receiving most recent treatment regimen for locally advanced or metastatic disease. Subjects must have received both of the following:
    a. Prior treatment with osimertinib. Subjects receiving an EGFR TKI at the time of signing informed consent should continue to take the EGFR TKI until 5 days prior to Cycle 1 Day 1.

Subjects in South Korea known to harbor a clinically actionable genomic alteration in addition to EGFR mutation (eg, anaplastic lymphoma kinase [ALK] or ROS1 protocol oncogene 1 [ROS1] fusion) for which treatment is available must have also received prior treatment with at least 1 approved genotype-directed therapy, unless unable (ie, if contraindicated). No new testing for these genomic alterations (eg, ALK or ROS1 fusion) is required for Screening.

    b. Systemic therapy with at least 1 platinum-based chemotherapy regimen.
5. Documentation of an EGFR-activating mutation detected from tumor tissue or blood sample: exon 19 deletion or L858R.
6. At least 1 measurable lesion confirmed by BICR as per RECIST v1.1 (see Section 10.4)
7. Consented and willing to provide required tumor tissue of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by H&E staining at the central laboratory). Required tumor tissue can be provided as either:
    a. Pretreatment tumor biopsy from at least 1 lesion not previously irradiated and amenable to core biopsy

OR

b. Archival tumor tissue collected from a biopsy performed within 3 months prior to signing of the tissue consent and since progression while on or after treatment with the most recent cancer therapy regimen.

8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at Screening (see Section 10.3.3).

9. Has adequate bone marrow reserve and organ function, based on local laboratory data within 14 days prior to Cycle 1 Day 1:

Laboratory Test	**Laboratory Value**
Platelet count	≥100 000/mm^3 or ≥100 × 10^9/L (platelet transfusions are not allowed up to 14 days prior to Cycle 1 Day 1 to meet eligibility)
Hemoglobin	≥9.0 g/dL (transfusion and/or growth factor support is allowed)
Absolute neutrophil count	≥1500/mm^3 or ≥1.5 × 10^9/L
Serum creatinine OR creatinine clearance	SCr ≤1.5 × ULN, OR CrCl ≥30 mL/min as calculated using the Cockcroft-Gault equation or measured CrCl
Aspartate aminotransferase/ Alanine aminotransferase	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN if no liver metastases (<3 × ULN in the presence of documented Gilbert's syndrome [unconjugated hyperbilirubinemia] or liver metastases)
Serum albumin	≥2.5 g/dL
PT or PT-INR and aPTT/PTT	≤1.5 × ULN, except for subjects on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-INR within therapeutic range as deemed appropriate by the Investigator

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; SCr = serum creatinine; ULN = upper limit of normal.

10. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and must be willing to use highly effective birth control, as detailed in Section 10.3.4, upon enrollment, during the Treatment Period, and for 7 months following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with surgery at least 1 month before the first dose or confirmed by follicle stimulating hormone (FSH) test. See Section 8.4.2 Pregnancy Test for further details regarding confirmation of post-menopausal status.

11. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

12. If male, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.4) upon enrollment, during the treatment period, and for at least 4 months following the last dose of study drug.
13. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.
14. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

5.2. Exclusion Criteria

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

1. Any previous or current histologic or cytologic evidence of small cell OR combined small cell/non-small cell disease in the archival tumor tissue or pretreatment tumor biopsy.
2. Any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current interstitial lung disease (ILD), or is suspected to have such disease by imaging during Screening.
3. Clinically severe respiratory compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
   a. Any underlying pulmonary disorder (eg, pulmonary emboli within 3 months prior to the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion);
   b. Any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (eg, rheumatoid arthritis, Sjogren's syndrome, sarcoidosis);

   OR prior complete pneumonectomy.
4. Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory or any form of immunosuppressive therapy prior to enrollment. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
5. Evidence of any leptomeningeal disease
6. Evidence of clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive or treated brain metastases who are asymptomatic (ie, without neurologic signs or symptoms and not requiring treatment with corticosteroids or anticonvulsants) may be included in the study. Subjects must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1.
7. Inadequate washout period prior to Cycle 1 Day 1, defined as:
   a. Whole brain radiation therapy <14 days or stereotactic brain radiation therapy <7 days;

b. Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), <14 days or 5 half-lives, whichever is longer;
c. Monoclonal antibodies, other than immune checkpoint inhibitors, such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFR) <28 days;
d. Immune checkpoint inhibitor therapy <21 days;
e. Major surgery (excluding placement of vascular access) <28 days;
f. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <14 days; or
g. Chloroquine/hydroxychloroquine ≤14 days.

8. Prior treatment with an anti-HER3 antibody or single-agent topoisomerase I inhibitor.
9. Prior treatment with an ADC that consists of any topoisomerase I inhibitor.
10. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible at the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee.
11. Has history of other active malignancy within 3 years prior to enrollment, except:
    a. Adequately treated non-melanoma skin cancer;
    b. Superficial bladder tumors (Ta, Tis, T1);
    c. Adequately treated intraepithelial carcinoma of the cervix uteri;
    d. Low risk non-metastatic prostate cancer (with Gleason score <7, and following local treatment or ongoing active surveillance);
    e. Any other curatively treated in situ disease.
12. Uncontrolled or significant cardiovascular disease prior to Cycle 1 Day 1, including:
    a. QT interval corrected with Fridericia's formula (QTcF) prolongation interval of >470 ms for females and >450 ms for males;
    b. Left ventricular ejection fraction (LVEF) <50% by either ECHO or MUGA scan;
    c. Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg;
    d. Myocardial infarction within 6 months;
    e. New York Heart Association (NYHA) Classes 2 to 4 congestive heart failure (See Section 10.3.2) within 28 days;
    f. Uncontrolled angina pectoris within 6 months;
    g. Cardiac arrhythmia requiring antiarrhythmic treatment.
13. Active hepatitis B and/or hepatitis C infection, such as those with serologic evidence of viral infection within 28 days of Cycle 1 Day 1.
    a. Subjects with past or resolved HBV infection are eligible if:
        i. Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) positive; **OR**
        ii. HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to

the viral load evaluation with normal transaminases values (in the absence of liver metastasis); **OR**

iii. HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation for subjects with liver metastasis and abnormal transaminases with a result of AST/ALT <3 × ULN.

b. Subjects with a history of hepatitis C infection will be eligible for enrollment only if the viral load according to local standards of detection is documented to be below the level of detection in the absence of anti-viral therapy during the previous 12 weeks (ie, sustained viral response according to the local product label but no less than 12 weeks, whichever is longer).

14. Subject with any human immunodeficiency virus (HIV) infection.
15. Any evidence of severe or uncontrolled diseases including active bleeding diatheses, active infection, psychiatric illness/social situations, geographical factors, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
16. History of hypersensitivity to either the drug substance or any excipients in patritumab deruxtecan.
17. Female who is pregnant or breast-feeding or intends to become pregnant during the study.
18. Prior or ongoing clinically relevant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's opinion, could affect the safety of the subject; alter the absorption, distribution, metabolism or excretion of the study drug; or confound the assessment of study results.
19. Has clinically significant corneal disease.

5.3. Screening Failures, Rescreening, and Subject Replacement

The study will allow rescreening once for any subject who failed to meet eligibility criteria upon initial Screening or whose Screening window has elapsed. The Investigator will consult with the Sponsor prior to making the decision to rescreen a subject. A unique subject identification number will be assigned at the time of rescreening. The initial reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log at the site and will be entered into the clinical database. If a subject undergoes rescreening, the subject must repeat all out of window assessments (ie, procedures performed beyond the specified window prior to Cycle 1 Day 1).

6. STUDY TREATMENT(S)

See Figure 1.1 for treatment sequence.

6.1. Study Drug(s) Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of patritumab deruxtecan (U3-1402).

Table 6.1: Study Drug Dosing Information

Study Drug Name	Patritumab Deruxtecan (U3-1402) for Injection 100 mg
Dosage Formulation	Patritumab deruxtecan (U3-1402) drug product will be provided as 100 mg of lyophilized-drug powder (Lyo-DP) in single-use amber glass vials of sterile drug product to be reconstituted with 5 mL water for injection to 20 mg/mL prior to use.
Dosage Level(s)	**Fixed dose regimen**: 5.6 mg/kg **Up-titration dose regimen**: Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg
Route of Administration	Intravenous (IV)
Dosing	One IV infusion every 3 weeks on Day 1 of each 21-day cycle
Duration	Patritumab deruxtecan (U3-1402) will be infused as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. In the absence of infusion-related reaction (IRR), the subsequent doses will be infused over approximately 30 minutes. In case of IRR at any time during treatment, subsequent doses will be infused over 90 minutes.
Packaging	Patritumab deruxtecan (U3-1402) will be supplied by the Sponsor. Study drug will be packaged in cartons containing 1 vial of patritumab deruxtecan for Injection 100 mg (lyophilized powder). Each vial is single use only.
Labeling	Patritumab deruxtecan (U3-1402) packaging will be labeled as required per local regulatory requirement.

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

Preparation, Handling, and Disposal

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

Prepared medicinal solutions should be used immediately. Refer to the Dose Preparation Instructions for detailed information about preparation and administration of patritumab deruxtecan.

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

Administration

The selected dose of patritumab deruxtecan will be reconstituted with 5 mL water for injection to 20 mg/mL prior to use. Following the reconstitution in 5 mL water for injection the product will be diluted in 5% dextrose solution for infusion. Patritumab deruxtecan will be administered as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no

infusion-related reactions after the initial dose, subsequent doses of patritumab deruxtecan will be infused over approximately 30 minutes on Day 1 of each subsequent cycle Q3W. Refer to Table 6.4 for additional information on drug administration following infusion-related reactions.

Subjects should receive the study drug within 3 days of randomization/enrollment. The subject's weight at baseline (defined as the last measurement on or prior to Cycle 1 Day 1) will be used to calculate the initial dose. The subject's weight will be determined at the beginning of each cycle. If during Cycle 1 Day 1 or throughout the course of treatment, the subject's weight changes by ≥10% from the baseline weight, the dose will be recalculated using this new weight and will be considered the new baseline for all subsequent dosing calculations.

The drug formulation used in this study will be Lyo-DP.

Storage

Patritumab deruxtecan vials must be stored in a secure, limited access storage area under the recommended storage conditions noted on the label and protected from light: Lyo-DP should be stored at 5°C±3°C (between 2°C and 8°C).

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

See the Pharmacy Manual for additional information on storage conditions of the study drug.

Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug against the shipping documentation.

The Receipt of Shipment Form should be faxed as instructed on the form unless receipt is controlled by interactive response technology (IRT). The original will be retained at the study site.

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

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

At the end of the study or as directed, all unused, used and/or partially used patritumab deruxtecan will be destroyed at the site as per site policy or local laws (and documented). As applicable, the study site must file a copy of the appropriate institution policy (and certificate of destruction) within their Investigator site file and provide a copy to the Sponsor. Please see the Pharmacy Manual for details.

6.3. Measures to Minimize Bias: Randomization and Blinding

Method of Treatment Allocation

This will be an open-label study. Initially, subjects will be randomized to one of the 2 arms (5.6 mg/kg fixed dose regimen [Arm 1] or up-titration dose regimen [Arm 2]) in a 1:1 ratio until

a decision is made based on data from the U31402-A-U102 study to continue enrollment in Arm 1, Arm 2, or in both arms. A maximum of 3 days is allowed between randomization and Cycle 1 Day 1 of the treatment in the study.

An independent biostatistician from the CRO, not otherwise part of the Sponsor study team, will generate the randomization list. Based on this information, the system will assign a unique randomization number and dose group for that subject.

Overall enrollment will be managed through the IRT for subjects meeting all eligibility criteria. The instructions on how to use the system will be provided in the IRT Manual.

Blinding

This is an open-label study; therefore, no blinding will be used.

6.4. Treatment Compliance

Patritumab deruxtecan will be administered as an IV infusion to subjects under the supervision of study site personnel. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for administration of study drug. Start and stop date/time of injection and amount of drug administered must be recorded in the electronic case report form (eCRF).

6.5. Guidelines for Dose Modification

All dose modifications (ie, dose interruption, dose reduction, and/or treatment discontinuation) should be based on the worst preceding toxicity (NCI-CTCAE v5.0). Possible exceptions to the dose modification criteria may be allowed on a case-by-case basis after discussion and agreement between the Investigator and Sponsor. The agreement must be documented. Dose modification decisions may be based on local laboratory results.

All dose modifications must be recorded on the adverse event (AE) and drug administration eCRF pages. If study drug is interrupted, missed doses will not be made up.

Dose modifications are applicable only to TEAEs that are assessed as related to use of patritumab deruxtecan by the Investigator(s). For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

Dose Delay Guidelines

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

Dose Reduction Guidelines

If dose reduction is required, patritumab deruxtecan dosing should be reduced by 1 dose level at a time (Table 6.2). Once the dose of patritumab deruxtecan has been reduced due to an AE, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required.

Dose reductions for the fixed dose 5.6 mg/kg regimen are described in Table 6.2.

Table 6.2: Dose Reductions for the Fixed Dose 5.6 mg/kg Regimen

Starting Dose (0)	5.6 mg/kg IV infusion Q3W
Dose Level (− 1)	4.8 mg/kg IV infusion Q3W
Dose Level (− 2)	3.2 mg/kg IV infusion Q3W

IV = intravenous; Q3W = every 3 weeks.

In the up-titration regimen, subjects will undergo up-titration as follows: Cycle 1 at 3.2 mg/kg, Cycle 2 at 4.8 mg/kg, Cycle 3 and subsequent cycles at 6.4 mg/kg Q3W. The recommended dose reduction is described in Table 6.3. If a TEAE requiring dose reduction occurs during up-titration (ie, Cycles 1 or 2), a further increase in dose is prohibited.

Table 6.3: Dose Reductions for the Up-titration Dose Regimen

Starting Dose (0)	6.4 mg/kg IV Q3W	4.8 mg/kg Q3W	3.2 mg/kg Q3W
Dose Level (− 1)	4.8 mg/kg IV Q3W	3.2 mg/kg Q3W	Discontinue
Dose Level (− 2)	3.2 mg/kg IV Q3W	Discontinue	Discontinue

IV = intravenous; Q3W = every 3 weeks.

Subjects will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Dose Modification Guidelines

Table 6.4 provides schedule modifications for specific toxicities.

Table 6.4: Dose Modifications for Non-Hematologic and Hematologic Toxicity Related to Patritumab Deruxtecan

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
General disorders and administration site conditions		
Infusion-related reaction (eg, same reduced rate as previous infusion)	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 must be reduced by 50% and subject must be closely monitored. If no other reactions appear, the subsequent infusion rate can be resumed at the initial planned rate.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
	Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] injection fluids); prophylactic medications indicated for ≤24 hours	Patritumab deruxtecan infusion must be interrupted. Symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids) must be started. If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. Upon restart, if Grade 2 symptoms recur, no further patritumab deruxtecan must be administered at that visit. The amount of patritumab deruxtecan infused must be recorded in the eCRF. Subsequent infusions must be conducted at the 50% reduced infusion rate (ie, same reduced rate as previous infusion).
	Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4 Life-threatening consequences, urgent intervention indicated	Administration of patritumab deruxtecan must be discontinued immediately and permanently. Urgent intervention is indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation, etc., must be administered as clinically indicated.
Fatigue/Asthenia/ Malaise	Grade 3	Delay dose until resolved to ≤Grade 1, then: • If resolved to ≤Grade 1 or baseline values in ≤14 days, resume patritumab deruxtecan; • If resolved to ≤Grade 1 or baseline values in >14 days, reduce patritumab deruxtecan by 1 dose level and resume.
Blood and lymphatic system disorders		
Neutrophil count decreased	Grade 3 (500 to <1000/mm^3; 0.5-1 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then resume patritumab deruxtecan.
	Grade 4 (<500/mm^3; <0.5 × 10^9/L)	Delay dose until resolved to ≤Grade 2; then reduce patritumab deruxtecan by 1 dose level.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
Febrile neutropenia (ANC <1000/mm^3; <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	Grade 3	Delay dose until resolved; then resume patritumab deruxtecan. Consider reducing patritumab deruxtecan by 1 dose level. Consider administration of G-CSF as prophylaxis for all subsequent cycles and according to local guidelines.
Febrile neutropenia (ANC <1000/mm^3; <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	Grade 4	Delay dose until resolved, then reduce patritumab deruxtecan by 1 dose level and resume. Administer G-CSF as prophylaxis for all subsequent cycles and according to local guidelines.
Lymphocyte count decreased[a]	Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then: • If resolved in ≤14 days, resume patritumab deruxtecan. • If resolved in >14 days; reduce patritumab deruxtecan by 1 dose level and resume.
Anemia	Grade 3 (Hemoglobin <8.0 g/dL)	Delay dose until resolved to ≤Grade 2 or baseline; then resume patritumab deruxtecan. For recurrent anemia, delay dose until resolved ≤Grade 2 or baseline, then reduce patritumab deruxtecan by 1 dose level and resume. Consider transfusion per institutional guidelines.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay dose until resolved to ≤Grade 2 or baseline, then reduce patritumab deruxtecan by 1 dose level and resume. Consider transfusion per institutional guidelines.
Platelet count decreased	Grade 3 (Platelet <50 – 25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then: • If resolved in ≤14 days, resume patritumab deruxtecan; • If resolved in >14 days, patritumab deruxtecan may be resumed. Consider reducing patritumab deruxtecan by 1 dose level. Consider transfusion per institutional guidelines.
	Grade 4 (Platelet <25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then reduce patritumab deruxtecan by 1 dose level and resume. Consider transfusion per institutional guidelines.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab Deruxtecan
Cardiac disorders		
Heart failure	Grade ≥2 (Symptoms with moderate activity or exertion)	Cardiologist consultation as necessary. Delay dose until resolved to ≤Grade 1, then reduce patritumab deruxtecan by 1 dose level.
Ejection fraction decreased	Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	Continue patritumab deruxtecan.
	LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	Continue patritumab deruxtecan. Repeat LVEF assessment within 3 weeks.
	LVEF 40% to ≤45% and decrease is ≥10% to 20% (absolute value) from baseline	Delay patritumab deruxtecan. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment.
	LVEF <40% or >20% (absolute value) drop from baseline	Delay patritumab deruxtecan. Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% (absolute value) drop from baseline is confirmed, discontinue patritumab deruxtecan. Cardiologist consultation as necessary.
Electrocardiogram QT corrected interval prolonged	Grade 3 (Average QTcF ≥501 ms; >60 ms change from baseline)	Delay patritumab deruxtecan until resolved to ≤Grade 1 (QTcF ≤ 480 ms). Determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If QTcF prolongation is attributed to patritumab deruxtecan, then reduce patritumab deruxtecan by 1 dose level. Cardiologist consultation as necessary.
	Grade 4 (Torsades de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue subject from patritumab deruxtecan. Cardiologist consult as necessary.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab Deruxtecan
Respiratory, thoracic and mediastinal disorders		
Pulmonary toxicity	See next column	If a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD. If ILD is suspected, delay patritumab deruxtecan dosing pending further evaluation and start corticosteroid treatment promptly unless clinically contraindicated.[45] Evaluations must include CT (preferably high-resolution CT), and pulmonologist consultation (when the Investigator is not a pulmonologist). The following evaluations must also be obtained, as indicated: • Infectious disease consultation as clinically indicated • Blood culture and CBC (other blood tests could be considered as needed) • Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests • Pulse oximetry (SpO_2) • Arterial blood gases, as clinically indicated • Diffusing capacity of the lungs for carbon monoxide (DLCO), as clinically indicated • One blood sample collection for PK analysis as soon as ILD is suspected, if feasible • Other tests, as clinically indicated If a non-inflammatory/infectious etiology is confirmed by the Investigator, treat accordingly and resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
	Grade 1	The administration of patritumab deruxtecan must be delayed. Patritumab 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. Toxicity Management: • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines (if subject is asymptomatic, then subject must still be considered as Grade 1 even if steroid treatment is given).
	Grade 2	Permanently discontinue subject from study treatment. Toxicity Management: • Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by 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 IV (eg, methylprednisolone). – Re-consider additional work-up for alternative etiologies as described above. – Escalate care as clinically indicated.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
	Grade 3 or 4	Permanently discontinue subject from study treatment. Toxicity Management: • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, – Re-consider additional work-up for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.
Eye disorders		
Ocular	Grade 3	Delay dose until resolved to ≤Grade 2, then: • If resolved in ≤7 days, resume patritumab deruxtecan; • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level. Ophthalmologist consultation as necessary.
	Grade 4	Discontinue subject from patritumab deruxtecan. Ophthalmologist consultation as necessary.
Renal and urinary disorders		
Creatinine increased	Grade 3 (>3.0 × baseline; >3.0 – 6.0 × ULN)	Delay dose until resolved to ≤Grade 1 or baseline, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (>6.0 × ULN)	Discontinue subject from patritumab deruxtecan.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
Hepatobiliary disorders		
AST or ALT increased without total bilirubin (TBL) increased	Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	Continue patritumab deruxtecan. In subjects **without** liver metastasis, monitor AST/ALT 24 to 72 hours later, and continue regular monitoring until resolution.
	Grade 3 (>5.0 – 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 x ULN.	Delay patritumab deruxtecan dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, resume patritumab deruxtecan; • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	>8.0 - 20.0 x 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 x ULN.	Delay patritumab deruxtecan dose until resolved to ≤baseline level, then: • If resolved in ≤7 days, resume patritumab deruxtecan; • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from patritumab deruxtecan. Gastroenterologist or hepatologist consultation as necessary.
TBL increased	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 patritumab deruxtecan until resolved to ≤Grade 1, then: • If resolved in ≤7 days, resume patritumab deruxtecan; • If resolved in >7 days, reduce patritumab deruxtecan by 1 dose level. If documented Gilbert's syndrome or liver metastases at baseline, continue patritumab deruxtecan.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab 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, delay patritumab deruxtecan dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, reduce patritumab deruxtecan by 1 dose level; • If resolved in >7 days, discontinue subject from patritumab deruxtecan. If documented Gilbert's syndrome or liver metastases at baseline, delay patritumab deruxtecan dose until resolved to ≤Grade 2, then: • If resolved in ≤7 days, reduce patritumab deruxtecan by 1 dose level; • If resolved in >7 days, discontinue subject from patritumab deruxtecan.
	Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from patritumab deruxtecan.
AST or ALT increased and TBL increased	AST or ALT ≥3 × ULN with simultaneous TBL >2 × ULN	Delay patritumab deruxtecan until drug-induced liver injury can be ruled out. The Investigator must consult with a gastroenterologist or hepatologist as needed, and the subject must be treated accordingly. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes, such as viral or autoimmune hepatitis, alcoholic liver injury, biliary tract disorders, or hemodynamic abnormalities. Results from diagnostic workup (including, for example: INR, direct bilirubin, serologic tests for hepatitis A, B, and C; alcohol use, ultrasound, MRI, CT scan, concomitant medication use, immunoglobulin levels, ECHO) must be recorded within the eCRF. If drug-induced liver injury is ruled out, the subject must be treated accordingly, and resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor. Patritumab deruxtecan will be permanently discontinued if drug-induced liver injury cannot be ruled out from diagnostic workup.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	**Schedule Modification for Patritumab Deruxtecan**
AST or ALT> 3.0 x ULN (if liver metastases are present, >5 ×ULN) with known Hepatitis B and/or Hepatitis C infection at baseline	--	Delay patritumab deruxtecan until reactivation of Hepatitis B and/or Hepatitis C can be ruled out. Perform HBV DNA and/or HCV RNA to rule out reactivation of Hepatitis B and/or Hepatitis C, respectively. Hepatologist and infectious disease consultations are recommended. If reactivation of Hepatitis B and/or Hepatitis C is confirmed, permanently discontinue patritumab deruxtecan.
Gastrointestinal disorders		
Nausea	Grade 3 (inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition [TPN], or hospitalization indicated)	Delay patritumab deruxtecan until resolved to ≤ Grade 1, and consider treatment with anti-emetics and/or corticosteroids as per Investigators judgement and local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤14 days, resume patritumab deruxtecan. • If does not resolve to ≤Grade 1 in >14 days, reduce patritumab deruxtecan by 1 dose level.
Vomiting	Grade 3 (tube feeding, TPN, or hospitalization indicated)	Delay patritumab deruxtecan until resolved to ≤Grade 1, and consider treatment with anti-emetics and/or corticosteroids as per Investigators judgement and local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤7 days, resume patritumab deruxtecan; • If does not resolve to ≤Grade 1 in >7 days, reduce patritumab deruxtecan by 1 dose level.
	Grade ≥4	Discontinue subject from patritumab deruxtecan
Based on currently available clinical safety data for patritumab deruxtecan, it is recommended that subjects receive premedication with antiemetic agents. Suggested agents include a 5-HT3 blocker in combination with another antiemetic or corticosteroid approximately 30 minutes prior to patritumab deruxtecan infusion. Choice of agents is based on Investigator's discretion as per local/institutional guidelines. Investigators must also consider providing subjects with an antiemetic regimen for subsequent use as needed.		
Diarrhea/Colitis	Grade 3	Delay patritumab deruxtecan until resolved to ≤Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤7 days, resume patritumab deruxtecan; • If resolved to ≤Grade 1 in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from patritumab deruxtecan.

	Worst Toxicity NCI-CTCAE v5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab Deruxtecan
Mucositis oral	Grade 3	Delay patritumab deruxtecan until resolved to ≤Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤14 days, resume patritumab deruxtecan; • If resolved to ≤Grade 1 in >14 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from patritumab deruxtecan.
Other Adverse Events (Non-laboratory or Laboratory)	Grade 3	Delay patritumab deruxtecan until resolved to ≤Grade 1, or baseline level, then: • If resolved in ≤7 days, resume patritumab deruxtecan; • If resolved >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from patritumab deruxtecan.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; eCRF = electronic case report form; G-CSF = granulocyte colony stimulating factor; HBV = hepatitis B virus; HCV = hepatitis C virus; ILD = interstitial lung disease; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NCI = National Cancer Institute; NSAIDs = non-steroidal anti-inflammatory drugs; PK = pharmacokinetic; QTcF = corrected QT using Fridericia's formula; RNA = ribonucleic acid; SpO_2 = peripheral oxygen saturation; TBL = total bilirubin; ULN = upper limit of normal.

[a] There will be no dose interruptions for Grade 1 to Grade 3 lymphocyte count decreases. All dose interruptions must be based on the worst preceding toxicity.

During study treatment, subjects who develop systolic and/or diastolic hypertension that is deemed by the Investigator to be clinically significant should receive treatment with anti-hypertensive therapy according to the Investigator's judgement and local institutional guidelines.

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

Therapies used from the time the subject signs the main ICF for study participation to the 40-Day Follow-up Visit (+7 days) after the last administration of patritumab deruxtecan will be recorded in the eCRF. Prophylactic therapies (including any required premedication), prior therapies and all concomitant therapies will be recorded in the eCRF. Based on currently available clinical safety data for patritumab deruxtecan, it is recommended that subjects receive premedication with antiemetic agents. Refer to Table 6.4.

All therapies received by the subjects within 35 days prior to enrollment will be recorded as prior therapies. Concomitant therapies include all prescription, over-the-counter, and herbal remedies.

Therapies Requiring a Washout Period Before Enrollment

The following medications/therapies and products require a washout period before enrollment:

- Whole brain radiation therapy ≥14 days or stereotactic brain radiation therapy ≥7 days;
- Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), ≥14 days or 5 half-lives, whichever is longer;
- Monoclonal antibodies, other than immune checkpoint inhibitors, such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFR) ≥28 days;
- Immune checkpoint inhibitor therapy ≥21 days;
- Major surgery (excluding placement of vascular access) ≥28 days;
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation ≥28 days or palliative radiation therapy ≥14 days.
- Chloroquine or hydroxychloroquine >14 days.

Prohibited Therapies/Products

The following medications/therapies and products will be prohibited during the Treatment Period through 40 days after the last dose of patritumab deruxtecan:

- Other anticancer therapy, including cytotoxic, immune checkpoint inhibitors, or targeted agents;
- Chloroquine and hydroxychloroquine;
- Live virus vaccination (beginning from 28 days prior to Cycle 1 Day 1);
- Other investigational therapeutic agents;
- Radiotherapy, except palliative radiation (as long as the radiation field does not include a measurable lesion or does not interrupt treatment for more than 28 days from the planned date of administration [ie, 49 days from the last infusion date]).
- Radiotherapy to the thorax is also prohibited. See “Permitted Therapies/Products” section below for exceptions on palliative radiation;
- Concomitant use of chronic systemic (IV or oral) corticosteroids (ie, >10 mg prednisone or equivalent anti-inflammatory) or other immunosuppressive medications except for managing AEs.

Restricted Therapies/Products

Subjects are permitted to receive the following only when absolutely necessary:

- Investigators' discretion/clinical judgement is recommended in accordance with the institutional guidelines for the following:
  - Prophylactic or supportive treatment for expected toxicities, including management of study drug;
  - Hematopoietic growth factors used for prophylaxis or treatment;
  - Bisphosphonates (eg, pamidronate or zoledronate) or denosumab for pain management and palliation of bony metastases, or treatment of osteoporosis.
- Subjects who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE Grade ≤2) while receiving treatment until at least 1 week after symptoms have resolved. If a subject has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥3) ocular events they must discontinue wearing their contact lenses until at least 1 week after treatment is permanently discontinued. Subjects must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by a study doctor, at any time during the study and for ≥1 week after permanent discontinuation of study treatment.

Permitted Therapies/Products

Subjects are permitted to receive prophylactic or supportive treatment as standard of care during the Treatment Period, per Investigator's discretion and institutional guidelines.

- Palliative radiation to known metastatic sites as long as the radiation field does not include a measurable lesion or interrupt treatment for more than 28 days from the planned date of administration (ie, 49 days from the last infusion date). Palliative radiotherapy to the thorax is permitted one week after infusion; however, the next infusion should start at least two weeks after the radiotherapy. Whenever possible, subjects should have a tumor assessment of the lesion(s) prior to receiving radiotherapy in order to rule out progression of disease. In cases of progression of disease, subjects should be discontinued from patritumab deruxtecan.
- Inhaled or topical steroids or intra-articular steroid injections
- Inactive/killed virus vaccinations
- Menstruating females may receive Depo-Provera or another suppressant of menses during the entire course of study treatment. In addition, after completion of study treatment, suppression of menses should be continued until the platelet count is ≥50,000/mm^3 without transfusion support
- Subjects taking warfarin should be monitored regularly for changes in PT or INR.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

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

- Death
- Adverse Event
- Progressive Disease per RECIST v1.1
- Clinical Progression: provide date (ie, definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for PD according to RECIST v1.1)
- Withdrawal by the 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

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 1.2).

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 EOT evaluation should be performed as described in the SoE (Table 1.2);
- A safety follow-up evaluation should be performed approximately 40 days (+7 days) after the last dose of study drug as described in the SoE (Table 1.2);
- If subject has discontinued study drug for any reason other than progressive disease or criteria specified below in Section 7.2, tumor assessments and survival follow-up should be continued as described in the SoE (Table 1.2);
- Long-term follow-up evaluations will be performed to assess survival as described in the SoE (Table 1.2).

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

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

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. If a subject does not come back to the study site, every effort should be made to contact the subject to gain required information, such as the approaches listed below.

- 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 in the eCRF. See Section 7.2 for definition of withdrawal by the 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 the 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 progressive disease or adverse event. 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 1.2) 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

A subject 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, text messages, emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

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

8. STUDY PROCEDURES

See the SoE in Table 1.1 for study procedures during the Screening Period and the first 3 cycles of Treatment Period, and Table 1.2 for study procedures during Cycle 4 and the subsequent cycles of the Treatment Period, EOT, and the Follow-up Period.

8.1. Eligibility Assessment

Review the subject's demographics, medical and NSCLC history, prior medications, non-drug therapies and radiotherapy, vital signs, and results of tests (physical examination, height, weight, peripheral oxygen saturation (SpO_2), ECOG PS, ophthalmologic assessment, 12-lead ECG, ECHO/MUGA scan, and clinical laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2). See Section 5.3 for (re-screening/subject replacement).

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.

Qualifying Tumor Tissue Specimen

A pretreatment tumor biopsy or archival tumor tissue is required to be collected from all subjects after signing tumor tissue ICF and prior to enrollment of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by H&E staining at central laboratory).

- A baseline pretreatment tumor biopsy must be of the primary (if intact) and/or metastatic lesion(s) not previously irradiated and amenable to core biopsy. Any serious adverse event (SAE) directly related to the new biopsy should be reported as outlined in Section 8.4.1.1.
- Archival tumor tissue must be collected from a biopsy performed within 3 months prior to signing of the tissue consent and since progression while on or after treatment with the most recent cancer therapy regimen.

Biomarker analysis details are provided in Section 8.7 and the Laboratory Manual.

Non-small Cell Lung Cancer History

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

Actionable Mutation Status

Subjects must have documented test results indicating presence of an EGFR-activating mutation (exon 19 deletion or L858R), as detected from tumor tissue or blood sample, in order to be enrolled into the study. If tests result(s) for EGFR-activating mutations are not available,

subjects are required to undergo testing for these genomic alterations using assays approved in their country of testing.

HER3 Expression Status

HER3 protein expression level will be retrospectively assessed as an exploratory marker and the result will not be required for eligibility.

General Medical History and Baseline Conditions

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

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of NSCLC/vital signs that are out of range) that were diagnosed or known to exist prior to signing the ICF 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 patritumab 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

HIV antibody test should be performed, prior to enrollment, as required by local regulations or independent Institutional Review Boards (IRBs)/Ethics Committees (ECs).

Hepatitis Screening

Hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) must be performed prior to enrollment.

- Subjects with past or resolved HBV infection are eligible if:
  - Hepatitis surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) positive; **OR**
  - HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation with normal transaminases values (in the absence of liver metastasis); **OR**
  - HBsAg positive and HBV DNA viral load is documented to be ≤2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation for subjects with liver metastasis and abnormal transaminases with a result of AST/ALT <3 x ULN.
- Subjects with a history of hepatitis C infection will be eligible for enrollment only if the viral load according to local standards of detection is documented to be below the level of detection in the absence of anti-viral therapy during the previous 12 weeks

(ie, sustained viral response according to the local product label but no less than 12 weeks, whichever is longer).

8.2. Randomization/Enrollment

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 have met all eligibility criteria, eligible subjects will be randomized to 1 of the 2 following dose regimens:

- Fixed dose regimen: 5.6 mg/kg (Arm 1)
- Up-titration dose regimen (Arm 2): Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg

Following a decision based on the benefit/risk from the U31402-A-U102 study, subsequent subjects will be enrolled into the selected optimal dose regimen (Arm 1 or Arm 2).

Randomization/enrollment is defined as the time point at which the Investigator has determined the subject has met all eligibility criteria and has registered the transaction through the IRT.

If subjects do not meet eligibility criteria on the day of randomization/enrollment, they will not be randomized/enrolled into the study.

Subjects should receive the study drug on the same day as randomization/enrollment. The subject's weight at baseline (defined as the last measurement on or prior to Cycle 1 Day 1) will be used to calculate the initial dose. The subject's weight will be determined at the beginning of each cycle. If during Cycle 1 Day 1 or throughout the course of treatment, the subject's weight changes by ≥10% from the baseline weight, the dose will be recalculated using this new weight and will be considered the new baseline for all subsequent dosing calculations.

8.3. Efficacy Assessments

Radiographic Tumor Assessments

Radiographic tumor assessments (computed tomography [CT]/magnetic resonance imaging [MRI]) will include all sites of disease identified at Screening, and any newly suspected disease sites, as per RECIST v1.1 (Section 10.4). Imaging must include chest, abdomen, pelvis, and brain for all subjects.

The CT scans should be performed with contrast agents unless contraindicated for medical reasons; follow the local label/package insert/summary of product characteristics (SmPC) or institutional guidelines for allergic reactions to contrast agents.

Baseline tumor assessment must be performed within 28 days of enrollment and confirmed for measurable disease by BICR. A tumor assessment performed to assess for disease progression on the prior therapy will be acceptable as baseline if performed within 28 days of enrollment and after signing the main ICF.

A complete set of 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. SpO_2 should be conducted with CT/MRI per Investigator discretion.

Antitumor activity will be assessed at baseline (Screening), and every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days), independent of treatment cycle, until documented disease progression by BICR per RECIST v1.1, death, lost to follow-up, or withdrawal of consent (Table 1.1 and Table 1.2). Subjects who discontinue study treatment for any reasons other than documented disease progression by BICR or are withdrawn from study for criteria specified in Section 7.2 will continue to undergo tumor assessments at the same frequency of every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days) during the Follow-up Period. Imaging timing should follow calendar days relative to Cycle 1 Day 1. Imaging time points will be projected from Cycle 1 Day 1 and should not be adjusted for delays in cycle start. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Tumor assessments will be performed as per RECIST v1.1 (see Section 10.4). Objective responses (CR or PR) must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point).

The same imaging technique (with or without contrast) used to characterize each identified and reported lesion at baseline will be employed in the subsequent tumor assessments, unless medically infeasible (ie, newly developed AE or allergy to contrast agent).

Bone scan (using ^{99m}technetium polyphosphonate scintigraphy, whole body bone MRI, ^{18}F-NaF positron emission tomography [PET]/CT or ^{18}F-fluorodeoxyglucose [FDG] PET/CT) should be performed within 6 weeks prior to Cycle 1 Day 1 (historical scans are acceptable). Thereafter, a bone scan should be performed every 24 weeks (±7 days) from Cycle 1 Day 1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan should be required at confirmation of CR to exclude new bone metastases. Lesions detected on bone scans must be followed with cross-sectional imaging.

When tumor assessments at a visit are performed over multiple days, the date of response for that assessment (CR, PR, stable disease [SD], Non-CR/Non-PD [subjects with non-target lesions (NTL) only] 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 progression (PD) should be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

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

Response Assessment

Assessment of response will be made by BICR and Investigator based on RECIST v1.1 (Section 10.4). However, tumor assessments will continue until disease progression is confirmed by BICR.

Subsequent Anticancer Treatments

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

Survival Follow-up

All subjects should be followed for survival at least every 3 months after discontinuing study drug (see Table 1.2). Survival monitoring will continue until the overall end of the study.

8.4. Safety Assessments

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 patritumab 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 AESIs and Serious Adverse Events

All SAEs occurring after the subject signs the main ICF and up to 47 days after the last dose of study medication (ie, from the beginning of the Screening Period to the end of the Follow-up Period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event eCRF. Any serious, adverse event that may occur subsequent to the 40-day (+7 days) follow-up reporting period that the Investigator assesses as related to study drug should also be reported as an SAE. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

When an AE of potential ILD (Section 8.4.1.2) is observed after 47 days since the last dose of patritumab deruxtecan, the AE (serious or non-serious) should be reported and recorded in AE eCRF if it is considered related to patritumab deruxtecan.

All non-serious AEs occurring after the subject has taken the first dose of patritumab deruxtecan until 47 days after the last dose of study medication will be recorded on the Adverse Event eCRF.

Exacerbation of a pre-existing medical condition and symptom after the first dose of patritumab 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 adverse events of special interest [AESIs] and SAEs) and medication errors including overdose 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 the study drug patritumab 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.

Additional relevant information regarding the AESIs, ILD, and all hepatic events which meet an elevated ALT or AST $\geq 3 \times$ upper limit of normal (ULN) and an elevated total bilirubin $> 2 \times$ ULN that may occur simultaneously or at different time points during the study for the patritumab deruxtecan clinical program regardless of seriousness, is to be collected through the targeted questionnaires within the clinical study database.

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 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 hours of awareness:

- SAEs (Section 10.5.2)
- All potential ILD cases should be reported within 24 hours, including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of Preferred Terms]) (as defined in Section 8.4.1.2).
- Hepatic events (both serious and non-serious) meeting the laboratory criteria of a potential Hy's Law criteria (as defined in Section 8.4.1.2 for details).
- 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.

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.

In the event that the eCRF is unavailable, report SAEs by faxing or emailing the serious adverse event report (SAVER) Form to the CRO 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

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

The Sponsor and 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.[42]

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 events upgraded to fatal/life threatening must be followed up and addressed promptly. The Investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information. Other follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.4.1.1.1. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to the CRO within 24 hours of awareness. Overdose will be reported via eCRF.

An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

Occupational exposures must be reported via the SAVER form.

8.4.1.2. Adverse Events of Special Interest

Interstitial Lung Disease

Interstitial lung disease is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential ILD cases reviewed by the independent ILD Adjudication Committee (AC), available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[42]

If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD. If ILD is suspected, delay patritumab deruxtecan dosing pending further evaluation and start corticosteroid treatment promptly per consensus statement[45] unless clinically contraindicated. Refer to Table 6.4 for guidance on further evaluation and management of ILD.

If a non-inflammatory/infectious etiology is confirmed by the Investigator, treat accordingly; resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor.

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

Interstitial Lung Disease Adjudication Committee

An independent ILD AC for patritumab deruxtecan is responsible for reviewing all cases of potential ILD. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This data collection will be triggered for AEs reported using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) from the current ILD Standard MedDRA Query (SMQ) and the PTs of acute respiratory failure and respiratory failure.

Combined Elevations of Aminotransferases and Bilirubin

Elevations of aminotransferase(s) and bilirubin in association with patritumab deruxtecan are considered to be an important potential risk based on a comprehensive cumulative review of the available safety data from the clinical development program, the available pre-clinical data, review of the cumulative literature and review of available information for products of the same class. Refer to the current IB for a summary of preliminary clinical study data.[42]

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.[46] These events must be reported via eCRF, with the Investigator's assessment of seriousness, severity, causality, and a detailed narrative for SAEs and AESIs. These events should be reported within 24 hours of Investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

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

Follow the management guidance outlined in the designated "Hepatobiliary disorders" dose modification section of the study protocol (Table 6.4).

8.4.2. Pregnancy

The Sponsor must be notified of any female subject who becomes pregnant while receiving or within 7 months of last dose of patritumab deruxtecan. The Sponsor must be notified of any male subject whose female partner becomes pregnant while the subject is receiving, or within 4 months of discontinuing patritumab 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 hours of learning of the pregnancy.

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

Pregnancy Test

For women of childbearing potential (as defined in Section 5.1): document the results of a negative serum pregnancy test within 28 days of Cycle 1 Day 1. Within 72 hours prior to infusion of each cycle (including prior to Cycle 1 Day 1) and at the EOT Visit, a urine or serum pregnancy test per institutional guidelines must be performed for all female subjects of childbearing potential (Table 1.1). A positive urine pregnancy test result must immediately be confirmed using a serum test. Results are required prior to administration of study treatment. Cycle 1 Day 1 assessment does not need to be repeated if Screening assessment was performed within 72 hours of Cycle 1 Day 1 infusion.

A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with surgery at least 1 month before the first dose or confirmed by FSH test (FSH >40 mIU/mL and estradiol <40 pg/mL [<147pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study.

Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to first dose of patritumab deruxtecan treatment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

8.4.3. Clinical Laboratory Evaluations

The clinical laboratory tests including hematology, coagulation, blood chemistry, and urinalysis will be performed as per the SoE by the local laboratory (Table 1.1 and Table 1.2). 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, an SAE should be reported in the eCRF and other relevant procedures must be followed (see Section 8.4.1.1).

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

8.4.4. Other Safety

Physical Examinations

Physical examinations should be performed as per the SoE (Table 1.1 and Table 1.2). 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 and Table 1.2). Vital signs will include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, temperature, SpO_2, height (obtained once, prior to dosing), body weight. Blood pressure and pulse rate will be measured after the subject has rested in a supine/semi-recumbent position for 5 minutes or more and prior to laboratory draws. SpO_2 should be conducted with CT/MRI per Investigator discretion.

Electrocardiograms

12 lead-ECGs will be performed and recorded for every subject as per the SoE (Table 1.1 and Table 1.2). Subjects should rest supine/semi-recumbent for at least 10 minutes prior to the ECG.

The same test must be used for Screening, EOT, and as clinically indicated. Assessment for the EOT Visit may be performed with a window up to 7 days. 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 post-baseline will be reported as AEs.

Multi-gated Acquisition Scan or Echocardiogram

MUGA/ECHO must be performed as per the SoE and must be performed within 28 days of enrollment (Table 1.1 and Table 1.2). Subjects must have a LVEF ≥50% to be eligible for the study. The same test must be used for screening, EOT, and as clinically indicated. Assessment for the EOT Visit may be performed with a window of up to 7 days.

ECOG PS

Assess and record the subject's ECOG PS as per the SoE (Table 1.1 and Table 1.2). See Section 10.3.3 for the ECOG PS scale.

Ophthalmologic Assessments

The ophthalmologic assessment must be performed as per the SoE (Table 1.1 and Table 1.2) and must include a visual acuity test (Early Treatment Diabetic Retinopathy Study [ETDRS], Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry. Assessment may be repeated as clinically indicated as part of a scheduled or unscheduled visit.

8.5. Pharmacokinetic (PK) Assessment(s)

Blood samples for patritumab deruxtecan PK analyses will be obtained at the time points specified in the SoE (Table 1.1 and Table 1.2). Additionally, samples may be obtained at any time during the study if deemed clinically necessary. At each time point, blood will be collected for patritumab deruxtecan PK analysis. Instructions for the collection and handling of blood samples and shipping of serum samples for patritumab deruxtecan PK analysis are included in the Laboratory Manual. The actual time of patritumab deruxtecan administration (Pre-Infusion and Post-Infusion) and the exact time of blood sampling for patritumab deruxtecan PK analysis must be recorded on the eCRF.

If time points coincide for different blood samplings, the PK samples should be taken at the exact nominal time point, followed by serum chemistry, hematology, and then biomarker samples. If time points of procedures coincide with blood sampling, vital signs should be taken immediately prior to PK sampling time.

The patritumab deruxtecan PK samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory. Serum concentrations of patritumab deruxtecan (intact ADC) and total anti-HER3 antibody (naked antibody plus intact ADC) will be measured with validated analyte-specific ligand binding assays. Serum concentrations of released payload MAAA-1181a will be measured with validated liquid chromatography/mass spectrometry assay.

Blood samples for PK analyses will be obtained at the time points shown in Table 1.1 and Table 1.2.

8.5.1. Immunogenicity

Blood samples for serum anti-drug antibody (ADA) analyses will be collected in all subjects as per the SoE (Table 1.1 and Table 1.2) at the following time points:

- Within 8 hours before infusion of patritumab deruxtecan at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, then every 2 cycles on Day 1 from Cycle 6 to EOT (ie, Cycle 6, Cycle 8, Cycle 10, etc.)
- At Cycle 1 Day 8 (± 1 day)
- At the EOT Visit
- For subjects with a positive anti-drug antibody (ADA) on-study, an additional plasma ADA sample must be collected every 3 months (± 14 days) up to 1 year from the last dose of patritumab deruxtecan, or until the ADA becomes negative, or the ADA titer becomes less than baseline, or the subject starts another anticancer therapy, or the subject withdraws consent from the study, whichever occurs first.

Details for ADA plasma sampling, processing, and storage will be provided in the Laboratory Manual.

The ADA testing will be performed using a validated ADA assay following tiered assay steps including Screening, confirmatory as well as titer determination. If ADA is confirmed, the sample will be banked for neutralizing antidrug-antibody (NAB) when the NAB assay is available. Serum concentrations of patritumab deruxtecan (intact ADC, total anti-HER3 antibody, and released payload MAAA-1181a) may also be measured using the same ADA samples for the purpose of ADA assessment.

8.6. Pharmacodynamic Assessment(s)

Not applicable.

8.7. Biomarker Assessment(s)

8.7.1. Biomarker Assessments in Blood Samples

Biomarkers (such as HER3 extracellular domain [ECD], cell-free deoxyribonucleic acid [cfDNA] and cell-free ribonucleic acid [cfRNA]) will be analyzed with the intent of monitoring the biological or antitumor impact of treatment with patritumab deruxtecan.

Other biomarkers in addition to or in place of these may be considered as suggested by updated literature.

At Cycle 1 Day 1 pre-infusion, a minimum of 34 mL of blood is required to be drawn. This includes 20 mL for cfDNA, 10 mL for cfRNA, and 4 mL for HER3 ECD. At all other time points, a minimum 24 mL of blood is required to be drawn. This includes 10 mL for cfDNA, 10 mL for cfRNA, and 4 mL for HER3 ECD. These biomarkers will be assessed in blood collected at the following time points (see the SoE in Table 1.1 and Table 1.2), using validated assays:

- Pre-infusion Cycle 1 Day 1

- Pre-infusion Cycle 2 Day 1
- Pre-infusion Cycle 3 Day 1, Cycle 4 Day 1, and subsequent cycles
- EOT

One or more of the aforementioned biomarkers may also be explored for predictive value.

Biomarker samples will be shipped to a central laboratory. Sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

8.7.2. Biomarker Assessments in Tissue

Biomarker analyses will be used to investigate the effect of patritumab deruxtecan at the molecular and cellular level as well as to determine how changes in the biomarkers may relate to exposure and clinical outcomes. The tumor biopsy will be performed if medically feasible. The exploratory biomarker analyses may be performed using methods such as protein, ribonucleic acid (RNA), or DNA analysis in tissue. The following samples for biomarker research are required and will be collected from all subjects in this study as specified in Table 1.1 and Table 1.2:

- Pretreatment tumor biopsy or archival tumor tissue of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by H&E staining at the central laboratory) collected prior to study entry. Pretreatment tumor biopsy is required but subjects may be exempted from the requirement to provide a pretreatment tumor biopsy if the archival tumor tissue was collected within 3 months prior to signing of tissue consent and since progression while on or after the most recent cancer therapy. The pretreatment tumor tissue biopsy or archival tumor tissue sample(s) will be stained for HER3 expression using IHC. HER3 expression will be assessed as an exploratory biomarker at a later date.
- Other potential exploratory biomarkers will be analyzed as well. Archival samples can be formalin-fixed, paraffin-embedded (FFPE) tissue block(s), prepared by the standard procedure at the study site. Additional information on tumor tissue collection, processing and immediate shipping procedures is included in the Laboratory Manual.

In addition to the biomarkers specified above, additional exploratory biomarker may be evaluated on any of the collected samples. The following samples for biomarker research should be collected from study subjects where possible:

- Optional EOT tumor biopsy will be performed at the time of progression or discontinuation from study treatment. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. The tumor biopsy should be obtained from the primary tumor or metastatic site, preferably from a site of recent radiographic progression, within 40 days of the last dose of patritumab deruxtecan, and prior to starting any new anticancer treatment.

These studies would extend the search for other potential biomarkers relevant to the effects of patritumab deruxtecan and/or the resistance to the treatment. This may include the development of ways to detect, monitor, or treat malignancies. These additional investigations would be

dependent upon clinical outcome, reagent, and sample availability. If the subject agrees, samples may be stored for a maximum of 15 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis and address scientific questions.

The sample collection information as required should be recorded on the eCRF pages and central laboratory requisition forms. Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

8.8. Pharmacogenomic (Inherited Genetic) Analysis

If a subject provides consent, a single blood sample (3 mL) for pharmacogenetic analysis will be collected from each subject. The pharmacogenomic blood sample will be scheduled for Cycle 1 Day 1 post-dose (see Table 1.1) but may be collected at any time after the first dose of patritumab deruxtecan. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Laboratory Manual.

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 8.8.1 for performing future pharmacogenetic analysis. Otherwise, all remaining DNA samples will be destroyed.

8.8.1. Banking of Specimens for Inherited Genetic Analysis

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

The banked samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of patritumab deruxtecan. Additionally, samples may be analyzed for genes involved in patritumab deruxtecan-related signaling pathways, or to examine diseases or physiologic processes or safety related to patritumab deruxtecan. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug.

Storage and Disposal of Specimens

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

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

Disclosure of the Results of Future Pharmacogenetic Analysis

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

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

The DCO date for the primary analysis will occur when all enrolled subjects have either a minimum of 9 months of follow-up or have discontinued from the study earlier. All data collected up to the DCO date will be included in the primary analyses. The primary analysis will be included in the CSR.

The final analysis of the study will occur after all subjects have discontinued from the study. Data collected beyond the primary analysis DCO will be presented as appropriate in a CSR addendum if deemed necessary.

Descriptive statistics on continuous data will include mean, median, standard deviation, and range (as well as geometric mean and geometric coefficient of variation for PK data). Categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. Time-to-event endpoints except for time to response (TTR) will be reported using Kaplan-Meier estimates.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken prior to Cycle 1 Day 1 will be used as the baseline value, unless otherwise specified. In general, missing data will not be imputed for the purpose of data analysis, unless otherwise specified.

Efficacy endpoints will be analyzed based on Efficacy Analysis Set. Safety analyses will be performed based on the Safety Analysis Set. Analysis of PK data will use the PK Analysis Set. Data from all sites will be pooled for the analyses. The analyses will be performed by treatment arm.

9.2. Statistical Hypothesis

The primary objective of this study is to investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R). The primary efficacy endpoint is ORR as assessed by BICR per RECIST v1.1. ORR is defined as the proportion of subjects with a best overall response (BOR) of confirmed CR or confirmed PR according to RECIST v1.1.

The following statistical hypothesis will be tested at 2-sided significance level of 5%:

$$H_0: \text{ORR} = 26.4\% \text{ vs. } H_1: \text{ORR} \neq 26.4\%$$

The null hypothesis of 26.4% is the upper bound of the exact 95% CI of the ORR (23%) observed in the ramucirumab plus docetaxel arm from the REVEL trial.[22]

9.3. Sample Size Determination

The primary efficacy endpoint of ORR is used for sample size determination. From the REVEL trial, the ORR of 23% from the ramucirumab plus docetaxel arm was observed (upper bound of exact 95% CI = 26.4%).[22] A clinically meaningful ORR of 37% is expected from patritumab deruxtecan. The one-sample exact binomial test for single proportion with a nominal 2-sided

significance level of 5% will have approximately 91% power to detect the difference between a null hypothesis (H_0) of ORR = 26.4% and an alternative hypothesis (H_1) of ORR = 37% when the sample size is 210. Table 9.1 below displays the exact 95% CI at various ORRs. When the observed ORR is greater than or equal to 32.9%, the lower bound of the 95% CI excludes 26.4%.

Table 9.1: Exact 95% Confidence Intervals for Sample Size of 210 Subjects at Various Observed ORRs

Sample Size	Number of Responders	Observed ORR (%)	Exact 95% CI
210	63	30.0	23.9, 36.7
	69	32.9	26.6, 39.7
	70	33.3	27.0, 40.2
	77	36.7	30.1, 43.6
	84	40.0	33.3, 47.0
	93	44.3	37.5, 51.3
	105	50.0	43.0, 57.0

CI = confidence interval; ORR = objective response rate

Up to approximately 420 subjects may be randomized/enrolled depending on whether and when one dose arm is dropped or not during the study. The sample size computation is performed using exact test for single proportion in nQuery v8.5.2.

The exact 95% CIs for the observed ORRs are based on binomial distribution and calculated using SAS® v9.4.

No formal comparison between the two treatment arms is planned, and sample size is calculated for each arm individually.

9.4. Population for Analysis Sets

Analysis Sets

- The **Full Analysis Set (FAS)** will include all subjects who are randomized or dosed (for non-randomized subjects) in this study. Following the Intent-to-Treat (ITT) principle, the randomized subjects will be analyzed according to the treatment assigned during the randomization process.
- The **Safety Analysis Set** will include all subjects who received at least one dose of study treatment. Subjects will be summarized according to the treatment received. Treatment received is the randomized/assigned treatment if the subject took at least 1 dose of the randomized/assigned study drug; otherwise the first treatment received will be used.
- The **Efficacy Analysis Set (EAS)** will include all subjects in the FAS who received at least 1 dose of study treatment. Subjects who have been randomized but not dosed

will be excluded from the EAS. In this study, the EAS is the same as the Safety Analysis Set. The EAS will use the actual treated arm.

- The **PK Analysis Set** will include all subjects in the Safety Analysis Set who had at least one PK sample with a measurable concentration of intact patritumab deruxtecan ADC, total anti-HER3 antibody, or released payload MAAA-1181a.

9.5. Statistical Analysis

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

9.5.1. Efficacy Analyses

Table 3.1 lists the primary and secondary endpoints and their corresponding definitions of all endpoints. Additional details for the analysis and censoring rules will be specified in the SAP. The EAS will be used for all efficacy analyses, unless otherwise specified.

9.5.1.1. Primary Efficacy Analyses

The primary efficacy endpoint of ORR is defined as the proportion of subjects who achieved a BOR of confirmed CR or PR as assessed by BICR per RECIST v1.1. The primary efficacy analysis will be based on the EAS.

The BOR will be determined using tumor assessments at different evaluation time points until documented disease progression or start of any further anticancer treatment that is expected to affect the assessment of tumor response to study drug, whichever is earlier. Clinical deterioration will not be considered as disease progression.

ORR will be presented with exact 95% CI using the Clopper-Pearson method.[47] If the lower bound of the 95% CI is higher than the null hypothesis of 26.4%, then the null hypothesis is rejected. For the computation of ORR, subjects with BOR of NE will be considered as non-responders. Data will be summarized by treatment arm. No formal comparisons between the two arms are planned.

9.5.1.2. Secondary Efficacy Analyses

Secondary efficacy endpoints include ORR as assessed by Investigator per RECIST v1.1; best percentage change in the sum of diameters (SoD) of measurable tumors, disease control rate (DCR), DoR, TTR, and PFS as assessed by BICR and Investigator per RECIST v1.1, and OS.

A brief description of each endpoint is provided below:

- DoR is defined as the time from the date of the first documentation of response (confirmed CR or PR) to the date of the first documentation of PD or death due to any cause, whichever occurs first. Duration of response will be measured for responding subjects (subjects with confirmed CR or PR) only. Detailed censoring rules for DoR will be specified in the SAP.

- Best percentage change in the SoD of measurable tumors is defined as the percentage change in the smallest SoD from all post-baseline tumor assessments, taking as reference the baseline SoD.
- DCR is defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or SD.
- PFS is defined as the time from the start date of study treatment to the earlier of the dates of the first documentation of PD or death due to any cause. Detailed censoring rules for PFS will be specified in the SAP.
- TTR is defined as the time from the start date of study treatment to the date of the first documentation of response (confirmed CR or PR). The TTR will be measured for responding subjects (subjects with confirmed CR or PR) only.
- OS is defined as the time from the start date of study treatment to the date of death due to any cause. If there is no death reported for a subject before the DCO for the OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

Response endpoints (ORR and DCR) will be analyzed in the same manner as the primary efficacy endpoint. Distribution of time to event endpoints (DoR, PFS, and OS) will be estimated using the Kaplan-Meier method and results presented graphically. Median event time with a 2-sided 95% CI will be calculated using Brookmeyer and Crowley methods. In addition, the event-free probability at different time points (eg, 3, 6, 9 months, etc.) will be estimated with corresponding 2-sided 95% CIs using Greenwood's formula. TTR will be summarized using descriptive statistics.

Descriptive statistics for the best percent change from baseline in the SoD will be provided. A waterfall plot of the best percentage change in the SoD for each subject will be presented.

9.5.1.3. Exploratory Analyses

Not applicable.

9.5.1.4. Multiplicity Adjustment

Not applicable.

9.5.2. Safety Analyses

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. Safety analyses will be performed using the Safety Analysis Set and subjects will be analyzed according to their actual treatment received.

The overall study period will be divided into 3 mutually exclusive segments for statistical analysis and reporting purposes:

- Pre-treatment period: from date of informed consent (inclusive) to the start date of study treatment −1

- On-treatment period: from the start date of study treatment (inclusive) to 47 days after the end date of study treatment (inclusive)
- Post-treatment period: starting from 48 days after the end date of study treatment.

Only data from the on-treatment period will be summarized, unless otherwise specified, except in cases where data from the pre-treatment period will be used for baseline determination.

Adverse Events

Adverse events will be coded using MedDRA and graded using NCI-CTCAE v5.0.

A TEAE is defined as an AE with a start or worsening date during the on-treatment period.

The TEAEs will be summarized using system organ class (SOC) and/or PTs. Additional summaries will be provided by the worst CTCAE grade, relationship to the study treatment (ie, regardless of relationship to study drug, study drug related), seriousness, actions taken with study treatment (ie, associated with dose reduction, dose interruption, study treatment discontinuation), and fatality.

If a subject reports more than one AE with the same PT, the AE with the worst CTCAE grade will be presented. If a subject reports more than one AE within the same primary SOC, the subject will be counted only once with the worst CTCAE grade at the SOC level, where applicable.

AESIs will also be summarized.

All AEs will be listed, including, but not limited to, verbatim term, PT, SOC, CTCAE grade, relationship to study drug, start and end dates, and outcome. Non-TEAEs will be flagged in the listing.

SAEs starting or worsening after the on-treatment period, if reported as related to the study treatment, will be summarized.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and chemistry) and changes from baseline by scheduled time of evaluation, including the EOT Visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE v5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

ECG

A listing of ECG data will be provided.

Vital Signs

Descriptive statistics will be provided for the vital sign measurements and changes from baseline by scheduled time of evaluation, including the EOT Visit. A listing of vital sign data will be generated.

Other

Listings of all other safety data (eg, physical examination findings including ECOG PS, ECHO/MUGA, and ophthalmologic findings) will be generated.

9.5.3. Other Analyses

The following other analyses are planned in this study.

Pharmacokinetics

Serum concentrations for intact patritumab deruxtecan ADC, total anti-HER3 antibody and released payload MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each time point of each dosing arm using the PK Analysis Set.

The Population PK (PopPK) analysis to evaluate the effect of intrinsic and extrinsic factors of intact patritumab deruxtecan ADC, and if appropriate, total anti-HER3 antibody and released payload MAAA-1181a may be characterized and may also include available PK data from the Phase 1 studies (U31402-A-J101 and U31402-A-U102). After establishment of the PopPK model, a PopPK/exposure-response model may be developed to evaluate the relationship between exposure and efficacy and toxicity. If conducted, the results of the nonlinear mixed effects PopPK and PopPK/exposure-response models will be reported separately from the CSR.

Immunogenicity

Immunogenicity will be assessed through characterization of prevalence, incidence and titer of ADA. The number and percentage of subjects with treatment-emergent ADA will be calculated. Treatment-emergent ADA positive is defined as subjects who were ADA negative at baseline and became ADA positive (ie, confirmed positive ADA) post-treatment or ADA positive at baseline and post-treatment and had an increase in ADA titer from baseline to post-treatment that meets the cut off value of fold change, or had missing ADA data at baseline and became ADA positive post-treatment.

Concentrations and PK parameters of total anti-HER3 antibody, intact patritumab deruxtecan ADC, and released payload MAAA-1181a may be summarized by status of ADA, if data allows. ADA titer will be determined for samples confirmed ADA positive. When neutralizing antibody assay becomes available, confirmed ADA positive samples may be analyzed for neutralizing activity.

Pharmacodynamics

Not applicable.

Biomarker

Biomarker data include IHC HER3 expression data and genomic alterations data from tumor tissue. HER3 expression data will be summarized and plotted if data permits. HER3 expression and genomic alteration data will be presented in listings. Other biomarker data, if analyzed, may be reported separately (ie, not in the CSR).

Inherited Genetics

A pharmacogenomics analysis may be conducted in combination with data from other studies. If conducted, results of the analysis will be reported separately.

9.6. Interim Analyses

There is no formal interim analysis planned for futility or superiority in this study.

This Phase 2 study will start with 2 randomized dose arms (5.6 mg/kg fixed dose regimen and up-titration dose regimen) with a 1:1 randomization ratio. In the ongoing U31402-A-U102 study, the same population is being studied in multiple expansion cohorts: Cohort 3a and 3b (with 45 subjects planned to be randomized to each dose regimen, 5.6 mg/kg Q3W or up-titration) and Cohort 1 (45 subjects dosed with 5.6 mg/kg Q3W). If, during the conduct of the current trial (U31402-A-U201), analyses from the U31402-A-U102 study indicate that one dose regimen provides clear advantages over the other in terms of benefit/risk, further enrollment into one arm may be discontinued.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

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

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

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

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

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

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

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

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

Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, Independent Ethics Committees (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 informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed ICF should be provided to the subject. The date that informed consent was signed must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the 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 2016/679/General Data Protection Regulation on the protection of individuals with regard to the processing of personal data and the free movement of such data.

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

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

10.1.4. Data Integrity and Quality Assurance

Monitoring and Inspections

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

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

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

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

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

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

Data Collection

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

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

Data Management

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

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

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

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

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

10.1.5. Committees

Interstitial Lung Disease Adjudication Committee

An external ILD AC will be used for this study. Details on the membership, responsibilities, and working procedures of the external ILD AC will be described in its own charter, provided as a separate document. The ILD AC will adjudicate all cases of potential ILD on an ongoing basis.

Adjudication of ILD cases will be based on evaluation of eCRFs and source documents including, but not limited to, chest high-resolution CT, arterial blood gases, and carbon monoxide diffusing capacity. The ILD AC will review ongoing cases of ILD to make the final determination of ILD diagnoses to guide Sponsor decisions regarding study suspension or study discontinuation and to provide assessment of ILD prevalence at the end of the study. Findings of the ILD AC with its recommendations will be provided to the Sponsor.

Mechanisms of Safety Oversight by the Sponsor

In Version 1.0 of U31402-A-U201 study protocol dated 26 Jun 2020, an external independent DMC was included to provide interim safety review of this Phase 2 U31402-A-U201 study to supplement safety and efficacy data obtained from the Phase 1 U31402-A-U102 study.

Subsequently, an external independent DMC was deemed not to be necessary with the following rationale: the Sponsor has determined that the combined safety and efficacy data from the Phase 1 U31402-A-U102 study will be sufficient to support any potential selection of a preferred dosing regimen while the Phase 2 U31402-A-U201 study is ongoing; the primary endpoint of ORR as assessed by BICR in this non-comparative Phase 2 study does not require DMC oversight; the lack of any a priori serious safety concern, besides ILD which is accounted for by the ILD adjudication committee; and the robust internal pharmacovigilance oversight that is part of the standard Daiichi Sankyo safety monitoring for clinical studies.

The Sponsor has in place a multi-layered process for ensuring subject safety through the Safety Management Team (SMT) through close collaboration of study site Investigators, the Sponsor study team, and the Sponsor Clinical Safety and Pharmacovigilance (CSPV). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

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

To support safety oversight, the Sponsor has established ongoing processes for collection, review, analysis, and submission of all AEs reported in the study and their aggregate analyses. Because this is an open-label study, the clinical scientist/leader, the Sponsor medical monitor, and the Investigators will have access to all data necessary for safety evaluation.

10.1.6. Study Documentation and Storage

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

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

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

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

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

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, 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.

10.1.7. Finances

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

Reimbursement, Indemnity, and Insurance

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

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

10.1.8. Publication and Public Disclosure Policy

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.

In order to ensure compliance with the public disclosure policies and the International Council of Medical Journal Editors recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on

data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

10.1.9. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the 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 hours and in accordance with the clinical study agreement between the parties.

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

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

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

10.1.10. Study and Site Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the 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

Study termination may also be requested by (a) competent authority/ies.

At the time of study closure, any subjects who are continuing treatment with patritumab deruxtecan and who are judged by the Investigator to have ongoing benefit may continue to receive treatment with patritumab deruxtecan through a rollover protocol or another mechanism consistent with local requirements.

10.1.11. Product Complaints

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

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

10.2. Appendix 2: Central and/or Local Laboratory

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

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry	albumin alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bilirubin (total) bilirubin (direct and indirect) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine estradiol (if indicated)	FSH (follicle-stimulating hormone; if indicated) lactate dehydrogenase (LDH) magnesium (Mg) phosphorus potassium (K) protein (total) sodium (Na)
Hematology	hemoglobin hematocrit platelet count mean platelet volume (if available) reticulated platelet fraction (if available) red blood cell (RBC) count white blood cell (WBC) count mean corpuscular volume (if available)	differential WBC count (absolute and percent): basophils eosinophils lymphocytes monocytes neutrophils
Coagulation	prothrombin time (PT)/international normalized ratio (INR) partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT)	
Urinalysis (abbreviated)	bilirubin glucose ketone bodies occult blood microscopic assessments (if indicated) pH protein	urobilinogen sediments: casts RBC WBC specific gravity

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds):[48]

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. New York Heart Association (NYHA)

The NYHA classifications are summarized below.[49]

Table 10.2: New York Heart Association Classifications

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

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

10.3.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status scale scores are summarized below.[50]

Table 10.3: Eastern Cooperative Oncology Group Performance Status

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

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

10.3.4. Highly Effective Contraception

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 for at least 4 months for males and for at least 7 months for females after the last dose of study drug. Methods considered to be highly effective contraception include:[51]

- 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
- True abstinence: when this is in line with the preferred and usual lifestyle of the subject

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, v1.1.[52] 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 of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Special Notes on the Assessment of Target Lesions

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

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

the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness.) The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error.

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

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

Evaluation of Non-Target Lesions

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 complete response. 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 the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR or PR is required in this study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time Point Response

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

All post-baseline scans must be anchored against the baseline (Cycle 1 Day 1) scan.

Table 10.4: Time Point Response: Subjects With Target (±Non-Target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	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 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 BOR when confirmation of CR or PR is required is displayed in Table 10.5.

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

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable 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 subject 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 (v1.1). Table 3. Euro J 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 patritumab 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 every 6 weeks ±7 days from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days) thereafter, independent of treatment cycle, until documented disease progression by BICR per RECIST v1.1, death, lost to follow-up, or withdrawal of consent as specified in the SoE or sooner if clinically indicated (see Table 1.1 and Table 1.2). Tumor assessments should not be delayed by dose interruptions; they are timed relative to randomization. The interval between scans is based on the last scan visit. When tumor assessments at a visit are performed over multiple days, the date of response for that assessment (CR, PR, SD, Non-CR/Non-PD [subjects with NTL only] or NE) should be recorded as the date of the last radiographic evaluation included in the series for that assessment, and the date of progression (PD) should be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

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, and CT or MRI of the brain. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

10.5. Appendix 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.[53]

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically relevant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Serious Adverse Event

A serious adverse event 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

Disease progression is a component of efficacy endpoints such as PFS. With one exception, disease progression should not be reported as an AE or SAE. However, when a death occurs due to disease progression with no other immediate cause, then disease progression should be reported as an SAE and should be recorded in the designated eCRF; in this circumstance, the SAE will be processed and be reported as per local regulatory requirements and institutions, as applicable.[53]

10.5.3. Grade Assessment

The severity of AEs will be graded using the latest NCI-CTCAE (v5.0). For each episode, the highest severity grade attained should be reported.

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

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

Difference Between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe 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.

10.5.4. Causality Assessment

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

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

    or

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

10.5.5. Action Taken Regarding Study Drug(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

10.5.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over the counter medication was required to treat the adverse event.
- Other.

10.5.7. Adverse Event Outcome

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

10.6. Appendix 6: Key Data Analysis Requirements

Table 10.6: Key Data Requirements

Endpoint/Analysis	Key Data Requirements
Primary Analysis	All electronic case report form (eCRF) collected data and key external source data (eg, tumor data as assessed by blinded independent central review [BICR], interstitial lung disease [ILD], laboratory data, pharmacokinetic [PK] data, protocol deviation, human epidermal growth factor receptor 3 [HER3] expression data) collected up to the data cut-off date are required for the primary analysis.
Primary Endpoint – objective response rate (ORR)	All tumor assessment data (eg, target, non-target, new lesion, overall response) as assessed by BICR and Investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) is required.

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

Due to the potential impact of coronavirus disease 2019 (COVID-19; due to severe respiratory syndrome coronavirus 2 [SARS-CoV-2]), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with patritumab deruxtecan. 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 COVID-19

If COVID-19 infection is suspected, interrupt patritumab deruxtecan and evaluate for COVID-19 according to local standards.

- If COVID-19 infection is ruled out, follow dose modification and management guidance as outlined in Table 6.4.
- If COVID-19 infection is confirmed or is still suspected after evaluation, continue to delay patritumab deruxtecan dosing and manage COVID-19 infection according to local standards until recovery. Recovery from COVID-19 infection is defined as the absence of signs or symptoms of COVID-19 infection and at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result. A chest CT must be performed in all subjects at the time of presumed recovery, and the results should be taken into consideration by the investigator when confirming recovery of COVID-19 infection. If recovery from COVID-19 infection is confirmed, follow the dose modification guidelines as summarized in Table 10.7 below.
- Dosing of patritumab deruxtecan may be delayed for up to 28 days from the planned date of administration (ie, 49 days from the last infusion date). If a subject is judged by the investigator to require a dose delay of longer than 28 days, the subject must be discontinued from the study treatment.

- 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 a drug-related ILD, manage per protocol ILD management guideline (see Table 6.4).

Table 10.7: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI-CTCAE (Version 5.0 Grade unless otherwise specified)	Schedule Modification for Patritumab Deruxtecan
Grade 1	Resume study drug at the same dose level after the subject has recovered from COVID-19 infection. [a]
Grade 2	Resume study drug at the same dose level after the subject has recovered from COVID-19 infection and if chest CT findings thought to be related to this infection are completely resolved.[a] Reduce by 1 dose level after the subject has recovered from COVID-19 infection and if residual chest CT findings related to the infection are observed but are not indicative of active infection.[a]
Grade 3	Reduce by 1 dose level if chest CT findings related to the infection are completely resolved.[a] Discontinue study drug if chest CT findings related to the infection are **not** completely resolved.
Grade 4	Discontinue study drug.

COVID-19 = coronavirus disease 2019; CT = computed tomography; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] Closely monitor signs/symptoms after resuming patritumab deruxtecan, initially with a phone call every 3 days for the first week and then with a weekly phone call thereafter for a total of 6 weeks.

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.2).
  - If treatment is absolutely required for COVID-19, patritumab deruxtecan must be interrupted.
  - If administered, then a washout period of more than 14 days is required before resumption of patritumab deruxtecan.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected from each subject who provides consent, if chloroquine or hydroxychloroquine is administered for COVID-19 infection, at the time points specified in the Schedule of Events (Table 1.1 and Table 1.2).

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

COVID-19 Assessment(s)

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT PCR test is not available at the site, a sample kit will be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory.

Serum samples will be used for COVID-19 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, at the time points specified in the Schedule of Events (Table 1.1 and Table 1.2), shipped to a central laboratory, and stored there until the tests become available.

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

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

Statistical Analysis - Assessment of the Impact of COVID-19

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the statistical analysis plan.

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICR	blinded independent central review
BOR	best overall response
cfDNA	cell-free deoxyribonucleic acid
cfRNA	cell-free ribonucleic acid
CI	confidence interval
Cmax	maximum concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CSPV	Clinical Safety and Pharmacovigilance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cut-off
DCR	disease control rate
DFCI	Dana-Farber Cancer Institute
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DoR	duration of response
EC	Ethics Committee

Abbreviation	Definition
ECD	extracellular domain
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor-mutated
EIU	exposure in utero
EOS	End of Study
EOT	End of Treatment
ERBB3	ERB-B2 receptor tyrosine kinase 3
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GGFG	glycine-glycine-phenylalanine-glycine
H_0	null hypothesis
H_1	alternative hypothesis
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HER3	human epidermal growth factor receptor 3
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
H&E	hematoxylin and eosin
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized-drug product
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid;
MUGA	multigated acquisition
NAB	neutralizing antidrug-antibody
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	not evaluable
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NTL	non-target lesion
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time/ preferred term
PTT	partial thromboplastin time
Q3W	every 3 weeks

Abbreviation	Definition
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RDE	recommended dose for expansion
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS1	ROS protocol-oncogene 1
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	suspected severe acute respiratory syndrome coronavirus 2
SAVER	serious adverse event report
SCr	serum creatinine
SD	stable disease
SID	subject identification
SMT	Safety Management Team
SoE	Schedule of Events
SOP	standard operating procedures
SpO_2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitors
TTR	time to response
ULN	upper limit of normal
US	United States
v	version