CLINICAL STUDY PROTOCOL

A MULTI-CENTER, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE SAFETY AND EFFICACY OF U3-1402 IN SUBJECTS WITH ADVANCED OR METASTATIC COLORECTAL CANCER (CRC)

U31402-A-U202

IND NUMBER 148299

EudraCT NUMBER 2019-004418-32

VERSION 4.0, 24 NOV 2020

DAIICHI SANKYO. INC.

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INVESTIGATOR AGREEMENT

A Multi-Center, Open-Label, Phase 2 Study to Evaluate Safety and Efficacy of U3-1402 in Subjects with Advanced or Metastatic Colorectal Cancer (CRC)

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	24-Nov-2020
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

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

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

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

SUMMARY OF CHANGES

The summary of changes below is a top-line summary of main changes in the current U31402-A-U202 clinical study protocol (Version 4.0) dated 24 November 2020 by section, as compared to Version 3.0, dated 24 August 2020.

Amendment Rationale:

This amendment provides greater uniformity in the enrolled population by ensuring the prior use of a BRAF inhibitor in patients whose tumors express a BRAF V600E mutation. It also provides further specification regarding the required antibody washout period, conditions under which tumor assessments should be conducted, screening, rescreening, and study closure procedures. Other minor editorial changes are provided to enhance clarity.

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

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in the Summary of Changes.
Minor edits, such as an update to language that does not alter original meaning, an update to version numbering, formatting, a change in font color, a correction to a typographical error, the use of abbreviations, moving verbiage within a section or table, a change in style or numbering, or a change in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Synopsis, Study Design Section 3.1 Study Design Section 3.1.2 Duration of Subject Participation Section 5.7 Discontinuation of Study Drug Section 6.3.1 Cycle 1 and Subsequent Cycles Section 6.5 40-day Post-treatment Follow-up Section 7.1 Tumor Assessments for Efficacy	Specified that tumor assessments should continue until documented disease progression (RECIST v1.1) by BICR, death, lost to follow-up, or withdrawal of consent by subject.	To specify the correct conditions under which tumor assessments should be conducted.
Synopsis Study Objectives, Outcome Measures, and Endpoints Table 2.1 Description of Objectives, Outcome Measures, and Endpoints Section 11.5.2.5 Other	Revised the definition of ADA-positive and ADA-negative subjects.	To align with the current Daiichi Sankyo definition.

Section # and Title	Description of Change	Brief Rationale
Synopsis, Subject Eligibility Criteria: Key Exclusion Criteria Section 4.2 Exclusion Criteria	Revised exclusion criterion 2 from "OR prior pneumonectomy" to "OR prior complete pneumonectomy."	To specify that subjects with prior partial pneumonectomy or prior lobectomy will not be excluded.
Synopsis, Subject Eligibility Criteria: Key Exclusion Criteria Section 4.2 Exclusion Criteria Section 5.6 Prior, Concomitant and Prohibited Medications	Specified that subjects who require use of topical steroids may be included in the study.	Topical steroids generally do not represent significant systemic exposure; therefore, the risks to subjects are low with use of topical steroids.
Synopsis, Study Eligibility Criteria Section 4.1, Exclusion Criteria	Clarified exclusion criterion 5 to state that subjects who are asymptomatic (ie, without neurologic signs or symptoms and do not require treatment with corticosteroids or anticonvulsants) may be included in the study and added that "Subjects must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1."	To align with current U3-1402 product safety requirements.
Synopsis, Subject Eligibility Criteria: Key Exclusion Criteria Section 4.2 Exclusion Criteria Section 5.6 Prior, Concomitant and Prohibited Medications	Added exclusion criterion 6c regarding the required washout period: "Monoclonal antibodies other than immune checkpoint inhibitors, such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFRs) <28 days" and included a specification for these therapies in Section 5.6: Therapies Requiring a Washout.	In consideration for the long half-lives typically observed with monoclonal antibodies and the ascertainment that this interval is consistent with ensuring patient safety.
Synopsis, Subject Eligibility Criteria: Key Exclusion Criteria Section 4.2 Exclusion Criteria	Removed terminology of uncontrolled hypertension from exclusion criterion 10c.	To correct an error in the description of systolic and diastolic blood pressure thresholds.
Synopsis, Indication Under Investigation Synopsis, Study Design Synopsis, Subject Eligibility Criteria: Key Inclusion Criteria Section 3.1 Overall Design Figure 3.1 Study Design Schema Section 4.1 Inclusion Criteria	Added to inclusion criterion 4 to state that patients must have previously received treatment with a BRAF inhibitor, if clinically indicated (eg, BRAF V600E positive).	To ensure that patients with BRAF V600E-positive tumor expression have previously received approved therapy with a BRAF inhibitor to align with current treatment guidelines.

Section # and Title	Description of Change	Brief Rationale
Synopsis, Subject Eligibility Criteria: Key Inclusion Criteria Section 4.1 Inclusion Criteria	Removed "(eg, RAS/BRAF wildtype)" as provided examples of an anti-EGFR agent.	To provide greater flexibility for the use of an anti-EGFR agent according to local institutional standards.
Section 3.1.2 Duration of Subject Participation Schedule of Events Section 6.3.1 Cycle 1 and Subsequent Cycles Section 6.5 40-day Post-treatment Follow-up Section 7.1 Tumor Assessments for Efficacy	Removed new anticancer treatment as a reason to discontinue tumor assessments.	To obtain all of the relevant scans until verification that criteria for terminating the serial evaluation of tumor response has been verified.
Section 3.1.2 Duration of Subject Participation Section 5.6 Prior, Concomitant and Prohibited Medications Section 6.1.2 Screening Schedule of Events	The Screening period has been extended from 28 days to 35 days.	To accommodate the potential for necessary administrative delays that might occur during the Screening period; however, all protocol-specified windows for specific assessments remain the same.
Section 3.1.3 Definition of the End of Study Section 13.2.10 Study and Site Closure	To add the following statement: "At the time of study closure, any subjects who are continuing treatment with U3-1402 and who are judged by the Investigator to have ongoing benefit may continue to receive treatment with U3-1402 through a rollover protocol or another mechanism consistent with local requirements."	To specify the procedure for the potential continuation of treatment with U3-1402 for subjects receiving U3-1402 at the time of study closure.
Schedule of Events	Added that the PK samples in subjects who are administered chloroquine or hydroxychloroquine will be collected if the subject provides consent.	To specify that subjects must provide consent for this testing within the appropriate ICF.
Schedule of Events	Specified the cycles that PK samples will be collected prior to infusion.	To align the footnote with the Schedule of Events.

Section # and Title	Description of Change	Brief Rationale
Schedule of Events Section 7.1 Tumor Assessments for Efficacy	Modified the text to include that use or nonuse of IV contrast is appropriate unless medically infeasible, ie, newly developed AE or allergy to contrast agent.	To specify that subjects with a newly developed AE or allergy to contrast agent are not required to receive IV contrast if medically infeasible.
Synopsis Key Exclusion Criteria Section 4.2 Exclusion Criteria Section 5.6 Prior, Concomitant and Prohibited Medications	Clarified that concomitant use of chronic systemic (IV or oral) corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory activity are prohibited.	To distinguish anti-inflammatory activity from mineralocorticoid activity, which may have a different conversion, and to align with exclusion criterion 3.
Section 5.2.4 Administration Schedule of Events	Revised the description for the recalculation of weight-based dosing.	To correct an error in the description for the recalculation of weight-based dosing.
Section 5.4 Dose Modifications (Dose Delay, Reduction, and/or Discontinuation)	Deleted the following statement: "Discussion and agreement between the Investigator and Sponsor are required before discontinuation of study treatment due to an AE."	The current dose modification guidelines no longer require discussion/agreement with Sponsor prior to dose reduction/discontinuation.
Section 5.8.4 Subject Rescreening Procedures	Revised text pertaining to circumstances for subject rescreening.	To specify that rescreening is allowed once if a subject fails to meet any eligibility criterion rather than to restrict rescreening to those who fail only transient or reversible eligibility criteria. The text was also updated to clarify the rescreening process requiring consultation with the Sponsor and assessments required at the time of rescreening.
Section 6.1.2 Screening Section 6.4 End of Treatment Section 9.10 Electrocardiograms Table 13.1 Schedule of Events	Clarified instruction for ECG collection.	To correct an error in the description of ECG collection: single and not triplicate ECGs will be obtained.

Section # and Title	Description of Change	Brief Rationale
Section 6.3.1 Cycle 1 and Subsequent Cycles Section 6.5 40-day Post-treatment Follow-up Section 7.1 Tumor Assessment for Efficacy	Clarified that imaging of the brain is required at Screening and will only be required at subsequent imaging assessments if there is a brain lesion present at baseline, within 1 week of achievement of CR, or if symptoms are present.	To correct an error in the description of the imaging assessment procedure.
Section 8.3.2 Tumor Sample Collection Section 8.3 Biomarker Assessment(s)	To specify that tumor biopsy will be performed if medically feasible.	To specify that the Investigator has discretion based on the medical feasibility of the on treatment biopsy.
Section 9.12 Other Safety Assessments	Specified that all ophthalmologic assessments must be evaluated by an ophthalmologist or other qualified practitioner rather than by the Investigator or delegate.	To specify the healthcare professionals required to perform ophthalmologic assessments.
Section 9.6 Pregnancy	To revise the text from "The Sponsor must be notified of any female subject or partner of a male subject who becomes pregnant while receiving or within 7 months of last dose of U3-1402." to "The Sponsor must be notified of any female subject who becomes pregnant while receiving or within 7 months of the last dose of U3-1402. 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, U3-1402."	To correct an error in the reporting requirements for pregnancy in order to align with current U3-1402 product safety requirements.
Section 9.10 Electrocardiograms	To remove the following statement: "Please refer to the Investigator Site Manual for additional information on the collection of ECGs."	To correct an error in Section 9.10, as no Investigator Site Manual for ECGs is provided for this study.
Section 11.5.2.1 Adverse Event Analyses	SAEs starting or worsening after the on-treatment period, if reported as related to the study treatment, will be listed separately.	To align with the current Daiichi Sankyo definition of a TEAE.

ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; CR = complete response; CT = computed tomography; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VEGF = vascular endothelial growth factor

PROTOCOL SYNOPSIS

EudraCT:	2019-004418-32
IND Number:	148299
Protocol Number:	U31402-A-U202
Investigational Product:	U3-1402
Active Ingredient(s)/ INN:	U3-1402 consists of an antibody component (patritumab) covalently conjugated to a drug-linker (MAAA-1162a) containing a topoisomerase I inhibitor drug component (MAAA-1181a).
Study Title:	A Multi-Center, Open-Label, Phase 2 Study to Evaluate Safety and Efficacy of U3-1402 in Subjects with Advanced or Metastatic Colorectal Cancer (CRC)
Study Phase:	Phase 2
Indication Under Investigation:	U3-1402 will be evaluated in adult subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of therapy, that must include all of the following agents: fluoropyrimidine, irinotecan, platinum agent, an anti-epidermal growth factor receptor (EGFR) agent (if clinically indicated), an anti-vascular endothelial growth factor (VEGF) agent (if clinically indicated), an immune checkpoint inhibitor (if clinically indicated), and a BRAF inhibitor (if clinically indicated).
Study Objectives, Outcome Measures, and Endpoints:	The table below lists primary and secondary study objectives and endpoints which have outcome measures:

Objectives	Outcome Measures	Endpoints	Category
Primary			
To assess the antitumor activity of U3-1402 in subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of therapy (see Inclusion Criteria in Section 4.1)	**Title:** ORR **Description:** Tumor response as assessed by BICR per RECIST v1.1. **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or PR.	Efficacy
Secondary			

To investigate the durability of U3-1402 antitumor activity in subjects with advanced or metastatic CRC	**Title:** DoR **Description:** Tumor response as assessed by BICR per RECIST v1.1 and death date reported by investigator **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject. Death date is collected until the subject discontinues the study.	DoR is defined as the time from the first documented response (CR or PR) to the date of disease progression or death due to any cause.	Efficacy
To further investigate the antitumor activity of U3-1402 in subjects with advanced or metastatic CRC	**Title:** ORR **Description:** Tumor response as assessed by the Investigator per RECIST v1.1. **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or PR.	Efficacy
	Title: DoR **Description:** Tumor response as assessed by Investigator per RECIST v1.1 and death date reported by Investigator **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject. Death date is collected until the subject discontinues the study.	DoR is defined as the duration from the first documented response to the date of disease progression or death due to any cause.	Efficacy
	Title: DCR **Description:** Tumor response 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 disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	DCR is defined as the proportion of subjects who achieved a confirmed BOR of CR, PR, or SD.	Efficacy

	Title: TTR **Description:** Tumor response 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 disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	TTR is defined as the time from the start of study treatment to the date of the first documentation of objective response (CR or PR) that is subsequently confirmed.	Efficacy
	Title: PFS **Description:** Tumor response as assessed by BICR and Investigator per RECIST v1.1 and death date reported by Investigator **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent 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 date of the first documentation of objective PD or death due to any cause, whichever is earlier.	Efficacy
	Title: OS **Description:** Death date as reported by Investigator **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 evaluate the safety and tolerability of U3-1402 in subjects with advanced or metastatic CRC	**Title:** TEAEs and other 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. AEs 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:** Based on a descriptive summary of the efficacy endpoints and HER3 status, a correlative analysis between HER3 protein expression level (as determined by HER3 IHC assay) and efficacy may be performed. **Time frame:** Efficacy data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject. HER3 data are collected at baseline (archival and pre-treatment tumor biopsy) and at Cycle 2.	HER3 protein expression in tumor tissue (as determined by IHC) and correlation with efficacy	Efficacy/ Biomarker
To assess the immunogenicity incidence against U3-1402	**Title:** Immunogenicity **Description:** ADA prevalence, incidence, and titer for U3-1402 **Time frame:** Data are collected from the start of study treatment until the end of treatment. Additional timepoints are specified in Table 13.1.	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 becomes available, confirmed ADA-positive samples may be analyzed for neutralizing activity.	Immunogenicity

To characterize the 3 PK analytes of U3-1402 in subjects with advanced or metastatic CRC	**Title:** PK endpoints **Description:** Serum concentration and PK parameters of U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a) **Time frame:** Data are collected at baseline, then from the start of study treatment until Cycle 8. Additional timepoints are specified in Table 13.1.	Cmax, Tmax, Ctrough, AUClast, and AUCtau	PK

ADA = anti-drug antibody; ADC = antibody drug conjugate; AESIs = adverse events of special interest; AUClast = area under the serum concentration-time curve up to the last quantifiable time ; AUCtau = area under the serum concentration-time curve during dosing interval; BICR = blinded independent central review; BOR = best overall response; Cmax = maximum serum concentration; CR = complete response; CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; Ctrough = trough serum concentration; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; 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; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; SD = stable disease; TBL = total bilirubin; TEAEs = treatment-emergent adverse events; Tmax = time to reach maximum serum concentration; TTR = time to tumor response; v = version.

Study Design: Phase 2, global, multicenter, open-label, 2-cohort study of U3-1402 monotherapy in subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of systemic therapy, that must include all of the following agents: a fluoropyrimidine, irinotecan, a platinum agent, an anti-EGFR agent (if clinically indicated), an anti-VEGF agent (if clinically indicated), an immune checkpoint inhibitor (if clinically indicated), and a BRAF inhibitor (if clinically indicated).

Part 1

Archival tumor biopsy and pre-treatment tumor biopsy will be collected from all subjects at the time of screening, and human epidermal growth factor receptor 3 (HER3) protein expression will be measured by an investigational device (HER3 immunohistochemistry [IHC] assay).

Results of the prospective HER3 IHC assay from the pre-treatment tumor biopsy will be used to assign subjects into 1 of 2 cohorts:

- Cohort 1: HER3 High (IHC 3+, 2+) (approximately 24 treated subjects) or,
- Cohort 2: HER3 Low/Negative (IHC 1+, 0) (approximately 12 treated subjects).

Subjects will be treated on Day 1 of each 21-day cycle (every 3 weeks [Q3W]) with U3-1402 5.6 mg/kg intravenous (IV).

Interim Analysis

For each study cohort, review of the preliminary data from Part 1 will be used to determine whether to open Part 2. The decision to advance from Part 1 to Part 2 will be made separately in Cohort 1 and Cohort 2; the interim futility analysis will be conducted with approximately 24 subjects in Cohort 1 and approximately 12

	subjects in Cohort 2 after all subjects have had the opportunity to complete two tumor assessments. The tumor assessment period may be extended if emerging data show responses are occurring later, or if the tumor assessment for the final evaluated subject in each cohort is delayed. At the time of the interim analysis for each cohort, enrollment into the respective cohort will be paused until the determination that criteria for advancement to Part 2 have been achieved. Note it is possible for the futility criterion to be passed before the above specified analysis timing. These analyses will be conducted based on BICR assessment in the Full Analysis Set (FAS). After review of the data from Part 1 based on criteria outlined in Section 11.6, if the Sponsor decides to enroll subjects irrespective of HER3 expression status in Part 2 (ie, Scenario 1 below, continuing enrollment of Cohort 2 into Part 2), the decision and preliminary data from Cohort 2 Part 1 will be provided as part of a protocol amendment. **Part 2** • Dose: U3-1402 5.6 mg/kg IV Q3W – **Scenario 1**: Enrollment continues in Cohort 1 and Cohort 2: approximately 44 subjects will be enrolled, regardless of HER3 IHC status, and receive treatment with U3-1402. – **Scenario 2**: Enrollment continues in Cohort 1 only: approximately 44 subjects with HER3 High (IHC 3+, 2+) status will be enrolled and receive treatment with U3-1402. Treatment with U3-1402 in all cohorts will continue until the time of progressive disease (PD) per RECIST v1.1, unacceptable toxicity, withdrawal of consent, death, termination of the study by Sponsor, or the occurrence of any of the other events specified in Section 5.7. If PD is suspected by Investigator tumor assessment, imaging must be submitted to blinded independent central review (BICR) for expedited confirmation of disease progression. The decision to discontinue U3-1402 is according to Investigator judgment and should consider BICR assessment.
Study Duration:	The study start date is the date when the first subject has signed an 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 from the subject, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed. The enrollment period is approximately 15 months. For each cohort, enrollment will occur in 2 parts separated by an interim futility analysis. The estimated treatment period is approximately 8 months and the follow-up period is approximately 4 months. The total estimated duration of the study is approximately 27 months. The primary analysis data cut-off will occur when all subjects have had a minimum of 9 months of follow-up or have discontinued from the study earlier. The DCO may be shifted if emerging data indicate responses are occurring at a different time. The final analysis will be performed after all subjects have discontinued from the study for any reason.

	The Sponsor may terminate the study at any time, and study termination may also be requested by a competent authority.
Study Sites and Location:	The study will be conducted at approximately 40 sites in the United States, Europe, and Asia, including Japan. Additional study sites may be added as needed.
Subject Eligibility Criteria:	**Key Inclusion Criteria** • Subject has provided written informed consent prior to the start of any study-specific procedures. • Subjects ≥18 years (follow local regulatory requirements if the legal age of consent for study participation is >18 years old). • Pathological/histological confirmation of advanced or metastatic colon or rectal adenocarcinoma. • Must be resistant, refractory, or intolerant to at least 2 prior lines of systemic therapy, that must include all of the following agents: a. Fluoropyrimidine b. Irinotecan c. Platinum agents (eg, oxaliplatin) d. An anti-EGFR agent, if clinically indicated e. An anti-VEGF agent, if clinically indicated (eg, bevacizumab) f. An immune checkpoint inhibitor, if clinically indicated (eg, microsatellite instability-high [MSI-H] status) g. A BRAF inhibitor, if clinically indicated (eg, BRAF V600E positive) • Has at least 1 measurable lesion confirmed by BICR as per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1. • Willing to provide a required pre-treatment tumor biopsy and an additional archival tissue sample for the assessment of HER3 expression levels by IHC and exploratory biomarkers, defined as: a. Pre-treatment tumor biopsy. Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity (2 cores or 20 slides with adequate tumor tissue content). b. An additional archival tissue sample collected greater than 3 months prior to screening must be available and of sufficient quantity, as defined above, at the time of screening. If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment tumor biopsy is obtained and after discussion and agreement from Sponsor (Medical Monitor or designee). c. Consent to provide on-treatment tumor biopsy. When at least 10 on-treatment tumor biopsies per cohort have been collected, the Sponsor will provide written notification of a change to the requirement. • Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

- Life expectancy ≥3 months.
- Has adequate bone marrow reserve and organ function at baseline based on local laboratory data defined as follows within 14 days prior to Cycle 1 Day 1:

Parameter	**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
SCr **OR** CrCl	SCr ≤ 1.5 × ULN, OR CrCl ≥ 30 mL/min as calculated using the Cockcroft-Gault equation or measured CrCl; confirmation of CrCl is only required when creatinine is >1.5 × ULN
Alanine aminotransferase /aspartate 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

- 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 pulmonary compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
    a. any underlying pulmonary disorder (eg, pulmonary emboli, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion)
    b. any autoimmune, connective tissue or inflammatory disorder with pulmonary involvement (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis)

OR prior complete pneumonectomy.

- Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory activity or any form of immunosuppressive therapy prior to Cycle 1 Day 1. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
- Evidence of 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 do not require 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 of U3-1402:
    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 <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-EGFRs) <28 days;
    d. Immune checkpoint inhibitor therapy <21 days;
    e. Major surgery (excluding placement of vascular access) <4 weeks;
    f. Radiotherapy treatment to >30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <14 days;
    g. Chloroquine or hydroxychloroquine ≤14 days.
- Prior treatment with an anti-HER3 antibody and/or antibody drug conjugate (ADC) that consists of an exatecan derivative that is any topoisomerase I inhibitor (eg, trastuzumab deruxtecan).
- 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.
- Had primary malignancies other than CRC within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
- Uncontrolled or significant cardiovascular disease prior to Cycle 1 Day 1, including:

a. QT interval corrected for heart rate using Fridericia's formula prolongation interval of >470 ms for females and >450 ms for males within 28 days;
b. Left ventricular ejection fraction (LVEF) <50% by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within 28 days;
c. Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg;
d. Myocardial infarction within 6 months;
e. New York Heart Association Classes 2 to 4 congestive heart failure (See Section 13.5) within 28 days;
f. Uncontrolled angina pectoris within 6 months;
g. Cardiac arrhythmia requiring antiarrhythmic treatment within 28 days.

- 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 hepatitis B virus (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 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**
     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).

- Subject with any human immunodeficiency virus (HIV) infection.
- Any evidence of severe or uncontrolled disease (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.

Dosage Form, Dose and Route of Administration:	U3-1402 will be supplied as a 100 mg sterile lyophilized powder (Lyo-DP) to be reconstituted with 5 mL of commercially available water for injection to 20 mg/mL prior to use. Each vial of sterile U3-1402 drug product is designed for single use only and is not to be used to treat more than 1 subject. Once reconstituted, U3-1402 Lyo-DP will be diluted with 250 mL commercially available 5% dextrose injection infusion and dosed at 5.6 mg/kg as an intravenous (IV) infusion administered on Day 1 of each 21-day cycle.
Planned Sample Size:	In Part 1 of the study, approximately 36 subjects will be evaluated in the two cohorts. If both Cohort 1 and Cohort 2 advance to Part 2 of the study, approximately 44 additional subjects will be enrolled in Part 2 (regardless of HER3 IHC status). In such a circumstance, approximately 80 subjects will be enrolled in total. If only Cohort 1 advances to Part 2 of the study, approximately 44 additional subjects will be enrolled in Part 2. In such a circumstance, approximately 80 subjects will be enrolled in total (68 of 80 subjects will have HER3 high expressing tumors). The clinically meaningful objective response rate (ORR) is considered as 20%, and the ORR based on historical data is considered as 5%. With sample size of 68 subjects, if 8 responses are observed, the observed ORR will be 11.8% with a 95% exact confidence interval (CI) of (5.2%, 21.9%). The probability of observing 8 or more responders in 68 subjects is approximately 97.4% when the true ORR is 20%. If the true ORR is 5%, the probability of observing 8 or more responders in 68 subjects is approximately 2%. With a sample size of 80 subjects, if 9 responses are observed, the observed ORR will be 11.25% with a 95% exact CI of (5.3%, 20.3%). The probability of observing 9 or more responders in 80 subjects is approximately 98.7% when the true ORR is 20%. If the true ORR is 5%, the probability of observing 9 or more responders in 80 subjects is approximately 1.8%.
Statistical Analyses:	**Primary and Final Analyses** • The primary analysis data cut-off will occur when all subjects have either a minimum of 9 months of follow-up or have discontinued from the study earlier. The DCO may be shifted if emerging data indicate responses are occurring at a different time. The primary analysis will be included in the clinical study report. • The final analysis will be performed after all subjects have discontinued from the study for any reason. **Interim Analysis** For each study cohort, review of the preliminary data from Part 1 will be used to determine whether to open Part 2. The decision to advance from Part 1 to Part 2 will be made separately in Cohort 1 and Cohort 2; the interim futility analysis will be conducted with approximately 24 subjects in Cohort 1 and approximately 12 subjects in Cohort 2 after all subjects have had the opportunity to complete two tumor assessments. The tumor assessment period may be extended if emerging data show responses are occurring later, or if the tumor assessment for the final evaluated subject in each cohort is delayed. At the time of the interim analysis for each cohort, enrollment into the respective cohort will be paused until the determination that

criteria for advancement to Part 2 has been achieved. Note it is possible for the futility criterion to be passed before the above specified analysis timing. These analyses will be conducted based on BICR assessment in the FAS.

Cohort 1 Decision Criteria at Interim:

1. If at least 3 responders out of 24 subjects in Cohort 1 are observed, then further enrollment in this cohort may proceed.
2. If 0 or 1 responder out of 24 subjects in Cohort 1 is observed at the interim, then further enrollment in this cohort may stop.
3. If 2 responders out of 24 subjects in Cohort 1 are observed, then a decision will be made, after further review of the data, to either continue or stop further enrollment in this cohort.

Cohort 2 Decision Criteria at Interim:

1. If at least 2 responders out of 12 subjects in Cohort 2 are observed, further enrollment in this cohort may proceed after submission of a protocol amendment which includes the preliminary data from Cohort 2 Part 1.
2. If 0 responder out of 12 subjects in Cohort 2 is observed at the interim, then further enrollment in this cohort may stop.
3. If 1 responder out of 12 subjects in Cohort 2 is observed, then a decision will be made, after further review of the data, to either continue or stop further enrollment in this cohort. Further enrollment will be contingent upon submission of a protocol amendment which includes the preliminary data from Cohort 2 Part 1.

The determination of whether to advance a cohort to Part 2 of the study may also take into consideration the PK properties of U3-1402 among subjects enrolled in this study, the subject or disease characteristics of enrolled subjects, among others. The decision to advance the study to Part 2 might be deferred based on the collective evaluation of such information. If indicated, the Sponsor may amend the protocol to evaluate other doses, dose regimens, or selected subject populations with advanced or metastatic CRC prior to advancing the study to Part 2.

Efficacy Analyses

The primary efficacy endpoint is ORR as assessed by BICR per RECIST v1.1. ORR is defined as the proportion of subjects who achieve a best overall response (BOR) of complete response (CR) or partial response (PR). CR/PR will be confirmed with a follow-up tumor assessment at least 4 weeks apart. ORR as assessed by BICR will be summarized with the 2-sided 95% CI using the Clopper-Pearson method in the FAS. For the computation of ORR, subjects with BOR of "not evaluable (NE)" will be included in the FAS and will be considered non-responders. Data will be summarized by cohort if applicable. No formal comparison between the 2 cohorts is planned.

The key secondary efficacy endpoint is duration of response (DoR) as assessed by BICR per RECIST v1.1. Its distribution will be estimated using Kaplan-Meier method and results will be presented graphically. Median DoR and its 2-sided 95% CIs will be calculated using Brookmeyer and Crowley methods. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding 2-sided 95% CIs using the Greenwood formula for variance derivation. Other secondary efficacy endpoints include DoR as assessed by

Investigator, ORR as assessed by Investigator, disease control rate (DCR), time to response (TTR), PFS as assessed by BICR and Investigator, and overall survival (OS). 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 analyzed in the same manner as the key secondary endpoint (DoR by BICR). TTR will be summarized using descriptive statistics.

Descriptive statistics for the best percent change from baseline in the sum of diameters will be provided by cohort if applicable. A waterfall plot of the best percent change in the sum of diameters and a swimmer's plot for response over time will be also prepared for each cohort if applicable.

No formal comparison between the 2 cohorts is planned.

Safety Analyses

Safety analyses in general will be descriptive and will be presented in tabular format with summary statistics presented by treatment group for the Safety Analysis Set (defined as all subjects who receive at least 1 dose of study drug).

Pharmacokinetic Analyses

Serum concentrations for U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a) will be listed, plotted, and summarized using descriptive statistics. PK parameters will be listed and summarized by treatment group using descriptive statistics.

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ABBREVIATION	DEFINITION
Ab	antibody
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUClast	area under the serum concentration-time curve up to the last quantifiable time
AUCtau	area under the serum concentration-time curve during dosing interval
BCRP	breast cancer resistance protein
BI	before infusion
BICR	blinded independent central review
BOR	best overall response
CA 19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
cfRNA	circulating free RNA
CI	confidence interval
Cmax	maximum serum concentration
COVID-19	coronavirus 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	trough serum concentration

ABBREVIATION	DEFINITION
DCO	data cut-off
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
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
EIU	exposure in utero
EOI	end of infusion
EOT	end of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
F/U	Follow-up (Visit)
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
HER3	human epidermal growth factor receptor 3
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

ABBREVIATION	DEFINITION
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
Kel	elimination rate constant associated with the terminal phase
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP-1	Multidrug resistance-associated protein-1
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

ABBREVIATION	DEFINITION
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
SD	stable disease
SOC	system organ class
SoD	sum of diameters
SOP	standard operating procedure
SpO_2	peripheral oxygen saturation
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum serum concentration
TTR	time to tumor response
ULN	upper limit of normal
US	United States
v	version
VEGF	vascular endothelial growth factor

1. INTRODUCTION

1.1. Background

1.1.1. Colorectal Cancer Background and Treatments

Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer death worldwide. In 2020, it is projected that approximately 147,950 individuals will be newly diagnosed in the United States with an estimated 53,200 cancer deaths (including 17,930 cases and 3,640 deaths in patients <50 years).[1] CRC incidence rates vary regionally, with higher rates observed in East Asia and Europe (13.1% and 11.8%, respectively, of the total cancer incidence in these regions) compared to lower rates observed in North America (7.6% the total cancer incidence).[2] At diagnosis, 39% of patients with CRC have localized disease, 35% of patients have regional stage disease, and 22% are diagnosed with distant metastases. The 5-year survival rate in localized disease is approximately 90%; fewer than 20% of patients with metastatic CRC are expected to survive 5 years.[3]

Current guidelines for the management of metastatic CRC recommend a multidisciplinary approach that involves surgical resection, chemotherapy with or without targeted therapy, and/or radiation therapy, as appropriate.[4,5] Individual patient data from 22 first-line metastatic CRC trials demonstrated a median overall survival (OS) of 18.2 months and progression-free survival (PFS) of 8.3 months.[6] First-line combination treatments have yielded median OS durations of up to 30 months.[7,8] Approved agents in the third-line and higher treatment setting following treatment with fluoropyrimidine, irinotecan, oxaliplatin, and anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) antibody (Ab) therapy include regorafenib (a multi-kinase inhibitor) and Trifluridine/Tipiracil (TAS-102; a thymidine-based nucleoside analog/thymidine phosphorylase inhibitor). The RECOURSE trial of the TAS-102 arm in patients with refractory metastatic CRC demonstrated an OS of 7.1 months, an objective response rate (ORR) of 1.6% (compared to 0.4% for placebo), a PFS of 2.0 months, and a disease control rate (DCR) of 44%.[9] The CORRECT trial results of regorafenib demonstrated an OS of 6.4 months, an ORR of 1% (compared to 0.4% for placebo), a PFS of 1.9 months, and a DCR of 41%.[10] Thus, among patients with previously treated locally advanced or metastatic CRC, the prognosis remains poor. [11]

1.1.2. Human Epidermal Growth Factor Receptor 3

Human epidermal growth factor receptor 3 (HER3), a member of the human epidermal growth factor receptor (HER) family of proteins, is known to mediate oncogenic transformation in multiple tumor types.[11,12] There is mechanistic evidence also for the role of HER3 in CRC. In CRC cells, HER3 promotes cell proliferation and mediates resistance to cytotoxic chemotherapy and to targeted therapeutics.[13] In vitro, ERBB3 (the gene encoding the HER3 protein) knockdown decreases cell proliferation, induces apoptosis, and blocks the migration of colon cancer cells.[14] Moreover, in BRAF-V600E mutant colon cancer stem cells, HER3 mediates cellular proliferation and is associated with resistance to the BRAF inhibitor vemurafenib.[14]

Multiple lines of evidence indicate that HER3 signaling is functionally important in mediating resistance to standard cancer treatment.[13,15,16,17] Elevated expression of the HER3 protein in multiple tumor types has been observed in approximately 69%-83% of CRC patients.[18,19,20]

Elevated HER3 expression has been associated with worse clinical outcome in CRC.[21,22] A meta-analysis of the association between the high expression of HER3and clinical pathologic features and prognosis of CRC showed that there was a significant association between an increase in HER3 expression and tumor differentiation, tumor, node, metastasis tumor stage, and anatomic location.[13] Patients with high expression of HER3 demonstrated an inferior tumor response and OS after treatment with cetuximab.[13]

1.1.3. U3-1402

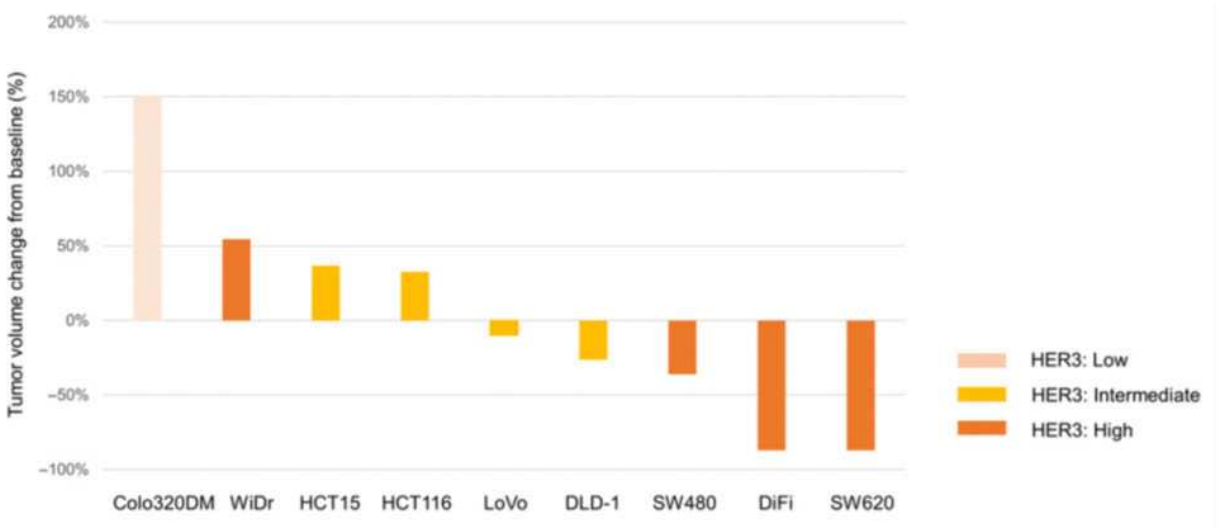
U3-1402 is an antibody drug conjugate (ADC) comprised of a recombinant fully human anti-HER3 immunoglobulin G1 monoclonal Ab (patritumab, U3-1287) covalently linked to MAAA-1162a (glycine-glycine-phenylalanine-glycine) tetrapeptide linker containing a topoisomerase I inhibitor [MAAA-1181a]). MAAA-1181a is a derivative of the topoisomerase I inhibitor exatecan (DX-8951f),[23,24,25] which has shown activity in a wide range of advanced solid tumors. MAAA-1181a is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I.

1.1.4. In Vivo and In Vitro Models

Nonclinical studies have shown that U3-1402 binds specifically to the HER3 extracellular domain and does not bind to other HER family proteins. U3-1402 exhibited HER3 expression-dependent cell growth inhibition activity in multiple HER3-expressing in vivo CRC models in various molecular sub-types. Antitumor activity was demonstrated following different prior treatments, including several that were derived from irinotecan refractory tumors, with a trend toward higher antitumor activity in higher HER3-expression models. Therefore, U3-1402 is expected to show antitumor activity in HER3-expressing tumors. For additional details, refer to Section 1.2.1 of the Investigator's Brochure (IB).[26]

To evaluate antitumor activity in a tumor xenograft model, U3-1402 was administered at 10 mg/kg every 3 weeks (Q3W) (Days 0, 7, and 14).[26] Activity of U3-1402 was assessed by the maximum tumor regression during the treatment (Figure 1.1).[27] Tumor regression was observed in xenografted tumors derived from 5 of the 9 cell lines (DiFi, DLD-1, LoVo, SW480, and SW620). The highest regression was seen in tumors from SW620 cells (high HER3 with KRAS G12C activation mutation) and DiFi (high HER3 expression with KRAS wild type and EGFR gene amplification). These results showed that antitumor activity of U3-1402 was associated with higher levels of HER3 expression in xenograft models, regardless of the KRAS mutation status.

Figure 1.1: Waterfall Plot for Tumor Xenograft Models.



HER3 = human epidermal growth factor receptor 3; Q3W = every 3 weeks.
U3-1402 (10 mg/kg) was administered Q3W (Days 0, 7, and 14) via intraperitoneal injection.
Source: Koganemaru 2019[27]

1.1.5. Clinical Studies

For additional details regarding the studies summarized below, refer to Section 1.3.2 of the IB.[26]

Study U31402-A-J101 Breast Cancer (Ongoing)

Study U31402-A-J101 is a Phase 1/2, multicenter, open-label, multiple-dose, first-in-human study of U3-1402 in subjects with HER3-positive metastatic breast cancer. The study design includes a Dose Escalation Part to identify the maximum tolerated dose (MTD) of U3-1402; a Dose Finding Part to determine the recommended doses for expansion (RDEs) of U3-1402 and to assess multiple drug administration schedules, to determine the safety of alternative dosing schedules; and a global Dose Expansion Part to evaluate the safety and efficacy of U3-1402 at the RDEs for subjects with HER3-positive metastatic breast cancer. As of the data cut-off (DCO) date of 05 Aug 2019, 144 of the 145 subjects enrolled had received U3-1402. At the DCO, 50 subjects were continuing study drug and 94 subjects had discontinued treatment including 74 subjects due to disease progression (68 subjects due to progressive disease [PD] by Response Evaluation Criteria in Solid Tumors [RECIST] and 6 subjects due to clinical PD), 10 subjects due to an adverse event (AE), 4 subjects due to withdrawal by subject, 5 subjects due to other reasons, and 1 due to death. Treatment-emergent adverse events (TEAEs), all grades regardless of causality, were reported in 141 (97.9%) treated subjects; nausea (113 [78.5%] subjects) and decreased appetite (74 [51.4%] subjects) were experienced by >50% of subjects. TEAEs of Grade 3 or higher were reported in 92 (63.9%) subjects. The most common Grade ≥3 TEAEs experienced by >5% of subjects were neutrophil count decreased (37 [25.7%] subjects), platelet count decreased (32 [22.2%] subjects), anaemia (25 [17.4%] subjects), white blood cell count decreased (21 [14.6%] subjects), thrombocytopenia (12 [8.3%] subjects), neutropenia (11 [7.6%] subjects), hypokalaemia (10 [6.9%] subjects), and aspartate aminotransferase (AST) increased (8 [5.6%] subjects).

Efficacy data are available as of the previous DCO (8 Nov 2018) and are as follows: subjects from Dose Escalation and Dose Finding (N=42) demonstrated a confirmed ORR of 42.9%, a DCR of 90.5%, and a median PFS of 8.3 months (median follow-up of 10.5 months).[28]

Study U31402-A-U102 (Ongoing)

Study U31402-A-U102 is a multicenter, open-label, Phase 1 study of U3-1402 in subjects with metastatic or unresectable non-small cell lung cancer (NSCLC). This study includes a Dose Escalation Part in which subjects receive intravenous (IV) U3-1402 in 21-day cycles with a starting dose of 3.2 mg/kg, and a Dose Expansion Part in which subjects receive U3-1402 at the RDE determined in the Dose Escalation Part. As of the DCO date of 05 Aug 2019, 36 subjects had received U3-1402 in the Dose Escalation Part. Four subjects were enrolled in the 3.2 mg/kg cohort, 15 subjects were enrolled in the 4.8 mg/kg cohort, 12 subjects were enrolled in the 5.6 mg/kg cohort, and 5 subjects were enrolled in the 6.4 mg/kg cohort. At the DCO, 12 subjects were continuing study drug. Eighteen subjects had discontinued due to disease progression, 2 subjects due to clinical progression, 1 subject due to death caused by disease progression, 2 subjects due to an AE, and 1 subject had discontinued due to withdrawal of consent by subject. All (100%) subjects had at least one TEAE; nausea (23 [63.9%] subjects) and vomiting (15 41.7%] subjects) were experienced by >40% of subjects. TEAEs of Grade 3 or higher were reported in 16 (44.4%) subjects as of 05 Aug 2019. The most common Grade ≥3 TEAEs reported 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).

Preliminary efficacy data are available as of the previous DCO (May 2019) and are as follows: of the 26 efficacy-evaluable patients, 6 had confirmed partial responses (PRs; 2 each at 4.8, 5.6, and 6.4 mg/kg). Median best percentage change in sum of diameters (SoD) was −25.7% (range, −82.6% to 13.3%), including decreases in SoD in patients with CDK4 amplification (–25.7% and -17.8%), human epidermal growth factor receptor 2 (HER2) amplification (–28.6%), and both CCNE1 amplification and PIK3CA mutation (-28.8%).[29]

1.2. Study Rationale

In the setting of advanced or metastatic CRC conventional approved therapies as well as targeted therapies confer minimal efficacy[29] (Section 1.1.1). Further, limited effective targeted options for this disease have become available over the last decade and very few experimental compounds are in development in the advanced setting. Therefore, there is a great unmet medical need in advanced or metastatic CRC as the standard of care is insufficient for treatment in this patient population.

In CRC cells, HER3 promotes cell proliferation and mediates resistance to cytotoxic chemotherapy and to targeted therapy. High expression of HER3 has been shown to be associated with tumor differentiation. There is a large patient population with metastatic CRC with high prevalence of HER3 expression. HER3 is expressed in a majority of CRC patients (~50%-75% immunohistochemistry [IHC] 3+ and 2+) (Section 1.1.2).[18,19,20]

Due to the high prevalence of HER3 expression, U3-1402 in advanced or metastatic CRC is hypothesized to show efficacy based on the following:

- Significant tumor regression with U3-1402 was observed in several tumor xenograft models with both KRAS wild type and KRAS mutant (Section 1.1.4).[30]
- Topoisomerase I inhibition with irinotecan is one of the cornerstones of systemic therapy regimens in advanced or metastatic CRC. Exatecan (DX-8951f), a compound from which the topoisomerase I inhibitor payload (MAAA-1181a) of U3-1402 is derived, showed proof of activity in a CRC study with an irinotecan resistant patient population.[30] The exatecan conjugate (MAAA-1181a) payload of the U3-1402 ADC has a similar mechanism of action and may, therefore show activity in patients whose tumors express HER3.
- Preliminary clinical evidence from the studies of U3-1402 in metastatic breast cancer (U31402-A-J101) and in NSCLC (U31402-A-U102) is consistent with this hypothesis where a high rate of HER3 expression and tumor reduction is observed in a majority of subjects. U3-1402 has also demonstrated a manageable safety profile in U31402-A-J101 and U31402-A-U102 (Section 1.1.5).[28,29]

The large population of patients with advanced or metastatic CRC for whom clinical outcomes remain poor due to minimally efficacious standard of care options, the high prevalence of HER3-expressing tumors in CRC, the clinical activity of exatecan (from which MAAA-1118a was derived) in irinotecan-resistant CRC, and preliminary clinical evidence of safety and efficacy of U3-1402 in metastatic breast cancer and NSCLC highlights the opportunity for U3-1402 to improve the care of patients with advanced or metastatic CRC.

This Phase 2, multicenter, open-label study was designed to primarily evaluate the safety and efficacy of U3-1402 in subjects with advanced or metastatic CRC who have received at least 2 prior lines of therapy and will explore clinical benefit according to HER3-expression level in otherwise refractory tumors.

1.2.1. Justification for Dose Selection for Study

The regimen to be evaluated will be a fixed dose of 5.6 mg/kg administered as a continuous IV infusion on Day 1 of each 21-day cycle.

Data from two studies have been considered for the selection of the 5.6 mg/kg dose. Study U31402-A-J101 included 1.6 mg/kg, 3.2 mg/kg, 6.4 mg/kg and 8.0 mg/kg Q3W in subjects with breast cancer, the MTD was established at 6.4 mg/kg. Study U31402-A-U102 included 3.2-mg/kg, 4.8 mg/kg, 5.6 mg/kg and 6.4 mg/kg Q3W in NSCLC patients, the MTD was established at 5.6 mg/kg. In addition, 4.2 mg/kg every 2 weeks and an up-titration dose regimen were studied in the J101 study, with 3.2 mg/kg in Cycle 1, 4.8 mg/kg in Cycle 2, and 6.4 mg/kg in Cycle 3 and after. Exposure of intact U3-1402 ADC, total anti-HER3 Ab and released payload MAAA-1181a increased as dose increased. Population pharmacokinetics (PK), and exposure response analyses for efficacy and safety were conducted using data from both the U31402-A-J101 and U31402-A-U102 studies. Exposure-efficacy relationship was established for intact U3-1402 ADC and the exposure safety relationship was established for released payload MAAA-1181a.

The rationale for the selection of 5.6 mg/kg is based on an exposure-response analysis of efficacy, and 5.6 mg/kg is predicted to provide a lower probability of ≥Grade 3 thrombocytopenia compared to 6.4 mg/kg, and an improved ORR compared to 4.8 mg/kg.

More data are being collected in the ongoing U3-1402 studies to further evaluate this dosing regimen.

1.2.2. Benefit/Risk Assessment for Study Subjects

U3-1402 is being developed for the treatment of HER3-expressing malignant tumors.

Nonclinical studies have demonstrated the antitumor activity of U3-1402 in HER3 tumor-bearing mouse models. Thus, U3-1402 is hypothesized to demonstrate efficacy in treating HER3-expressing tumors in patients.

In nonclinical toxicology studies, intestinal toxicity, lymphatic/hematopoietic system toxicity, skin toxicity, pulmonary toxicity, reproductive and accessory organ toxicities, hepatic toxicity, cardiotoxicity, and renal toxicity were found in association with the administration of U3-1402.

As with any therapeutic Abs, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions to U3-1402. Considering the toxicity data from the nonclinical studies, the important potential risk is hepatotoxicity, and the potential risks are infusion-related reaction, dry eye, keratitis, photosensitivity, dry skin, rash, rash maculopapular, and skin pigmentation in humans from exposure to U3-1402, and these have been closely monitored and evaluated in the U3-1402 clinical development program.

Based on the preliminary clinical safety data from the ongoing U3-1402 studies, the important identified risk is interstitial lung disease (ILD); the important potential risk is hepatotoxicity, and the identified risks are nausea, decreased appetite, platelet count decreased/thrombocytopenia, white blood cell count decreased/leukopenia, neutrophil count decreased/neutropenia, vomiting, anemia, diarrhea, fatigue, malaise, stomatitis, constipation, alanine aminotransferase (ALT) increased, AST increased, febrile neutropenia, and alopecia, and will continue to be closely monitored and evaluated in the U3-1402 clinical development program.

Preliminary data as of 06 Nov 2018 from the ongoing study U31402-A-J101 in breast cancer subjects from Dose Escalation and Dose Finding (N=42) demonstrated a confirmed ORR of 42.9%, a DCR of 90.5%, and a median PFS of 8.3 months (median follow-up of 10.5 months).[28] Further, preliminary data as of May 2019 from the ongoing study U31402-A-U102 are as follows: of the 26 efficacy-evaluable patients, 6 had confirmed PRs (2 each at 4.8, 5.6, and 6.4 mg/kg). Median best percentage change in SoD was -25.7% (range, -82.6% to 13.3%), including decreases in SoD in patients with CDK4 amplification (-25.7% and -17.8%), HER2 amplification (-28.6%), and both CCNE1 amplification and PIK3CA mutation (-28.8%).[29]

In conclusion, based on the efficacy and safety data from the nonclinical studies and the preliminary clinical safety and efficacy data from the ongoing studies, the benefit/risk balance supports continued clinical development of U3-1402.

See the current IB for updated benefit/risk assessment.[26]

2. STUDY OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives and endpoints as well as outcome measures are described in Table 2.1. See Section 11 for further description of the endpoint analyses and definitions.

Table 2.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measures	Endpoints	Category
Primary			
To assess the antitumor activity of U3-1402 in subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of therapy (see Inclusion Criteria in Section 4.1)	**Title:** ORR **Description:** Tumor response as assessed by BICR per RECIST v1.1 **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or PR.	Efficacy
Secondary			
To investigate the durability of U3-1402 antitumor activity in subjects with advanced or metastatic CRC	**Title:** DoR **Description:** Tumor response as assessed by BICR per RECIST v1.1 and death date reported by Investigator **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject. Death date is collected until the subject discontinues the study.	DoR is defined as the time from the first documented response (CR or PR) to the date of disease progression or death due to any cause.	Efficacy
To further investigate the antitumor activity of U3-1402 in subjects with advanced or metastatic CRC	**Title:** ORR **Description:** Tumor response as assessed by the Investigator per RECIST v1.1. **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject.	ORR is defined as the proportion of subjects with a BOR of confirmed CR or PR.	Efficacy
	Title: DoR **Description:** Tumor response as assessed by Investigator per	DoR is defined as the duration from the first documented response to	Efficacy

Objectives	Outcome Measures	Endpoints	Category
	RECIST v1.1 and death date reported by Investigator **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject. Death date is collected until the subject discontinues the study.	the date of disease progression or death due to any cause.	
	Title: DCR **Description:** Tumor response 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 disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	DCR is defined as the proportion of subjects who achieved a confirmed BOR of CR, PR, or SD.	Efficacy
	Title: TTR **Description:** Tumor response 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 disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject.	TTR is defined as the time from the start of study treatment to the date of the first documentation of objective response (CR or PR) that is subsequently confirmed.	Efficacy
	Title: PFS **Description:** Tumor response as assessed by BICR and Investigator per RECIST v1.1 and death date reported by Investigator. **Time frame:** Data are collected at baseline, then from the start of study treatment until disease progression by BICR, death, lost to follow-up, or withdrawal of consent by the subject. Death date is collected until the subject discontinues the study.	PFS is defined as the duration from the start of study treatment to the date of the first documentation of objective PD or death due to any cause, whichever is earlier.	Efficacy

Objectives	Outcome Measures	Endpoints	Category
	Title: OS **Description:** Death date as reported by Investigator **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 evaluate the safety and tolerability of U3-1402 in subjects with advanced or metastatic CRC	**Title:** TEAEs and other 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. AEs 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:** Based on a descriptive summary of the efficacy endpoints and HER3 status, a correlative analysis between HER3 protein expression level (as determined by HER3 IHC assay) and efficacy may be performed. **Time frame:** Efficacy data are collected at baseline, then from the start of study treatment until disease progression or death, lost to follow-up, or withdrawal of consent by the subject. HER3 data are collected at baseline (archival and pre-treatment tumor biopsy) and at Cycle 2.	HER3 protein expression in tumor tissue (as determined by IHC) and correlation with efficacy	Efficacy/ Biomarker

Objectives	Outcome Measures	Endpoints	Category
To assess the immunogenicity incidence against U3-1402	**Title:** Immunogenicity **Description:** ADA prevalence, incidence, and titer for U3-1402 **Time frame:** Data are collected from the start of study treatment until the end of treatment. Additional timepoints are specified in Table 13.1.	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 becomes available confirmed ADA-positive samples may be analyzed for neutralizing activity.	Immuno-genicity
To characterize the 3 PK analytes of U3-1402 in subjects with advanced or metastatic CRC	**Title:** PK endpoints **Description:** Serum concentration and PK parameters of U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a) **Time frame:** Data are collected at baseline, then from the start of study treatment until Cycle 8. Additional timepoints are specified in Table 13.1.	Cmax, Tmax, Ctrough, AUClast, and AUCtau	PK
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

Objectives	Outcome Measures	Endpoints	Category
To explore potential additional biomarkers that may aid in identifying subjects who will derive optimal therapeutic benefit from U3-1402	Not applicable	Potential patient selection biomarkers (gene expression, genomic alteration, gene signatures) will be assessed in association with U3-1402 clinical activity.	Biomarker
To explore the impact of intrinsic and extrinsic factors of the PK of U3-1402 in subjects with advanced or metastatic CRC	Not applicable	Population PK analysis	PK
To evaluate the Exposure-Response for efficacy and safety endpoints	Not applicable	Exposure-Response for efficacy and safety analysis	Efficacy

ADA = anti-drug antibody; ADC = antibody drug conjugate; AESIs = adverse events of special interest; AUClast = area under the serum concentration-time curve up to the last quantifiable time ; AUCtau = area under the serum concentration-time curve during dosing interval; BICR = blinded independent central review; BOR = best overall response; Cmax = maximum serum concentration; CR = complete response; CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; Ctrough = trough serum concentration; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; HER3 = human epidermal growth factor receptor 3; ICF = informed consent form; ICF = informed consent form; IHC = immunohistochemistry; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; mRNA = messenger ribonucleic acid; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; SD = stable disease; TBL = total bilirubin; TEAEs = treatment-emergent adverse events; Tmax = time to reach maximum serum concentration; TTR = time to tumor response; v = version.

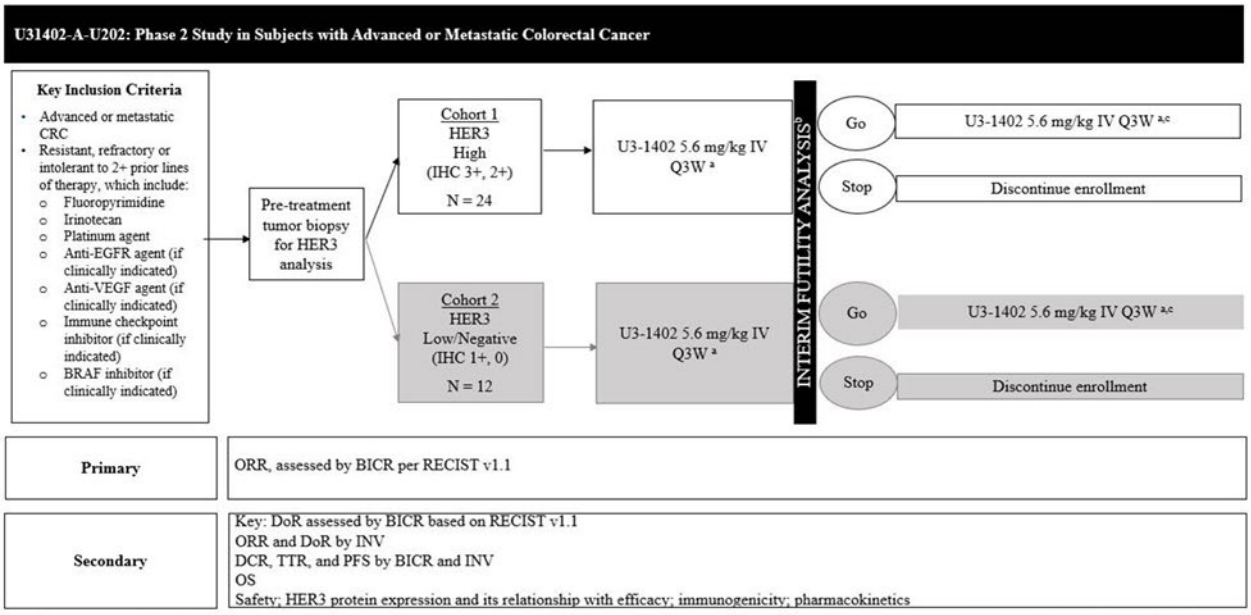
3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2, multicenter, open-label, 2-cohort study of U3-1402 single agent therapy in subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of systemic therapy that must include all of the following agents: fluoropyrimidine, irinotecan, platinum agent, an anti-EGFR agent (if clinically indicated), an anti-VEGF agent (if clinically indicated), an immune checkpoint inhibitor (if clinically indicated), and a BRAF inhibitor (if clinically indicated). Figure 3.1 shows the study design.

This study will be conducted at approximately 40 sites in the United States, Europe, and Asia (including Japan). Additional sites may be added as needed.

Figure 3.1: Study Design Schema



a. Treatment with U3-1402 in all cohorts will continue until the time of progressive disease (PD), unacceptable toxicity, withdrawal of consent, death, termination of the study by Sponsor, or the occurrence of any of the other events specified in Section 5.7.
b. An interim futility analysis will be conducted after approximately 24 subjects in Cohort 1 have had the opportunity to complete two tumor assessments. Separately in Cohort 2, an interim futility analysis is planned with approximately 12 subjects. For further details, see Section 11.6.
c. A total of 44 subjects will be enrolled in Part 2. For details regarding sample size in Part 2, see Section 11.3.

BICR = blinded independent central review; CRC = colorectal cancer; DCR = disease control rate; DoR = duration of response; EGFR = epidermal growth factor receptor; HER3 = human epidermal growth factor receptor 3; IHC = immunohistochemistry; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to tumor response; VEGF = vascular endothelial growth factor.

Part 1

Archival tumor biopsy and pre-treatment tumor biopsy will be collected from all subjects at screening and HER3 protein expression will be measured by an investigational device (HER3 IHC assay).

Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if the archival tumor tissue:

- Was collected within 3 months of screening during or after treatment with the last prior cancer treatment and
- Is of sufficient quantity, defined as 2 cores or 20 slides with adequate tumor tissue content.

Results of the prospective HER3 IHC assay from the pre-treatment tumor biopsy will be used to assign subjects into 1 of 2 cohorts:

- Cohort 1: HER3 High (IHC 3+, 2+) (approximately 24 treated subjects), **or**
- Cohort 2: HER3 Low/Negative (IHC 1+, 0) (approximately 12 treated subjects).

See Section 8.3.1 for additional details regarding the HER3 IHC assay.

Subjects will be treated on Day 1 of each 21-day cycle with U3-1402 5.6 mg/kg IV.

For each study cohort, review of the preliminary data from Part 1 will be used to determine whether to open Part 2. The decision to advance from Part 1 to Part 2 will be made separately in Cohort 1 and Cohort 2; the interim futility analysis will be conducted with approximately 24 subjects in Cohort 1 and approximately 12 subjects in Cohort 2 after all subjects have had the opportunity to complete two tumor assessments. The tumor assessment period may be extended if emerging data show responses are occurring later, or if the tumor assessment for the final evaluated subject in each cohort is delayed. At the time of the interim analysis for each cohort, enrollment into the respective cohort will be paused until the determination that criteria for advancement to Part 2 have been achieved. Note it is possible for the futility criterion to be passed before the above specified analysis timing. These analyses will be conducted based on BICR assessment in the Full Analysis Set (FAS).

After review of the data from Part 1 based on criteria outlined in Section 11.6, if the Sponsor decides to enroll subjects irrespective of HER3 expression status in Part 2 (ie, Scenario 1 below, continuing enrollment of Cohort 2 into Part 2), the decision and preliminary data from Cohort 2 Part 1 will be provided as part of a protocol amendment.

Part 2

- Dose: U3-1402 5.6 mg/kg IV Q3W
  - **Scenario 1**: Enrollment continues in Cohort 1 and Cohort 2: approximately 44 subjects will be enrolled, regardless of HER3 IHC status, and receive treatment with U3-1402.

    Total sample size at end of study: approximately 80 = Part 1 (Cohort 1 [approximately 24 subjects] + Cohort 2 [approximately 12 subjects]) + Part 2 (Cohorts 1 and 2 [approximately 44 subjects])
  - **Scenario 2**: Enrollment continues in Cohort 1 only: approximately 44 subjects with HER3 High (IHC 3+, 2+) status will be enrolled and receive treatment with U3-1402.

    Total sample size at end of study: approximately 80 = Part 1 (Cohort 1 [approximately 24 subjects] + Cohort 2 [approximately 12 subjects]) + Part 2 (Cohort 1 [approximately 44 subjects])

Treatment with U3-1402 in all cohorts will continue until the time of PD (confirmed by BICR) per RECIST v1.1, unacceptable toxicity, withdrawal of consent, death, termination of the study by Sponsor, or the occurrence of any of the other events specified in Section 5.7. 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 U3-1402 is according to Investigator judgment and should consider BICR assessment.

3.1.1. Duration of the Study

The study start date is the date when the first subject has signed an informed consent form (ICF).

The enrollment period is approximately 15 months. It will occur in 2 parts separated by an interim futility analysis for each cohort. The estimated treatment period is approximately 8 months, and the follow-up period is approximately 4 months.

The total estimated duration of the study is approximately 27 months. The primary analysis data cut-off will occur when all subjects have had either a minimum of 9 months of follow-up or have discontinued from the study earlier. The DCO may be shifted if emerging data indicate responses are occurring at a different time. The final analysis will be performed after all subjects have discontinued from the study for any reason. In addition, the Sponsor may terminate the study at any time and study termination may also be requested by a competent authority; in such an instance the data cut-off date will be the date of study termination.

3.1.2. Duration of Subject Participation

The screening period is up to 35 days. Each cycle of treatment will be 21 days. The number of treatment cycles with U3-1402 is not limited. Subjects may continue study treatment until the time of progressive disease per RECIST v1.1, unacceptable toxicity, withdrawal of consent, death, termination of the study by Sponsor or the occurrence of any of the other events specified in Section 5.7. If PD is suspected by Investigator tumor assessment, imaging must be submitted to BICR for expedited confirmation of disease progression. The decision to discontinue U3-1402 is according to Investigator judgment and should consider BICR assessment.

Tumor assessments will be performed 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 Version (v) 1.1 , death, lost to follow-up, or withdrawal of consent.

There is an End-of-Treatment (EOT) Visit that takes place within 7 days after the final dose of U3-1402 or before the start of new anticancer treatment, whichever comes first. Subjects will be asked to attend a 40-Day Follow-up (F/U) Visit (+7 days) 40 days after the last U3-1402 administration. If the subject begins another anticancer therapy before the end of the 40 days (+7 days), every effort will be made to complete all of the F/U assessments prior to starting the new therapy. For further details concerning assessments performed at the EOT and F/U Visits refer to the Schedule of Events (Table 13.1).

After discontinuation from study treatment, follow-up information for determining anti-drug antibodies (ADAs) as well as survival information and subsequent anticancer therapy, if available, should be collected every 3 months (±14 days). Survival F/U contact can occur via telephone contact or unscheduled visit and will continue until death, withdrawal of consent, lost

to follow-up, or study closure, whichever occurs first. Refer to Table 13.1 for details. 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.

3.1.3. Definition of the End of Study

The overall end of study will occur after the last subject last visit has occurred; or after all subjects have discontinued from the study or have died; or an alternative study becomes available for subjects continuing to derive benefit from treatment with U3-1402 where the drug is offered to these subjects; or the study is discontinued by the Sponsor for other reasons.

At the time of study closure, any subjects who are continuing treatment with U3-1402 and who are judged by the Investigator to have ongoing benefit may continue to receive treatment with U3-1402 through a rollover protocol or another mechanism consistent with local requirements.

4. STUDY POPULATION

Each subject will sign and date a study ICF provided by the site. A subject is considered enrolled in the study upon the Investigator or a designee obtaining written informed consent from the subject at the time of screening and upon determination that all inclusion and exclusion criteria have been satisfied.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited subject information and outcome of the screening process (ie, enrollment in the study, reason for ineligibility, withdrew consent).

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

4.1. Inclusion Criteria

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

1. Sign and date the ICF prior to the start of any study-specific qualification procedures.
2. Male or female subjects ≥18 years (follow local regulatory requirements if the legal age of consent for study participation is >18 years old).
3. Pathological or histological confirmation and documentation of colon or rectum adenocarcinoma with advanced or metastatic disease.
4. Must be resistant, refractory, or intolerant to at least 2 prior lines of therapy, that must include all of the following agents:
    a. Fluoropyrimidine
    b. Irinotecan
    c. Platinum agents (eg, oxaliplatin)
    d. An anti-EGFR agent, if clinically indicated
    e. An anti-VEGF agent, if clinically indicated (eg, bevacizumab)
    f. An immune checkpoint inhibitor, if clinically indicated (eg, microsatellite instability-high [MSI-H] status)
    g. A BRAF inhibitor, if clinically indicated (eg, BRAF V600E positive)
5. Has at least 1 measurable lesion confirmed by BICR as per RECIST v1.1.
6. Willing to provide a required pre-treatment tumor biopsy and an additional archival tissue sample for the assessment of HER3 expression levels by IHC and exploratory biomarkers, defined as:
    a. Pre-treatment tumor biopsy. Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity (2 cores or 20 slides with adequate tumor tissue content).
    b. An additional archival tissue sample collected greater than 3 months prior to screening must be available and of sufficient quantity, as defined above, at the time of screening. If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment

tumor biopsy is obtained and after discussion and agreement from Sponsor (Medical Monitor or designee).

c. Consent to provide on-treatment tumor biopsy. When at least 10 on-treatment tumor biopsies per cohort have been collected, the Sponsor will provide written notification of a change to the requirement.

7. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.
8. Life expectancy ≥3 months.
9. Has adequate bone marrow reserve and organ function, based on local laboratory data, defined as within 14 days prior to Cycle 1 Day 1:

Parameter	**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
SCr **OR** CrCl	SCr ≤ 1.5 × ULN, OR CrCl ≥ 30 mL/min as calculated using the Cockcroft-Gault equation or measured CrCl; confirmation of CrCl is only required when creatinine is >1.5 × ULN
Alanine aminotransferase /aspartate 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 a highly effective form of birth control as detailed in Section 13.8, 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 9.6 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 contraception (Section 13.8) 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 for 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.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be denied entry to the study:

1. Any history of ILD (including pulmonary fibrosis or radiation pneumonitis), has current ILD, or is suspected to have such disease by imaging during screening.
2. Clinically severe pulmonary compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
    a. any underlying pulmonary disorder (eg, pulmonary emboli, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion)
    b. any autoimmune, connective tissue or inflammatory disorder with pulmonary involvement (eg, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis)

    OR prior complete pneumonectomy.
3. Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory activity or any form of immunosuppressive therapy prior to Cycle 1 Day 1. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
4. Evidence of leptomeningeal disease
5. 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 do not require 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.
6. Inadequate washout period prior to Cycle 1 Day 1 of U3-1402:

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 <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-EGFRs) <28 days;
d. Immune checkpoint inhibitor therapy <21 days;
e. Major surgery (excluding placement of vascular access) <4 weeks;
f. Radiotherapy treatment to >30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <14 days;
g. Chloroquine /Hydroxychloroquine ≤14 days.

7. Prior treatment with an anti-HER3 antibody and/or ADC that consists of an exatecan derivative that is any topoisomerase I inhibitor (eg, trastuzumab deruxtecan).

8. 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.

9. Had primary malignancies other than CRC within 3 years prior to Cycle 1 Day 1, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.

10. Uncontrolled or significant cardiovascular disease prior to Cycle 1 Day 1, including:

    a. QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation interval of >470 ms for females and >450 ms for males within 28 days;
    b. Left ventricular ejection fraction (LVEF) <50% by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within 28 days;
    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 (See Section 13.5) within 28 days;
    f. Uncontrolled angina pectoris within 6 months;
    g. Cardiac arrhythmia requiring antiarrhythmic treatment within 28 days.

11. 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 hepatitis B virus (HBV) infection are eligible if:
        i. Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody positive; **OR**
        ii. 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**
        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).

12. Subject with any human immunodeficiency virus (HIV) infection.
13. Any evidence of severe or uncontrolled systemic 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.
14. Has history of hypersensitivity to either the drug substances or inactive ingredients in the drug product.
15. Female who is pregnant or breastfeeding or intends to become pregnant during the study.
16. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator
17. Has clinically significant corneal disease.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments

5.1.1. Treatment Group(s)/Sequences

All subjects will receive treatment with U3-1402 5.6 mg/kg IV Q3W.

5.1.2. Method of Treatment Allocation

Subjects must meet all eligibility criteria and provide signed informed consent prior to initiating any study-specific procedures.

Part 1

Prior to interim futility analysis, results of the prospective HER3 IHC assay from the pre-treatment tumor biopsy will be used to assign subjects to the following cohorts:

- Cohort 1 – HER3 High (IHC 3+, 2+)
- Cohort 2 – HER3 Low/Negative (IHC 1+, 0)

All subjects will receive treatment with U3-1402 5.6 mg/kg IV Q3W.

Part 2

Post interim futility analysis, all subjects will receive treatment with U3-1402 5.6 mg.kg Q3W.

- Enrollment continues in Cohort 1 and Cohort 2, regardless of HER3 IHC status
  - Cohort 1 – HER3 High (IHC 3+, 2+)
  - Cohort 2 – HER3 Low/Negative (IHC 1+, 0)
- Enrollment continues in Cohort 1 only
  - Cohort 1 – HER3 High (IHC 3+, 2+)

5.1.3. Blinding

This study has an open-label design, and no blinding will be performed.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug(s)

5.2.1. Description

U3-1402 for Injection 100 mg (Lyo-DP) is a sterile lyophilized powder in an amber glass vial for intravenous infusion that must be stored at 5°C ±3°C and protected from light. Each vial of sterile U3-1402 drug product is designed for single use only and is not to be used to treat more than 1 subject.

5.2.2. Labeling and Packaging

U3-1402 for Injection 100 mg will be supplied by the Sponsor and will be packaged and labeled in compliance with local regulatory requirements. The packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations.

5.2.3. Preparation

Preparation of U3-1402 will be conducted in accordance with instructions detailed in the Dose Preparation Instructions provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site.

Prior to use, Lyo-DP will be reconstituted with 5 mL of commercially available water for injection to provide a solution with the concentration of 20 mg/mL U3-1402 at a pH range of 5.4 ± 0.5 formulated with L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 20. Five mL of reconstituted solution is withdrawn from each vial to deliver 100 mg of U3-1402. Following reconstitution, U3-1402 will be diluted in dextrose solution and dosed at 5.6 mg/kg. Please reference the Pharmacy Instructions for specific details.

5.2.4. Administration

U3-1402 will be infused as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after this initial dose, then subsequent doses of U3-1402 will be infused over approximately 30 minutes on Day 1 of each subsequent cycle Q3W. Record start and stop times and amount of drug administered. Refer to Table 5.2 for additional information on drug administration following infusion-related reactions.

The subject's weight at Screening (baseline) 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 weight for all subsequent dosing calculations.

5.2.5. Storage

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

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

Refer to the Pharmacy Instructions for more information regarding drug storage.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, and check the drug expiration date. In addition, the Investigator or designee shall contact the Sponsor and CRO as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be maintained for the investigational product. The record must be kept current and should contain the dates and quantities of drug received, subject's information for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and the remaining quantity.

At the end of the study, or as directed, all unused, used and/or partially used U3-1402 will be destroyed at the site per institutional policy (and documented). If the site's institutional policy does not allow for destruction on site, U3-1402 will be returned to a designee as instructed by the Sponsor or destroyed in accordance with the Sponsor's instructions. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational product must be documented, and the documentation included in the shipment. At the end of the study, a final investigational product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator and the supervisor of investigational products in Japan when approved in writing by the Sponsor, and after the Sponsor has received copies of the site's drug handling and disposition SOPs.

All investigational product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator or supervisor of investigational products in Japan is responsible for the accountability of all used and unused study supplies at the site.

5.3. Control Treatment

Not applicable.

5.4. Dose Modifications (Dose Delay, Reduction, and/or Discontinuation)

All dose modifications (delay, reduction and/or discontinuation) should be based on the worst grade toxicity of the event preceding the dose modification. Dose modifications are applicable only to TEAEs that are assessed as related to use of U3-1402 by the Investigator(s). For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary. All dose modifications must be recorded on the AE and drug administration electronic case report form (eCRF) pages.

5.4.1. Dose Delay and Reductions

5.4.1.1. Dose Delay and Discontinuation

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.

5.4.1.2. Dose Reductions

If dose reduction is required, U3-1402 dosing should be reduced by 1 dose level at a time (Table 5.1). Once the dose of U3-1402 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 5.1.

Table 5.1: Dose Reductions for the Fixed Dose 5.6 mg/kg Regimen

Starting Dose	Dose Level -1	Dose Level -2
5.6 mg/kg IV infusion Q3W	4.8 mg/kg IV infusion Q3W	3.2 mg/kg IV infusion Q3W

IV = intravenous; Q3W = every 3 weeks

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

5.4.1.3. Dose Modifications

Table 5.2 provides schedule modifications for specific toxicities.

Table 5.2: Dose Modification Criteria

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
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 infusion, the rate must be reduced by 50% and subjects must be closely monitored. If no other reactions appear, the subsequent infusion rate can be resumed at the initial planned rate.
	Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] injection fluids); prophylactic medications indicated for ≤24 hours	U3-1402 infusion must be interrupted. Symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids) administered as needed. 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 U3-1402 must be administered at that visit. The amount of U3-1402 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).

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	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 U3-1402 must be discontinued immediately and permanently. Urgent intervention 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 or baseline values, then: • If resolved to ≤Grade 1 or baseline values in ≤14 days, resume U3-1402; • If resolved to ≤Grade 1 or baseline values in >14 days, reduce U3-1402 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 U3-1402.
	Grade 4 (<500/mm^3; <0.5 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then reduce U3-1402 by 1 dose level and resume.
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 U3-1402. Consider reducing U3-1402 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 U3-1402 by 1 dose level and resume. Administer G-CSF as prophylaxis for all subsequent cycles and according to local guidelines.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Lymphocyte count decreased	Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then: • If resolved in ≤14 days, resume U3-1402. • If resolved in >14 days, reduce U3-1402 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 U3-1402. For recurrent anemia, delay dose until resolved to ≤Grade 2 or baseline, then reduce U3-1402 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 U3-1402 by 1 dose level and resume. Consider transfusion per institutional guidelines.
Platelet count decreased	Grade 3 (Platelets <50 - 25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then: • If resolved in ≤14 days, resume U3-1402; • If resolved in >14 days, U3-1402 may be resumed. Consider reducing U3-1402 by 1 dose level. Consider transfusion per institutional guidelines.
	Grade 4 (Platelets <25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then reduce U3-1402 by 1 dose level and resume. Consider transfusion per institutional guidelines.
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 U3-1402 by 1 dose level and resume.
Ejection fraction decreased	Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	Continue U3-1402.
	LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	Continue U3-1402. Repeat LVEF assessment within 3 weeks.
	LVEF 40% to ≤45% and decrease is 10% to 20% (absolute) from baseline	Delay U3-1402 dosing. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	LVEF <40% or >20% (absolute) drop from baseline	Delay U3-1402 dosing. Repeat LVEF assessment within 3 weeks; if LVEF <40% or >20% (absolute) drop from baseline is confirmed, discontinue U3-1402. Cardiologist consultation as necessary.
Electrocardiogram QT corrected interval prolonged	Grade 3 (Average QTcF ≥501 ms; >60 ms change from baseline)	Delay U3-1402 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 U3-1402, then reduce U3-1402 by 1 dose level. Cardiologist consultation as necessary.
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue subject from U3-1402. Cardiologist consultation as necessary

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Respiratory, thoracic and mediastinal disorders		
Pulmonary toxicity	See next rows	If a subject develops radiographic changes potentially consistent with ILD or 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 U3-1402 dosing pending further evaluation and start corticosteroid treatment promptly per consensus statement [39] unless clinically contraindicated. Evaluation 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 U3-1402 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 Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	Grade 1	The administration of U3-1402 must be delayed. U3-1402 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 CT chest findings, followed by gradual taper over at least 4 weeks.
		• Monitor symptoms closely.
		• Re-image as clinically indicated.
		• If worsening or no improvement in diagnostic observations in 5 days,
		  • Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone).
		  • Re-consider additional work-up for alternative etiologies as described above.
		  • Escalate care as clinically indicated.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402

	Grade 3 and 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 U3-1402; • If resolved in >7 days, then reduce U3-1402 by 1 dose level. Ophthalmologist consultation as necessary.
	Grade 4	Discontinue subject from U3-1402. 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 U3-1402 by 1 dose level.
	Grade 4 (>6.0 × ULN)	Discontinue subject from U3-1402.
Hepatobiliary disorders		
AST or ALT increased without TBL increased	Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	Continue U3-1402. In subjects **without** liver metastasis, monitor AST/ALT 24 to 72 hours later, and continue regular monitoring until resolution.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	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 U3-1402 dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, resume U3-1402; • If resolved in >7 days, then reduce U3-1402 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 U3-1402 dose until resolved to ≤ baseline level, then: • If resolved in ≤7 days, resume U3-1402; • If resolved in >7 days, then reduce U3-1402 by 1 dose level.
	Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from U3-1402. 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 U3-1402 dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, resume U3-1402; • If resolved in >7 days, reduce U3-1402 by 1 dose level. If documented Gilbert's syndrome or liver metastases at baseline, continue U3-1402.
	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 U3-1402 dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, reduce U3-1402 by 1 dose level; • If resolved in >7 days, discontinue subject from U3-1402. If documented Gilbert's syndrome or liver metastases at baseline, delay U3-1402 dose until resolved to ≤Grade 2, then: • If resolved in ≤7 days, reduce U3-1402 by 1 dose level; • If resolved in >7 days, discontinue subject from U3-1402.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from U3-1402.
AST or ALT increased and TBL increased	AST or ALT ≥3 × ULN with simultaneous TBL >2 × ULN	Delay U3-1402 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 U3-1402 may occur after discussion between the Investigator and Sponsor. U3-1402 will be permanently discontinued if drug induced liver injury cannot be ruled out from diagnostic workup.
AST or ALT > 3.0 x ULN (if liver metastases are present, >5 ×ULN) for those subjects with known Hepatitis B and/or Hepatitis C infection at baseline	--	Delay U3-1402 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 U3-1402.
Gastrointestinal disorders		
Nausea	Grade 3 (inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated)	Delay U3-1402 until resolved to ≤Grade 1, and consider treatment with anti-emetics and/or corticosteroids as per Investigator's judgment and local/institutional guidelines, then: • If resolved to ≤Grade 1 in ≤14 days resume U3-1402; • If does not resolve to ≤Grade 1 in >14 days reduce U3-1402 dose by 1 level.

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Vomiting	Grade 3 (Tube feeding, TPN, or hospitalization indicated)	Delay U3-1402 until resolved to ≤Grade 1, and consider treatment with antiemetics and/or corticosteroids as per Investigator's judgment and local/institutional guidelines, then: • If resolved to ≤Grade 1 in ≤7 days, resume U3-1402; • If does not resolve to ≤Grade 1 in >7 days, reduce U3-1402 by 1 dose level.
	Grade 4	Discontinue subject from U3-1402
Based on currently available clinical safety data for U3-1402, 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 U3-1402 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 U3-1402 until resolved to ≤Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤7 days, resume U3-1402; • If resolved to ≤Grade 1 in >7 days, then reduce U3-1402 by 1 dose level.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue subject from U3-1402.
Mucositis oral	Grade 3	Delay U3-1402 until resolved to ≤Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤Grade 1 in ≤14 days, resume U3-1402; • If resolved to ≤Grade 1 in >14 days, then reduce U3-1402 by 1 dose level.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue subject from U3-1402.
Other adverse events (non-laboratory or laboratory)	Grade 3	Delay U3-1402 until resolved to ≤Grade 1, or baseline level, then: • If resolved in ≤7 days, resume U3-1402; • If resolved in >7 days, then reduce U3-1402 by 1 dose level.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue subject from U3-1402.

ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CBC = complete blood count; CT = computerized tomography; DNA = deoxyribonucleic acid; ECHO = echocardiogram; eCRF = electronic case report form; G-CSF = granulocyte-colony stimulating factor; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; ILD = interstitial lung disease;

LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; QTcF = QT interval corrected for heart rate using Fridericia's formula; RNA = ribonucleic acid;SpO_2 = peripheral capillary oxygen saturation; TBL = total bilirubin; TPN = total parenteral nutrition; ULN = upper limit of normal.

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 judgment 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 Daiichi Sankyo's Medical Monitor or designee.

5.5. Method of Assessing Treatment Compliance

All drugs used for the study treatment will be administered by the Investigator or other designated study personnel. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for the administration of study treatment.

5.6. Prior, Concomitant and Prohibited Medications

Therapies used from the time the subject signs the ICF for study participation to the 40-Day F/U Visit (+ 7 days) after the last administration of U3-1402 will be recorded in the eCRF. Prophylactic therapies (including any required premedications), prior therapies and all concomitant therapies will be recorded in the eCRF. Based on currently available clinical safety data for U3-1402, it is recommended that patients receive premedication with antiemetic agents. Refer to Table 5.2.

All therapies received by 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, ≥14 days or 5 half-lives, whichever is longer;
- Monoclonal antibodies other than immune checkpoint inhibitors, such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFRs) ≥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 U3-1402:

- Other anticancer therapy, including cytotoxic chemotherapy, immune checkpoint inhibitors, or targeted agents
- Live virus vaccination (beginning from 28 days prior to Cycle 1 Day)
- Other investigational therapeutic agents
- Radiotherapy, except for 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.
- Concomitant use of chronic systemic (IV or oral) corticosteroids (ie, >10 mg prednisone or equivalent anti-inflammatory activity) or other immunosuppressive medications except for managing AEs
- Chloroquine or hydroxychloroquine

Refer to Section 13.9 for further instructions.

Restricted Therapies/Products

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

- Investigators' discretion/clinical judgment 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 upon by a study doctor, at any time during the study and ≥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 interrupts 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 U3-1402.
- 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 $\geq$50,000/mm^3 without transfusion support
- Subjects taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio.

5.6.1. Membrane Transport Inhibitors

A clinical drug-drug interaction study (DS8201-A-A104) fam-trastuzumab deruxtecan, an ADC that shares the same linker and payload (MAAA-1181a) as U3-1402, showed that co-administration of ritonavir (a dual inhibitor of OATP1B/CYP3A) or itraconazole (a strong CYP3A inhibitor) increased the MAAA-1181a AUC by 22% and 18%, respectively. This magnitude of increase of MAAA-1181a is not considered to indicate a clinically meaningful impact on the PK of DS-8201. Although a dedicated study with a P-glycoprotein (P-gp) inhibitor was not conducted, since itraconazole and ritonavir have been reported to be strong P-gp inhibitors[31], the increases in exposure of MAAA-1181a (22% and 18%) can be considered as a summed impact of a strong CYP3A4 inhibitor and strong P-gp inhibitor. Therefore, the impact of a strong P-gp inhibitor alone on the exposure of MAAA-1181a is expected to be no greater than that observed for a dual inhibitor such as itraconazole or ritonovir.

Although MAAA-1181a was identified in vitro to be a substrate of the efflux transporters breast cancer resistance protein (BCRP) and multidrug resistance-associated protein-1MRP-1, no dedicated study was conducted to evaluate the effects of BCRP and MRP-1 inhibitors on the exposure of MAAA-1181a. Ritonavir has been reported to be an inhibitor of BCRP[32,33] and MRP1[34], supporting the conclusion that BCRP and MRP-1 inhibitors are also unlikely to have a clinically meaningful effect on exposure of MAAA-1181a. In addition, since the expression of MRP-1 in the liver (which mediates the efflux of glucuronidated or sulfateds bile salt conjugates[35]) is low[36], the inhibition of MRP1 is expected to have a low impact on the exposure of MAAA-1181a.

In rats, the major excretion pathway of radiolabeled MAAA-1181a was feces via the biliary route, and the urinary excretion of MAAA-1181a is low[37,38]. MATE2-K (which is involved in the excretion of substrates into urine) is expected to have minimal impact on the exposure of MAAA-1181a in patients.

Section 13.10 provides a link to a Food and Drug Administration list of clinical inhibitors for transporters.

5.7. Discontinuation of Study Drug

The primary reason for permanent discontinuation of U3-1402 treatment administration must be recorded. Reasons for treatment discontinuation include:

- PD 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)
- AE (See Section 5.4)
- Death
- Pregnancy
- Withdrawal by subject (**to discontinue study drug**). NOTE: In this section, this is only withdrawal for treatment with study drug and is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including survival follow-up).
- Lost to follow-up
- Protocol violation (specify)
- Study terminated by Sponsor
- Other, specify (eg, Investigator discretion)

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

Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.8. Subject Withdrawal/Discontinuation from the Study

5.8.1. Reasons for Withdrawal

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

- Death
- Withdrawal by subject (**from the study**). NOTE: This indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival.
- Lost to follow-up
- Study terminated by Sponsor
- Other, specify

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are PD or AE. If the 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.

5.8.2. 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.
- If consent for 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 the Schedule of Events (Table 13.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

5.8.3. Subject Replacement

Subjects will not be replaced.

5.8.4. Subject Rescreening Procedures

The study will allow rescreening once for any subject who has failed to meet the eligibility criteria during the time of 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 that the subject was 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, as specified in the protocol (i.e., procedures performed beyond the specified window prior to Cycle 1 Day 1).

5.8.5. 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, using telephone calls, texts, emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

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

6. STUDY PROCEDURES

6.1. Screening

6.1.1. Tissue Requirement

All subjects will be required to provide a pre-treatment tumor biopsy and archival tumor sample prior to Cycle 1 Day 1. A HER3 IHC assay will be used to assign subjects to cohorts.

The following procedures should be conducted for all subjects:

Before enrollment

- Obtain a separate signed and dated ICF for tumor screening before any study-related procedures or assessments are performed.
- Perform a pre-treatment tumor biopsy and request an archival tumor tissue sample (see details in Section 8.3.2).
  - Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if the archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity defined as 2 cores or 20 slides with adequate tumor tissue content.
  - An additional archival tissue sample collected greater than 3 months prior to screening must be available and of sufficient quantity, as defined above, at the time of screening. If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment tumor biopsy is obtained and after discussion and agreement from Sponsor.
- Send tumor tissue to the IHC central testing lab for determination of the HER3 status. Refer to the Laboratory Manual for information regarding archival and pre-treatment tumor tissue requirements and shipping.

6.1.2. Screening

The following activities and/or assessments will be performed during the Eligibility Screening period. The Screening period is 35 days; however, a more restrictive window may be specified for certain Screening assessments prior to the first dose (see the Schedule of Events [Table 13.1] for detailed information):

- Have the subject sign the appropriate ICF(s) prior to initiating any study procedures.
- Review the subject's demographics, medical and target disease history, and results of tests done as part of routine care. Assess whether subject meets inclusion/exclusion criteria specified in Section 4.
- Subject's medical history, prior cancer history, prior cancer biomarker history, and prior cancer medical therapy will be obtained by the Investigator or a qualified designee.

- Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of CRC/vital signs that are out of range) that were diagnosed or known to exist prior to the main ICF signature will be recorded in Medical History in the eCRF. Record the start date of any medical occurrence that started after the ICF was signed and is ongoing at the time of the Cycle 1 Day 1 on the AE eCRF.
- Perform tumor assessment by computed tomography (CT) or magnetic resonance imaging MRI scans of the brain, chest, abdomen, pelvis, and any other sites of disease within 28 days prior to Cycle 1 Day 1 (Section 13.4).
- Perform Hepatitis B (Hepatitis B surface antigen [HBsAg]) and Hepatitis C virus (HCV Ab) and viral load assessment (if indicated) as described in the eligibility criteria within 28 days prior to Cycle 1 Day 1 (see Section 4.2).
- An HIV Ab test is optional unless required by local regulations or Institutional Review Board (IRB)/Independent Ethics Committee (IEC). If required, perform within 28 days prior to Cycle 1 Day 1.
- Urinalysis (Section 9.8). Urinalysis assessment should be performed within 72 hours 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 clinically indicated.
- Obtain a serum sample for pregnancy testing in women of childbearing potential within 72 hours of enrollment for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours before infusion (BI) of each cycle and at end of treatment.
- Vital sign assessments include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes. Vital sign assessments should be performed within 28 days prior to Cycle 1 Day 1 (Section 9.9).
- Peripheral oxygen saturation (SpO_2) within 28 days prior to Cycle 1 Day 1 (Note: When CT/MRI is conducted, SpO_2 should also be obtained per Investigator discretion.) (Section 9.12)
- Ophthalmologic assessments include visual acuity test (Early Treatment Diabetic Retinopathy Study [ETDRS], Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry and have to occur within 7 days prior to Cycle 1 Day 1. Assessment may be repeated as clinically indicated as part of an unscheduled visit. (Section 9.12).
- Perform a complete physical examination and record weight and height within 28 days prior to Cycle 1 Day 1 (Section 9.11).
- Assess functional status using the ECOG PS Scale within 28 days prior to Cycle 1 Day 1 (Section 13.6).
- Perform a 12-lead electrocardiogram (ECG) within 28 days prior to Cycle 1 Day 1. Subjects should rest supine for at least 10 minutes prior to the ECG assessment. The same test must be used for screening, EOT, and as clinically indicated (Section 9.10).

- LVEF measured by ECHO or MUGA within 28 days prior to Cycle 1 Day 1. The same test must be used for the subject at screening, EOT, and as clinically indicated. (Section 9.12).
- Obtain blood samples for safety laboratories (Section 9.8). Hematology/chemistry assessments should be obtained within 14 days prior to Cycle 1 Day 1.
- Assess for AEs/serious adverse events (SAEs) and review prior medications (Section 9).
- Coagulation test 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.

6.2. Randomization

Randomization is not applicable for this study.

6.3. Study Assessments

6.3.1. Cycle 1 and Subsequent Cycles

The following activities and/or assessments will be performed during the Treatment Period (details are provided in the Schedule of Assessments; see Table 13.1).

Day 1; BI (all cycles)

- Obtain a urine sample for pregnancy testing in women of childbearing potential within 72 hours of enrollment for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours before infusion of each cycle and at end of treatment.
- Complete physical examination and record weight (Section 9.11).
- Assess functional status using the ECOG PS Scale (Section 13.6).
- Carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), C-reactive protein (CRP) (Section 9.8).
- Obtain blood samples for safety laboratories (Section 9.8). Collect additional safety samples on Cycle 1 Day 1, Day 8, Day 15, Cycle 2 Day 1, and Cycle 3, Day 1, Day 8 and Day 15, Cycle 4 and subsequent cycles on Day 1.
- Obtain the biomarker samples Day 1 of each cycle and on Cycle 2 Day 3 (rather than Day 1) to coincide with collection of the on-treatment tumor biopsy (Section 8.3).
- Administer U3-1402 (Section 5.2.4)

Day 1; BI and/or end of infusion (EOI; per cycle)

- Obtain blood samples for PK analyses (Section 8.1) on visits per the Schedule of Events (Table 13.1).

  - Initial 12 subjects in each cohort (12 subjects in Cohort 1 and 12 subjects in Cohort 2): Prior to interim futility analysis, PK blood samples will be collected intensively in Cycle 1 and 3 and sparsely in Cycles 2, 4, 6 and 8 (for specific PK sampling timepoints, see Table 13.1).
  - Blood samples for PK from all other subjects in each cohort will be collected under a less-intensive schedule (see Table 13.1).
- Vital signs including SpO_2 measured BI and EOI on Day 1 of all cycles and additionally on Day 8 and Day 15 of Cycle 1 (Section 9.9). Assessments will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes.

Other

- Collect a single blood sample for pharmacogenomic analysis at EOI on Cycle 1 Day 1 or at any time during the study (Section 8.4.1).
- Collect blood samples for ADA analysis on Cycles 1 and 2, Day 1 (BI), on Cycle 1 Day 8, and on Cycle 4, Day 1 (-5 days), and every 2 cycles thereafter (Section 8.4).
- Collect on-treatment tumor biopsy Cycle 2, Day 3 (±1 day) (Section 8.3.2). The on-treatment tumor biopsy sample (with minimum of 2 cores or 20 slides) will be analyzed for HER3 protein expression using IHC and ribonucleic acid (RNA) expression profiling and genomic alteration using next generation sequencing (NGS). One core will be flash frozen for analysis of MAAA-1181a using fit-for-purpose qualified assay at the bioanalytical laboratory. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Soft tissue tumor biopsy should be obtained from the primary tumor or metastatic site. Blood for hematology must be obtained within 2 days of the tumor biopsy and results must be reviewed by the Investigator prior to obtaining a tumor biopsy. After approximately 10 on-treatment tumor biopsies per cohort have been collected, the Sponsor will notify the Investigator of a change in this requirement. If the subject does not consent to the mandatory on-treatment tumor biopsy, blood sample for biomarkers will be collected on Cycle 2 Day 1. If consent is not obtained to perform the mandatory on-treatment tumor biopsy, the PK sample at Cycle 2 Day 3 is not needed.
- Perform tumor assessment by CT or MRI scans of the brain (if stable brain metastasis was present at baseline), chest, abdomen, pelvis, and any other sites of disease 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 (Section 7.1).
- AE/SAE assessments at all visits and review concomitant medications (Section 9).

6.4. End of Treatment

The EOT is defined as the date the Investigator decides to discontinue study treatment. The following EOT procedures will be performed as specified in the Schedule of Events. This visit occurs within 7 days after the final dose of U3-1402 or before the start of new anticancer treatment, whichever comes first. If the decision to withdraw/discontinue U3-1402 occurs more than 7 days after the final dose of U3-1402, then this visit should occur within 7 days after this decision or before the start of new anticancer treatment; whichever comes first. If the EOT assessments have been performed within 30 d (± 7 d) of their last treatment, they can be considered to be the EOT data and there is no need to repeat them; otherwise, these assessments need to be repeated. If the EOT Visit occurs ≥40 days after the final dose of U3-1402, the 40-Day F/U Visit does not need to be conducted.

The following procedures should be obtained/performed per the Schedule of Events (Table 13.1):

- On-treatment tumor biopsy (optional) (Section 8.3.2). An optional EOT on-treatment tumor biopsy will also be performed at the time of progression or discontinuation from study treatment with minimal 2 cores or 20 slides (if provided as slides). 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 U3-1402, and prior to starting any new anticancer treatment.
- Collect urine for urinalysis (Section 9.8).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential within 72 hours of enrollment for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test. Perform repeat pregnancy tests (urine or serum test per institutional guideline) 72 hours before infusion of each cycle and at end of treatment.
- Complete physical examination and record weight (Section 9.11).
- Vital signs (Section 9.9). Assessments will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes.
- Perform SpO_2 (Section 9.12). When CT/MRI is conducted, SpO_2 should also be obtained per Investigator discretion.
- Assess functional status using the ECOG PS Scale (Section 13.6).
- Obtain blood samples for the following:
  - Safety laboratories (Section 9.8);
  - Biomarkers (Section 8.3);
  - CEA, CA 19-9, CRP (Section 9.8);
  - ADA (Section 8.4);

  - PK analysis (Section 8.1). PK assay can be performed on the ADA sample collected.

- LVEF measured by ECHO or MUGA. The same test must be used for the subject at screening, EOT, and as clinically indicated. (Section 9.12).
- Perform a 12-lead ECG. Subjects should rest supine for at least 10 minutes prior to the ECG assessment. The same test must be used for screening, EOT, and as clinically indicated (Section 9.10).
- Ophthalmologic assessments include visual acuity test (ETDRS, Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry. A 40 +7-Day F/U assessment is only required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
- AEs/SAEs assessment and review concomitant medications (Section 9).

6.5. 40-day Post-treatment Follow-up

Assessments to monitor ongoing safety, and immunogenicity in the follow-up period will be performed 40 days (+7 days) after the last dose of U3-1402 or before starting new anticancer treatment, whichever comes first. For detailed explanations of the timing and nature of assessments performed, refer to the Schedule of Events (Table 13.1).

- Perform tumor assessment by CT or MRI scans of the brain (if stable brain metastasis was present at baseline), chest, abdomen, pelvis, and any other sites of disease 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.
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential within 72 hours of enrollment for all female subjects of childbearing potential. A positive urine pregnancy test result must immediately be confirmed using a serum test.
- Complete physical examination and record weight (Section 9.11).
- Vital signs (Section 9.9). Assessments will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes
- Perform SpO_2 (Section 9.12). When CT/MRI is conducted, SpO_2 should also be obtained per Investigator discretion.
- Assess functional status using the ECOG PS Scale (Section 13.6).
- Obtain blood samples for the safety laboratories (Section 9.8);
- AEs/SAEs assessment and review medications (Section 9).

6.6. Every 3 Month Follow-up

All subjects should be followed for survival at least every 3 months (±14 days) after discontinuing study drug.

For detailed explanations of the timing and nature of assessments performed in the follow-up period refer to the Schedule of Events (Table 13.1).

- For subjects with positive ADA, additional serum ADA samples should be collected every 3 months (± 30 days) for up to 1 year after the last dose of U3-1402, 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 (Section 8.4).
- Obtain blood samples for the PK analysis per the cohort's specifications in Table 13.1 (see Section 8.1). The PK assay can be performed on the ADA sample collected.
- Survival monitoring will continue until death, withdrawal of consent by subject from the study (Note: this indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival), lost to follow-up, or study termination by Sponsor, whichever event occurs earlier.
- Review new anticancer treatment.

7. EFFICACY ASSESSMENTS

7.1. Tumor Assessments for Efficacy

Clinical activity of U3-1402 will be assessed by evaluating tumor response.

Tumor assessments will be conducted as indicated in the Schedule of Events (Table 13.1). At screening, perform radiographic tumor assessments (CT/MRI) of the chest, abdomen, pelvis, brain, and all sites of disease. Investigator determined tumor radiologic assessments of the brain (if stable brain metastasis was present at baseline), chest, abdomen, and pelvis and other relevant anatomic locations where imaging was performed at screening or newly suspected disease should be performed 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, and will continue to be performed until documented disease progression by BICR per RECIST v1.1 (Section 13.4), death, lost to follow-up, or withdrawal of consent (withdrawal by subject from the study as indicated on the end of study form: NOTE: This indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term 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 same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse 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 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 13.4).

Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Also, perform CT or MRI of the brain within a target of 1 week after a subject achieves a complete response (CR).

7.2. Appropriateness of Selected Efficacy Assessment(s)

Considerable medical need in advanced or metastatic CRC and lack of effective treatment options underpin the urgency for finding new effective therapeutic agents.

ORR as assessed by BICR per RECIST v1.1 was selected as the primary endpoint for this study. Although OS is considered the most reliable efficacy endpoint for cancer trials, this endpoint requires a large sample size and long waiting times for an event to happen and is more appropriate for randomized controlled studies. Replacing OS by a surrogate survival endpoint such as ORR or PFS allows determination of the effects of a new treatment in less time, using a smaller sample size and potentially with fewer confounding effects from prior lines of treatment.[40,41]

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

Blood samples for U3-1402 PK analyses will be obtained at the time points specified in the Schedule of Events (Table 13.1). Additionally, samples may be obtained at any time during the study if deemed clinically necessary. At each time point, blood will be collected for U3-1402 PK analysis. Instructions for the collection and handling of blood samples and shipping of serum samples for U3-1402 PK analysis are included in the Laboratory Manual. The actual time of U3-1402 administration (start of infusion and EOI) and the exact time of blood sampling for U3-1402 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, ECG and vital signs should be taken immediately prior to PK sampling time.

The U3-1402 PK samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory. Serum concentrations of U3-1402 (ADC) and total anti-HER3 antibody (naked antibody plus ADC) will be measured with validated analyte-specific ligand binding assays. Serum concentrations of the released payload MAAA-1181a will be measured with validated liquid chromatography/mass spectrometry assay.

The serum PK parameters listed in Table 8.1 of U3-1402 (ADC, total anti-HER3 antibody and MAAA-1181a) will be estimated using standard noncompartmental methods:

- Cmax = maximum serum concentration;
- Tmax = time to reach maximum serum concentration;
- Ctrough = trough serum concentration;
- AUClast = area under the serum concentration-time curve up to the last quantifiable time;
- AUCtau = area under the serum concentration-time curve during dosing interval.

The other PK parameters (elimination rate constant associated with the terminal phase [Kel], terminal elimination half-life, total body clearance, volume of distribution based on the terminal phase, and volume of distribution at steady state) will be calculated if data permit.

Initial 12 subjects in each cohort (12 subjects in Cohort 1 and 12 subjects in Cohort 2): Pharmacokinetic blood samples will be collected intensively prior to the interim futility analysis during Cycles 1 and 3 and sparsely in Cycles 2, 4, 6 and 8 (before and at EOI) (see the Schedule of Events in Table 13.1).

PK samples from all other subjects, in each cohort, will be collected under a less-intensive schedule (see the Schedule of Events in Table 13.1).

Table 8.1: Pharmacokinetic Parameters

Subject Population	Analyte	PK parameters
Initial 12 subjects in Cohort 1 and initial 12 subjects in Cohort 2	U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a)	Cmax, Tmax, Ctrough, AUClast, and AUCtau
All other subjects	U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a)	Cmax, Tmax, Ctrough

ADC = antibody drug conjugate; AUClast = area under the serum concentration-time curve up to the last quantifiable time; AUCtau = area under the serum concentration-time curve during dosing interval; Cmax = maximum serum concentration; Ctrough = trough serum concentration; HER3 = human epidermal growth factor receptor 3; Tmax = time to reach maximum serum concentration.

8.2. Pharmacodynamic Assessment(s)

Not applicable.

8.3. Biomarker Assessment(s)

Subjects will be requested to provide a tumor sample for assessing HER3 expression and other biomarkers at study entry, during the treatment period, and at EOT; see the Schedule of Events (Table 13.1) for details of assessments and timings.

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

All subjects will be asked to provide written consent to provide tumor tissue (archival tissue, pre-treatment tumor biopsy, and on-treatment tumor biopsy) and blood samples for research purposes prior to study entry. The tumor biopsy will be performed if medically feasible.

In addition, biomarker research including analysis of genes or DNA, RNA, proteins and metabolites may be conducted on blood/tumor tissue. This research would extend the search for other potential biomarkers related to the effects of U3-1402 treatment. See Section 8.4.1.3 for storage and disposal of specimens.

8.3.1. HER3 Protein Expression

The level of HER3 protein expression will be assessed using the archival and pre-treatment biopsy provided by the subject. Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if the archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity (defined as 2 cores or 20 slides with adequate tumor tissue content). An additional archival tissue sample collected greater than 3 months prior to screening must be available and of sufficient quantity, as defined above, at the time of screening. If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment tumor biopsy is obtained and after discussion and agreement from the Sponsor. The level of HER3 expression in pre-study treatment, on-study treatment, and post-study treatment will be assessed with the tumor biopsy sample.

The slides from all subjects will be stained using an investigational device to measure HER3 protein expression. Subjects will be designated to each cohort based on the HER3 expression as (3+, 2+, 1+ or 0) using the algorithm that has been established for HER2 IHC testing in gastric cancer.[42]

8.3.2. Tumor Sample Collection

Refer to the Laboratory Manual for instructions regarding archival and pre-treatment tumor tissue handling and shipping.

Study Entry

All subjects are required to provide archival tumor tissue and a pre-treatment biopsy with adequate tumor tissue content, defined as 2 cores or 20 slides. Biopsies will be taken from soft tissue. Subjects may be exempted from the requirement to provide a pre-treatment tumor biopsy if the archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity, as defined above. An additional archival tissue sample collected greater than 3 months prior to screening should be submitted along with the mandatory pre-treatment tumor biopsy sample (or archival tumor tissue sample if collected within 3 months of screening). If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment tumor biopsy is obtained and after discussion and agreement from Sponsor (Medical Monitor or designee).

The pre-treatment biopsy and archival tissue will be analyzed for HER3 protein expression at the time of enrollment. Tumor samples must be obtained after the date of informed consent for tumor screening. The pre-treatment tumor biopsy should be obtained from a primary tumor or metastatic site, not previously irradiated, and preferably from a site of disease progression. Any tumor material left after HER3 protein expression analysis will be used for exploratory biomarker assessment such as gene mutation analysis, gene expression as well as other immune marker analyses.

On-treatment Biopsy

All subjects will be required to consent to an on-treatment tumor biopsy to understand HER3 expression dynamics and correlation of HER3 expression with MAAA-1181a delivery, and double-stranded-DNA damage. The biopsy should be performed on Cycle 2, Day 3 (±1 day). Collection of the on-treatment biopsy is mandatory (if medically feasible) for all subjects unless communicated otherwise from the Sponsor. Tumor tissue for this biopsy should be obtained from the primary tumor or metastatic site. The on-treatment tumor biopsy samples will be analyzed for HER3 expression with IHC, other immune marker, and RNA expression profiling using NGS. One core will be flash frozen for analysis of MAAA-1181a using validated assays at the bioanalytical laboratory. Consent for this biopsy should be documented in the tissue consent portion of the ICF. After at least 10 on-treatment tumor biopsies per cohort have been collected, sites will be notified of a change to the requirement.

End-of-treatment Biopsy

An **optional** EOT tumor biopsy may be performed at the time of progression or discontinuation from study treatment. Consent for optional EOT biopsy should be documented in the tissue

consent portion of the ICF. Tumor biopsy should be obtained from the primary tumor or a metastatic site, preferably from a site of recent radiographic progression, within 40 days of the date of discontinuation, and prior to starting any new anticancer treatment. This sample will be tested for exploratory purpose such as gene mutation analysis, gene expression as well as other immune marker analysis.

8.3.3. Biomarker Assessments in Tumor Tissue and Blood Samples

Potential patient selection biomarkers (including HER3 expression using IHC) will be analyzed with the intent of identifying those subjects with advanced or metastatic CRC who will most likely derive clinical benefit from U3-1402, to support future subject selection strategies for advanced or metastatic CRC subjects. These potential biomarkers will be assessed in archival and pre-treatment tumor tissue.

Further exploratory archival, pre-treatment, on-treatment, and end-of-treatment tissue (eg, RNA, DNA, and other immune marker IHC) or blood-based biomarkers (eg, soluble protein markers, circulating free DNA [cfDNA] and circulating free RNA [cfRNA]) will be analyzed based on emerging scientific knowledge to better understand the target disease and also to evaluate the effects of study treatment (pharmacodynamic effect and effects associated with U3-1402 clinical activity). The exploratory biomarker analyses may be performed using methods other than IHC (eg, protein, RNA, or DNA analysis). Blood for biomarkers assessment (eg, soluble protein, markers, cfDNA, cfRNA) should be collected as per the Schedule of Events (Table 13.1). If consent is obtained to perform the mandatory on-treatment tumor biopsy, a tumor biopsy will be collected on Cycle 2 Day 3. Blood sample for biomarkers will also be collected on Cycle 2 Day 3. If consent is not obtained to perform the mandatory on-treatment tumor biopsy, blood sample for biomarkers will be collected on Cycle 2 Day 1. Moreover, blood samples may be used to measure soluble CRC markers, such as carcinoembryonic antigen, CA 19-9, and C-reactive protein, but not limited to these markers only.

The results from exploratory biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be verified in future studies.

8.4. Immunogenicity

Blood samples for ADA assessment will be obtained at the time points specified in the Schedule of Events (Table 13.1) and will be analyzed at the central laboratory. The PK assay can be performed on the ADA sample collected. The details on immunogenicity blood sample collection, handling and shipment are described in the Laboratory Manual. The immunogenicity testing will be performed using a validated ADA assay comprised of tiered steps including screening, confirmatory, and titer determination. ADA samples confirmed positive will be banked until availability of a neutralizing ADA assay. Serum concentrations of U3-1402 may be measured using the same ADA samples collected for the purpose of ADA assessment at the EOT and the long-term follow-up visits that occur every 3 months.

For subjects with positive ADA at the EOT visit, additional serum ADA samples should be collected every 3 months (±14 days) for up to 1 year after the last dose of U3-1402, unless 1 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.

8.4.1. Genomic or Genetic Banking and Analysis

8.4.1.1. Sample Collection and Analysis

An optional single blood sample for pharmacogenetics analysis should be collected on Cycle 1 Day 1 or at any time during the study from subjects who provide consent.

Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of the study drug. Additionally, samples may be analyzed for genes involved in study drug-related signaling pathways, or to examine diseases or physiologic processes related to the study drug. Subject samples will not be sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

8.4.1.2. Instructions for Collection of Specimens

Instructions for collection of biospecimens are included in the Laboratory Manual.

8.4.1.3. Storage and Disposal of Specimens

Any remaining biosamples 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 analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic) to U3-1402, or in case serious adverse drug reactions are noted in a clinical study and biomarker 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.

8.4.1.4. Disclosure of the Results

Any data obtained from exploratory research will not be disclosed to the subject or Investigators.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will include SAEs, TEAEs, adverse events of special interest (AESIs), physical examination findings (including ECOG PS), vital sign measurements, and standard clinical laboratory parameters. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded using NCI-CTCAE v5.0.

9.2. Adverse Event Collection and Reporting

All clinical AEs occurring after the subject signs the main study ICF and up to 47 days after the last dose of study drug (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF. When an AE of potential ILD (Section 9.3.1) is observed after 47 days since last dose of U3-1402, the AE (serious or non-serious) should be reported and recorded in AE eCRF if it is considered related to U3-1402. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

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

All clinical laboratory results, vital signs, and ECG results or findings should be appraised and documented by the Investigator to determine their clinical significance. Isolated abnormal clinical 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, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each time point, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each time point. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator 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 U3-1402. The Investigator's assessment must be clearly documented in the study site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for definitions).

All SAEs, potential ILD cases, overdoses, and hepatic events (both serious, non-serious, and clinical laboratory results) that meet the criteria of elevated (ALT or AST) ≥3 × upper limit of normal (ULN) and an elevated total bilirubin >2 × ULN should be reported within 24 hours of awareness (see Sections 9.3.1, 9.3.2, and 9.5.1 for definitions).

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

Progressive disease is a study endpoint and, consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "Progressive disease" should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. Unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, will be followed until resolution or until they become clinically not relevant.

9.3. Adverse Events of Special Interest

9.3.1. Pulmonary Toxicity (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.

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 U3-1402 dosing pending further evaluation and start corticosteroid treatment promptly per consensus statement[39] unless clinically contraindicated. Refer to Table 5.2 for guidance on further evaluation and management of ILD.

If a non-inflammatory/infectious etiology is confirmed by the Investigator, treat accordingly; resumption of U3-1402 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.

9.3.1.1. Interstitial Lung Disease Adjudication Committee

An independent ILD AC for U3-1402 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 MedDRA preferred terms (PTs) from the current ILD Standard MedDRA Query (SMQ) and the PTs of acute respiratory failure and respiratory failure.

9.3.2. Elevation of Aminotransferase(s) and Bilirubin: Hepatic Events

Elevation of aminotransferase(s) and bilirubin in association with U3-1402 is 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 trial data.

All hepatic events (serious, non-serious, and clinical laboratory results) that meet criteria of elevated ALT or AST ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study, should be reported as an AE (serious or non-serious) and as an AESI to closely monitor potential Hy's law, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction, or dose delay, require corrective treatment, constitute an AE in the Investigator's clinical judgment, and/or are related to disease progression. A detailed narrative and confirmations with repeated laboratory assessment(s) should also be provided. Such events should be reported within 24 hours of Investigator's awareness of the event.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and 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 (International Council for Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

All AEs will be graded according to the NCI-CTCAE v5.0:

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

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

9.4.4. Causality Assessment

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

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

9.4.5. Action Taken Regarding Study Drug(s)

- Dose not changed: No change in study drug dosage was made.
- Drug withdrawn: The study drug was permanently stopped.
- Dose reduced: The dosage of study drug was reduced.
- Drug interrupted: The study drug was temporarily stopped.
- Not applicable.

9.4.6. Other Action Taken for Event

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

9.4.7. Adverse Event Outcome

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

9.5. Serious Adverse Events Reporting Procedure For Investigators

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

Serious events that are also efficacy endpoints (disease progression) will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, if a subject dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE and captured on the AE eCRF.

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

- SAEs (see Section 9.4.2 for definition)
- 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 PTs) (see Section 9.3.1 for details)
- All hepatic events (both serious and non-serious, and clinical laboratory results) that meet criteria of elevated ALT or AST ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study should be reported as an AE (serious or non-serious) and as an AESI, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction or dose delay, require corrective treatment, constitute an AE in the Investigator's clinical judgment and/or are related to disease progression (see Section 9.3.2 for details).
- Overdose (see Section 9.5.1 for a definition)

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

Additional relevant information regarding the AESIs of ILD, and all hepatic events that meet the criteria of an elevated ALT or AST ≥ 3 × ULN and an elevated total bilirubin > 2 × ULN that may occur simultaneously or at different time points during the study for the U3-1402 clinical program, regardless of seriousness, is to be collected through the targeted questionnaires within the clinical study database.

Urgent safety queries and follow-up information such as those upgraded to fatal/life threatening case must be followed up and addressed promptly. The investigator will submit any updated SAE data to the sponsor and/or 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. In the event that an eCRF is unavailable, report SAEs, overdoses, potential cases of ILD, and hepatic events that meet criteria of elevated ALT or AST ≥3 × ULN and an elevated total bilirubin >2 × ULN on a Serious Adverse Event Report (SAVER) form. All completed SAVER forms must be signed by the Investigator and e-mailed or faxed to the Sponsor or the CRO using the provided fax transmittal form and the appropriate fax number provided for your country. Once EDC becomes available, please enter events reported on the SAVER Form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

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

9.5.1. 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. An "excessive and medically important" overdose includes any overdose in which an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant (ie, it poses an actual or potential risk to the subject). All occurrences of overdose must be reported to the CRO or Sponsor within 24 hours of awareness. Overdose will be reported via the SAVER form or eCRF.

9.6. Pregnancy

The Sponsor must be notified of any female subject who becomes pregnant while receiving or within 7 months of the last dose of U3-1402. 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, U3-1402.

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 or 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 4.1): document the results of a negative serum pregnancy test. For eligibility, if not performed as a part of routine care within 72 hours prior to Cycle 1 Day 1, a serum pregnancy test must be performed with the results available (Table 13.1). A positive urine pregnancy test must immediately be confirmed using a serum test. Repeat pregnancy test (urine or serum per institutional guidelines) must be performed 72 hours before infusion at each cycle and at the EOT visit.

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 the first dose of U3-1402 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.

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

Daiichi Sankyo and/or CRO will inform Investigators and regulatory authorities of any suspected unexpected serious adverse reactions occurring in study sites or other studies of U3-1402, as appropriate per institutional and/or local reporting requirements.

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

9.8. Clinical Laboratory Evaluations

Clinical laboratory measurements will be conducted at the local laboratory. The following items will be measured. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used. Refer to the Schedule of Events (Table 13.1) for timing of these assessments.

Table 9.1: Clinical Laboratory Tests

Laboratory tests	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, mean platelet volume (if available), reticulated platelet fraction (if available), and differential white blood cell count (absolute and percent) (ie, neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood Chemistry	Total protein, albumin, ALP, ALT, AST, bicarbonate, TBL, direct bilirubin, indirect bilirubin, BUN/urea, calcium, chloride, creatinine, LDH, magnesium, potassium, sodium, CEA[a], CA19-9[a], and CRP[a]
Coagulation (only at screening)	Prothrombin time or prothrombin time-international normalized ratio, and activated partial thromboplastin time/partial thromboplastin time
Urinalysis	Protein, glucose, blood, bilirubin, glucose, ketone bodies, leukocyte esterase, occult blood, pH, urobilinogen, microscopic assessment of urine sediment (casts, RBC, WBC), and specific gravity

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CRP = C-reactive protein; LDH = lactate dehydrogenase; RBC = red blood cell; TBL = total bilirubin; WBC = white blood cell
[a] Assessed at the central laboratory

In addition, a pregnancy test (serum) for all female subjects of childbearing potential must be performed during the Screening Period and at the visits (serum or urine) indicated in the Schedule of Events. A positive urine pregnancy test result must be confirmed immediately using a serum test.

All laboratory values must be appraised by the Investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the Investigator should be recorded on the AE eCRF. If the abnormal laboratory value constitutes an SAE, it should be reported by the Investigator with a targeted questionnaire that is in-built as an eCRF or a SAVER form within 24 hours of awareness and other relevant procedures must be followed (see Section 9.5). Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

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

Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes.

9.10. Electrocardiograms

Standard supine/semi-recumbent 12-lead ECG prior to blood draws and will be performed as described in the Schedule of Events (Table 13.1). The ECG will be measured after the subject has rested supine for at least 10 minutes prior to the ECG assessment. ECGs must be recorded

on an ECG machine and reviewed by the Investigator or delegated physician for the presence of abnormalities. The same test must be used for Screening, EOT, and as clinically indicated.

Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Whether or not the measurement is performed, the date the ECG is to be performed, heart rate, PR interval, RR interval, QRS duration, QT interval, QTcF interval, and results will be recorded in the eCRF.

9.11. Physical Examinations

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

9.12. Other Safety Assessments

Cardiac assessments:

- LVEF
  - LVEF will be measured by either ECHO or MUGA, as described in the Schedule of Events (Table 13.1). All ECHO/MUGA assessments must be evaluated by the Investigator or delegate. The same modality (ECHO or MUGA) should be used for the subject throughout the study.
  - Refer to Section 13.5 for the NYHA Functional Capacity and Objective Assessment.

Ophthalmologic assessments:

- Ophthalmologic assessments will include a visual acuity test (ETDRS, Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry as indicated in the Schedule of Events (Section 13.1). All ophthalmologic assessments must be evaluated by an ophthalmologist or other qualified practitioner. More frequent examinations may be performed at the discretion of the Investigator and if indicated.

Pulmonary assessments:

- SpO_2 should be measured along with tumor assessments per Investigator discretion and as indicated in the Schedule of Events (Section 13.1). Additional testing to investigate pulmonary disorders may be performed, eg, chest radiograph, functional/blood-gas examination, pulmonary function testing, or serological examinations, at the Investigator's discretion as described in Table 5.2. An ILD AC has been set up for this study. Additional details regarding the ILD AC are available in Section 9.3.1.1.

10. OTHER ASSESSMENTS

10.1. Patient Reported Outcomes

Not applicable.

10.2. Pharmacoeconomic Assessments

Not applicable.

11. STATISTICAL CONSIDERATIONS

11.1. General Statistical Considerations

The primary analysis DCO will occur when all subjects have either a minimum of 9 months follow-up or have discontinued from the study earlier. The DCO may be shifted if emerging data indicate responses are occurring at a different time. The final analysis will occur when all subjects have discontinued from the study for any reason. The primary analysis will be included in the CSR.

Descriptive statistics on continuous data will include mean, median, standard deviation, and range (as well as geometric means and geometric coefficient of variation for PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

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 before start of study treatment will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized before database lock.

11.2. Statistical Hypothesis

No statistical testing is planned for this study.

11.3. Sample Size Determination

In Part 1 of the study, approximately 36 subjects will be evaluated in the two cohorts. If both Cohort 1 and Cohort 2 advance to Part 2 of the study, approximately 44 additional subjects will be enrolled in Part 2 (regardless of HER3 IHC status). In such a circumstance, approximately 80 subjects will be enrolled in total. If only Cohort 1 advances to Part 2 of the study, approximately 44 additional subjects will be enrolled in Part 2. In such circumstance, approximately 80 subjects will be enrolled in total (68 of 80 subjects will have HER3 high expressing tumors).

The total sample size is shown in Table 11.1.

Table 11.1: Total Sample Size Pre- and Post-futility Analysis

	Scenario 1 Enrollment continues in both Cohorts		Scenario 2 Enrollment continues in Cohort 1 only	
	Cohort 1	**Cohort 2**	**Cohort 1**	**Cohort 2**
Futility decision per cohort	Go	Go	Go	Stop
Sample size up to futility	24	12	24	12
Additional sample size after futility	44[a]		44	NA
Cohort sample size	80 [a]		68	12
Total sample size for the study	80 [a]		80	

HER3 = human epidermal growth factor receptor 3; IHC = immunohistochemistry; NA = not applicable
[a] All comers will be enrolled regardless of HER3 IHC status

If the criteria to continue enrollment are not met at interim futility analysis in either cohort, further enrollment will be stopped. In this scenario, the total sample size for the study will be approximately 36 subjects (Cohort 1: 24 subjects, Cohort 2: 12 subjects).

Table 11.2 presents the minimum number of responders at various sample sizes for the 95% exact CIs lower bound to be above 5%.

The clinically meaningful ORR is considered as 20% and the ORR based on historical data is considered as 5%.[9,10]

With a sample size of 68 subjects, if 8 responses are observed, the observed ORR will be 11.8% with a 95% exact confidence interval (CI) of (5.2%, 21.9%). The probability of observing 8 or more responders in 68 subjects is approximately 97.4% when the true ORR is 20%. If the true ORR is 5%, the probability of observing 8 or more responders in 68 subjects is approximately 2%.

With a sample size of 80 subjects, if 9 responses are observed, the observed ORR will be 11.25% with a 95% exact CI of (5.3%, 20.3%). The probability of observing 9 or more responders in 80 subjects is approximately 98.7% when the true ORR is 20%. If the true ORR is 5%, the probability of observing 9 or more responders in 80 subjects is approximately 1.8%.

Table 11.2: Statistical Properties for Different Sample Sizes

N	Number of Responders (x)	Observed ORR	95% Exact CI	P ($X \geq x \mid p = 0.2$)	P ($X \geq x \mid p = 0.05$)
68	8	11.8%	(5.2%, 21.9%)	97.4%	2.0%
80	9	11.25%	(5.3%, 20.3%)	98.7%	1.8%

CI = confidence interval; ORR = objective response rate.

Table 11.3 summarizes the exact two-sided 95% CIs for the observed ORR ranging from 5% to 20% approximately (with an increment of approximately 5%) at various sample sizes.

Table 11.3: Exact Confidence Interval for Different Observed Objective Response Rates

N=68		N=80	
Number of Responders (Observed ORR)	**95% Exact CI**	**Number of Responders (Observed ORR)**	**95% Exact CI**
4 (5.9%)	(1.6%, 14.4%)	4 (5%)	(1.4%, 12.3%)
7 (10.3%)	(4.2%, 20.1%)	8 (10%)	(4.4%, 18.8%)
11 (16.2%)	(8.4%, 27.1%)	12 (15%)	(8%, 24.7%)
14 (20.6%)	(11.7%, 32.1%)	16 (20%)	(11.9%, 30.4%)

CI = confidence interval; ORR = objective response rate.

All calculations were performed using the SAS 9.4 software.

11.4. Population for Analysis Sets

FAS will include all subjects who received at least one dose of study drug. Efficacy analyses will be performed using FAS.

Safety Analysis Set will include all subjects who received at least one dose of study drug.

PK Analysis Set will include all subjects in the Safety Analysis Set who have at least one PK sample with measurable concentration for U3-1402 (ADC, total anti-HER3 Ab, or MAAA-1181).

11.5. Statistical Analyses

11.5.1. Efficacy Analyses

11.5.1.1. Primary Efficacy Analyses

The primary efficacy endpoint is ORR (the proportion of subjects with a best overall response [BOR] of CR or PR) as assessed by BICR per RECIST v1.1. CR/PR will be confirmed with a follow-up tumor assessment at least 4 weeks apart.

ORR will be summarized with the 2-sided 95% CI using the Clopper-Pearson method in the FAS. For the computation of ORR, subjects with BOR of "not evaluable (NE)" will be included in the FAS and will be considered non-responders. Data will be summarized by cohort if applicable. No formal comparison between the 2 cohorts is planned.

11.5.1.2. Secondary Efficacy Analyses

The key secondary efficacy endpoint is duration of response (DoR), defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression or death due to any cause, as assessed by BICR per RECIST v1.1. DoR will be calculated for responding subjects (PR or CR) only. Subjects who are progression-free at the time of the analyses will be censored on the date of the last adequate tumor assessment (CR, PR, or stable disease [SD]).

Other secondary efficacy endpoints include:

- ORR as assessed by Investigator per RECIST v1.1 will be analyzed in the same manner as the primary efficacy endpoint.
- DoR as assessed by Investigator per RECIST v1.1 will be analyzed in the same manner as the key secondary efficacy endpoint.
- DCR is defined as the proportion of subjects who achieved a confirmed BOR of CR, PR, or SD as assessed by BICR and Investigator per RECIST v1.1. It will be analyzed in the same manner as the primary efficacy endpoint.
- Time to response (TTR) is defined as the time between the start of study treatment to the date of the first documentation of objective response (CR or PR) that is subsequently confirmed. TTR will be assessed by BICR and Investigator per RECIST v1.1. TTR will be calculated for responding subjects (BOR of PR or CR) only.
- PFS is defined as the time from start of study treatment to the first objective documentation of radiological disease progression or death due to any cause. Subjects who are progression-free at the time of the analyses will be censored on the date of the last adequate tumor assessment (CR, PR, or SD).
- OS is defined as the time from the start of study treatment to the date of death due to any cause. Subjects who are alive at the time of the analyses will be censored on the last contact date at which the subject is known to be alive.

Distribution of time-to-event endpoints (DoR, PFS, and OS) will be estimated using the Kaplan-Meier method and results will be presented graphically. Median DoR and its 2-sided 95% CIs will be calculated using Brookmeyer and Crowley methods. In addition, the event-free probability at different time points (eg, 3, 6, 9, 12 months) will be estimated with corresponding 2-sided 95% CIs using the Greenwood formula for variance derivation. TTR will be summarized using descriptive statistics. Censoring rules for the time-to-event endpoints (DoR, PFS and OS) will be specified in the SAP.

No formal comparison between the two cohorts is planned.

Descriptive statistics for the best percent change from baseline in the SoD will be provided by cohort, if applicable. A waterfall plot of the best percent change in the SoD and a swimmer's plot for response over time will also be prepared.

The correlation between HER3 protein expression level (as determined by HER3 IHC assay) and efficacy will be assessed.

11.5.1.3. Exploratory Efficacy Analyses

Analyses to explore the relationship between exposure and efficacy may be conducted using data from this study, or may be conducted using pooled data with other studies. If conducted, such analyses will be reported separately and will therefore not be part of the CSR.

11.5.1.4. Multiplicity Adjustment

Not applicable.

11.5.2. Safety Analyses

Safety analyses will be performed using the Safety Analysis Set and in general will be descriptive. Additional details regarding safety analyses will be described in the SAP.

The overall study period will be divided into three mutually exclusive segments:

- Pre-treatment period: from date of study 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.

Safety summaries will include assessments collected during the on-treatment period unless otherwise specified. Data will be summarized by cohort if applicable. All assessments will be listed.

11.5.2.1. Adverse Event Analyses

TEAEs are defined as those AEs with a start or worsening date during the on-treatment period.

AEs will be coded using MedDRA and graded based on v5.0 of NCI-CTCAE.

The number and percentage of subjects with TEAEs will be summarized by system organ class (SOC), and/or PT. 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.

AESIs will also be summarized.

All deaths and on-treatment deaths will be summarized by primary cause of death. All deaths will be listed.

A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, PT, SOC, NCI-CTCAE grade, and relationship to study drug. SAEs, AESIs and TEAEs associated with treatment discontinuation will be listed.

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

11.5.2.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for clinical laboratory test results (hematology and chemistry) and changes from baseline by scheduled time of evaluation, including EOT. The baseline value is defined as the last non-missing value before the start of study treatment.

Abnormal 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. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

11.5.2.3. ECG

A listing of ECG data will be generated.

11.5.2.4. Vital Signs

Descriptive statistics will be provided for the vital sign measurements and the change from baseline by scheduled time of evaluation, including EOT. The baseline value is defined as the last non-missing value before the start of study treatment. A listing of vital sign data will be generated.

11.5.2.5. Other

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

Immunogenicity (Anti-Drug Antibody) Analyses

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 U3-1402 ADC, and released payload MAAA-1181a may be summarized by status of ADA, if data allow. 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.

11.5.3. Other Analyses

11.5.3.1. Pharmacokinetics

Data will be summarized by cohort if applicable.

PK Analyses as Secondary Objective

PK parameters will be listed and summarized using descriptive statistics.

Serum concentration-time data for U3-1402 (ADC, total anti-HER3 antibody and MAAA-1181a) will be listed, plotted, and summarized using descriptive statistics at each time point.

Exploratory PK Analyses

Serum concentration data may be used to perform a population PK modeling. The influences of intrinsic or extrinsic factor will be assessed in the population PK analysis. Population PK and exposure-response analyses for U3-1402 (ADC, total anti-HER3 antibody, and MAAA-1181a) may be performed to characterize the relationship between dose and exposure and between exposure and efficacy and/or safety endpoints. If performed, results of population PK analyses will be reported separately (ie, not in the CSR).

11.5.3.2. Pharmacodynamics

Not applicable.

11.5.3.3. Biomarker Analyses

HER3 protein expression in tumor tissue (as determined by IHC) may be summarized descriptively, and the correlation with efficacy parameters may be analyzed if data permits.

11.6. Interim Analyses

For each study cohort, review of the preliminary data from Part 1 will be used to determine whether to open Part 2. The decision to advance from Part 1 to Part 2 will be made separately in Cohort 1 and Cohort 2; the interim futility analysis will be conducted with approximately 24 subjects in Cohort 1 and approximately 12 subjects in Cohort 2 after all subjects have had the opportunity to complete two tumor assessments. The tumor assessment period may be extended if emerging data show responses are occurring later, or if the tumor assessment for the final evaluated subject in each cohort is delayed. At the time of the interim analysis for each cohort, enrollment into the respective cohort will be paused until the determination that criteria for advancement to Part 2 has been achieved. Note it is possible for the futility criterion to be passed before the above specified analysis timing. These analyses will be conducted based on BICR assessment in the FAS.

Cohort 1 Decision Criteria at Interim:

1. If at least 3 responders out of 24 subjects in Cohort 1 are observed, then further enrollment in this cohort may proceed.
2. If 0 or 1 responder out of 24 subjects in Cohort 1 is observed at the interim, then further enrollment in this cohort may stop.
3. If 2 responders out of 24 subjects in Cohort 1 are observed, then a decision will be made, after further review of the data, to either continue or stop further enrollment in this cohort.

Cohort 2 Decision Criteria at Interim:

1. If at least 2 responders out of 12 subjects in Cohort 2 are observed, further enrollment in this cohort may proceed after submission of a protocol amendment which includes the preliminary data from Cohort 2 Part 1.
2. If 0 responder out of 12 subjects in Cohort 2 is observed at the interim, then further enrollment in this cohort may stop.
3. If 1 responder out of 12 subjects in Cohort 2 is observed, then a decision will be made, after further review of the data, to either continue or stop further enrollment in this cohort. Further enrollment will be contingent upon submission of a protocol amendment which includes the preliminary data from Cohort 2 Part 1.

The exact decision rules will depend on the actual number of subjects at the respective interim analysis.

If the criterion to pass futility is met at interim for Cohort 2 but not Cohort 1, all data will be reviewed thoroughly to decide the next step for the study.

The criterion for interim analysis is constructed as follows: based on the interim data, if in a cohort there is less than 10% probability for the true ORR to be above 20% (clinically meaningful ORR), then U3-1402 is considered futile in this cohort and further enrollment may not be warranted. If there is at least 10% probability for the true ORR to be above 20% and at least 80% probability for the true ORR to be above 5% (ORR based on historical data)[9,10] then promising efficacy is demonstrated in this cohort and further enrollment in this cohort may proceed.

If the true ORR is 20%, then the probability of observing at least 3 responders out of 24 subjects in Cohort 1 at the interim analysis will be 88.5% and the probability of observing at least 2 responders out of 12 subjects in Cohort 2 at the interim analysis will be 72.5%. If the true ORR is 5%, then the probability of observing 0 or 1 responder out of 24 subjects in Cohort 1 at the interim analysis will be 66.1% and the probability of observing 0 responders out of 12 subjects in Cohort 2 at the interim analysis will be 54%.

The determination of whether to advance a cohort to Part 2 of the study may also take into consideration the PK properties of U3-1402 among subjects enrolled in this study, and the subject or disease characteristics of enrolled subjects, among others. The decision to advance the study to Part 2 might be deferred based on the collective evaluation of such information. If indicated, the Sponsor may amend the protocol to evaluate other doses, dose regimens, or selected subject populations with advanced or metastatic CRC prior to advancing the study to Part 2.

11.7. Statistical Analysis Process

Data from the clinical study will be analyzed by the Sponsor and/or its agent/CRO.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy, safety, PK, and other data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

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

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13. APPENDICES

13.1. Schedule of Events

Table 13.1: Schedule of Events

	Tissue Requirement	Screening	Cycle 1				Cycle 2				Cycle 3				Cycle 4 and Subsequent Cycles		EOT[a]	40-Day post-Tx F/U[b]	q3 mo. F/U
			D1		D8	D15	D1		D3	D15	D1		D8	D15	D1				
			BI	EOI			BI	EOI			BI	EOI			BI	EOI			
Visit Window (days)		(-35)			(±1)		(±1)				(±1)				(±1)			(+7)	(±14)
Tissue Informed Consent	X																		
Study Informed Consent		X																	
Archival Tumor Tissue [c]	X																		
Pre-Treatment Tumor Biopsy [d]	X																		
On Treatment Tumor Biopsy									X[e]								X[f]		
Demography		X																	
Medical History		X																	
Inclusion/ Exclusion		X																	
Prior Cancer History		X																	
Prior Cancer Biomarker History		X																	
Prior Cancer Medical Therapy		X																	
HIV Ab Test [g]		X																	
HBsAg, HBV DNA, HCV Ab, HCV RNA [g]		X																	
Urinalysis [h]		X															X		
Pregnancy Test [i]		X	X				X				X				X		X	X	
Physical Examination		X[j]	X				X				X				X		X	X	
Vital Signs (including SpO_2)[k]		X	X	X	X	X	X	X			X	X			X	X	X	X	
Height		X[j]																	

	Tissue Requirement	Screening	Cycle 1				Cycle 2				Cycle 3				Cycle 4 and Subsequent Cycles		EOT[a]	40-Day post-Tx F/U[b]	q3 mo. F/U
			D1		D8	D15	D1		D3	D15	D1		D8	D15	D1				
			BI	EOI			BI	EOI			BI	EOI			BI	EOI			
Visit Window (days)		(-35)			(±1)		(±1)				(±1)				(±1)			(+7)	(±14)
Weight		X[j]	X				X				X				X		X	X	
ECOG PS		X[j]	X				X				X				X		X	X	
Hematology & Chemistry		X[k]	X[l]		X	X	X[l]				X[l]		X	X	X[l]		X	X	
Coagulation [m]		X																	
12-lead ECG [n]		X															X		
ECHO/MUGA (LVEF) [o]		X															X		
COVID-19 Sample [p]			X												X Starting at Cycle 5, Day 1 and every 4 cycles thereafter		X		
Ophthalmologic Assessment [q]		X															X[r]		
U3-1402 Administration [s]			X				X				X				X				
Blood Sample for Biomarkers [t]			X				X[u]		X[u]		X				X		X		
Blood Sample for PGx				X[v]															
Carcino-embryonic Antigen (CEA), CA 19-9, CRP			X				X				X				X		X		
ADA Blood Sample			X		X		X								X Cycle 4, Day 1 (-5 days) and every 2 cycles thereafter		X		X[w]
PK Blood Sample (Intensive for initial 12 subjects in each cohort)			X[x]	X[y]	X	X	X[x]	X[z]	X[aa]	X	X[x]	X[y]	X	X	X[x] Cycle 4, 6, & 8	X[z] Cycle 4, 6, & 8	X[bb]		X[bb]

	Tissue Requirement	Screening	Cycle 1				Cycle 2				Cycle 3				Cycle 4 and Subsequent Cycles		EOT[a]	40-Day post-Tx F/U[b]	q3 mo. F/U
			D1		D8	D15	D1		D3	D15	D1		D8	D15	D1				
			BI	EOI			BI	EOI			BI	EOI			BI	EOI			
Visit Window (days)		(-35)			(±1)		(±1)				(±1)				(±1)			(+7)	(±14)
PK Blood Sample (Less intensive for all other subjects)			X[x]	X[cc]	X	X	X[x]	X[z]	X[aa]		X[x]	X[cc]	X	X	X[x] Cycle 4, 6, & 8	X[z] Cycle 4, 6, & 8	X[bb]		X[bb]
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 (if subject provides consent): • 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 U3-1402 resumption, after the CQ/HCQ washout period[dd], (within 8h BI of U3-1402).																
Tumor Assessment (CT/MRI) [ee]		X[ff]	X[gg] 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.															
Prior/ Concomitant Medications			X																
AE SAEs[hh]			X																
AE Non-SAEs[ii]			X																
New Cancer Treatment																			X[ij]
Survival F/U																			X[ij]

Ab = antibody; ADA = anti-drug antibody; AE= adverse event; BI= before infusion; BICR = blinded independent central review; C = cycle; CA 19-9 = cancer antigen 19-9; cfDNA = circulating free DNA; cfRNA = circulating free RNA; CRP = C-reactive protein; CT = computed tomography; CQ = chloroquine; COVID-19 = coronavirus 2019; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EOI= end of infusion; EOT = end of treatment; ETDRS = Early Treatment Diabetic Retinopathy Study; F/U = follow up; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCQ = hydroxychloroquine; HCV = hepatitis C virus; HER3 = human epidermal growth factor receptor 3; FFPE = formalin-fixed paraffin-embedded; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; IHC = immunohistochemistry; IRB = Institutional Review Board; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA= multigated acquisition; NGS = next generation sequencing; PD = progressive disease; PGx = pharmacogenomics; PK= pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE= serious adverse evet; SpO_2 = peripheral oxygen saturation; q3 mo= every 3 months; 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 EOT assessments have been performed within 30 d (± 7 d) of their last treatment, they can be considered to be the EOT data and there is no need to repeat them; otherwise, these assessments need to be repeated.

[b] 40 days (+ 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If the EOT Visit occurs ≥40 days after the final dose of U3-1402, the 40-Day F/U Visit does not need to be conducted.

[c] Archival tumor tissue is required with minimal 2 cores or 20 slides with adequate tumor tissue content. FFPE block is preferred. An additional archival tissue sample collected greater than 3 months prior to screening must be available and of sufficient quantity, as defined above, at the time of screening. If an archival tissue sample (collected greater than 3 months prior to screening) is not available, a subject may be included provided the pre-treatment tumor biopsy is obtained and after discussion and agreement from Sponsor (Medical Monitor or designee).

[d] Pre-treatment tumor biopsy is required and should be obtained from a primary tumor or metastatic site, and not previously irradiated. Exception: Pre-treatment tumor biopsy may not be required if the archival tumor tissue was collected within 3 months of screening during or after treatment with the last prior cancer treatment and is of sufficient quantity, defined as 2 cores or 20 slides with adequate tumor tissue content.

[e] An on-treatment tumor biopsy is required to be performed on Cycle 2 Day 3 (± 1 day). On-treatment tumor biopsy sample (with minimum of 2 cores) will be analyzed for HER3 protein expression using IHC and RNA expression profiling and genomic alteration using NGS. One core will be flash frozen for analysis of MAAA-1181a using fit-for-purpose qualified assay at the bioanalytical laboratory. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Soft tissue tumor biopsy should be obtained from the primary tumor or metastatic site. A blood for hematology must be obtained within 2 days of the tumor biopsy and results must be reviewed by the Investigator prior to obtaining a tumor biopsy. After approximately 10 on-treatment tumor biopsies per cohort have been collected, the Sponsor will notify the Investigator of a change in this requirement. If the subject does not consent to the mandatory on-treatment tumor biopsy, a blood sample for biomarkers will be collected on Cycle 2 Day 1.

[f] An optional EOT on-treatment tumor biopsy will also be performed at the time of progression or discontinuation from study treatment with minimal 2 cores or 20 slides (if provided as slides). 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 U3-1402, and prior to starting any new anticancer treatment.

[g] Perform Hepatitis B (HBsAg), Hepatitis C (HCV Ab), and HIV viral load assessments (if indicated) as described in the eligibility criteria within 28 days prior to Cycle 1 Day 1 (see Section 4.2)

[h] Urinalysis assessment should be performed within 72 hours 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.

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

[j] Screening: Within 28 days prior to Cycle 1 Day 1.

[jk] Screening assessment should be peformed within 28 days prior to Cycle 1 Day 1. Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate should be measured after the subject has rested in a supine position for 5 minutes. When CT/MRI is conducted, SpO2 should also be obtained per Investigator discretion.

[k] Screening: Within 14 days prior to Cycle 1 Day 1.

[l] Should be performed ≤ 2 days of scheduled visit. Results are required prior to study treatment.

[m] Screening assessment should be peformed 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.

[n] Screening assessment should be peformed within 28 days prior to Cycle 1 Day 1. ECG: Subjects should rest supine for at least 10 minutes prior to the ECG 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.

[o] Screening assessment should be peformed within 28 days prior to Cycle 1 Day 1. ECHO or MUGA: The same test must be used for the subject at screening, EOT, and as clinically indicated. Assessment for EOT Visit may be performed with a window up to 7 days.

[p] 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 13.9.

[q] Ophthalmologic assessments (− 7 days) include visual acuity test (ETDRS, Snellens, or Landolt), slit lamp examination, fundoscopy, and tonometry. Assessment may be repeated as clinically indicated as part of an unscheduled visit.

[r] Ophthalmologic assessments: A 40 +7-Day F/U assessment is only required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

[s] The subject's weight at Screening (baseline) 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 weight for all subsequent dosing calculations. U3-1402 will be infused 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 U3-1402 will be infused over approximately 30 minutes on Day 1 of each subsequent cycle Q3W. Refer to Table 5.2 for additional information on drug administration following infusion-related reactions. Refer to the Pharmacy Manual for information on storage and preparation of U3-1402.

[t] Blood samples will be drawn to derive serum for HER3 extracellular domain or plasma for liquid biopsy, such as cfDNA and cfRNA

[u] If consent is not obtained to perform the mandatory on-treatment tumor biopsy, a blood sample for biomarkers will be collected on Cycle 2 Day1. If consent is obtained to perform the mandatory on-treatment tumor biopsy, a blood sample for biomarkers will be collected on Cycle 2 Day 3.

[v] An optional single blood sample for PGx analysis should be collected on Cycle 1 Day 1 or at any time during the study.

[w] For subjects with positive ADA, additional serum ADA samples should be collected every 3 months (± 30 days) for up to 1 year after the last dose of U3-1402, 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.
[x] − 8 to 0 hours BI on Day 1 of Cycles 1, 2, 3, 4, 6, and 8.
[y] Within 15 minutes of EOI, then 1,2, 4, 8 hours (± 15 minutes) after the EOI.
[z] Within 15 minutes of the EOI only.
[aa] If consent is not obtained to perform the mandatory on-treatment tumor biopsy, the PK sample at C2D3 is not needed.
[bb] PK assay can be performed on the ADA sample collected.
[cc] Within 15 minutes of EOI, then 4 hours (± 15 minutes) after the EOI.
[dd] If subject provides consent, samples should be collected. A washout period of no less than 14 days is required before restarting U3-1402.
[ee] Screening assessment should be peformed within 28 days prior to Cycle 1 Day 1. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse 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 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 13.4) and submitted for BICR.
[ff] CT or MRI of the brain should be performed for all subjects as well as the abdomen, pelvis, chest and any other sites of disease.
[gg] Perform radiographic tumor assessments (CT/MRI) of the chest, abdomen, pelvis, CT or MRI of the brain (required at baseline), all sites of disease, and other areas where scans were performed at screening or newly suspected disease as per RECIST v1.1 (Section 13.4). Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Also, perform CT or MRI of the brain within a target of 1 week after a subject achieves a CR.
[hh] Any SAEs after signing the appropriate ICF should be reported until 47 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.
[ii] Any AEs after signing of the main ICF until 47 days after the last dose of the study drug should be followed until resolution or stabilized.
[jj] Survival F/U contact can occur via telephone contact or unscheduled visit and will continue until death or withdrawal of consent.

13.2. Regulatory and Ethical Considerations

13.2.1. Regulatory Compliance

The study protocol, the Investigator's Brochure, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the independent IRB or IEC 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 IEC.

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

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for 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;
- United States (US) Food and Drug Administration GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 (27 Mar 1997) and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 (25 Nov 2014);
- Other applicable local regulations.

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

Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study,

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.

13.2.2. 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 and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the 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).

13.2.3. Subject Confidentiality

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

For European Union (EU) study sites, the Sponsor will observe the rules laid down in the EU Regulation 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 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.

13.2.4. Data Integrity and Quality Assurance

Monitoring and Inspections

The Sponsor 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 subject identification.

To ensure the quality of clinical data across all subjects and study sites, a Sponsor/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 (WHO-DD) Dictionary.

13.2.5. 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 trial suspension or trial 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.

13.2.6. 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, Investigator's Brochure, 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.

13.2.7. Finances

Prior to starting the study, the Principal Investigator and/or Institution will sign a clinical study agreement with the Sponsor. 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.

13.2.8. 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 (ICMJE).

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

13.2.9. 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.

13.2.10. 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.

At the time of study closure, any subjects who are continuing treatment with U3-1402 and who are judged by the Investigator to have ongoing benefit may continue to receive treatment with U3-1402 through a rollover protocol or another mechanism consistent with local requirements.

13.2.11. 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.

13.3. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight, where weight is lean body mass in kilograms (1 kilogram = 2.2 pounds)[43]:

Conventional: serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

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

Female:

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

13.4. Response Evaluation Criteria in Solid Tumors, Version 1.1

13.4.1. Measurability of Tumor at Baseline

13.4.1.1. Definitions

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

13.4.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan

(CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in F/U, 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.

13.4.1.1.2. Non-measurable

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

13.4.1.1.3. Special Considerations Regarding Lesion Measurability

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

13.4.1.1.3.1. Bone Lesions

- Bone scan, positron emission tomography 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.

13.4.1.1.3.2. Cystic Lesions

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

13.4.1.1.3.3. Lesions with Prior Local Treatment

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

13.4.1.2. Specifications by Methods of Measurements

13.4.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 30 days before the first dose of U3-1402.

13.4.1.2.2. Method of Assessment

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

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

13.4.2. Tumor Response Evaluation

13.4.2.1. Assessment of Overall Tumor Burden and Measurable Disease

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

Only subjects with measurable disease at baseline should be included in the study.

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

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (representative of all involved organs) should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

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

13.4.2.3. Response Criteria

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

13.4.2.3.1. Evaluation of Target Lesions

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

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

Progressive disease: 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).

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

13.4.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be 0 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 progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

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

13.4.2.3.3. Evaluation of Non-target Lesions

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

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

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

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

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

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

"increase" in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

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

13.4.2.3.5. New Lesions

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and F/U 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.

13.4.2.4. Evaluation of Overall Response

13.4.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 13.2 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Table 13.2: Overall Response: Subjects with Target (± Non-target) Disease

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
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

13.4.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements 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 progressive disease. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved progressive disease status, regardless of the contribution of the missing lesion.

13.4.2.4.3. Best Overall Response: All Time Points

Best response determination in trials where confirmation of complete or partial response is required: when SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline, 6 weeks (−1 week). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Table 13.3.

Table 13.3: Best Overall Response when Confirmation of CR and PR Required

Overall Response – First Time Point	Overall Response – Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, PD
CR	PD	SD provided minimum criteria for SD duration met, PD
CR	NE	SD provided minimum criteria for SD duration met, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, PD
PR	NE	SD provided minimum criteria for SD duration met, NE
NE	NE	NE

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

[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 (6 weeks) 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.

13.4.2.4.4. Special Notes on Response Assessment

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

13.5. New York Heart Association

The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released 14 Mar 1994.[44] The new classifications are summarized below for the many physicians and scientists who use them to describe the status of individual patients.

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

13.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

The Eastern Cooperative Oncology Group performance status scale[45] is summarized in Table 13.4.

Table 13.4: Eastern Cooperative Oncology Group Performance Status Scale Grade Description

GRADE	DESCRIPTION
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

13.7. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0

1. Toxicity Grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 different criteria Grades might be applicable for rating a particular toxicity, or similar toxicities, the more severe Grade should be used.
3. Any toxicity resulting in death is defined as Grade 5.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. For links to the NCI-CTCAE v5.0, please refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

13.8. 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 male and for at least 7 months for female after the last dose of study drug. Methods considered to be highly effective contraception include:[46]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence

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

Due to the potential impact of coronavirus disease 2019 (COVID-19, due to severe acute respiratory syndrome coronavirus 2 [SARS CoV-2]), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with U3-1402. 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 U3-1402 and rule out SARS-CoV-2 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 5.2.
- If COVID-19 is confirmed or is still suspected after evaluation, follow dose modification as outlined in Table 13.5 below and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no signs/symptoms of COVID-19, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 13.5: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI-CTCAE (Version 5.0 Grade unless otherwise specified)	**Schedule Modification for U3-1402**
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved[a]
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved[a] Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

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

[a] Closely monitor signs/symptoms after resuming U3-1402, 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.

In addition to the recommendations outlined in Table 13.5, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 5.2).

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 4.2).
  - If treatment is absolutely required for COVID-19, U3-1402 must be interrupted.
  - If administered, then a washout period of no less than 14 days is required before resumption of U3-1402.

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 13.1).

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 (the participant must not have any signs or symptoms of COVID-19 infection for at least 2 weeks and nearly or completely resolved chest CT findings) 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 13.1), shipped to a central laboratory, and stored there until the tests become available.

If the subject consents, 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.

13.10. Membrane Transport Inhibitors

A list of membrane transport inhibitors is available at the link provided:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2.