SARAH CANNON
Development Innovations

BRE 354

A Phase II Study of U3-1402 (Patritumab Deruxtecan) in Patients with Metastatic Breast Cancer

DEVELOPMENT INNOVATIONS STUDY NUMBER:	BRE 354
STUDY DRUG:	U3-1402 (Patritumab Deruxtecan)
SPONSOR:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd., Suite 800 Nashville, TN 37203 USA 615-329-7274
STUDY CHAIR:	Erika Hamilton, MD Director, Breast Cancer and Gynecologic Cancer Research Program Sarah Cannon Research Institute 250 25th Ave North, Suite 200 Nashville, TN 37203 USA 615-524-4092 Office
MEDICAL MONITOR:	Lola Dosunmu, MD, MPH Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd., Suite 800 Nashville, TN 37203 USA 615-329-7274 (Office) 615-454-0272 (Cell)
DATE FINAL:	23 September 2020

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	17 November 2020
AMENDMENT NUMBER:	2	**AMENDMENT DATE:**	14 December 2021
AMENDMENT NUMBER:	3	**AMENDMENT DATE:**	23 May 2022
AMENDMENT NUMBER:	4	**AMENDMENT DATE:**	06 February 2023
AMENDMENT NUMBER:	5	**AMENDMENT DATE:**	28 June 2023

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Clinical Study Statement of Compliance

BRE 354

A Phase II Study of U3-1402 (Patritumab Deruxtecan) in Patients with Metastatic Breast Cancer

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulations (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug (IND) Application**
  - **Title 45CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Clinical Study Approval Page

BRE 354

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Erika Hamilton

Study Chair Erika Hamilton, MD Director, Breast Cancer and Gynecologic Cancer Research Program Sarah Cannon Research Institute	**Study Chair Signature**	**Date**

Lola Dosunmu

Sarah Cannon Development Innovations, LLC Lola Dosunmu, MD, MPH Senior Director, Medical and Clinical Science	**Sarah Cannon Development Innovations, LLC Representative Signature**	**Date**

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Clinical Study Principal Investigator Signature Form

BRE 354

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: BRE 354 Study Team
Nashville, TN 37203

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Development Innovations

CLINICAL PROTOCOL AMENDMENT SUMMARY OF CHANGES

BRE 354

AMENDMENT NUMBER: 5 **AMENDMENT DATE:** 28 June 2023

Additions to the text are **bolded**, and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global changes:

Introductory pages: Dr. Lola Dosunmu's credentials were updated to **Senior** Director.

U3-1402: transitioning to consistently using patritumab deruxtecan instead of U3-1402 within the text and in the title. Please note: patritumab deruxtecan will still be provided to sites labeled as "U3-1402".

Summaries of Changes for Previous Protocol Amendments (1 through 4) are now located in Appendix F.

Section 1.1.1 HER3

Activation of the PI3K/Akt pathway and **proto-oncogene** SRC signaling are major determinants of trastuzumab-induced resistance based on data from preclinical studies (Mishra et al. 2018).

Section 1.1.5 Study Rationale

The efficacy of ADCs with a similar payload directed against a novel target is unknown; hence it is of interest to evaluate patritumab deruxtecan, a HER3-targeted ADC with topoisomerase 1 inhibitor as the payload, in a patient population whose disease has progressed on ~~T-DXd~~**an ADC. Recent research highlights both cross-resistance to an ADC after ADC therapy in patients with MBC and durable responses on latter lines of ADC therapy, particularly if a different antibody target is utilized. Further research is needed to understand the mechanisms of clinical resistance and to guide optimal sequencing of ADC-based treatment options (Abelman et al. 2023).**

Section 2 Study Objectives and Endpoints

Table 1 Headings were corrected to distinguish between Objectives and Primary Objective.

Synopsis and Section 3.1.1 Inclusion criteria for Parts A and B (HER2-negative) and Part Z (HER2-positive) cohorts:

4 Triple-negative breast cancer **(TNBC)** patients should have received at least 1 but no more than ~~3~~ **5** prior lines of chemotherapy in the metastatic setting.

5 **Parts A and B patients only: Patients with** HR+ **HER2-negative MBC** should have received prior treatment with endocrine therapy +CDK 4/6 inhibitor. No limit to prior endocrine therapy regimens, but no more than 2 prior chemotherapy regimens in the metastatic setting **are allowed**. **HR+ = ER and/or PgR positivity that are defined as ≥1% of cells expressing HR via IHC analysis. HER2 negativity is defined as either of the following: IHC 0, IHC 1+, or IHC 2+/in situ hybridization (ISH) negative.**

6 **Part B patients only: Patients with HER2-negative MBC will be included into one of the following 2 subgroups: 1) MBC HR+, HER2-, regardless of HER3 expression, who have received trastuzumab deruxtecan and/or sacituzumab govitecan, or, 2) mTNBC, regardless of HER3 expression, who have received sacituzumab govitecan and/or datopotamab deruxtecan**.

9 **At least 1 ~~M~~m**easurable **lesion**~~disease~~ per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (bone-only disease excluded)

Synopsis Exclusion criteria for Part A and B (HER2-negative) and Part Z (HER2-positive) cohorts (to align with the Section 3.2.1)

9. ~~Any of the following cardiac criteria currently or within the last 6 months~~ **Uncontrolled or significant cardiovascular disorder prior to Cycle 1 Day 1, including**:

Synopsis and Section 3.2.2 Additional exclusion criteria only for Part A and B (HER2-negative) cohorts:

~~15. Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g., T-DXd, DS-1062a, and DS-7300a)~~

15. Patients with HER2+ breast cancer per ASCO-CAP guidelines

16. **Part A only:** Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g., trastuzumab deruxtecan, DS-1062a **[datopotamab deruxtecan]**, and DS-7300a **[B7-H3 DXd-ADC]**)

17. **Part B patients only: Prior treatment with trastuzumab deruxtecan, sacituzumab govitecan, and/or datopotamab deruxtecan with any of the following**:

- **A severe reaction or severe tolerability issues that necessitated stopping treatment with the therapy**
- **Any unresolved toxicities from the prior therapy greater than Grade 1, with the exception of alopecia**

Synopsis and Section 5 Study Design

Part B will enroll an additional 20 patients in**to** each **of 2** subgroup**s** that w**ere**~~ill be~~ defined from the Part A (based on ER/PR/HER2/HER3 expression)~~. Patients will be identified by prospective~~ evaluation of biomarker expression in pre-treatment biopsy samples or in tissue from a biopsy done within 2 months prior to consent. A total of up to 40 patients ~~(i.e., maximum of 2 subgroups)~~ will be enrolled **into the following 2** Part B subgroups:

- **MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan therapy**
- **mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan therapy**

Figure 1 Study Scheme Parts A and B was updated to include a description of the Part B subgroups.

Section 5.1 Treatment Plan

Patritumab deruxtecan (U3-1402**)** 5.6 mg/kg IV will be administered Day 1 Q3W.
Patritumab deruxtecan~~U3-1402~~ will be prepared and administered via IV infusion according to the details in Section 8.1.2~~the Pharmacy Manual~~.

Section 6.1 Dose Modifications Due to Hematologic Toxicity

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Patients whose treatment is delayed due to toxicity will discontinue study drug or will proceed with treatment when toxicity has improved (as long as the toxicity resolves within **126 days from the time of the last administration of patritumab deruxtecan**~~4 weeks~~) according to the dose modifications below.

Table 3 Dose Modifications Due to Hematologic Toxicities

Febrile neutropenia was updated to give the same guidance for Grade 3 and Grade 4: **Delay dose until resolved, then reduce patritumab deruxtecan by 1 dose level and resume.**

Administration of G-CSF as prophylaxis for all subsequent cycles is recommended.

Section 8.1.1 Labelling, Packaging, and Supply

~~U3-1402~~**Patritumab deruxtecan** will be supplied ~~as vials in cartons~~ by Daiichi Sankyo as vials **in cartons labelled as "U3-1402"**.

Section 10.1 Statistical Design

This is a Phase II open-label study of ~~U3-1402~~**patritumab deruxtecan** in patients with ~~metastatic breast cancer (~~MBC~~) who have received no prior anti-HER2 therapy. This study~~ that will be conducted in 3 parts. Part A will enroll up to 60 patients with HER2- MBC. **Part B will enroll an additional 20 patients into each of 2 subgroups that were defined from the Part A (based on ER/PR/HER2/HER3 expression) evaluation of biomarker expression in pre-treatment biopsy samples or in tissue from a biopsy done within 2 months prior to consent. A total of up to 40 patients will be enrolled into the following 2 Part B subgroups:**

- **MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan therapy**
- **mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan therapy**

The primary objective of this study is to evaluate overall response rate (ORR) and progression-free survival at 6 months (PFS-6) of single agent ~~U3-1402~~ **patritumab deruxtecan** in patients with ~~HER2-~~ MBC.

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BRE 354 CONTACT INFORMATION

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Study Chair:	Erika Hamilton, MD Director, Breast Cancer and Gynecologic Cancer Research Program Sarah Cannon Research Institute 250 25th Ave North, Suite 200 Nashville, TN 37203 USA 615-524-4092 Office
Medical Monitor:	Lola Dosunmu, MD, MPH Senior Director, Medical and Clinical Science Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd., Suite 800 Nashville, TN 37203 USA 615-329-7274 (Office) / 615-454-0272 (Cell)
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BRE 354 PROTOCOL SYNOPSIS

Title of Study: A Phase II Study of U3-1402 (Patritumab Deruxtecan) in Patients with Metastatic Breast Cancer

Development Innovations Study Number: BRE 354

Sponsor: Sarah Cannon Development Innovations, LLC – Nashville, TN 37203

Study Duration: The total duration of the study is planned to be approximately 46 months.

Phase of Study: II

Study Centers: This study will be conducted at approximately 10 sites in the United States.

Number of Patients: Up to 121 patients are planned to be enrolled in this study.

Objectives:

Primary Objective

The primary objective of this study is:

- To evaluate overall response rate (ORR) and progression-free survival at 6 months (PFS-6) of single agent U3-1402 (patritumab deruxtecan) in patients with HER2- metastatic breast cancer (MBC)

Secondary Objective

The secondary objectives of this study are:

- To assess the safety and tolerability of patritumab deruxtecan in patients with MBC
- To estimate the duration of response (DoR) and PFS in patients with MBC
- To estimate the clinical benefit rate (CBR) in patients with MBC
- To evaluate ORR and PFS-6 of single agent patritumab deruxtecan in patients with HER2+ MBC after progression on trastuzumab deruxtecan

Exploratory Objective

The exploratory objectives of this study are:

- To evaluate HER3 protein expression and its relationship with efficacy
- To identify biomarkers associated with clinical efficacy in patients with MBC
- To evaluate PK (pharmacokinetics) and ADA (anti-drug antibody) in patients with MBC

Study Design: This is a Phase II open-label study of patritumab deruxtecan in patients with MBC and will be conducted in 3 parts. Part A will enroll up to 60 patients with HER2- MBC. All enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done within 2 months prior to consent and tissue from this biopsy is available) to determine if patients with expression of the following biomarkers as determined by immunohistochemistry (IHC) (ER/PR/HER2/HER3) show response to treatment after all patients in Part A have completed 2 tumor assessments. Blood samples and on-treatment biopsy samples will be collected from all patients for additional correlative analyses. PK and ADA blood samples will be taken from all patients.

Part B will enroll an additional 20 patients into each of 2 subgroups that were defined from the Part A (based on ER/PR/HER2/HER3 expression) evaluation of biomarker expression in pre-treatment biopsy samples or in tissue from a biopsy done within 2 months prior to consent. A total of up to 40 patients will be enrolled into the following 2 Part B subgroups:

- MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan therapy

- mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan therapy

Patients enrolled in Part A will be included along with Part B patients of their respective subgroups in the final statistical analysis for efficacy.

Part Z will enroll an additional 21 patients with HER2+ MBC. All enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done while on or after trastuzumab deruxtecan therapy within 3 months prior to consent and tissue from this biopsy is available) for biomarker analysis. Blood samples and on-treatment biopsy samples will be collected from all patients for additional correlative analyses, unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor. Blood samples for PK and ADA will be collected from all patients.

Patients will have computed tomography (CT) scans every 6 weeks (±5 days) from Cycle 1 Day 1 for the first 6 months, then every 9 weeks (±5 days) thereafter. Patients will be allowed to continue on therapy as long as they have no disease progression, have not withdrawn from the study, have not met other protocol-defined criteria for treatment discontinuation, and are considered, by the Investigator, to still be receiving clinical benefit.

Study Drugs, Doses, and Modes of Administration: Patritumab deruxtecan 5.6 mg/kg will be administered through IV on Day 1 of each cycle (every 3 weeks).

Inclusion Criteria:

Patients must meet the following criteria in order to be included in the research study:

Inclusion criteria for Parts A and B (HER2-negative) and Part Z (HER2-positive) cohorts:

1. Written informed consent, according to local guidelines, signed and dated by the patient or by a legal guardian prior to the performance of any study-specific procedures, sampling, or analyses
2. Women and men at least 18 years-of-age at the time of signature of the informed consent form
3. Histologically documented locally advanced or metastatic breast cancer
4. Triple-negative breast cancer (TNBC) patients should have received at least 1 but no more than 5 prior lines of chemotherapy in the metastatic setting
5. **Parts A and B patients only:** Patients with HR+ HER2-negative MBC should have received prior treatment with endocrine therapy +CDK 4/6 inhibitor. No limit to prior endocrine therapy regimens, but no more than 2 prior chemotherapy regimens in the metastatic setting are allowed. HR+ = ER and/or PgR positivity that are defined as ≥1% of cells expressing HR via IHC analysis. HER2 negativity is defined as either of the following: IHC 0, IHC 1+, or IHC 2+/in situ hybridization (ISH) negative.
6. **Part B patients only**: Patients with HER2-negative MBC will be included into one of the following 2 subgroups:
   1) MBC HR+, HER2-, regardless of HER3 expression, who have received trastuzumab deruxtecan and/or sacituzumab govitecan, or, 2) mTNBC, regardless of HER3 expression, who have received sacituzumab govitecan and/or datopotamab deruxtecan.
7. **Part Z patients only:** should have documented HER2-positive expression as per American Society of Clinical Oncology – College of American Pathologists guidelines based on local testing.
8. **Part Z patients only:** should have had prior treatment with at least 2 anti-HER2 therapies, 1 of which must be trastuzumab deruxtecan. These patients must have experienced disease progression after receiving trastuzumab deruxtecan.
9. At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (bone-only disease excluded)
10. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed ≥4 weeks prior to initiation of study treatment (2 weeks for patients who received palliative radiation

therapy), there is no evidence of central nervous system disease progression on a scan or mild neurologic symptoms, and there is no requirement for chronic corticosteroid therapy for the treatment of brain metastases.

11. Willingness to undergo pre-treatment biopsy and on-treatment biopsies. Must have a tumor amenable to pre-treatment biopsy (unless archived tissue is available and was obtained within 2 months prior to starting treatment) and on-treatment biopsy (excludes bone lesions and previously irradiated lesions).
12. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A)
13. Has adequate organ function within 7 days before the start of study treatment, defined as:
    - Platelet count $\geq 100 \times 10^9$/L
    - Hemoglobin ≥9 g/dL (transfusion and/or growth factor support allowed)
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5 × the upper limit of normal (ULN), except for patients on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-international normalized ratio (INR) within therapeutic range as deemed appropriate by the Investigator.
    - Serum creatinine ≤1.5 × ULN, or creatinine clearance ≥50 mL/min as calculated using the modified Cockcroft-Gault equation; confirmation of creatinine clearance is only required when creatinine is >1.5 × ULN.
    - Aspartate aminotransferase/alanine aminotransferase ≤3 × ULN (if liver metastases are present, ≤5 × ULN)
    - Total bilirubin ≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome or liver metastases
    - Serum albumin ≥2.5 g/dL
14. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of acceptable contraception (Appendix C), including one barrier method, during their participation in the study and for at least 7 months following last dose. Male patients must also refrain from donating sperm during their participation in the study.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from study entry:

Exclusion criteria for Part A and B (HER2-negative) and Part Z (HER2-positive) cohorts:

1. Treatment with any of the following:
    - Any systemic anti-cancer chemotherapy, small molecule, biologic, hormonal agent, or immune checkpoint inhibitor therapy from a previous treatment regimen or clinical study within 21 days prior to the first dose of patritumab deruxtecan
    - Prior treatment with any HER3-targeting agent
    - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug treatment
    - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug treatment, or palliative radiation therapy within 2 weeks of the first dose of study drug treatment

- Chloroquine/hydroxychloroquine ≤14 days prior to the first dose of study drug treatment.

2. Has any hypersensitivity to drug substances or inactive ingredients in drug product.
3. Has any clinically significant interstitial lung disease (ILD) (including pulmonary fibrosis or radiation pneumonitis) or is suspected to have such disease by imaging during screening. If imaging findings are unlikely to indicate a history of pneumonitis, then the Investigator should discuss the considerations with the Medical Monitor about potential enrollment and record the reasoning in the source documentation.
4. Clinically severe pulmonary compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:

- Any underlying pulmonary disorder (e.g., pulmonary emboli, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion)
- Any autoimmune, connective tissue or inflammatory disorder with pulmonary involvement (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis)

OR

- Prior pneumonectomy

5. With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or baseline at the time of starting study treatment. Note: patients with chronic Grade 2 toxicities who are asymptomatic or adequately managed with stable medication may be eligible with approval by the Medical Monitor.
6. Leptomeningeal metastases or evidence of spinal cord compression or brain metastases, defined as being clinically active and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Patients with clinically inactive or treated brain metastases who are asymptomatic (i.e., without neurologic signs or symptoms and do not require treatment with corticosteroids or anticonvulsants) may be included in the study. Patients must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1.
7. Women who are pregnant, nursing, or plan to become pregnant while in the study and for at least 7 months after the last administration of study treatment
8. Men who plan to father a child while in the study and for at least 7 months after the last administration of study treatment
9. Uncontrolled or significant cardiovascular disorder prior to Cycle 1 Day 1, including:

- Mean resting corrected QT interval using Fridericia's formula (QTcF) prolongation to >470 ms for females and >450 ms for males in three successive screening measurements
- Patients with a left ventricular ejection fraction <50%
- Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
- Documented myocardial infarction within 6 months.
- Congestive heart failure (New York Heart Association ≥ Grade 2 [Appendix D]) within 28 days

10. Has known clinically significant corneal disease from prior therapies such as drug-induced keratitis
11. 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. Patients who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.

12. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding diatheses, or active infection, including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions is not required.
13. Presence of other active invasive cancers other than the one treated in this study within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.

Additional exclusion criteria only for Part A and B (HER2-negative) cohorts:

15. Patients with HER2+ breast cancer per ASCO-CAP guidelines
16. **Part A only:** Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g., trastuzumab deruxtecan, DS-1062a [datopotamab deruxtecan], and DS-7300a [B7-H3 DXd-ADC])
17. **Part B patients only:** Prior treatment with trastuzumab deruxtecan, sacituzumab govitecan, and/or datopotamab deruxtecan with any of the following:

- A severe reaction or severe tolerability issues that necessitated stopping treatment with the therapy
- Any unresolved toxicities from the prior therapy greater than Grade 1, with the exception of alopecia

Additional exclusion criteria only for Part Z (HER2-positive) cohort:

18. Treatment with any of the following:

- Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor except trastuzumab deruxtecan
- Prior treatment with trastuzumab deruxtecan within 4 weeks prior to the first dose of patritumab deruxtecan

19. Uncontrolled or significant cardiovascular disease, including history of myocardial infarction within 6 months before enrollment
20. A severe reaction or severe tolerability issues that necessitated stopping treatment with trastuzumab deruxtecan
21. Any unresolved toxicities from prior therapy with trastuzumab deruxtecan greater than Grade 1 with the exception of alopecia.

Correlative Testing: Correlative testing will be done on tissue and blood samples collected prior to starting treatment. All patients in Part A will have an on-treatment biopsy in Cycle 2 between Days 1-7. Patients in Part B will have biopsies in Cycle 2 between Days 1-7 except for patients with HER3 expression who will follow a different schedule. The first 10 patients in Part B with HER3 expression will have the on-treatment biopsy in Cycle 1 between Days 15-21 and the next 10 patients with HER3 expression will have the on-treatment biopsy in Cycle 2 between Days 1-7. All patients in Part Z will have an on-treatment biopsy in Cycle 2 between Days 1-7 unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor.

1. Pre-treatment biopsy (not required if tissue was acquired within previous 2 months for Part A and B patients and 3 months for Part Z patients and tissue from this biopsy is available) and on-treatment biopsy. Biomarker analyses may include:

- IHC: ER/PR/HER2/HER3 expression
- Fluorescence in situ hybridization (FISH): HER2 amplification

- RNA sequencing and DNA extraction for future analysis
- HER3 signaling marker analysis
- DNA damaging marker such as γH2AX
- Immuno-oncology related markers (such as PD-L1, PD-1, CD8, CD4, CD68, CD163)
- Novel DXd sensitive and resistant marker
- Samples for future research related to the biology of breast cancer and action of the drug

2. Blood sample for Part A patients

    - cell-free RNA (cfRNA)
    - circulating-tumor DNA (ctDNA) panel

3. Blood sample for Parts B and Z patients

    - circulating-tumor DNA (ctDNA) panel

Statistical Methodology: Sixty patients will be enrolled into Part A, and the sizes of the biomarker expression-defined subgroups will not be restricted. Evaluation of biomarker expression-defined subgroups to carry forward into Part B will be based on evaluation of ORR, PFS-6, and results from correlative tests.

Patients in the subgroups from Part A that are expanded in Part B will be included in a combined subgroup for presentation (e.g., if 12 ER high/HER-3 high patients are treated in Part A, and that subgroup treats 20 additional patients in Part B, they would be added to the affiliated Part B subgroup for a total of 32 in analysis). Part Z will enroll an additional 21 patients with HER2+ MBC.

PFS-6 will be a binary endpoint with patients surviving progression-free for at least 6 months considered successes; otherwise, patients will be considered failures (including patients who withdraw from the study prior to six months). The ORR and six-month PFS will be presented with two-sided 95% confidence intervals (CIs) (calculated based on the Clopper-Pearson method). The table below shows the precision of the estimates for the two endpoints across a range of sample sizes and ORR or PFS-6 rates.

Projected CIs for ORR and PFS-6

Approximate ORR or PFS-6	N	Percentage (95% CI)†	Width of 95% CI†
0.20	20	0.20 (0.06, 0.44)	0.38
	25	0.20 (0.07, 0.41)	0.34
	30	0.20 (0.08, 0.39)	0.31
	35	0.20 (0.08, 0.37)	0.28
	40	0.20 (0.09, 0.36)	0.27
0.30	20	0.30 (0.12, 0.54)	0.42
	25	0.32 (0.15, 0.54)	0.39
	30	0.30 (0.15, 0.49)	0.35
	35	0.31 (0.17, 0.49)	0.32
	40	0.30 (0.17, 0.47)	0.30
0.40	20	0.40 (0.19, 0.64)	0.45
	25	0.40 (0.21, 0.61)	0.40
	30	0.40 (0.23, 0.59)	0.37

Approximate ORR or PFS-6	N	Percentage (95% CI)†	Width of 95% CI†
	35	0.40 (0.24, 0.58)	0.34
	40	0.40 (0.25, 0.57)	0.32
0.50	20	0.50 (0.27, 0.73)	0.46
	25	0.52 (0.31, 0.72)	0.41
	30	0.50 (0.31, 0.69)	0.37
	35	0.51 (0.34, 0.69)	0.35
	40	0.50 (0.34, 0.66)	0.32

†Based on Clopper-Pearson.

BRE 354 SCHEDULE OF ASSESSMENTS (SOA)

Study period	**Screening**		**Treatment Cycles**				**EOT[s,r]**	**40-Day (+7 days) Safety FU[t]**	**FU**
Cycle[a]			**C1**	**C2**	**C3**	**C4+**			
Visit number	**1**		**2**	**3**	**4**	**5+**			
Treatment day	**-28 days[b]**	**-7 days[b]**	**1**	**1 (±2)**	**1 (±2)**	**1 (±2)**		**+1 week**	
Informed consent[b]	X								
Inclusion/exclusion criteria	X								
Medical history and demographics[c]		X							
Physical examination, height (screening only), and weight[c,d]		X	X	X	X	X	X	X	
ECOG performance status[c,d]		X	X	X	X	X	X	X	
12-lead electrocardiograms (triplicate)[c,e]	X		X	X	X	X	X		
Ophthalmologic assessments[f]	X						X[f]		
Vital signs[c, g]		X	X	X	X	X	X	X	
Serum/urine pregnancy test[c,h]		X	X	X	X	X	X	X	
Safety laboratory (hematology, biochemistry)[c, i, j]		X	X	X	X	X	X	X	
Safety laboratory (coagulation - aPTT/PTT and INR/PT)[c]		X	X	X	X	X	X	X	
Safety laboratory (urine)[c]		X	X	X	X	X	X	X	
Tumor assessment[k]	X[k]			Every 2 cycles for the first 6 months of treatment and every 3 cycles thereafter[k]					
Pre-treatment/EOT blood sampling for cfRNA and ctDNA biomarker[l] – Arm A only			X				X		

Study period	**Screening**		**Treatment Cycles**				**EOT[s,r]**	**40-Day (+7 days) Safety FU[t]**	**FU**
Cycle[a]			**C1**	**C2**	**C3**	**C4+**			
Visit number	**1**		**2**	**3**	**4**	**5+**			
Treatment day	**-28 days[b]**	**-7 days[b]**	**1**	**1 (±2)**	**1 (±2)**	**1 (±2)**		**+1 week**	
Pre-treatment/EOT blood sampling for ctDNA biomarker[l] – Part B and Part Z patients only			X				X		
Pre-treatment tumor sample[m]	X								
Pharmacokinetic Samples			X[n]	X[n]		X[n]			
ADA			X[o]	X[o]			X		
On-treatment tumor biopsy - Part A patients and Part B patients except for first 10 patients in Part B with HER3 expression				X (between D1-7)[p]			X (Optional)[p]		
On-treatment blood sample for cfRNA and ctDNA - Part A				X (between D1-7)[p]					
On-treatment tumor biopsy - first 10 patients in Part B with HER3 expression			X (between D15-21)[p]				X (Optional)[p]		
On-treatment tumor biopsy - Part Z patients				X (between D1-7)[v]					
BRCA1/*BRCA2* mutational status[q]	X								
U3-1402 (patritumab deruxtecan)			X	X	X	X			
Concomitant medications	X		X	X	X	X	X	X	
Adverse Events	X		X	X	X	X	X[r]	X	
PFS Follow Up									X[u]

ADA= anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; cfRNA = cell-free RNA; CK = creatine kinase; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; ETDRS = early treatment diabetic retinopathy study; FU = follow-up; INR = international normalized ratio; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SOA = Schedule of Assessments, WBC = white blood cells

Schedule of Assessments Footnotes

a Treatment cycles are 21 days (3 weeks). Patients may continue treatment with patritumab deruxtecan as long as they are deriving clinical benefit according to the Investigator's judgment.

b Informed consent should take place within 28 days of start of study treatment. Tumor assessments (scans) and ECGs should be performed ≤28 days prior to initiation of treatment. Evaluations that should be recorded ≤7 days prior to initiation of treatment are listed in footnote c and Section 7.2.

c Safety laboratory assessments, including hematology, biochemistry, coagulation, serum pregnancy test, and urinalysis, will be performed locally. The following screening assessments should be done ≤7 days prior to initiation of treatment: medical history and demographics, physical examination (including height and weight), ECOG performance status, vital signs, hematology, biochemistry, coagulation, urinalysis, and screening pregnancy test. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of ECOG performance status, an abbreviated physical examination, and vital signs.

d Physical examinations, including the measurements of height (screening only) and weight, and ECOG performance status will be done at screening, on Day 1 of each treatment cycle, at the EOT visit, and at the 40-day safety FU visit.

e Triplicate 12-lead ECGs will be done at the time points outlined in the SOA.

f Ophthalmologic exams will take place at screening (≤28 days prior to Cycle 1 Day 1) and EOT, and if clinically indicated. Ophthalmologic exams include a visual acuity test (early treatment diabetic retinopathy study [ETDRS] or Snellens), slit lamp examination, fundoscopy, and tonometry. Assessments may be repeated as clinically indicated as part of a scheduled or unscheduled visit. A 40 (+7) Day FU assessment is required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

g Vital signs (blood pressure, body temperature, heart and respiratory rate) are checked at every visit prior to administration of treatment and at the discretion of the Investigator. On days that ECGs are taken, vital signs should be taken after the patient has been resting in the supine position prior to ECGs and administration of treatment.

h Pregnancy tests are mandatory for women of child-bearing potential. A serum (β-HCG) pregnancy test must be done at screening. Thereafter, this test can be done with either serum or urine on Day 1 of each cycle, at the EOT visit, and at the 40-day FU visit.

i Hematology blood tests include including red blood cell (RBC) count, hemoglobin (Hb) hematocrit, reticulocytes, total white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, 5-part differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils), and platelet count.

j Biochemistry blood tests include sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3 or CO_2, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase (ALT), alkaline phosphatase ALP), bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase (CK: if CK is elevated, then CK-MB, Troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted), serum urea nitrogen, and serum uric acid).

k Tumor assessments should be done according to RECIST v 1.1 (see Appendix B) and should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not otherwise confirmed) bone metastasis at screening, tumor assessment at screening should include a bone scan. Correlative imaging should then be repeated at each tumor assessment (see Appendix B). Assessments will be performed by the

Investigator ≤28 days prior to initiation of treatment and every 2 cycles (6 weeks ±5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter, and at the discretion of the Investigator.

l Blood sampling for cfRNA and ctDNA biomarkers for Part A patients will be taken at pre-dose on Cycle 1 Day 1 and EOT or disease progression. Blood sampling for ctDNA biomarkers for Part B and Part Z patients will be taken at pre-dose on Cycle 1 Day 1 and EOT or disease progression.

m If medically feasible, all patients should provide a pre-treatment biopsy. If it is not medically feasible to provide a pre-treatment biopsy, archival biopsy tissue that was taken 2 months prior to consent in Part A and Part B and 3 months prior to consent in Part Z should be provided. This sample should be obtained from a primary tumor or metastatic site, and not previously irradiated.

n A serum PK sample to be collected at Cycle 1 at the end of infusion with a window of 0-4 hours after end of infusion. PK samples will also be taken Cycle 2 and Cycle 4 predose and at the end of infusion with a window of 0-4 hours after end of infusion.

o An ADA sample to be collected pre-dose at Cycle 1 and Cycle 2; and at EOT.

p All patients in Part A will have an on-treatment biopsy in Cycle 2 between Days 1-7. Patients in Part B will have biopsies taken in Cycle 2 between Days 1-7 except for patients with HER3 expression who will follow a different schedule. The first 10 patients in Part B with HER3 expression will have the on-treatment biopsy in Cycle 1 between Days 15-21 and the next 10 patients with HER3 expression will have the on treatment biopsy in Cycle 2 between Days 1-7. Patients will also be asked to have an optional biopsy at EOT or progression.

- The study team leader will track patient enrollment across multiple sites and track on-treatment biopsy collection.
- Once the 10th patient (Part B) on-treatment sample is collected and analyzed, an Investigator letter will be sent to the sites that the first 10 patients evaluable tumor requirement criteria have been met and sites are to proceed with the on-treatment biopsy schedule for Patients 11-20.

q *BRCA1/BRCA2* mutational status should be provided at Screening. If status is unknown, cannot be obtained from archival tissue or a blood sample, or patient refuses to be tested, they can still enroll in the study.

r Adverse events and SAEs will be followed for 40 days (+7 days) after the last dose of the study drug.

s An EOT visit should be performed for all patients who permanently discontinue study treatment. If the decision to permanently discontinue treatment is made at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment).

t A 40-day safety FU visit should take place before any other anti-cancer treatment starts.

u If the patient discontinues treatment without having PD, tumor assessment/imaging should continue to be performed per standard of care until progression, withdrawal of consent, subsequent treatment, or the study is stopped. Follow-up for progression may be done by review of medical records every 3 months to confirm patient status.

v- All patients in Part Z will have an on-treatment biopsy in Cycle 2 between Days 1-7 unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADC	Antibody drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
cfRNA	Cell-free RNA
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulation-tumor DNA
Development Innovations	Sarah Cannon Development Innovations, LLC
DMC	Data Monitoring Committee
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End-of-treatment (visit)
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HER3	Receptor tyrosine-protein kinase erbB-3
HIPAA	Health Insurance Portability and Accountability Act
HR	Hormone receptor
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator study file
IV	Intravenous
MBC	Metastatic breast cancer
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Overall response rate

Abbreviation or special term	Explanation
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PK	Pharmacokinetic
PR	Partial response
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SOA	Schedule of Assessments
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
T-DXd	Trastuzumab deruxtecan
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal
USPI	United States Package Insert

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

1.1 Background and Study Rationale

1.1.1 HER3

Receptor tyrosine-protein kinase erbB-3 (HER3) protein that is encoded by the *ERBB3* oncogene is highly expressed in many cancers, including breast cancer (Lee-Hoeflich et al. 2008). Unlike the other members of the HER family, HER3 is unique in that it has minimal intrinsic kinase activity. The HER3 receptor forms heterodimers with other RTKs, most notably with HER2, and the subsequent downstream signaling promotes tumorigenesis and metastasis (Mota et al. 2017; Mishra et al. 2018; Lyu et al. 2018).

The heterodimerization of HER3 with RTKs activates oncogenic signaling via the PI3K/Akt and the MAPK/ERK and other pathways. Inhibition of these pathways using MEKi, PI3Ki, mTOR and AKTi leads to HER3 upregulation (Gala & Chandarlapaty 2014). This upregulation leads to sustained PI3K/AKT signaling, resulting in tumor survival (Gala & Chandarlapaty 2014; Mishra et al. 2018).

Increased levels of circulating HER3 ligand HRG may also lead to HER3 activation and treatment resistance. Multiple studies indicate that HER3 activation plays a key role in treatment resistance to EGFR and anti-estrogen therapies. Fulvestrant resistant MC-7 cells were shown to be dependent on HER3 and NRG-2 (a HER3 ligand) expression for sustained growth and survival (Frogne T et al. 2009). Activation of the PI3K/Akt pathway and proto-oncogene SRC signaling are major determinants of trastuzumab-induced resistance based on data from preclinical studies (Mishra et al. 2018). Thus HER3 appears to play an important role in both HER2+ and ER+ breast cancer. Furthermore, HER3 has been shown to be upregulated in chemotherapy-resistant breast cancer. Finally, a meta-analysis across multiple tumor types demonstrated that higher expression of HER3 correlates with poorer outcomes in cancer patients (Ocana et al. 2013).

Thus HER3 is a valid therapeutic target in cancer and drugs targeting HER3 have employed different strategies. These include mono- and bi-specific antibodies targeting multiple HER3 domains, bi-specific ligand traps for HER3, small molecule inhibitors against HER3 pseudokinase activity and HER3 peptide vaccines, which are in various stages of clinical development.

1.1.2 U3-1402 (patritumab deruxtecan)

Patritumab deruxtecan is an antibody drug conjugate (ADC) comprising a recombinant fully human anti-HER3 IgG1 monoclonal antibody (patritumab, U3-1287) covalently linked to MAAA-1162a (glycine-glycinephenylalanine-glycine [GGFG]) tetrapeptide linker containing a topoisomerase I inhibitor [MAAA-1181a]). MAAA-1181a is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I. Patritumab deruxtecan has exhibited specific binding activity to human HER3.

1.1.3 Clinical Safety

The safety and preliminary efficacy of patritumab deruxtecan were evaluated in the on-going Phase I/II Study U31402-A-J101 in US and Japan in patients with metastatic breast cancer (MBC). The trial enrolled advanced/unresectable MBC patients (irrespective of subtype) with HER3 positive tumors who were refractory/intolerant to standard therapy in the dose escalation

phase. Patients with HER3-positive MBC who had received ≥2 and ≤6 prior chemotherapy regimens were then enrolled in the dose-finding phase and subsequent expansion phase. The expansion phase included HR+/HER2- and triple negative MBC patients with HER3 high expression and HR+/HER2- MBC patients with HER3 low expression. Two different doses of patritumab deruxtecan, 4.8 mg/kg and 6.4 mg/kg, were evaluated.

As of the data cut-off date of 05 August 2019, 144 of 145 patients enrolled in Study U31402-A-J101 had received patritumab deruxtecan: 34 patients in the dose escalation part, 32 patients in the dose-finding part, and 78 patients in the dose expansion part. A total of 141 (97.9%) patients had experienced at least 1 treatment-emergent adverse event (TEAE) and 138 (95.8%) patients had experienced at least 1 TEAE considered related to study drug by the Investigator. The most frequent TEAEs (in >20% of patients), all grades, regardless of causality and noted in descending order of frequency, included nausea (113 [78.5%] patients), decreased appetite (74 [51.4%] patients), platelet count decreased (65 [45.1%] patients), neutrophil count decreased (61 [42.4%] patients), vomiting (57 [39.6%] patients), white blood cell count decreased (53 [36.8%] patients), anemia (52 [36.1%] patients), diarrhea (50 [34.7%] patients), aspartate aminotransferase (AST) increased (41 [28.5%] patients), fatigue (40 [27.8%] patients), alanine aminotransferase (ALT) increased (36 [25.0%] patients), stomatitis (36 [25.0%] patients), constipation (32 [22.2%] patients), and alopecia and malaise (31 [21.5%] patients each).

There were 92 (63.9%) patients with TEAEs of Grade 3 or higher, including most commonly (in >5% of patients), neutrophil count decreased (37 [25.7%] patients), platelet count decreased (32 [22.2%] patients), anemia (25 [17.4%] patients), white blood cell count decreased (21 [14.6%] patients), thrombocytopenia (12 [8.3%] patients), neutropenia (11 [7.6%] patients), hypokalemia (10 [6.9%] patients), and AST increased (8 [5.6%] patients).

Forty-six (31.9%) of the 144 treated patients had a treatment-emergent serious adverse event (SAE), including 31 (21.5%) patients with study drug-related SAEs. The most common SAEs reported in more than 1 patient, in descending order of frequency, included platelet count decreased (8 [5.6%] patients); vomiting (6 [4.2%] patients); decreased appetite (5 [3.5%] patients); nausea and thrombocytopenia (4 [2.8%] patients each); pneumonitis (3 [2.1%] patients); and febrile neutropenia, mental status changes, and urinary tract infection (2 [1.4%] patients each).

Treatment-emergent AEs were associated with a dose interruption in 68 (47.2%) patients and a dose reduction in 22 (15.3%) patients. Twelve (8.3%) patients discontinued study drug due to a TEAE.

Ten (6.9%) of the 144 treated patients experienced a potential interstitial lung disease (ILD) event (1 per patient) requiring ILD adjudication as of the data cut-off date, including 6 (4.2%) patients with pneumonitis (3 Grade 2 and 3 Grade 3), and 4 (2.8%) patients (1 patient each) with ILD (Grade 2), radiation pneumonitis (Grade 3), radiation fibrosis-lung (Grade 1), and respiratory failure (Grade 2). Treatment-emergent AEs in 7 of the above 10 patients (6 pneumonitis and 1 ILD) were considered as related to patritumab deruxtecan by the Investigators.

1.1.4 Clinical Efficacy

As of the data cut-off date of 06 November 2018, the median follow-up time was 10.5 months for patients with MBC (N=42, the dose escalation phase and the dose finding phase, 1.6 to 8.0 mg/kg) in Study U31402-A-J101. The preliminary efficacy reported on treatment with single agent patritumab deruxtecan per Investigator assessment showed an ORR of 42.9% (4.8 mg/kg: 40.0% [6/15], 6.4 mg/kg: 60.0% [9/15]). The median progression-free survival (PFS) was 8.3 months (range: 1.2, 16.8+), median duration of response (DoR) was not reached (range: 2.8, 13.8+).

1.1.5 Study Rationale

The safety and preliminary efficacy reported with single agent patritumab deruxtecan in Study U31402-A-J101 and benefit/risk balance support further exploration of patritumab deruxtecan in the MBC patient population to determine the subset of patients that are likely to derive the greatest benefit.

As noted above, HER3 is an important dimerization partner for HER2 and this heterodimerization leads to oncogenic signaling via the PI3K/Akt and the MAPK/ERK and other pathways. Trastuzumab deruxtecan (DS-8201a) is a HER2-targeted ADC with a topoisomerase 1 inhibitor as the payload. Trastuzumab deruxtecan has revolutionized the treatment of HER2+ MBC by significantly prolonging PFS in heavily pretreated and 3L HER2+ MBC (Modi et al. 2020; Cortes et al. 2022).

There are multiple ADCs in development against novel targets like Trop 2, Nectin 4, and HER3 with either similar or novel payloads. The efficacy of ADCs with a similar payload directed against a novel target is unknown; hence it is of interest to evaluate patritumab deruxtecan, a HER3-targeted ADC with topoisomerase 1 inhibitor as the payload, in a patient population whose disease has progressed on an ADC. Recent research highlights both cross-resistance to an ADC after ADC therapy in patients with MBC and durable responses on latter lines of ADC therapy, particularly if a different antibody target is utilized. Further research is needed to understand the mechanisms of clinical resistance and to guide optimal sequencing of ADC-based treatment options (Abelman et al. 2023).

1.2 Potential Risks and Benefits of the Treatment Regimen

Patritumab deruxtecan is being developed for the treatment of HER3-expressing malignant tumors. The product is in the early stages of development.

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

Based on the preliminary clinical safety data from the ongoing patritumab deruxtecan studies, nausea, decreased appetite, platelet count decreased/thrombocytopenia, white blood cell count decreased/leukopenia, neutrophil count decreased/neutropenia, vomiting, anemia, diarrhea, fatigue, malaise, stomatitis, constipation, ALT increased, AST increased, and alopecia are identified risks and will continue to be closely monitored and evaluated in the patritumab deruxtecan clinical development program.

Based on clinical data and safety information available as of the 05 August 2019 data cut-off, ILD/pneumonitis was added as an adverse drug reaction associated with the use of patritumab

deruxtecan and considered an important identified risk. The reported ILD events were generally manageable via close monitoring and by following the ILD management plan in the protocol.

In conclusion, based on the efficacy and safety data from the nonclinical studies and the preliminary clinical safety data from ongoing studies, the benefit/risk balance supports continued clinical development of patritumab deruxtecan. For more information on the non-clinical and clinical studies, see the current patritumab deruxtecan Investigator's Brochure (IB).

1.3 Rationale for the dose

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 patritumab deruxtecan ADC, total anti-HER3 antibody 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 J101 and U102 studies. Exposure-efficacy relationship was established for intact patritumab deruxtecan 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 patritumab deruxtecan studies to further evaluate this dosing regimen.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Corresponding Endpoints

Objectives:	**Endpoints/Variables:**
Primary Objective:	**Endpoints/Variables:**
Evaluate ORR and PFS-6 of single agent patritumab deruxtecan in patients with HER2-MBC	ORR defined as the proportion of patients with confirmed CR or PR (i.e., confirmation at least 4 weeks apart) and 6-month PFS as defined by defined as the proportion of patients who survive progression-free for at least 6 months per RECIST version (v) 1.1.

Objectives:	Endpoints/Variables:
Secondary Objectives:	**Endpoints/Variables:**
Assess the safety and tolerability of patritumab deruxtecan in patients with MBC	AEs/SAEs Vital signs Clinical chemistry/hematology parameters ECGs
Estimate the DoR	Duration of response
PFS in patients with MBC	PFS
Clinical Benefit Rate (CBR)	CBR defined as the proportion of patients with CR, PR or best overall response of SD for ≥ 6 months according to the RECIST v 1.1 criteria.
Evaluate ORR and PFS-6 of single agent patritumab deruxtecan in patients with HER2+ MBC after progression on trastuzumab deruxtecan	ORR defined as the proportion of patients with confirmed CR or PR (i.e., confirmation at least 4 weeks apart) and 6-month PFS as defined by defined as the proportion of patients who survive progression-free for at least 6 months per RECIST version (v) 1.1.
Exploratory Objectives:	**Endpoints/Variables:**
Evaluate HER3 protein expression and its relationship with efficacy	HER3 protein expression, ORR, PFS-6
Identify biomarkers associated with clinical efficacy in patients with MBC	Assays of these samples will include HER3 protein expression, and immune cell markers.
Evaluate PK (pharmacokinetics) and ADA (anti-drug antibody) in patients with MBC	Serum concentration of patritumab deruxtecan (antibody conjugated MAAA-1181a, total anti-HER3 antibody, and MAAA-1181a) and population PK analysis and incidence and titer of ADA in serum via validated assay

AE = adverse event; DoR = duration of response; ECG = electrocardiogram; MBC = metastatic breast cancer; ORR = Overall response rate; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

3.1.1 Inclusion criteria for <u>Part A and B (HER2-negative) and Part Z (HER2-positive)</u> cohorts:

1. Written informed consent, according to local guidelines, signed and dated by the patient or by a legal guardian prior to the performance of any study-specific procedures, sampling, or analyses

2. Women and men at least 18 years-of-age at the time of signature of the informed consent form (ICF)
3. Histologically documented locally advanced or metastatic breast cancer
4. Triple-negative breast cancer (TNBC) patients should have received at least 1 but no more than 5 prior lines of chemotherapy in the metastatic setting
5. **Parts A and B patients only:** Patients with HR+ HER2-negative MBC should have received prior treatment with endocrine therapy +CDK 4/6 inhibitor. No limit to prior endocrine therapy regimens, but no more than 2 prior chemotherapy regimens in the metastatic setting are allowed. HR+ = ER and/or PgR positivity that are defined as ≥1% of cells expressing HR via IHC analysis. HER2 negativity is defined as either of the following: IHC 0, IHC 1+, or IHC 2+/in situ hybridization (ISH) negative.
6. **Part B patients only**: Patients with HER2-negative MBC will be included into one of the following 2 subgroups: 1) MBC HR+, HER2-, regardless of HER3 expression, who have received trastuzumab deruxtecan and/or sacituzumab govitecan, or, 2) mTNBC, regardless of HER3 expression, who have received sacituzumab govitecan and/or datopotamab deruxtecan.
7. **Part Z patients only:** should have documented HER2-positive expression as per American Society of Clinical Oncology – College of American Pathologists guidelines based on local testing.
8. **Part Z patients only:** should have had prior treatment with at least 2 anti-HER2 therapies, 1 of which must be trastuzumab deruxtecan. These patients must have experienced disease progression after receiving trastuzumab deruxtecan.
9. At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (bone-only disease excluded)
10. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed ≥4 weeks prior to initiation of study treatment (2 weeks for patients who received palliative radiation therapy), there is no evidence of central nervous system disease progression on a scan or mild neurologic symptoms, and there is no requirement for chronic corticosteroid therapy for the treatment of brain metastases.
11. Willingness to undergo pre-treatment biopsy and on-treatment biopsies. Must have a tumor amenable to pre-treatment biopsy (unless archived tissue is available and was obtained within 2 months prior to starting treatment) and on-treatment biopsy (excludes bone lesions and previously irradiated lesions).
12. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A)

13. Has adequate organ function within 7 days before the start of study treatment, defined as:
    - Platelet count ≥100 × 10^9/L
    - Hemoglobin (Hb) ≥9 g/dL (transfusion and/or growth factor support allowed)
    - Absolute neutrophil count ≥1.5 × 10^9/L
    - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5 × the upper limit of normal (ULN), except for patients on coumadin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-international normalized ratio (INR) within therapeutic range as deemed appropriate by the Investigator.
    - Serum creatinine ≤1.5 × ULN, or creatinine clearance ≥50 mL/min as calculated using the modified Cockcroft-Gault equation; confirmation of creatinine clearance is only required when creatinine is >1.5 × ULN.
    - AST/ALT ≤3 × ULN (if liver metastases are present, ≤5 × ULN)
    - Total bilirubin ≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of documented Gilbert's syndrome or liver metastases
    - Serum albumin ≥2.5 g/dL
14. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of acceptable contraception (Appendix C), including one barrier method, during their participation in the study and for at least 7 months following last dose. Male patients must also refrain from donating sperm during their participation in the study.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

3.2.1 Exclusion criteria for Parts A and B (HER2-negative) and Part Z (HER2-positive) cohorts:

1. Treatment with any of the following:

- Any systemic anti-cancer chemotherapy, small molecule, biologic, hormonal agent, or immune checkpoint inhibitor therapy from a previous treatment regimen or clinical study within 21 days prior to the first dose of patritumab deruxtecan
- Prior treatment with any HER3-targeting agent
- Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug treatment
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug treatment, or palliative radiation therapy within 2 weeks of the first dose of study drug treatment
- Chloroquine /hydroxychloroquine ≤14 days prior to the first dose of study drug treatment

2. Has any hypersensitivity to drug substances or inactive ingredients in drug product
3. Has any history of ILD (including pulmonary fibrosis or radiation pneumonitis), has clinically significant ILD, or is suspected to have such disease by imaging during screening. If imaging findings are unlikely to indicate a history of pneumonitis, then the

Investigator should discuss the considerations with the Medical Monitor about potential enrollment and record the reasoning in the source documentation

4. Clinically severe pulmonary compromise (based on Investigator's assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
   a. any underlying pulmonary disorder (e.g., 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 (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis)

   OR prior pneumonectomy
5. With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or baseline at the time of starting study treatment. Note: patients with chronic Grade 2 toxicities who are asymptomatic or adequately managed with stable medication may be eligible with approval by the Medical Monitor.
6. Leptomeningeal metastases or evidence of spinal cord compression or brain metastases, defined as being clinically active and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Patients with clinically inactive or treated brain metastases who are asymptomatic (i.e., without neurologic signs or symptoms and do not require treatment with corticosteroids or anticonvulsants) may be included in the study. Patients must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1.
7. Women who are pregnant, nursing, or plan to become pregnant while in the study and for at least 7 months after the last administration of study treatment
8. Men who plan to father a child while in the study and for at least 7 months after the last administration of study treatment
9. Uncontrolled or significant cardiovascular disorder prior to Cycle 1 Day 1, including:
   - Mean resting corrected QT interval using Fridericia's formula (QTcF) prolongation to >470 ms for females and >450 ms for males in three successive screening measurements
   - Patients with a left ventricular ejection fraction (LVEF) <50%
   - Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
   - Documented myocardial infarction within 6 months.
   - Congestive heart failure (New York Heart Association ≥ Grade 2 [Appendix D]) within 28 days
10. Has known clinically significant corneal disease from prior therapies such as drug-induced keratitis
11. 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. Patients who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.

12. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, uncontrolled diabetes mellitus, active bleeding diatheses, or active infection, including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions is not required.
13. Presence of other active invasive cancers other than the one treated in this study within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.

3.2.2 Additional exclusion criteria only for Parts A and B (HER2-negative) cohorts:

15. Patients with HER2+ breast cancer per ASCO-CAP guidelines
16. **Part A only:** Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g., trastuzumab deruxtecan, DS-1062a [datopotamab deruxtecan], and DS-7300a [B7-H3 DXd-ADC])
17. **Part B patients only:** Prior treatment with trastuzumab deruxtecan, sacituzumab govitecan, and/or datopotamab deruxtecan with any of the following:
    - A severe reaction or severe tolerability issues that necessitated stopping treatment with the therapy
    - Any unresolved toxicities from the prior therapy greater than Grade 1, with the exception of alopecia

3.2.3 Additional exclusion criteria only for Part Z (HER2-positive) cohort:

18. Treatment with any of the following:
    - Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor except trastuzumab deruxtecan
    - Prior treatment with trastuzumab deruxtecan within 4 weeks prior to the first dose of patritumab deruxtecan
19. Uncontrolled or significant cardiovascular disease, including history of myocardial infarction within 6 months before enrollment
20. A severe reaction or severe tolerability issues that necessitated stopping treatment with trastuzumab deruxtecan
21. Any unresolved toxicities from prior therapy with trastuzumab deruxtecan

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression (Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after consultation with the Medical Monitor.)
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient lost to follow-up
- Patient requests to discontinue treatment
- Patient withdraws consent from study treatment or study participation altogether
- Pregnancy
- Study termination

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 40 days (+7 days) after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records.

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute [NCI] CTCAE Version 5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, and the potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee/institutional review board (IRB) approval of this protocol and any associated ICFs is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled by each site following the patient registration instructions provided by the Sarah Cannon Development Innovations, LLC (Development Innovations) study contact. Patient registration follow-up and/or confirmation will be provided via email within approximately 48 hours or by the next business day.

5. STUDY DESIGN

This is a Phase II open-label study of patritumab deruxtecan in patients with MBC and will be conducted in 3 parts. Part A will enroll up to 60 patients with HER2- MBC. All enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done within 2 months prior to consent) to determine if patients with expression of the following biomarkers as determined by IHC (ER/PR/HER2/HER3) show response to treatment after all patients in Part A have completed 2 tumor assessments. Blood samples and on-treatment biopsy samples will be collected from all patients for additional correlative analyses.

Part B will enroll an additional 20 patients into each of 2 subgroups that were defined from the Part A (based on ER/PR/HER2/HER3 expression) evaluation of biomarker expression in pre-treatment biopsy samples or in tissue from a biopsy done within 2 months prior to consent. A total of up to 40 patients will be enrolled into the following 2 Part B subgroups:

- MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan therapy
- mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan therapy

Patients enrolled in Part A will be included along with Part B patients of their respective subgroups in the final statistical analysis for efficacy.

Part Z will enroll an additional 21 patients with HER2+ MBC. All enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done while on or after trastuzumab deruxtecan therapy within 3 months prior to consent and tissue from this biopsy is available) for biomarker analysis. Blood samples and on-treatment biopsy samples will be collected from all patients for additional correlative analyses, unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor. PK and ADA blood samples will be collected from all patients.

The study schema is presented in Figure 1.

Figure 1 Study Schema Parts A and B

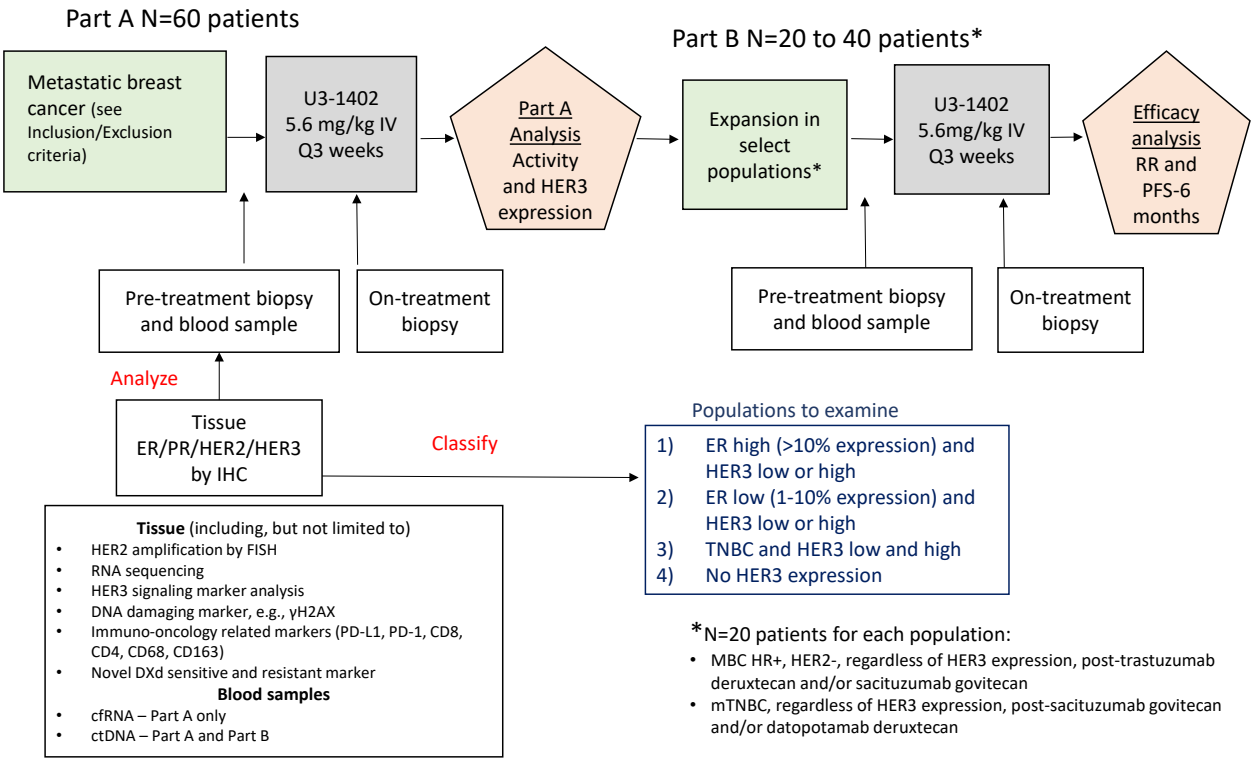
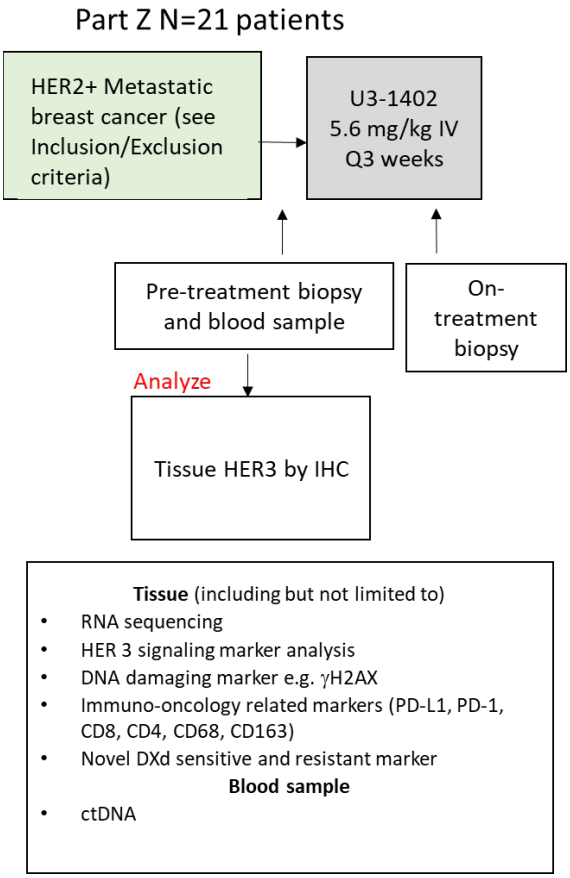

Part A N=60 patients
Metastatic breast cancer (see Inclusion/Exclusion criteria)
U3-1402 5.6 mg/kg IV Q3 weeks
Part A Analysis Activity and HER3 expression
Part B N=20 to 40 patients*
Expansion in select populations*
U3-1402 5.6mg/kg IV Q3 weeks
Efficacy analysis RR and PFS-6 months
Pre-treatment biopsy and blood sample
On-treatment biopsy
Pre-treatment biopsy and blood sample
On-treatment biopsy
Analyze
Tissue ER/PR/HER2/HER3 by IHC
Classify
Populations to examine
1) ER high (>10% expression) and HER3 low or high
2) ER low (1-10% expression) and HER3 low or high
3) TNBC and HER3 low and high
4) No HER3 expression
Tissue (including, but not limited to)
• HER2 amplification by FISH
• RNA sequencing
• HER3 signaling marker analysis
• DNA damaging marker, e.g., γH2AX
• Immuno-oncology related markers (PD-L1, PD-1, CD8, CD4, CD68, CD163)
• Novel DXd sensitive and resistant marker
Blood samples
• cfRNA – Part A only
• ctDNA – Part A and Part B
*N=20 patients for each population:
• MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan
• mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan

Figure 2 Study Schema Part Z



All eligible patients will receive patritumab deruxtecan 5.6 mg/kg intravenous (IV) on Day 1 of each cycle (every 3 weeks [Q3W]). Patients will have computed tomography (CT) scans every 6 weeks (±5 days) from Cycle 1 Day 1 for the first 6 months, then every 9 weeks (±5 days) thereafter. Patients will be allowed to continue on therapy as long as they have no disease progression, have not withdrawn from the study, have not met other protocol-defined criteria for treatment discontinuation, and are considered by the Investigator to still be receiving clinical benefit. Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after disease progression after consultation with the Medical Monitor.

5.1 Treatment Plan

Patritumab deruxtecan (U3-1402) 5.6 mg/kg IV will be administered Day 1 Q3W. Patritumab deruxtecan will be prepared and administered via IV infusion according to the details in Section 8.1.2.

5.2 Treatment Duration

The **start of the study** is defined as the date when the first patient in the whole study signs informed consent.

The **end of the study** is defined as the date of the last visit (including all follow-up visits) of the last patient in the whole study.

5.3 Concomitant Medications

Patients will be asked about prior medications during screening and instructed not to take any additional medications during the course of the study without prior consultation with the study team. At each visit, the patient will be asked about any new medications he or she is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is recommended.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate (such as pamidronate or zolendronic acid) use or denosumab for pain management and palliation of bone metastases, or treatment of osteoporosis, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines
- Hematopoietic growth factors used for prophylaxis or treatment
- Patients taking warfarin should be monitored regularly for changes in PT or INR.

Supportive care and other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator, with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study treatments should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Live virus vaccination (beginning from 28 days prior to Cycle 1 Day 1)
- Radiotherapy, except for palliative radiation (as long as the radiation field does not include the only measurable lesion or does not interrupt treatment for more than 28 days from the planned date of administration [i.e., 49 days from the last infusion date of patritumab deruxtecan])
- Radiotherapy to the thorax is also prohibited once a patient is screened and enrolled into the study.
- Concomitant use of chronic systemic (intravenous (IV) or oral) corticosteroids (i.e., >10 mg prednisone or equivalent) or other immunosuppressive medications except for managing AEs
- Herbal preparations/medications that could potentially interact with patritumab deruxtecan may not be allowed throughout the study. Any use of these substances will require discussion with the Medical Monitor. These herbal medications include, but are not limited

to: St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, cannabis and other medical marijuana products, and ginseng. Patients may need to stop using these herbal medications ≥7 days prior to the first dose of the study drug.

5.3.3 Restricted Therapies/Products

Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate symptoms (CTCAE Grade ≤2) while receiving treatment until at least 1 week after symptoms have resolved. If a patient 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. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless approved by a study doctor, at any time during the study and ≥1 week after permanent discontinuation of study treatment.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded using the NCI CTCAE Version 5.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of patritumab deruxtecan will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary, they will be permanent for the remainder of the treatment. Any patient requiring a toxicity-related dose delay of more than 18 weeks (126 days) from the last patritumab deruxtecan dose must be discontinued from the study, unless discussed with the Medical Monitor for extenuating circumstances. During the time of any dose delay, scheduled CT/MRI scans should continue as per protocol, and subjects should fulfill all of the following criteria:

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

If toxicities occur that are ≤ Grade 2, they should be managed symptomatically, if possible, and the patient should be re-treated without a dose reduction. If toxicities occur that are ≥ Grade 3, treatment should be withheld until resolution to ≤ Grade 1 or to the baseline value (if the baseline value was > Grade 1). Treatment should then be re-instituted, if medically appropriate, at the next lower dose level (see Table 2).

The dose level reductions to be used in this study are presented in Table 2.

Table 2 Dose Level Modifications

Dose Level	Patritumab deruxtecan
Starting Dose	5.6 mg/kg
Dose Level -1	4.8 mg/kg
Dose Level -2	3.2 mg/kg

6.1 Dose Modifications Due to Hematologic Toxicity

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Patients whose treatment is delayed due to toxicity will discontinue study drug or will proceed with treatment when toxicity has improved (as long as the toxicity resolves within 126 days from the time of the last administration of patritumab deruxtecan) according to the dose modifications below.

Table 3 Dose Modifications Due to Hematologic Toxicities

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	**Schedule Modification for patritumab deruxtecan**
Blood and lymphatic system disorders		
Neutrophil count decreased	Grade 3 (500 - <1000/mm^3; 0.5-1 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then resume patritumab deruxtecan.
	Grade 4 (<500/mm^3; <0.5 × 10^9/L)	Delay dose until resolved to ≤Grade 2, study treatment may be resumed after discussion and agreement between the Investigator and Medical Monitor. If treatment is resumed, then reduce by at least 1 dose level.
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 and 4	Delay dose until resolved, then reduce patritumab deruxtecan by 1 dose level and resume. Administration of G-CSF as prophylaxis for all subsequent cycles is recommended.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for patritumab deruxtecan
Anemia	Grade 3 (Hgb <8.0 g/dL)	Delay dose until resolved to ≤ Grade 2 or baseline, then resume patritumab deruxtecan. For recurrent anemia, delay dose until resolved ≤Grade 2 or baseline, then reduce patritumab deruxtecan dose by 1 level. Consider transfusion according to institutional guidelines.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce patritumab deruxtecan dose by 1 level. Consider transfusion according to institutional guidelines.
Platelet count decreased	Grade 3 (<50 - 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then: • If resolved in ≤14 days, resume patritumab deruxtecan. • If resolved in >14 days, patritumab deruxtecan may be resumed. Consider reducing patritumab deruxtecan by 1 dose level. Consider transfusion according to institutional guidelines.
	Grade 4 (<25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce patritumab deruxtecan by 1 dose level. Consider transfusion according to institutional guidelines.
Lymphocyte Count Decreased	Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤ Grade 2, then: • If resolved in ≤14 days, resume patritumab deruxtecan. • If resolved in >14 days, then reduce patritumab deruxtecan by 1 dose level.

6.2 Dose Modifications due to Non-Hematologic Toxicity

Table 4 Dose Modifications Due to Non-Hematologic Toxicities

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
General disorders and administration site conditions		

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Infusion related reaction (e.g., same reduced rate as previous infusion)	Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and patients should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
	Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV injection fluids); prophylactic medications indicated for ≤24 hours)	Patritumab deruxtecan infusion should be interrupted. Symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids) should be started. If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. Upon restart, if Grade 2 symptoms recur, no further patritumab deruxtecan should be administered at that visit. The amount of patritumab deruxtecan infused must be recorded in the eCRF. Subsequent infusions should be conducted at the 50% reduced infusion rate.
	Grade 3 (Prolonged [e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae) Grade 4 (Life-threatening consequences; urgent intervention indicated)	Administration of patritumab deruxtecan should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc., should be administered as clinically indicated.
Fatigue/ Asthenia/Malaise	Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline, then: • If resolved to ≤ Grade 1 or baseline in ≤14 days, resume patritumab deruxtecan. • If resolved to ≤ Grade 1 or baseline in >14 days, then reduce patritumab deruxtecan by 1 dose level.
Cardiac disorders		

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Heart failure	Grade ≥2 (Symptoms with moderate activity or exertion)	Cardiologist consultation as necessary. Delay dose until resolved to ≤ Grade 1, then reduce patritumab deruxtecan by 1 dose level.
Ejection fraction decreased	Decrease in LVEF 10% - 20% (absolute value), but LVEF >45%	Continue patritumab deruxtecan.
	LVEF 40% - ≤45% and decrease is <10% (absolute value) from baseline	Continue patritumab deruxtecan. Repeat LVEF assessment within 3 weeks.
	LVEF 40% - ≤45% and decrease is ≥10% to 20% (absolute value) from baseline	Delay patritumab deruxtecan. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue patient from study treatment.
	LVEF <40% or >20% (absolute value) drop from baseline	Delay patritumab deruxtecan. Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% (absolute value) drop from baseline is confirmed, discontinue patritumab deruxtecan. Cardiologist consultation as necessary.
Electrocardiogram QT corrected interval prolonged	Grade 3 (Average QTcF ≥501 ms; >60 ms change from baseline)	Delay patritumab deruxtecan until resolved to ≤ Grade 1 (QTcF ≤480 ms). Determine if another medication the patient was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If QTcF prolongation is attributed to patritumab deruxtecan, then reduce patritumab deruxtecan by 1 dose level. Cardiologist consultation as necessary.
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue patient from patritumab deruxtecan. Cardiologist consultation as necessary.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Respiratory, thoracic and mediastinal disorders		
ILD	See next column	If a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD. If ILD is suspected, delay patritumab deruxtecan dosing pending further evaluation and start corticosteroid treatment promptly per consensus statement[a] unless clinically contraindicated. Evaluations must include CT (preferably high-resolution CT), and pulmonologist consultation (when the Investigator is not a pulmonologist). The following evaluations should 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/pneumonitis is suspected, if feasible • Other tests, as clinically indicated If a non-inflammatory/infectious etiology is confirmed by the Investigator, treat accordingly and resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

a Kubo K, Azuma A, Kanazawa M, et al. Japanese Respiratory Society Committee. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respir Investig. 2013; 51(4):260-77.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Respiratory, thoracic and mediastinal disorders - ILD		
	Grade 1	The administration of patritumab deruxtecan must be delayed. Patritumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤28 days from day of onset, maintain dose. • If resolved in >28 days from day of onset, reduce dose 1 level. Toxicity Management: • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If there is worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines (if patient is asymptomatic, then patient should still be considered as Grade 1 even if steroid treatment is given).

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Respiratory, thoracic and mediastinal disorders - ILD		
	Grade 2	Permanently discontinue patient from study treatment. Toxicity Management: • Promptly start systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (e.g., methylprednisolone). – Re-consider additional work-up for alternative etiologies as described above. – Escalate care as clinically indicated.
	Grade 3 and 4	Permanently discontinue patient from study treatment. Toxicity Management: • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for 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 immunosuppressants and/or treat per local practice.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Eye disorders		
Ocular	Grade 3	Delay dose until resolved to ≤Grade 2, then: • If resolved in ≤7 days, resume patritumab deruxtecan. • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level. Ophthalmologist consultation as necessary.
	Grade 4	Discontinue patient from patritumab deruxtecan. Ophthalmologist consultation as necessary.
Renal and urinary disorders		
Creatinine increased	Grade 3 (>3.0 × baseline; >3.0-6.0 × ULN)	Delay dose until resolved to ≤ Grade 1 or baseline, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (>6.0 × ULN)	Discontinue patient from patritumab deruxtecan.
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 patritumab deruxtecan. In patients **without** liver metastasis, monitor AST/ALT 24 to 72 hours later, and continue regular monitoring until resolution.
	Grade 3 (>5.0-20.0 × ULN if baseline was normal; >5.0-20.0 × baseline if baseline was abnormal). In patients without liver metastases and patients with liver metastases and baseline level ≤ 3 x ULN.	Delay patritumab deruxtecan dose until resolved to ≤ Grade 1, then: • If resolved in ≤7 days, resume patritumab deruxtecan. • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	>8.0-20.0 × ULN if baseline was normal; >8.0-20.0 × baseline if baseline was abnormal. In patients with liver metastases, if the baseline level was > 3 × ULN.	Delay patritumab deruxtecan dose until resolved to ≤ baseline level, then: • If resolved in ≤7 days, resume patritumab deruxtecan. • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
	Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue patient from patritumab deruxtecan. Gastroenterologist or hepatologist consultation as necessary.
TBL increased	Grade 2 (>1.5-3.0 × ULN if baseline was normal; >1.5-3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay patritumab deruxtecan dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, resume patritumab deruxtecan. • If resolved in >7 days, then reduce patritumab deruxtecan by 1 dose level. If documented Gilbert's syndrome or liver metastases at baseline, continue patritumab deruxtecan.
	Grade 3 (>3.0-10.0 × ULN if baseline was normal; >3.0-10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay patritumab deruxtecan dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then reduce patritumab deruxtecan by 1 dose level. • If resolved in > 7 days, discontinue patritumab deruxtecan. If documented Gilbert's syndrome or liver metastases at baseline, delay patritumab deruxtecan dose until resolved to ≤ Grade 2, then: • If resolved in ≤7 days, then reduce patritumab deruxtecan by 1 dose level. • If resolved in >7 days, discontinue patritumab deruxtecan.
	Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue patient from patritumab deruxtecan.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
AST or ALT increased and TBL increased	AST or ALT ≥3 × ULN with simultaneous TBL >2 × ULN	Delay patritumab deruxtecan until drug-induced liver injury can be ruled out. The Investigator should consult with a gastroenterologist or hepatologist as needed, and the patient should 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) should be recorded within the eCRF. If drug-induced liver injury is ruled out, the patient should be treated accordingly, and resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor. Patritumab deruxtecan will be permanently discontinued if drug induced liver injury cannot be ruled out from diagnostic workup.
AST or ALT > 3.0 x ULN (if liver metastases are present, >5 ×ULN) with known hepatitis B and/or hepatitis C infection at baseline	--	Delay patritumab deruxtecan until reactivation of Hepatitis B and/or Hepatitis C can be ruled out. Perform HBV DNA and/or HCV RNA to rule out reactivation of Hepatitis B and/or Hepatitis C, respectively. Hepatologist and infectious disease consultations are recommended. If reactivation of Hepatitis B and/or Hepatitis C is confirmed, permanently discontinue patritumab deruxtecan.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
Gastrointestinal disorders		
Nausea	Grade 3 (Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition [TPN], or hospitalization indicated)	Delay patritumab deruxtecan until resolved ≤ Grade 1, and consider treatment with antiemetics and/or corticosteroids as per Investigator's judgement and local practice/guidelines, then: • If resolved to ≤ Grade 1 in ≤14 days, resume patritumab deruxtecan. • If resolved to ≤ Grade 1 in >14 days, then reduce patritumab deruxtecan by 1 dose level.
Vomiting	Grade 3 (Tube feeding, TPN, or hospitalization indicated)	Delay patritumab deruxtecan until resolved ≤ Grade 1, and consider treatment with antiemetics and / or corticosteroids as per Investigator's judgement and local practice/guidelines, then: • If resolved to ≤ Grade 1 in ≤7 days, resume patritumab deruxtecan. • If resolved to ≤ Grade 1 in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade ≥4	Discontinue patient from patritumab deruxtecan.
Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV).		
Diarrhea/ Colitis	Grade 3	Delay patritumab deruxtecan until resolved ≤ Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤ Grade 1 in ≤7 days, resume patritumab deruxtecan. • If resolved to ≤ Grade 1 in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue patient from patritumab deruxtecan.
Mucositis oral	Grade 3	Delay patritumab deruxtecan until resolved ≤ Grade 1, and consider treatment per local practice/guidelines, then: • If resolved to ≤ Grade 1 in ≤14 days, resume patritumab deruxtecan. • If resolved to ≤ Grade 1 in >14 days, then reduce patritumab deruxtecan by 1 dose level.

	Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for Patritumab deruxtecan
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue patient from patritumab deruxtecan.
Other adverse events (Non-laboratory or Laboratory)	Grade 3	Delay patritumab deruxtecan until resolved ≤ Grade 1, or baseline, then: • If resolved in ≤7 days, resume patritumab deruxtecan. • If resolved to in >7 days, then reduce patritumab deruxtecan by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue patient from patritumab deruxtecan.

6.2.1 Specific Recommendations for ILD

If a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever, rule out ILD.

If ILD is suspected, delay patritumab deruxtecan dosing pending further evaluation and start corticosteroid treatment promptly unless clinically contraindicated.

Evaluation must include CT (preferably high-resolution CT) and pulmonologist consultation (when the Investigator is not a pulmonologist). The following evaluations should also be obtained, as indicated:

- Infectious disease consultation as clinically indicated
- Blood cultures and CBC (other blood tests could be considered as needed)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests
- Pulse oximetry (peripheral capillary oxygen saturation [SpO_2])
- Arterial blood gases, as clinically indicated
- Diffusing capacity 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 the AE is confirmed to be ILD, follow the management guidance outlined in Table 4. If a non-inflammatory/infectious etiology is confirmed by the Investigator, treat accordingly and resumption of patritumab deruxtecan may occur after discussion between the Investigator and Sponsor.

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

6.2.2 Specific Recommendations for Liver Function Test Abnormalities

For patients with Grade 3 liver enzyme elevations (AST/ALT), patritumab deruxtecan should be held until the values recover to ≤ Grade 1. Patients with an elevation of ALT/AST ≥3 × ULN in conjunction with a bilirubin ≥2 × ULN may remain in the study if a correctable, non-drug-related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the study.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments (SOA) for this study is presented at the beginning of this protocol. The key procedures required in this study include:

- Reporting of all AEs occurring after the first dose of study treatment
- Pre-treatment and on-treatment blood biomarker assessments
- Tumor biopsy biomarker assessments
- Tumor assessments (based on CT/positron emission tomography [PET]/ and/or magnetic resonance imaging [MRI] scan) according to RECIST v 1.1 (see Appendix B).

A cycle of treatment is scheduled to last 3 weeks (21 calendar days). Multiple procedures may be scheduled at the same time point relative to patritumab deruxtecan dosing. Vital signs and ECG assessments should be performed prior to specimen collections.

7.2 Screening

At enrollment, each potential research subject will provide written informed consent ≤28 days prior to initiation of treatment and prior to starting any study-specific procedures. Upon signature of the ICF, patients will be assigned a unique patient number as enrollment (screening) occurs.

The screening assessments described in the SOA will be collected, reviewed, and determined to be acceptable by the site Principal Investigator or designee after obtaining informed consent prior to the initiation of treatment.

The following screening assessments should be performed and recorded ≤28 days prior to initiation of treatment:

- Ophthalmologic exam
- 12-lead ECG triplicate
- CT scan of chest, abdomen, and pelvis
- Bone scan if bone metastasis is suspected

Ophthalmologic exams include a visual acuity test (early treatment diabetic retinopathy study [ETDRS] or Snellens), slit lamp examination, fundoscopy, and tonometry. Assessments may be

repeated as clinically indicated as part of a scheduled or unscheduled visit. A 40 (+7) day FU assessment is required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

The following screening assessments should be recorded ≤7 days prior to initiation of treatment:

- Medical history and demographics
- Physical examination (including height and weight)
- ECOG performance status
- Vital signs
- Hematology including red blood cell (RBC) count, hemoglobin (Hb), hematocrit, reticulocytes, total white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, 5-part differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils), and platelet count
- Biochemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3 or CO_2, albumin, total protein, AST, ALT, alkaline phosphatase [ALP], bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, and serum uric acid)
- Coagulation test - aPTT/PTT and INR/PT
- Urinalysis
- Screening pregnancy test (blood)

If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1, with the exception of the ECOG performance status, an abbreviated physical examination, vital signs, and triplicate ECGs.

Concomitant medications present at study entry and/or during screening that are relevant to the patient's safety during the study as judged by the Investigator will be recorded in the electronic case report form (eCRF) (see Section 5.3 for details on concomitant medications).

7.3 Assessments During Study Treatment

Patients will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit and the criteria listed in Section 3.3 Discontinuation from Study Treatment are not met. Please refer to the SOA for detailed outlines of each visit during the treatment period for each part of the study.

7.3.1 Response Assessments

Patients will be re-evaluated for response to treatment every 2 cycles (6 weeks ±5 days) for the first 6 months, and every 3 cycles (9 weeks ±5 days) thereafter. Patients with PD or unacceptable toxicity should be discontinued from the study. Patients who are receiving clinical benefit in the opinion of the treating Investigator may be allowed to stay on study after consultation with the Medical Monitor. Patients with SD or response to therapy will continue treatment. The assessments to be performed at this time are specified in the SOA. Please refer

to Appendix B Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 for further instructions on evaluating response (e.g., PD, SD).

The following assessments will be performed if abnormal at baseline or if clinically indicated:

- CT scan of chest, abdomen, and pelvis
- CT scan head/MRI brain if history of central nervous system metastases

7.4 Follow-Up Periods and Study Completion

7.4.1 End-of-Treatment Visit

The end-of-treatment (EOT) visit will be performed as soon as possible (preferably within 7 days but no later than 14 days) after the Investigator decided with the patient to permanently discontinue the study treatment or when the Investigator became aware that the study treatment, had been discontinued.

If the patient discontinues treatment without having PD, tumor assessment/imaging should continue to be performed as outlined in the protocol until progression.

7.4.2 Forty-Day Safety Follow-Up

All patients will be followed after discontinuing study treatment until all treatment-related toxicity resolves or for at least 40 days (+7 days) post-study drug discontinuation or until the start of another anti-cancer treatment. Any concomitant medications received up to 30 days after the last dose of study medication should be recorded.

7.4.3 Progression-free Survival Follow-Up

If the patient discontinues treatment without having PD, tumor assessment/imaging should continue to be performed per standard of care until progression, withdrawal of consent, subsequent treatment, or the study is stopped. Follow-up for progression may be done by review of medical records every 3 months to confirm patient status.

7.5 SARS-CoV-2

For patients with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Appendix E.

7.6 Pharmacokinetic and Anti-Drug Antibody Assessments

Patients will have PK and ADA blood samples collected at the times noted in the SOA.

Population PK and exploratory exposure-response analyses may be performed to characterize the relationships between dose and exposure and between exposure and efficacy and/or safety endpoints. If performed, results of population PK or exposure-response analyses will be reported separately from the Clinical Study Report.

The ADA testing will be performed using a validated ADA assay following tiered assay steps including Screening, confirmatory as well as titer determination. If ADA is confirmed, further analysis to profile immunogenicity of patritumab deruxtecan (e.g., neutralizing antibody assay) will be conducted. Serum concentrations of intact patritumab deruxtecan ADC, total anti-HER3 antibody and released payload MAAA-1181a may also be measured using the same ADA samples for purpose of ADA assessment.

Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual.

7.7 Biomarker Assessments

Tissue and blood will be collected for correlative testing prior to starting treatment.

7.7.1 Biomarker Tissue Samples

7.7.1.1 Fresh Biopsies

If medically feasible, all patients will have a pre-treatment biopsy. If it is not medically feasible to provide a pre-treatment biopsy, archival biopsy tissue that was taken 2 months prior to consent in Part A and Part B and 3 months prior to consent in Part Z should be provided. This sample should be obtained from a primary tumor or metastatic site, and not previously irradiated. All fresh biopsies will be processed according to the laboratory manual.

All patients in Part A will have an on-treatment biopsy in Cycle 2 between Days 1 and 7. Patients in Part B will have biopsies in Cycle 2 between Days 1 and 7 except for patients with HER3 expression who will follow a different schedule. The first 10 patients in Part B with HER3 expression will have the on-treatment biopsy in Cycle 1 between Days 15 and 21 and the next 10 patients with HER3 expression will have the on treatment biopsy in Cycle 2 between Days 1 and 7. The study team leader will track patient enrollment across multiple sites and track on-treatment biopsy collection. Once the 10th patient (Part B) on-treatment sample is collected and analyzed, an Investigator letter will be sent to the sites that the first 10 patients evaluable tumor requirement criteria have been met and sites are to proceed with the on-treatment biopsy schedule for patients 11-20.

All patients in Part Z will have an on-treatment biopsy in Cycle 2 between Days 1-7 unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor.

Pre-treatment biopsies will be used to determine ER/PR/HER2/HER3 expression for Part A and Part B patients and HER2/HER3 expression for Part Z patients but will not be limited to markers mentioned here. Baseline, on-treatment, and EOT/PD samples will be used to evaluate RNA, protein and/or DNA for gene expression/mutation changes and exploratory protein biomarkers. The status of gene/protein expression including ER/PR/HER2/HER3 by IHC, HER2 amplification by fluorescence in situ hybridization (FISH), DNA/RNA sequencing, HER3 signaling analysis, DNA damaging marker such as γH2AX, immune related markers such as PD-L1, PD-1 CD4, CD8, CD68, CD163 and novel DXd sensitivity and resistance markers may be tested to explore whether these are correlated with the response to treatment. The EOT/PD biopsies are optional for the patient.

If possible, sites should collect pre-treatment, on-treatment, and EOT/PD biopsies from the same tumor lesion. Accessible lesions are defined as tumor lesions that can be biopsied and that are amenable to repeat biopsy. Failure to obtain a sufficient tumor sample after making best efforts to biopsy the tumor will not be considered a protocol deviation.

Biopsies should be obtained through non-significant risk procedures. Sampling should be undertaken by experienced physicians in appropriate settings.

Instructions regarding sample collection, sample handling/storage/processing, and sample shipping are provided in the Laboratory Manual.

7.7.2 Biomarker Blood Samples

Blood samples will be collected for exploratory analysis of circulating tumor DNA (ctDNA) and cell-free RNA (cfRNA) to explore changes in the molecular repertoire of HER3 genes at C1D1 and EOT. Blood samples will be analyzed using next-generation sequencing (NGS) of ctDNA. The clearance (disappearance) and emergence of new gene alterations before and following treatment will be explored.

Circulating tumor DNA (ctDNA) and cfRNA blood samples will be taken at the following time points for **Part A** patients:

- Cycle 1 Day 1 pre-dose for Part A patients
- Cycle 2 between Days 1 and 7 for Part A patients
- EOT visit or at disease progression for Part A and Part B patients

Circulating tumor DNA (ctDNA) blood samples will be taken at the following time points for **Part B** and **Part Z** patients:

- Cycle 1 Day 1 pre-dose for Part B and Part Z patients
- EOT visit or at disease progression for Part B and Part Z patients

Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual.

7.7.3 *BRCA1/BRCA2* mutational status

BRCA1/BRCA2 mutational status should be provided at Screening. If status is unknown, cannot be obtained from archival tissue or a blood sample, or patient refuses to be tested, they can still enroll in the study.

7.7.4 Biosample storage for future analysis

If the patient agrees, the remaining biomarker samples (tumor, blood or other specimen obtained in the study) may be stored for up to 15 years, and/or as per local regulation, and further analyzed to address scientific questions related to study drug(s) and/or relevant cancer indications.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 U3-1402 (patritumab deruxtecan)

Investigational Product	Dosage Form and Strength	Manufacturer
Patritumab deruxtecan	100 mg	Daiichi Sankyo

8.1.1 Labelling, Packaging, and Supply

Patritumab deruxtecan will be supplied by Daiichi Sankyo as vials in cartons labelled as "U3-1402".

The batch number of the study drug should be entered on the eCRF, if applicable.

The immediate packaging will contain a statement to conform with US Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows: "Caution: New Drug - Limited by federal (or United States) law to investigational use."

All study drugs must be kept in a secure, limited access place under appropriate storage conditions. Storage conditions for patritumab deruxtecan are included on the investigational product label and pharmacy manual.

Development Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of Patritumab deruxtecan (U3-1402)

Patritumab deruxtecan (U3-1402) is administered as an 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 patritumab deruxtecan will be infused over approximately 30 minutes on Day 1 of each subsequent cycle (Q3W).

Preparation and administration instructions will be provided in the pharmacy manual.

8.1.3 Precautions and Risks Associated with Patritumab deruxtecan

Precautions and risks are located in the IB.

8.2 Accountability for All Study Drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by Development Innovations or its representatives and regulatory agency inspectors upon request.

Throughout the study and at its completion, Development Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by Development Innovations. Please contact Development Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using RECIST Version 1.1 (see Appendix B). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a Phase II open-label study of patritumab deruxtecan in patients with MBC that will be conducted in 3 parts. Part A will enroll up to 60 patients with HER2- MBC. Part B will enroll an additional 20 patients into each of 2 subgroups that were defined from Part A (based on ER/PR/HER2/HER3 expression) following evaluation of biomarker expression in pre-treatment

biopsy samples or in tissue from a biopsy done within 2 months prior to consent. A total of up to 40 patients will be enrolled into the following 2 Part B subgroups:

- MBC HR+, HER2-, regardless of HER3 expression, post-trastuzumab deruxtecan and/or sacituzumab govitecan therapy
- mTNBC, regardless of HER3 expression, post-sacituzumab govitecan and/or datopotamab deruxtecan therapy

The primary objective of this study is to evaluate overall response rate (ORR) and progression-free survival at 6 months (PFS-6) of single agent patritumab deruxtecan in patients with MBC.

10.2 Sample Size Considerations

Sixty patients will be enrolled into Part A, and the sizes of the biomarker expression-defined subgroups will not be restricted. Evaluation of biomarker expression-defined subgroups to carry forward into Part B will be based on evaluation of overall response rate (ORR), PFS-6, and results from correlative tests.

Patients in the subgroups from Part A that are expanded in Part B will be included in a combined subgroup for presentation (e.g., if 12 ER high/HER-3 high patients are treated in Part A, and that subgroup treats 20 additional patients in Part B, they would be added to the affiliated Part B subgroup for a total of 32 in analysis). Part Z will enroll an additional 21 patients with HER2+ MBC.

PFS-6 will be a binary endpoint with patients surviving progression-free for at least six month considered successes; otherwise, patients will be considered failures (including patients who withdraw from the study prior to six months). The ORR and six-month PFS will be presented with two-sided 95% confidence intervals (CIs) (calculated based on the Clopper-Pearson method). Table 5 below shows the precision of the estimates for the two endpoints across a range of sample sizes and ORR or PFS-6 rates.

Table 5 Projected CIs for ORR and PFS-6

Approximate ORR or PFS-6	n	Percentage (95% CI)†	Width of 95% CI†
0.20	20	0.20 (0.06, 0.44)	0.38
	25	0.20 (0.07, 0.41)	0.34
	30	0.20 (0.08, 0.39)	0.31
	35	0.20 (0.08, 0.37)	0.28
	40	0.20 (0.09, 0.36)	0.27
0.30	20	0.30 (0.12, 0.54)	0.42
	25	0.32 (0.15, 0.54)	0.39
	30	0.30 (0.15, 0.49)	0.35
	35	0.31 (0.17, 0.49)	0.32
	40	0.30 (0.17, 0.47)	0.30
0.40	20	0.40 (0.19, 0.64)	0.45
	25	0.40 (0.21, 0.61)	0.40

Approximate ORR or PFS-6	n	Percentage (95% CI)†	Width of 95% CI†
	30	0.40 (0.23, 0.59)	0.37
	35	0.40 (0.24, 0.58)	0.34
	40	0.40 (0.25, 0.57)	0.32
0.50	20	0.50 (0.27, 0.73)	0.46
	25	0.52 (0.31, 0.72)	0.41
	30	0.50 (0.31, 0.69)	0.37
	35	0.51 (0.34, 0.69)	0.35
	40	0.50 (0.34, 0.66)	0.32

†Based on Clopper-Pearson.

10.3 Analysis Populations

The following analysis populations will be used:

- **Safety Analysis Set** will include all patients who received at least one dose of study treatment. For this study, the FAS and safety analysis set are identical.
- **Full Analysis Set (FAS)** will be comprised of all patients who received at least one dose of study treatment. For this study, the FAS and Safety Analysis Set are identical.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations, and ranges for all continuous measures, will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to event endpoints will be reported using Kaplan-Meier estimates, with 95% CIs for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients who were screened, enrolled, treated, and discontinued the treatment/study for any reasons will be presented overall and also by biomarker-defined subgroups.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Full Analysis Set. Results will be presented overall and by biomarker-defined subgroup.

- Objective Response Rate (ORR), defined as the proportion of patients with confirmed CR or PR (i.e., confirmation at least 4 weeks apart) according to RECIST Version 1.1 criteria (see Appendix B). Patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responders.

- Clinical Benefit Rate (CBR), defined as the proportion of patients with CR, PR or best overall response of SD for ≥ 6 months according to the RECIST v 1.1 criteria.

- Progression Free Survival (PFS) is defined as the time from start of study treatment to the date of event defined as the first documented radiological progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

- Six-month PFS (PFS-6) rate is defined as the proportion of patients who survive progression-free for at least 6 months. Patients who discontinue the study prior to 6 months or do not have post-6 months tumor evaluations will be considered failures.

- Duration of response (DOR) is defined as the duration from the first documented response to the date of progression or death due to any cause. In case a patient does not have progression or die, DoR is censored at the date of last adequate tumor assessment (defined as an assessment of CR, PR or SD). Duration of response analysis will include only responders.

For ORR and PFS-6, estimates and the associated 95% CIs (based on the Clopper-Pearson method) in each biomarker-defined subgroup will be calculated.f

For PFS, Kaplan-Meier curves will be generated, and the median time to event and the associated 95% CIs will be provided.

For DoR, Kaplan-Meier estimates will be generated and descriptive statistics (e.g., number of patients ongoing at time of cutoff, the number of patients with DoR ≥6 months) will be provided.

10.4.3 Safety Analysis

All safety endpoints, including laboratory results, vital signs, and ECG findings, will be summarized for patients in the Safety Analysis Set.

Adverse Events

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy up to 40 days (+ 7 days) after last day of treatment and will be graded according to NCI CTCAE Version 5.0. Serious adverse events starting or worsening after the on-treatment period, if reported as related to the study treatment, are also TEAEs. The AE summary will include only TEAEs.

The AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/about-meddra/) and summarized using system organ class and preferred term overall and by biomarker-defined subgroup for all patients in the Safety Analysis Set. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented overall and by biomarker-defined subgroup.

Clinical Laboratory Tests

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

Abnormal laboratory results will be graded according to NCI CTCAE Version 5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst on-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results ≥ Grade 3 will be listed.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD; https://www.who-umc.org/), and they will be listed and summarized by overall and by biomarker-defined subgroup.

Vital Signs

Descriptive statistics will be provided for the vital sign measurements and changes from baseline by scheduled time of evaluation, including the EOT visit.

Electrocardiogram Analyses

Descriptive statistics will be provided for ECG parameters and changes from baseline, including the EOT visit. In addition, the number and percentage of patients meeting the following criteria will be tabulated for QT and QTcF: ≤450 msec, >450 to ≤480 msec, >480 msec to ≤500 msec, and >500 msec, and change from baseline ≥30 msec and ≥60 msec.

The QT intervals will be corrected for heart rate by Fridericia's formula (QTcF =QT/[RR]1/3).

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur when all patients have had the opportunity to be observed for at least 6 months for ORR and PFS.

10.5.2 Planned Interim Analysis

An interim analysis will be conducted after all patients in Part A have completed 2 tumor assessments or have discontinued from treatment. 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 is delayed. Results from Part A will be used to inform the selection of biomarker-defined subgroups in Part B.

10.5.3 Efficacy Review

No formal efficacy review planned. However, results from Part A will be used to inform the selection of biomarker-defined subgroups in Part B.

10.5.4 Pharmacokinetic and Anti-Drug Antibody Analysis

Plasma concentration-time data will be listed, plotted, and summarized using descriptive statistics at each time point.

PK parameters will be listed and summarized using descriptive statistics.

The number and percentage of subjects who have a positive ADA result will be summarized with regards to: baseline prevalence of ADA (prior to first dose administration) – if applicable, post-baseline incidence of ADA (both total and in subjects with positive result at baseline), treatment-emergent incidence of ADA (positive post-baseline result where baseline result was negative or missing or ADA titer increased following positive baseline result).

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology and clinical chemistry laboratory findings, vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Development Innovations Safety Department (see Section 11.1.5). It is Development Innovations' responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of each IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization of at least 24 hours or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered "serious." Seriousness serves as the guide for defining regulatory reporting obligations and is based on a patient/event outcome or an action usually associated

with events that pose a threat to a patient's life or vital functions. For example, nausea that persists for several hours may be considered "severe" nausea but may not be considered an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. "Severity" and "seriousness" should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which means any AE caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5.0, and changes will be documented.

If the AE is serious, it should be reported immediately to Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment and/or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs, regardless of seriousness or relationship to patritumab deruxtecan treatment (called study treatment), spanning from the start of study treatment until 40 calendar days (+7 days) after discontinuation or completion of study treatment as defined by the clinical study for that patient

after his/her last dose of study drug, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies is/are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

After 40 days after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory tests, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as "serious" require expeditious handling and reporting to the Development Innovations Safety Department in order to comply with regulatory requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 40-day follow-up period after the last study treatment. **The Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE Report Form should be sent to the Development Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

Sarah Cannon Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Development Innovations Safety Department as soon as it is available; these reports should also be submitted using the Development Innovations SAE Report Form.

11.2.1 Investigator Reporting After Study Discontinuation

Forty days after completing protocol-specific treatment or study discontinuation, treatment-related AEs, SAEs, or deaths determined by the Investigator as treatment-related are to be reported directly to the Sponsor (Development Innovations).

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of an appropriate method (e.g., as per RECIST criteria for solid tumors; see Appendix B), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should be recorded only once on the SAE Report Form and/or the AE eCRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form and/or AE eCRF.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "End of Study" eCRF. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" ("death, cause unknown") on the AE eCRF. During post-study survival follow-up, deaths attributed to progression of disease will be recorded on the "Follow-up Summary" and "Death Page" eCRFs.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in a hospitalization of >24 hours or prolongation of a pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care, or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form which is a paper report form, not available within the eCRF should be completed and faxed to the Development Innovations Safety Department. The Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria and should therefore be expeditiously reported as an SAE using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Patritumab deruxtecan Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Development Innovations Safety Department no later than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of patritumab deruxtecan, see the IB.

11.4 Protocol-Defined Adverse Events of Special Interest

For the patritumab deruxtecan clinical program, based on the available pre-clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, the following events are considered to be AESIs, and will need to be reported expeditiously (see Section 11.1.5). These events include the following:

- Interstitial lung disease/pneumonitis
- Elevations of aminotransferases and bilirubin suggestive of Potential Hy's Law

11.4.1 Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for patritumab deruxtecan is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be

brought for adjudication. This data collection will be triggered for adverse events reported using MedDRA preferred terms (PTs) from the current ILD Standard MedDRA Query (SMQ) and the PTs of acute respiratory failure and respiratory failure.

11.4.2 Elevations of Aminotransferase(s) and Bilirubin

All hepatic events (serious, non-serious, and clinical laboratory results) which meet 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, should be reported as an AE (serious or non-serious) and as an AESI to closely monitor potential Hy's law patients, 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.

Such events should be reported within 24 hours of Investigator's awareness of the event with the Investigator's assessment of seriousness, causality, and a detailed narrative and confirmed with repeated laboratory assessment(s).

11.5 Funding Partner Serious Adverse Event Reporting Requirements

The Development Innovations Safety Department will forward SAE information to Daiichi Sankyo Safety Department, Cognizant_book-in@dsi.com, within 7 days for Fatal-Life Threatening SUSARS and 15 days for all other SAEs or AESIs on CIOMS I form Development Innovations for which is acceptable by its IRB and the FDA.

Development Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Council for Harmonisation (ICH) guidelines and FDA regulations.

11.5.1 Sponsor Assessment of Unexpected

The Sponsor is responsible for assessing an AE or suspected AE as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert [USPI])
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug or that occur with members of the drug class, but have not previously been observed under investigation.

When applicable, a UAE may also apply to an event that is not listed in the current USPI or to an event that may be mentioned in the USPI but differs from the event because of greater severity or specificity.

Known as suspected unexpected serious adverse reactions (SUSARs), these events suspected (by the Investigator or Sponsor) to be related to the study drug are unexpected (not listed in the IB or USPI) and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (for fatal or life-threatening events) or 15 days (for all serious

events) or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

11.5.2 Funding Partner Reporting for Clinical Studies under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Development Innovations Safety Department must also be distributed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply:

Daiichi Sankyo Safety Department

Safety Dept. Email: cspv_aggregatereport@dsi.com

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet Sponsor, Good Clinical Practice (GCP), ICH, and, when appropriate, regulatory guidelines.

12.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by Development Innovations or its representative(s), government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, eCRFs). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of Development Innovations, Source Document Verification may be performed on partial or all data items as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB(s), and/or Development Innovations or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of GCP outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulation (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients, and documentation

evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for patritumab deruxtecan will be prepared by the Sponsor or its representative as required for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure that all legal aspects are covered and that approval of the appropriate regulatory bodies has been obtained prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happens only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this study

- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information and that if the information is disclosed, the information may no longer be protected by federal or state privacy laws
- That the information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR, it is a requirement that the Investigator and institution permit authorized representatives of Development Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF or other documents submitted to Development Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Development Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Development Innovations database and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, Development Innovations shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by Development Innovations. All amendments require review and approval of all pharmaceutical companies providing funding for the study and of the Principal Investigator supporting the study. The written amendment must be reviewed and approved by Development Innovations and submitted to the IRB at the Investigator's facility for the board's approval.

Items requiring a protocol amendment approved by the IRB of record for the Investigator's facility and the FDA or other regulatory authorities include but are not limited to the following:

- Change to study design
- Risk to patients
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of an Investigator.

The amendment will be submitted formally to the IRB and the FDA or other regulatory authorities by Development Innovations.

It should be further noted that if an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patients' consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd. Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include but are not limited to the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by those laboratories
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved ICF containing permission for audit by representatives of Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)

- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patients' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patients' eCRF data are obtained. These can include but are not limited to hospital records, clinical and office charts, laboratory results, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, and correspondence.

The Principal Investigator and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, the protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain the Principal Investigator name, the date drug shipped/received, and the date, quantity, and batch/code or lot number for the identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and readily available.

Development Innovations shall maintain adequate investigational product and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21 CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA or, in the event that the marketing application

has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRF records and medical records), all original signed ICFs, copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, Development Innovations must be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Development Innovations. The Investigator must obtain Development Innovations' written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by Development Innovations throughout the study and will be held by Development Innovations at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language except for patient questionnaires for non-English speaking patients and should be kept current to enable Development Innovations to review the patients' status throughout the course of the study. In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Development Innovations and be replaced instead with the patient number and other identifier (i.e., patient initials) as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the test was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF have been assessed. Each completed eCRF will be signed and dated by the Principal Investigator once all data for that patient are final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the study design, the analysis or interpretation of data, or the drafting and/or critical revision of any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at the research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data have been received, the Investigator shall have the right to publish his/her results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract, or other written or oral material that describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Development Innovations confidential information from all publications.

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16. APPENDICES

Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
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 (e.g., 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

Appendix B: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

This appendix details the general implementation of RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1) guidelines (Eisenhauer et al 2009) for the study with regards to Investigator assessment of tumor burden.

Definition of Measurable and Non-measurable Lesions

Only patients with at least one measurable tumor lesion or malignant lymph node that can be accurately assessed at baseline should be included in the study. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable:

Tumor lesions: To be considered measurable disease, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography/MRI (CT/MRI scan slice thickness/interval no greater than 5 mm)

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 follow-up, only the short axis will be measured and followed.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline).
- Truly non-measurable lesions include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions or lesions subjected to other local-regional therapy.

Special Consideration Regarding Lesion Measurability:

Bone lesions

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

Cystic lesions

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Definition of Target and Non-Target Lesions

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all involved organs should be identified as target lesions at baseline. Pathological lymph 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. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), 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.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are selected as measurable lesions, only the short axis is added into the sum, even if the nodes regress to below 10 mm in the study. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Special cases:

- If a target lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- 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 to not overstate progression should it be based on increase in size of the nodes.
- If a target lesion splits into two or more parts, then record the sum of the diameters of those parts. If two or more target lesions merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

Non-target lesions:

All other lesions (or sites of disease) including pathological lymph nodes (those with short axis ≥10 mm but <15 mm) should be identified as non-target lesions (NTLs) and should also be recorded at baseline. Nodes that have a short axis <10 mm are considered non-pathological and

should not be recorded or followed. In addition, it is possible to record multiple NTLs involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

CT, MRI: CT scanning with IV contrast 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. If IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray. MRI is also acceptable and can be used when CT is not feasible or is medically contraindicated.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examination can, however, be used to identify the presence of new lesions. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is required.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques alone will not be used for objective tumor response measurements.

FDG-PET: FDG-PET scans may be used as a method for identifying new lesions in the assessment of progression, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion by CT/MRI at the same visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions by CT/MRI then follow-up CT/MRI assessments

should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumor response evaluation

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

Evaluation of target lesions:

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or nadir (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.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable. Note: If the sum of diameters of assessed lesions meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits.
Progression (PD)	Unequivocal progression of existing non-target lesions indicative of a substantial worsening in non-target disease. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of

therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New lesions: The presence of one or more new lesions is assessed as disease progression. A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Evaluation of overall response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	Non-CR/Non-PD
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (relevant when no target lesions/non-target lesions at baseline).

Special notes on response evaluation

Missing assessments and non-evaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Symptomatic progression: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD 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 treatment.

Confirmation of response: Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

References

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Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 7 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Male Partner Sterilization When there is appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 7months after the last dose of the study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

Unacceptable Contraception Methods for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breast-feeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the Development Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 6 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the **Development Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as follows:

- Women are considered post-menopausal and not of childbearing potential if they have had continuous 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
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.	Objective evidence of minimal cardiovascular disease.
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.	Objective evidence of moderately severe cardiovascular disease.
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.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

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

Due to the potential impact of SARS-CoV-2, i.e. COVID-19, on patient safety, the Sponsor recommends the following dose modification and management plan for patients with confirmed or suspected SARS-CoV-2 while being treated with patritumab deruxtecan. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate SARS-CoV-2.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

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

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

- If SARS-CoV-2 is ruled out, follow dose modification and management guidance as outlined in Table 4.
- If SARS-CoV-2 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 6 below and manage SARS-CoV-2 per local guidance until recovery of SARS-CoV-2. SARS-CoV-2 recovery is defined as no signs/symptoms of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 6 SARS-CoV-2 Dose Modification Criteria

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

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

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

In addition to the recommendations outlined in Table 6, Investigators may consider dose modifications of the study drug according to the patient's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD, manage per protocol ILD management guideline (Table 4).

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.3.2.
  - If treatment is absolutely required for SARS-CoV-2, patritumab deruxtecan must be interrupted.
  - If administered, then a washout period of 14 days is required before resumption of patritumab deruxtecan

SARS-CoV-2 Assessment(s)

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a patient presents to the clinic with symptoms suggestive of SARS-CoV-2, the clinic should follow its standard of care practice.

Appendix F: Summaries of Changes from Previous BRE 354 Protocol Amendments

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	17 November 2020

Additions to the text are **bolded**, and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global Changes made from FDA review

Section 3.2 Exclusion Criteria and Synopsis:

- amended #1 and #2 to clarify –

1. Treatment with any of the following:
   - ~~Prior treatment with any anti HER2 therapy in any setting~~

2. Patients with HER2-positive breast cancer per ASCO-CAP guidelines

Section 7.7.3 *BRCA1/BRCA2* mutational status and **Schedule of Assessments:**

- Amended to clarify ***BRCA1/BRCA2* mutational status should be provided at Screening. If status is unknown, cannot be obtained from archival tissue or a blood sample, or patient refuses to be tested, they can still enroll in the study**.

Additions to the text are **bolded**, and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Schedule of Assessments and Section 7 Study Assessments and Evaluations –

Footnote b and Section 7.2 Screening – clarified that ECGs should be performed **≤28** days prior to initiation of treatment

Footnote f and Section 7.2 Screening – clarified that ophthalmologic exams will take place **≤28** days prior to Cycle 1 Day 1 and removed Landolt exam

Footnote g – clarified that **on days that ECGs are taken, vital signs should be taken after the patient has been resting in the supine position prior to ECGs and administration of treatment**.

Footnote j and Section 7.2 Screening – amended to clarify that HCO_3 **or CO_2** can be collected

Footnote l – clarified that blood samples are to be taken for **cfRNA pre-dose on Cycle 1 Day 1**

Footnote m and Section 7.7.1.1 – clarified that **if medically feasible**, all patients will have a pre-treatment biopsy. **If it is not medically feasible to provide a pre-treatment biopsy, archival tissue** ~~unless archived tissue~~ that was taken within 2 months of treatment **should be provided** ~~starting is available~~.

Footnote p and Section 7.7.1.1 – clarified the following:

- **The study team leader will track patient enrolment across multiple sites and track on-treatment biopsy collection.**
- **Once the 10th patient on-treatment sample is collected and analyzed, an Investigator letter will be sent to the sites that the first 10 patients evaluable tumor requirement criteria have been met and sites are to proceed with the on-treatment biopsy schedule for patients 11-20.**

Section 1.1.1 HER3 was amended to clarify that **- Receptor tyrosine-protein kinase erbB-3 (HER3) protein that is encoded by the *ERBB3*** oncogene is **highly** expressed ~~overexpressed~~ in many cancers, including breast cancer (Lee-Hoeflich et al. 2008).

Section 3.2 Exclusion Criteria and Synopsis – amended to clarify that

10) Any of the following cardiac criteria currently or within the last 6 months:

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age ~~or any concomitant medication known to prolong the QT interval~~

Section 5 Study Design and Synopsis were amended to clarify that all enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done within 2 months prior to consent) to determine if patients with particular biomarker expression (ER/PR/HER2/HER3) show

~~preliminary~~ **response to treatment after all patients in Part A have completed 2 tumor assessments** ~~efficacy after an analysis is performed at 24 weeks.~~

Section 5.3.2 Prohibited Concomitant Medications amended to clarify that –

- Radiotherapy to the thorax is also prohibited **once a patient is screened and enrolled into the study**. ~~See Section 5.3.1 above for exceptions on palliative radiation.~~

Section 7.5 SARS-CoV-2

~~If patient provides consent, samples should be collected prior to study drug infusion at Cycle 1 Day 1, Cycle 5 Day 1, and every 4 cycles thereafter (Cycle 9, Cycle 13, etc.).~~ For patients with suspected or confirmed SARS-CoV-2 infections, follow the dose modifications in Appendix E. ~~If the patient consents, the remaining serum samples will also be stored for future analysis.~~

Section 7.6 Pharmacokinetic and Anti-drug Antibody Assessments updated the language for ADA assessments to state - **The ADA testing will be performed using a validated ADA assay following tiered assay steps including Screening, confirmatory as well as titer determination. If ADA is confirmed, further analysis to profile immunogenicity of U3-1402 (e.g., neutralizing antibody assay) will be conducted. Serum concentrations of intact U3-1402 (patritumab deruxtecan) ADC, total anti-HER3 antibody and released payload MAAA-1181a may also be measured using the same ADA samples for purpose of ADA assessment.** ~~Immunogenicity will be assessed through characterization of prevalence, incidence and titer of ADA. The number and percentage of subjects will be calculated for ADA (presence and absence) before and after the start of study drug administration. Positive ADA samples will be stored for possible further analysis for characterization of immunogenicity.~~

Section 7.7.1 Biomarker tissue samples was amended to clarify that pre-treatment biopsies will be used to determine ER/PR/HER2/HER3 expression **but will not be limited to markers mentioned here**. Baseline, on-treatment, and EOT/PD samples will be used to evaluate RNA, protein and/or DNA for gene expression/mutation changes and exploratory protein biomarkers. **The status of gene/protein expression including ER/PR/HER2/HER3 by immunohistochemistry (IHC), HER2 amplification by fluorescence in situ hybridization (FISH), RNA sequencing, HER3 signaling analysis, DNA damaging marker such as γH2AX, immune related markers such as PD-L1, PD-1 CD4, CD8, CD68, CD163 and novel DXd sensitivity and resistance markers may be tested to explore whether these are correlated with the response to treatment**. The EOT/PD biopsies are optional for the patient.

Section 7.7.4 – Biosample storage for future analysis added to clarify that **-If the subject agrees, the remaining biomarker samples (tumor, blood or other specimen obtained in the study) may be stored for up to 15 years, and/or as per local regulation, and further analyzed to address scientific questions related to study drug(s) and/or relevant cancer indications.**

Section 10.5.2 Planned Interim Analysis – clarified that **an interim analysis will be conducted after all patients in Part A have completed 2 tumor assessments or have discontinued from treatment. 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 is delayed. Results** from Part A will be used to inform the selection of biomarker-defined subgroups in Part B.

Section 10.5.4 **Pharmacokinetic and Anti-drug Antibody Analysis** clarified that **serum** concentration-time data will be listed, plotted, and summarized using descriptive statistics at each time point.

Also, updated ADA analysis language to state the following - **The ADA prevalence, which is the percentage of subjects who were ADA positive at any time point (baseline or post-baseline), will be summarized. The ADA incidence will also be reported, which is the proportion of subjects having treatment-emergent ADA during the study period. Treatment-emergent ADA includes subjects who were ADA negative at baseline and became ADA positive post-baseline (treatment-induced ADA), subjects who were ADA positive at baseline and post-baseline but had an increase in ADA titer of at least 4-fold from baseline to post-baseline (treatment-boosted ADA), and subjects who had missing ADA data at baseline and were ADA positive post-baseline.**

Appendix E Related to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was amended as follows**:**

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a patient presents to the clinic with symptoms suggestive of SARS-CoV-2, **the clinic should follow its standards of care practice**. ~~but the real-time RT-PCR test is not available at the site, a nasopharyngeal swab or saliva sample kit will be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory~~.

~~Serum samples will be used for SARS-CoV-2 testing from each patient who provides consent. Samples will be collected prior to the study drug infusion, shipped to a central laboratory, and stored there until the tests become available.~~

~~If the patient consents, the remaining serum samples will also be stored for future analysis.~~

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

Additions to the text are **bolded**, and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global Changes

Section 1.1.5 Study Rationale was amended to add - **As noted above, HER3 is an important dimerization partner for HER2 and this heterodimerization leads to oncogenic signaling via the PI3K/Akt and the MAPK/ERK and other pathways. Trastuzumab deruxtecan (T-DXd) is a HER2-targeted ADC with a topoisomerase 1 inhibitor as the payload. T-DXd has revolutionized the treatment of HER2+ MBC by significantly prolonging PFS in heavily pretreated and 3L HER2+ MBC (Modi et al. 2020; Cortes et al. 2022).**

There are multiple ADCs in development against novel targets like Trop 2, Nectin 4 and HER3 with either similar or novel payloads. The efficacy of ADCs with a similar payload directed against a novel target is unknown; hence it is of interest to evaluate U3-1402, a HER3-targeted ADC with topoisomerase 1 inhibitor as the payload, in a patient population whose disease has progressed on T-DXd.

Section 2 Study Objectives and endpoints, Section 10 Statistical Considerations and Synopsis were amended to add the definition for ORR and PFS-6 to the study endpoints as follows –

- ORR **defined as the proportion of patients with confirmed CR or PR (i.e., confirmation at least 4 weeks apart)** and 6-month PFS **defined as the proportion of patients who survive progression-free for at least 6 months per** RECIST version (v) 1.1.

To add the following objectives and endpoints –

- **To estimate the clinical benefit rate (CBR) in patients with MBC. CBR defined as the proportion of patients with CR, PR or best overall response of SD for ≥ 6 months according to the RECIST v 1.1 criteria.**
- **To evaluate ORR and PFS-6 of single agent U3-1402 in patients with HER2+ MBC after progression on trastuzumab deruxtecan (T-DXd). ORR defined as the proportion of patients with confirmed CR or PR (i.e., confirmation at least 4 weeks apart) and 6-month PFS as defined by defined as the proportion of patients who survive progression-free for at least 6 months per RECIST version (v) 1.1**.

And to remove cfRNA as an exploratory endpoint and clarify that the serum concentration of U3-1402 to be evaluated includes **antibody conjugated MAAA-1181a**, **total anti-HER3 antibody** ~~intact ADC~~, and MAAA-1181a.

Section 3.1.1 Inclusion criteria for Part A and B (HER2-negative) and Part Z (HER2-positive) cohorts was amended to add criteria for Part Z patients –

> 6. **Part Z patients only should have documented HER2-positive expression as per American Society of Clinical Oncology – College of American Pathologists guidelines based on local testing.**

7. **Part Z patients only should have had prior treatment with at least 2 anti-HER2 therapies, 1 of which must be T-DXd. These patients must have experienced disease progression after receiving T-DXd**.

8. Part Z patients only can have had up to 6 prior lines of therapy in the metastatic setting.

Section 3.2.1 Exclusion criteria for Part A and B (HER2-negative) and Part Z (HER2-positive) cohorts was amended to clarify that –

1. Treatment with any of the following:

- Any systemic anti-cancer chemotherapy, small molecule, biologic, hormonal agent, or immune checkpoint inhibitor therapy from a previous treatment regimen or clinical study within 21 days prior to the first dose of U3-1402.
- Prior treatment with any HER3 targeting agent
- ~~Prior treatment with an ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g. DS-8201a, DS-1062a, and DS-7300a)~~
- Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug treatment
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug treatment, or palliative radiation therapy within 2 weeks of the first dose of study drug treatment
- Chloroquine /hydroxychloroquine ≤14 days prior to the first dose of study drug treatment.

2. ~~Patients with HER2-positive breast cancer per ASCO-CAP guidelines~~

6 Leptomeningeal metastases or ~~spinal cord compression due to disease~~ **evidence of spinal cord compression or brain metastases, defined as being clinically active and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Patients with clinically inactive or treated brain metastases who are asymptomatic (i.e., without neurologic signs or symptoms and do not require treatment with corticosteroids or anticonvulsants) may be included in the study. Patients must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1**.

9. **Uncontrolled or significant cardiovascular disorder prior to Cycle 1 Day 1, including** ~~Any of the following cardiac criteria currently or within the last 6 months~~:

- Mean resting corrected QT interval using Fridericia's formula (QTcF) prolongation to >470 ms for females and >450 ms for males in three successive screening measurements
- Patients with a left ventricular ejection fraction (LVEF) <50%
- **Resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).**
- **Documented myocardial infarction within 6 months.**
- ~~Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting electrocardiograms (ECGs), e.g., complete left bundle branch block, third-degree heart block~~

- Congestive heart failure (New York Heart Association ≥ Grade 2 [Appendix D]) **within 28 days**
- ~~Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age~~

11 **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. Patients who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.**

Section 3.2.2 <u>Additional exclusion criteria only for Part A and B (HER2-negative) cohorts:</u>

15 Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor (e.g., T-DXd, DS-1062a, and DS-7300a)

16 Patients with HER2+ breast cancer per ASCO-CAP guidelines

<u>Section 3.2.3 Additional exclusion criteria only for Part Z (HER2-positive) cohort:</u>

17 Treatment with any of the following:

- **Prior treatment with an antibody drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor except T-DXd**
- **Prior treatment with T-DXd within 4 weeks prior to the first dose of U3-1402**

18 Uncontrolled or significant cardiovascular disease, including history of myocardial infarction within 6 months before enrollment

19 A severe reaction or severe tolerability issues that necessitated stopping treatment with T-DXd

20 Any unresolved toxicities from prior therapy with T-DXd.

Section 5 Study Design, Section 10 Statistical Considerations and Synopsis were amended to add an additional cohort, Part Z.

This is a Phase II open-label study of U3-1402 in patients with MBC ~~who have received no prior anti-HER2 therapy. This study~~ **and** will be conducted in ~~2~~ **3** parts. Part A will enroll up to 60 patients with **HER2-** MBC…

Part B will enroll an additional 20 patients in each subgroup that will be defined from Part A (based on ER/PR/HER2/HER3 expression). Patients will be identified by prospective evaluation of biomarker expression in pre-treatment biopsy samples or in tissue from a biopsy done within 2 months prior to **consent**~~starting treatment~~. A total of up to **40**~~60~~ patients (i.e., maximum of **2**~~3~~ subgroups) will be enrolled in Part B.

Part Z will enroll an additional 21 patients with HER2+ MBC. All enrolled patients will undergo pre-treatment biopsies (unless a biopsy was done while on or after T-DXd therapy within 3 months prior to consent and tissue from this biopsy is available) for biomarker analysis. Blood samples and on-treatment biopsy samples will be collected from all patients for additional correlative analyses, unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor. PK and ADA blood samples will be collected from all patients.

Section 6.2 Dose Modifications due to Non-Hematologic Toxicity, Table 4 was amended to clarify that for nausea and vomiting: **premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK-1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV)**. ~~Based on currently available clinical safety data for U3-1402, it is recommended that patients 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 patients with an antiemetic regimen for subsequent use as needed.~~

Section 7.7.1.1 Fresh biopsies and footnote 'm' clarified that if medically feasible, all patients will have a pre-treatment biopsy. If it is not medically feasible to provide a pre-treatment biopsy, archival **biopsy** tissue that was taken **2 months prior to consent in Part A and Part B and 3 months prior to consent in Part Z** should be provided.

Section 7.7.1.1 Fresh biopsies and footnote 'v' clarified that **all patients in Part Z will have an on-treatment biopsy in Cycle 2 between Days 1-7 unless not technically feasible or unsafe for the patient after discussion with the Medical Monitor.**

Section 7.7.1.1 Fresh biopsies was amended to clarify that pre-treatment biopsies will be used to determine ER/PR/HER2/HER3 expression **for Part A and Part B patients** and HER2/HER3 expression **for Part Z patients** but will not be limited to markers mentioned here.

Section 7.7.2 Biomarker blood samples and footnote 'l' clarified that **patients in Part B and Part Z will have ctDNA blood samples taken predose on Cycle 1 Day 1 and at EOT**.

Section 7.7.2 Biomarker blood samples and footnote 'p' clarified that patients in Part B will not have cfRNA blood samples taken.

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Synopsis and Section 3.1.1 Inclusion criteria for Part**s** A and B (HER2-negative) and Part Z (HER2-positive) cohorts:

5 **Parts A and B (HER2-negative, ER-positive) patients only:** HR+ breast cancer patients should have received prior treatment with endocrine therapy +CDK 4/6 inhibitor. No limit to prior endocrine therapy regimens, but no more than 2 prior chemotherapy regimens in the metastatic setting.

~~8 Part Z patients only can have had up to 6 prior lines of therapy in the metastatic setting.~~

Section 6 Dose modifications

Doses of U3-1402 will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary, they will be permanent for the remainder of the treatment. Any patient requiring a toxicity-related dose delay of more than **18 weeks (126 days) from the last U3-1402 dose**~~28 days from the intended day of the next scheduled dose~~ must be discontinued from the study, unless discussed with the Medical Monitor for extenuating circumstances. **During the time of any dose delay, scheduled CT/MRI scans should continue as per protocol, and subjects should fulfill all of the following criteria:**

- **Study drug may be resumed with confirmation of continued benefit per RECIST 1.1. Scans should be performed at the frequency defined per protocol while the drug is being held.**
- **At minimum, 1 restaging scan must be done within 6 weeks prior to restarting the study drug.**
- **Investigational product is restarted within the guidance of the treatment management guidelines for U3-1402, if appropriate.**
- **No prohibited concomitant medications have been administered since the last dose of U3-1402.**