A Phase 1b/2, First-in-Human, Dose Escalation and Expansion Study of XMT-1536 In Patients with Solid Tumors Likely to Express NaPi2b

Sponsor Protocol ID:	MER-XMT-1536-1
Final Date, Version:	20 April 2022, Version 10.0
Phase:	1b (First-in-human) / 2
IND Number:	135,571
EUDRACT Number:	2020-000630-17
Investigational Product(s):	XMT-1536 Antibody Drug Conjugate
Marketed Study Drug(s):	Not Applicable
Medical Monitor:	Study Medical Monitor information can be found on the Contact List
Sponsor:	Mersana Therapeutics, Inc. 840 Memorial Drive Cambridge, MA, USA - 02139
Sponsor Contact:	Leslie DeMars, MD, Executive Medical Director, Clinical Development Mersana Therapeutics, Inc.
Amendment(s):	Supersedes Versions: 02 September 2021-Version 9.0 (Global), 9.2 (FIN), 9.1 (CZ) 31 January 2021 – Version 8.1 (Global), 8.2 (SWE), and 8.3 (NOR) 03 November 2020 – Version 7.1 14 August 2020 – Version 7.0 20 November 2019 - Version 6.0 18 March 2020 - Version 6.1, EU only 28 April 2020 - Version 6.2, GOG only 12 October 2020 - Version 6.3, United Kingdom 13 December 2020 – Version 6.4, Germany 11 November 2019 - Version 5.2, Canada only 12 July 2019 - Version 5.1, United States 13 June 2019 - Version 5.0, United States 18 February 2019 - Version 4.0, United States 13 August 2018 - Version 3.0, United States 19 October 2018 - Version 2.0, United States
GOG	3048
ENGOT	ova67/AGO

SPONSOR AGREEMENT

My signature below confirms that this protocol is written to comply with the U.S. Code of Federal Regulations applicable to clinical studies (45 CFR and 21 CFR including parts 50 and 56 regarding informed consent and Institutional Review Board Regulations and U.S. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessments.) Further, I consent to ensure to the best of my ability that Mersana Therapeutics, Inc., and all designees who perform management, reporting, and data handling functions of this study on behalf of Mersana, will abide by this protocol and associated governance documents. All pivotal non-clinical and clinical data presented in support of clinical trial applications for this protocol (MER-XMT-1536-1) have been produced in accordance with the U.S. Code of Federal Regulations Title 21 Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies, Organization for Economic Co-operation and Development (OECD) Principles of GLP and ICH E6 Guideline on GCP.

20 Apr 2022

Leslie DeMars, MD, Executive Medical Director, Clinical Development
Mersana Therapeutics, Inc.

Date

INVESTIGATOR AGREEMENT

My signature below constitutes that I have read and understood the intentions and logistics involved with conducting this protocol. I consent to provide assurance that this trial will be conducted in strict accord with the provisions of the protocol, the Investigators Brochure, and applicable U.S federal and local regulations and ICH guidelines. Further, I will also ensure that:

- All applicable regional regulatory approvals are received prior to trial conduct, for example from the governing Institutional Review Board or Independent Ethics Committee;
- Local stipulations will be followed such as, but not limited to practices and policies of local hospital and medical review boards;
- I will personally conduct or oversee the conduct of this trial and ensure that all staff to whom study responsibilities are delegated are properly credentialed and trained to perform these tasks.

_____ _____

Principal Investigator Signature Date

_____

Principal Investigator Name

AMENDMENT SUMMARY OF CHANGES

This table provides a summary of the changes implemented as of Amendment 10. The main changes to this amendment include modification of the UPLIFT cohort ITT analysis population to reflect the starting dose of 36 mg/m^2 q4wk (capped at a BSA of 2.2 m^2), revisions to the dose modification plan, and addition of a PK/ECG timepoint in the QTc sub-study. Given the nature of these changes, this amendment is considered substantial.

Table 1: Amendment 10 Summary of Changes

Section #, Name	Change	Rationale
Title page, sponsor agreement	Sponsor contact information changed.	New Mersana Medical Director assigned
1.1, Synopsis, Investigational product and mode of administration	Product lot numbers removed from investigational product dosage description.	Removal of duplicate information as this is provided in the pharmacy manuals.
1.2, Schedule of Events	Table 1: Window for ECGs at screening revised to 0-28 days (vs. 0-14 days).	Reduction of burden on participants and sites as remaining assessments deemed sufficient data for pop PK.
	Table 2 (SoE for Annotation for EXP and UPLIFT) updated	Clarification of protocol instructions and correction of errors.
	Cycle 3, Day 2 lab visit removed.	Based on available data, data collection for the specific time point deemed unnecessary
1.3, Schedule events QTc Sub-study	Added Cycle 1 D5 (±1 day) timepoint.	Regulatory agency request.
1.4, Study Schema	Figure note added to indicate the UPLIFT sample size represents the planned participants enrolling at the starting dose of 36 mg/m^2	Analysis population refined to clarify that only those at updated starting dose of 36 mg/m^2 will be included.
2.5.7., Rationale for Correlative Studies	Language on optional EOT biopsies revised to indicate only for DES & EXP.	Enhanced clarity of protocol instructions and correction of errors.
2.6.2, Clinical Risk Assessment	Reference statement to the IB added.	Provide direction on the location of updated safety information.
4.1., Overall Study Design 1.1., Synopsis, Methodology	Sentence added to the Expansion description to indicate EXP will end once all patients have completed study treatment and sufficient data have been collected for the key study endpoints.	Enhanced clarity of study timeline.
4.3.4, Ocular	Additional information added to provide	Clarifies the medical personnel

Section #, Name	Change	Rationale
Examinations and Schedule of Events	revision from ophthalmologist requirement to medically qualified personnel for conduct of exams. Footnote I revised according to above change.	appropriate to conduct ocular exams.
4.6., Dose Reduction, Modification, and Delay Criteria After Completion of Cycle 1 and Beyond	Revisions to the dose modification plan for: Grade 3 ALT Elevation Grade 2 ILD/Pneumonitis Grade 2 and Grade 3 Proteinuria Grade 3 Ocular Toxicity Grade 3 and Grade 4 Other Related AEs	Following discussion with a regulatory agency to provide monitoring and management of safety events.
1.1., Synopsis, Ovarian Cancer Eligibility Criteria for UPLIFT, General Exclusion Criteria Generic to all Segments of the Study 5.3.3, Selection and Withdrawal of subjects	Ovarian Cancer Eligibility Criteria for UPLIFT: Inclusion #3 revised to provide explicit instructions for patients in Finland to have exhausted other treatment options for HGSOC. General Exclusion Criteria Generic to all Segments of the Study: Addition of inclusion #15 to provide explicit instructions for vaccine windows for Czech Republic.	Updated to be consistent with regulatory requirements in participating countries. Please see Appendix 8 for additional rationale.
1.1., Synopsis, 5.3.2., General Inclusion and Exclusion Criteria Generic to all Segments of the Study 5.3.4., Eligibility Criteria for QTc Sub-study 6.3.1., Strong inducers and inducers to Cytochrome P450 Appendix 5., Strong Inhibitors and Inducers of Cytochrome P450	General Exclusion criteria #13 revised from Cytochrome P450 to Cytochrome P450 3A.	Update across the program based on the result of a nonclinical study
6.3.5, Vaccinations	Section updated to include Czech Republic specific instructions to restrict patients	Updated to be consistent with regulatory requirements in

Section #, Name	Change	Rationale
	from receiving live vaccinations consistent with Exclusion #15.	participating countries. Please see Appendix 8 for additional rationale.
7., Study Drug Materials and Management	Study drug preparation language revised to align with Pharmacy Manual and Investigator's Brochure.	Revised for clarity.
1.1., Synopsis, Objectives (UPLIFT) 11., Statistics	Revised UPLIFT cohort ITT Population, ITT-NaPi2b Positive Population, and Per Protocol Population to restrict to patients with a starting dose of 36 mg/m^2 q4wk (capped at a BSA of 2.2 m^2) only.	Updated to reflect that the revised efficacy analysis populations will be based on the 36 mg/m^2 starting dose regimen.
11.4.2.1 Definition of Efficacy Endpoints	Revised definition of DCR for UPLIFT exploratory analysis to remove requirement for SD to be maintained for at least 4 months after initiation of study treatment.	Updated for consistency with DES and EXP definition of DCR.
11.4.3.5 Additional Analyses	Revised additional exploratory analyses to exclude analysis of ORR using simple logistic regression models.	Updated to focus exploratory subgroup analyses on descriptive summaries.
Appendix 1, AE: Definitions and Procedures for Recording, Evaluating, Follow-up, and reporting	Section text revised to indicate that SAE forms (in addition to eCRFs) can be used as a record method for relevant AE/SAE information Table 26: SAE Reporting to the Sponsor of Designee via an Electronic Data Collection Tool removed	Mersana decision to update AE reporting guidelines to improve accuracy of reporting among sites

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Mersana Therapeutics, Inc.	
Name of Investigational Product: XMT-1536 - Upifitamab rilsodotin Antibody Drug Conjugate (ADC)	**Country(ies) of Study:** Dose Escalation: United States Expansion and UPLIFT: Global
Name of Active Ingredient(s): XMT-1536 Antibody Drug Conjugate	**Protocol ID:** MER-XMT-1536-1-version 10.0 (Global) GOG: 3048 ENGOT: ova67/AGO
Title of Study: A Phase 1b/2, First-in-Human, Dose Escalation and Expansion Study of XMT-1536 In Patients with Solid Tumors Likely to Express NaPi2b	
Study center(s): Three to 7 centers in Dose Escalation; Approximately 140 global centers for the Expansion and UPLIFT segments.	
Investigators: Multi-center	
Study period (years): First patient enrolled: December 2017 Primary Completion Date: 30 April 2023 Study Completion Date: 31 December 2024	**Clinical Phase:** 1b/2, First-in-Human

Methodology:

This trial is an open label, multi-center study of XMT-1536 administered as an intravenous infusion once every 28 days (q28d). This study is comprised of three patient cohorts as illustrated in Figure 1.

The Dose Escalation (DES; Cohort 1) segment of the study was completed and established the XMT-1536 MTD of 43 mg/m^2 q28d. The cancer types studied were: salivary duct carcinoma (n=1); papillary renal (n=2); endometrial (n=8); non-small cell lung cancer or NSCLC (n=11); and ovarian cancer (n= 40).

The Expansion (EXP; Cohort 2) segment of the study consists of 2 parallel patient populations:

- Cohort 2A - patients with HGSOC (both platinum-resistant and platinum-sensitive) and
- Cohort 2B - patients with NSCLC, adenocarcinoma subtype.

Cohort 2A completed enrollment in April 2021 (N=97) and Cohort 2B (NSCLC) completed enrollment June 2021 (N=45). The EXP portion of the study will end once all patients have completed study treatment and sufficient data have been collected for the key study endpoints.

Dosing began in Cohort 3, known as "UPLIFT", in April 2021. The UPLIFT cohort (Cohort 3) is for patients with platinum-resistant HGSOC, including cancers of ovarian, fallopian tube or primary peritoneal origin. Site approval of Version 8.1 of the protocol implemented the UPLIFT cohort.

Prior to the implementation of Version 9 of the protocol, 32 patients were enrolled in the UPLIFT cohort and dosed at 43 mg/m^2. Following implementation of Version 9.0, all patients enrolled in the UPLIFT cohort (the only cohort remaining open for enrollment), have received a starting dose of upifitamab

rilsodotin 36 mg/m^2 (capped at BSA 2.2 m^2) q4wk. Any patients remaining on treatment at 43 mg/m^2 from the DES and EXP segments of the study were switched to 36 mg/m^2 (capped at BSA 2.2 m^2) q4wk. This dose change was informed by a review of the ongoing safety and efficacy data of the OC patients from the DES and EXP segments of the study along with a preliminary population pharmacokinetic analysis. Available data suggest that changing the starting dose to 36 mg/m^2 could lead to optimization of the benefit/risk of profile of upifitamab rilsodotin by improving the overall safety profile while maintaining robust anti-tumor activity.

As of Version 9.0, a QTc Sub-study, to be conducted at selected sites, has been added. In this segment, approximately 25 evaluable patients with HGSOC (UPLIFT Cohort 3) at selected research sites who agree to the sub-study specific eligibility criteria are eligible for enrollment. These research sites will offer participation within the QTc evaluation sub-study to all eligible patients in order to avoid bias in patient selection. In the event that enrollment in UPLIFT is completed, enrollment of patients into the QTc sub-study will continue until the target number of evaluable patients is met. Data will be collected and processed by an external vendor with experience in conducting central cardiac reads in accordance with the international regulatory standards for reporting QTc safety assessments.

All adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria version (CTCAE v5.0). In DES, the observation period for DLTs was 28 days, between Day 1 through end of Cycle 1 which included the pre-dose assessments before receiving the Cycle 2 dose. In general, adverse events ≥ Grade 3 were evaluated as DLTs with some modifications for the following criteria: hematologic toxicities, hepatic toxicities, and electrolyte imbalances. See Section 9.5 for a full description of the conditions when an adverse event became a DLT. Any XMT-1536-related toxicity that delayed initiation of Cycle 2 by more than 2 weeks, caused hospitalization to treat an infusion-related reaction, and any toxicity that prompted modification of the dose level to be administered in Cycle 2 were also DLTs.

In the DES, EXP, and UPLIFT segments, blood sampling is performed to determine plasma PK parameters of XMT-1536, its release product XMT-1267, the antibody scaffold XMT-1535, and select metabolites. Testing for anti-drug antibodies (ADA) and neutralizing antibodies (nAb) will be performed.

Tumor responses will be Investigator-assessed using Response Evaluation Criteria in Solid Tumors (RECIST), v 1.1, 2009 in DES, EXP and UPLIFT. In UPLIFT, tumor responses will also undergo independent radiology review (IRR) assessed using RECIST v 1.1.

Refer to Section 4.5 for ongoing Safety Review Committee (SRC) procedures and Appendix 10 for the study history and changes made via protocol amendments.

The DES and EXP patients were dosed with the Phase (Ph) 1 liquid XMT-1536 formulation. Patients enrolled in the UPLIFT segment will use the lyophilized form of XMT-1536 (upifitamab rilsodotin).

Number of patients (planned):

DES: Sixty-two patients were dosed and will be followed to study conclusion.

EXP: 97 patients with ovarian cancer and 45 patients with NSCLC were dosed and will be followed to study conclusion.

UPLIFT: Approximately 180 to 240 patients with platinum resistant HGSOC, including cancers of ovarian, fallopian tube, or primary peritoneal origin.

QTc: Approximately 25 evaluable patients will be enrolled across 10 to 15 selected research sites. Patients who are candidates for UPLIFT will have to meet additional eligibility criteria to be candidates for

enrollment into the QTc sub-study. Patients enrolled into the QTc cohort will also be part of the UPLIFT cohort, unless UPLIFT has completed enrollment.

Objectives (DES and EXP):

Primary in Dose Escalation (DES):

- Determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of XMT-1536 administered intravenously once every 28 days
- Assess the safety and tolerability of XMT-1536

Primary in Expansion (EXP):

- Assess further the safety and tolerability of XMT-1536 administered at the MTD/RP2D identified in the DES
- Assess the preliminary anti-neoplastic activity of XMT-1536

Secondary in DES:

- Assess the preliminary anti-neoplastic activity of XMT-1536

Secondary in DES and EXP:

- Assess the pharmacokinetics (PK) of XMT-1536, its release product, and selected metabolites
- Assess the development of anti-drug antibodies to XMT-1536
- Assess the association of tumor expression of NaPi2b and objective tumor response to XMT-1536
- Assess safety and efficacy in ovarian cancer subpopulations, including patients previously treated and failed therapy with bevacizumab and patients with and without Breast Cancer type 1 susceptibility gene (BRCA) mutation who were previously treated and failed therapy with poly ADP ribose polymerase inhibitors (PARPi).

Exploratory in DES, EXP and UPLIFT:

- Retrospectively evaluate the association of objective response with tumor expression of genes other than NaPi2b, or other tumor molecular and histologic features

Refer to Section 3 and Section 11 for a full description of the objectives and endpoints.

Objectives (UPLIFT):

Primary in Pivotal Cohort (UPLIFT):

- Determine the confirmed investigator-assessed objective response rate of XMT-1536 (upifitamab rilsodotin) at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 in patients with higher (TPS ≥75) sodium-dependent phosphate transport protein 2b (NaPi2b) expressing platinum-resistant high-grade serous ovarian cancer (HGSOC), including cancers of ovarian, fallopian tube or primary peritoneal origin

Secondary in UPLIFT:

- Assess the confirmed investigator-assessed objective response rate of XMT-1536 (upifitamab rilsodotin) regardless of NaPi2b expression.
- Assess the confirmed objective response rate by independent radiology review (IRR) for patients with HIGH NaPi2b (TPS ≥75) and overall.

- Assess the duration of objective response (DOR) in patients who achieve a response.
- Assess the incidence and severity of adverse events (AEs).

Exploratory in DES, EXP and UPLIFT:

- Retrospectively evaluate the association of objective response with tumor expression of genes other than NaPi2b, or other tumor molecular and histologic features

Exploratory in UPLIFT:

- Assess the disease control rate (DCR)
- Assess the progression-free survival (PFS)
- Assess the overall survival (OS)
- Assess the population PK
- Assess the relationship of XMT-1536 (upifitamab rilsodotin) exposure to efficacy and safety outcomes.
- Assess development of anti-drug antibody and neutralizing antibody in response to XMT-1536 (upifitamab rilsodotin) exposure

Refer to Section 3 and Section 11 for a full description of the objectives and endpoints.

Objectives (QTc Sub-Study):

Primary in QTc sub-study:

- Evaluation of the concentration-response analysis of XMT-1536 versus the change in QTcF values

Secondary in QTc Sub-study:

- Evaluation of the effect of XMT-1536 on QTcF in patients with platinum-resistant HGSOC by timepoint analysis
- Evaluation of the effect of XMT-1536 on the PR-interval (PR), QRS duration (QRS), Heart Rate (HR), and ECG morphology.

Refer to Section 3 and Section 11 for a full description of the objectives and endpoints.

General Inclusion and Exclusion Criteria Generic to all Segments of the Study:

Refer to Section 5 of the protocol for general discussion points on the eligibility criteria. Participants will have met all inclusion and none of the exclusion criteria as noted below as well as any cohort/sub-study specific criteria.

General Inclusion Criteria:

1. Females and males, aged ≥18 years old
2. ECOG performance status 0 or 1
3. Measurable disease as per RECIST, version 1.1
4. Resolution of all acute toxic effects of prior therapy or surgical procedures to ≤Grade 1 except alopecia, stable immune-related toxicity such as hypothyroidism on hormone replacement, adrenal insufficiency on ≤10 mg daily prednisolone (or equivalent), chronic Grade 2 peripheral sensory neuropathy after prior taxane therapy.

5. Cardiac left ventricular ejection fraction (LVEF) ≥50% or ≥ the institution's lower limit of normal by either Echo or MUGA scan
6. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥1500 cells/mm3
    b. Platelet count ≥100,000/mm3
    c. Hemoglobin ≥9 g/dLP[a]
    d. In patients not on anticoagulation therapy: INR, activated partial thromboplastin time (aPTT), and prothrombin time (PT) all within 1.2 times the institutional upper limit of normal (ULN). Patients on anticoagulation therapy are allowed if their relevant laboratory values are within the therapeutic window.
    e. Estimated glomerular filtration rate (GFR) ≥45 mL/minP[b]
    f. Total bilirubin ≤ULN
    g. Patients with asymptomatic elevations in unconjugated bilirubin due to Gilbert syndrome or stable chronic hemolytic anemia (e.g., hereditary spherocytosis, sickle cell disease, thalassemia intermedia) may be eligible after discussion with the Sponsor Medical Monitor.
7. Aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) ≤1.5 times the institutional ULN.
8. Albumin ≥3.0 g/dL
9. During the study, female study participants of child-bearing potential must use a highly effective non-hormonal form of contraception for the duration of study drug administration and for at least 6 months after the last dose of study drug. Please see Appendix 7 for examples of non-hormonal highly effective contraceptive methods.
10. Male study participants must use barrier contraception (condoms) for the duration of study drug and for at least 6 months after the last dose of study drug. The WOCBP partners of male study participants must use highly effective contraception for the duration of study drug and for at least 6 months after the last dose of study drug (Appendix 7).
11. Able to provide informed consent.

General Exclusion Criteria:

1. Major surgery within 28 days of starting study treatment, systemic anti-cancer therapy within the lesser of 28 days or 5 half-lives of the prior therapy before starting study treatment (14 days or 5 half-lives for small molecule targeted therapy), or recent radiation therapy with unresolved toxicity or within a time window of potential toxicity (consultation with the Sponsor Medical Monitor is recommended).
2. Patients with untreated CNS metastases (including new and progressive brain metastases), history of leptomeningeal metastasis or carcinomatous meningitis.
    a. Patients are eligible if CNS metastases are adequately treated, and patients are neurologically stable for at least 2 weeks prior to enrollment.
    b. In addition, patients must be either off corticosteroids, or on a stable/decreasing dose of ≤ 10 mg daily prednisone (or equivalent). Anticonvulsants are allowed except for those drugs associated with liver toxicity. See Appendix 4.

3. Untreated, known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). In addition, negative serology is required during screening (baseline) for HBV and HCV:
    a. HBV: Patients with serologic evidence of chronic HBV infection should have an HBV viral load below the limit of quantification to be eligible.
    b. HCV: Patients with a history of HCV infection should have completed curative antiviral treatment and HCV viral load below the limit of quantification.
    c. Screening for HIV is not required except if mandated by local regulations or indicated based on clinical assessment
4. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease) or intercurrent illness that could increase risk of adverse events, whether or not potentially related to study treatment (in unclear cases, consultation with the Medical Monitor is recommended). Further, patients are excluded with the following characteristics:
    a. A baseline prolongation of QTcF interval >CTCAE G1: repeated demonstration of a QTcF interval >480 milliseconds (ms) using Frederica's QT correction formula.
    b. A history of additional risk factors for Torsade's de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
5. History of cirrhosis, hepatic fibrosis, esophageal or gastric varices, or other clinically significant liver disease. Testing beyond laboratory studies otherwise defined in the eligibility criteria, to diagnose potentially clinically significant liver disease based on risk factors such as hepatic steatosis or history of excessive alcohol intake, will be based on clinical judgement of the investigator.
6. Patients cannot receive drugs associated with hepatotoxicity concurrent with XMT-1536 administration (refer to Appendix 4). Patients may receive acetaminophen/paracetamol for a limited time but at a total daily dose of ≤ 2 g per day. Use of NSAIDs or steroids for treatment of fever is encouraged.
7. Current use of either constant or intermittent supplementary oxygen therapy.
8. History of or suspected pneumonitis or interstitial lung disease.
9. Oxygen saturation on room air <93%.
10. Pregnant or nursing women
11. Diagnosis of additional malignancy that progressed or required active treatment within the last 2 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix
12. Active corneal disease, or history of corneal disease within 12 months prior to enrollment.
13. Use of strong CYP450 3A inhibitors or inducers that cannot be discontinued while receiving study treatment (refer to Appendix 5)
14. Known sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
15. In the Czech Republic, patients cannot be enrolled if they have received a live/attenuated vaccine within 30 days of study entry or if they plan to receive a live/attenuated vaccine while on treatment through 90 days post the last dose of study medication.

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[a] Prophylactic transfusion of blood (or blood components) within 14 days prior to initial dosing cannot be used to meet enrollment criteria. Transfusion of blood (or blood components) to manage treatment-emergent anemia or other cytopenias is permissible and should be recorded as a concomitant medication. Growth factor prophylaxis cannot be used prior to XMT-1536 administration in any cycle. However, the use of growth factors as treatment for cytopenia is allowed. Please contact the Medical Monitor if this is necessary. If cytopenia occurs after administration of Cycle 1, use of growth factors may be administered prophylactically in subsequent cycles at the discretion of the Investigator and after consultation with the Medical Monitor.

[b] Calculated using CKD-EPI Creatinine Equation https://www.kidney.org/content/ckd-epi-creatinine-equation-2009 or institutional standard method.

Ovarian Cancer Inclusion and Exclusion Criteria for UPLIFT – Cohort 3

Refer to Section 5 of the protocol for general discussion points on the eligibility criteria. Participants will have met all inclusion and none of the exclusion criteria as noted in the overall MER-XMT-1536-1 protocol as well as the additional criteria below:

Inclusion:

1. Histological diagnosis of high grade serous ovarian cancer, which includes fallopian tube, or primary peritoneal cancer, that is metastatic or recurrent.
2. Platinum-resistant disease:
    a. Patients who have only had 1 line of platinum-based therapy must meet all of the below criteria:
        - have received at least 4 cycles of platinum-containing chemotherapy,
        - have had a response [complete response/remission (CR) or partial response/remission (PR)]
        - have progressed between 3 months and ≤ 6 months after the date of the last dose of platinum
    b. Patients who have received 2 to 4 lines of prior platinum-based therapy must have received at least 4 cycles of platinum-containing chemotherapy within their last platinum-based regimen and then progressed within 6 months after the date of the last dose of platinum.

    Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic image showing progression. Patients who progressed within 3 months of front-line platinum-based therapy are excluded. If radiographic progression was not documented, the date of progression based on biopsy can be used for calculation.
3. One to 4 prior lines of systemic therapy for ovarian cancer:
    a. Prior treatment with bevacizumab is required for patients with 1 to 2 prior lines of therapy.
    b. In France, patients must have received at least 2 lines of systemic therapy and must not be candidates for surgery.
    c. Definitions for prior lines of therapy:
        i. Adjuvant ± neoadjuvant considered one line of therapy as long as they are the same regimens (e.g., platinum/taxane for 4 cycles before surgery followed by platinum/taxane for 4 cycles after surgery)
        ii. Maintenance therapy (e.g., bevacizumab, PARPi, endocrine therapy) will be considered as part of the preceding line of therapy (i.e., not counted independently)

iii. Therapy given for only 1 cycle and discontinued due to toxicity in the absence of progression will not be counted as a new line of therapy; therapy given for 2 or more cycles will be counted as a line of therapy. Substitutions of different platinum agents or taxanes will not be counted as new lines.

iv. Hormonal therapy (e.g., tamoxifen, letrozole) will be counted as a separate line of therapy unless it was given as maintenance.

d. In Sweden, patients must have received prior treatment with pegylated liposomal doxorubicin or paclitaxel, if not contraindicated

e. In Finland, patients must have exhausted available curative, effective, or suitable treatment options for HGSOC (e.g., have received paclitaxel, pegylated doxorubicin or topotecan).

4. Patients must be willing to provide an archival tumor tissue block or slides or if not available, undergo procedure to obtain a new tumor biopsy using a low-risk, medically routine procedure.

Exclusion

1. Low-grade, clear cell, endometrioid, mucinous, carcinosarcoma, germ-cell, mixed histology, or stromal tumors
2. Prior treatment with mirvetuximab soravtansine or another ADC containing an antitubulin payload
3. Lack of response to front-line, platinum-containing therapy or progression less than 3 months after completing front-line, platinum-containing therapy.
4. Participation in DES or EXP segments of this study

Eligibility Criteria for QTc Sub-study

Participants will have met all inclusion and none of the exclusion criteria as noted in the overall MER-XMT-1536-1 protocol as well as the additional criteria below, specific to this sub-study:

QTc Inclusion Criteria:

1. Study patient has agreed to remain in the clinic for the additional QTc related study activities on the Day 1 of Cycle 1 and Cycle 3 (approximately 4-6 hours following XMT-1536 administration).

QTc Exclusion Criteria:

1. Use of strong CYP450 3A inducers, as provided in Appendix 5, dosed for systemic exposure 7 days prior to the first dosing and through to Day 9.
2. Uncontrolled cardiac arrhythmias, for example, atrial fibrillation with a ventricular response at rest > 100 beats per minute. left bundle branch block (LBBB)
3. Known abnormality of any cardiac valve (either stenosis or regurgitation) that is greater than moderate in severity.
4. Subjects not in sinus rhythm at screening with HR >45- <100
5. Any ECG abnormality that can interfere with the measurement of the QT interval

Ovarian Cancer Inclusion and Exclusion Criteria for Expansion – Cohort 2A

Obsolete as of Version 9.0 as enrollment has been closed. Please refer to prior version of the protocol if needed.

NSCLC Inclusion and Exclusion Criteria for Expansion – Cohort 2B

Obsolete as of Version 9.0 as enrollment has been closed. Please refer to prior version of the protocol if needed.

Investigational product and mode of administration:

Cohort 2A and 2B – EXP: The Phase 1 XMT-1536 drug product is provided as colorless to light yellow frozen liquid in 5 mL vials with a rubber stopper sealed by a green or gray flip-off cap. Each vial contains 2.5 mL of XMT1536 at a concentration of 10 mg/mL of ADC, pH of 4.0 to 6.0. Vials must be stored at -20°C (±5°C) in a temperature-monitored freezer. Each dose will be prepared in 100 mL 0.9% normal saline total volume and administered by IV infusion over 90 minutes in all patients for Cycle 1. If well tolerated, subsequent doses can be administered over 30 to 90 min. Patients may receive study drug treatment on an outpatient basis, but during Cycles 1 and 3 will be monitored for approximately 6 hours following XMT-1536 administration for safety assessments and PK sampling. XMT-1536 will be dosed according to body surface area (BSA). Calculate the patient's BSA and prepare the dose solution from the contents of the XMT-1536 stock vial as described in the Pharmacy Manual. Refer to Section 6.4 for more information.

Cohort 3 – UPLIFT: The XMT-1536 drug product (upifitamab rilsodotin) to be used in UPLIFT is provided as a single-dose, white to off-white powder in 10mL vials with a rubber stopper sealed with a blue flip-off cap. Each vial contains 80 mg of XMT-1536 (upifitamab rilsodotin) for reconstitution with 8 mL of water for injection (WFI), USP or Sodium Chloride Injection, USP. The XMT-1536 DP once reconstituted, yields a solution concentration of 10 mg/mL of ADC, pH 4.5 – 5.0. The XMT-1536 drug product (upifitamab rilsodotin) vial must be stored between 2 - 8°C in a temperature monitored refrigerator.

Investigational product dosage:

Following implementation of Version 9.0, all patients enrolled in the UPLIFT cohort (the only cohort remaining open), will receive a starting dose of upifitamab rilsodotin 36 mg/m^2 (capped at BSA 2.2 m^2) q4wk. Each dose will be prepared in 100 mL 0.9% normal saline total volume and administered by IV infusion over 90 minutes (± 10 minutes) in all patients for Cycle 1. If well tolerated, subsequent doses can be administered over 30 to 90 min. If the XMT-1536 dose is reduced due to unacceptable toxicity (see Section 4.6), the BSA dose cap at 2.2 m^2 will remain in effect for any lower dose that is administered.

For all patients dosed, including those participating in both EXP cohorts and UPLIFT, the BSA adjusted dose will be calculated following each institution's standard practice. When possible, the Mosteller Formula will be used. The starting dose level will be calculated based on height and weight collected within 14 days of the first dose and can be collected on the day of first dose. Dose calculations in subsequent cycles should be made for weight changes ≥5% from most recent dose calculation.

Customary supportive care medications may be used for treatment of concurrent, acute conditions that are associated with dosing, e.g., hypersensitivity reaction, emesis, diarrhea, and fever. Recommended prophylactic treatments to be administered before any patient's first dose and/or subsequent doses depending on each patient's prior response to XMT-1536 infusion(s) are outlined in Section 4.6 of the protocol. The type of prophylactic treatment to be used is at the discretion of the Investigator and should be informed by the patient's past response to chemotherapy treatment and their medical history. Treatment with anti-emetic and anti-pyretic medications may be indicated for several days after infusion and may be used before the first dose. Dose adjustments after Cycle 1 are permitted under specific circumstances; these are described in Section 4.6.

The SRC will continue to review data of patients in the EXP and UPLIFT segments of the study to assess safety and tolerability (see Section 4.5.2).

Reference therapy, dosage and mode of administration:

Not Applicable.

Duration of treatment:

Treatment may continue indefinitely unless one of the following occurs:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse events or pregnancy
- Patient non-compliance with study instructions
- Patient withdraws consent for participation from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator

Patients can be continued on XMT-1536 following disease progression if the Investigator perceives the potential for the patient to derive benefit from continued exposure, after discussion with the Sponsor Medical Monitor.

Criteria for evaluation:

In the DES, EXP, and UPLIFT segments of the study, assessments with computerized tomography (CT) scans or magnetic resonance imaging (MRI) and using RECIST v 1.1 criteria (see Appendix 3) will be performed every 8 weeks ± 3 days beginning with the date of Cycle 1 Day 1 until week 24 followed by every 12 weeks +/- 7 days thereafter, even if a subsequent cycle is delayed. The use of positron emission tomography – CT (PET-CT) imaging during the study must first be reviewed and approved by the Sponsor Medical Monitor. The same imaging modality should be used throughout the study per patient. Patients who achieve a response (i.e., CR or PR) will be assessed for response confirmation per RECIST v 1.1 as soon as 26 days but no later than 42 days post first determination of response. Subsequent scans will be conducted every 8 weeks ± 3 days from the date of the confirmation scan. If the patient has been on study treatment for ≥24 weeks, subsequent scans can be conducted 12 weeks ± 7 days from the date of the confirmation scan (depending on time elapsed since Cycle 1 Day 1).

Patients will be continuously evaluated for adverse events, the use of concomitant medications, and the occurrence of infusion reactions in all cycle. Pharmacokinetic profiles of XMT-1536 and select release products/metabolites and the development of anti-drug antibodies will be evaluated. The objective response rate (ORR – rate of complete response [CR] and partial response [PR]) and disease control rate (DCR: CR + PR + stable disease [SD]) will be measured for each cohort. Response duration, progression-free survival (PFS), and overall survival (OS) will be estimated using the Kaplan-Meier method.

In the QTc sub-study (selected sites only), a 12-lead ECG will be obtained in triplicate according to the schedule presented in the protocol. The following parameters will be collected or calculated: ventricular rate (beats per minute), PR interval, QRS duration, QT/QTc interval, QTcF, and RR interval. Potential effects will be assessed by analysis of central tendency, the incidence of clinical noteworthy ECG values, morphological assessments, rhythm abnormalities, and an analysis of upifitamab rilsodotin concentration and baseline-corrected QT interval (corrected using Fridericia's formula) (QTcF). All ECG interval data will represent the means of up to three individual tracings, based on electrocardiograms (ECGs) taken

approximately one minute apart. The concentration-QTcF change from baseline (ΔQTcF) analysis and analysis of central tendency for ΔQTcF will be summarized, along with evaluations of cardiac safety as outlined in the ECG Statistical Analysis Plan.
Statistical methods: Separate Statistical Analysis Plans (SAPs) will be written for the analyses of data from DES (Cohort 1), EXP (Cohort 2A and 2B), and UPLIFT (Cohort 3). All 3 SAPs will be final before the study database is locked and will address the analysis of all clinical, safety, and laboratory data collected for the study. Descriptive statistics will be used to display the results. Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. Time-to-event data will be summarized using the Kaplan--Meier method. ORR, DCR, and Duration of Response (DOR) will be reported. Separate Clinical Study Reports will be written for each Cohort. See Section 11.3 for a full description of the analysis of safety, primary efficacy, pharmacokinetics, and NaPi2b expression data.
Data Publication: Mersana follows ICMJE criteria and ensures authors have participated sufficiently in the development of the publication data to take responsibility for content. Mersana will publish the data from this study, whether positive or negative, at the end of the study. This study was posted on www.ClinicalTrials.gov in Oct 2017 when it was initiated: Identifier NCT03319628.

1.2. Schedule of Events

This section contains the schedules of events for all segments of the study (Table 2), the QTc sub-study that will be conducted at selected sites (Table 4), and all relevant notes and considerations.

For Cycle 1 and Cycle 3 PK and ECG timepoints, the QTc schedule of events (Table 4) must be used for PK and ECG sampling timepoints for all patients enrolled in the sub-study.

This section should be referenced along with Appendix 8 that outlines country-specific requirements that differ from the overall global conduct of the study due to differences in regional practices and regulations.

Table 2: Schedule of Events for EXP Cohorts 2A, 2B, and UPLIFT Cohort 3

	Study Visits *(A)*	**Tumor Imaging** *(D)*	**BX** *(E)*	**Inclusion Exclusion** *(F)*	**Med Hx Demog** *(G)*	**ECOG**	**PE & VS** *(H)*	**Ocu Tests** *(I)*	**CV** *(J)*	**Safety Labs** *(K)*	**CA 125** *(L)*	**PK Labs** *(M)*	**ADA** *(N)*	**AE & Con Med** *(O)*
1	Screen Day-28 to Day -1	X	X					X	MUGA/ Echo and ECG	Viral serology	X			
2	Screen Day -14 to Day -1			Confirm Eligibility	X	X	Full PE & VS			CBC, Chem, UA, Coag, hCG, Troponin				CM only
Key screen data is relayed to Mersana for Medical Monitor review prior to administering the first dose of XMT-1536 to any patient. *(A)*														
CYCLE 1														
3	Dose – Day 1						Pre-Dose: Brief PE & VS VS: EOI & EOI+4 h EOD*		ECG: Pre, EOI	Chem, CBC, hCG, Coag, UA, and Troponin		*Pre dose EOI EOI+4 h	X	X
4	Day 2						VS			CBC, Chem		X		X
6	Day 8						Brief PE & VS			CBC, Chem		X		X
7	Day 15						VS			CBC, Chem		X		X
8	Day 21						VS			CBC, Chem		X		X
9	Day 28-End of Cycle						Full PE & VS			CBC, Chem	X	§		X

Table 2: Schedule of Events for EXP Cohorts 2A, 2B, and UPLIFT Cohort 3 (Continued)

	Study Visits *(A)*	**Tumor Imaging** *(D)*	**BX** *(E)*	**Inclusion Exclusion** *(F)*	**Med Hx Demog** *(G)*	**ECOG**	**PE & VS** *(H)*	**Ocu Tests** *(I)*	**CV** *(J)*	**Safety Labs** *(K)*	**CA 125** *(L)*	**PK Labs** *(M)*	**ADA** *(N)*	**AE & Con Med** *(O)*
CYCLE 2														
10	Dose – Day 1					Pre-Dose	VS: Pre & EOI, EOD		ECG: Pre &EOI	Chem, CBC, hCG, UA, Coag. Troponin		Pre dose EOI	x	X
11	Day 2 Lab Visit									CBC, Chem		X		
12	Day 8 Lab Visit									CBC, Chem		X		
13	Day 15 Lab Visit									CBC, Chem		X		
15	Day 28-End of Cycle	X					Full PE & VS	X	MUGA or Echo	CBC, Chem	X	§		X
CYCLE 3 (P)														
16	Dose – Day 1					Pre-Dose	VS: Pre & EOI, EOD		ECG: Pre & EOI	Chem, hCG, CBC, UA, Coag, Troponin		Pre dose EOI EOI+4 h	x	X
17	Day 8 Lab Visit									CBC, Chem		X		
18	Day 15 Lab Visit									CBC, Chem		X		
20	Day 28-End of Cycle						Full PE & VS			CBC, Chem	X	§		X

Table 2: Schedule of Events for EXP Cohorts 2A, 2B, and UPLIFT Cohort 3 (Continued)

	Study Visits *(A)*	**Tumor Imaging** *(D)*	**BX** *(E)*	**Inclusion Exclusion** *(F)*	**Med Hx Demog** *(G)*	**ECOG**	**PE & VS** *(H)*	**Ocu Tests** *(I)*	**CV** *(J)*	**Safety Labs** *(K)*	**CA 125** *(L)*	**PK Labs** *(M)*	**ADA** *(N)*	**AE & Con Med** *(O)*
CYCLE 4 & SUBSEQUENT CYCLES (P)														
21	Dose – Day 1					Pre-Dose	VS: Pre & EOI, EOD		ECG: Pre &EOI	Chem, CBC, hCG, UA, Coag^, Troponin		Pre dose EOI	Even Cy	X
22	Day 8 Lab Visit through C12									CBC, Chem		X		
25	Day 28-End of Cycle	X					Full PE & VS			CBC, Chem	X	§		X
26	End of Treatment (B)	X			Confirm		Full PE & VS	X	ECG MUGA or Echo	CBC, Chem, UA, hCG, Coag, Troponin	X		X	X
27	Post Treatment & Survival Follow-up (C)	X								hCG through 6 months post last dose				X Phone

ABBREVIATIONS: AE = Adverse Event; BX = Biopsy; CA 125 = Cancer antigen 125; CBC = Complete blood count; Chem = Chemistry; Coag = Coagulation blood parameters; Cy = Cycle; CM = Concomitant Medication; EOC=End of Cycle; EOD = End of Day, defined as the timepoint following completion of all study procedures and prior to patient departure from site; EOI = End of Infusion; Ocu = Ocular; PE = Physical Examination; VS = Vital Signs

§ PK ASSESSMENTS: Obtain sample at EOC. If the EOC visit is on the same day as the start of the next cycle, the pre-dose PK sample will serve as the end of prior cycle sample.

^ Coagulation parameters are not collected after Cycle 4 unless medically necessary.

Schedule of Events Annotations

Table 3: Schedule of Events Annotations for EXP Cohorts 2A, 2B, and UPLIFT Cohort 3

(A) Study Visits	• The following screen results will be submitted via IXRS or clinical database for Mersana's review at least 2 days before the intended day of first dose, in accord with local laws and regulations: diagnostic report regarding the primary tumor (including histology results and mutation status, if possible), medical history including demography and current and prior medications and prior cancer therapies; physical examination and vital signs; ECG and MUGA or Echo; ocular examinations, all safety labs; tumor imaging results, and confirmation of the availability of the archive tissue, pathology report associated with the archive tissue sample and the pre dose biopsy if done. If the pre dose biopsy is not medically feasible, ensure that written approval to proceed with dosing from Sponsor or CRO has been sent. • The End of Cycle assessments can be performed on the same day as dosing in the next cycle provided safety lab results are obtained, reviewed, and found to be within acceptable parameters prior to initiating the next dose. • Patients who undergo dose reduction (Section 4.6) will follow the schedule of events outlined in the cycle during which the dose reduction occurs. • On Cycle 1 Day 15 and Day 21, a ±1-day window is allowed to accommodate patient or site scheduling. • After Cycle 1, a ±2-day window is allowed for dosing visits. While on treatment, a window of ±2 days is allowed for any assessments to accommodate patient or site scheduling, except as noted below for specific assessments (e.g., pre-dose safety & lab assessments, ECG, and PK assessments).
(B) End of Treatment (EOT) **Row 26**	• Perform the assessments indicated if the End of Treatment visit does not coincide with an End of Cycle visit. Further, these procedures can be done on the same day a patient is in-clinic for some other scheduled or unscheduled visit. • Perform the tumor imaging disease assessment if the patient is due for disease scans according to the tumor imaging schedule. • The following EOT assessments should be obtained at any EOT visit (±7 days from the time that end of treatment is determined): safety labs, physical examination, adverse event review, vital sign collection, and ADA plasma sample. • The EOT ophthalmic exam or disease assessment may be performed ±7 days from the EOT visit.

(C) Post Treatment and Survival Follow-up **Row 27**	• The Post Treatment follow-up will be completed via phone call with the study patient, although a family member is permitted to provide the requested information. • The Post Treatment follow-up call window is 30 (±7) days after the last dose of XMT-1536 is administered. • As outlined in (K), pregnancy testing must be conducted at EOT and continue every month for 6 months following the last dose of study medication during the Follow-up period. If a patient discontinues study participation prior to the 6-month period following the last dose of study medication, they should be advised that continuation of pregnancy testing is recommended. • A second call will be conducted approximately 60 (±7) days (approximately 5 half-lives) after the last dose of XMT-1536. In France, this must be conducted via visit and all procedures conducted at EOT must be performed, except for tumor imaging. Safety data obtained during these calls will be entered into the study database. If a serious AE is reported during these calls, follow the SAE Reporting process in Appendix 1. • Following the second Post Treatment follow-up call, patients will be followed for overall survival. This data will be collected by phone approximately every 3 months and recorded in the database until consent is withdrawn or the patient expires. • The end of the trial is defined as the last patient visit or follow-up telephone call for Overall Survival.
(D) **Tumor Imaging** **Rows 1, 15, 25, 26**	• Protocol mandated re-staging CT or MRI scans should encompass the chest, abdomen, and pelvis. Patients with history of metastasis that cannot be assessed by CT/MRI chest/abdomen/pelvis need additional imaging for complete tumor evaluation on study. For example: – Patients with known brain metastasis will undergo brain imaging (i.e., MRI) every 8 weeks ± 3 days as part of complete tumor evaluation. Patients with signs/symptoms concerning for CNS metastasis while on study treatment should also undergo additional imaging as determined by the treating physician. – Patients with known bone metastasis will undergo nuclear medicine bone scan every 8 weeks ± 3 days as part of complete tumor evaluation. Patients with signs/symptoms concerning for bone metastasis while on study treatment should also undergo additional imaging as determined by the treating physician. • Either contrast CT or contrast MRI technique will be selected for the screen images and will continue to be consistently used for each patient for the duration of their study participation. PET-CT can be used throughout the study if first approved by the Sponsor Medical Monitor. The same modality must be used throughout the study per patient. • Tumor imaging will be interpreted using RECIST v. 1.1. (Appendix 3).

	• Tumor imaging will be conducted every 8 weeks ± 3 days from Cycle 1 Day 1, even if dose administration is delayed in a subsequent cycle(s). The window of ± 3 days is provided to accommodate patient schedules if necessary. If the patient has been on study for ≥24 weeks, scans can be conducted every 12 weeks ± 7 days. • A confirmation CT or MRI scan after the initial PR or CR may be done as early as 26 days but no later than 42 days post first determination of response as per RECIST guidelines. Subsequent scans will be conducted every 8 weeks ± 3 days from the date of the confirmation scan. If the patient has been on study treatment for ≥24 weeks, subsequent scans can be conducted 12 weeks ± 7 days from the date of confirmation (depending on time elapsed since Cycle 1 Day 1). • Patients who have stopped dosing for any reason should have periodic tumor assessments per RECIST as per the schedule outlined above (every 8 weeks ± 3 days until 24 weeks post C1D1, then every 12 weeks ± 7 days). These tumor assessments should continue until the patient progresses, withdraws consent, begins a new chemotherapy, or expires. These data will be recorded in the database. • UPLIFT only: Tumor images will be remitted periodically to the central read facility where central, independent radiology review will be conducted.
(E) Biopsies (BX) Row 1	• EXP: a recent biopsy will be obtained prior to first dose if medically feasible. Contact the Sponsor Medical Monitor for approval if a recent biopsy is not feasible. • UPLIFT: A recent biopsy will be obtained prior to first dose if the patient is unable to provide an archival tumor tissue block or slides. Please refer to the Lab Manual for full instructions for collection of adequate tissue samples. • Fresh tumor biopsies should be done according to local routine clinical practice and according to institutional standards. Fresh tumor sample will be obtained from recurrent/metastatic lesions, using standard institutional procedures if this is deemed by the clinical investigator to be medically feasible and if it can be done with minimal risk to the patient. High risk procedures such as core needle biopsies of lung nodules should not be performed to obtain tissue on this protocol (Levit, et al., 2019) • The type of biopsy is at the discretion of the Investigator. However, the Sponsor's order of preference for specimen type, from most preferred to least: (1) surgical resection, (2) core biopsy, and last a fine-needle aspirate. If an ascites sample is the only method possible to obtain a fresh biopsy, this is allowed. The sample should be evaluated to ensure there is a sufficiently sized cell pellet for analysis. • All biopsy tissue samples, archive and recent, should be accompanied by a pathology report. Reports with all patient information redacted will be sent to the Sponsor as soon as available. If the biopsy sample is part of

	eligibility criteria, the pathology report will be sent to the Sponsor prior to approval to dose, unless otherwise indicated in writing by the Sponsor Medical Monitor. • Biopsy tissue samples will be tested to determine the expression of NaPi2b in all patients enrolled in this study. In UPLIFT, the research site and sponsor will remain blinded to the NaPi2b expression for all patients until the entire database for this study has been locked at which time the NaPi2b expression for each patient enrolled in UPLIFT will be sent to the study site for the study file.
(F) Inclusion/Exclusion Criteria: **Row 2**	• Formal confirmation that inclusion criteria were met, and no exclusion criteria were met will be documented in each patient's study source file. • Ovarian Cancer: prior lines of therapy include all systemic regimens used to treat ovarian cancer, e.g., chemotherapy, immunotherapy. Treatments given as maintenance, e.g., bevacizumab or a PARP inhibitor following platinum-based therapy for patients in response, are not counted as prior lines of therapy. Intraperitoneal and neoadjuvant or adjuvant therapies are counted as one line of therapy. • NSCLC: prior lines of therapy include all systemic and oral regimens including chemotherapy, tyrosine kinase inhibitors and immunotherapy. • If the Investigator is unclear about how to count prior lines of therapy, the Investigator should contact the Medical Monitor during screening.
(G) Medical History and Demography **Rows 2 and 26**	• Ongoing medical conditions must be noted in Medical History, including any unresolved treatment effects from prior clinical study participation. Sometimes during study participation, the Research Staff become aware of pre-existing conditions, prior medications, etc., that are pertinent to study participation. The initial eligibility criteria and medical history obtained pre-study will be confirmed at the end of study and annotations will be made accordingly in the database. • Complete collection of prior oncology therapies as specified in the database (includes regimen, dates, best overall response, and progression dates) is of critical importance and may require contacting the referring physician for clarifying information.
(H) Physical Examinations & Vital Signs **All Rows, except 1 and 27**	• Peripheral neuropathy evaluations will be included in at least all full PEs. Refer to Section 4.3.1 for a complete description of full vs. brief PEs. Vital signs include blood pressure, pulse rate, respiration rate, oxygen saturation, and temperature.

	• Any clinically relevant findings from PE or neurological examination before the first dose will be recorded in the medical history section of the CRF. Any clinically relevant changes after the first dose of study treatment will be recorded in the AE section of the eCRF (Section 9.2.2) • Pre-dose PE may be performed up to 2 days prior to dosing. • Pre-dose vital signs should be performed prior to infusion, on the same day as dosing. • For post-dose vital signs on Cycle 1 Day 1, perform within 30 minutes after the end of the infusion and 4 hours (240 ±15 minutes) after the end of infusion. For subsequent cycles, perform within 30 minutes after the end of the infusion and prior to patient discharge. • For all PE and Vital signs on non-dosing days, a window of ±2 days is allowed to accommodate patient or site scheduling. At EOT, a window of ±7 days is allowed.
(I) Ophthalmic Exams Rows 1,12,26	• Screening and on-study ophthalmic exams may be performed by any health care professional licensed to perform such procedures. A participant with ocular symptoms, clinically significant ocular findings on exam, or clinically significant medical history of eye disease must be evaluated by an ophthalmologist. • An ophthalmic exam, to include at a minimum a slit-lamp examination, visual acuity test, and optical coherence tomography (OCT) assessments, is required during screening as a baseline measurement, at the EOC2, and EOT, regardless of whether ocular symptoms are present. The Cycle 2 examination can be ± 7 days from the EOC visit. At EOT, a window of ± 7 days from the EOT visit is allowed. The Cycle 3 dose will not be held until after the EOC2 examination if a patient is asymptomatic. • Patients from sites in France are also required to undergo ophthalmic exams at the end of Cycle 6 (± 7 days). • Additional evaluations during study participation will be required if the patient is complaining of ocular toxicities (e.g., eye pain). For these patients, a slit-lamp examination, visual acuity test, and OCT should be conducted after symptom onset but before the next dose of study drug, then at the end of every even numbered cycle, or more frequently as clinically indicated, until symptoms resolve. Additional eye tests may be conducted based on the patient's symptoms and medical discretion of the ophthalmologist.
(J) Cardiovascular (CV) Rows 1, 2, 3, 10, 15, 16, 21, 26	• Baseline, EOC2, and EOT MUGA or Echo will be obtained for all patients. The Cycle 2 MUGA or ECHO can be obtained ± 7 days from the EOC visit. At EOT, a window of ± 7 days from the EOT visit is allowed for MUGA or ECHO. If symptoms indicate possible emerging or advancing cardiovascular disease, a patient may be asked to undergo unscheduled test(s). The same technology as used during the baseline assessment will be used for any second or subsequent scans.

	• Electrocardiograph: A 12-lead ECG single read out of acceptable quality obtained at every time point noted. The read out will be retained in the study patient's source documentation. Predose ECGs must be performed on the day of dosing. End of Infusion ECGs have a window of ± 5 minutes. ECGs must be performed prior to blood draws at the same time point (e.g., PK sample) and after the patient has been at rest for at least 3 minutes. Any clinically relevant changes occurring after the first dose will be recorded in the AE section of the eCRF (Section 9.2.2). The ECG will be repeated if any results are considered to be clinically significant. • For patients enrolled in the QTc sub-study: please refer to Table 4 for specific instructions
(K) Safety Assessments **All rows noted**	• Baseline serology testing for viral hepatitis will be performed as described in exclusion criterion 3. For HBV, required testing includes HBsAg and anti-HBc, with reflex testing of HBV DNA if anti-HBc is positive; for HBC, anti-HCV antibody is required, with reflex testing for HCV RNA if the antibody is positive. HIV testing is not mandated except by local regulations. • Coagulation parameters collected, at a minimum: INR/PT (or INR only), aPTT, and fibrinogen. Additional evaluations will be performed based on clinical signs and symptoms as appropriate, e.g., disseminated intravascular coagulation. CBC are analyzed locally and must include at a minimum: WBC with differential (absolute), RBC, hematocrit, hemoglobin, platelet. • hCG levels will be measured via a serum pregnancy test in women of childbearing potential (WOCBP) during screen. In WOCBP, urine or serum pregnancy tests will be conducted monthly prior to each dose, and where applicable due to local regulations. For WOCBP, pregnancy testing must be conducted at EOT and continue every month for 6 months following the last dose of study medication during the Follow-up period. If a patient discontinues study participation prior to the 6-month period following the last dose of study medication, they should be advised that continuation of monthly pregnancy testing is recommended (through 6 months post the last dose of study medication). • Blood chemistries must include at a minimum: potassium, sodium, chloride, carbon dioxide, glucose, albumin, blood urea nitrogen (BUN), total protein, creatinine, total bilirubin, calcium, alkaline phosphatase, magnesium, phosphorus, LDH, AST, and ALT. The Sponsor will acknowledge in writing if local practices preclude the collection of any of the specified analytes. Alternative analytes may be requested in this circumstance. • Troponin I or T obtained at baseline, pre dose on Cycles 1 to 4, and EOT will be analyzed locally. Additional troponin tests will be performed based on medical judgement for additional diagnostic evaluation of signs and symptoms indicating the possibility of cardiac disorder.

	• Urinalysis via dip stick will be conducted within 14 days prior to receiving first dose, before dose commences at each subsequent cycle, and at EOT. • If the patient resides a significant distance from the research facility such that return is a hardship, arrangements can be made to have a local blood draw with the results and local normal range returned to the Study Investigator for monitoring. • On dosing days, safety labs (Chem, CBC, hCG, UA, Coag, Troponin) must be performed pre-dose and can be performed up to 2 days prior to dosing. For all safety labs on non-dosing days, a window of ±2 days is allowed to accommodate patient or site scheduling. At EOT, a window of ±7 days is allowed.
(L) Cancer Antigen 125 **Rows 1, 9,15,20, 25, 26**	• CA 125 samples will be collected only from study patients with ovarian cancer if it is known to be previously elevated. Obtain a sample at EOT if this visit does not coincide with another study visit or if EOT occurs > 2 weeks after the last CA125 assessment was obtained. CA 125 will be analyzed locally.
(M) PK Lab Sampling **All rows noted**	• For dosing days, obtain pre-infusion PK sample up to 60 minutes pre-dose on the day of infusion, obtain the end of infusion PK sample within 10 minutes at the end of infusion, obtain the 4 hours-post infusion within a ±30 minute window. • On Cycle 1 Day 2, obtain PK samples within 23-25 hours after the end-of-infusion on Day 1 • On Cycle 1 Day 5, Day 15, and Day 21, a ±1-day window is allowed to accommodate patient or site scheduling. • Obtain all samples for Day 8, Day 15, and Day 21 in any cycle within a 4-hour window of the time the dose infusion ended for that cycle (time infusion ended +/- 2 hours). For Cycle 2 and beyond, Day 15 PK sample may be collected within a +/- 1 day window from the time the infusion ended. • Refer to the Laboratory Manual for detailed instructions on sample collection, processing, and shipment.
(N) Anti-Drug Antibody (ADA) **Rows 3, 10, 16, 21, 26**	• Samples will be collected before first dose in Cycle 1, before dose in Cycles 2, 3, 4 and all even numbered cycles thereafter. Samples taken on dosing days should be taken up to 60 minutes pre-dose. A final EOT ADA sample will be obtained if the EOT visit does not coincide with the visit at the end of an even numbered cycle when the ADA sample is required. These samples will also be tested for neutralizing antibodies if ADA positive.
(O) Adverse Events & Concomitant Medications	• AE assessment will be conducted at each visit by asking a general question about the patient's health status and record all reports in the study database. AEs that may be shared by the patient during lab visits, phone calls,

All Rows except 1	telemedicine visits or other unscheduled contacts will also be recorded in the study database. Once an AE has been documented, directly follow it until resolution or the end of study participation. For additional information on SAE reporting, refer to Section 9.2. • On Cycle 1 Day 1, patients will remain in the dosing clinic for observation for a minimum of 2 hours post end of infusion (EOI). After this period, patients may leave the infusion clinic to another suitable location in the hospital based on local practices but must return in time for all subsequent study assessments. • Collect the use of concomitant medications from 30 days before date of first study visit. Record the use of OTC drugs, vitamins, and herbal preparations as concomitant medications throughout the study.
(P) Cycle 3 and Beyond	• Beginning with Cycle 4 and all subsequent even-numbered cycles, each patient's weight will be rechecked for dose preparation purposes unless a site-specific standard BSA recheck process is in use. • See Section D regarding scans for response confirmation.

Alterations to the Schedule of Events

1. Based on the Investigator's medical judgment and his or her Institution's practices, additional safety assessment may be performed at any time to monitor an emergent safety concern. These unscheduled assessments will be recorded in the study database.
2. The Sponsor recognizes that occasionally extenuating circumstances may occur that delay a scheduled study assessment, e.g., delays due to holidays, severe weather, or an event in a patient's personal life. These delays are permitted at the discretion of the Investigator provided the minor alteration in the schedule does not place the study patient at increased risk. If this occurs, please notify the Clinical Trial Manager and your CRA in advance of the delay if at all possible.
3. In March 2020, a COVID-19 Mitigation Schedule of Events was sent to all research sites. Once approved by IRB/IEC, this schedule can be followed until such time that the Sponsor indicates it is no longer needed, which will be made in accord with public health recommendations and local institutional policies. Changes in the Schedule of Events may be made to immediately protect patient safety or in the event of catastrophic events, e.g., natural disasters, wars. Changes made under these circumstances must be reported to the governing IRB/IEC and Mersana immediately or as soon as possible.

1.3. Schedule of Events – QTc Sub-Study

Table 4: Pharmacokinetic and Electrocardiogram Schedule for the QTc Sub-Study

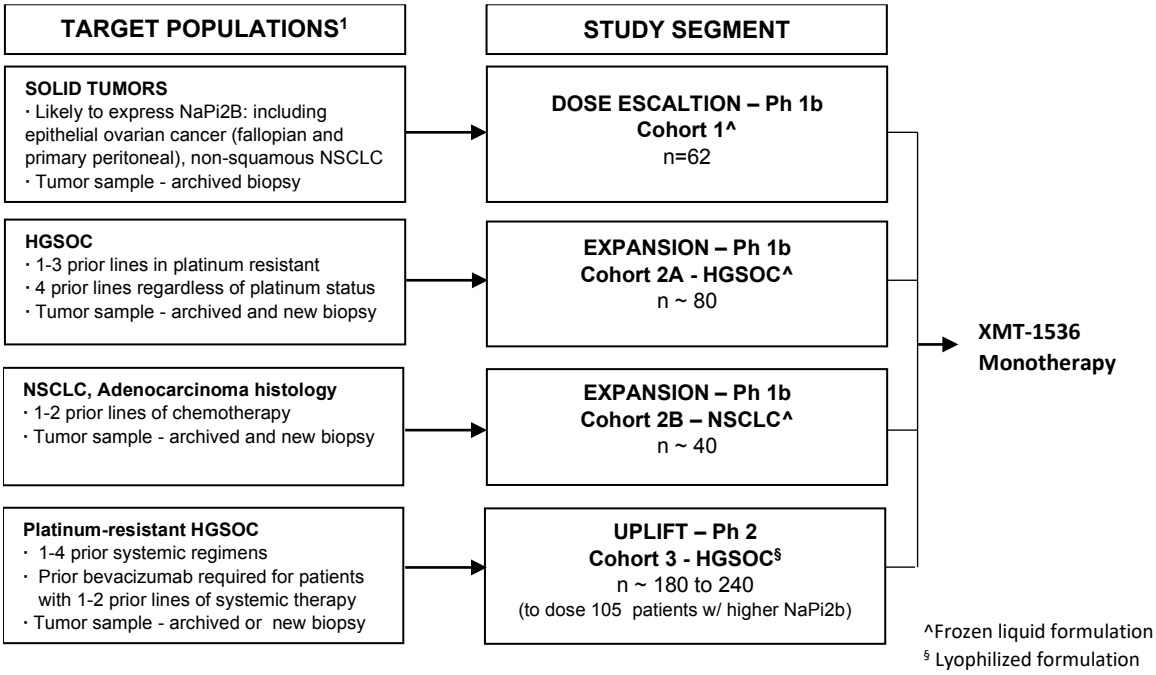
Visit/Cycle	Cycle 1												Cycle 3			
Study Day	Day 1		Day 2		Day 5[1]		Day 8		Day 15[1]		Day 21[1]		Day 1		Day 2	
Assessment	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]	ECG[2]	Blood[3]
Pre-dose																
60-65 min prior to infusion start	X	X											X	X		
45-50 min prior to infusion start	X	X											X	X		
30-35 min prior to infusion start	X	X											X	X		
Post-dose																
2 hrs after EOI (±5 min)	X	X											X	X		
3 hrs after EOI (±5 min)	X	X														
4 hrs after EOI (±5 min)	X	X											X	X		
5 hrs after EOI (±5 min)	X	X														
6 hrs after EOI (±5 min)	X	X														
26 hrs after EOI (±5 min)			X	X											X	X
28 hrs after EOI (±5 min)			X	X												
≤2 hrs after nominal time of infusion from Day 1 (±5 min)					X	X	X	X	X	X	X	X				

Abbreviations: CxDx = Cycle x, Day x; ECG = electrocardiogram; EOI = end of infusion; hr = hour(s); min = minute(s); PK = pharmacokinetics.

[1] On Cycle 1 Day 5, Day 15 and Day 21, a ±1-day window is allowed to accommodate patient or site scheduling. On these days, PK blood samples will be obtained immediately following the triplicate ECG collection.
[2] Pharmacokinetic blood samples will be obtained immediately following the triplicate ECG collection.
[3] All ECGs will be performed in triplicate. ECGs should be performed prior to PK sampling. The ECG procedure should be started in enough time to enable the PK samples to be taken within the windows stated above. ECGs should be completed within enough time to allow the PK sampling to be conducted within the window.

1.4. Study Schema – DES, EXP, and UPLIFT

Figure 1: Study Cohorts



[1]Refer to Section 5.3 for complete inclusion and exclusion criteria.
Note: For the UPLIFT cohort, the number of planned participants represents the number to enroll at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2.
Enrollment has been completed in the DES and EXP segments of the study by the time of Version 9.0.

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2. INTRODUCTION

2.1. NaPi2b and Antibody Drug Conjugates

NaPi2b (SLC34A2) is a member of the SLC34 family of sodium-dependent phosphate transporters which are expressed on apical membranes of epithelial cells, where they regulate absorption and homeostasis of inorganic phosphate (Biber, 1996). NaPi2b is expressed in normal lung tissue in several epithelial tissues including type II pneumocytes, the intestinal brush border, and surface epithelium of the uterus and fallopian tube (Hilfiker, et al., 1998), (Feild, et al., 1999), (Xu, et al., 1999), (dos Santos, et al., 1999).

Antibody-drug conjugates (ADCs) combine a monoclonal antibody to a cell-surface antigen on tumor cells with a potent cytotoxic molecule (payload) in order to specifically target tumor cells for killing. The ideal ADC target would be expressed on a variety of tumor cell types with no expression in normal tissues; however, all ADCs developed to date have targeted proteins with some degree of normal tissue expression (Damelin, et al., 2015). Nonetheless, toxicities of clinical-stage ADCs have often been driven by the ADC platform (linker and payload) rather than to normal tissue expression of the target. For instance, ocular toxicities, peripheral neuropathy and neutropenia have been seen with a number of microtubule-directed ADCs with different target antigens (de Goeij, 2016).

NaPi2b was identified as a potential ADC target by Lin et al., who reported expression of NaPi2b protein in ovarian epithelial cancer, nonsquamous NSCLC, and papillary thyroid cancer (Lin, et al., 2015). The authors generated an anti-NaPi2b ADC using the monomethyl auristatin E (MMAE) payload, which had activity in xenograft models of NaPi2b-expressing tumors. Preclinical toxicology studies revealed platform-mediated toxicity (neutropenia and anemia) but little or no evidence of lung toxicity, despite high levels of NaPi2b RNA expression in the lung. Subsequently, the anti-NaPi2b ADC, lifastuzumab vedotin, was tested clinically and was found to have activity in ovarian and, to a lesser extent, nonsquamous lung cancers, with overall response rates of 41% and 10%, respectively, in patients whose tumors were positive for NaPi2b by IHC and who were treated at the RP2D (Burris, 2014).

2.2. XMT-1536 Overview

XMT-1536 is an ADC developed to target NaPi2b-expressing tumors. The drug comprises XMT-1535, a humanized IgG1 anti-NaPi2b monoclonal antibody, conjugated with the active payload XMT-1267 (Auristatin-F hydroxypropylamide or AF-HPA) via a biocompatible, biodegradable polymer. (Bodyak et al. 2021)

After binding NaPi2b, XMT-1536 is internalized into the cell and traffics to the lysosome. The active drug XMT-1267 is released in the lysosomal compartment by intracellular enzymes that cleave the linker attaching XMT-1267 to the polymer. The active cytotoxin XMT-1267 is a tubulin-targeting anti-mitotic that is highly toxic to dividing cells. It readily diffuses across the plasma membrane, so that released XMT-1267 can kill neighboring cells in a NaPi2b-independent manner. This is referred to as “bystander-effect” killing. XMT-1267 is further metabolized to XMT-1521 (Auristatin F), which is markedly less cell permeable than XMT-1267 and is significantly less cytotoxic as a free drug. Bio-distribution studies in tumor-bearing mice have indicated that while high and sustained tumor concentrations of XMT-1267 are achieved,

the exposure to XMT-1267 in other tissues is much lower as it is metabolized to the less toxic XMT-1521, potentially mitigating normal tissue toxicity due to released drug payload.

2.3. Nonclinical Pharmacology

2.3.1. XMT-1535 – NaPi2b Binding and Internalization

XMT-1535 readily internalizes into NaPi2b-expressing cells. As an IgG1, XMT-1535 shows antibody dependent cell-mediated cytotoxicity (ADCC). XMT-1535 binds to the extracellular domain of human, cynomolgus monkey, rat and mouse NaPi2b with similar potency. None of the properties of XMT-1535 are adversely impacted upon drug conjugation to form XMT-1536, other than ADCC, which is moderately reduced with XMT-1536 compared to XMT-1535.

2.3.2. XMT-1536 Potency

XMT-1536 has potent cytotoxicity activity in the NaPi2b expressing cell line, OVCAR3, with an IC50 in the sub-nanomolar range. On average, XMT-1536 showed greater than 50 times selectivity compared to a non-binding control ADC. The unconjugated antibody XMT-1535 had no cytotoxic effect.

2.3.3. Xenograft Efficacy Studies

Several murine tumor xenograft studies have been conducted using both tumor cell line and patient derived models. XMT-1536 showed targeted, dose-dependent, anti-tumor activity in NaPi2b-positive tumor models. XMT-1536 induced partial tumor regressions in the OVCAR3 ovarian cancer cell line model after a single dose of 3 mg/kg (0.21 mg/kg payload equivalent dose), and complete tumor regressions after a single dose of 5 mg/kg (0.36 mg/kg payload dose) or 3 weekly doses of 3 mg/kg.

The anti-tumor activity of XMT-1536 was also evaluated in seven patient-derived xenograft models of NSCLC adenocarcinoma, chosen for high NaPi2b expression and representing a spectrum of oncogenic driver mutations prevalent in NSCLC adenocarcinoma (including tumors without oncogenic drivers). XMT-1536 was administered at 3 mg/kg intravenously, once weekly for 3 weeks (last dose on Day 14). Experiments ran until tumor growth past a pre-specified endpoint or Day 60. At the 3 mg/kg dose, XMT-1536 was active in 6/7 models, with complete tumor regression in 3 models, partial tumor regression in 1 model, and significant tumor growth inhibition in 2 models. In 3 of the 4 models where XMT-1536 induced tumor regression, regressions were durable, with most of the animals maintaining partial or complete regression at Day 60.

XMT-1536 was also evaluated in a set of 20 patient-derived xenograft models of ovarian carcinoma, which represented both pretreated and untreated cancers and were chosen without regard to expression of NaPi2b. XMT-1536 induced at least 50% reduction in tumor volume relative to baseline in 10/20 (50%) models when administered at a dose of 3 mg/kg once weekly for 3 weeks These findings lend strong support for the potential for clinical activity of XMT-1536 in patients with ovarian cancer.

2.4. Nonclinical Toxicology

The safety of XMT-1536 was studied in rat and cynomolgus monkey repeat-dose toxicology studies, with the monkey being the more sensitive species. In the repeat-dose GLP study in the rat, adverse target organ effects occurred mainly at the highest dose (6 mg/kg) and were seen in the testis, kidney, sciatic nerve, and mammary gland. In the repeat-dose monkey GLP study, the target organs were liver, kidney, spleen, thymus and, to a lesser extent, bone marrow (hypercellularity); none of the effects in these organs were considered severely toxic. Observed findings in the target organs in both species have been dose-dependent, monitorable and generally reversible.

In the rat study, there was a death of one animal treated at the highest dose (6 mg/kg); the cause of death was considered to be septicemia, without an evident focus of infection, and the relationship with XMT-1536 could not be established. In the monkey study, one animal treated at the highest dose (3 mg/kg) developed clinical signs of ataxia and decreased proprioception and was euthanized early due to clinical deterioration. Clinical pathology and microscopic findings were not obviously distinct from other animals treated at the same dose; hence, the cause of clinical deterioration was unclear and may have been multifactorial. Relationship of these events to XMT-1536 could neither be established nor ruled out.

Liver findings were observed in both rat and monkey repeat-dose toxicology studies, more prominently in the monkey. In the monkey dose-ranging study, there was fulminant liver failure at the highest doses (4 and 8 mg/kg), leading to premature deaths of several animals. In GLP studies in monkey and rat, liver was a target organ, although none of the effects were considered severely toxic. In the monkey GLP study, dose-dependent increases in AST, ALT, alkaline phosphatase and bilirubin were observed at the higher doses, peaking 7 days after dosing, with partial to complete recovery at later times. Microscopically, degeneration/regeneration was seen in the liver at higher doses. Similarly, in the rat GLP study, there were dose-related increases in AST, ALT, alkaline phosphatase and GGT. Microscopic findings included hepatocellular single cell necrosis at higher doses, increased mitoses, and mixed cell infiltration, but none of these were considered adverse findings.

Kidney findings were also observed in both species, with the rat being the more affected species. Microscopic findings in the rat included mild to moderate tubular degeneration, mild single cell necrosis, and mild glomerulopathy. In the monkey, there was dose-dependent, mild to moderate degeneration/regeneration and hyaline casts in the tubules, and mild glomerulopathy. Proteinuria was observed in both species, consistent with the histological findings. NaPi2b is expressed in rat, monkey and human kidney tubules, raising the possibility that the effects in the kidney tubules were target-dependent.

Hematologic effects of XMT-1536 administration consisted mainly of decreased red cell mass and apparently increased leukopoiesis, but none of the hematologic findings were considered severe. In rats, there was decreased red cell mass with reticulocytosis, increases in platelets and white blood cells, increased hematopoiesis in the spleen, and extramedullary hematopoiesis in other organs. In monkeys, there was decreased red cell mass with reticulocytosis, mildly to moderately decreased platelets, and increased white blood cell populations, accompanied by increased cellularity in the spleen and bone marrow. In the monkey GLP study there was also

evidence of an acute phase response, with increased fibrinogen, globulins, and triglycerides, and decreased albumin.

Ocular toxicities have been observed with ADCs, particularly with those using auristatin F. In the XMT-1536 studies there were no findings in the eye other than in the Harderian gland in the rat, which does not have a human equivalent. However, the tissue cross-reactivity study found plasma membrane expression of NaPi2b in the corneal and conjunctival epithelium in human tissue, but not in monkeys or rats, raising the possibility that target-mediated ocular toxicity could occur in humans that would not be detected in animal studies.

Peripheral neuropathy has been associated with several microtubule-targeting ADCs. Sciatic nerve findings were noted in rat GLP toxicology study of XMT-1536, mainly at the highest dose tested (6 mg/kg), including mild to moderate axonal degeneration and minimal to mild mononuclear cell infiltration, with partial or complete recovery. The only corresponding clinical observation was decreased hind limb movement, with complete recovery, in one high-dose rat.

NaPi2b protein is expressed in human, monkey, and rat lung tissues, specifically in pneumocytes and bronchial epithelium. In the rat GLP study, XMT-1536 was associated with dose-dependent increased interstitial cellularity and alveolar interstitial histiocytic infiltration, with complete or partial recovery. These findings were not considered adverse. There were increases in lung weight in monkeys that were fully reversible, but there was no microscopic correlate and no other evidence of lung pathology. Hence, the preclinical toxicology studies did not identify lung as a target organ for XMT-1536, perhaps because the toxin targets dividing cells, and the NaPi2b-expressing cell types in lung tissue are not normally undergoing active cell division in healthy tissue. However, the high expression of NaPi2b in human lung tissue raises a theoretical possibility of XMT-1536-mediated tissue damage under conditions of cell division such as inflammation and tissue repair.

XMT-1536 showed approximately dose proportional increases in C_{max} and AUC in plasma pharmacokinetic studies performed in rats and cynomolgus monkeys. In both species, the ratio of total XMT-1267 payload to free XMT-1267 has been greater than 1000-fold for both C_{max} and AUC. These data indicate that the drug linker is highly stable in plasma with minimal exposure to free drug payload. In rats, exposure to XMT-1535 antibody and XMT-1267 drug payload was dose proportional after the first administration of study drug, but less than dose proportional after the second administration, with higher doses showing greater loss of exposure. This is potentially indicative of the development of anti-drug antibodies against XMT-1536 in the rat. Assays to detect anti-drug antibodies were not conducted as part of the nonclinical testing program for XMT-1536.

Based on the totality of data in both rats and monkeys, the monkey was determined to be the more sensitive species, based primarily on the clinical deterioration and resulting euthanasia of one monkey dosed at 3 mg/kg in the GLP toxicity study, for which the contribution of XMT-1536 could neither be established nor excluded. The starting dose was therefore based on the highest non-severely toxic dose (HNSTD) in monkeys, which was 1.5 mg/kg. Using one-sixth the HNSTD and applying a scaling factor and dosing by body surface area yields a starting dose for the first-in-human trial of 3 mg/m^2.

Please refer to the Investigator's Brochure for a more detailed description of XMT-1536 nonclinical toxicology.

2.5. Rationale for Clinical Trial

2.5.1. Rationale for Starting Dose and Dose Escalation Design

XMT-1536 representative of the Phase 1 drug product was tested in repeat-dose GLP toxicology studies in cynomolgus monkey and rat (summarized in Section 2.4). Per ICH Guidance S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, XMT-1536 was administered intravenously on Days 1 and 22 in both species to support once every three-week dosing in humans. As described in Section 2.4, the HNSTD of XMT-1536 administered to cynomolgus monkey was 1.5 mg/kg (18 mg/m^2 after applying an allometric scaling factor of 12). The human starting dose was one-sixth the HNSTD per ICH S9. Therefore, the starting dose was 3 mg/m^2 administered intravenously every three weeks.

The DES segment of the study utilized a modified version of Simon's accelerated titration design (ATD) (Simon & Freidlin, 1997) in which single patients were treated at each of the first two doses, followed by the traditional 3+3 design starting at Dose Level 3. This design minimized the number of patients who were treated at low doses that were likely to be tolerable but unlikely to yield clinical responses. An FDA analysis of phase 1 study outcomes of ADCs found a narrow range of MTDs for ADCs using the same platform and concluded that prior clinical data could inform the design of phase 1 studies for ADCs that share the same small molecule drug, linker, and ratio of small molecule to monoclonal antibody (mAb) (Saber & Leighton, 2015). These properties are identical between XMT-1536 and XMT-1522, an anti-HER2 ADC used in a previous study, in patients with HER2-positive indications including breast, gastric, and lung cancers.

In the Phase 1 study of XMT-1522, doses up to and including 52 mg/m^2 were evaluated. Preclinical toxicology studies of the two ADCs, using essentially identical designs, yielded a higher HNSTD for XMT-1536 than XMT-1522.

Hence, as it was likely that XMT-1536 would be well-tolerated at doses up to at least 12 mg/m^2, 1 patient was initially enrolled at each of the first two dose levels of 3 and 6 mg/m^2 in order to avoid unnecessary exposure of additional patients at these doses. In the event of moderate toxicity at either of these doses, conversion to a 3 + 3 dose escalation design would have occurred.

2.5.2. Rationale for Study Population

This study will enroll patients with tumor types that have shown to have expression of NaPi2b. The priority for enrollment is ovarian cancer and NSCLC, adenocarcinoma subtype, because:

- NaPi2b is expressed on a high proportion of these tumor types (Lin, et al., 2015).
- Primary xenograft models of these tumor types have shown robust responses to XMT-1536, as described above.
- Clinical activity was seen with the anti-NaPi2b ADC lifastuzumab vedotin in patients with these cancers (Burris, et al., 2014).
- Early data from this study demonstrate tumor shrinkage in both populations, as well as ovarian cancer with low NaPi2b expression. (Tolcher et al., 2019; Richardson et al., 2020; Richardson, et al., 2020; Hamilton et al., 2020).

High-Grade Serous Ovarian Carcinoma

Ovarian Cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States. The majority of ovarian malignancies (90%) are derived from epithelial cells (epithelial ovarian cancer); the remainder arise from other ovarian cell types (non-epithelial ovarian cancer) [Kim et al., 2018; Chen et al., 2003].

Diagnosis is made histologically, and evaluation is commonly performed following surgical removal of an ovary or fallopian tube or biopsies of the peritoneum. Infrequently (approximately 20% with advanced disease), the diagnosis is based upon tissue or fluid obtained via image-guided biopsy, paracentesis, or thoracentesis [Diaz et al., 2010; Hewitt et al., 2007; Mehdi et al., 2010].

By report, NaPi2b is detected in serous carcinoma, a histologic subset of overall ovarian carcinoma. NaPi2b expression has also been documented in some of the less common histologies, such as clear cell and endometrioid, although much less information is available for these subsets. Conversely, mucinous carcinoma, which represents 10% of all epithelial tumors, has a much less frequent rate of expression.

NaPi2b expression can be detected in a well-defined set of normal tissues (Lin, et al., 2015) and expression appears to be retained in the tumors which arise from these tissue types. The variation in NaPi2b expression rates between different epithelial tumor histologies may be attributed to the differences in the cell of origin of these tumors. Formerly, the majority of ovarian epithelial tumors were believed to arise from the ovarian surface epithelium, but current understanding suggests that ovarian epithelial tumors have a variety of normal progenitor tissues. This oncogeny may explain why the majority of high-grade serous tumors, which are now considered to arise in NaPi2b expressing fallopian tube epithelium, also express NaPi2b, while some mucinous tumors, which may arise from various tissues including mucinous epithelium in synchronous teratomas (Wang et al., 2015), do not.

NaPi2b is expressed in some subtypes of epithelial ovarian carcinomas and is therefore a potential target for the development of therapeutic treatment options and optimized diagnoses (Gryshkova, 2009).

Current treatment options include debulking surgery and systemic chemotherapy; however, there is a significant unmet medical need in patients who become resistant to platinum-based therapy and therefore have few options for additional treatment.

Non-small Cell Lung Cancer, Adenocarcinoma Subtype

Worldwide, lung cancer occurred in approximately 2.1 million patients in 2018 and caused an estimated 1.7 million deaths. In the United States, there will be approximately 230,000 new cases of lung cancer and over 140,000 deaths annually (Siegel 2019).

Approximately 95% of all lung cancers are classified as either small cell lung cancer or NSCLC. This distinction is required for proper staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung.

For patients with NSCLC, initial management is largely determined by the stage of disease. Surgical resection offers the best opportunity for long-term survival and cure in patients with resectable NSCLC. The appropriateness of surgical resection of candidates with known or

suspected NSCLC includes preoperative staging and an assessment of performance status with concurrent comorbidities and pulmonary function to allow prediction of postoperative function.

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localized disease is the same, the molecular characterization of tumor tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy. However, treatments that provide meaningful clinical benefit with acceptable safety profiles remain a significant unmet need.

NaPi2b is expressed in a high proportion of NSCLC (adenocarcinoma subtype) (Lin, et al., 2015) and primary xenograft models of this subtypes have shown robust response to XMT-1536 and is therefore a potential target for the development of therapeutic treatment options and optimized diagnoses.

Beyond these primary indications, DES was open to several additional, rarer tumor types in which the available evidence suggests that expression of NaPi2b is a common event. Publicly available RNA expression data from The Cancer Genome Atlas (http://www.cbioportal.org) suggested that NaPi2b may be expressed in papillary renal and endometrial cancers at levels comparable to the level found in lung adenocarcinoma and ovarian and papillary thyroid cancers. We have recently verified expression at the protein level in these cancers using IHC, supporting the inclusion of these indications in the trial. (Data on file.) We also found robust expression of NaPi2b protein in papillary thyroid cancer, as reported previously. (Lin, et al., 2015). Finally, a patient-derived xenograft model of salivary duct carcinoma showed responsiveness to XMT-1536, supporting the inclusion of this very rare cancer type in the trial. (Data on file.) However, as of Protocol version 4.0, only serous ovarian and NSCLC, adenocarcinoma subtypes are being enrolled.

The EXP segment included patient cohorts with HGSOC and NSCLC, adenocarcinoma subtype to further evaluate safety and tolerability and gain an initial assessment of efficacy.

UPLIFT is the pivotal cohort segment of this study and will analyze the primary and secondary efficacy and safety endpoints in patients with platinum-resistant HGSOC. This study segment may form the basis of a BLA submission to the US FDA and may be supportive of future applications.

2.5.3. Rationale for Dose Expansion Design

The EXP initiated enrollment of patients with OC and NSCLC at 36 mg/m^2 dosed every 28 days (q28d), the MTD was then determined to be 43 mg/m^2 q28d and patients were enrolled at 43 mg/m^2 q28d with a BSA dose cap at 1.8 m^2. Enrollment in Expansion is now completed.

2.5.4. Rationale for UPLIFT Design

UPLIFT is designed as a Phase 2 pivotal cohort of patients with platinum-resistant ovarian cancer, a serious, life-threatening condition for which there is substantial unmet medical need. This design is based on preliminary clinical activity and favorable safety profile observed with XMT-1536 (upifitamab rilsodotin) in patients with ovarian cancer (OC), including fallopian tube and primary peritoneal cancer. In DES, XMT-1536 yielded 5 confirmed tumor responses in patients with OC with a trend toward a higher response rate observed with increasing doses of

XMT-1536 (upifitamab rilsodotin) and in tumors with positive NaPi2b expression (i.e., NaPi2b IHC H-score ≥ 110, defined as the lowest H-score at which a response was observed in DES). These early signs of dose proportional response led to the decision to implement EXP as there is a substantial unmet medical need in these patients with limited, if any, treatment options and response rates to these limited therapies are low. Historical data in this population treated with available therapy show response rates in the range of 4-12% and median progression-free survival (PFS) of 3 to 4 months (Pujade-Lauraine et al., 2019; Gaillard et al., 2016; Moore et al., 2019).

As reported by Hamilton et al. at ESMO 2020, the activity of XMT-1536 was further observed in patients with OC demonstrating an ORR of 34% including 2 patients with CR and a DCR of 79%. Responses were observed for patients dosed at 36 mg/m^2 q28d and 43 mg/m^2 capped at 1.8 m^2 q28d. The OC EXP NaPi2b-positive population (employing the same definition used in DES and defined as NaPi2b IHC H-score ≥ 110) demonstrated an ORR of 35% and DCR of 85%. The OC EXP lower NaPi2b population (also employing the same definition used in DES and defined as NaPi2b IHC H-score < 110) demonstrated an ORR of 29% and DCR of 57%.

Safety data from a pooled analysis of 123 (DES n=62; EXP n=61) patients with solid tumors likely to express NaPi2b who received at least one dose of XMT-1536 in the ongoing Phase 1 clinical study indicate XMT-1536 is safe and tolerable (see Section 2.6.2 for additional information).

Together, these safety and early clinical efficacy data support further study of XMT-1536 in patients with OC.

2.5.4.1. Rationale for NaPi2b Threshold

In UPLIFT, subjects will be enrolled unselected relative to NaPi2b expression. NaPi2b-positive will be defined using an immunohistochemical (IHC) assay and scored using a tumor proportion score (TPS) method. Evaluation of the efficacy/expression relationship will be done retrospectively, to a pre-defined cut-point of TPS ≥75.

The TPS ≥75 cutoff was chosen following retrospective evaluation of tumor tissue from an independent cohort of ovarian cancer participants relative to the UPLIFT cohort in Study MER-XMT-1536-1. In these prior cohorts, a clinical research IHC assay was used to retrospectively evaluate the NaPi2b biomarker cutoff. The TPS methodology was selected over the previously reported H-Score methodology in order to maximize reproducibility across readers and laboratories. The enrichment for response in NaPi2b-positive expressors in the early study is shown in Table 5 (data cut-off 03 December 2020).

The UPLIFT cohort will validate the predictive value of the TPS Score method, as determined by a NaPi2b IHC assay being developed.

Table 5: Best Response in Evaluable Patients with Ovarian Cancer, relative to a TPS ≥75 cut-off (n=47)

	All (n=47)	**NaPi2b-Positive (≥75) (n=26)**	**NaPi2b-Negative (<75) (n=18)**	**NaPi2b Not Yet Determined (n=3)**
CR; n(%)	2 (4)	2 (8)	0	0
PR; n(%)	11 (23)	8 (31)	2 (11)	1 (33)
SD; n(%)	19 (40)	11 (42)	7 (39)	1 (33)
ORR; n(%)	13 (28)	10 (38)	2 (11)	1 (33)
DCR; n(%)	32 (68)	21 (81)	9 (50)	2 (67)

2.5.5. Rationale for Recommended Phase 2 Dose in UPLIFT

A comprehensive review of clinical safety and efficacy data and PK (NCA and Pop PK) of the patients with ovarian cancer from the dose escalation and expansion segments of the ongoing MER-XMT-1536-1 study was conducted. The NCA and Pop PK data was reviewed along with exposure and safety/response analyses for OC patients treated at all doses in order to assess the optimal starting dose to maximize benefit risk profile of upifitamab rilsodotin.

Review of the safety data indicated that the 43 mg/m^2 Q4W dose capped at 1.8 m^2 (N=48) and uncapped (N=41) had an increased risk for Grade ≥3 adverse events characteristic of treatment with ADCs. Grade ≥3 thrombocytopenia occurred in 17% of patients at the 43 mg/m^2 capped dose and 12% of patients at 43 mg/m^2 uncapped dose compared to the 36 mg/m^2 dose (0%). Additionally, Grade ≥3 AST (43 mg/m^2, capped=35% and 43 mg/m^2, uncapped=39%) and fatigue (43 mg/m^2, capped=13% and 43 mg/m^2, uncapped=22%) occurred at higher rates compared to the 36 mg/m^2 dose group (increased AST =21% and fatigue=5%).

Dose reductions due to treatment-related AEs also differed between the dose groups: 30% of patients in 43 mg/m^2 dose groups required dose reductions compared to 11% of patients in the 36 mg/m^2 dose group.

The Pop PK analysis demonstrated the probability of observing Grade ≥2 ILD/pneumonitis, Grade ≥3 ILD/pneumonitis or other Grade ≥3 AEs was positively associated the AUC.

Both conjugated and free drug time averaged AUC demonstrated a small positive relationship with ORR.

Simulations of the impact of a BSA cap on the levels of conjugated and free XMT-1267 were conducted at both 1.8 and 2.2 m^2. Overall, BSA capping lowers the levels of conjugated and free XMT-1267 in the largest patients and the BSA cap of 2.2 m^2 limits the degree of potential under exposure of conjugated and free XMT-1267 compared to the current BSA cap of 1.8 mg/m^2.

Thus, the determination has been made to change the starting dose of upifitamab rilsodotin to 36 mg/m^2 Q4w with the inclusion of a BSA cap at 2.2 m^2. This dose change is intended to optimize

the benefit/risk profile of upifitamab rilsodotin by improving the overall safety profile while maintaining robust anti-tumor activity.

2.5.6. Rationale for QTc Sub-study

A sub-study will be conducted to assess the potential risk of XMT-1536 on corrected QT interval (QTc) prolongation. The International Council for Harmonisation (ICH) E14 guidance (ICH, 2017) recommends careful clinical testing in a thorough QT/QTc interval study whenever feasible. When thorough QT studies cannot be implemented, such as with oncologic therapies, the ICH guidance allows for alternative methods.

Overall, there were no nonclinical findings that would suggest a risk of QTc prolongation with clinical doses of XMT-1536. Cardiovascular safety was assessed in a 4-week repeat-dose Good Laboratory Practice toxicity study in cynomolgus monkeys. XMT-1536 was administered at 0.75, 1.5, and 3 mg/kg via intravenous infusion. Electrocardiogram (ECG) assessments were conducted once at pretreatment and during Weeks 4 and 7. Results demonstrated that there were no changes in heart rate or blood pressure related to treatment with XMT-1536. All ECG results were qualitatively and quantitatively within normal limits. No treatment-related effects on RR interval, PR interval, QRS duration, QT interval, or QTc interval were observed at any dose level based on comparison of predose and postdose group mean values and control values. Additionally, there were no changes in body temperature related to upifitamab rilsodotin.

As the preclinical data suggests that the risk of cardiac effects is low, dedicated ECG monitoring supported by concentration-QTc modeling will be employed to investigate the potential for drug-induced cardiac effects; an approach consistent with other oncology therapies. (Chari et al. 2021; Garg et al. 2013; Moore et al. 2019)

2.5.7. Rationale for Correlative Studies

Pharmacokinetic studies will be performed to measure blood levels of total XMT-1535 monoclonal antibody, antibody-conjugated and/or total XMT-1267 drug payload, free XMT-1267 drug payload, and free XMT-1521, a major metabolite of XMT-1267. These measurements will be used to evaluate maximum concentration (C_{max}) and exposure measured as area under the curve (AUC) to constituents of XMT-1536. These parameters will be compared to safety and efficacy measurements to identify potential safety/exposure or efficacy/exposure relationships.

Assays to detect anti-drug antibodies against XMT-1536 will be performed at baseline and at regular intervals during the study. The incidence of ADA development against XMT-1536 will be estimated. The correlation of development of ADA to pharmacokinetics, safety and efficacy parameters will be explored.

XMT-1536 has induced tumor regressions in mouse xenograft models in tumors representing a range of NaPi2b expression levels, with results from patient-derived ovarian cancer models suggesting that tumors without evidence of NaPi2b expression by IHC may not be responsive to XMT-1536, as would be expected from the mechanism of action. Patients will not be pre-screened for NaPi2b expression in their tumors, but NaPi2b staining by IHC will be analyzed retrospectively to assess whether this testing could be used to identify patients likely to have clinical responses to XMT-1536.

Pre-treatment tumor tissue specimens are being required to evaluate methods for quantifying NaPi2b protein expression. NaPi2b messenger RNA levels may be evaluated as a potential tool for identifying patient populations for treatment with XMT-1536. In conjunction with measurement of NaPi2b, the expression of additional genes related to tumor subsets, immunologic status of the tumor, and sensitivity to the auristatin payload class may be measured. In addition, tumor samples may be evaluated using assays to estimate overall mutation burden, to detect mutations in a panel of genes related to DNA repair and oncogenesis (for example, BRCA1 and 2, TP53, KRAS, etc.), and to measure proliferation index. Measures of clinical benefit (Overall Response Rate [ORR], disease control rate [DCR]) will be evaluated as a function of NaPi2b expression as determined by IHC, or other research methods, expression of other genes or groups of genes, and gene mutation status of genes with tumor-associated mutations. These potential additional tumor tests are outlined as exploratory objectives for the specific segments of the study and information will be included in the Informed Consent form.

A subset of patients may experience clinical benefit from XMT-1536, manifested by objective response or unexpected duration of disease stabilization. For the DES and EXP portions of the study, if an Investigator identifies a patient who in his/her opinion has experienced clinical benefit from XMT-1536, that patient will be asked to undergo an optional end-of-treatment biopsy, preferably from a progressing lesion amenable to biopsy. This tissue will be analyzed to understand potential mechanisms of acquired resistance to XMT-1536, including evaluation of NaPi2b expression or other biomarkers potentially associated with resistance to the auristatin F payload class (for example, expression of drug efflux transporters, immunologic features etc.). This end of treatment biopsy does not apply to the UPLIFT cohort.

Where allowed by local regulations, pharmacodynamic/biomarker samples may be stored beyond the end of the study for potential future research, if consented to by subjects. The duration and the intention will be outlined in the Informed Consent form, along with the intended research objective.

2.6. Benefit/Risk Assessment

2.6.1. Nonclinical Risk Assessment

XMT-1536 and related molecules have been evaluated in a comprehensive panel of in vitro pharmacology, in vivo pharmacology, pharmacokinetic, and toxicology studies generally conducted in accordance with ICH S9 Nonclinical Evaluation of Anticancer Pharmaceuticals.

A benefit-risk assessment was conducted based on the totality of the XMT-1536 nonclinical data package. First, it was demonstrated that the plasma exposure of conjugated drug at a tolerated dose in Cynomolgus monkeys was comparable to the plasma exposure at a dose that induced significant anti-tumor activity against human tumor xenografts in mice. This analysis suggested a therapeutic window in the nonclinical studies. Second, the toxicity profile of XMT-1536 in rats and monkeys was considered in the context of potential risks for clinical development. The nonclinical toxicity profile suggests that potential adverse events in the clinic are readily monitorable and generally reversible. In particular, the principal histological changes included dose-dependent increases in mitosis/single cell necrosis and vasculopathy in various organs with associated inflammation, hemorrhage, and/or thrombosis; these changes occurred in conjunction with readily monitorable changes in clinical pathology parameters. Taken together, the benefit-

risk assessment based on the totality of the nonclinical data supports the clinical development of XMT-1536.

The data from the pharmacology program is summarized in Section 2.3 and the toxicology data in Section 2.4.

The XMT-1536 toxicology program does not raise particular safety concerns for its intended use in this first-in-human study. Based on the findings from the nonclinical toxicology studies in rats and monkeys, specific surveillance, rapid-reporting and toxicity management parameters are included in the study protocol for the following adverse events of clinical interest:

- infusion-related reactions
- hemorrhage dysfunction
- hepatic toxicity

Additional surveillance and monitoring parameters are also included for ocular toxicity and neuropathy, as these findings have been associated with other ADCs based on other platforms.

As findings in both male and female reproductive organs have been seen with treatment with XMT-1536 or XMT-1267, pregnancy monitoring and contraception parameters are included in the clinical program.

Additional monitoring is in place through systematic review of adverse event data along with other study outcomes by a Safety Review Committee.

2.6.2. Clinical Risk Assessment

XMT-1536 as evaluated in patients with solid tumors likely to express NaPi2b has demonstrated a favorable safety profile to date. Please refer to the Investigator's Brochure for a detailed description of the most recent data on safety.

As of 10 June 2021, a total of 200 patients have been dosed with XMT-1536 (n=62 DES and n=97 EXP-OC; n=41 EXP-NSCLC) across a variety of cancer types. In DES, the cancer types studied included: salivary duct carcinoma (n=1); papillary renal (n=2); endometrial (n=8); non-small cell lung cancer or NSCLC (n=11); and ovarian cancer (n= 40).

Treatment-related AEs (TRAE) have been reported in 179/200 (90%) patients (79%; n=49 of patients in DES and 94%; n=130 of patients in EXP). Most TRAEs are mild or moderate (Grade 1 or 2) in severity; no severe (≥ Grade 3) TRAEs of neutropenia, peripheral neuropathy, or ocular toxicity have been reported.

The most frequently occurring TRAEs reported in ≥20% of patients (all grades) were fatigue (62%); nausea (54%); AST increased (49%); decreased appetite (32%); vomiting (27%); headache (27%); pyrexia (26%); diarrhea (25%); anemia (24%); platelet count decreased (23%); and blood alkaline phosphatase increased (21%).

Dose limiting toxicities in DES included AST elevation (at dose levels 5A at 30 mg/m2 q28d; 6 at 40mg/m2 q21d; 6A at 36 mg/m2 q28d), fatigue (at dose level 8A 52 mg/m^2 q28d capped at 1.8 m^2), and thrombocytopenia (at dose level 8A 52 mg/m^2 q28d capped at 1.8 m^2).

Transient AST elevation as determined by laboratory assessment was observed in a majority of patients dosed with XMT-1536, peaking at Day 8 of each cycle with levels returning to baseline

or Grade 1 by the start of the next cycle. There were no associated increases in other liver enzymes (including total bilirubin, ALT, alkaline phosphatase).

The previously presented preliminary efficacy data presented an ORR of 29% and DCR of 71% in the OC population in EXP (n=65). Two (7%) evaluable patients with platinum-resistant OC experienced a complete response (CR). Forty-two out of 65 (65%) were patients with platinum-resistant (including platinum refractory) ovarian cancer who had received up to 3 prior lines of systemic therapy while 23/65 (35%) were patients who had received 4 or 5 prior lines of systemic therapy (Richardson 2021). The efficacy data remains stable in this ongoing study.

This preliminary efficacy data is considered to provide a meaningful clinical benefit given that there is a substantial unmet medical need in these patients with limited, if any, treatment options and response rates to these limited therapies are low.

2.6.3. Risk Assessment Specific to the Concomitant Administration of COVID-19 Vaccine

Although data is limited, interactions between XMT-1536 and the COVID-19 vaccine are not expected. In patients who have received the COVID-19 vaccine, it is not expected that overall safety risks from treatment with XMT-1536 would be increased. Patients on XMT-1536 are permitted to receive vaccinations (including COVID-19, influenza, pneumococcal, HSV, shingles, etc.) while on study at the discretion of the treating physician. Additional guidance can be found in Section 6.3.5.

2.6.4. Overall Benefit/Risk Assessment

The safety is monitored and reviewed regularly by the sponsor in conjunction with a Safety Review Committee. Taken together, the ongoing safety and efficacy profile of XMT-1536 suggests the potential for benefit from treatment for the protocol population.

3. TRIAL OBJECTIVES

Table 6: Trial Objectives and Endpoints

	OBJECTIVES	ENDPOINTS
DES	**Primary:** Determine the MTD or RP2D of a once every 4-week administration of XMT-1536 Assess the safety and tolerability of XMT-1536	**Primary:** MTD, RP2D Safety and tolerability measures
	Secondary: Assess preliminary anti-neoplastic activity of XMT-1536 Assess PK of XMT-1536, its release product, and selected metabolites Assess the development of anti-drug antibodies and neutralizing antibodies Assess the association of tumor expression of NaPi2b and objective tumor response	Secondary: Objective response rate (ORR) Duration of response (DOR) Disease control rate (DCR) = CR + PR + SD (any duration) PK profile of XMT-1536, its release product, and metabolites Anti-drug antibody levels and nAb levels NaPi2b protein or RNA levels measured in tumor samples
	Exploratory: Retrospectively evaluate the association of objective response with tumor expression of genes other than NaPi2b, or other tumor molecular and histologic features. Mutation analysis for cancer-related genes.	*Exploratory:* Correlative measure for ORR and DCR, and alternative assays for measurement of NaPi2b expression, expression of other genes, or tumor gene mutations
EXP	**Primary:** Assess further safety and tolerability using the MTD or RP2D identified in DES Assess the preliminary anti-neoplastic activity of XMT-1536	**Primary:** Safety and tolerability measures ORR, DCR
	Secondary: Assess PK of XMT-1536, its release product, and selected metabolites Assess the development of anti-drug antibodies Assess the association of tumor expression of NaPi2b and objective tumor response Further assessment of preliminary anti-neoplastic activity in the treated population and defined sub-groups.	Secondary: PK profile of XMT-1536, its release product, and metabolites Anti-drug antibody levels and nAb levels NaPi2b protein or RNA levels measured in tumor samples Analyze the effect of NaPi2b expression on objective response DOR, PFS, OS

	OBJECTIVES	ENDPOINTS
		Sub-group analyses of responses in ovarian cancer patients including patients previously treated and failed therapy with bevacizumab and patients with and without BRCA mutation who were previously treated and failed therapy with PARP inhibitors.
	Exploratory: Retrospectively evaluate the association of objective response with tumor expression of genes other than NaPi2b, or other tumor molecular and histologic features. Mutation analysis for cancer-related genes.	*Exploratory:* Correlative measure for ORR, DCR, and alternative assays for measurement of expression of other genes, or tumor gene mutations.
UPLIFT	**Primary:** Determine the confirmed investigator-assessed objective response rate of XMT-1536 (upifitamab rilsodotin) at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 in patients with sodium-dependent NaPi2b (TPS ≥75) expressing platinum-resistant high-grade serous ovarian cancer (HGSOC), including cancers of ovarian, fallopian tube or primary peritoneal origin	**Primary:** Confirmed investigator-assessed ORR in the ITT-NaPi2b Positive (≥75) population (Positive [≥75]and negative NaPi2b [<75] status will have been defined prior to sample testing and based on data from a separate subject group.)
	Secondary: Assess the confirmed investigator-assessed objective response rate of XMT-1536 (upifitamab rilsodotin) regardless of NaPi2b expression. Assess the confirmed ORR by independent radiology review (IRR) for patients with higher NaPi2b and overall.	Secondary: Confirmed investigator-assessed ORR in the entire ITT population Confirmed ORR by IRR in the ITT-NaPi2b Positive population; Confirmed ORR by IRR in the entire ITT population
	Assess the DOR of XMT-1536 (upifitamab rilsodotin) among patients who achieved objective response. Assess the incidence and severity of adverse events	DOR in the ITT-NaPi2b Positive population; DOR in the entire ITT population Safety and tolerability measures

	OBJECTIVES	ENDPOINTS
UPLIFT	*Exploratory:* Assess the DCR	*Exploratory:* DCR in the ITT-NaPi2b Positive population; DCR in the entire ITT population
	Assess PFS	PFS in the ITT-NaPi2b Positive population; PFS in the entire ITT population
	Assess OS	OS in the ITT-NaPi2b Positive population; OS in the entire ITT population
	Evaluate expression of NaPi2b and other cancer-related genes in relationship to outcome.	Correlate NaPi2b expression and other cancer-related genes with BOR, PFS, ORR, OS.
	Assess the population PK	PK profile of XMT-1536 (upifitamab rilsodotin), its release product, and metabolites
	Assess relationship of XMT-1536 (upifitamab rilsodotin) exposure to efficacy and safety outcomes.	PK covariate analyses with selected safety and efficacy parameter
	Assess development of ADA and nAb in response to XMT-1536 (upifitamab rilsodotin) exposure.	Determine anti-drug antibody (ADA) and neutralizing antibody (nAb) levels in response to XMT-1536 (upifitamab rilsodotin) exposure.
QTc Sub-study	**Primary:** Evaluation of the concentration-response analysis of XMT-1536 versus the change in QTcF values	**Primary:** Concentration-response analysis of the change from baseline in the QTcF vs concentration of upifitamab rilsodotin
	<u>Secondary:</u> Evaluation of the effect of XMT-1536 on QTcF in patients with platinum-resistant HGSOC by timepoint analysis Evaluation of the effect of XMT-1536 on the PR-interval (PR), QRS duration (QRS), Heart Rate (HR), and ECG morphology.	<u>Secondary:</u> Change in the duration of ventricular repolarization using QTcF between baseline to post dose C1D1 and C3D1 at each of the post baseline ECG sampling timepoints

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This trial is an open label, multi-center study of XMT-1536 administered as an intravenous infusion once every four weeks. The dose escalation (DES) part of the study established the maximum tolerated dose (MTD) for XMT-1536 in patients with a number of tumor types likely to express NaPi2b, with a focus on patients with platinum-resistant, high-grade serous ovarian cancer and non-squamous non-small cell lung cancer (NSCLC), adenocarcinoma subtype. (Refer to Section 2.5.2). The MTD was defined as the highest dose of XMT-1536 that did not cause unacceptable toxicities defined by the protocol-specific dose limit-toxicity criteria in Section 9.5.

The dose selected for the EXP was 43 mg/m^2 q28d with a cap of BSA at 1.8 m^2 with the potential for further exploration of the dose for determination of an RP2D depending on the safety and efficacy response observed.

Patients may continue to receive XMT-1536 until disease progression provided the drug is well-tolerated and patients continue to derive clinical benefit in the opinion of the Investigator.

The EXP segment of the study (Cohort 2) consists of 2 parallel patient populations:

- Cohort 2A: Patients with HGSOC (including epithelial ovarian, fallopian tube, and primary peritoneal cancer).
- Cohort 2B: Patients with NSCLC, adenocarcinoma subtype.

Cohort 2A completed enrollment in April 2021 and Cohort 2B (NSCLC) completed enrollment June 2021. Dosing began in Cohort 3, known as “UPLIFT”, in April 2021. The EXP portion of the study will end once all patients have completed study treatment and sufficient data have been collected for the key study endpoints.

The UPLIFT cohort (Cohort 3) is for patients with platinum-resistant HGSOC. Site approval of Version 8.1 of the protocol implemented the UPLIFT cohort with a starting dose of upifitamab rilsodotin 43 mg/m2 (capped at BSA 1.8m2) q4wk.

Following implementation of Version 9.0, all patients enrolled in the UPLIFT cohort (the only cohort remaining open), received a starting dose of upifitamab rilsodotin 36 mg/m^2 (capped at BSA 2.2) q4wk. Any patients remaining on treatment from the DES and EXP segments of the study were switched to this dose. This dose change was informed by a review of the ongoing safety and efficacy data of the OC patients from the DES and EXP segments of the study along with a preliminary population pharmacokinetic analysis. This shift to the dosing paradigm is intended to optimize the overall benefit/risk profile of upifitamab rilsodotin by improving the overall safety profile while maintaining robust anti-tumor activity.

As of Version 9.0, a QTc Sub-study has been added, to be conducted at selected sites. In this segment, approximately 25 evaluable patients with HGSOC (UPLIFT Cohort 3) at selected research sites who agree to the sub-study specific eligibility criteria are eligible for enrollment. These research sites will offer participation within the QTc evaluation sub-study to all eligible patients in order to avoid bias in patient selection. In the event that enrollment in UPLIFT is completed, enrollment of patients into the QTc sub-study will continue until the target number of

evaluable patients is met. Data will be collected and processed by an external vendor with experience in conducting central cardiac reads to the international regulatory standards for reporting QTc safety assessments.

4.2. Number of Subjects

Sixty-two patients were enrolled in Cohort 1, DES.

Expansion Cohort 2A completed enrollment in April 2021 (N=97) and Cohort 2B (NSCLC) completed enrollment June 2021 (N=45).

Cohort 3, UPLIFT, will enroll approximately 180 to 240 patients with platinum resistant HGSOC, including cancers of ovarian, fallopian tube or primary peritoneal origin, for analysis.

The QTc sub-study will enroll approximately 25 evaluable patients across 10 to 15 selected research sites. Patients who are candidates for UPLIFT are candidates for enrollment into the QTc prolongation sub-study, if they meet the eligibility criteria for both UPLIFT and the QTc sub-study. Enrollment in the QTc sub-study will continue should enrollment in UPLIFT complete.

4.3. Clinical Evaluations

The Investigator will evaluate every patient prior to initiating a dose of XMT-1536. Patients will be evaluated for the occurrence of new and/or worsening toxicities at every visit. All adverse events will be graded according to NCI, CTCAE v5.0.

4.3.1. Physical and Neurological Examinations

A full physical examination (PE) consists of examining:

- Head/ears/eyes/nose/throat (HEENT),
- Palpable tumors,
- Neurological and muscular systems,
- Pulmonary and cardiovascular systems,
- Abdomen and lower extremities.

A brief physical examination consists of examining:

- HEENT,
- Pulmonary and cardiovascular systems.

The investigator (or designee) is responsible for performing the physical and neurological examinations. If the appointed designee is to perform these examinations, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. Whenever possible, the same individual should perform all physical and neurological examinations.

Any condition present at the post-treatment physical and neurological examinations that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

4.3.2. Vital Sign Measurements

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

Vital signs will be measured with the subject in a supine or a sitting/semi-recumbent position after 5 minutes rest.

A properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring blood pressure and heart rate is acceptable, although, when done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

Body temperature will be measured with either an oral (temperature taken at floor of the mouth) or tympanic thermometer.

Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF.

4.3.3. Electrocardiograms (All subjects)

Electrocardiogram recordings will be obtained after the subject has been at rest for at least 5 minutes, preferably 10 minutes. Additional ECGs may be obtained at the investigator's discretion and should always be obtained in the event of early termination. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF. The ECG will be repeated if any results are considered to be clinically significant (i.e., AEs).

At selected sites, a central ECG service will be used for reading all ECGs of patients enrolled in the QTc sub-study in order to standardize interpretations for the safety analysis; these sites will also have machines provided by the Sponsor/designee for use during the conduct of the study.

4.3.4. Ocular Examinations

Screening and on-study ophthalmic examinations may be performed by any health care professional licensed to perform such procedures. Any participant with ocular symptoms, clinically significant ocular findings on the exam (i.e., AEs), or clinically significant medical history of eye disease (medical history entry into the CRF) must be evaluated by an ophthalmologist.

Ophthalmic exams will include the following tests at a minimum: slit lamp examinations, visual acuity and ocular coherence tomography (OCT)conducted during the screen period, at the end of Cycle 2 and End of Treatment, regardless of the occurrence of symptoms such as eye pain.

Patients from sites in France are also required to undergo ophthalmic exams at the end of Cycle 6 (± 7 days).

Additional evaluations during study participation will be required if a patient complains of ocular toxicities and based on the discretion of the treating physician. For these patients, visual acuity, slit-lamp, and OCT examinations should be conducted after symptom onset, then at the end of every even numbered cycle, or more frequently as clinically indicated, until symptoms resolve.

4.3.5. Clinical Safety Laboratory Assessments

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal (i.e., AEs) during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

Additional details about safety laboratory assessments are provided in Section 8.

4.4. Dose Escalation

The DES segment of the study utilized an accelerated titration design (Simon & Freidlin, 1997) and for the first 2 dose levels, 1 patient was treated at each dose level. Initially, the following doses were studied at a q21d regimen: DL1, 3 mg/m^2; DL2, 6 mg/m^2; DL3, 12 mg/m^2, DL4, 20 mg/m^2; DL5, 30 mg/m^2; DL6, 40 mg/m^2. The following dose levels were also studied in DES at a q28 d regimen: DL4A, 20 mg/m^2; DL5A, 30 mg/m^2; DL6A, 36 mg/m^2; DL7A, 43 mg/m^2, and DL8A, 53 mg/m^2.

Following completion of the DES segment of the study, the dose escalation data of DL6A 36 mg/m^2 q28d was reviewed and the SRC recommended opening the EXP cohorts for ovarian cancer and NSCLC adenocarcinoma. In April 2020, the SRC declared 43 mg/m^2 q28d as the MTD based on 2 patients who experienced a DLT at DL8A, 52 mg/m^2 q28d (Grade 3 fatigue leading to dose reduction at Cycle 2 and Grade 3 thrombocytopenia leading to dose reduction at Cycle 2). Moving forward, the SRC will continue to review data of patients in the EXP and UPLIFT segments of the study.

4.5. Safety Review Committee (SRC) and Safety Review Meetings

4.5.1. Dose Escalation Safety Review Process

Following are the rules that were observed during the conduct of the DES segment of the study. Any dose level with 2 or more DLTs occurring in 6 or fewer treated patients would be considered to exceed the MTD and subsequent patients would be enrolled at lower dose level(s). In the absence of this, decisions about whether to escalate to the next dose level or continue the evaluation of the current dose level were made by the Safety Review Committee (SRC). The decision-making portion of the SRC consisted of: (1) all Principal Investigators, regardless of whether their sites enrolled a patient in the dose level to be evaluated; (2) the designated Medical Monitor, and (3) Mersana CMO and/or designated Medical Director.

Relevant safety data as outlined in the Charter was shared with the SRC prior to the meeting. These data were reviewed, compared against the rules for DLTs, and discussed by this group before the SRC made the decision whether to:

- Escalate the dose to the next planned level or a higher dose level that is less than the planned increase based on the data demonstrating drug tolerability.
- Add patients to a current level for additional evaluation
- De-escalate to a lower dose level for further evaluation; either a previously stipulated dose level or new lower dose level may be chosen based on patient safety data.

The discussion and decision that resulted from each Safety Review Meeting (SRM) was documented and distributed to all research sites who then shared this information internally and/or with their IRB/IEC according to local requirements. If an important medical trend was observed during data surveillance, an ad hoc SRM comprised of the Investigators, CRO Medical Monitor, and Sponsor Medical Monitors could be convened.

If one of the optional patients experienced a DLT after the SRC had cleared the next higher dose level and enrollment had commenced, an ad hoc meeting of the SRC was convened to review these data and determine the next steps. During the ad hoc review period, no new patients would receive the next higher dose. Patients receiving XMT-1536 at dose levels below or at the dose that was administered to the optional patient(s) with a DLT were allowed to continue the study during this period.

4.5.2. Expansion and UPLIFT Safety Review Process

Routine monitoring of safety data and review will continue throughout the study to ensure patient safety. Safety review meetings will be held among Investigators, the Sponsor personnel, and the Sponsor designee (i.e. SRC) to review safety data periodically as outlined in the charter.

4.6. Dose Reduction, Modification, and Delay Criteria After Completion of Cycle 1 and Beyond

All toxicity grades referred to in this section are from CTCAE Version 5.0. Patients should continue to be followed to resolve or return to baseline after any toxicity event along with following the guidance provided below.

4.6.1. Dose Reduction General Description

Investigators should refer to the sections and corresponding tables below for guidance related to specific events. If not specifically indicated in the sections and corresponding tables below for specific events, dose adjustments may be made by the investigator if a patient experiences toxicity despite appropriate use of supportive medication and would benefit from further treatment with XMT-1536 in the opinion of the Investigator.

In such cases, if the toxicity is >Grade 2, treatment at a reduced dose may commence if the observed toxicity resolves to Grade 1 or Grade 2. Dose reductions made at the discretion of the Investigator must be discussed with and approved by the Medical Monitor.

If a patient requires additional dose reduction while receiving 20 mg/m^2, study treatment should be discontinued. The dose cap at 2.2 m^2 is maintained for all dose reductions. See Table 7.

Table 7: Dose Reduction for Toxicity

Dose Reduction Steps	Dose To Be Administered
Starting Dose	36 mg/m^2, IV, every 28 days (capped at BSA of 2.2 m^2)
First dose reduction	30 mg/m^2, IV, every 28 days (capped at BSA of 2.2 m^2)
Second dose reduction	20 mg/m^2, IV, every 28 days (capped at BSA of 2.2 m^2)

4.6.2. AST/ALT Elevation

Elevations in AST and ALT have been observed in participants treated with XMT-1536. AST elevation with and without ALT elevation peaks at Day 8 of each cycle and recovers before the next dose. As outlined in Table 8, participants who experience ALT/AST elevation levels of Grade 3 will be retested within 7 days until levels return to ≤ Grade 2 and monitored at least weekly until the levels return to ≤ Grade 1 or to that participant's baseline. If the participant resides a significant distance from the research facility such that return is a hardship, arrangements can be made to have a local blood draw with the results and local normal range returned to the Study Investigator for monitoring.

Any events of suspected Hy's Law cases (unexplained aminotransferase increases to >3×ULN and simultaneous serum total bilirubin to >2×ULN) should be reported as serious adverse events as outlined in Appendix 1 (FDA, 2009).

Table 8: Dose Modification for Hepatotoxicity - AST and ALT

Grade	Threshold	Action
Grade 1	• If normal at baseline: >ULN - 3.0 x ULN • If baseline was abnormal: 1.5 - 3.0 x baseline	No dose adjustment is required.
Grade 2	• If normal at baseline: >3.0 – 5.0 x ULN • If baseline was abnormal: >3.0 – 5.0 x baseline	• No dose adjustment is required but repeat testing within 7 days • Withhold/delay XMT-1536 until toxicity resolves to Grade ≤1 or baseline. • Resume at same dose
Grade 3	• If normal at baseline: >5.0 – 20.0 x ULN • If baseline was abnormal: >5.0 – 20.0 x baseline	**AST Elevation:** • Repeat testing within 7 days • Monitor and withhold until toxicity resolves to Grade ≤1 or baseline. If recovery occurs: o ≤ 28 days from last dose, resume at same dose o >28 days from last dose, resume at next lower dose
		ALT Elevation: • Repeat testing within 7 days • For first occurrence: Monitor and withhold until toxicity resolves to Grade ≤1 or baseline. If recovery occurs: o ≤ 28 days from last dose, resume at same dose o > 28 days from last dose, resume at next lower dose • If Grade 3 recurs, resume at next lower dose level once toxicity resolves to Grade ≤1 or baseline
Grade 4	• If normal at baseline: >20.0 x ULN • If baseline was abnormal: > 20.0 x baseline	• Permanently discontinue XMT-1536

4.6.3. Interstitial Lung Disease (ILD)/Pneumonitis

Patients will be closely monitored throughout the study to allow for the early detection of symptoms that may be indicative of ILD/pneumonitis.

Symptoms may include hypoxia, dyspnea, cough, fever, or acute worsening of a baseline pulmonary condition. Comprehensive evaluation should be performed if a participant develops radiographic changes potentially consistent with ILD/pneumonitis or develops acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea or cough.

In the presence of these symptoms, immediate consultation with other specialists (for example, Infectious Disease and especially Pulmonology) is encouraged to rule out infectious, neoplastic,

and/or other causes. High-resolution CT radiographs of the chest should be obtained soon after the development of symptoms. Other evaluations to be considered include the following:

- Blood cultures, complete blood count, and other blood tests as appropriate
- Bronchoscopy and bronchoalveolar lavage if clinically feasible and warranted
- Pulmonary function test and pulse oximetry
- Arterial blood gases if clinically indicated

Treatment considerations should include the use of corticosteroids as soon as ILD/pneumonitis is suspected. If an etiology other than ILD/pneumonitis is diagnosed, follow the standard clinical practice. Refer to Table 9 for treatment management and dose modification rules if ILD/pneumonitis is suspected.

Table 9: Dose Modification and Management for ILD/Pneumonitis

Grade	Description	Dose Modification Actions	Additional Management Actions
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Resume XMT-1536 at the next lower dose.	• Contact the Medical Monitor immediately • Report as AECI • Monitor and closely follow-up for at least 7 days for onset of clinical symptoms, physical 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
Grade 2 Grade 3 Grade 4	Symptomatic; medical intervention indicated; limiting instrumental ADL Severe symptoms; limiting self-care ADL; oxygen indicated Life-threatening respiratory compromise: urgent intervention indicated (e.g., tracheotomy or intubation)	• Permanently discontinue use of XMT-1536. • Follow the participant until symptoms resolve or return to baseline	• Contact the Medical Monitor immediately • Report as AECI (and SAE, if the event meets any of seriousness criteria) • Promptly start systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks. • Monitor symptoms closely • Re-image as clinically indicated • If participant's condition worsens or demonstrates no improvement within 5 days, – Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and/or switching to intravenous administration (e.g. methylprednisolone) – Re-consider additional work-up for alternative etiologies as described above • Escalate care as clinically indicated

4.6.4. Hematologic Toxicity

The following guidance in Table 10 will be observed in the presence of adverse events of thrombocytopenia and anemia. No dose modification is required for Grade 1 or Grade 2 events.

Thrombocytopenia has been observed in patients treated with XMT-1536. Platelet count nadirs on Day 8 of each cycle and recovers to >100K before the next dose. Additional evaluation and treatment for thrombocytopenia should be considered in the setting of appropriate clinical signs and symptoms.

Table 10: Dose Modification for Hematologic Toxicity

Grade	Threshold	Actions
Anemia		
Grade 3	• Hemoglobin < 8.0 g/dL; transfusion indicated	• Consider transfusion • Withhold/delay dose until resolved to Grade ≤ 2, then resume at the same dose
Grade 4	• Life threatening consequences; urgent intervention indicated	• Transfuse • Withhold/delay dose until resolved to Grade ≤ 2, then resume next lower dose
Platelet Count Decreased		
Grade 3	• Platelets < 50 – 25 x 10P9P/L	• Repeat testing within 7 days and order additional evaluation based on clinical signs and symptoms • Monitor and if toxicity resolves to Grade ≤ 1 or baseline. If recovery occurs within: o ≤ 28 days from last dose, resume at same dose o >28 days from last dose, resume at next lower dose
Grade 4	• Platelets < 25 x 10^9/L	• Withhold/delay dose until resolved to Grade ≤1 or baseline, then resume at next lower dose

4.6.5. Proteinuria

Proteinuria has been observed in patients treated with XMT-1536. The guidance presented in Table 11 should be followed.

In the case of proteinuria detected by dipstick, repeat urine dipstick tests with clean or midstream urine collection is recommended.

If a participant experiences Grade 2 or 3 proteinuria confirmed by 24-hour urine collection, a referral to nephrology is required and the participant should be managed according to Table 11.

Participants with severe proteinuria (urinary protein ≥ 3.5 g/24 hrs) together with hypoalbuminemia (< 3 g/dL) and peripheral edema should permanently discontinue upifitamab rilsodotin as this could be signs/symptoms of nephrotic syndrome.

Table 11: Dose Modification for Proteinuria

Grade	Definition	Action
Grade 1	• 1+ proteinuria or urinary protein ≥ULN - <1.0 g/24 hr	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	• 2+ and 3+ proteinuria* or urinary protein 1.0 - <3.5 g/24 hr	• Assess proteinuria based on 24-hr urine collection before additional dosing decisions are made • If Grade 2 proteinuria confirmed by 24-hour urine protein level, withhold/delay XMT-1536 until toxicity resolves to Grade ≤1 or baseline. If recovery occurs: o within ≤ 28 days, resume at same dose o in >28 days, resume at next lower dose
Grade 3	• 4+ proteinuria or urinary protein ≥3.5 g/24 hr	• Assess proteinuria based on 24-hr urine collection before additional dosing decisions are made • If Grade 3 proteinuria confirmed by 24-hour urine protein level, withhold/delay dose until resolved to Grade ≤1, then resume at next lower dose. • Permanently discontinue XMT-1536 in patients with a combination of Grade 3 proteinuria (urinary protein ≥3.5 g/24 hrs; 4+ proteinuria), hypoalbuminemia (< 3 g/dL) and peripheral edema

*For Grade 2 proteinuria detected by urine dipstick in 2 consecutive cycles, treatment should be withheld while 24-hr urine collection is performed to make a further dosing decision. The patient may be monitored frequently by urine dipstick to watch for resolution, but confirmation of resolution to ≤ Grade 1 by 24-hr urine protein assessment is required for the patient to resume treatment.

4.6.6. Infusion-Related Reactions

Infusion-related reactions (IRRs) may occur several minutes into an infusion, during an infusion, or after it has been completed. IRRs can present with the following symptoms: fever, chills, dyspnea, hypotension, tachycardia, skin rashes, headache, nausea, or vomiting. The response to the reaction will be based on the severity of the symptoms. IRR management guidelines are found in Table 12 and Table 13.

Table 12: Initial IRR Management

Grade	Threshold	Action
Grade 1	Transient reaction: infusion interruption not indicated; intervention not indicated	• Continue infusion at present rate • Administer diphenhydramine and/or acetaminophen (or NSAIDs)
Grade 2	Infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	• Interrupt infusion and treat symptoms while observing response. If symptoms resolve rapidly, restart infusion at <50% of prior delivery rate. Consider increasing the infusion rate by 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate during the next cycle. • Administer diphenhydramine and acetaminophen (or NSAIDs) • Administer as needed: IV fluids, narcotics
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	• If the IRR is prolonged and symptoms do not rapidly respond to treatment, stop infusion. Determine if inpatient hospitalization is needed until resolution. • Infusion must not be restarted. Patient must not be retreated with XMT-1536. • Administer diphenhydramine and acetaminophen (or NSAIDs) • Administer as needed: IV fluids, narcotics, corticosteroids, beta-agonists, supplemental oxygen
Grade 4	Life-threatening consequences; urgent intervention indicated	• Discontinue treatment • Contact Medical Monitor

Table 13: Subsequent Dosing After IRR Occurrence

Prior IRR Severity	Infusion
Grade 1	• Pre-medicate (regimen may include antihistamines, antipyretics, and corticosteroids) prior to all subsequent doses. • Deliver the next infusion over 90 (±10) minutes. If no IRR, subsequent doses can be delivered over 30 min.
Grade 2	• Consult with the Medical Monitor if additional infusions are appropriate. If yes, pre-medicate prior to all subsequent doses. Deliver the infusion over 90 (±10) minutes.
Grade 3 or Grade 4	• Participant must be discontinued from the study. If possible, the participant will remain in the study and undergo all specified assessments through the end of that cycle and then End of Study Assessments. Refer to Section 1.3

4.6.7. Other Related Adverse Events and Ocular AEs

A participant with ocular symptoms, clinically significant ocular findings on exam, or clinically significant medical history of eye disease must be evaluated by an ophthalmologist. Other observed toxicities (i.e., AEs) that are considered related by the Investigator should be managed as per Table 14 and Table 15 below.

Table 14: Dose Modification for Ocular AEs

Grade	Actions
Grade 1 or 2	• For ocular symptoms, hold study treatment until participant has undergone complete examination by an ophthalmologist.
Grade 3	Consult with the Medical Monitor prior to withholding/delaying study treatment. • Hold study treatment until resolution to Grade ≤2 or Grade ≤1 as per consultation with the Medical Monitor. • Following resolution, resume study treatment at the next lower dose. • If Grade 3 recurs, resume study treatment at the next lower dose following resolution of additional occurrence.
Grade 4	• Consult with the Medical Monitor prior to permanently discontinuing study treatment.

Table 15: Dose Modification for Other Related AEs

Grade	Actions
Grade 1 or 2	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3	• Consult with the Medical Monitor prior to withholding/delaying XMT-1536. Hold XMT-1536 until resolution to Grade ≤2 or Grade ≤1 as per consultation with the Medical Monitor. • Resume at same dose • If Grade 3 recurs, resume XMT-1536 at the next lower dose
Grade 4	• Consult with the Medical Monitor prior to permanently discontinuing XMT-1536

4.6.8. Dose Delays

Delays in dosing may occur up to 8 weeks. Patients must discontinue if the dose must be delayed for more than 8 weeks unless discussed with the Sponsor Medical Monitor. During this period, tumor imaging will continue at the frequency outlined in Section 6.2.

4.7. Trial Definitions

4.7.1. End of Treatment

End of treatment is defined as the last dose of study treatment administered while a patient is on study.

4.7.2. End of Study

End of Study is defined as the last data collection point for each patient, defined as the last follow-up for Overall Survival.

4.7.3. End of Trial

The End of trial is defined as the last data collection point for the last patient on the trial, defined as the last follow-up for Survival captured for the last patient. Follow-up for survival will be for 12 months after the last dose of study medication for the last patient enrolled.

4.8. Study Termination

Mersana reserves the right to terminate the study at an any time for any reason at their sole discretion. Study sites will be closed upon study completion. The study may be terminated due to discontinuation of further study treatment development.

If the study is prematurely terminated or suspended, Mersana shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient(s) and assure appropriate patient therapy and/or follow-up.

In the case that the trial is terminated early by the Sponsor, accommodations will be made for patients, who are without alternative validated therapeutic options and who continue to derive benefit from XMT-1536, to have access to XMT-1536. These accommodations will be made on a case-by-case basis and in accordance with local regulations.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Patient Selection - Global

Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator and Sponsor Medical Monitor to ensure that the inclusion and exclusion criteria have been satisfied and that the patient is eligible for participation. The following screen data will be shared, in redacted form, with Sponsor for review and approval prior to a patient receiving his or her first dose, in accordance with local privacy rules:

- diagnostic report regarding the primary tumor (including histology results and mutation status)
- medical history
- demography
- current and prior medications, and prior cancer treatments
- physical examination and vital signs
- ECG and MUGA or Echo
- ophthalmic examinations including slit lamp, visual acuity and OCT
- all safety labs
- tumor imaging results
- confirmation of the availability of archive tissue, and the pathology report for the archived sample. If tissue for a recent biopsy can be submitted, that pathology report will also be sent to the Sponsor.

Note: If a fresh tumor sample is to be obtained, the tumor sample should be collected from a recurrent/metastatic lesions, using standard institutional procedures if this is deemed by the clinical investigator to be medically feasible and if it can be done with minimal risk to the patient. High risk procedures such as core needle biopsies of lung nodules should not be performed to obtain tissue on this protocol (Levit, et al., 2019).

5.2. Patient Selection – QTc Sub-study

Evaluation of overall eligibility will be conducted by the Investigator to ensure that the participant meets all of the inclusion criteria and none of the exclusion criteria as stated in the synopsis and Section 5.3 of the MER-XMT-1536-1 protocol. Additionally, patients participating in the QTc Sub-study must meet the cardiovascular criteria at study entry as described in Section 5.3.4.

Approximately 25 evaluable patients are expected to be enrolled in this sub-study. These patients will sign a separate consent form to participate in this sub-study. Based on historical oncology clinical studies with QTc sub-studies, the planned number of participants to be included is considered to be suitable for this QTc evaluation (Chari et al. 2021; Garg et al. 2013; Moore et al. 2019)

5.3. Subject Inclusion and Exclusion Criteria

5.3.1. General Inclusion Criteria Specific to all Segments of the Study

1. Females and males, age ≥ 18 years old.
2. ECOG performance status 0 or 1.
3. Measurable disease as per RECIST, version 1.1.
4. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 except alopecia, stable immune-related toxicity such as hypothyroidism on hormone replacement, adrenal insufficiency on ≤ 10 mg daily prednisolone (or equivalent), chronic Grade 2 peripheral sensory neuropathy after prior taxane therapy.
5. Cardiac left ventricular ejection fraction (LVEF) ≥ 50% or ≥ the institution's lower limit of normal by either Echo or MUGA scan.
6. Adequate organ function as defined by the following criteria:
   a. Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3
   b. Platelet count ≥ 100,000/mm^3
   c. Hemoglobin ≥ 9 g/dL[a]
   d. In patients not on anticoagulation therapy: INR, activated partial thromboplastin time (aPTT), and prothrombin time (PT) all within 1.2 times the institution's upper limit of normal (ULN). Patients on anticoagulation therapy are allowed if their relevant laboratory values are within the therapeutic window.
   e. Estimated glomerular filtration rate (GFR) ≥45 mL/min[b].
   f. Total bilirubin ≤ the ULN
      - Patients with asymptomatic elevations in unconjugated bilirubin due to Gilbert syndrome or stable chronic hemolytic anemia (e.g., hereditary spherocytosis, sickle cell disease, thalassemia intermedia) may be eligible after discussion with the Sponsor Medical Monitor.
7. Aspartate aminotransferase (AST or SGOT), and alanine aminotransferase (ALT or SGPT) ≤ 1.5 times the institutional ULN.
8. Albumin ≥ 3.0 g/dL
9. During the study, female study participants of child-bearing potential must use a highly effective non-hormonal form of contraception for the duration of study drug administration and for at least 6 months after the last dose of study drug. Please see Appendix 7 for examples of non-hormonal highly effective contraceptive methods.
10. Male study participants must use barrier contraception (condoms) for the duration of study drug and for at least 6 months after the last dose of study drug. The WOCBP partners of male study participants must use highly effective contraception for the duration of study drug and for at least 6 months after the last dose of study drug (Appendix 7).
11. Able to provide informed consent.

[a] Prophylactic transfusion of blood (or blood components) within 14 days prior to initial dosing cannot be used to meet enrollment criteria. Transfusion of blood (or blood components) to manage treatment-emergent anemia or other cytopenias is permissible and will be recorded as a concomitant medication. Growth factor prophylaxis cannot be used prior to XMT-1536 administration in any cycle. However, the use of growth factors as treatment for cytopenia is allowed. Please contact the Sponsor Medical Monitor if this is necessary. If cytopenia occurs after administration of Cycle 1, use of growth factors may be administered prophylactically in subsequent cycles at the discretion of the Investigator and after consultation with the Medical Monitor.

[b] Calculated using CKD-EPI Creatinine Equation https://www.kidney.org/content/ckd-epi-creatinine-equation-2009 or institutional standard method.

5.3.2. General Exclusion Criteria Generic to all Segments of the Study

1. Major surgery within 28 days of starting study treatment or systemic anti-cancer therapy within the lesser of 28 days or 5 half-lives of the prior therapy before starting study treatment (14 days or 5 half-lives for small molecule targeted therapy); or recent radiation therapy with unresolved toxicity or within a time window of potential toxicity (consultation with the Sponsor Medical Monitor is recommended).
2. Patients with untreated CNS metastases (including new and progressive brain metastases), history of leptomeningeal metastasis or carcinomatous meningitis.
    a. Patients are eligible if CNS metastases are adequately treated, and patients are neurologically stable for at least 2 weeks prior to enrollment.
    b. In addition, patients must be either off corticosteroids, or on a stable/decreasing dose of ≤ 10 mg daily prednisone (or equivalent). Anticonvulsants are allowed except for those drugs associated with liver toxicity. See Appendix 4.
3. Untreated, known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). In addition, negative serology is required during screening (baseline) for HBV and HCV:
    a. HBV: Patients with serologic evidence of chronic HBV infection should have an HBV viral load below the limit of quantification to be eligible.
    b. HCV: Patients with a history of HCV infection should have completed curative antiviral treatment and HCV viral load below the limit of quantification.
    c. HIV: Screening for HIV is not required except if mandated by local regulations or indicated based on clinical assessment.
4. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease) or intercurrent illness that could increase risk of adverse events, whether or not potentially related to study treatment (in unclear cases, consultation with the Medical Monitor is recommended). Further, patients are excluded with the following characteristics:
    a. A baseline prolongation of QTcF interval >CTCAE G1: repeated demonstration of a QTcF interval >480 milliseconds (ms) using Frederica's QT correction formula.
    b. A history of additional risk factors for Torsade's de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
5. History of cirrhosis, hepatic fibrosis, esophageal or gastric varices, or other clinically significant liver disease. Testing beyond laboratory studies otherwise defined in the eligibility criteria, to diagnose potentially clinically significant liver disease based on

risk factors such as hepatic steatosis or history of excessive alcohol intake, will be based on clinical judgement of the investigator.

6. Patients cannot receive drugs associated with hepatotoxicity concurrent with XMT-1536 administration (refer to Appendix 4). Patients may receive acetaminophen/paracetamol for a limited time but at a total daily dose of ≤ 2 g per day. Use of NSAIDs or steroids for treatment of fever is encouraged.
7. Current use of either constant or intermittent supplementary oxygen therapy.
8. History of or suspected pneumonitis or interstitial lung disease.
9. Oxygen saturation on room air <93%.
10. Pregnant or nursing women.
11. Diagnosis of additional malignancy that progressed or required active treatment within the last 2 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix
12. Active corneal disease, or history of corneal disease within 12 months prior to enrollment.
13. Use of strong CYP450 3A inhibitors or inducers that cannot be discontinued while receiving study treatment. Refer to Appendix 5.
14. Known sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
15. In the Czech Republic, patients cannot be enrolled if they have received a live/attenuated vaccine within 30 days of study entry or if they plan to receive a live/attenuated vaccine while on treatment through 90 days post the last dose of study medication.

5.3.3. Ovarian Cancer Eligibility Criteria for UPLIFT – Cohort 3

Inclusion Criteria:

1. Histological diagnosis of high grade serous ovarian cancer, which includes fallopian tube, or primary peritoneal cancer, that is metastatic or recurrent.
2. Platinum-resistant disease:
   a. Patients who have only had 1 line of platinum-based therapy must meet all of the below criteria:
      - have received at least 4 cycles of platinum-containing chemotherapy,
      - have had a response [complete response/remission (CR) or partial response/remission (PR)],
      - have progressed between 3 months and ≤ 6 months after the date of the last dose of platinum
   b. Patients who have received 2 to 4 lines of prior platinum-based therapy must have received at least 4 cycles of platinum-containing chemotherapy within their last platinum-based regimen and then progressed within 6 months after the date of the last dose of platinum.

Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic image showing progression. Patients who progressed within 3 months of front-line platinum-based therapy are excluded. If radiographic progression was not documented, the date of progression based on biopsy can be used for calculation.

3. One to 4 prior lines of systemic therapy for ovarian cancer:
    a. Prior treatment with bevacizumab is required for patients with 1 to 2 prior lines of therapy.
    b. In France, patients must have received at least 2 lines of systemic therapy and must not be candidates for surgery.
    c. Definitions for prior lines of therapy:
        i. Adjuvant ± neoadjuvant considered one line of therapy as long as they are the same regimens (e.g., platinum/taxane for 4 cycles before surgery followed by platinum/taxane for 4 cycles after surgery)
        ii. Maintenance therapy (e.g., bevacizumab, PARPi, endocrine therapy) will be considered as part of the preceding line of therapy (i.e., not counted independently)
        iii. Therapy given for only 1 cycle and discontinued due to toxicity in the absence of progression will not be counted as a new line of therapy; therapy given for 2 or more cycles will be counted as a line of therapy. Substitutions of different platinum agents or taxanes will not be counted as new lines.
        iv. Hormonal therapy (e.g., tamoxifen, letrozole) will be counted as a separate line of therapy unless it was given as maintenance.
    d. In Sweden, patients must have received prior treatment with pegylated liposomal doxorubicin or paclitaxel, if not contraindicated
    e. In Finland, patients must have exhausted available curative, effective, or suitable treatment options for HGSOC (e.g., have received paclitaxel, pegylated doxorubicin or topotecan)
4. Patients must be willing to provide an archival tumor tissue block or slides or if not available, undergo procedure to obtain a new tumor biopsy using a low-risk, medically routine procedure.

Exclusion Criteria:

1. Low-grade, clear cell, endometrioid, mucinous, carcinosarcoma, germ-cell, mixed histology, or stromal tumors.
2. Prior treatment with mirvetuximab soravtansine or another ADC containing an antitubulin payload.
3. Lack of response to front-line, platinum-containing therapy or progression less than 3 months after completing front-line, platinum-containing therapy.
4. Participation in DES or EXP segments of this study.

5.3.4. Eligibility Criteria for QTc Sub-study

Participants will have met all inclusion and none of the exclusion criteria as noted in the overall MER-XMT-1536-1 protocol as well as the additional criteria below, specific to this sub-study:

QTc Inclusion Criteria:

1. Study patient has agreed to remain in the clinic longer on the Day 1 of Cycle 1 and Cycle 3 (approximately 4-6 hours following XMT-1536 administration).

QTc Exclusion Criteria:

1. Use of strong CYP450 3A inducers, as provided in Appendix 5, dosed for systemic exposure 7 days prior to the first dosing and through to Day 9.
2. Uncontrolled cardiac arrhythmias, for example, atrial fibrillation with a ventricular response at rest > 100 beats per minute. left bundle branch block (LBBB)
3. Known abnormality of any cardiac valve (either stenosis or regurgitation) that is greater than moderate in severity.
4. Subjects not in sinus rhythm at screening with HR >45- <100
5. Any ECG abnormality that can interfere with the measurement of the QT interval

5.3.5. Ovarian Cancer Eligibility Criteria for Expansion – Cohort 2A

Obsolete as of Version 9.0 as enrollment has been closed. Please refer to prior version of the protocol if needed.

5.3.6. NSCLC Eligibility Criteria for Expansion – Cohort 2B

Obsolete as of Version 9.0 as enrollment has been closed. Please refer to prior version of the protocol if needed.

5.4. Subject Withdrawal Criteria, Overall Survival and Long-Term Follow-up

5.4.1. Discontinuation from Study Treatment

Patients may be discontinued from study treatment at any time and continue in the study for long-term follow up. Specific reasons for discontinuing study treatment include the following:

- Unacceptable toxicity
- Risk to the patient as judged by the Investigator, Sponsor, or both
- Severe non-compliance with protocol as judged by the Investigator, Sponsor, or both
- Pregnancy
- Withdrawn consent
- Loss to follow-up
- Death

Resignation from treatment will allow a patient to remain in the study for safety evaluations and efficacy assessments and not undergo further biopsies or routine laboratory testing. Safety labs may be drawn at the discretion of the Investigator. All patients who resign from treatment will be requested to continue follow-up through at least 60 days (approximately 5 half-lives) post dose for safety monitoring purposes. WOCBP should have monthly pregnancy testing through 6 months post the last dose of study treatment as noted elsewhere in the protocol.

5.4.2. Progression Free Survival

To assess progression free survival after a patient has stopped dosing with XMT-1536 for any reason, the interval for ongoing tumor imaging assessments and evaluation per RECIST should be performed as outlined in Section 6.2 if a dose delay occurs. Patients will continue with tumor imaging until disease progression, they withdraw consent, begin receiving a different cancer treatment, or expire.

Entrance into hospice care preempts this request. Refer to Section 1.2 for a complete description of the assessments to be conducted at the End of Treatment.

In all cases, the reason for withdrawal from study treatment must be recorded in the eCRF. If the reason is initially unknown, the patient should be followed to establish whether the reason was an adverse event. If yes, this event will be recorded as the reason for study treatment termination.

5.4.3. Discontinuation from the Study

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Loss to follow-up
- Death from any cause
- Sponsor’s decision to terminate study
- Investigator’s decision

A patient may withdraw from the study at any time at their own request or may be withdrawn at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an EOT visit should be conducted as outlined in Table 2.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

5.4.4. Duration of treatment:

Treatment may continue indefinitely unless one of the following occurs:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse events or pregnancy

- Patient non-compliance with study instructions
- Patient withdraws consent for participation from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator

Patients can be continued on XMT-1536 following disease progression if the Investigator perceives the potential for the patient to derive benefit from continued exposure, after discussion with the Sponsor Medical Monitor.

6. TREATMENT OF SUBJECTS

6.1. Randomization and Blinding

All segments of this study are open-label. There are no steps provided for randomization or blinding of study drug. However, Sponsor and Research Site personnel will remain blinded to NaPi2b expression levels in patients participating in the UPLIFT cohort until the study database has been locked.

6.2. Tumor Measurements

Protocol mandated re-staging CT or MRI scans should encompass the chest, abdomen, and pelvis. Either contrast CT or contrast MRI technique will be selected for the screen images and will continue to be consistently used for each patient for the duration of their study participation. PET-CT can be used throughout the study if first approved by the Sponsor Medical Monitor. The same modality must be used throughout the study per patient

Patients with history of metastasis that cannot be assessed by CT/MRI chest/abdomen/pelvis need additional imaging for complete tumor evaluation on study. For examples refer to Table 2 Section D Tumor Imaging.

Tumor imaging will be conducted every 8 weeks ± 3 days from Cycle 1 Day 1, even if dose administration is delayed in a subsequent cycle(s). Tumor imaging will be conducted every 12 weeks ±7 days after 24 weeks on study. Tumor imaging will be interpreted using RECIST v. 1.1. (Appendix 3).

Patients who achieve a response (i.e., CR or PR) will be assessed for response confirmation per RECIST v 1.1 as soon as 26 days but no later than 42 days post first determination of response as per RECIST v1.1 guidelines. Subsequent scans will be conducted every 8 weeks ± 3 days from the date of the confirmation scan from the date of the confirmation scan. If the patient has been on study treatment for ≥24 weeks, subsequent scans can be conducted every 12 weeks ± 7 days (depending on time elapsed since Cycle 1 Day 1) from the date of the confirmation scan.

6.2.1. Independent Radiology Review

Investigator assessed tumor imaging pre dose and all points after dosing with XMT-1536 (upifitamab rilsodotin) will be conducted at each research site in accord with RECIST v 1.1 and the local policies. These results will be recorded in the clinical database and used for the primary endpoint. Tumor images will also be sent to a central overread facility and these results will be used to conduct a supplementary analysis for patients participating in UPLIFT, Cohort 3.

6.3. Concomitant Medications and Therapies

6.3.1. Strong Inhibitors and Inducers to Cytochrome P450 3A

Patients should not be using strong inhibitors of CYP450 3A for 14 days before initiation of XMT-1536 dosing and until 14 days after the last dose. A strong inhibitor is defined as one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance. Refer to Appendix 5 for the CYP450 3A Interactions chart governing this protocol.

Additionally, for patients enrolled in the QTc Sub-study, strong inducers of CYP450 3A should be avoided. Similar to inhibitors, a strong inducer A strong inhibitor is defined as one that

causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance. Please refer to Appendix 5 for examples of these inducers to be avoided during participation in the QTc sub-study.

6.3.2. Use of Drugs Associated with Hepatotoxicity

Drugs Categorized as "Most DILI Concern" and "Not Withdrawn or Discontinued" (Appendix 4) by the FDA are those drugs most likely to possibly cause drug-induced liver injury (DILI). These drugs should be used with caution if required per standard of care. If a drug on this list must be used during the study to render appropriate medical care and for which no alternative is available, the Medical Monitor may be contacted to discuss, if desired.

6.3.3. Other Oncology Therapies

Other experimental or approved treatments including cytotoxic regimens, chemotherapy, immunotherapy, hormonal therapy or biological agents cannot be used during this trial or for 28 days or 5 half-lives, whichever is shorter, prior to Cycle 1, Day 1. Refer to Section 5.3 for specific inclusion and exclusion criteria related to prior anti-cancer therapies in PROC (Section 5.3.5) and NSCLC (Section 0).

6.3.4. Palliative Radiotherapy and Bisphosphonates

Palliative radiotherapy treatment can be used to treat symptomatic bone metastases. Please contact the Medical Monitor prior to administration. Bisphosphonates or denosumab to prevent or control bony metastases, treat osteoporosis, or address bone pain may be used. Before initiating treatment with bisphosphonates or denosumab with a study patient, approval must be obtained from the Study Medical Monitor.

6.3.5. Vaccinations

Patients on XMT-1536 are permitted to receive live/attenuated or non-live vaccinations (including COVID-19, influenza, pneumococcal, HSV, shingles, etc.) before study entry or while on study, if the vaccine is administered in line with standard of care as per the discretion of the treating physician and as per local or institutional policies, except in the Czech Republic. Patients in the Czech Republic must not receive live/attenuated vaccines within 30 days of study entry, or plan to receive a live/attenuated vaccine while on treatment through 90 days post the last dose of study treatment.

Where allowed, administration of vaccinations will be recorded on concomitant medication page in the study database.

Positive COVID-19 tests will be recorded in the AE module of the study database. Patients who test positive may remain on study, however, clinic visits and treatment should follow institutional guidelines for cancer patients. If quarantine is required, study treatment will be withheld. When the patient has completed quarantine and the patient is clinically appropriate for further treatment as determined by the treating oncologist, then study treatment may resume.

A negative COVID test is not mandated by the study Sponsor and such testing should follow institutional guidelines. Delays in dosing may occur up to 8 weeks. Patients must discontinue if the dose must be delayed for more than 8 weeks unless discussed with the Sponsor Medical Monitor.

For additional information on COVID-19 vaccinations and cancer treatment, refer to the most recent version of the NCCN guidance on COVID-19 vaccinations in people with cancer.

6.3.6. Use of Drugs Associated with QT Prolongation

This section is applicable to all patients enrolled in the QTc sub-study. For those patients, drugs known to cause QT prolongation should not be used during study participation in the QTc sub-study or for 30 days prior to study entry. A non-comprehensive list of these medications is provided in Table 16 (Nachimuthu, Assar, and Schussler 2012). If a drug to prolong QT must be used during the study to render appropriate medical care and for which no alternative is available, the investigator should contact the Medical Monitor to discuss the circumstance, particularly for patients participating in the QTc sub-study.

Table 16: Examples of Drugs Known to Cause QTc Prolongation

Generic Name	Generic Name
Amiodarone	Ibogaine
Anagrelide	Ibutilide
Azithromycin	Levofloxacin
Bepridil	Levomepromazine
Cesium chloride	Levosulpiride
Chloroquine	Meglumine
Chlorpromazine	Methadone
Chlorprothixene	Moxifloxacin
Cilostazol	Nifekalant
Ciprofloxin	Papaverine hydrogen chloride
Citalopram	Pentamidine
Clarithromycin	Pimozide
Cocaine	Procainamide
Disopyramide	Propofol
Dofetilide	Quinidine
Domperidone	Roxithromycin
Donepezil	Sertindole
Dronedarone	Sevoflurane
Droperidol	Sotalol
Erythromycin	Sulpiride
Escitalopram	Sultopride
Flecainide	Terlipressin
Halofantrine	Terodiline
Hydroquinidine	Thioridazine
Hydroxychloroquine	

6.3.7. Additional Lifestyle Considerations for Patients Enrolled in the QTc Sub-Study

On the days those patients are to undergo matching ECG/PK assessments within the QTc sub study, they are encouraged to avoid food and beverages containing xanthines/caffeine for 24 hours prior to these assessments. Small amounts of caffeine derived from normal food stuffs e.g., 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the

exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction.

Additionally, patients are encouraged to avoid food and beverages containing grapefruit/Seville orange during the conduct of the QTc sub-study.

6.4. XMT-1536 Administration

After the patient has been authorized to dose, research personnel will enter the requested information into the randomization system for all EXP patients and into the study specific system for all UPLIFT patients. A drug vial number will be issued, and this will be provided to the pharmacist to initiate dose preparation.

XMT-1536 is administered intravenously via peripheral IV or in-dwelling venous catheter (port-a-cath). Administration procedures will ensure that the entire scheduled dose is delivered and that no part of the scheduled dose remains in the infusion line.

The initial dose for each patient will be administered over 90 min. If no infusion-related reaction (IRR) occurs, all subsequent doses can be administered over 30 to 90 min. Treatment of IRRs should be according to institutional standards, or the guidelines given in Section 4.6.6. Any treatment for an IRR will be recorded as a Concomitant Medication.

~~6.5.~~ Supportive Care

XMT-1536 will be administered intravenously in a clinic setting with rapid access to trained emergency personnel and the customary equipment used for emergency treatment. Beyond the planned assessments, patients will be generally monitored for emergent infusion reactions, e.g., hypersensitivity, by medical personnel for the first 90 minutes after the first infusion and for 30 minutes after administration of the second and subsequent doses. Patients will be monitored for longer periods where required by local regulations. After the monitoring period, patients will be instructed to remain on the dosing clinic premises until all study assessments have been completed for each dosing visit (about 4 hours after infusion for Dose 1 and Dose 3, and about 1 or 2 hours after infusion for all other doses).

6.5.1. Prophylaxis and Standard Post-Treatment Regimens

Prophylaxis for IRRs, particularly for nausea and vomiting, and fever is recommended prior to the first dose of XMT-1536. The type of prophylaxis for nausea and vomiting will be commensurate with the patient's reaction to prior anticancer therapies. Suggested therapies should follow consensus guidelines (e.g., NCCN, ASCO) and may include 5-HT3 receptor antagonists and/or dexamethasone, with the choice of agent(s) and dosage at the Investigator's discretion. Treatment of nausea and vomiting should be according to institutional standards. Typical IRRs (occurring during or within hours of infusion) have been very rare with XMT-1536 treatment. Delayed fever has occurred in several patients, and prophylactic medication to prevent fever, before infusion and/or for several days after infusion, should also be considered (e.g., dexamethasone 8-10 mg IV). Fever may be treated with NSAIDs or steroids, but the use of acetaminophen (paracetamol) is discouraged and should be limited to ≤2 g per day due to the risk of liver enzyme elevations or hepatotoxicity. See Table 32 for guidance on prophylactic medications appropriate in this study.

If a patient experiences an IRR after the first administration or subsequent dosing, refer to Section 4.6.6 for guidelines on IRR treatment and subsequent dosing.

Consider use of proton-pump inhibitors for the prevention of gastritis and/or upper gastrointestinal bleeding in patients receiving ibuprofen and corticosteroids, particularly in participants with other underlying risk factors such as history of gastro-esophageal reflux or peptic ulcer disease; or such as concomitant use of anti-coagulants.

Prophylactic transfusion of blood (or blood components) prior to initial dosing cannot be used to meet enrollment criteria. Transfusion of blood (or blood components) to manage treatment-emergent anemia or other cytopenias is permissible and should be recorded as a concomitant medication. Growth factor prophylaxis cannot be used prior to XMT-1536 administration in any cycle.

All medications used pre-or post-treatment for managing infusion reactions will be recorded in the eCRF in the correct category, per completion instructions. Concomitant medication use is monitored frequently, and the protocol will be clarified or amended should a specific recommendation or regimen be warranted.

6.5.2. Criteria for Continued Dosing in Cycle 2 and Beyond

In Cycle 2 and beyond, the Investigator or designee should review End of Cycle/pre-dose clinical and laboratory findings before proceeding with study drug administration. All liver enzymes should have recovered to Grade 1 or lower, or to the patient's baseline, before proceeding. Laboratory data, particularly liver tests, should be compared to the patient's baseline, and delay of dosing should be considered to allow for more complete recovery of liver function or to allow resolution of other AEs, e.g., nausea, vomiting, anorexia, or fatigue. Refer to guidance on dose modifications and delays due to various toxicities in Section 4.6.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

XMT-1536 will be supplied by Mersana via Almac Distribution Services (ALMAC). The CRA will review each site's practices to confirm GCP compliance before vials are received and regularly review the inventory and tracking throughout the study. Refer to the Pharmacy Manual for detailed instructions on the use of the interactive dose registering software or IXRS for UPLIFT patients and WebEZ™ for EXP patients. Both are hosted by ALMAC. Vial assignment and detailed instructions on study drug handling, accountability, and re-ordering. information below is provided as an overview.

7.2. Study Drug Packaging and Labeling

The lyophilized formulation of XMT-1536 (upifitamab rilsodotin) to be use for Injection in UPLIFT. Cohort 3 is provided as a white to off-white powder in 10mL glass tubing vials with a gray chlorobutyl rubber stopper sealed with a blue flip-off cap. Each single-dose vial contains 80mg of XMT-1536 antibody drug conjugate for reconstitution with 8.0 mL of WFI or Sodium Chloride Injection, USP yielding a concentration of 10 mg/mL and pH of 4.5 to 5.0.

The liquid formulation of XMT-1536 to be used for injection in Cohort 2A and 2B EXP is provided as a colorless to yellow to brown liquid in a 5mL, round, flint glass tubing vial with a gray chlorobutyl rubber stopper with a barrier film covered by a 20mm aluminum, green or gray flip-off cap. Each single use vial contains 2.5 mL of XMT-1536 antibody drug conjugate at concentration of 10 mg/mL and pH of 4.0 to 5.0.

7.3. Study Drug Storage

- Cohort 3 UPLIFT vials must be stored at 2 – 8° C in a secure, temperature-controlled refrigerator.
- Cohort 2 EXP vials must be stored at -20°C (± 5°C) in a secure, temperature-controlled freezer.

XMT-1536 vials will be inventoried and controlled using the institution's standard pharmacy procedures for control of a research substance. The assigned CRA will review storage conditions and the maintenance of these conditions during periodic on-site visits.

7.4. Study Drug Preparation

- Each XMT-1536 (upifitamab rilsodotin) individual lyophilized drug product vial used for UPLIFT (Cohort 3) must equilibrate to room temperature for at least 30 min (up to 24 hours) followed by reconstitution with 8.0 mL of diluent before preparing a patient's dose. Inspect reconstituted vials before use: the liquid should be colorless to light yellow with essentially no visible particulates.
- Each XMT-1536 individual liquid drug product vial used for Cohort 2 EXP will be allowed to thaw at room temperature for up to 120 min before preparing a patient's dose. Inspect thawed vials before use: the liquid should be colorless to yellow to brown with essentially no visible particulates.

Vials must not be shaken or placed in direct sunlight. Once the dose for infusion has been prepared, it can be retained at room temperature, under typical room lighting conditions, for a maximum of 12 hours before administration.

XMT-1536 will be administered according to body surface area (BSA) with a maximum dose capped at BSA of 2.2 m^2 for every patient's starting dose and subsequently if dose reduction occurs. The BSA adjusted dose will be calculated following each institution's standard practice. When possible, the Mosteller Formula will be used. The starting dose will be calculated based on height and weight collected within 14 days of the first dose (can be collected the day of first dose). Dose calculations in subsequent cycles should be made for weight changes ≥5% from most recent dose calculation.

Each dose will be prepared in a 100 mL, 0.9% NS polyvinyl chloride (PVC) or 0.9% NS ethylene vinyl acetate (EVA) infusion bags. Dose preparation will be performed according to Investigational Site procedures. Refer to Pharmacy Manual for detailed instructions. Dose preparation will be documented in each patient's study participation record and follow all institutional practices including quality assurance checks.

7.5. Administration

The initial dose for each patient will be administered over 90 min. If no infusion-related reaction (IRR) occurs, all subsequent doses can be administered between a duration of 30 to 90 min at the discretion of the Investigator.

Once a patient completes Cycle 1, dose adjustments may be made if a patient experiences intolerable toxicity but would benefit from further treatment with XMT-1536, in the opinion of the Investigator. Refer to Section 4.6 for additional information.

7.6. Study Drug Handling and Disposal

Clinical Trial Material (CTM) accountability standards and processes in use at the research centers will be deployed for the control of XMT-1536 study drug. The appointed pharmacist, or designee, will maintain a record of:

- Confirmation of upload from the electronic temperature monitoring device used in each shipment of XMT-1536 and any consequent communication from ALMAC (refer to Pharmacy Manual).
- Clinical trial material delivery (including dates, quantities, batch record number, and any notations about vial appearance).
- Calculations to create a patient-specific dose and accompanying dose preparation steps,
- Distribution to study patients, and unused portions of dose vials.

The assigned CRA will review drug accountability forms to ensure accuracy and confirm absence of drug diversion at least quarterly. A member of the research site will contact either the CRO or Sponsor immediately should he or she become aware of the possibility of drug diversion.

Refer to the Pharmacy Manual for additional details on drug receipt, accountability, dose preparation and administration, and final CTM disposition instructions.

8. LABORATORY ASSESSMENTS

Refer to the Laboratory Manual for a detailed description of all collection, processing and shipment procedures. The normal ranges used by each local laboratory will be collected for each site involved in the study.

8.1. Blood Sample Collection for Safety and PK

Safety laboratory samples will be analyzed by the CLIA laboratory associated with each research center. CA 125 levels will be analyzed according to local procedures. These data will be manually entered into the clinical trial database. Sponsor/designee will collect the normal ranges pertinent to each laboratory.

Collection and shipping kits for PK and PD laboratory samples will be provided by Sponsor/designee. After processing, samples will be returned as per the Lab Manual instructions where they will be sent to the appropriate reference labs for analysis.

8.2. Urine Sample Collection for Safety

Urine samples will be analyzed at each site using the Institution's standard of practice for dip stick analysis.

8.3. Tissue Sample Collection

Instructions for collection and shipping are found in the Laboratory Manual.

8.4. Sample Analysis & Review

Safety laboratory results will be reviewed by the Investigator in charge of treating a study patient within a short period of time after received in accord with each Institution's standard practices and prior to administration of a next dose of XMT-1536. Key safety lab results by patient will be reviewed during the SRMs.

Pharmacokinetic results will be reviewed periodically during the Investigator Review calls that will be held throughout the study or during SRMs.

Exploratory results will be reviewed by Mersana and may be shared with the Investigators if needed. Exploratory assessments are not safety related.

Refer to the Laboratory Manual provided by Mersana for detailed information on laboratory sample collection, processing, and shipment.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

Safety parameters will be monitored throughout the study during the Investigator Review calls which will occur approximately every 2 weeks during DES and not longer than every quarter during EXP (see Section 4.5). SRMs will continue to be conducted during the UPLIFT segment of the study as per the schedule outlined in the charter.

Emergent, unexpected, and/or important safety information will be sent to all Investigators and research centers as it occurs, including information about serious adverse events. Ad hoc SRM(s) will be conducted if necessary.

9.2. Adverse and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 1.

All AEs that occur after any patient has received any part of the first dose of XMT-1536 will be reported by the subject (or when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) during the study.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible forfollowing up AEs that are serious, considered related to the study treatment or trial procedures, or that caused the subject to discontinue study treatment (see Appendix 1).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Assessments (Section 1.2).

At Post Treatment visit (60 ±7 days from End of Treatment Visit), the Investigator will report any AEs/SAEs regardless of causality. After this Post Treatment Visit, the Investigator will only report SAEs related to the study treatment or if it is learned the patient has died.

All SAEs will be recorded and reported to the Sponsor within 24 hours, as indicated in Appendix 1.

9.2.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 1.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire aboutAE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to follow each subject proactively at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Appendix 1.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor/designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and thesafety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review, acknowledge, and then file it along with the Investigator's Brochure and willnotify the IRB/IEC, if appropriate according to local requirements.

9.3. Adverse Events of Clinical Interest

Information on adverse events of clinical interest (AECI) will be reported to the Pharmacovigilance Vendor via the AECI/SAE paper form first observation by research site staff, e.g., within 3 business days. Real-time signal monitoring will be performed on these events and a cumulative and by-dose level summary of any AECI reports will be shared as part of each SRM. In the EXP segment of the study, quarterly signal detection meetings will be held and the following AECIs will be included in the aggregate data package. See Section 4.5 for additional information on SRMs and periodic safety reviews. AECI categories for the anti-tubulin drug class and based on prior observations from this study are as follows:

- Infusion-related reactions
- Grade 4 thrombocytopenia
- Corneal disorders
- Grade 3 fatigue, nausea, and vomiting
- Pneumonitis

9.4. Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of IMP and until the final contact at End of Study. At a minimum, monthly pregnancy tests will be completed throughout the trial for all women of childbearing potential. During periods where monthly visits are not scheduled, female subjects can choose to visit the site for the test or complete the test via a remote option.

If a pregnancy is reported, the investigator should inform the medical monitor within24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth,congenital anomalies, ectopic pregnancy) are considered SAEs.

9.5. Dose Limiting Toxicity in DES

Dose limiting toxicities were followed during the DES segment of the trial. Dose-limiting toxicities are not evaluated for EXP or UPLIFT. However, thorough safety monitoring continues in EXP and UPLIFT with safety review meetings conducted at the frequency outlined in the charter (see Section 4.5).

9.5.1. Dose Limiting Toxicity Observation Period

The DLT Observation Period is end of Cycle 1 in DES only. Patients received at least 80% of their planned dose and completed Cycle 1 in order to be considered evaluable for tolerability, unless dose reduction, interruption, or discontinuation was the result of a DLT. A DLT is defined as any of the following treatment-related toxicities occurring within the DLT Observation Period.

9.5.1.1. Non-hematological DLTs

All non-hematological toxicities that are Grade ≥ 3 and are not due to disease progression or another clearly identifiable cause are DLTs, with the following modifications:

- Any case consistent with Hy's Law
  - AST or ALT > 3 X ULN *and*
  - Total bilirubin > 2 X ULN *and*
  - Alkaline phosphatase < 2 X ULN *and*
  - No other reason for liver injury.
- Grade 3 AST increase lasting >5 days, or Grade 4 increase of AST of any duration
- Grade ≥ 3 increase of ALT, ALP, or bilirubin of any duration.
- Grade 3 fatigue that persists for ≥ 1 week is a DLT, or Grade 4 of any duration.
- Grade ≥ 3 neutropenic fever is a DLT.
- An infusion-related reaction that requires hospitalization for treatment is a DLT.
- Any death not clearly due to the underlying disease or extraneous causes is a DLT.

The following are **not** DLTs:

- Grade 3 nausea, vomiting, or diarrhea persisting for < 72 hours with adequate antiemetic and other supportive care.
- Grade ≥ 3 electrolyte abnormality lasting < 72 hours and that resolves spontaneously or responds to conventional medical interventions.
- Alopecia of any grade.
- Asymptomatic changes in lipid profiles or blood glucose.

9.5.1.2. Hematological DLTs

- Grade ≥ 3 thrombocytopenia with significant bleeding is a DLT.
- Grade 4 neutropenia or thrombocytopenia for > 7 days is a DLT.

9.5.1.3. Dosing Delays Due to XMT-1536 Treatment-related Toxicity

- Any toxicity related to XMT-1536 that delays start of Cycle 2 by more than 2 weeks or an XMT-1536 related toxicity that prompts modification of the dose given in Cycle 2 is a DLT.

10. QTC SUB-STUDY CRITERIA FOR EVALUATION

10.1. ECG Assessments

A 12-lead ECG will be obtained according to the schedule presented in Table 3.

For QTc sub-study sites, ECGs must be obtained in triplicate using the machines provided by Sponsor/designee for the conduct of the study as per the schedule provided in Section 1.3 . The following parameters will be collected or calculated: ventricular rate (beats per minute), PR interval, QRS duration, QT/QTc interval, QTcF, and RR interval.

Potential effects will be assessed by analysis of central tendency, the incidence of clinical noteworthy ECG values, morphological assessments, rhythm abnormalities, and an analysis of upifitamab rilsodotin concentration and baseline-corrected QT interval (corrected using Fridericia's formula) (QTcF). All ECG interval data will represent the means of up to three individual tracings, based on ECGs taken approximately one minute apart. The concentration-QTcF change from baseline (ΔQTcF) analysis and analysis of central tendency for ΔQTcF will be summarized, along with evaluations of cardiac safety as outlined in the ECG Statistical Analysis Plan.

ECGs for the QTc sub-study will be acquired from the ECG machines provided by the Sponsor/designee and instructions for conduct outlined in the ECG manual will be followed.

Measures will be taken to eliminate baseline tremor as it may interfere with the quality of the ECG interpretation.

All QTc sub-study ECGs will be interpreted at the central cardiac laboratory by cardiovascular physicians at the ECG vendor in a blinded fashion. All of the ECGs obtained from a particular subject on a given day will be read by the same cardiovascular physicians. The ECGs will be analyzed manually utilizing validated digital techniques. The QT intervals will be measured using a high-resolution manual on-screen caliper method in compliance with the suggested standards set forth in ICH E14.

The measurements will be made using the global 12-lead median beat display, and all fiducial points for all ECGs will be confirmed or adjusted by a cardiologist. The RR interval will be the average of the beats within the 10-second acquisition. Within a 5-minute extraction window, it is highly unlikely that three 10-second tracings will not be retrieved.

10.2. Assessment of Safety

Consistent with the overall conduct of Study MER-XMT-1536-1, safety parameters will be collected/monitored throughout the QTc sub-study. Emergent, unexpected, and/or important safety information will be sent to all Investigators and research centers as it occurs, including information about SAEs. Ad hoc Safety Review Meeting(s) will be conducted if necessary. Further details regarding the assessment of safety are described in Section 9 of the MER-XMT-1536-1 protocol.

11. STATISTICS

11.1. Determination of Sample Size

11.1.1. Dose Escalation

It was anticipated that up to 8 dose escalation levels would be required to determine the MTD, thereby enrolling up to 60 patients during the DES phase. The Dose Limiting Toxicity was met at DLA8A, 52 mg/m^2 q28d and the MTD was declared at 43 mg/m^2 q28d. The number of patients dosed in DES was 62. The MTD that was selected in the 3 + 3 design had an upper bound of 0.33 for the probability of dose-limiting toxicity. Simulation studies indicated that the selected dose in this design has toxicity probability of 0.2 (Lin & Shih, 2001).

11.1.2. Expansion

A total of 97 patients in ovarian cancer and 45 in NSCLC have been enrolled and dosed in the EXP phase.

11.1.2.1. Sample Size and Efficacy

While the sample sizes for the study are based on typical practice in Phase 2 studies, these sample sizes can be determined to rule out certain levels of true adverse event rate or ORR based on the observed proportions for these events. Using one-sided exact binomial test, statistical power to rule out certain level of true rates for a given sample size, observed rate and significance level is calculated for a range of values (Saber & Guid, 2015).

With an expansion cohort size of 80 patients for ovarian cancer and 40 patients for NSCLC, we assume a target response rate of 20% for ovarian cancer and 25% for NSCLC and an uninteresting rate of 10% for both populations. Under these assumptions, the following patient counts for alpha (1-sided), the false positive rate, and power (Power %) are provided in Table 17. Literature suggests an overall response rate to current standard of care between approximately 10% to 25% for ovarian cancer and NSCLC, (Hanna, et al., 2004), (Garon, 2014), (Pujade-Lauraine, et al., 2014), (Gordon, et al., 2001), (Sehouli, et al., 2011), (Ferrandina, 2008), after frontline standard of care treatment has failed. Therefore, a response rate of 10% to XMT-1536 would not constitute an improvement over available treatment options and the Sponsor may not pursue developing this treatment for these indications. However, if a response rate of ≥ 20% in ovarian cancer and ≥25% in NSCLC is achieved, this would indicate a drug response of interest and the Sponsor may investigate further development.

The minimum number of responses for success are in Table 17 and Table 18.

Table 17: Efficacy Sample Size in Expansion, Ovarian Cancer

Type	Sample Size	Target Response Rate (%)	Uninteresting Response Rate (%)	Minimum Number of Responses	Alpha 1-Sided	Power (%)
Ovarian	80	20	10	15	0.025	65.7
Ovarian	80	20	10	14	0.05	74.8
Ovarian	80	20	10	13	0.075	83.5

Table 18: Efficacy Sample Size in Expansion, NSCLC

Type	Sample Size	Target Response Rate (%)	Uninteresting Response Rate (%)	Minimum Number of Responses	Alpha 1-Sided	Power (%)
NSCLC	40	25	10	9	0.025	69.9
NSCLC	40	25	10	8	0.05	81.5
NSCLC	40	25	10	7	0.1	90.8

11.1.2.2. Sample Size and Safety

Approximately 120 patients, 80 patients in the ovarian cancer cohort and 40 patients in the NSCLC cohort, were to be enrolled and dosed in the EXP phase. For a sample size of 120 and a selected adverse event, the following rates apply. See Table 19 and Table 20.

Table 19: Safety Sample Size in Expansion

Total Patients	Adverse Events	Adverse Event Rate (%)	Count of Patients Upper 95% C.I.	Count of Patients Upper 90% C.I.	Percent of Patients Upper 95% C.I.	Percent of Patients Upper 90% C.I.
120	0	0	4	3	3	2.5
120	1	0.8	6	5	4.6	3.9
120	2	1.7	8	7	5.9	5.2
120	3	2.5	9	8	7.1	6.3
120	4	3.3	10	9	8.3	7.5
120	5	4.2	12	11	9.5	8.6
120	6	5	13	12	10.6	9.6
120	7	5.8	14	13	11.6	10.7
120	8	6.7	16	14	12.7	11.7
120	9	7.5	17	16	13.8	12.7
120	10	8.3	18	17	14.8	13.7
120	15	12.5	24	23	19.8	18.6
120	20	16.7	30	28	24.6	23.3
120	30	25	41	39	33.7	32.3
120	40	33.3	51	50	42.5	41.1
120	50	41.7	62	60	51	49.6

[1]CI = Confidence Interval

Thus, for a selected AE, if there are no such events, an underlying event rate of up to about 3% cannot be ruled-out. For a putative event rate of about 20%, 10 or fewer events out of 120 patients are required to rule-out a 14.8% or higher true underlying event rate.

Table 20: Safety Event Rate Estimate

Event Rate (%)	Number of Patients	Probability of Observing at Least One Event (%)
0.01	120	1.19
0.05	120	5.82
0.1	120	11.31
0.2	120	21.36
0.5	120	45.2
1.0	120	70.06
2.0	120	91.15
3.0	120	97.41
4.0	120	99.25
5.0	120	99.79

11.1.3. UPLIFT

In patients with platinum-resistant ovarian cancer, literature suggests an ORR to current standard of care of approximately 4% - 12% (Moore et al., 2019; Gaillard et al., 2016; Pujade-Lauraine et al., 2019). Therefore, a response rate of 12% to XMT-1536 (upifitamab rilsodotin) would not constitute an improvement over available treatment options.

A sample size of 105 patients at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 with higher NaPi2b expression will provide at least 90% power to rule out the uninteresting ORR of 12% when the true ORR for XMT-1536 (upifitamab rilsodotin) is 24% or higher using a one-sided 97.5% exact binomial confidence interval (Clopper-Pearson method).

Assuming approximately 60% of HGSOC patients have higher NaPi2b expression, a total sample size of approximately 175 patients will need to be enrolled and treated at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 to have at least 105 patients in the ITT-NaPi2b Positive population. If we assume that the target ORR for XMT-1536 (upifitamab rilsodotin) in the overall ITT population is 21%, then the sample size of 175 patients at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 will have at least 87% power to rule out the uninteresting ORR of 12% using a one- sided 97.5% exact binomial confidence interval (Clopper-Pearson method).

11.1.4. QTc Sub-study (selected sites only)

Approximately 25 evaluable patients are expected to be enrolled in this sub-study. Based on historical oncology clinical studies with QTc sub-studies, the planned number of participants to be included is considered to be suitable for this QTc evaluation (Chari et al. 2021; Garg et al. 2013; Moore et al. 2019).

11.2. Statistical Analysis

11.2.1. Statistical Analysis Overview

Separate Statistical Analysis Plans (SAPs) will be written for the analyses of data from DES (Cohort 1), from EXP (Cohorts 2A and 2B), and from UPLIFT (Cohort 3). The SAPs will address the analyses of data recorded in the clinical database as well as laboratory data and other

data transferred. Separate Clinical Study Reports (CSRs) will be written for each segment of the study. The final tables, listings and figures (TLFs) and CSRs for each segment will be prepared after data from the segment have been cleaned and locked. Any deviations from the planned analyses will be described in the final study report.

Clinical data will be transferred to PK vendor to support PK analysis. A separate analysis plan addressing the PK profile of XMT-1536, its release product and metabolites will be prepared.

Data from DES will be adequately summarized and reviewed with the SRC, at a minimum, before EXP dosing begins. Based on review of DES data, a protocol amendment may be created and submitted for approval prior to initiating the EXP segment. Statistical analyses will be carried out using SAS Version 9.3 or higher.

Continuous variables, including baseline characteristics, will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum.

Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of patients within a category. Time-to-event data will be summarized using the Kaplan-Meier method.

Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last available observation prior to the first administration of study drug on Cycle 1, Day 1.

The handling of missing data will be specified in the SAP along with the methods used for reporting the endpoints.

11.2.2. QTc Sub-study Analysis

The primary and secondary endpoints are as defined in Section 3. Data will be presented as measures of central tendency (mean, SD, median, 2-sided 90% CI) for both the raw values and changes from baseline.

11.3. Analysis Data Sets

11.3.1. Dose Escalation and Expansion

For the purposes of this study, the Enrolled analysis set consists of patients who are registered to participate in this trial with informed consent signed and have undergone the inclusion/exclusion criteria assessment. At the time of enrollment, the patient's study identification code and dose cohort will be assigned. The demographic and baseline characteristics, medical history and pre-existing conditions of patients in the Enrolled analysis set will be summarized and listed.

Safety analyses will be conducted on the Safety analysis set, i.e., patients receiving any amount of an XMT-1536 dose (partial or complete). Patients completing Cycle 1 in the absence of a DLT, will be considered to have tolerated the XMT-1536 regimen. Patients must receive at least 80% of their planned dose of XMT-1536 and complete Cycle 1 in order to be considered evaluable for tolerability, unless dose reduction, interruption, or discontinuation was the result of a DLT.

The enrolled patients who receive any amount of their assigned dose of XMT-1536 and have an adequate number of concentration determinations to allow for PK calculations will comprise the

PK analysis set. Analysis of PK concentration data per dose level, per indication, and per patient results will be provided.

The Efficacy analysis set will be comprised of treated patients. The efficacy response evaluable set includes a subset of the efficacy analysis set for whom baseline response assessment and at least one post-baseline response assessment are available.

Safety data from DES and EXP will be reported for all patients in the safety analysis set.

11.3.1.1. Dose Escalation and Expansion Safety Analysis

The number and percent of patients who experienced DLT by dose cohort and across all dose cohorts in the DES phase will be reported. All Adverse Events and AECIs will also be reported by dose cohort and across all dose cohorts in the DES phase.

In the EXP phase, all adverse events and AECIs will be reported by dose and across all doses. The seriousness, CTCAE severity grading, and Investigator-reported relationship of adverse events to study drug will be summarize and listed. Safety laboratory data will be summarized and listed.

11.3.2. UPLIFT

The following analysis populations are defined for this segment of the study:

11.3.2.1. Intent-to-Treat (ITT)

All patients enrolled who received a starting dose of 36 mg/m^2 q4wk (capped at a BSA of 2.2 m^2) and who received at least 1 dose of study drug. Patients who were enrolled in the study with other histologies (do not have HGSOC) or who do not have measurable disease at baseline, will be excluded from the ITT population.

11.3.2.2. Intent-to-Treat-NaPi2b Positive (ITT–NaPi2b Positive):

All patients in the ITT population who have a NaPi2b expression value at or above the higher NaPi2b threshold. Subjects who have insufficient tissue for performing the NaPi2b IHC assay or who have inconclusive assay results will not be included in the ITT-NaPi2b Positive population. NaPi2b Positive and Negative status will have been defined prior to sample testing and based on data from a separate sample group.

11.3.2.3. Per Protocol

All dosed patients who received a starting dose of 36 mg/m^2 q4wk (capped at a BSA of 2.2 m^2) and satisfy all inclusion and none of the exclusion criteria and who do not have major protocol deviations impacting assessments of efficacy. The list of major protocol deviations that exclude patients from the PP population will be provided in the Statistical Analysis Plan (SAP). Patients who are lost to follow-up before their first scan and patients who do not have a valid NaPi2b result will not be included in the PP analysis.

11.3.2.4. Safety

All subjects who received any amount of study drug, regardless of their starting dose will be included in the Safety analysis set.

11.3.2.5. Pharmacokinetic (PK)

All patients with at least one post-infusion sample with a measurable concentration.

11.3.3. QTc Sub-study

The QTc-evaluable patient population is defined as all subjects who have received XMT-1536 and have at least one time-matched ECG evaluation and PK sample.

11.3.4. UPLIFT Safety Analysis

All patients who receive at least one dose of study treatment will be evaluated for safety. Summaries will be provided by starting dose level (i.e., 36 mg/m^2 q4wk, capped at a BSA of 2.2 m^2, and 43 mg/m^2 q4wk capped at a BSA of 1.8 m^2) and overall. The incidence rates of treatment emergent adverse events, treatment related adverse events, serious treatment emergent adverse events (SAEs) and AECIs will be summarized by MedDRA preferred terms and system organ class (SOC). The frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity) and maximum relationship to study treatment will also be described.

Listings of laboratory test results and CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented. Additionally, the prevalence and incidence of ADA and nAB levels will be reported.

Exploratory analyses will also be performed on other safety parameters, as deemed appropriate. Exposure to study treatment over time will be summarized with time on treatment and total amount of administered treatment.

11.4. Primary Efficacy Analysis

11.4.1. Dose Escalation and Expansion.

The primary endpoint is ORR by Investigator radiologic review and is defined as the proportion of patients who achieve a confirmed PR or CR per RECIST v 1.1. A secondary endpoint is the DCR which is defined as the proportion of patients who achieve complete response, partial response, and/or stable disease of any duration per RECIST v 1.1. The number and percentage of patients achieving response or clinical benefit will be summarized and an exact 95% confidence interval (CI) will be provided.

Analysis of other efficacy endpoints including duration of response (DOR), progression-free survival (PFS) and overall survival (OS) will also be reported, wherever possible according to standard response criteria. Kaplan-Meier estimates of medians and quartiles with 95% CIs will be reported for these statistics.

The efficacy endpoints will be analyzed using both the efficacy analysis set and the efficacy evaluable analysis set in each cancer type cohort.

11.4.2. UPLIFT

11.4.2.1. Definition of Efficacy Endpoints

The primary efficacy endpoint is confirmed investigator-assessed objective response rate (ORR) per RECIST v1.1 in the ITT- NaPi2b Positive population.

Confirmed ORR is defined as the proportion of patients who have achieved a confirmed complete response (CR) or partial response (PR) per RECIST v1.1 after the initiation of study treatment. Confirmed responses are those that persist on repeat imaging at least 26 days (28 days minus 2-day window) after initial response.

The secondary efficacy endpoints are:

- Confirmed investigator-assessed ORR per RECIST v1.1 in the ITT population
- Confirmed ORR by independent radiology review (IRR) per RECIST v1.1 in the ITT-NaPi2b Positive population
- Confirmed ORR by IRR per RECIST v1.1 in the ITT population
- Duration of response (DOR) is defined as the time interval from the time that the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that progressive disease (PD) is objectively documented in patients who have achieved confirmed response. DOR will be analyzed in the ITT-NaPi2b Positive and the overall ITT populations.

The exploratory efficacy endpoints are:

- Disease control rate (DCR) is defined as the proportion of patients who have achieved CR, PR or SD. DCR will be analyzed in the ITT-NaPi2b Positive and ITT populations.
- Progression-free survival is defined as the time interval from the date of the first dose of the study treatment until the first date at which disease progression is objectively documented or death due to any cause, whichever occurs first. PFS will be censored on the date of the last evaluable scan for patients without documented disease progression or who do not die prior to the end of the study. Patients with 2 consecutive scheduled non-evaluable scans will be censored at the last scan immediately prior to the 2 consecutive non-evaluable scans. PFS will be analyzed in the ITT-NaPi2b Positive and ITT populations.
- Overall survival (OS) is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. OS will be censored on the date of last contact for those patients who are alive at the end of the study. OS will be analyzed in the ITT-NaPi2b Positive and ITT populations.

Unless otherwise stated, secondary and exploratory efficacy endpoints will use investigator assessments with supplementary analyses performed using the IRR assessments.

Details of censoring for time to event endpoints will be provided in the SAP.

11.4.2.2. Data Handling Rules for Efficacy Analyses

A patient will be considered as non-evaluable (NE) for response per RECIST v1.1 at a protocol specified time point if no imaging/measurement is done or only a subset of lesion measurements is made unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

A patient will be considered to have a response if the criteria for response have been met per RECIST v1.1.

All patients will be assigned to one of the following best overall response categories: CR, PR, SD, PD, or NE.

Examples of reasons patients are categorized as NE are early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (including patients with 2 or more consecutive scheduled non-evaluable post-baseline disease assessments).

All patients whose best overall response is not CR or PR will be classified as non-responders in the calculation of ORR.

Scans before Day 35 are evaluable only if they are PD, PR or CR. SD scans before Day 35 are considered non-evaluable. Confirmation scans per RECIST v1.1 must be done at least 26 days (28 days minus 2-day window) after the initial response.

SD measurements must have met the SD criteria at least once after study entry at a minimum interval of 35 days.

11.4.3. UPLIFT Efficacy Endpoint Analyses

The analyses corresponding to the primary and secondary efficacy objectives of the study are provided below using the structured framework specified in the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials, 2020.

11.4.3.1. Primary Efficacy Endpoint

The estimand used to address the primary objective is defined by the following:

- Treatment: XMT-1536 (upifitamab rilsodotin) at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 administered as an IV infusion q28d
- Population: Patients in the ITT-NaPi2b Positive population
- Variable: A binary response variable indicating success if patients achieve confirmed objective response (CR or PR) assessed by the investigator per RECIST v1.1, after the initiation of study treatment.
- Intercurrent events:
    - If a patient discontinues treatment prematurely or the dose is reduced or delayed, use observed objective response
    - If a patient is lost to follow-up, discontinues from the study prematurely or dies prior to the patient's first scan, then assume the patient did not have an objective response
    - If a patient has no adequate post-baseline response assessment, then assume the patient did not have an objective response. Scans that are missing or cannot be assigned a time point response will be considered non-evaluable (NE) for that time point. Patients who have a sequence of CR/PR followed by NE followed by CR/PR will be considered as confirmed CR/PR provided that the first and 3rd time points in the sequence are 26 days (28 days minus 2-day window) or more days apart. Patients with 2 consecutive NE assessments will be considered as non-responders.
- Population-level summary: Proportion of patients with confirmed CR or PR (i.e., ORR) assessed by the investigator, per RECIST v1.1. An exact one-sided 97.5% confidence

interval for the ORR will be calculated based on the binomial distribution using the Clopper-Pearson method.

11.4.3.2. Key Secondary Efficacy Endpoint

Confirmed investigator-assessed ORR per RECIST v1.1 in the ITT population will be analyzed in the same manner as the primary efficacy endpoint, but the analysis will be conducted in the entire ITT population.

11.4.3.3. Other Secondary Efficacy Endpoints

1. Confirmed ORR by IRR per RECIST v1.1 in the ITT-NaPi2b Positive population will be analyzed in the same manner as the primary efficacy endpoint, but the ORR will be based on IRR assessments.
2. Confirmed ORR by IRR per RECIST v1.1 in the ITT population will be analyzed in the same manner as the primary efficacy endpoint, but the ORR will be based on IRR assessments and the analysis will be conducted in the entire ITT population.
3. The estimand used to address the secondary objective evaluating DOR is:
    - Treatment: XMT-1536 (upifitamab rilsodotin) at a starting dose level of 36 mg/m^2 q4wk capped at 2.2 m^2 administered as an IV infusion q28d
    - Population: Patients in the ITT-NaPi2b Positive population who had a confirmed CR or PR
    - Variable: Time from when the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the progressive disease is objectively documented per RECIST v1.1.
    - Intercurrent events:
        - If a patient discontinues treatment prematurely or the dose is reduced or delayed, use observed outcome
        - If a patient is lost to follow-up or discontinued from the study prematurely prior to documentation of PD, DOR is censored on the last scan date
        - If a patient dies prior to documentation of PD, DOR is reached on the date of death
        - DOR will be censored on the date of last scan for patients who do not have documented PD at database lock.
        - If a patient has 2 consecutive scheduled non-evaluable scans, DOR will be censored at the last scan date immediately prior to the 2 consecutive non-evaluable scans.

- Population-level summary: Median DOR. The median, 25th and 75th percentiles for DOR and the corresponding two-sided 95% confidence intervals for the median will be estimated using the Kaplan-Meier method in the ITT-NaPi2b Positive population in patients with a confirmed objective response.

A similar analysis for DOR will be conducted in the entire ITT population.

Unless otherwise stated, secondary efficacy endpoints will use investigator assessments with supplementary analyses performed using the IRR assessments.

11.4.3.4. Exploratory Efficacy Endpoints

Description of the analyses of the exploratory efficacy endpoints, DCR, PFS and OS, will be provided in the SAP.

11.4.3.5. Additional Analyses

Exploratory analyses for ORR will be performed for the ITT population within subgroups defined by age, race, geographic region, prior lines of therapy, prior anticancer therapies, BRCA1/2 mutation status and other prognostic factors. An additional subgroup analysis will be performed by starting dose (36 mg/m^2 and 43 mg/m^2) for all dosed patients.

11.4.4. Multiplicity Adjustments

No adjustments for multiplicity will be made for the evaluation of efficacy in this single-arm cohort.

11.4.5. Interim Analysis

An interim analysis of the efficacy data in the ITT population may be conducted when approximately half of the patients have been enrolled. No efficacy analysis by NaPi2b status will be conducted at this time. Furthermore, no changes to the study design will be made based on the interim analysis results.

11.4.6. Pharmacokinetics Analysis

The PK profile of the active ingredient of XMT-1536, its release product and selected metabolites will be determined for each patient by non-compartmental analysis using standard PK software (e.g., Phoenix WinNonlin). PK parameters per patient will include time of maximum observed concentration (t_{max}), maximum concentration (C_{max}), and area under the concentration curve for the last measurable concentration ($AUC_{0\text{-}last}$). When the terminal elimination phase can be identified, additional parameters such as elimination half-life, clearance, and volume of distribution will be determined.

The handling of missing concentration and covariate data, outliers and values below the limit of quantification as well as details of the modeling for dose-response and PK parameter-response relationships will be provided in the PK analysis plan.

11.4.7. Objective Response Rate and Alternative Assays for Measurement of NaPi2b Expression

NaPi2b expression status will be confirmed by central laboratory testing. In addition, alternative methods for measuring NaPi2b expression may be used. BOR, PFS, ORR, OS, and DOR (with associated confidence intervals) will be reported by patients stratified by central NaPi2b status, and status assessed by other methods of NaPi2b measurement.

12. DATA COLLECTION AND MANAGEMENT

Only data collected and treated via the following process will be used for study analysis and reporting.

12.1. Confidentiality

Patient names will not be supplied to Mersana. Only the patient number will be used in the case report form. If the patient's name appears on any other document (e.g., x-ray report), it must be obliterated before a copy of the document is supplied to Sponsor/designee. Study findings stored on a computer will be stored in accordance with local data protection laws. Patients will be told that representatives of Mersana, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws

12.2. Original Data Records and Monitoring

Clinical Research Associates (CRAs) who have been appropriately trained in GCP compliance, oncology research, and the protocol will corroborate 100% of the data that have been entered in the clinical trial database against original records. Original records, also known as source documents include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records and other records retained at the pharmacy, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files and records retained at the laboratories and other technical departments involved in the clinical study that pertain to a study patient during the course of the clinical study. Monitors and auditors must have access to original records. If the point of first record of this information is an electronic medical record, e.g., EPIC, the CRA must either have access to this database for each study patient or a printout of the original data. If the latter, a validation certificate stating the paper copy is an exact representation of the medical record database will be on file in the study binder. Changes to any originally recorded data should be traceable, allow the original record to be visible after the change was made, and explained briefly. If documents are electronically maintained, an audit trail describing all data manipulations must be available and stored with the data.

CRAs will also periodically ensure that each research site has correctly retained requisite study documents per ICH E6, Section 4, and confirm that drug accountability is without error. This work will be conducted in an ongoing fashion both remotely and on-site. Each site visit is described in a standardized site visit report. These procedures are outlined and will proceed as outlined in the Monitoring Plan.

Domestic and foreign regulatory authorities, the IEC/IRB, and an auditor(s) authorized by Mersana may request access to all source documents, access to the eCRF, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator. Medical records and other study documents may be copied during audit or inspection if patient names are obliterated on the copies to ensure confidentiality.

If the Investigator is informed of an impending regulatory authority audit, Sponsor/designee must be notified within 24 hours of the Investigator's notification by the inspecting authority.

12.3. Data Entry and Management

A study-specific electronic database that conforms to 21CFR Part 11 and other FDA and ICH data handling conventions, i.e., unique user ID/passwords, PI signatures, will be deployed. The point of study data entry will be at the research site using an eCRF portal. The CRO will prepare a data entry instruction manual specifically for this study for use by the research site personnel and CRAs. Specifications for entering local lab data, RECIST measurements, pre-existing conditions, AEs secondary to other medical events, etc., are defined therein.

Data will be entered remotely by each research center after Sponsor/designee has confirmed each site adequately meets the technology and regulatory prerequisites for direct data entry.

12.4. Data Review and Finalization

A comprehensive Data Management Plan (DMP) will be prepared which outlines all data entry, handling, correction, coding, review, and reporting activities to be performed by the CRO and Sponsor.

Upload of any data from the point of entry at the research site that are inconsistent with specifications as outlined in the Data Management Plan will trigger automated data queries to be issued immediately to research site personnel for resolution.

Data will be reviewed periodically. Any inconsistencies noted during this remote cleaning and/or auditing process will be sent to the research site for clarification via a GCP compliant data query and resolve process.

All study data generated at central testing facilities will be transferred to the study database electronically and not recorded by research site staff in the eCRF. These data will be communicated to each Investigator in a timely fashion during active protocol conduct.

As a final step in the data management process, a 100% quality check will be performed on pre-study identified key efficacy and safety parameters as outlined in the DMP. In addition, a random patient sample (10 to 20%) will be selected in order to perform a partial audit of all remaining data. The purpose of this audit is to detect systematic and random errors. Any errors found from this audit will be corrected and, if the error rate is greater than 10 errors per 10,000 fields (0.1%), a systematic review of the database will be undertaken, and corrections will be made to achieve an error rate of <0.1%.

- The Adverse events and medical history entries will be coded using MedDRA
- Concomitant medications will be coded using WHO-ATC
- The Safety Database and clinical database will be reconciled periodically for key data fields as outlined in the DMP

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Mersana, or their designees, may conduct a quality assurance audit. You will be given ample notice of the request to audit and a mutually agreed upon time frame will be decided.

Research centers agree to immediately notify Sponsor/designee if informed by a Regulatory Agency of a pending audit that includes data or information from this study. If a Regulatory Agency arrives unannounced, the research center will immediately contact Sponsor/designee.

Research centers also agree to notify Sponsor/designee within a reasonable timeframe if informed by a Regulatory Agency of a pending audit that does not include data or information from this study.

14. ETHICAL CONSIDERATIONS AND REGULATORY REQUIREMENTS

14.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The research site must submit written approval to Sponsor/designee and in turn be authorized to begin study conduct before they enroll any patients into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with information on any reportable serious adverse drug reactions from any other study conducted with the investigational product. Mersana will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable laws and regulations, regulatory requirements, Sponsor/designee SOPs, and Mersana's policy on clinical trial conduct. The Investigator will also specially abide by all mandates on the FDA Form 1572 and/or other national and local regulatory body, including, but not limited to the following principles.

- Ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.
- Be responsible for supervising anyone to whom study activities have been delegated.
- The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom significant trial-related duties have been delegated.
- Should notify the patient's primary physician about participation in the trial.
- Agrees to abide by all IRB/IEC-specific reporting requirements for the duration of the trial and must submit annual update reports (at a minimum) and a final study report according to the IRB/IEC's standards. If the trial is prematurely terminated by either the Sponsor or the Investigator, the Investigator will promptly inform his or her IRB/IEC and the study patients.
- The Investigator will abide by the financial provisions agreed to between his or her institution and the Sponsor.

An FDA Form 3454 Financial Disclosure Form will also be collected prior to study participation. Investigators are responsible for submitting a revised form(s) if any substantive

changes occur. Updated forms will be collected at the end of the study or if a research center discontinues participation.

14.3. Patient Information and Informed Consent Process

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions of appropriately trained personnel and allowed time to consider the information provided before signing the consent.

The patient's signed and dated informed consent must be obtained before conducting any study procedures, even if oral consent is given orally, e.g., a visually impaired patient. A legally recognized alternative signature will be acceptable, e.g., thumb print or character mark.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

14.4. Protocols and Amendments

The Investigator will not alter this clinical study protocol without obtaining the written agreement of the Sponsor/designee. All protocol amendments will be approved by the IRB/IEC unless the Investigator implements a change to avoid an immediate safety concern for a patient. Any such change will be reported immediately to the IRB/IEC and Sponsor or CRO.

The Investigator should also promptly report to the IRB/IEC in accord with local standards and the Sponsor, if it is not already aware, if any of the following observations are made:

- Changes increasing the risk to patient and/or affecting significantly the conduct of the trial
- All adverse events that are both serious and unexpected
- Any new information that may affect adversely the safely of the study patients or the conduct of the trial

14.4.1. Study Record Retention

Accurate and complete source documents will be retained by the Investigator. The following records must be retained by the Investigator/institution for a minimum of 2 years after the Sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed informed consent documents for all patients.
- Patient identification code list, screening log (if applicable), and enrollment log.
- Record of all communications between the Investigator and the IEC/IRB.
- Records of all documents pertaining to IRB review / approval of study related protocols/amendments, Investigator's Brochures, sample Informed Consent Forms and amendments, and any other documents that pertain to patient information, recruitment methods, advertisements.

- Composition of the IEC/IRB or other applicable statement.
- Record of all communications between the Investigator and Sponsor (or contract research organization).
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and of documentation of corrections for all patients.
- Drug accountability records.
- Record of any body fluids or tissue samples retained.
- All other source documents (patient records, hospital records, laboratory records, etc.).
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records.

Typically, study records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented in writing to the Sponsor.

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16. APPENDICES

APPENDIX 1. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

Table 21: Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial subject, temporallyassociated with the use of trial treatment, whether or not considered related to the trial treatment. • NOTE: Signs and symptoms and/or abnormal laboratory test results indicating a commonunderlying pathology/diagnosis should be reported as a single AE.

Table 22: Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those thatworsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase infrequency and/or intensity of the condition. • New conditions detected or diagnosed after trial treatment administration even though it mayhave been present before the start of the trial. • Signs, symptoms, or the clinical manifestations of a suspected drug-drug interaction. • Signs, symptoms, or the clinical manifestations of a suspected overdose of either trial treatmentor a concomitant medication. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reportedas an AE or SAE. Such instances will be captured in the efficacy assessments.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if seriousconditions are met (e.g., hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

Table 23: Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose, that meets one or more of the criteria listed:
a. Results in death
b. Is considered life-threatening by the investigator or the sponsor The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at riskof death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not havebeen appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria,the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is notconsidered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such asuncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is considered a significant medical event by the Investigator or the sponsor Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include intensive treatment in an emergency roomor at home for allergic bronchospasm or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

Table 24: Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation(eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms,and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
• The investigator will then record all relevant AE/SAE information in the SAE form/eCRF.
  o Nonserious AEs that are identified at any time during the trial must be recorded on theAE eCRF with the current status noted. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk- related behavior, family history and occupation).
  o If updated information (eg, resolved status) on SAE status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject islost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the pointthe event has resolved or stabilized, or the subject is lost to follow-up, or has died.
  o Any new SAEs reported to the investigator that occur after the last scheduled contactand are determined by the investigator to be related to the use of the IMP, should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs identified after the defined trial period and continueto report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the subject's medical records tothe sponsor or designee in lieu of completion of the AE/SAE eCRF page.
• There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsoror designee.

Table 24: Recording and Follow-Up of AE and/or SAE (Continued)

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the trial andassign it to 1 of the following categories:
Assessment of Causality
• The investigator is obligated to assess the relationship between trial treatment and eachoccurrence of each AE/SAE. • The investigator will assess the relationship as either of the following: o **Related**: An AE will be considered "related" to the use of the IMP if there *a reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. o **Not Related**: An AE will be considered "not related" to the use of the IMP if there isno plausible causal relationship between the IMP and the AE. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors,as well as the temporal relationship of the event to trial treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, formarketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she hasreviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every eventbefore the initial transmission of the SAE data to the sponsor or designee.** • The investigator may change his/her opinion of causality in light of follow-up information andsend a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reportingrequirements.

Table 25: Follow-Up of AEs and SAEs

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. Thismay include additional laboratory tests or investigations, histopathological examinations, orconsultation with other health care professionals. • If a subject dies during participation in the trial or during a recognized follow-up period, theinvestigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed SAE form/eCRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hoursof receipt of the information.

Table 26: SAE Reporting to the Sponsor or Designee via Paper Form

SAE Reporting to the Sponsor or Designee via Paper Form
• the site will use the paper SAEform. The SAE paper form should be used to electronically transmit this informationto the sponsor or designee. • Contacts for electronic transmission of the paper SAE form are provided in the Investigator Binder. • In rare circumstances and in the absence of facsimile equipment, notification by telephone isacceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete andsign the appropriate SAE form within the designated reporting time frames.

APPENDIX 2. THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

The ECOG Scale of Performance Status (Table 27) will be used to qualify patients for enrollment and as a general status evaluation tool during XMT-1536 dosing (Oken, 1982).

Table 27: ECOG Performance Scale

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

APPENDIX 3. RECIST CRITERIA

New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) (Eisenhauer, 2009).

Smartphone and tablet applications exist that provide instructions on the basic process and definition of the steps involved with a RECIST measurement, how to measure tumor size via RECIST criteria, integrating old and new target lesions, and a direct link to the European Journal of Cancer publication. Examples are found below.

Android:

https://play.google.com/store/apps/details?id=appinventor.ai_louis_lassalle.RECIST_1_1_Calc&hl=en

iPhone IOS:

http://apk4iphone.com/RECIST-1-1-Calculator.html

https://recist.eortc.org/recist-1-1-2/

APPENDIX 4. DRUGS ASSOCIATED WITH LIVER TOXICITY

The list provided below if from FDA web site "Drug Induced Livery Injury Rank (DILI rank) Dataset, located at: https://www.fda.gov/ScienceResearch/BioinformaticsTools/LiverToxicityKnowledgeBase/ucm604985.htm.

Drugs categorized at "Most-DILI-concern" cannot be used on the day of or after XMT-1536 has been administered or for 21 days after the last dose of XMT-1536. Below is the list of 130 drugs that are in this category. See Table 28.

Table 28: Drugs Categorized as Most DILI Concern and Not Withdrawn or Discontinued

4-aminosalicylic acid	estramustine	minocycline
abacavir	ethambutol	nandrolone decanoate
acarbose	etodolac	natalizumab
acetaminophen	etravirine	nefazodone
acetazolamide	exemestane	nevirapine
acitretin	febuxostat	niacin
albendazole	felbamate	nilutamide
allopurinol	fenoprofen	nitrofurantoin
amiodarone	fluconazole	nortriptyline
asparaginase	flutamide	orlistat
atomoxetine	fosphenytoin	oxaliplatin
atorvastatin	gefitinib	oxandrolone
azathioprine	gemcitabine	oxymetholone
bexarotene	gemfibrozil	papaverine
bicalutamide	gemtuzumab ozogamicin	pazopanib
bortezomib	griseofulvin	peginterferon alfa-2b
bosentan	hydroxyurea	pentostatin
busulfan	imatinib	phenytoin
carbamazepine	indomethacin	propylthiouracil
chlorzoxazone	infliximab	raltegravir
ciprofloxacin	interferon alfa-2a, recombinant	rifampin
clarithromycin	interferon alfa-2b	riluzole
clomipramine	interferon alfacon-1	ritonavir

Table 28: Drugs Categorized as Most DILI Concern and Not Withdrawn or Discontinued (Continued)

clozapine	interferon beta-1a	sorafenib
cyclosporine	interferon beta-1b	stavudine
cytarabine	isoniazid	sulfasalazine
dacarbazine	isotretinoin	sulindac
dactinomycin	itraconazole	sunitinib
danazol	ketoconazole	tamoxifen
dantrolene	labetalol	telithromycin
darunavir	lamotrigine	terbinafine
deferasirox	lapatinib	testosterone
diclofenac	leflunomide	thiabendazole
didanosine	levofloxacin	ticlopidine
diflunisal	maraviroc	tipranavir
diltiazem	mefenamic acid	tizanidine
disulfiram	mercaptopurine	tolcapone
divalproex sodium	methimazole	tolvaptan
dronedarone	methotrexate	valproic acid
duloxetine	methyldopa	voriconazole
efavirenz	mexiletine	zafirlukast
eltrombopag olamine	micafungin	zidovudine
erlotinib	milnacipran	zileuton
erythromycin		

APPENDIX 5. STRONG INHIBITORS AND INDUCERS OF CYTOCHROME P450 3A

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g., making it ineffective. Table 29 has a list of examples of strong inhibitors that should be avoided for 14 days before initiation of XMT-1536 dosing and until 14 days after the last dose. A strong inhibitor is defined as one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

Additionally, strong inducers of CYP450 3A should be avoided. Similar to inhibitors, a strong inducer is defined as one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance. Please refer to Table 30 for examples of these inducers to be avoided during participation in the QTc sub-study.

Table 29: Strong Inhibitors of Cytochrome P450 3A

3A	Clarithromycin indinavir itraconazole ketoconazole nefazodone nelfinavir ritonavir saquinavir idelalisib ribociclib telithromycin

Note: Several valid interaction tables are recognized references for medical practice. This protocol will use the following reference: Flockhart D.A., (2007). Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. https://drug-interactions.medicine.iu.edu/MainTable.aspx Accessed 31 August 2020. Additionally, the FDA Drug Development and Drug Interactions Table of Substrates, Inhibitors, and Inducers is used as reference for the strength of interaction (accessible at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3).

Table 30: Strong Inducers of Cytochrome P450 3A

3A	Apalutamide Carbamazepine Enzalutamide Mitotane Phenytoin Rifampin St John’s wort

Note: Several valid interaction tables are recognized references for medical practice. This protocol will use the following reference: Flockhart D.A., (2007). Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. https://drug-interactions.medicine.iu.edu/MainTable.aspx Accessed 31 August 2020. Additionally, the FDA Drug Development and Drug Interactions Table of Substrates, Inhibitors, and Inducers is used as reference for the strength of interaction (accessible at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3

APPENDIX 6. GUIDANCE ON PREMEDICATIONS AND SUPPORTIVE MEDICATIONS

Table 31: List of Acceptable Pre-medications Given Prior to Infusion of XMT-1536

Adverse Event	Example Regimen and Dose
NauseaP[a]	**5-HT3 receptor antagonist** • Granisetron 2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous[a] • Ondansetron Single 24-mg dose administered by tablets, successive oral dissolving tablets, or oral dissolving film applications before the start of chemotherapy, or 8 mg or 0.15 mg/kg IV (max 8mg/day).[a] • Palonosetron 0.25 mg IV **Neurokinin-1 (NK1) receptor antagonist** • Aprepitant 125 mg oral or 130 mg IV • Fosaprepitant 150 mg IV • Netupitant-palonosetron 300 mg netupitant/0.5 mg palonosetron oral in single capsule • Fosnetupitant-palonosetron 235 mg fosnetupitant/0.25 mg palonosetron IV • Rolapitant 180 mg oral **Steroids** • Dexamethasone 8-12 mg oral or IV **Other** • Olanzapine 10 mg or 5 mg oral Dexamethasone 8-12 mg oral or IV
Fever	• NSAIDs preferred • Acetaminophen allowed up to 2 grams/day
Rash/Hypersensitivity reaction	• H1/H2 antagonists (e.g., diphenydramine plus ranitidine)
[a]Based on ASCO Guideline Update on Antiemetics. Paul J. Hesketh, Mark G. Kris, Ethan Basch, Kari Bohlke, Sally Y. Barbour, Rebecca Anne Clark-Snow, Michael A. Danso, Kristopher Dennis, L. Lee Dupuis, Stacie B. Dusetzina, Cathy Eng, Petra C. Feyer, Karin Jordan, Kimberly Noonan, Dee Sparacio, and Gary H. Lyman. Journal of Clinical Oncology 2020 38:24, 2782-2797	

[a] This medication should not be used for patients enrolled in the QTc sub-study.

Table 32: List of Acceptable Supportive Prophylactic Medications After Infusion of XMT-1536

Adverse Event	Example Regimen and Dose[a]
Nausea/Vomiting	• Dopamine antagonists (e.g, metoclopramide, haloperidol, olanzapine)[b] • Antihistamines (e.g., promethazine) • Serotonin (5HT3) antagonists (e.g., palonosetron)[c] • Other agents (e.g., anticholinergics, steroids, neurokinin-1 antagonists, benzodiazepines for anticipatory nausea)
Pyrexia[d]	• Nonsteroidal anti-inflammatory drugs (NSAIDs) • Acetaminophen/paracetamol – limit to ≤2 grams in 24 hour period • Low dose steroids
Fatigue[e]	• Stimulants (e.g., methylphenidate as per standard of care) • Steroids • Complementary medicine (e.g., gingseng, vitamins)

[a] Discuss with Medical Monitor if your preferred medication is not listed.
[b] The use of haloperidol and olanzapine should be avoided for patients enrolled in the QTc sub-study
[c] The use of ondasetron and granisetron should be avoided for patients enrolled in the QTc sub-study.
[d] Rule out infectious causes; consider admission to hospital if systemically unwell, and for Grade 3 or 4
[e] Treat other factors that may contribute to or exacerbate fatigue (eg, anemia, electrolyte abnormalities, etc)

APPENDIX 7. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

a. Documented hysterectomy
b. Documented bilateral salpingectomy
c. Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

1. Postmenopausal female: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Highly Effective Form(s) of Contraception allowed while on study

The following non-hormonal highly effective forms of contraception are allowed while on study and for the 6 months post the last dose of study medication as required:

- Intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner
- Female sterilization
- Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

Note: Periodic abstinence (calendar, symptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception

Contraception and Pregnancy Avoidance Procedures

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered a WOCBP following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Sterilized male subjects should be at least 1-year post bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this trial. This applies only to male subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial treatment by the investigator will be reported to the sponsor as described in Section 9.4. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the trial will discontinue trial treatment and be withdrawn from the trial.

APPENDIX 8. COUNTRY-SPECIFIC REQUIREMENTS

This appendix is intended to outline country-specific requirements that differ from the overall global conduct of the study due to differences in regional practices and regulations. All sites are advised to refer to this appendix in addition to the overall study plan to ensure adherence to the protocol.

Table 33: Table of Country-Specific Requirements

Country of Origin	Request	Required Action
Czech Republic	Include an HIV test among the screening examinations to determine eligibility as per the study global exclusion criteria	Participating sites in the Czech Republic must screen for HIV as part of the confirmation of eligibility. Patients with confirmation of HIV status completed within 30 days of screening do not need to complete a new HIV screening test
Czech Republic	FSH examination is required to confirm that female subjects are postmenopausal	Participating sites in the Czech Republic must provide determination of an FSH level in the postmenopausal range via a laboratory test for females with 12 months of amenorrhea. Additional information about this procedure is found in Appendix 7.
Czech Republic	Patients are required to be monitored for at least 4 hours after the first and second cycle	Participating sites in the Czech Republic must monitor patients for at least 4 hours after the first and second dose of XMT-1536
Czech Republic	In compliance with the standard procedures applicable to oncology studies in the Czech Republic, patients must not receive live attenuated vaccines 30 days prior to study entry or receive live/attenuated vaccines 30 days prior to study entry or receive live/attenuated vaccines while on treatment through 90 days after administration of the last dose of the study medication.	Patients in the Czech Republic must adhere to the additional exclusion of restriction of receipt of live vaccinations as specified in Exclusion 15, applicable to Czech Republic only and referenced in Section 6.3.5 Vaccinations.
France	The eligibility criteria are requested to be modified so that platinum-resistant patients can only be included following receipt of at least 2 prior systemic lines. Additionally, patients eligible for surgery should not be enrolled.	Participating sites in France cannot enroll patients with platinum-resistant disease who have had not received at least 2 prior systemic lines of therapy or who are eligible for surgery.

France	Safety follow-up visit should be conducted 60 days following study treatment discontinuation for all patients	Participating sites in France should have a safety follow-up visit conducted 60 days after study treatment discontinuation. The same assessments as the EOT visit, except tumor imaging, should be conducted.
France	Ophthalmic Exams	Patients from sites in France are also required to undergo ophthalmic exams at the end of Cycle 6 (± 7 days) in addition to the timepoints included in the Schedule of Events.
Finland	The eligibility criteria are required to be modified to indicate that patients must have exhausted other effective treatments for HGSOC prior to inclusion in the trial.	Ovarian Cancer Eligibility Criteria for UPLIFT, Inclusion #3 revised to provide explicit instructions for patients in Finland to have exhausted other treatment options for HGSOC.

APPENDIX 9. ABBREVIATIONS

Table 34: Abbreviations

Abbreviation	Full Term	Abbreviation	Full Term
ADA	Anti-drug antibodies	ICF	Informed consent form
ADC	Antibody drug conjugate	IHC	immunohistochemistry
ADL	Activities of daily living	HNSTD	Highest non-severely toxic dose
ADCC	Antibody-dependent cell-medicated cytotoxicity	KRAS	Kirsten rat sarcoma (oncogene)
AE	Adverse Event	LDH	Lactate dehydrogenase
ALK	Anaplastic lymphoma kinase (marker)	mAb nAb	Monoclonal antibody Neutralizing antibody
ALT (SGPT)	Alanine transaminase or alanine aminotransferase, or serum glutamate-pyruvate transaminase	MedDRA	Medical Dictionary for Regulatory Activities
ALP	Alkaline phosphatase	Med Hx	Medical history
ANC	Absolute neutrophil count	MRI	Magnetic Resonance Imaging
AST (SGOT)	Aspartate transaminase or aspartate aminotransferase, or serum glutamic oxaloacetic transaminase	MTD	Maximum tolerated dose
$AUC_{0\text{-}Last}$	Area under the curve from time 0 to the last measurable concentration.	MUGA	Multi gated acquisition scan
BRCA	Breast Cancer type 1 susceptibility gene	NaPi2b	Sodium-dependent phosphate transport protein 2B
BSA	Body surface area	NCI	National Cancer Institute
BUN	Blood urea nitrogen	NK1	Neurokinan-1
CBC	Complete blood count	NSCLC	Non-small cell lung cancer
CI	Confidence interval	OCT	Ocular coherence tomography
CISH	Chromogenic in situ Hybridization	ORR	Objective response rate (CR+PR)
CMO	Chief Medical Officer	OS	Overall survival
Con Med	Concomitant Medication	PARPi	poly ADP ribose polymerase inhibitors
C_{max}	Concentration at maximum level	PD-1/PD-L1	Programmed death-1/ Programmed death ligand-1
CPN	Chronic progressive neuropathy	PE	Physical exam
CR	Complete response	PFS	Progression-free survival
CT	Computerized tomography	PK	Pharmacokinetics
CTCAE	Common Toxicity Criteria for Adverse Events	PR	Partial response
DCR	Disease control rate	RP2D	Recommended Phase 2 Dose
DES	Dose escalation	RECIST	Response Evaluation Criteria in Solid Tumors
DL	Dose Level	SD	Stable disease
DILI	Drug induced liver injury	SRC	Safety Review Committee
DLT	Dose limiting toxicity	SRM	Safety Review Meeting
DOR	Duration of response	t_{max}	Time to maximum concentration
ECHO	Echocardiogram	TP53	Tumor protein p53
eCRF	Electronic case report form	UA	Urinalysis
EGRF	Epidermal growth factor receptor	ULN	Upper limit of normal
EXP	Expansion	UpRi	Upifitamab rilsodotin
FIH	First-in-human	VS	Vital signs
		WHO-ATC	World Health Organization Anatomical Therapeutic Committee

APPENDIX 10. PROTOCOL HISTORY

Table 35: Protocol History

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
Original Protocol 15 September 2017	Dose Levels: 21-day cycles • DL1: 3 mg/m^2 • DL2: 6 mg/m^2 • DL3: 12 mg/m^2 • DL4: 20 mg/m^2 • DL5: 30 mg/m^2 • DL6: 40 mg/m^2 • DL&: 53 mg/m^2	• DLT evaluation period: 21 days • Any dose level with 2 or more DLTs in 6 or fewer treated patients will be considered to have exceeded the MTD	• This version was submitted in the IND application and never sent for IRB approval or used for patient participation.
Original Protocol to Version 2 19 October 2017 First protocol used for patient participation	Dose Levels: 21-day cycles • DL1: 3 mg/m^2 • DL2: 6 mg/m^2 • DL3: 12 mg/m^2 • DL4: 20 mg/m^2 • DL5: 30 mg/m^2 • DL6: 40 mg/m^2 (1 patient dosed at this level)	• DLT evaluation period: 21 days • Any dose level with 2 or more DLTs in 6 or fewer treated patients will be considered to have exceeded the MTD	• Implemented inclusion and exclusion changes from FDA sent during the IND review period. • Defined MTD and RP2D.
Version 3 13 August 2018	Dose Levels: 28-day cycles • DL4A: 20 mg/m^2 (additional patients dosed at this level) • DL5A: 30 mg/m^2 • DL6A: 36 mg/m^2 • DL7A: 43 mg/m^2 (maximum dose)	• DLT evaluation period: Cycle 1 and Cycle 2 (56 days) • Any dose level with 2 or more DLTs in 6 or fewer treated patients will be considered to have exceeded the MTD	• Added eligibility criteria to rule out enrollment of patient with chronic liver disease. • Incorporated use to FDA DILI concern drug list. • Added more lab sampling to monitor changes in hepatic function. • Certain DLT criteria and rules for redosing after certain adverse events are more restrictive.
Version 4 18 February 2019	Same as Version 3.	• DLT evaluation period: 28 days (Day 1 through end of cycle 1, including pre-dose assessments prior to Cycle	• The patient populations where restricted to those most likely to express NaPi2b and therefore more likely to response to XMT-1536. • Modifications to the DLT criteria were made to allow

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
		2) • Grade 3 AST elevations that return to Grade 2 in ≤5 days will not be assessed as a DLT • Any dose level with 2 or more DLTs in 6 or fewer treated patients will be considered to have exceeded the MTD	safe exploration of higher doses until MTD was met or RP2D was determined.
Version 5.0 13 June 2019	DL8A: 52 mg/m^2, 28-day Cycle	Same as Version 4	• Refined requirements to conduct the expansion (EXP) segment of the study, refining the inclusion exclusion criteria to study ovarian cancer and NSCLC patients. • Allowed the Safety Review Committee to select an EXP dose after the completion of DL6A. • Provide ongoing safety review in EXP by the Safety Review Committee in lieu of the DES SRC activities.
Version 5.1 12 July 2019	Same as Version 5.0	Same as Version 5.0	• Tests for fibrinogen and d-dimer was added to the following visits: baseline, Cycles 1, 2, 3, 4 and beyond: days 8, 15, 21, and 28 and at the End of Treatment visit.
Version 5.2 11 November 2019	Same as Version 5.0	Same as Version 5.0	• This version was created for submission to Health Canada. No changes were made from version 5.1
Version 6.0 19 November 2020	• 36 mg/m^2 selected as EXP dose • Allows for dose escalation beyond DL7A of ≤20% at the discretion of the SRC	Same as Amendment 5	• Inclusion criteria was changed regarding prior lines of therapy for ovarian cancer and NSCLC patients. • EXP commenced at 36 mg/m2 and in parallel, dose escalation continued.
Version 6.0 – COVID-19 Mitigation 23 March 2020	Same as Version 6.0	Same as Version 6.0	• Options for study visits allowed if acceptable to a local site and their IRB. • Laboratory samples obtained between dosing visits could be done at regional facilities close to a patient's home. • On-site visits could be replaced by telemedicine visits. If done, lab sampling between dose visits

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
			could be skipped if deemed medically appropriate by the Investigator.
Version 6.1 19 March 2020	Same as Version 6.0	Same as Version 6.0	• One change was made: the EudraCT identification was added.
Version 6.2 29 April 2020	Same as Version 6.0	Same as Version 6.0	• One change was made: The Gynecological Oncology Group (GOG) protocol identification number was added.
Version 6.3	Same as Version 6.0	Same as Version 6.0	• Changes implemented to address comments from MHRA.
Version 6.4	Same as Version 6.0	Same as Version 6.0	• Changes implemented to address comments from PEI.
Version 7.0 31 August 2020	Expansion Dose: 43 mg/m^2, q28d	DLT criteria and DES data review meetings are no longer applicable and are replaced by Quarterly Safety Review meetings conducted and published to all investigators.	• Eligibility criteria were clarified. • Overall survival and progression free survival data to be collected were elaborated. • Additional countries for EXP conducted were added. • The justification for additional patient enrollment was provided.
Version 7.1	Expansion Dose: 43 mg/m^2, q28d	Same as Version 7.1	• Added criteria for dose reduction due to ILD/pneumonitis.
Version 8.0 (Created only for regulatory review) And Version 8.1 – for use by Research Sites to conduct the study after IRB/IEC and other required local Approvals	Expansion Dose: 43 mg/m^2, q28d, considered the Recommended Phase 2 Dose	Same as Version 7.1	• The rationale, eligibility criteria and sample size justification were added for the Ph 2, pivotal ovarian cancer Cohort 3, also referred to as UPLIFT, segment of the study. • Statistical analysis parameters were added for use in UPLIFT data analysis. • Additional guidance for treatment and continued dosing after certain Gr 2 or Gr 3 adverse events is now included in Section 4. • Baseline and post dose ocular evaluations now include visual acuity test, and optical coherence tomography (OCT) assessments in addition to the slit lamp evaluation. • Guidance for the use of prophylactic medications is now provided.

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
			• Clarification on the timing of tumor evaluations for RECIST evaluation has been added. • The DES segment of the study has concluded, and this is indicated throughout the text.
Version 8.2 29 April 2021	Same as Version 8.1	Same as Version 8.1	• Protocol changes implemented for Sweden only • Benefit/Risk Assessment added • Frequency of pregnancy tests amended to comply with local guidelines • New section added, 4.7 Trial Definitions • Eligibility criterion #3 for Cohort 3 revised to include additional guidance as to allowable prior treatments • SUSAR definition and procedure added to Section 9.2.1.1 • Section 13.2 revised to clarify local and national laws and regulations apply
Version 8.3 11 June 2021	Same as Version 8.1	Same as Version 8.1	• Protocol changes implemented for Norway only • Benefit/Risk Assessment added • Frequency of pregnancy tests amended to extend 6 months beyond last dose of study medication • New section added, 4.7 Trial Definitions • Exclusion criterion #13 added to General Exclusion Criteria for DES, EXP, and UPLIFT
Version 9.0 26 July 2021	Same as Version 8.1	Same as Version 8.1	• All protocol changes from Versions 8.2 and 8.3 were incorporated into Global version • Language was incorporated into the protocol to denote the current status of the DES, EXP, and UPLIFT segments of the study, including Background Information, Methodology, and Eligibility Criteria • QTc Sub-study was incorporated into the protocol to provide additional safety information for the protocol, inclusive of additional subsections for study considerations; criteria for evaluation; and schedule of events

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
			• Discrepancies between synopsis and protocol body were corrected, along with other errors noted during review and implementation of Version 8.1 at sites • Inclusion Criteria #2 and #3 for UPLIFT were clarified to provide more specific instruction as to the prior lines of therapy and instructions for counting lines of platinum therapy • Exclusion Criterion #3 for UPLIFT was revised to be more specific • Section 9.2.2 was updated to remove the contact information from reporting as it will be captured in the Safety Manual. • Throughout the protocol, specific reference to CROs was removed to make the protocol less directive as the information will be captured in other study documents • Exclusion #13 added to general exclusion criteria consistent with requests from country • Exclusions #14 and 15 added to general exclusion criteria to provide mor stringent guidance for potential for ILD/pneumonitis • The Adverse Event and Safety Reporting sections were revised in alignment with updated processes • Appendix for Contraception and Pregnancy Information added • Appendix to address country-specific requirements added • D-dimer was removed from collection in SoA table.
Version 9.1	Same as Version 8.1	Same as Version 8.1	• Czech Republic only – exclusion added to the global criteria for patients in this country prohibiting use of live vaccines from 30 days prior to study entry through 90 days after the last dose of study medication. • Statement added to Section 6.3.5 Vaccinations to be

Protocol Version	Dose Levels & Cycle Length	Dose Limiting Toxicity Criteria	Summary of Changes
			consistent with exclusion criteria. • Country specific requirements table updated
Version 9.2	Same as Version 9.0	Same as Version 8.1	• Finland only: inclusion #3 added to the Ovarian Cancer Specific Eligibility Criteria for UPLIFT to state that patients must have exhausted other treatment options for HGSOC prior to inclusion in the trial • Country specific requirements table updated
Version 10	Sane as Version 9.2.	Same as version 9.2.	• Sponsor contact information updated • General Exclusion criteria #13 and Appendix 5 revised from Cytochrome P450 to Cytochrome P450 3A throughout protocol. • Description of Expansion timeline added for clarification in 1.1. Synopsis (Methodology) and 4.1. Overall Study Design • Refinements to the efficacy analysis definitions were incorporated • Efficacy analysis population refined to clarify that only those at updated starting dose of 36 mg/m2 will be included. • 1.3, SoA Table updated o Window for ECGs at screening revised to 0-28 days (vs. 0-14 days) o Cycle 3, Day 2 lab visit removed to reduce burden on participants. • Table 4: Pharmacokinetic and Electrocardiogram Schedule for the QTc Sub-Study: timepoint at Cycle 1 Day 5 ± 1 day added • Appendix to address country-specific requirements updated. • Dose reduction, modification, and delay criteria updated following discussion with regulatory agency. • EDC Tool removed from AE/SAE reporting guidelines