A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Upifitamab Rilsodotin (XMT-1536) as Post-Platinum Maintenance Therapy for Participants with Recurrent, Platinum-Sensitive Ovarian Cancer (UP-NEXT)

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In this study, we look at how safe the new medicinal product XMT-1536 is for the treatment of ovarian cancer and how well it works. We compare the effect of XMT-1536 with the effect of a placebo. A placebo is a product without the active ingredient...

Ethical review	Approved WMO
Status	Pending
Health condition type	Reproductive neoplasms female benign
Study type	Interventional

Summary

ID

NL-OMON53654

Source
ToetsingOnline

Brief title
MER-XMT-1536-3 UP-NEXT

Condition

- Reproductive neoplasms female benign

Synonym
ovarian cancer

Research involving

Human

Sponsors and support

Primary sponsor: Mersana Therapeutics, Inc.
Source(s) of monetary or material Support: industry sponsored trial by Mersana Therapeutics;Inc.

Intervention

Keyword: MER-XMT-1536-3, Ovarian Cancer, upifitamab rilsodotine, UP-NEXT

Outcome measures

Primary outcome

Primary Objective:

• Demonstrate superiority in Progression-free Survival (PFS) as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 of upifitamab rilsodotin versus placebo as maintenance therapy

Secondary outcome

Key Secondary Objective:

• Compare Overall Survival (OS) of upifitamab rilsodotin versus placebo as maintenance therapy

Other Secondary Objectives:

• Compare PFS as assessed by Investigator using RECIST v1.1 of upifitamab rilsodotin versus placebo as maintenance therapy

• Compare the Objective Response Rate (ORR) as assessed by Investigator using RECIST v1.1 of upifitamab rilsodotin versus placebo as maintenance therapy

• Evaluate safety and tolerability in participants treated with upifitamab

rilsodotin versus placebo as maintenance therapy

Study description

Background summary

You are being asked to participate in this study because you have been diagnosed with platinum-sensitive high-grade serous ovarian cancer. Platinum-sensitive high-grade serous ovarian cancer is a type of cancer that responds at first to treatment with drugs that contain the metal platinum, but then cancer comes back within a certain period. For example, ovarian cancer that comes back in 6 or more months after treatment is considered platinum sensitive. You recently received treatment with chemotherapy containing a platinum chemotherapy drug and your cancer did not worsen while on that treatment. You have also participated in the pre-screening testing which showed that your tumor has high levels of NaPi2b.

XMT-1536 (upifitamab rilsodotin) is the investigational drug. This means it has not been approved as a treatment for cancer in any country. XMT-1536 is a *targeted therapy*, which means that it is directed specifically at a tumor. It is a type of antibody drug conjugate; this means it has 2 parts that are joined together into one drug product. The first part is an antibody that binds to NaPi2b (sodium-dependent phosphate transporter), a protein on the surface of the cells of your tumor. The second part is a cancer medicine that is attached to the antibody. When the antibody binds to NaPi2b, it carries the cancer medicine directly into the tumor cells to kill them.

Study objective

In this study, we look at how safe the new medicinal product XMT-1536 is for the treatment of ovarian cancer and how well it works.
We compare the effect of XMT-1536 with the effect of a placebo. A placebo is a product without the active ingredient: a 'fake medicinal product'.
The purpose of the study is to:
• Compare progression free survival (the length of time that patients live without their disease getting worse) for patients with ovarian cancer with high NaPi2b level on their tumor cells treated with XMT-1536 versus placebo, following standard chemotherapy.
• Compare response to treatment and overall survival.
• Compare safety and tolerability of treatment with XMT-1536 versus treatment with placebo.
• Compare the time to the start of next cancer treatment after study treatment with XMT-1536 or placebo and the time to worsening of patients* cancers following next cancer treatment.

• Understand quality of life through patient questionnaires.
• Evaluate if blood levels of XMT-1536 and proteins your body may produce against XMT-1536 are related to response to treatment or side effects of treatment.

Study design

This is a double-blind, randomized, placebo controlled (2:1 upifitamab rilsodotin: placebo), Phase 3 study in participants with recurrent, platinum-sensitive high-grade serous ovarian cancer (HGSOC) including fallopian tube and primary peritoneal cancer in the maintenance setting.
Participants must have had in their most recent treatment regimen 4 to 8 cycles of platinumbased chemotherapy, including carboplatin or cisplatin ±: paclitaxel, docetaxel, pegylated liposomal doxorubicin or gemcitabine in the 2nd - 4th line setting for the treatment of platinumsensitive recurrent disease, with no evidence of disease (NED)/complete response (CR)/partial response (PR)/ or stable disease (SD) as best response. Participant*s disease must be NaPi2bpositive (TPS >=75), as measured by central laboratory (archived or recent biopsy).

Approximately 350 participants will be randomized 2:1 (upifitimab rilsodotin:placebo) into this study. An imbalanced randomization ratio of 2:1 for the experimental arm over the control arm was selected balancing the principle of equipoise in clinical trial research with acceptability to prospective study participants. This randomization ratio has been utilized in other ovarian cancer maintenance trials.

Randomization of participants will be stratified based on their response to last platinum-based regimen (NED or CR versus PR versus SD), number of prior lines of platinum-based therapy (2 versus 3 or 4) and previous treatment with a PARPi (yes or no).

Intervention

The study is divided into several sections, or periods:

(Pre-)Screening
Pre-screening / Screening tests must be done before you receive any XMT-1536 (or placebo). These screening tests will help your study doctor determine if you have certain conditions or lab results that might prevent you from taking part in the study.

Treatment Cycles & End of Treatment, Safety Follow Up
• Treatment/Dosing up to 18 months with XMT-1536 (or placebo) into 2 groups: Group 1. The people in this group will get XMT-1536; Group 2. The people in this group will get placebo.

• Assessments via physical examinations, blood/tumor samples, ECG/eye exam, PRO questionnaires

Safety Follow Up, 30 days following your End of Treatment Visit, & Post Treatment Follow-up
Via phone calls, approximately 30 days after your last dose or after your End of Treatment visit and then every 90 days

Study burden and risks

There are risks, discomforts, and inconveniences associated with any research study. Side effects may be experienced from taking part in this study, although not everybody does. Side effects are mostly reversible and not all require treatment. It is very important that any side effects, reactions, or discomforts experienced between visits to the hospital are mentioned to the study doctor or nurses.

The side effects of the treatment and possible discomforts you may experience with assessments during the study are further explained in section 6 and 7 of the patient information and informed consent form.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Participants must be at least 18 years of age, and female.
2.Participant must have an ECOG performance status 0 or 1
3.Participant must have a histological diagnosis of high grade serous ovarian cancer, which includes fallopian tube and primary peritoneal cancer, that is metastatic or recurrent.
4.Participant must be able to understand the study procedures and agree to participate in the study by providing written informed consent.
5.Participant must have platinum-sensitive recurrent disease, defined as having achieved either a partial or complete response to 4 or more cycles in their penultimate platinum- containing regimen and their disease progressing more than 6 months after completion of the last dose of platinum containing therapy in the penultimate regimen.
6.Participant must have had 4 to 8 cycles of platinum-based chemotherapy in 2nd to 4th line setting in their most recent treatment regimen as defined below:
a. Platinum-based chemotherapy regimens allowed immediately preceding enrollment to the study: carboplatin or cisplatin ±: paclitaxel, docetaxel, pegylated liposomal doxorubicin or gemcitabine.
b. Participant must receive first study treatment infusion between 4 and 12 weeks after completing final dose of platinum in the most recent platinum-based regimen.
c. Definitions for prior lines of therapy:
-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)
-Maintenance therapy (e.g., bevacizumab, PARPi, endocrine therapy) will be considered as part of the preceding line of therapy (i.e., not counted independently)
- 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.
-Hormonal therapy (e.g., tamoxifen, letrozole) will be counted as a separate line of therapy unless given as maintenance.
7. Participant must have had as their best response to last line of treatment one of the following: No Evidence of Disease (NED); Complete Response (CR); Partial Response (PR); OR Stable Disease (SD)
8. Participants with NED, CR, or PR as their best response to most recent line

of treatment and who have not received treatment with a prior PARP inhibitor must have definitive BRCA1 and BRCA2 testing results that demonstrate no evidence of a deleterious BRCA1 or BRCA2 mutation. Somatic BRCA mutation testing is required for participants who are classified as not having a deleterious mutation by germline testing alone.
9. Participant must provide either a tumor tissue block or fresh cut slides for measurement of NaPi2b expression by a central laboratory. If sufficient archival tumor tissue is not available, then a tumor tissue block or slides must be obtained from a fresh biopsy and provided to the central laboratory. Confirmation of a NaPi2b-H/positive tumor by the central laboratory is required prior to randomization.
10. Participants with toxicity from prior therapy or surgical procedures must have recovered to Grade <=1. Participants with alopecia, stable immune-related toxicity such as hypothyroidism on hormone replacement, adrenal insufficiency treated with <=10 mg daily prednisone (or equivalent), or chronic Grade 2 peripheral sensory neuropathy after prior taxane therapy is an exception to this criterion and may qualify for this study.
11. Participants must have cardiac left ventricular ejection fraction (LVEF) >=50% or >= the institution's lower limit of normal as measured by either Echo or MUGA scan
12. Participants must have adequate organ function within 14 days prior to enrollment
13. During the study, female study participants of child-bearing potential (WOCBP) must a contraceptive method that is highly effective during study treatment and for at least 6 months after the last dose of study treatment.

Exclusion criteria

1. Participant has received prior treatment with mirvetuximab soravtansine or another ADC containing an auristatin or maytansinoid payload.
2. Participant has received bevacizumab in combination with last platinum-based regiment or plans to receive maintenance therapy outside the study intervention.
3. Participant has clinical signs or symptoms of gastrointestinal obstruction and/or requirement for parenteral hydration or nutrition.
4. Participant has ascites or pleural effusion managed with therapeutic paracentesis or thoracentesis within 28 days prior to signing the principal study consent form.
5. Participant has 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. Participants cannot receive drugs associated with hepatotoxicity concurrent with upifitamab rilsodotin administration except as outlined in Appendix 4.

7. Participant currently uses either constant or intermittent supplementary oxygen therapy.
8. Participant has history of or suspected pneumonitis or interstitial lung disease.
9. Participant has oxygen saturation on room air <93%.
10. Participant has had major surgery or systemic anti-cancer therapy within 28 days of starting study treatment.
11. Participant has a low-grade, clear cell, endometrioid, mucinous, carcinosarcoma, germ- cell, mixed histology, or stromal tumor.
12. Participant has untreated CNS metastases (including new and progressive brain metastases), history of leptomeningeal metastasis, or carcinomatous meningitis.
- Participants are eligible if CNS metastases are adequately treated and are neurologically stable for at least 2 weeks prior to enrollment.
- In addition, participants 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.
13. Participant has 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:
- HBV: Participants with serologic evidence of chronic HBV infection should have an HBV viral load below the limit of quantification to be eligible.
- HCV: Participants with a history of HCV infection should have completed curative antiviral treatment and HCV viral load below the limit of quantification.
- Screening for HIV is not required except if mandated by local regulations or indicated based on clinical assessment.
14. Participant has current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease) or intercurrent illness that could interfere with per-protocol evaluations. Further, participants are excluded with the following characteristics:
- A marked baseline prolongation of QTcF interval CTCAE Grade >1: repeated demonstration of a QTcF interval >480 milliseconds (ms) using Fridericia's QT correction formula.
- A history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).
15. Has a diagnosis of additional malignancy that required treatment within 2 years prior to screening, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix
16. Participant has clinically significant corneal disease.
17. Participant is unwilling to be transfused with blood components.
18. Participant is receiving concurrent anti-cancer therapy (e.g. chemotherapy, radiation therapy, biologic therapy, immunotherapy, hormonal therapy, investigational therapy).
19. Participant is unable or unlikely to comply with dosing schedule and study evaluations.

20. Participant is using strong CYP450 3A4 inhibitors or inducers that cannot be discontinued while receiving study treatment (see Appendix 5).
21. Participants who are WOCBP must not be pregnant or nursing. Pregnancy status must be confirmed with a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	10-04-2023
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Upifitamab rilsodotin Antibody Drug Conjugate
Generic name:	Upifitamab rilsodotin Antibody Drug Conjugate

Ethics review

Approved WMO

Date:	09-02-2023

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-005099-21-NL
ClinicalTrials.gov	NCT05329545
CCMO	NL82819.018.23