MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

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Primary Objective:• To compare the progression-free survival (PFS) of patients randomized to mirvetuximab soravtansine (MIRV) vs. Investigator*s choice of chemotherapy (IC Chemo) Key Secondary Objectives:• To compare the objective response rate (ORR...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55302

Source
ToetsingOnline

Brief title
MIRASOL

Condition

- Other condition
- Ovarian and fallopian tube disorders

Synonym
fallopian tube cancers, Ovarian Cancer

Health condition

Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers

Research involving
Human

Sponsors and support

Primary sponsor: Immunogen, Inc.
Source(s) of monetary or material Support: Immunogen;Inc.

Intervention

Keyword: Cancer, High Folate Receptor-Alpha Expression, Mirvetuximab Soravtansine, Platinum-Resistant

Outcome measures

Primary outcome

Primary Endpoint

• PFS, defined as the time from date of randomization until

Investigator-assessed progressive disease (PD) or death, whichever occurs

first. Results will be summarized by arm

* Kaplan-Meier method for survival function estimate

* Stratified Cox proportional hazard regression for hazard ratio (HR) estimate

* Stratified log-rank test for hypothesis testing

Secondary outcome

Key Secondary Endpoints

• Objective response includes best response of complete response (CR) or

partial response (PR) as assessed by the Investigator

* Stratified Cochran-Mantel-Haenszel (CMH) test for treatment comparison

* Clopper-Pearson method for 95% CI estimation

• OS defined as the time from date of randomization until the date of death. Patients alive at the time of analysis will be censored at the last known date known to be alive

* Kaplan-Meier method for survival function estimate

* Stratified Cox proportional hazard regression for HR estimate

* Stratified log-rank test for hypothesis testing

• Primary PRO assessment, defined as the number of patients achieving at least 15 point absolute improvement at Week 8 or Week 9 in the abdominal/GI scale of EORTC QLQ OV28

Other Secondary Endpoints

• DOR defined as the time from initial response until Investigator-assessed PD for all patients who achieve a confirmed objective response (PR or CR)

* Kaplan-Meier method for survival function estimate

* Unstratified Cox proportional hazard regression for HR estimate

* Unstratified log-rank test for hypothesis testing

• CA-125 response determined using the GCIG criteria defined in Section 8.14.2 of the protocol CA-125 response per GCIG criteria will be determined programmatically

• PFS2 defined as the time from date of randomization until second disease progression or death whichever occurs first. Results will be summarized by arm

• TEAEs, laboratory test results, physical examination findings, and vital signs

Exploratory Endpoints

Exploratory endpoints are provided below. The analysis and subsequent results of these assessments may be reported in separate documents and not included in the Statistical Analysis Plan or Clinical Study Report, respectively.

• EORTC QLQ-C30/OV-28, and EQ5D-5L

• PK parameters will not be calculated due to the use of a sparse sampling schedule. Summary statistics of intact ADC, total Ab, DM4 and S-methyl DM4 concentration data by time will be presented

• Immunogenicity is defined as the presence of ADA to MIRV. Based on seroconversion status, the impact of ADA on both efficacy and safety will be evaluated

• Identification of soluble FRα levels and other biomarkers, such as protein, genetic, and/or gene expression changes, related to solid malignancies and/or MIRV or IC Chemo mechanism of action

Study description

Background summary

Folate receptor alpha (FRα) is a glycosylphosphatidylinositol-anchored cell surface protein encoded by the folate receptor 1 (FOLR1) gene. FRα internalizes folate, which is an essential cofactor for one-carbon transfer reactions that are required for DNA and RNA synthesis, cell growth and proliferation. Marked upregulation of FRα occurs during neonatal development and in cancer, suggesting that the receptor functions primarily under conditions of high folate demand. In contrast, normal adult tissues generally lack FRα expression and employ alternative transporters such as folate receptor β, reduced folate carrier and proton-coupled folate transporter for folate uptake (Weitman 1992, Mantovani 1994, Elnakat 2004, Kelemen 2006, and Investigator Brochure). Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumors, particularly the serous and endometrioid

histologic subtypes of ovarian and endometrial cancers (Scorer 2010, Garin-Chesa 1993, Kalli 2008, Crane 2012, Dainty 2007, Jones 2008, Ab 2015, and Allard 2007). IHC results obtained from patients screened or enrolled in the Phase 1 Study
IMGN853-0401 and Phase 3 Study IMGN853-403 are generally consistent with the literature (Investigator Brochure). Assessment of the FRα distribution in the PROC expansion cohort of IMGN853-0401 demonstrated that approximately 40% of patients have high expression.
In vitro, MIRV binds cell surface FRα with high apparent affinity (<= 0.1 nM) and shows potent (IC50 <= 1 nM) and selective cytotoxicity against tumor cells expressing FRα. Cytotoxic effects of MIRV in vitro is related to the level of cell-surface expression of FRα (Ab 2015). MIRV additionally emonstrates significant activity against FRα positive xenografts, with partial and complete remissions observed in ovarian models (Ab 2015). Together with the selective upregulation of FRα in solid tumors, these results provide the rationale for exploring the clinical utility of MIRV.

Study objective

Primary Objective:
• To compare the progression-free survival (PFS) of patients randomized to mirvetuximab soravtansine (MIRV) vs. Investigator*s choice of chemotherapy (IC Chemo)
Key Secondary Objectives:
• To compare the objective response rate (ORR) of patients randomized to MIRV vs. IC Chemo
• To compare overall survival (OS) of patients randomized to MIRV vs. IC Chemo
• To compare the primary patient-reported outcome (PRO) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-OV28 (Abdominal/GI Symptom Scale) assessment from patients randomized to MIRV vs. IC Chemo
Additional Secondary Objectives:
• To compare the safety and tolerability of MIRV vs. IC Chemo
• To compare the duration of response (DOR) in patients randomized to MIRV vs. IC Chemo
• To compare the CA-125 response rate (RR) per Gynecologic Cancer Intergroup (GCIG) CA-125 criteria in patients randomized to MIRV vs. IC Chemo
• To compare the time to progression or death on the next line of treatment (PFS2) in patients randomized to MIRV vs. IC Chemo
Exploratory Objectives:
• To assess PRO using the EORTC QLQ-C30, EuroQol-5 Dimension 5-level (EQ-5D-5L) and Patient Global Impression of Severity (PGIS) questionnaires
• To evaluate concentrations of MIRV, total antibody (TAb), DM4 and S-methyl DM4, using sparse sampling
• To assess the immunogenicity of MIRV via anti-drug antibodies (ADAs)
• To evaluate potential biomarkers in blood and tumor tissue predictive of

response to MIRV

Study design

A Randomized, Open-label, Phase 3 Study :
This Phase 3 study is designed to compare the efficacy and safety of MIRV vs. IC Chemo in patients with platinum-resistant high-grade epithelial ovarian cancer (EOC), primary peritoneal, or fallopian tube cancer, whose tumors express a high-level of FRα. Patients will be, in the opinion of the Investigator, appropriate for single agent therapy for their next line of therapy. Folate receptor alpha (FRα) positivity will be defined by the Ventana FOLR1 (FOLR1-2.1) CDx assay.
Eligible patients (N = 430), who have provided informed consent and meet study entry criteria will be randomized (1:1) to one of two arms

Intervention

• Arm 1 (n = 215): MIRV 6 mg/kg adjusted ideal body weight (AIBW) every 3 weeks (Q3W)
• Arm 2 (n = 215): IC Chemo, at one of the following regimens as determined by the Investigator prior to randomization:
- Paclitaxel (Pac; 80 mg/m2) administered QW within a 4-week cycle
- Pegylated liposomal doxorubicin (PLD; 40 mg/m2) administered Q4W
- Topotecan (Topo; 4 mg/m2) administered either on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days (1.25 mg/m2 Days 1-5) Q3W

Study burden and risks

The burden and risk mainly consist out of extra time spent in comparison to standard treatment and side effects, and the risks of medical evaluation, including venapuncture, biopsy and MRI/CT scans.

Contacts

Public
Immunogen, Inc.

Winter Street 830
Waltham MA 02451
US
Scientific
Immunogen, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Female patients >= 18 years of age
2. Patients must have a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer
3. Patients must have platinum-resistant disease
a. Patients who have only had 1 line of platinum based therapy must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed between > 3 months and <= 6 months after the date last dose of platinum
b. Patients who have received 2 or 3 lines of platinum therapy must have progressed on or 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 imaging showing progression.; Patients who are platinum-refractory during front-line treatment are excluded (see exclusion criteria)
4. Patients must have progressed radiographically on or after their most recent line of therapy
Note: Progression must be determined radiographically and/or by CA-125 GCIG progression criteria
5. Patients must be willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy using a low risk, medically routine procedure for immunohistochemistry (IHC) confirmation of FRα positivity
6. Patient's tumor must be positive for FRα expression as defined by the Ventana FOLR1 (FOLR-2.1) CDx assay
7. Patients must have at least one lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the

Investigator)
8. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy is appropriate as the next line of treatment:
a. Adjuvant ± neoadjuvant considered one line of therapy
b. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered as part of the preceding line of therapy (ie, not counted independently)
c. Therapy changed due to toxicity in the absence of progression will be considered as part of the same line (ie, not counted independently)
d. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance.
9. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
10. Time from prior therapy:
a. Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)
b. Focal radiation completed at least 2 weeks prior to first dose of study drug
11. Patients must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities
12. Major surgery must be completed at least 4 weeks prior to first dose and have recovered or stabilized from the side effects of prior surgery
13. Patients must have adequate hematologic, liver and kidney functions defined as:
a. Absolute neutrophil count (ANC) >= 1.5 x 109/L (1,500/µL) without G-CSF in the prior 10 days or long-acting WBC growth factors in the prior 20 days
b. Platelet count >= 100 x 109/L (100,000/µL) without platelet transfusion in the prior 10 days
c. Hemoglobin >= 9.0 g/dL without packed red blood cell (PRBC) transfusion in the prior 21 days
d. Serum creatinine <= 1.5 x upper limit of normal (ULN)
e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3.0 x ULN
f. Serum bilirubin <= 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if total bilirubin < 3.0 x ULN)
g. Serum albumin >= 2 g/dL
14. Patients or their legally authorized representative must be willing and able to sign the informed consent form (ICF) and to adhere to the protocol requirements
15. Women of childbearing potential (WCBP) must agree to use highly effective contraceptive method(s) in while on study drug and for at least 3 months after the last dose of mirvetuximab soravtansine or at least 6 months after the last dose of Pac, PLD, or Topo
16. WCBP must have a negative pregnancy test within 4 days prior to the first dose of study drug

Exclusion criteria

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or lowgrade or borderline ovarian tumor
2. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first line platinum-containing chemotherapy
3. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
4. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
5. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision
6. Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
b. HIV infection
c. Active cytomegalovirus infection
d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug
Note: Testing at screening is not required for the above infections unless clinically indicated
7. Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
8. Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
a. Myocardial infarction <= 6 months prior to first dose
b. Unstable angina pectoris
c. Uncontrolled congestive heart failure (New York Heart Association > class II)
d. Uncontrolled >= Grade 3 hypertension (per CTCAE)
e. Uncontrolled cardiac arrhythmias
9. Patients assigned to PLD stratum only:
• Left ventricular ejection fraction (LVEF) below the institutional limit of normal as measured by echocardiography (ECHO) or multigated acquisition (MUGA) scan
10. Patients with a history of hemorrhagic or ischemic stroke within six months prior to randomization
11. Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)

12. Patients with a previous clinical diagnosis of non-infectious interstitial lung disease (ILD), including noninfectious pneumonitis
13. Patients with required use of folate-containing supplements (eg, folate deficiency)
14. Patients with prior hypersensitivity to monoclonal antibodies
15. Women who are pregnant or lactating
16. Patients with prior treatment with MIRV or other FRα-targeting agents
17. Patients with untreated or symptomatic central nervous system (CNS) metastases
18. Patients with a history of other malignancy within 3 years prior to randomization
Note: does not include tumors with a negligible risk for metastasis or death (eg, adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast)
19. Prior known hypersensitivity reactions to study drugs and/or any of their excipients
20. People who are detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who are unable to express their consent, and people who are subject to a legal guardianship order
21. Simultaneous participation in another research study, in countries or localities where this is the health authority guidance

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-06-2021

Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx
Generic name:	Doxorubicine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	mirvetuximab soravtansine
Generic name:	MIRV
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Abraxane
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Topotecan
Generic name:	Hycamtin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-08-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2022
Application type:	Amendment
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	EUCTR2019-003509-80-NL
ClinicalTrials.gov	NCT04209855
CCMO	NL72455.018.20