Primary Objectives: In the Dose Escalation Phase:
• To assess the safety and pharmacokinetics (PK) in order to determine a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of REGN4018 as monotherapy and in combination with cemiplimab.

Ethical review: Approved WMO
Status: Pending
Health condition type: Reproductive neoplasms female malignant and unspecified
Study type: Interventional

Summary

Source
ToetsingOnline

Brief title
R4018-ONC-1721

Condition
• Reproductive neoplasms female malignant and unspecified

Synonym
Recurrent Ovarian Cancer / Ovarian Cancer

Research involving
Human

Sponsors and support
Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Industry
**Intervention**

Keyword: Open-label, Ovarian Cancer, Phase 1/2, REGN4018

**Outcome measures**

**Primary outcome**

In the dose escalation phase:

Dose-limiting toxicities, treatment-emergent adverse events (TEAEs; including immune-related adverse events [imAEs]), serious AEs (SAEs), deaths, laboratory abnormalities (grade 3 or higher per CTCAE), and PK for monotherapy and in combination with cemiplimab.

In the dose expansion phase:

- ORR defined by RECIST 1.1 for both monotherapy and in combination with cemiplimab.

**Secondary outcome**

In the Dose Escalation Phase: ORR based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

In the Dose Expansion Phase:

- TEAEs; including immune-related, SAEs, deaths, and laboratory abnormalities (grade 3 or higher per CTCAE).
- Concentration of REGN4018 in serum over time.
- Change from baseline in QoL as measured by the European Organisation for...
Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 GHS/QoL score

- Change from baseline in physical functioning as measured by the EORTC QLQ-C30 physical functioning score
- Change from baseline in abdominal symptoms as measured by the Measure of Ovarian Symptoms and Treatment (MOST)-Abdominal index score (Not applicable to Endometrial Cancer Cohort)
- Time to deterioration in GHS/QoL, physical functioning, and abdominal symptoms
- Change from baseline in QoL as measured by EQ-5D

In both Dose Escalation and Dose Expansion Phases:

- ORR based on iRECIST, best overall response (BOR), duration of response (DOR), disease control rate, CR rate, PFS based on RECIST 1.1 and iRECIST, and CA-125 response
- Presence or absence of anti-drug antibodies against REGN4018 and cemiplimab

### Study description

### Background summary

REGN4018 is an antibody that targets 2 different proteins, namely, MUC16 and CD3, found on cells. Proteins are a part of each cell in the body, which work together like little machines for the cell to work. MUC16 is a protein that is found on the surface of some normal cells and cancer cells, like ovarian cancer cells. CD3 is a protein that is found on the surface of T-cells. T cells are apart of the immune system.

REGN4018 is intended to work by helping T cells find and kill the ovarian cancer cells. Cemiplimab is an antibody that works by blocking the immune checkpoint, a cell
receptor programmed cell death 1 (PD-1). on immune cells that is involved in preventing immune cells from destroying other cells. Blocking the receptor is expected to help immune cells attack cancer cells may increase the acidity of REGN4018.

**Study objective**

Primary Objectives
In the Dose Escalation Phase:
• To assess the safety and pharmacokinetics (PK) in order to determine a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of REGN4018 as monotherapy and in combination with cemiplimab
In the Dose Expansion Phase:
• To assess the preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab, (separately by cohort) as determined by the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary Objectives
In the Dose Escalation Phase:
To assess the preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab (separately by cohort) as determined by ORR by RECIST 1.1.
In the Dose Expansion Phase:
• To characterize the safety profile in each expansion cohort
• To characterize the PK of REGN4018 as monotherapy and in combination with cemiplimab
• To assess the effect of REGN4018 as monotherapy and in combination with cemiplimab on patient-reported outcomes (PROs), including health-related quality of life (HRQoL), functioning, and symptoms
In both the Dose Escalation and Dose Expansion Phases:
• To assess preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab (separately by cohort) as measured by ORR based on immune based therapy RECIST (iRECIST), best overall response (BOR), duration of response (DOR), disease control rate, CR rate, and progression-free survival (PFS) based on RECIST 1.1 and iRECIST
• To assess efficacy of REGN4018 as monotherapy and in combination with cemiplimab as measured by CA-125 level
• Immunogenicity of REGN4018 and cemiplimab

**Study design**

This is a phase 1/2, first-in-human (FIH), open-label, multicenter,
dose-escalation study with cohort expansion to investigate the safety, tolerability, efficacy, and PK of REGN4018, an anti-MUC16 x anti-CD3 bispecific antibody, administered as monotherapy and in combination with cemiplimab in patients with platinum-experienced and/or intolerant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with elevated serum CA-125 levels. With protocol amendment 8, a cohort(s) will be opened to evaluate REGN4018 in women with recurrent endometrial cancer after prior anti-PD-1 therapy and prior platinum-based chemotherapy.

**Intervention**

Monotherapy (REGN4018 administration): REGN4018 will be administered in a series of dose escalation and dose expansion cohorts by intravenous (IV) infusion and/or subcutaneous (SC) as described in the protocol during 6-week cycle (42 days).

Combination Therapy (REGN4018 and cemiplimab administration): REGN4018 will be administered in a series of dose escalation and dose expansion cohorts by intravenous (IV) infusion and/or subcutaneous (SC) as described in the protocol during 6-week cycle (42 days). Cemiplimab will be administered by IV infusion once a REGN4018 monotherapy dose has been selected.

Subcutaneous REGN4018 Initial and Transitional Dose cohorts: A cohort will be enrolled to explore SC administration of REGN4018 in week 1 (initial dose) and week 2 (transitional dose). REGN4018 2 mg will be administered by SC injection in week 1 and REGN4018 25 mg will be administered subcutaneously in week 2. With protocol amendment 8, additional cohort(s) will evaluate REGN4018 6 mg administered by SC injection in week 1 and REGN4018 25 mg administered subcutaneously in week 2. In these cohorts, the subsequent doses (including second transitional dose, if applicable, and full doses) will be administered by IV infusion up to 4 hours (including flush), once weekly.

Sarilumab prophylaxis cohort: Sarilumab 350 mg IV will be administered on cycle 1 day 1 before either the IV or SC initial dose of REGN4018. If sarilumab prophylaxis and/or SC initial and transitional doses are determined to significantly decrease grade 2 CRS, these treatments may be incorporated in expansion cohorts.

**Study burden and risks**

The study contains a screening phase, treatment phase and a follow-up phase.
The subject will have to undergo several examinations, tests and/or procedures before, during and after her treatment. Possible side effects that are already known.

Contacts

Public
Regeneron Pharmaceuticals, Inc.
Old Saw Mill River Road 777
Tarrytown 10591
US

Scientific
Regeneron Pharmaceuticals, Inc.
Old Saw Mill River Road 777
Tarrytown 10591
US

Trial sites

Listed location countries
Netherlands

Eligibility criteria

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

Inclusion criteria

1. Ovarian Cancer Cohorts Only: Patients with histologically or cytologically confirmed diagnosis of advanced, epithelial ovarian cancer (except carcinosarcoma), primary peritoneal, or fallopian tube cancer who have all of the following:
   a. serum CA-125 level >=2x upper limit of normal (ULN) (in screening)
b. has received at least 1 line of platinum-containing therapy or must be platinum-intolerant (applicable for dose escalation and non-randomized dose expansion cohorts)
c. documented relapse or progression on or after the most recent line of therapy
d. no standard therapy options likely to convey clinical benefit
2. Adequate organ and bone marrow function as defined in the protocol
3. Life expectancy of at least 3 months
4. Randomized phase 2 expansion cohort (Ovarian Cancer only):
   Platinum-resistant ovarian cancer patients who have had 1 to 3 lines of platinum-based therapy as defined in the protocol.
5. Endometrial Cancer Cohorts Only (supersedes criterion 2): histologically confirmed endometrial cancer that has progressed or recurrent after prior anti-PD-1 therapy and platinum-based chemotherapy

Note: Other protocol Inclusion Criteria apply

**Exclusion criteria**

1. Recent treatment with anti-Programmed Cell Death (PD-1)/PD-L1 therapy
2. Ovarian Cancer Expansion cohorts only: More than 4 prior lines of cytotoxic chemotherapy for platinum-experienced and/or intolerant disease
3. Prior treatment with a Mucin 16 (MUC16)-targeted therapy
4. Untreated or active primary brain tumor, central nervous system (CNS) metastases, or spinal cord compression
5. History and/or current cardiac findings as defined in the protocol
6. Severe and/or uncontrolled hypertension at screening. Patients taking anti-hypertensive medication must be on a stable anti-hypertensive regimen

Note: Other protocol Exclusion Criteria apply

**Study design**

**Design**

<table>
<thead>
<tr>
<th>Study phase</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Interventional</td>
</tr>
<tr>
<td>Masking</td>
<td>Open (masking not used)</td>
</tr>
<tr>
<td>Control</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Primary purpose</td>
<td>Treatment</td>
</tr>
</tbody>
</table>
Recruitment

NL
Recruitment status : Pending
Start date (anticipated) : 01-06-2023
Enrollment : 21
Type : Anticipated

Medical products/devices used

| Registration | No |
| Product type | Medicine |
| Brand name | Cemiplimab |
| Generic name | Cemiplimab |
| Registration | Yes - NL outside intended use |
| Product type | Medicine |
| Brand name | Kevzara |
| Generic name | Sarilumab |
| Registration | Yes - NL outside intended use |
| Product type | Medicine |
| Brand name | REGN4018 |
| Generic name | REGN4018 |

Ethics review

Approved WMO
Date : 13-02-2023
Application type : First submission
Review commission : METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO
Date : 10-07-2023
Application type : First submission
Review commission : METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO
Date : 08-01-2024
Application type : Amendment
Review commission : METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date : 04-03-2024
Application type : Amendment
Review commission : METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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

<table>
<thead>
<tr>
<th>Register</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>EudraCT</td>
<td>EUCTR2019-003298-24-NL</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
<td>NCT03564340</td>
</tr>
<tr>
<td>CCMO</td>
<td>NL83392.078.23</td>
</tr>
</tbody>
</table>