A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96 / ENGOT-ov65)

Published: 21-10-2021
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This study has been transitioned to CTIS with ID 2023-506177-35-00 check the CTIS register for the current data. Objective: To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ovarian and fallopian tube disorders
Study type	Interventional

Summary

ID

NL-OMON51981

Source
ToetsingOnline

Brief title
MK3475-B96

Condition

- Ovarian and fallopian tube disorders

Synonym
Ovarian Cancer, Ovarian carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: MSD / Merck Sharp & Dohme

Intervention

Keyword: Ovarian cancer, Pembrolizumab, Phase 3

Outcome measures

Primary outcome

Primary: To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by the investigator

Secondary outcome

Secondary:

- To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to overall survival (OS)

- To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to progression free survival (PFS)

- To evaluate the safety and tolerability of pembrolizumab in combination with paclitaxel with or without bevacizumab

- To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to Global

Health Status/Quality of Life (GHS/QoL) score

Study description

Background summary

Ovariumcarcinoma (OC) is the 20th most common cancer, with an estimated 295,414 new cases diagnosed worldwide. OC is typically diagnosed in advanced stages. The 5-year survival rate for patients with OC is only about 48%, and in patients with distant disease only 29%. Given the high toxicity with the current SOC chemotherapeutic regimens and no clear improvement in OS, there remains an urgent requirement for novel therapies to be identified for women with platinum-resistant disease. Due to over-expressed PD-LI in OC, the combination of chemotherapy and immune checkpoint blockade may be a rational approach for the treatment of recurrent OC.

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with ligand PD-L1 and ligand PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention of recurrent OC

Study objective

This study has been transitioned to CTIS with ID 2023-506177-35-00 check the CTIS register for the current data.

Objective: To compare pembrolizumab plus paclitaxel with or without bevacizumab to placebo plus paclitaxel with or without bevacizumab, with respect to progression-free survival (PFS) per RECIST 1.1 as assessed by the investigator.

Study design

This is an randomized, multicenter, double-blind, phase 3-study with pembrolizumab (MK3475) plus paclitaxel versus placebo plus paclitaxel, with or without bevacizumab for patient with Platinum-resistant Recurrent Ovarian Cancer.

Approximately 616 participants will be randomly assigned (1:1) to 1 of 2 treatment arms. Screening procedures must be completed within 28 days prior to treatment. Eligible participants are randomly assigned to Arm 1 or 2 to one fo the following study intervention groups until one of the conditions for discontinuation of study intervention is met.After the end-of-treatment, each participant will be followed for the
occurrence of adverse events and spontaneously reported pregnancy.

The Sponsor estimates that the study will require approximately 65 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant*s last study-related contact.All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Intervention

Arm 1:
Pembrolizumab 400 mg (Q6W, 18 cycles)
+
Paclitaxela 80 mg/m2 days 1, 8, 15 of each Q3W-cycle
(± bevacizumab 10 mg/kg Q2Wb)

Arm 2:
Placebo (Q6W, 18 cycles)
+
Paclitaxela 80 mg/m2 days 1, 8, 15 of each Q3W-cyclus
(± bevacizumab 10 mg/kg Q2Wb)

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, Biopsy (if applicable), CT-MRI or bone scans, physical exams, possibly confrontational questionnaires, and patients will be asked to visit the hospital regularly. Patients will be administered with different kinds of medication present in the different interventiongroups during sixweek cycles up to a maximum of 18 doses and 9 additional doses.

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an

investigational medicine. Pembrolizumab has been administered in a large number of cancer participants with a well characterized safety profile and has received regulatory approval for multiple malignancies. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W). Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The below-mentioned inclusion criteria are the most important ones. A complete list of cohort specific inclusion criteria can be found in the protocol.
1. Has histologically confirmed epithelial (including high-grade serous or predominantly

serous, low-grade serous, any-grade endometrioid, malignant mixed Müllerian tumors
[carcinosarcoma], or clear cell) ovarian, fallopian tube, or primary peritoneal carcinoma.
2. Has received 1 or 2 prior lines of systemic therapy for OC, including at least 1 prior
platinum-based therapy.
3. Has radiographic evidence of disease progression within 6 months (180 days) after the
last dose of platinum-based chemotherapy for OC (ie, platinum-resistant disease).
4. Is a candidate for paclitaxel chemotherapy (and bevacizumab, if using).
5. Is female, and at least 18 years of age, at the time of signing the informed consent.
6. Has an ECOG performance status of 0 to 1 assessed within 3 days before randomization.
7. A female participant is eligible to participate if she is not pregnant or breastfeeding
8. The participant (or legally acceptable representative) has provided documented informed
consent for the study
9. Has radiographically evaluable disease
10. Archival tumor tissue sample or newly obtained core or incisional/excisional biopsy of a
tumor lesion not previously irradiated has been provided
11. Have adequate organ function

Exclusion criteria

The below-mentioned exclusion criteria are the most important ones. A complete list of cohort specific exclusion criteria can be found in the protocol.
1. Has nonepithelial cancers (germ cell tumors and sex cord-stromal tumors), borderline
tumors (low malignant potential), mucinous, seromucinous that is predominantly mucinous, malignant Brenner*s tumor and undifferentiated carcinoma.
2. Has primary platinum-refractory disease, defined as disease that has progressed per
radiographic imaging while receiving or within 28 days of the last dose of first-line platinum-based therapy.
3. Has prior disease progression on weekly paclitaxel alone.
4. Has uncontrolled hypertension. Note: only for patients receiving bevacizumab
5. Has current, clinically relevant bowel obstruction. Note: only for patients receiving bevacizumab
6. Has a history of thrombotic disorders, hemorrhage, hemoptysis, or active gastrointestinal

bleeding within 6 months before randomization.Note: This applies only to participants who will receive bevacizumab.
7. Has received >2 prior lines of systemic therapy for OC
8. Has received prior systemic anticancer therapy, including investigational agents or maintanance therapy (including bevacizumab maintanance therapy) within 4 weeks before randomization
9. Has received prior radiation therapy within 2 weeks of start of study intervention.
10. Has not recovered adequately from surgery and/or any complications from the surgery.
11.Has received colony-stimulating factors within 4 weeks before randomization.
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of
study intervention
13. Has received an investigational agent or
has used an investigational device within 4 weeks prior to study intervention administration.
14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy within 7 days before the first dose of study medication.
15. Has a known additional malignancy that is progressing or has required active treatment
within the past 3 years.
16. Has known active CNS metastases and/or carcinomatous meningitis. Participants with
previously treated brain metastases may participate provided they are radiologically stable
17. Has severe hypersensitivity (>=Grade 3) to pembrolizumab, paclitaxel, or bevacizumab
18. Has an active autoimmune disease that has required systemic treatment in the past 2 years
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required
steroids or has current pneumonitis/interstitial lung disease.
20. Has an active infection requiring systemic therapy
21. Has a known history of HIV infection.
22. Has a known history of Hepatitis B or known active Hepatitis C virus
23. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study
24. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
25. Participant, in the judgement of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.
26. Has had an allogenic tissue/solid organ transplant

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:	Recruiting
Start date (anticipated):	17-03-2022
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin, Zirabev
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Paclitaxel, Paxene, Taxol, Pazenir

Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-02-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
EU-CTR	CTIS2023-506177-35-00
EudraCT	EUCTR2020-005027-37-NL
CCMO	NL79015.028.21