A Phase 3, Multicenter, Randomized, Open-Label Study of Avelumab (MSB0010718C) Alone or in Combination with Pegylated Liposomal Doxorubicin versus Pegylated Liposomal Doxorubicin Alone to In Patients with Platinum-Resistant/Refractory Ovarian Cancer

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Primary Objective* To demonstrate that avelumab given alone or in combination with Pegylatedliposomal doxorubicin (PLD) is superior to PLD alone in prolonging Overall Survival(OS) in patients with platinum -resistant/platinum-refractory ovarian...

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

Summary

ID

NL-OMON47622

Source
ToetsingOnline

Brief title
JAVELIN OVARIAN 200

Condition

- Ovarian and fallopian tube disorders

Synonym
Platinum-Resistant/Refractory Ovarian Cancer / ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: Avelumab, Ovarian cancer, Phase 3, Platinum

Outcome measures

Primary outcome

Primary Endpoint

* Overall Survival (OS).

* Progression Free Survival as determined by Blinded Independent Central Review

according to RECIST version 1.1.

Secondary outcome

Secondary Endpoints

* Efficacy: Objective response (OR), Duration of Response (DR), and Disease

Control (DC) as determined by Blinded Independent Central Review (BICR) and

Investigator [As assessed by RECIST version 1.1].

* PFS as determined by Investigator according to RECIST version 1.1.

* Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory

abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure,

pulse

rate); electrocardiograms (ECGs), ECHO or MUGA scans.

* Pharmacokinetics: PK parameters, including Ctrough and Cmax for avelumab:

Cmax, volume of

distribution (Vd), clearance (CL), area under the concentration-time curve

(AUC) for

doxorubicin (PLD samples).

* Immunogenicity: Incidence of anti-drug antibodies (ADA) and neutralizing

antibodies (Nab) against avelumab.

* Candidate predictive biomarkers in tumor tissue (including, but not limited

to, PD-L1

expression and tumor infiltrating CD8+ T lymphocytes as assessed by

immunohistochemistry (IHC)).

* Patient-Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L.

Study description

Background summary

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most
common cause of cancer mortality in women. The incidence of ovarian cancer increases
with age and is most prevalent in the eighth decade of life. The median age at the time of
diagnosis is 63 years, and 70% of patients present with advanced disease.3 Although
expectations for long-term survival can be very high if the cancer is identified and treated
early, the women diagnosed with advanced ovarian cancer continue to have less than
30% 5-year survival.
Patients are considered to have platinum-sensitive disease if they respond to first-line
platinum therapy and experience a relapse-free period of greater than 6 months following the
last dose of platinum therapy. Platinum-resistant disease is defined by relapse between 0 to
6 months after the last platinum dose. Platinum-refractory disease is defined

by lack of
response to platinum-based chemotherapy or recurrence prior to completion of platinum-based therapy.
There are no highly effective therapies in the platinum-resistant/refractory population,
although non-platinum-related agents have demonstrated modest antitumor efficacy in a
subset of these patients.
Programmed death ligand 1 (PD-L1, also called B7-H1 or CD274) and its receptor, PD-1,
have a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on
activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1
delivers a series of strong inhibitory signals to inhibit T-cell function.
Avelumab* (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor.
In preclinical
studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.1 Prelimenary data from the ongoing ovarian cancer Study EMR 100070-001, which
is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004) showed an Objective Response Rate (ORR) of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.
Certain chemotherapy agents, including doxorubicin, have been shown to have immunostimulatory properties.57 Preclinical evaluation of breast tumor and sarcoma
responses to anthracyclines suggested that immune mechanisms contribute to tumor growth
inhibition. In addition, expression of genes such as CD8*, CD8*, and IFN-* correlated with response to
anthracycline chemotherapy in breast cancer patients. Enhanced exposure of tumor antigens as a result of tumor cell kill may enhance the activity of immune checkpoint
blockade.50 In preclinical studies, combination of avelumab with chemotherapies showed
improved anti-tumor activity of chemotherapy (gemcitabine, oxaliplatin, 5FU).1
Taken together, these observations suggest that combination of anthracyclines with avelumab
may provide added clinical benefit relative to either agent alone.

Study objective

Primary Objective
* To demonstrate that avelumab given alone or in combination with Pegylated liposomal doxorubicin (PLD) is superior to PLD alone in prolonging Overall Survival

(OS) in patients with platinum -resistant/platinum-refractory ovarian cancer.
* To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging PFS in patients with platinumresistant/ platinum-refractory ovarian cancer.

Secondary Objectives
* To evaluate anti-tumor activity of avelumab given alone or in combination with PLD
versus PLD alone in ovarian cancer patients.
* To evaluate the overall safety profile of avelumab alone or in combination with PLD
versus PLD alone in ovarian cancer patients.
* To characterize the Pharmacokinetics (PK) of doxorubicin (PLD samples) and avelumab when administered in combination, and to assess the effect of avelumab on
the PK of doxorubicin (PLD samples) and the effect of PLD on PK of avelumab.
* To assess the immunogenicity of avelumab.
* To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab
alone or PLD in combination with avelumab in pre-treatment tumor tissue, that may
aid in the identification of patient subpopulations most likely to benefit from treatment.
* To compare the effect of avelumab alone or in combination with PLD versus PLD alone on patient-reported outcomes (PRO) in patients with ovarian cancer.

Study design

This is a Phase 3, multicenter, randomized, open-label, parallel 3-arm study in which
approximately 550 patients will be randomized in a 1:1:1 ratio to receive avelumab alone,
avelumab in combination with PLD, or PLD alone, as follows:
* Arm A: avelumab alone;
* Arm B: avelumab plus PLD;
* Arm C: PLD alone.
* Patients will be stratified according to platinum-refractory or platinum-resistant
status, number of prior regimens (*1 vs 2 or 3), and bulky disease (defined as presence of a tumor *5 cm) vs not.

Intervention

* Arm A: avelumab alone;
* Arm B: avelumab plus PLD;
* Arm C: PLD alone.

Study burden and risks

Information mentioned in the infomed consent form:

Risks Associated with Avelumab
Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion, and immune side effects. The following side effects have been observed among 1738 patients treated with avelumab according to the results from two oncology clinical studies in patients with various solid tumors.

Side effects observed in 10% or more of patients:
* General signs or symptoms: tiredness; nausea; loose or watery stools (diarrhea); constipation; reduced appetite; decrease in weight; vomiting; low number of red blood cells (anemia); belly pain; cough; fever; shortness of breath; swelling of feet and legs; back pain; joint pain.
* Reactions that occur during or following the infusion: may include chills or shaking, fever, flushing, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure, hives. These infusion reactions are mostly mild or moderate and generally resolve with a slowdown or discontinuation of the infusion and administration of medications such as anti-allergic and pain-killer drugs. In some cases these reactions may be severe or life-threatening (in less than 1% of patients) and can require intensive medical care.

Immune side effects
Immune side effects result from an increased activity of the immune system. Most of these side effects are reversible, which means they will stop once treatment with avelumab is discontinued. However, in some cases these reactions may be severe (approximately 2% of patients) and may lead to death in rare cases. The reactions that are more severe require treatment with drugs that decrease the immune system function, also called immunosuppressant drugs (like corticosteroids or more potent drugs).
No immune side effects were observed in 10% or more of patients.

Immune side effects observed in 5% to less than 10% of patients
* Abnormal function of the thyroid gland (could include low or high function or inflammation of the thyroid gland): may include rapid heartbeat; increased sweating; extreme tiredness; weight gain or weight loss; hair loss; changes in mood or behavior such as irritability or forgetfulness; feeling cold; constipation; voice gets deeper.
* Inflammation of the skin (rash): may include skin rash, itchy skin, skin redness, skin blisters, or peeling.

Immune side effects observed in 1% to less than 5% of patients
* Inflammation of the large intestine (colitis): may include diarrhea (loose

stools) or more frequent bowel movements than usual; blood in stools or dark, tarry, sticky stools; severe stomach area (abdomen) pain or tenderness.
* Inflammation of the lungs (pneumonitis): may include new or worsening cough, shortness of breath, chest pain.

Rare risks Associated with Avelumab

Immune side effects observed in less than 1% of patients:
* Inflammation of the liver (hepatitis): may include yellowing of skin or of the whites of eyes; severe nausea or vomiting; pain on the right side of stomach area (abdomen); drowsiness; dark urine (tea colored); bleeding or bruising more easily than normal; feeling less hungry than usual.
* Inflammation of the kidneys (nephritis): may include urinating less than usual; blood in urine; swelling in ankles; loss of appetite.
* Low function of the adrenal glands (glands on top of the kidneys), which may be due to the reduced function of the pituitary gland (a gland in the head): may include very low blood pressure; extreme tiredness.
* Increase in blood sugar (diabetes): may include urinating more often than usual; feeling more hungry or thirsty than usual, nausea or vomiting, stomach area (abdomen) pain.
* Inflammation of the eyes (uveitis): may include changes in eyesight.
* Inflammation of the muscles (myositis): may include severe or persistent muscle or joint pain; severe muscle weakness.
* Inflammation of the heart (myocarditis): may include chest pain or tightness; tiredness; changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation; swelling of feet and legs; trouble breathing.
* Inflammation of the nerves (Guillain-Barre syndrome): may include "pins and needles" sensations in arms and legs; weakness in legs that spreads to the upper body and may lead to temporary paralysis.

Vaccination Risks
Live vaccines (vaccines containing a living organism, such as a live virus) should not be given within 30 days prior to study entry and throughout the study

Risks Associated with PLD
Very Common (10% or more of subjects), leukopenia (decreased white blood cell count), nausea, anemia, stomatitis (inflammation of the mouth and lips, for example canker sores), neutropenia (low count of neutrophils, a type of white blood cell), vomiting, thrombocytopenia (low platelet count), alopecia (hair loss), anorexia, rash, constipation, asthenia (weakness), diarrhea, Hand-foot syndrome (redness, swelling, and pain on palms of the hands and/or the soles of the feet), mucous membrane disorder.

Common (observed in more than 1% but less than 10% of subjects) pharyngitis (sore throat), dry mouth, infection, flatulence (gas), oral moniliasis (yeast infection of the mouth and/or throat), gingivitis (gum

inflammation), herpes zoster, taste perversion, urinary tract infection, vesiculobullous rash (blisters), pruritus (skin itching), allergic reaction, exfoliative dermatitis (inflammatory skin disease), dehydration (lack of fluid in body), skin disorder, cachexia (muscle wasting), maculopapular rash, paresthesia (numbness or tingling on the skin), sweating, headache, acne, dizziness, skin ulcer, neuropathy (damage to nerves causing weakness, numbness and pain), dry skin, hypertonia (reduced ability of muscles to stretch), skin discoloration, zonjunctivitis (pinkeye), back pain
cardiovascular disorder, myalgia (muscle pain), vasodilation (widening of blood vessels), dysuria (painful or difficult urination), dyspnea, vaginitis (inflammation of vagina), increased cough, fever, somnolence (sleepiness), pain, abdominal pain, chills, dyspepsia (impaired digestion) chest pain, mouth ulceration, malaise (general feeling of discomfort), esophagitis (inflammation of the esophagus), peripheral edema (build-up of fluid that causes swelling), nausea and vomiting, weight loss, gastritis (inflammation of the stomach), dysphagia (difficulty in swallowing)

Special warnings for PLD:
Cardiomyopathy: Heart damage, including acute left ventricular failure are serious but uncommon risks that are related to how much PLD you have taken over time. Therefore, your heart function will be checked closely during the study.

Infusion-Related Reactions: Mild to severe reactions following an infusion have occurred in 1 in 11 patients receiving PLD. These may include; flushing, shortness of breath or difficulty breathing, facial swelling, headache, chills, chest pain, back pain, tightness of chest and throat, fever, rapid heartbeat, skin rash, cyanosis (blue or purple discoloration of the skin) , syncope (pass out), bronchospasm, asthma, apnea, and low blood pressure. Most of these occurred during the first infusion. You may receive against them an antihistamine drug (H1 blocker) and acetaminophen paracetamol or a similar drug prior to every PLD infusion.

OTHER RISKS
Since avelumab is investigational when taken alone or in combination with PLD, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. You should get medical help and contact the study doctor right away if you think you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck. Other allergic reactions may include rash, hives, or blisters.

Contacts

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US
Scientific
Pfizer

East 42nd Street 219
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer, including malignant mixed Müllerian tumors with highgrade serous component.;2. Platinum-resistant/refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-based therapy (refractory), respectively.;3. Received up to 3 lines of systemic anticancer therapy for platinum-sensitive disease, most recently platinum-containing, and no prior systemic therapy for platinum-resistant disease.;4. Measurable disease by investigator assessment with at least 1 unidimensional measurable lesion by RECIST v.1.1 that has not previously been irradiated.;5. At least 18 years of age (*20 years of age in Japan).;6. ECOG performance status (PS) 0 to 1.;7. Estimated life expectancy of at least 3 months.;8. Mandatory tumor biopsy must be performed prior to enrollment for all patients (unless there is a documented clinical contraindication). In addition, availability of archived FFPE tumor tissue should be confirmed. If a patient underwent tumor tissue collection within 3 months prior to enrollment with no intervening treatment, and the sample is provided, then a new de novo tumor biopsy is not required.;9.

Adequate bone marrow function, including:;a. Absolute neutrophil count (ANC) *1.5 x 10 to the power 9/L;;b. Platelet count *100 x 10 to the power 9/L;;c. Hemoglobin *9 g/dL (may have been blood transfused).;10. Adequate liver function, including:;a. Total bilirubin level *1.5 × the upper limit of normal (ULN).;b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) *2.5 x ULN.;11. Adequate renal function as evidenced by:;a. Creatinine clearance *50 mL/min as calculated using the Cockcroft-Gault equation.;12. Serum/urine pregnancy test (for females of childbearing potential) negative at screening.;13. Female patients, of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and after the last dose of assigned treatment for the following lengths of time.;a. Patients who receive avelumab only: for at least 60 days after the last avelumab dose.;b. Patients who receive PLD (alone or in combination with avelumab): for at least 6 months after the last PLD dose.;14. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.;15. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

Exclusion criteria

1. Non-epithelial tumor, or ovarian tumors with low malignant potential (ie, borderline tumors).;2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) antibody (including ipilimumab, tremelimumab or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).;3. Patients with PLD-resistant EOC, as evidenced by lack of response or progression within 6 months of the last dose of PLD.;4. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry and are neurologically stable.;5. Concurrent anticancer treatment within 28 days prior to study entry, eg, cytoreductive therapy, radiotherapy [with the exception of palliative radiotherapy], immunotherapy, or cytokine therapy (except for erythropoietin); major surgery within 28 days prior to study entry (excluding diagnostic biopsy); use of hormonal agents within 7 days prior to study entry; or use of any investigational drug within 28 days prior to study entry. Note: patients receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days prior to study entry.;6. Diagnosis of any other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix.;7. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation, bradycardia defined as <50 bpm), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association Class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.;8. Ongoing cardiac dysrhythmias of NCI CTCAE Grade *3, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (average of triplicate ECG).;9. Left ventricular ejection fraction (LVEF)

<50% by MUGA or 2-D echocardiography.;10. Prior anthracycline-related cardiotoxicity or prior anthracycline exposure approaching the lifetime limit.;11. Prior organ transplantation including allogeneic stem-cell transplantation.;12. Known history of a positive human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.;13. Active infection requiring systemic therapy.;14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).;15. Administration of a live vaccine within 30 days prior to study entry.;16. Current or prior use of immunosuppressive medication within 7 days prior to randomization. The following are exceptions to this exclusion criterion:;a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);;b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent;;c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).;17. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.;18. Known severe hypersensitivity reactions to monoclonal antibodies or liposomal preparations. Known hypersensitivity to any component of the Investigational Products.;19. Persisting Grade *2 toxicity related to prior therapy; however, Grade 2 sensory neuropathy or alopecia is acceptable.;20. Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry, uncontrolled diarrhea in the last 4 weeks prior to enrollment, or history of inflammatory bowel disease.;21. Other severe acute or chronic medical condition including pneumonitis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.;Please refer to the protocol for the rest of the exclusion criteria

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):	05-12-2016
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx
Generic name:	pegylated liposomal doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxil
Generic name:	pegylated liposomal doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	na
Generic name:	Avelumab

Ethics review

Approved WMO Date:	09-05-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	02-11-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO
Date: 22-12-2016

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 10-02-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 06-06-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 24-07-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 07-09-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 06-10-2017

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2015-003091-77-NL
ClinicalTrials.gov	NCT02580058
CCMO	NL56911.058.16