A Randomized, Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Avelumab (MSB0010718C) in Combination with and/or Following Chemotherapy in Patients with Previously Untreated Epithelial Ovarian Cancer

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Co Primary Objectives:1. To demonstrate that avelumab in combination with platinum based chemotherapy followed by avelumab maintenance (Arm C) is superior to platinum based chemotherapy alone followed by observation (Arm A) in prolonging progression...

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

Summary

ID

NL-OMON45949

Source
ToetsingOnline

Brief title
JAVELIN OVARIAN 100

Condition

- Ovarian and fallopian tube disorders

Synonym
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

Outcome measures

Primary outcome

The primary endpoint of the study is Progression-Free Survival (PFS).

Secondary outcome

Other efficacy endpoints include overall survival (OS), objective reponse (OR), and duration of response (DR). This study will also include additional efficacy endpoints, PFS2, pathological complete response (pCR) and PFS by GCIG criteria, as defined below.

PFS2: PFS2 is defined by the European Medicines Agency (EMA) guidance (EMA, 2012) as the time from randomization to second objective disease progression, or death from any cause, whichever occurs first. However, continued collection of scans and RECIST assessment after discontinuation from the study is logistically challenging. In the absence of reliable tumor assessments, the end of next line treatment has been proposed as a surrogate (EMA, 2012). In ovarian cancer patients, however, first subsequent treatment is anticipated to mostly consist of a fixed/ planned number of cycles and end of treatment therefore might not reflect disease progression. There is limited experience

with PFS2 in ovarian cancer, although it has been proposed as an endpoint to explore in future studies.

In this protocol, PFS2 is defined as time from randomization to the start of second subsequent treatment after first documentation of objective progression of disease, or death from any cause. In the setting of ovarian cancer, start of second subsequent therapy was deemed to be the most reliable and unequivocal evidence of second progression.

pCR: Compared to breast cancer, there is relatively little experience with using the rate of pCR as a surrogate endpoint in ovarian cancer. There are also challenges in standardization of pCR assessment, since unlike breast cancer it is difficult to accurately sample the entire tumor bed.

A recent study by Bohm et al, 2015,68 has tested and validated the prognostic significance of a 3 tier scoring system for grading pathological response to neoadjuvant therapy in patients with high grade pelvic serous carcinoma. The study included 60 patients in the test cohort and 71 patients in the validation cohort.
This 3 tier scoring system is reproducible, simple and easy to apply, and shows a significant association with clinical outcome when based on pathological assessment of omentum samples.

In this protocol, patients are eligible to enroll prior to receiving

neoadjuvant chemotherapy. Since neoadjuvant chemotherapy is one of the stratification factors, randomized groups of patients are expected to receive either chemotherapy alone or chemotherapy + avelumab in a 2:1 ratio. These patients will undergo interval debulking surgery after 3 cycles of chemotherapy. pCR will be assessed using the recently developed pathologic response score.

PFS by GCIG criteria will also be assessed in this study incorporating both RECIST 1.1 and CA 125.69

Study description

Background summary

Ovarian cancer (OC) is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. Fewer than 40% of women diagnosed with ovarian cancer are cured.1 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.2 Although expectations for long term survival can be very high if the cancer is identified and treated early, women who are diagnosed with advanced ovarian cancer continue to have poor long term survival due to refractory, resistant, or recurrent disease and most will die within 5 years.

Carboplatin in combination with paclitaxel is the current standard of care in the first line epithelial ovarian cancer (EOC) treatment setting following debulking surgery for patients with stage IC or higher, as well as selected stage IA B patients (those with high grade or clear cell histology). Chemotherapy is administered for a total of 6 8 cycles. Complete response is achieved in approximately 75% of patients, but most patients ultimately succumb to the disease with median progression free survival (PFS) of approximately 18 months.4 Therefore, there remains a high unmet need for newer agents with novel mechanisms of action and combination regimens able to modify the natural history of the disease.

Recently, the dose dense frontline chemotherapy regimen of weekly paclitaxel combined with Q3W carboplatin has been increasing in usage.

The current standard of care in the frontline maintenance treatment setting is region dependent. Some patients receive bevacizumab in combination with chemotherapy, followed by one year of bevacizumab maintenance in regions where bevacizumab is approved in this setting. For a significant number of newly diagnosed patients, the standard of care remains a platinum doublet chemotherapy followed by observation.

Programmed death ligand 1 (PD L1, also called B7 H1 or CD274) has 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 functions.

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, the combination of avelumab with chemotherapy (gemcitabine, oxaliplatin, 5FU) showed improved anti tumor activity over single agent chemotherapy.11 Preliminary 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 overall response rate (ORR) of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.

Preliminary subgroup analysis demonstrated increased activity in patients with lower tumor burden, lower number of prior therapies, and platinum sensitivity. Therefore, avelumab has the potential to change the natural history of disease in the maintenance setting following frontline chemotherapy, when tumor burden is small. Patients with minimal residual disease are thought of as the ideal candidates for immunotherapy approaches in ovarian cancer.

In addition, there are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy. Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells. In summary, avelumab demonstrated promising antitumor activity in heavily pretreated patients with ovarian cancer and has the potential to improve the durability of response to platinum based therapy in the frontline setting when combined with chemotherapy and in the maintenance setting.

Study objective

Co Primary Objectives:
1. To demonstrate that avelumab in combination with platinum based chemotherapy

followed by avelumab maintenance (Arm C) is superior to platinum based chemotherapy alone followed by observation (Arm A) in prolonging progression free survival (PFS) in patients with previously untreated epithelial ovarian cancer (EOC).
2. To demonstrate that platinum based chemotherapy alone followed by avelumab maintenance (Arm B) is superior to platinum based chemotherapy alone followed by observation (Arm A) in prolonging PFS in patients with previously untreated EOC.

Secondary Objectives
*To compare Arm C and Arm B to Arm A in patients with previously untreated EOC, with respect to overall survival (OS).
*To evaluate the anti tumor activity in each treatment arm.
*To evaluate the overall safety profile in each treatment arm.
*To evaluate the pharmacokinetics (PK) of paclitaxel and carboplatin alone and in combination with avelumab.
*To evaluate the PK of avelumab alone and in combination with carboplatin paclitaxel (Arms B and C).
*To evaluate the immunogenicity of avelumab alone and in combination with carboplatin paclitaxel (Arms B and C).
*To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in combination with and/or following carboplatin paclitaxel in pre treatment tumor tissue, that may aid in the identification of patient subpopulations most likely to benefit from treatment.
*To evaluate patient reported outcome (PRO) in each treatment arm in patients with previously untreated EOC including the assessment of treatment side effects and disease related symptoms.

Study design

This is a Phase 3, open label, international, multi center, efficacy, and safety study of avelumab in combination with and/or following platinum based chemotherapy. Eligible patients must have previously untreated, histologically confirmed Stage III IV epithelial ovarian (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) and be candidates for platinum based chemotherapy. In this Phase 3 trial, approximately 951 patients who are candidates for frontline platinum based chemotherapy will be randomized in a 1:1:1 ratio to the following treatment arms:
- Group A Chemotherapy alone followed by observation
- Groep B Chemotherapy alone followed by maintenance phase with Avelumab
- Groep C Chemotherapy + Avelumab followed by maintenance phase with Avelumab

The assignment to Arm A vs Arm B will be blinded at the time of randomization to patients, investigators, and the Sponsor until completion of chemotherapy as described in Section 5.1. Crossover between treatment arms will not be permitted.
Intravenous carboplatin paclitaxel will be used as the chemotherapy backbone,

consisting of Q3 week (Q3W) carboplatin and the investigator choice of either Q3W or weekly paclitaxel (see below). Once a paclitaxel regimen is selected for a given patient, it should not be changed for the duration of the study.

Patients may be enrolled either following primary debulking surgery, or prior to initiation of neoadjuvant chemotherapy. The latter group will undergo interval debulking surgery after 3 cycles of chemotherapy (plus or minus avelumab, depending on randomization) to be followed by the remainder of chemotherapy (plus or minus avelumab, depending on randomization).

Intervention

- Group A Chemotherapy alone followed by observation
- Groep B Chemotherapy alone followed by maintenance phase with Avelumab
- Groep C Chemotherapy + Avelumab followed by maintenance phase with Avelumab

Study burden and risks

Information mentioned in the infomed consent form:

Appendix E: Possible discomforts and risks related to the research study

Risks Associated with Avelumab
The study drug avelumab can have side effects There are 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.
Reactions (including allergic reactions) that occur during or following infusion (may include chills, fever, muscle pain, shortness of breath, low or high blood pressure), Tiredness.

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.

Immune side effects that are 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.

Risks Associated with Paclitaxel
Loss of hair, Tingling, numbness, burning pain in hands and feet, Lower blood counts which can lead to a risk of infection and bleeding, Gastrointestinal discomfort, Skin redness or rash, Fatigue, Nausea and/or vomiting, Diarrhea, Anemia, Headaches, Blurred vision, Skin or nail darkening, Aches and pains in muscle and joints, Swelling, Mouth sores, Changes in EKG, Slow heart rate, low blood pressure, Seizures, Non-itching lesions in mouth and/or mucous membranes,

Fever, Temporary changes in blood tests that measure liver function, Temporary *blind spots* in vision, Severe rash called Steven-Johnson syndrome which can cause fever and red sores in your mouth and eyes.

Severe allergic reactions due to paclitaxel
Paclitaxel may cause severe allergic reactions. If you develop such a reaction, you may experience shortness of breath, low blood pressure, swelling of the mouth, and rash. These reactions may very rarely be fatal.

Risk of fetal harm
Paclitaxel can cause fetal harm when administered to a pregnant woman.

Risks Associated with Carboplatin
Tingling, numbness, burning pain in hands and feet, Lower blood counts which can lead to a risk of infection and bleeding, Nausea and/or vomiting, fatigue, Loss of hair, Weakness, loss of strength
Pain, Mouth Sores, Mild allergic reactions (facial flusinh, rash, itching of the hands, feet and chest)
Moderate to severe allergic reactions (faster than normal heart rate, shortness of breath, high or low blood pressure, swelling of the face, and rash), Cardiovascular changes, Respiratory changes
Temporary changes in blood tests which measure kidney and liver function, Blurred vision
Hearing loss, Diarrhea.

Risk of fetal harm
Carboplatin can cause fetal harm when administered to a pregnant woman.

Risks associated with study procedures

Risks and possible discomforts you might experience from the study procedures include:
Blood draws: A blood draw may cause inflammation of the vein, pain, bruising, discomfort, redness, burning, or bleeding at the site where the needle is placed to draw the blood. You may feel dizzy or you may faint. There is a slight chance of infection.
Intravenous Catheter: The use of an intravenous catheter may cause pain, bruising, clotting, bleeding, leakage of drug solution, and possibly infection at the catheter site.
ECG: Risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches.
Bone Scan: A bone scan exposes you to a small dose of radiation. Although all radiation you receive builds up over your lifetime, small doses from bone scans should not create a significant risk to your health.
CT scans: You may experience fear of being in a narrow or enclosed space while having a CT/MRI scan. You will be asked not to move during the test and to relax and breathe normally. A CT scan exposes you to a small dose of radiation.

Although all radiation you receive builds up over your lifetime, this amount of radiation should not create a significant risk to your health.
Contrast dye for CT scans: Contrast dye is usually injected when you get a CT scan. The contrast dye may cause pain or burning when it is injected, and may worsen kidney function in patients who already have kidney disease or who are dehydrated (have not had enough liquids that day). The contrast dye may also cause an allergic reaction, which could be severe and life-threatening.
MRI: There are risks from an MRI if you are pregnant or have one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your body (including gun shot or shrapnel). You may also become anxious from lying in a tight space without moving. The MRI scan does not cause any pain and does not expose you to x-ray radiation.
Biopsy: The tumor biopsy procedures (to be carried out only in case an appropriate archived tumor sample is not available or if you agree to give additional samples) may be associated with pain, discomfort, bleeding, swelling, scarring, bruising, and infection. To reduce these risks, the site of the biopsy will be numbed and sterile techniques will be used.
Genetic Research Risks: The pharmacogenomics/biomarker research that may be performed using your tissue and blood samples may involve genetic testing. Procedures have been put into place to ensure that any results from genetic research cannot be linked to you. However, there is a remote possibility that information from your participation in this study could adversely affect you or your family in some way if a genetic disorder were discovered.
In addition, your doctor may require that you remain in the clinic until very late in the day or that you even stay overnight in order to comply with the requested procedures.

Other risks

Since avelumab is investigational when taken alone or in combination with chemotherapy, 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.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

Pregnancy Related Risks / Use of Birth Control
The effects of avelumab on a pregnancy or a nursing child are not fully known. Carboplatin and paclitaxel can cause fetal harm when given to pregnant women. If you are currently pregnant, planning to become pregnant or breastfeeding a

child, you should not join this study.

If you are able to have children and you are sexually active, you must use birth control consistently and correctly during the study and for 60 days after the last dose of avelumab (Arms B and C). The study doctor will discuss with you the two methods of birth control that you should use while you are in this study and will help you select the methods that are appropriate for you. The study doctor will also check that you understand how to use the birth control methods and may review this with you at each of your study visits.
Birth control methods, even when used properly are not perfect. If you become pregnant during the study, or you want to stop your required birth control during the study, you should tell the study doctor immediately. You will no longer be able to receive study drugs but may remain in the study if you stop using birth control or you become pregnant

Pregnancy Follow Up
If you become pregnant during the study or within 60 days after you have stopped taking avelumab or within 60 days after you have stopped taking carboplatin and paclitaxel, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this research study. The study doctor will ask if you or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you agree, this information will be provided to the study sponsor for safety monitoring follow-up.

Contacts

Public
Pfizer

East 42nd Street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically confirmed Stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (according to AJCC/UICC TNM and International Federation of Gynecology and Obstetrics (FIGO) Staging System 2014 edition), including malignant mixed Müllerian tumors with high grade serous component.
2. Patients must be candidates for platinum-based chemotherapy and previously untreated.
3. Patients must have completed a surgical debulking procedure, or be candidates for neoadjuvant chemotherapy.
a. For patients enrolling after debulking surgery, the following conditions must be met:
* The minimum surgery required is an abdominal surgery with an attempt at cytoreduction providing tissue for histologic evaluation and establishing and documenting the primary site and stage
* Patient must be randomized at a maximum of 8 weeks after surgery.
b. For patients who are candidates for neoadjuvant chemotherapy, the following conditions must be met:
* A core tissue (not fine needle aspiration) biopsy is required. The tissue must be consistent with a tumor of Müllerian origin.
* Stage IIIC*IV documented via imaging or surgery (without attempt at cytoreduction)
* Serum CA125/ CEA ratio > 25. If the serum CA125/CEA ratio is < 25, workup should be negative for the presence of a primary gastrointestinal or breast malignancy (< 6 weeks before randomization).
* Plan to receive carboplatin-paclitaxel neoadjuvant chemotherapy.
* Randomization must occur within 8 weeks after diagnosis.
4. Availability of an archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 15 slides. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accordance with local institutional practice for tumor biopsies.
5. Eastern Cooperative Group (ECOG) performance status 0-1
6. Age *18 years (or *20 years in Japan).
7. Adequate hematological function (ANC *1.5 x 10 to the power 9/L, Hgb *9.0 g/dL, and platelet count *100 x 10 to the power 9/L).
8. Adequate liver function tests (ALT/AST *2.5 x ULN, total serum bilirubin level *1.5 x ULN).
9. Adequate renal function by estimated creatinine clearance *50 mL/min as calculated using the Cockcroft-Gault method.

10. Estimated life expectancy of at least 12 weeks.
11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
12. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
13. Patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.
Patients of non-childbearing potential must meet at least one of the
following criteria:
* Have undergone a documented hysterectomy and/or bilateral oophorectomy;
* Have medically confirmed ovarian failure; or
* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state.

Exclusion criteria

1. Non-epithelial tumors, or ovarian tumors with low malignant potential (ie, borderline tumors).
2. Mucinous tumors.
3. Patients for whom, in the opinion of the Investigator, there is clinical benefit to administer bevacizumab as a first-line treatment and for whom bevacizumab is approved and available in this setting.
4. Cancer for which intraperitoneal cytotoxic chemotherapy is planned.
5. Prior systemic anti-cancer treatment for EOC, FTC, or PPC.
6. Prior immunotherapy with IL-2, IFN-*, or anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody (including ipilimumab), or any other antibody or drug specifically targeting T cell costimulation or immune checkpoint pathways.
7. Major surgery (other than debulking surgery) for any reason within 4 weeks prior to randomization and/or incomplete recovery from surgery.
8. Known brain, leptomeningeal, or spinal cord metastases.
9. Current or prior use of immunosuppressive medication within 7 days prior to randomization, except the following: intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); systemic corticosteroids at physiologic doses *10 mg/day of prednisone
or equivalent; steroids as premedication for hypersensitivity reactions [eg, computed tomography (CT) scan premedication].
10. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents except patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroidism not requiring immunosuppressive treatment.
11. Any of the following in the previous 6 months: myocardial infarction, severe/unstable

angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis or symptomatic pulmonary embolism.
12. Active and clinically significant bacterial, fungal or viral infection, any positive tests for hepatitis B (HBV), hepatitis C (HCV) indicating acute or chronic infection(positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive), known history of a positive human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness.
13. Administration of a live vaccine within 30 days prior to study entry.
14. Known severe hypersensitivity reactions to monoclonal antibodies, carboplatin, or paclitaxel or other platinum-containing compounds (NCI CTCAE v4.03 Grade *3).
15. Persisting NCI CTCAE v4.03 Grade >1 toxicity related to prior therapy.
16. Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of adequately treated basal or squamous cell carcinoma of the skin, cervical carcinoma in situ, lobular carcinoma in situ (LCIS), or ductal carcinoma in situ (DCIS).
17. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.
18. Participation in other clinical studies involving investigational drug(s) within 4 weeks prior to study randomization and/or during study participation.
19. Other severe/severe acute or chronic medical, including colitis, inflammatory bowel disease, and pneumonitis, or psychiatric condition, 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 investigational product 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.
20. Pregnant patients or breastfeeding patients.
21. Patients with bleeding tumors

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):	10-07-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Avelumab

Ethics review

Approved WMO Date:	12-07-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-01-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	06-10-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2015-003239-36-NL
ClinicalTrials.gov	NCT02718417
CCMO	NL58129.058.16

Study results

Summary results
Trial ended prematurely