An open-label, Phase I/II multicenter clinical trial of VXM01 in combination with avelumab in patients with progressive glioblastoma following standard treatment, with or without second surgery.

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Primary Objective:• Safety and tolerability of VXM01 in combination with avelumabSecondary Objectives:• Efficacy of VXM01 in combination with avelumab by assessment of tumor objective response rate (ORR) per Immunotherapy Response Assessment in...

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

Summary

ID

NL-OMON48738

Source
ToetsingOnline

Brief title
VXM01 plus Avelumab combination study in progressive glioblastoma

Condition

- Other condition

Synonym
brain tumour, Glioblastoma

Health condition

Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: VAXIMM GmbH
Source(s) of monetary or material Support: Merck,Pfizer,VAXIMM GmbH

Intervention

Keyword: Avelumab, Glioblastoma, VXM01

Outcome measures

Primary outcome

Primary Endpoint:

• Safety and tolerability up to 60 weeks after first IMP administration (incl.

EoS visit, week 60)

Secondary outcome

Secondary Endpoints:

• Best overall response (OR) and Duration of Response (DoR) on MRI according to

iRANO in subjects with or without surgery prior to trial entry (up to

re-operation)

• Clinical response as assessed by time to progression (TTP), progression free

survival (PFS), recurrence-free survival after re-operation (RFS) and overall

survival (OS) up to end of trial

Exploratory Endpoints:

• Patient-individual VEGFR-2 specific IFN-gamma T cell responses pre- and

post-vaccination, determined by Enzyme Linked Immuno Spot (ELISpot) using

cryopreserved peripheral blood mononuclear cells (all subjects)

• Frequency of peripheral regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) measured using flow cytometry analysis

• Tumor tissue immunohistochemistry / -fluorescence staining evaluations including, but not limited to, VEGFR-2 expression on tumor cells and tumor vasculature, effector T cell infiltration, Tregs, MDSCs, PD-1, PD-L1 (primary tumors of all subjects and recurrent tumors of re-operated subjects)

• Tumor PTEN mutation/deletion status (primary tumors of all subjects and recurrent tumors of re-operated subjects)

• Microsatellite instability (MSI) / DNA mismatch repair (MMR) status

• TCR sequencing of tumor infiltrating lymphocytes (TILs) and peripheral T cells.

• PK profile of avelumab in combination with VXM01

• Anti-avelumab anti-drug antibodies (ADA)

• Gut microbiome status

Study description

Background summary

VXM01 is an investigational oral cancer immunotherapeutic gene transfer medicinal product. It consists of a plasmid DNA, pVAX10.VR2-1, encoding an expression cassette for the human Vascular Endothelial Growth Factor-Receptor 2 (VEGFR-2). This DNA is delivered, after oral administration to the patient, by a live attenuated bacterium (Salmonella enterica subsp. enterica Serovar Typhi Strain Ty21a) serving as a living carrier. The biological activity of VXM01 is as follows:
1. Orally administered Salmonellae carrying the expression plasmid enter the host via M cells in the intestine. After transcytosis the bacteria are taken up by phagocytic cells such as macrophages and dendritic cells.
2. The expression plasmids are released followed by a transfer of the plasmids into the cytosol either via a specific transport system or by endosomal leakage.

3. The vector enters the nucleus and is transcribed, leading to antigen expression in the cytosol of the host cell. Infected macrophages go into apoptosis and are taken up by dendritic bystander cells which present antigens from apoptotic material on MHC-I.
4. These activated antigen presenting cells induce VEGFR-2-specific cytotoxic CD8+ T cells which subsequently target VEGFR-2 expressing cells of tumour vasculature or the tumour itself.
5. By targeting the tumour vasculature VXM01 elicits anti-angiogenic effects. In subjects expressing VEGFR-2 on tumor cells VEGFR-2 serves as tumor-associated antigen.
Results from previous and ongoing clinical trials with VXM01 revealed an acceptable safety profile. Treatment with VXM01 clearly elicited anti-VEGFR-2 specific T-cell immune responses in subjects particularly after administration of boosting immunizations. These immune responses were accompanied by changes in pharmacodynamic biomarkers indicating an anti-angiogenic activity of VXM01. Prolonged overall survival was associated with immune response to VXM01.
Based on the pharmacodynamic effects of VXM01 and avelumab a synergistic activity of both agents can be expected. VXM01 has been shown to induce target specific CD8+ T-cells in animals and cancer subjects. In the clinical trial VXM01-02-DE signals indicative for a beneficial effect of the treatment of subjects suffering from recurrent glioblastoma with VXM01 have been observed. The effect was apparent in particular in subjects with high expression of the target antigen VEGFR-2 in the tumor. The number of infiltrating T-cells in the tumor tissue from re-operation was increased compared to the primary tumor.
With action both at the level of binding of APC to T cells as well as in the tumor cell T cell compartment, avelumab increases the number of CD8+PD-1+ T cells as well as CD8+ effector memory T (TEM) cells and releases anti-tumor T cells from immune suppression by blocking the PD-1/PD-L1 interaction. Unlike perceived in the past, PD-L1 inhibition might be particularly effective.
It can therefore be anticipated that the number of VEGFR-2 specific CD8+ T-cells induced by VXM01 in the gut can be increased by concomitant treatment with avelumab and act more effectively in the brain microenvironment.

Study objective

Primary Objective:
• Safety and tolerability of VXM01 in combination with avelumab
Secondary Objectives:
• Efficacy of VXM01 in combination with avelumab by assessment of tumor objective response rate (ORR) per Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria and according to Okada et al., 2015 (see Appendix I) in non-resected and resected subjects (up to re-operation)
• Efficacy of VXM01 in combination with avelumab by assessment of clinical response
Exploratory Objectives:
• Effect of VXM01 plus avelumab on immuno- and biomarkers in tumor tissue and blood samples pre-and post-treatment

• To characterize the pharmacokinetics (PK) of avelumab in combination with VXM01
• To characterize the immunogenicity of avelumab in combination with VXM01
• To characterize the gut microbiome pre- and post treatment

Study design

This trial will be conducted as a multicenter, open-label, Phase I/II trial to evaluate the efficacy and safety of VXM01 in combination with avelumab in subjects with resectable and non-resectable progressive glioblastoma following tumor resection and radiochemotherapy containing temozolomide.
The trial will be performed in 30 subjects with progressive glioblastoma:
• 24 subjects who will not be candidates for a tumor re-operation (non-resectable subjects)
• 6 subjects who will be candidates for a tumor re-operation (resectable subjects)
Patients who are candidates for tumor re-operation but that for any reason do not have this routine surgical resection will be allowed to enter the non-resectable cohort, if this is agreed by the investigator and medical monitor.
The trial will start with a safety run-in to determine which dose of VXM01 (10^6 or 10^7 CFU/mL) in combination with avelumab (800 mg) to take forward. This part of the trial will be performed in the subjects with non-resectable glioblastoma only.
The trial, for each subject, will consist of a screening period, a treatment and observatioon phase of 60 weeks including, a treatment phase of up to 48 weeks with prime and boosting administrations of VXM01 in combination with avelumab and an observation phase of 12 weeks and with an end of trial visit at Week 60.
Subjects will be screened within approximately 3 weeks (Day -21 to Day - 1) prior to first trial drug administration. Inclusion will be performed at the inclusion visit (Day 0) after all screening and inclusion assessments have been completed and the patient is judged as eligible for this trial.
Subjects will receive VXM01 in combination with avelumab up to Week 48:
• VXM01 (10^6 or 10^7 CFU/mL) will be administered as 4 single oral prime administrations on Day 1, 3, 5 and 7, followed by single oral 4-weekly boosting administrations (from Week 4 to 48 in non-resectable subjects and from Week 8 to 48 in resectable subjects).
• Avelumab (800 mg) will be administered as single intravenous 2-weekly administrations (in resectable subjects the treatment will be stopped after the third dose on Day 29 due to re-operation and will be continued from Week 8 to 48).
The end of study (EoS) visit assessments will be performed Week 60.
Follow-up visits will be performed 1, 3, 6, 12, and 24 months after the EoS examination.
If the investigator deems appropriate, treatment with the combination of VXM01 and avelumab may continue beyond Week 48 and under a patient-specific

treatment prolongation phase. Subjects may continue to receive trial treatments as long as, in the investigator*s or delegate*s opinion, they are benefiting from treatment and do not meet any of the protocol specific discontinuation criteria, or withdrawal of consent. VXM01/avelumab combination should not be given concomitantly with other anti-cancer treatment.
During the prolongation phase VXM01 in combination with avelumab will be administered from Week 52 to Week 96 (VXM01 in a 4-weekly administration scheme and avelumab in a 2-weekly administration scheme). In this case the observation phase will be 8 weeks with the end of patient-specific treatment prolongation visit (EoP) performed at Week 104. Follow-up visits will be performed 1, 3, 6, 12, and 24 months after the end of patient-specific treatment prolongation visit.
In case of patient-specific treatment prolongation, the duration of the trial will be approximately 107 weeks (from screening to end of prolongation). The entire trial including follow-up will last approximately 5 years (recruitment phase of approximately 10 months, treatment phase of up to 24 months, follow-up phase of 24 months).
A Data Safety Monitoring Board (DSMB) will be convened to periodically assess the trial conduct and data in terms of risk-benefit balance and provide recommendations to Vaximm regarding the trial*s continuation or modification. Furthermore, the DSMB will be consulted in case a Treatment Limiting Toxicity (TLT) is classified as possibly related to either of the Investigational Medicinal Products (IMPs).
Safety Run-In: It is planned that the safety-run will investigate two doses of VXM01, 10^6 CFU/mL and VXM01 10^7 CFU/mL.
The first 3 non-resectable subjects treated with the VXM01 10^6 CFU/mL dose in combination with avelumab will be included in a staggered fashion (1+2). This means that for safety reasons there will be a time interval of at least 5 weeks between dosing of the first patient and the following 2 subjects (TLT observation period). Under condition that no TLTs are observed, the VXM01 dose will be increased to 107 CFU/mL.
Similarly, also the first 3 subjects treated with the VXM01 10^7 CFU/mL dose in combination with avelumab will be included in a staggered fashion (1+2). This means that for safety reasons there will be a time interval of at least 5 weeks between dosing of the first patient and the following 2 subjects. Under the condition that the safety and tolerability is considered acceptable for the VXM01 10^7 CFU/mL dose in combination with avelumab, all subjects treated with VXM01 10^6 CFU/mL dose in combination with avelumab can be treated with the higher dose (intra-subject dose escalation allowed) after approval by DSMB, at the discretion of the investigator.
Should any TLTs be observed in the first three subjects under VXM01 10^6 or 10^7 CFU/mL, respectively, an additional 3 subjects in this dose group will be included. After an additional time interval of 5 weeks and review of safety data, the start of the treatment with the 10^7 CFU/mL dose level (for subjects treated with the 10^6 CFU/mL dose) or the parallel inclusion of all remaining trial subjects (in case of treatment with the 10^7 CFU/mL dose) can be initiated after review by the DSMB.

In any case, the decision to dose escalate from the 10^6 CFU /mL to the 10^7 CFU /mL VXM01 dose and to proceed with the 10^7 CFU /mL beyond the run-in part of the trial, will be made after review by the DSMB,Vaximm and the Medical Monitor and will consider the *Discontinuation of Treatment* rules defined in the protocol.
In the unlikely case that two or more TLTs occur at the 10^6 CFU /mL dose level, a decision to dose de-escalate and at what dose or whether to continue the trial will also be taken after review by the DSMB, Vaximm and the Medical Monitor.

Intervention

Each non-resectable patient will receive a total of 4 prime doses and 12 boosting doses of VXM01 up to Week 48 and 25 doses of avelumab. In case of patient specific prolongation, additional 12 doses of VXM01 and additional 23 doses of avelumab will be given. Thus, a maximum dose of 28 doses VXM01 and 48 doses avelumab will be given.
Each resectable patient will receive a total of 4 prime doses and 11 boosting doses of VXM01 up to Week 48 and 21 doses of avelumab. In case of patient specific prolongation, additional 12 doses of VXM01 and additional 23 doses of avelumab will be given. Thus, a maximum dose of 27 doses VXM01 and 44 doses avelumab will be given.
A fixed dosing regimen of 800 mg administered as a 1 hour IV infusion Q2W will be utilized for avelumab.
Following avelumab infusions, patients must be observed for 60 minutes post infusion for potential infusion related reactions.

Study burden and risks

VXM01
In the first study with VXM01 in humans, the medication was tolerated well. No serious adverse drug reactions were reported that led to an interruption of the treatment. In addition, no death in causal connection with VXM01 was reported.
Very common side effects (>=1/10 users)
• Abdominal pain (27%, 27 out of 100),
• Diarrhoea (27%, 27 out of 100),
• Nausea and vomiting (both 13%, 13 out of 100).
• Reduced number of platelets (17%, 17 out of 100), and white blood cells (20%, 20 out of 100).
• Common side effects (>= 1/100 and < 1/10 users)
• High blood pressure
• Decreased number of red blood cells
• Increased creatinine
• Reduced number of platelets
Occasional side effects (>= 1/1000 and < 1/100 users)
A slight blood pressure increase and adverse drug reactions affecting renal

function have been reported in patients treated with VXM01, but also in similar numbers of patients treated with a dummy treatment, so the relation with VXM01 remains unclear. From animal studies we know that wounds may heal slower, but this is expected because of the way VXM01 works.
Carrier bacteria (such as "Typhoral" in typhoid vaccines) in humans
The following undesirable effects have been reported in clinical studies with "Typhoral" capsules:
Frequent (1-10%, 1-10 out of 100 users):
• Abdominal pain,
• nausea,
• vomiting,
• diarrhoea,
• fever,
• headache,
• rash
These symptoms resolved within a few days without treatment. No serious systemic reactions that affect the entire body were reported.
The following side effects are known from market survey whose incidence can not be calculated:
• Allergic reactions and severe allergic reactions
• Decreased appetite
• Paraesthesia, dizziness
• Flatulence
• Skin reactions like dermatitis, exanthema, pruritus and urticaria
• Joint pain, muscle pain and back pain
• Weakness
• Malaise
• Fatigue
• Chill
• Flu-like symptoms
Avelumab (Bavencio®)
Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion (so called infusion-related reactions), and immune side effects.
The following general side effects have been observed in >= 10 % of patients among 1738 patients treated with avelumab according to the results from two oncology clinical studies in patients with various solid tumors:
• Tiredness
• Nausea (feeling sick to the stomach)
• Diarrhoea (Frequent loose, watery stools)
• Constipation (difficulty passing stools)
• Decreased appetite
• Infusion related reaction
• Weight decreased
• Vomiting
• Anaemia (low number of red blood cells)
• Abdominal pain

• Cough
• Pyrexia (fever)
• Dyspnoea (shortness of breath)
• Pruritus (itching)
• Oedema peripheral (build up of fluid in the body causing swelling)
• Musculoskeletal pain (including back pain, neck pain)
• Arthralgia (joint pain)
• Dizziness
• Headache
• Hypertension (increase in blood pressure)
• Urinary tract infection
Allergic reactions or reactions in the context with the infusions might occur during or after the infusion. Although Avelumab is a fully human protein, the risk cannot be completely excluded. Symptoms may include chills or shaking, fever, flushing, back pain, belly pain, shortness of breath or wheezing, decrease in blood pressure, and hives. Infusion-related reactions have already been observed under treatment with Avelumab. In general, these reactions are mild to moderate and generally resolve with a slowdown or discontinuation of the infusion and with appropriate drugs, but in less than 1 % of patients severe to life-threatening reactions might occur, which require advanced cardiac life support and could potentially be fatal.
For the prevention of infusion-related adverse effects and possible allergic reactions patients will receive a premedication of an antihistamine drug (so-called H1 blocker) and an anti-inflammatory drug (paracetamol; in USA acetaminophen) 30 to 60 minutes before the first 4 infusions.
In addition, side effects resulting from an increased activity of the immune system have also been observed. The side effects listed below may be temporary, long term, permanent or result in death. However, most of these side effects are reversible depending on their severity and the patient*s health condition. That means they will stop once the drug is discontinued. 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).
The following immune-mediated side effects have been observed in patients receiving the study drug and might occur, such as:
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 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.
Single cases of immune-mediated pneumonitis, immune mediated hepatitis and immune-mediated myocarditis with fatal outcome have been observed with avelumab.
In addition, the study-related measurements (blood sampling, MRI scans, ECG) carried out as part of this clinical trial may lead to discomfort. See Appendix B of the Informed Consent Form for more information about other discomforts and risks that may occur as a result of undergoing the various examinations.

Contacts

Public
VAXIMM GmbH

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects who are able to understand and follow instructions during the trial
2. Ability and willingness to give written informed consent, signed and dated
3. Male or female subjects. Female subjects must be post-menopausal for at least 2 years or surgically sterile
4. Age >=18 years
5. Histologically diagnosed intracranial supratentorial malignant glioma (contrast-enhancing glioblastoma WHO Grade IV)
6. Evidence of tumor progression by RANO criteria following at least one prior therapy regimen that must have contained radiation and chemotherapy with temozolomide, as measured by MRI
* Radiotherapy must have been completed at least 3 months prior to the inclusion visit
7. Candidates for a tumor reoperation (for the resectable arm [n=6] only)
* Neurosurgical intervention should be postponable for 30 days
8. Adequate bone marrow function including: Absolute neutrophil count (ANC) >=1,500/mm3 or >=1.5 x 10^9/L; Platelets >= 100,000/mm3 or >=100 x 10^9/L; Hemoglobin >= 9 g/dL (may have been transfused); INR <1.5x ULN. Subjects with documented benign cyclical neutropenia are allowed if WBC count is >= 1.5 × 10^9/L with absolute neutrophil count >= 1.0 × 10^9/L and appropriate hematology parameters: leukocytes >=4.0 x 10^9 / L, lymphocytes >=0.6 x 10^9/L
9. Adequate hepatic function defined by a total bilirubin level <= 1.5 × the upper limit of normal range (ULN), an aspartate aminotransferase (AST), level <= 2.5 × ULN, and an alanine aminotransferase (ALT) level <= 2.5 × ULN or, for subjects with documented metastatic disease to the liver, AST and ALT levels <= 5 × ULN. Subjects with documented Gilbert disease are allowed if total bilirubin <= 3 x ULN

10. Adequate renal function defined by an estimated creatinine clearance >= 30 mL/min according to the Cockcroft-Gault formula
11. Patients must be able to undergo MRI
12. Absence of active bacterial infection requiring antibiotic treatment
13. Karnofsky performance status >=70
14. Primary (or most recently obtained available) tumor samples available for pathology review, panel sequencing, as well as central detection of T-cell responses in the peripheral blood and in the tumor tissue
15. No medical or social conditions that may interfere with trial outcome and follow-up

Exclusion criteria

1. Cardiovascular disease defined as:
a. Uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg)
b. Arterial thromboembolic event within 6 months before trial entry including:
* Myocardial infarction
* Unstable angina pectoris
* Cerebrovascular accident
* Transient ischemic attack
2. Congestive heart failure New York Heart Association grade III to IV
3. Serious ventricular arrhythmia requiring medication and arrhythmias requiring Implantable Cardioverter Defibrillator (ICDs)
4. Clinically significant peripheral artery disease > grade 2b according to Fontaine
5. History of relevant intracranial hemorrhage (not confined to susceptibility (iron) lesions on MRI only)
6. Hemoptysis within 6 months before trial entry
7. Known oesophageal varices
8. Upper or lower gastrointestinal bleeding within 6 months before inclusion (Day 0)
9. Significant traumatic injury or surgery within 4 weeks before trial entry
10. Non-healing wound, incomplete wound healing, bone fracture or gastrointestinal ulcers within three years before inclusion, or positive gastroscopy within 3 months before inclusion
11. Gastrointestinal fistula
12. Thrombolysis therapy within 4 weeks before trial entry
13. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that based on the investigators judgement provides a reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the trial results or render the patient at high risk for treatment complications
14. Previous malignant disease (other than the tumor disease for this trial)

within the last 5 years (except adequately treated non-melanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to trial entry and the subject was deemed to have been cured with no additional therapy required or anticipated to be required
15. Prior organ transplantation, including allogeneic stem cell transplantation
16. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable
17. History of uncontrolled intercurrent illness including but not limited to uncontrolled diabetes (e.g., hemoglobin A1c >= 8%)
18. Known prior hypersensitivity to investigational product or any component in its formulations or any other drug scheduled or likely to be given during the trial, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade >= 3)
19. Persisting toxicity related to prior therapy (NCI CTCAE v5.0 Grade > 1); however, alopecia, sensory neuropathy Grade <= 2, or other Grade <= 2 AEs not constituting a safety risk based on investigator*s judgment are acceptable
20. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with trial participation or trial treatment administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into this trial
21. Active infection requiring systemic therapy
22. Known history of human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome or multi-drug resistant gram-negative bacteria
23. 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)
24. Women of childbearing potential
25. History of serious ophthalmological diseases, e.g. optic neuropathy, retinal detachment, uveitis
26. Treatment in any other clinical trial within 30 days or within 5 half lives of any prior treatment, before screening
27. Any other condition or treatment that, in the opinion of the investigator, might interfere with the trial or current drug or substance abuse
28. Chronic concurrent therapy within 2 weeks before and during the treatment period with:
a. Corticosteroids (except steroids up to equivalent of dexamethasone 4 mg daily dose)

b. Immunosuppressive agents
c. Antibiotics
d. Bevacizumab or any other anti-angiogenic treatment
e. Any other anti-cancer therapy or concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative short course, limited field (ie, <= 10 fractions and <= 30% bone marrow involvement or per institutional standard) radiotherapy, which may be administered during the study. However dosing must be suspended at least 14 days prior to the start of radiotherapy and must not be resumed until at least 14 days after the last radiotherapy fraction], immune therapy, or cytokine therapy, except for erythropoietin)
f. Administration of live vaccines (other than VXM01) within 30 days prior to study treatment
29. Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines (other than VXM01)
30. Inability to understand the protocol requirements, instructions and trial-related restrictions, the nature, scope, and possible consequences of the trial
31. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial
32. Legal incapacity or limited legal capacity
33. Any condition which results in an undue risk for the patient during the trial participation according to the investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-09-2019

Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bavencio
Generic name:	Avelumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-06-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	17-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2017-003076-31-NL
ClinicalTrials.gov	NCT03750071
CCMO	NL64825.000.18