A phase I open-label clinical trial, evaluating the therapeutic vaccine hVEGF26-104/RFASE in patients with advanced solid tumors

Published: 11-07-2013
Last updated: 22-04-2024

Primary objectives- To investigate the safety and tolerability profile of hVEGF26-104/RFASE.- To determine the effective dose of hVEGF26-104/RFASE required to neutralize VEGF in serum, defined as a VEGF level below 9,0 pg/mL.Secondary objectives- To…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47883

Source
ToetsingOnline

Brief title
Phase I study on VEGF vaccination in metastatic solid tumors

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, Advanced solid tumor

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Immunovo BV

Intervention

Keyword: Angiogenesis, Cancer, Vaccine, VEGF

Outcome measures

Primary outcome

- Safety and tolerability of hVEGF26-104/RFASE, measured by the number of participants with serious and non-serious adverse events

- Neutralization of endogenous VEGF in serum, defined as a VEGF level below 9.0 pg/mL as determined by sandwich ELISA.

Secondary outcome

- Anti-VEGF antibody titer in serum, plasma and a platelet sample, as determined by indirect ELISA.

- VEGF concentration in plasma as determined by sandwich ELISA.

- VEGF concentration in a platelet sample as determined by sandwich ELISA.

- Functional VEGF neutralization, as determined in a Ba/F3-R2-R2 cell proliferation bio-assay.

- Cellular (T-cell) immune response, as determined by ELISPOT

- Immune modulation

- Angiogenesis suppression: Within the tumor, by assessing microvessel density (MVD), quantity of proliferating endothelial cells and pericyt coverage.

Study description

Background summary

Angiogenesis (the formation of new blood vessels from pre-existing blood vessels) plays an important role in the growth and spread of tumors. Angiogenesis is regulated by a balance of activators and inhibitors. One of the angiogenic activators is the vascular endothelial growth factor (VEGF, also referred to as VEGF-A). Over the past decade, several angiogenesis inhibitors have been discovered and implemented in the therapy of cancer patients. Bevacizumab (a humanized monoclonal antibody that inhibits VEGF-A) has been shown to improve survival in different tumor types in first and second line therapy when given in various chemotherapy combinations. Furthermore, research has shown a survival benefit of continued VEGF suppression with bevacizumab beyond first progression in metastatic colorectal cancer. So although repeated use of bevacizumab as a chronic therapy is much desired, currently this is not feasible because of substantial disadvantages of bevacizumab therapy. First, since bevacizumab only offers temporary VEGF neutralization, it needs frequent repeated administration. Secondly, bevacizumab is an intravenous therapy, which requires hospitalization on each administration. Third, bevacizumab has very high production costs.
These specific drawbacks of longer term monoclonal antibody therapy could be circumvented by the use of a therapeutic cancer vaccine targeting VEGF. A vaccine is able to induce sustained VEGF suppression and can be administered via an intramuscular (IM) injection. In addition, a vaccine will likely inhibit VEGF more effectively as compared to bevacizumab, because a vaccine induces a polyclonal antibody response, resulting in higher avidity binding. Furthermore, it is believed that endogenous antibodies have a better tumor penetrating capacity, as compared to exogenously administered antibodies.
The vaccine hVEGF26-104 is a truncated synthetic peptide mimic of the VEGF protein and consists of 79 amino acids (residue 26-104). The vaccine contains an antigen that directs the body*s own polyclonal antibody response towards the active site of the endogenous VEGF molecule. After binding of the antibodies to endogenous VEGF this hormone will no longer be able to bind to its receptors (VEGFR1 and VEGFR2) and consequently will no longer exert its pro-angiogenic effect. To enhance the immune response, RFASE, which belongs to the adjuvant group of sulpholipopolysaccharides, will be used as an adjuvant.

Study objective

Primary objectives
- To investigate the safety and tolerability profile of hVEGF26-104/RFASE.
- To determine the effective dose of hVEGF26-104/RFASE required to neutralize VEGF in serum, defined as a VEGF level below 9,0 pg/mL.
Secondary objectives
- To determine the anti-VEGF antibody titer, induced by hVEGF26-104/RFASE

administration.
- To determine the effective dose of hVEGF26-104/RFASE required to neutralize VEGF in plasma and in a platelet sample.
- To assess the effect of VEGF neutralization in a functional Ba/F3-R2 cell proliferation assay.
Exploratory objectives
- To assess the cellular anti-tumor immune response induced by hVEGF26-104/RFASE administration.
- To assess immunomodulatory effects upon hVEGF26-104/RFASE administration.
- To make a preliminary assessment of hVEGF26-104/RFASE to suppress angiogenesis within the tumor.
- To assess the immune infiltration and the regulation of endothelial cell adhesion molecules within the tumor.

Study design

This is an open label single center phase I study.

A *3 + 3 * dose escalation design will be used. The study will investigate sequential cohorts consisting of 3 patients to be enrolled and treated at the applicable dose level. The study medication consists of 1.0 mL hVEGF26-104 (in escalating doses of 62.5, 125, 250, 500, 1000, 2000 and 4000 µg). The lowest dose of RFASE is 20 mg and this can be escalated to 40 mg, 80 mg and max. 160 mg. Eligible subjects will receive three IM injections with hVEGF26-104/RFASE on days 0 (primer), 14 and 28 (boosters). To assess potential toxicity of the adjuvant RFASE, the 3 patients enrolled in the first cohort of the study (62.5 *g) will receive a single injection with RFASE (fixed dose of 20 mg) as a single agent 14 days prior to the first immunisation with hVEGF26-104/RFASE. If no DLT occurs within 14 days after the RFASE administration, the patients will continue with 3 immunisations hVEGF26-104/RFASE. If none out of 3 patients experiences a DLT at a certain dose level, one can proceed to the next dose level. If one patient experiences a DLT at a certain dose level, another 3 patients will be assigned at the same dose level. In the highest dose escalation cohort, at least 6 patients will be enrolled.
In case insufficient VEGF neutralization (< 50 % reduction in serum VEGF levels compared to pre-treatment) is achieved in dose cohort 3 (hVEGF26-104 250 ug) while administration of the vaccine showed to be safe (< DLT in this cohort), RFASE dose will be escalated to 40 mg while the dose of hVEGF26-104 will remain similar (250 ug) (dose cohort 3B). When there is again insufficient VEGF neutralization, RFASE dose can again be escalated to 80 mg (cohort 3C). The maximum RFASE dose that can be given in this study is 160 mg (cohort 3D).
In case of sufficient VEGF neutralization (> 50% reduction in serum VEGF levels compared to pre-treatment) and administration showed to be safe (< DLT in this cohort), hVEGF26-104 dose will be escalated to 500 ug (cohort 4), 1000 ug (cohort 5), 2000 ug (cohort 6) and 4000 ug (cohort 7) but RFASE dose will remain the same (40 mg).
If VEGF is no longer neutralized, but there is no sign of progression either;

the patient will receive another booster of hVEGF26-104/RFASE in order to achieve VEGF neutralization again. This booster can be repeated until progressive disease, death or other reasons for withdrawal from the study.

Intervention

Eligible subjects will receive three intramuscular injections with hVEGF26-104/RFASE in dose-escalation on days 0 (primer), 14 and 28 (boosters), followed by an observation period of 6 weeks. Blood will be drawn at given timepoints to assess safety, immunogenicity and angiogenesis parameters. At screening, a tumor biopsy will be performed for a baseline assessment of angiogenesis and immune infiltration. In the case that VEGF is neutralized 8 weeks after first hVEGF26-104 administration, the patient will be asked to undergo another biopsy at week 10 to assess any possible change in angiogenesis and immune infiltration in the tumor. In patients whom there is no VEGF neutralization 6 weeks after primer immunization, the DLT period will be terminated.
If VEGF is no longer neutralized, but there is no sign of progression either; the patient will receive another booster of hVEGF26-104/RFASE in order to achieve VEGF neutralization again.

Study burden and risks

Patients participating in the study will receive a total of 3 IM injections with hVEGF26-104/RFASE. Blood will be drawn at given timepoints to assess safety, immunogenicity, angiogenesis and effects on circulating immune effector subsets and endothelial cells and precursors. At baseline patients will be asked to undergo a tumor biopsy. If the blood work indicates VEGF neutralization, patients will be asked to undergo a second tumor biopsy at week 10. During the follow-up period, blood will be drawn every 4 weeks. Furthermore, radiological imaging will be performed every 8 weeks.

Given that this is the first study in which hVEGF26-104/RFASE is applied in man, there are no published data on the risks of this vaccine. However, pre-clinical research in mice and rats did not show any serious toxicity or adverse events. The most important side effects observed were a temporary rise in body temperature, erythema/edema at the injection site and an acute phase reaction observed in blood.
Since hVEGF26-104/RFASE is supposed to act on the same site of the VEGF molecule as bevacizumab, the potential side-effect profile is expected to be comparable. Side effects that can be expected include hypertension, impaired wound healing, bleeding events, thrombosis, proteinuria, leukopenia and bowel perforation.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically confirmed advanced, solid malignancy.
2. Refractory or not amenable to standard therapy
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Willing and able to give written informed consent
5. Patient is * 18 years of age at the time of signature of the informed consent
6. Adequate hematological function: Absolute neutrophil count (ANC) * 1.5 x 109/L, platelets * 100 x 109/L, Hemoglobin * 6.0 mmol/L.
7. Adequate hepatic function: serum bilirubin * 1.5 times the upper limit of normal (ULN), ALT and AST * 2.5 x ULN (or * 5 times ULN if liver metastases are present).
8. Adequate renal function: eGFR * 50ml/min
9. PT-INR/PTT < 1.5 x ULN, unless coumarin derivatives are used
10. Activated partial thromboplastin time (APTT) < 1.25 x ULN (therapeutic anticoagulation

therapy is allowed, if this treatment can be interrupted for a biopsy as judged by the treating physician)
11. Female patients of childbearing potential may be enrolled in the study, if the patient
- Has practiced adequate contraception for 30 days prior to first hVEGF26-104/RFASE administration.
- Negative pregnancy test
- Has agreed to continue adequate contraception for as long as VEGF is neutralized.

Exclusion criteria

1. Major surgery within 28 days before the initiation of study treatment
2. Any serious non-healing wounds, ulcers, or bone fractures within 28 days prior to the initiation of study treatment.
3. Deep venous thrombosis (DVT) or pulmonary embolus (PE) within 1 year prior to the initiation of study treatment.
4. Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
5. The patient is scheduled to receive another vaccination during the DLT period.
6. A previous serious allergic reaction to a vaccine such as angioedema and anaphylaxis.
7. Treatment with bevacizumab within 6 weeks prior to the initiation of study treatment.
8. Uncontrolled auto-immune diseases
9. Primary or secondary immunodeficiency, including HIV
10. Treatment with a glucocorticoid derivative in an equivalent dose of * 10mg prednisone a day.
11. Female patients: the patient is pregnant or lactating.
12. When the patient is scheduled to receive any other anticancer treatments.
13. Chemotherapy within 28 days prior to the initiation of study treatment.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-04-2014

Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	hVEGF26-104/RFASE

Ethics review

Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-10-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-11-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-07-2015
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-05-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	21-05-2019
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	EUCTR2013-002663-25-NL
ClinicalTrials.gov	NCT02237638
CCMO	NL45279.000.13

Study results

Date completed:	01-01-2020
Results posted:	25-11-2020
Actual enrolment:	27

First publication
19-11-2020