AN OPEN-LABEL, MULTICENTER, DOSE ESCALATION PHASE IB STUDY WITH EXPANSION COHORTS TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND THERAPEUTIC ACTIVITY OF RO7009789 (CD40 AGONISTIC MONOCLONAL ANTIBODY) OR BEVACIZUMAB (ANTI-VEGF MONOCLONAL ANTIBODY, PART II) IN COMBINATION WITH VANUCIZUMAB (ANTI-ANG2 AND ANTI-VEGF BI-SPECIFIC MONOCLONAL ANTIBODY) IN PATIENTS WITH METASTATIC SOLID TUMORS

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To evaluate the safety and tolerability of RO7009789 and vanucizumab when administered in combination To determine the maximum tolerated dose (MTD) (for the SC administration and potentially for the IV), route and recommended Phase II dose of...

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

Summary

ID

NL-OMON47188

Source
ToetsingOnline

Brief title
Phase Ib combination with RO7009789 (CD40 agonist) and bevacizumab

Condition

- Other condition

Synonym
Cancer, Solid tumors

Health condition

solide tumoren

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F.Hoffmann - La Roche

Intervention

Keyword: CD40 agonist, Phase Ib, Solid tumors

Outcome measures

Primary outcome

Safety is the primary endpoint and all efficacy endpoints are secondary. Among the efficacy endpoints, for the evaluation of the preliminary antitumor activity of RO7009789 in combination with vanucizumab/bevacizumab, best ORR, objective response rate, DCR, PFS, and OS (if data is mature at the time of analysis) according to RECIST v1.1 will be considered primary.

Secondary outcome

Best ORR, objective response rate, DCR, and PFS will also be assessed according

to irRC and will be considered secondary.

Study description

Background summary

Lack of immune cell infiltration in the majority of solid tumors is seen as a major barrier to the success of immunotherapy. Anti-angiogenic therapies such as bevacizumab and vanucizumab are thought to exert anti-tumor effects at least partly through normalization of tumor neovasculature, which could enhance tumor infiltration of immune cells stimulated by immunotherapy. In addition, there is substantial overlap between cell types and factors involved in immune suppression in the tumor microenvironment and the regulation of neovascularization. Thus, in the context of a RO7009789/vanucizumab combination, immune suppression and angiogenesis are considered to be related processes.

Study objective

*To evaluate the safety and tolerability of RO7009789 and vanucizumab when administered in combination
* To determine the maximum tolerated dose (MTD) (for the SC administration and potentially for the IV), route and recommended Phase II dose of RO7009789 when administered in combination with vanucizumab

Part I (Dose Escalation):
* To characterize the pharmacokinetic (PK) and pharmacodynamics (PD) effects of RO7009789 and vanucizumab when administered in combination
* To assess the biomarkers that might act as PD indicators of the immune modulatory effect and anti-tumor activity of RO7009789 alone and in combination with vanucizumab
* To evaluate the incidence of anti-drug antibodies (ADAs) against RO7009789 and vanucizumab and to assess their potential relationship with other outcome measures

Part II (Expansion Cohorts):
* To evaluate the clinical activity of RO7009789 when administered in combination with bevacizumab in patients with aPROC, HNSCC and NSCLC
* To evaluate the safety and tolerability of the combination RO7009789 and bevacizumab

Study design

This is a Phase Ib, open-label, multicenter, global study designed to assess the safety, tolerability and clinical activity of RO7009789 in combination with vanucizumab in patients with metastatic solid tumors (except prostate cancer and squamous non-small cell lung cancer [NSCLC]) that are not amenable to standard treatment. This study consists of two parts: The aim of Part I is to define the MTD for the SC route of administration (and potentially IV if injection site reactions are dose limiting when administered SC) and the RP2D of RO7009789 in combination with vanucizumab. Part II intends to investigate the clinical activity of RO7009789 in combination with bevacizumab in defined cancer types

Intervention

In Part I, cohorts of three patients will receive escalating doses of RO7009789 subcutaneously/intravenously every 28 days (Q4W) on Day 2 of Cycles 1 through 4, and thereafter on Day 2 of every third cycle (i.e. Cycle 7 Day 2, Cycle 10 Day 2, etc.). The starting dose RO7009789 administration will be 1 mg.
In the event that the SC MTD is determined by injection site reactions, the IV route of administration may be evaluated to establish if greater efficacy or safety can be achieved. The starting IV dose will be at most 50% of the SC MTD and not greater than 8 mg. At the MTD for both SC and IV, each cohort will be expanded to generate PD, PK and safety data to establish the most effective dose and route of administration for Part II.

In Part II, RO7009789 will be administered at RP2D defined in Part I Q4W on Cycle 1 Day 2 and then on Cycle 2 Day 2, on Cycle 3 Day 2 and on Cycle 4 Day 2. Thereafter RO7009789 will be given on Day 2 of every third cycle.

In Part I vanucizumab will be administered intravenously at the fixed dose of 2 g Q2W on Cycle 1 Day1.
In Part II (expansion) vanucizumab will be administered subcutaneously at the fixed dose of 2 g Q2W on Cycle 1 Day1. The dose of vanucizumab in Part II of this study may be adapted based on vanucizumab-related safety events or vanucizumab PK data emerging in Part I.

Treatment with RO7009789 and vanucizumab in Part I and RO7009789 and bevacizumab in Part II will be continued * potentially beyond radiographic disease progression * as long as the patient experiences clinical benefit in the opinion of the investigator. Treatment with RO7009789 and vanucizmuab/bevacizumab will be discontinued if the patient develops unacceptable toxicity or withdraws consent.

Study burden and risks

Infusion/Injection-related Reaction (IRR), Immune-mediated Side Events, High blood pressure, Lack of energy, Constipation, Diarrhea, Abdominal pain,

Vomiting, Nausea, Headache, Swelling of tissues, Cough, Fatigue, Pain in joint, Shortness of breath, Systemic Immune Activation (SIA), abnormal blood tests, procedural risks such as tumor biopsies and blood collection.
Severe side effects reported under treatment with vanucizumab include:
Gastrointestinal perforation (damage to any part of the wall of the stomach, small intestine or large bowel)
Fistula (an abnormal connection between two hollow organs such as blood vessels, intestines, or other hollow organs)
Bleeding
High blood pressure
Congestive heart failure (damage to the left heart chamber that pumps blood to the body and can cause fluid in the lungs, which makes breathing difficult)
Thrombotic microangiopathy (a rare disease that results in formation of blood clots in the smallest blood vessels causing a reduction of blood platelets and red blood cells and kidney failure)
RO7009789 in combination with vanucizumab could:
Cause venous and arterial blood clots. Blood exams will be closely monitored during the study and symptoms like breath shortness or leg pain or swelling will be carefully investigated.
Increase the body*s immune system which may give rise to autoimmune disorders. Therefore you will be closely monitored for autoimmune reactions (e.g., skin, digestive system, breathing, underactive thyroid, and liver disease).
Most of the patients who received RO7009789 subcutaneously developed injection site reactions such as redness, itching, swelling, induration, and tenderness 2 - 9 days later at the site of the injection.

Side effects related to Bevacizumab include:
* Bleeding from the rectum (rectal haemorrhage)
* Diarrhoea
* Nausea and vomiting
* Constipation
* Mucosal inflammation or inflammation of the mouth (stomatitis)
* Loss of appetite (anorexia)
* Abdominal pain
* Weight loss
* Low numbers of white blood cells (neutropenia, leukopenia) and potentially associated with fever (febrile neutropenia)
* Low numbers of platelets (thrombocytopenia)
* Dry skin, flaking and inflammation of the skin (exfoliative dermatitis)
* Change in skin colour (skin discoloration)
* Numbness or loss of feeling in the fingers or toes (peripheral sensory neuropathy)
* Change in the sense of taste (dysgeusia)
* High blood pressure (hypertension)
* Shortness of breath (dyspnoea)
* Pain, including headache and joint pain (arthralgia)
* Alteration in speech (dysarthria)

* Protein in urine
* Mucocutaneous bleeding, including nose bleed (epistaxis)
* Lack of energy, weakness (asthenia, fatigue)
* Fever (pyrexia)
* Runny nose (rhinitis)
* Eye disorder, watery eyes (lacrimation increased)
* Fertility problems in women (ovarian failure)
* Nail-related changes
* Delay in wound healing or failure of a wound to heal or spontaneous opening of a wound

Please refer to section 1.4 BENEFIT RISK ASSESSMENT in the protocol for the Benefit/Risk rationale.

Contacts

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Scientific
Roche Nederland B.V.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

* Part I: Advanced/metastatic histologically confirmed solid tumor (except prostate cancer and squamous NSCLC) not amenable to standard therapy
* Part II: Histologically confirmed diagnosis of advanced/metastatic aPROC, HNSCC and non-squamous NSCLC previously treated with anti-PD-L1 inhibitor alone or in combination
* Age * 18 years
* Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
* Life expectancy * 16 weeks
* Adequate hematologic and organ function
* Adequate cardiovascular function
* Measurable disease Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Exclusion criteria

* Patients with prostate cancer or squamous NSCLC
* Patients who have received prior systemic anti-cancer treatment within the following time frames (see protocol for details)
* Treatment with compounds targeting VEGF or VEGF-R within 12 months prior to enrolment (Part II only)
* Treatment with systemic immunosuppressive medications within 2 weeks prior to Cycle 1 Day 1
* Chronic daily treatment with non-steroidal anti-inflammatory drugs (NSAIDs). However, occasional use for the symptomatic relief of medical conditions (e.g. headache) is allowed
* Patients who have undergone major surgery within 4 weeks prior to study drug administration
* Patients who have undurgone any abdominal surgery or interventions (including colonoscopy)or
significant abdominal traumatic injury within 60 days prior to Day 1 of
Cycle 1
* Known clinically significant liver disease (with the exception of Gilbert's syndrome)
* History of peripheral venous thrombosis or thromboembolic event (within 12 months prior to Cycle 1 Day 1)
* History of hemoptysis (bronchopulmonary hemorrhage) NCI CTCAE * Grade 2 within 4 weeks prior to study drug administration;
* Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume
* Significant cardio- or cerebrovascular disease within 6 months prior to Cycle 1 Day 1
* History of intra-abdominal inflammatory process within 6 months prior to
Day 1 Cycle 1, including but not limited to: diverticulitis, peptic ulcer disease, colitis
* History of bowel obstruction and/or clinical signs or symptoms of

gastrointestinal obstruction including sub-occlusive disease, related to the underlying disease or a requirement for routine parenteral hydration, parenteral nutrition, or tube feeding. Patients with signs/symptoms of sub-/occlusive syndrome/bowel obstruction at time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
* Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
* Patients with colonic prosthesis (stent) implant in place (as applicable)
* Severe non-healing wound, active ulcer or untreated bone fracture
* Known primary CNS malignancy or symptomatic or untreated CNS metastases.
* Pregnancy, lactation, or breastfeeding
* History of autoimmune diseases
* Patient with HIV infection, active hepatitis B (chronic or acute), or hepatitis C infection
* Severe infections within 4 weeks prior to Cycle 1 Day 1

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):	10-05-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	NVT
Generic name:	vanucizumab

Ethics review

Approved WMO Date:	28-10-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-02-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-01-2017

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 16-02-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 19-02-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 31-07-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 03-08-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 24-09-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 27-09-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 21-12-2018

Application type: Amendment

Review commission: PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO
Date: 24-01-2019

Application type: Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
Other	clinicaltrials.gov
EudraCT	EUCTR2015-003480-11-NL
CCMO	NL55345.031.15