An open-label, multicenter, dose escalation and expansion Phase Ib study to evaluate the safety, pharmacokinetics and therapeutic activity of RO6958688 in combination with atezolizumab in patients with locally advanced and/or metastatic CEA-positive solid tumors

Published: 17-11-2015
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The primary objectives of this study are:* To establish the preliminary safety and tolerability profile of RO6958688 in combination with atezolizumab* To determine the maximum-tolerated dose (MTD) in cycle 1 and in later cycles, if achieved, of...

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

Summary

ID

NL-OMON47345

Source
ToetsingOnline

Brief title
WP29945 / CEA TCB

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 Ltd.

Intervention

Keyword: CEA positive, Dose escalation study part, Expansion study part, Solid tumors

Outcome measures

Primary outcome

Safety outcome measures

The safety outcome measures for this study are:

* Incidence and nature of DLTs

* Incidence and severity of adverse events and IRRs and cytokine-release

syndrome symptoms

* Incidence of laboratory abnormalities (hematology testing, coagulation, serum

chemistries, and urinalysis)

* Incidence of ADAs (anti-atezolizumab antibodies and anti-RO6958688 antibodies)

formation, detection of cytokine release and potential correlation with PK, PD,

safety,

and efficacy parameters

* Incidence of autoantibodies (anti-nuclear antibody, anti-double-stranded DNA,

cytoplasmic anti-neutrophil cytoplasmic antibody, and perinuclear

anti-neutrophil

cytoplasmic antibody) in comparison to baseline

* Changes in vital signs, physical findings and ECG findings.

Secondary outcome

Pharmacokinetic Outcome Measures

Pharmacokinetic (PK) concentration data of RO6958688 and atezolizumab will be summarized with the use of descriptive statistical methods

Pharmacodynamic Outcome Measures

The PD outcome measures for this study are the following and will be examined in patients enrolled in both Parts I and II:

* Whole blood samples: Peripheral blood immune cells will be assessed with respect to the changes in the characteristics of lineage (CD4+ T cells, CD8+ T cells, natural killer [NK] cells, monocytes, T-regulatory cells, and B cells), activation (including but not limited to CD25, CD69, etc.), and differentiation (including but not limited to CD45RO Ki67, PD1, TIM3, ICOS, etc.).

* determination of TCR V* sequencing (the CDR3-TCR beta chain repertoire) and TCR V* diversity .

* Serum or plasma samples: PD biomarkers such as cytokines and inflammation markers.

* Tumor biopsy: Biopsies will be assessed centrally for changes in immune cell numbers and activation characteristics as well as changes in tumor markers such as PD-L1.

* Positron Emission Tomography (PET): Baseline and on-treatment 2-[18F]-Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) will be

collected to determine changes in glucose metabolism of the tumor lesions.

* Original or archival tumor: Potential predictive/prognostic biomarkers such

as MMR status and CEA expression will be confirmed on archival tumor, if

available, or from the freshly obtained biopsy samples. These measurements will

assess the RO6958688 and atezolizumab CEA change over the course of the disease

and the stability of the measurements.

Study description

Background summary

Cancer is the leading cause of death worldwide.
Despite the advances in chemotherapy and targeted therapies, the prognosis of patients with advanced cancer remains poor in general. Consequently, there is a persisting and urgent medical need to develop new therapies that can be added to existing treatments to increase survival without causing unacceptable toxicity.

RO6958688 is a new T-cell bispecific antibody (TCB), which focuses on the carcinoantigeen (CEA) which is expressed on tumor cells for T cells. Upon binding of RO6958688, this leads to T cell activation and tumor cell lysis.

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that increases the tumor-specific T cell response by interference in the PDL1 (PD-1) and PDL1 B7.1(CD80, B7-1) interactions.

Clinical benefit from atezolizumab given as monotherapy or combined therapy was observed in a broad range of malignancies including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, urothelial bladder cancer (UBC), colorectal cancer (CRC), head and neck cancer, gastric cancer, breast cancer and sarcoma.

For more background infromation see protocol section 1.1-1.4

Study objective

The primary objectives of this study are:
* To establish the preliminary safety and tolerability profile of RO6958688 in combination with atezolizumab

* To determine the maximum-tolerated dose (MTD) in cycle 1 and in later cycles, if achieved, of RO6958688 in combination with atezolizumab
* To identify a recommended phase II dose and schedule (RP2D) of RO6958688 in combination with atezolizumab.

Secundary objectives
The secondary objectives for this study are:
* To describe the preliminary pharmacodynamic (PD) effects and duration of PD response for RO6958688 in combination with atezolizumab in mandatory paired tumor biopsies and paired blood samples on the basis of alterations in the quantity and quality of intratumoral T cells and peripheral blood cells (including but not limited to CD3+, CD4+, CD8+ T cells, and other immune cells that might act as potential predictors of anti-tumor activity of RO6958688 in combination with atezolizumab)
* To describe the pharmacokinetics (PK) of RO6958688 and atezolizumab when administered in combination
* To obtain preliminary anti-tumor activity data of RO6958688 in combination with atezolizumab on objective overall response rate (ORR), duration of response (DOR) and derived measures, disease control rate (DCR; defined as response rate [RR] + stable disease rate [SDR]), preliminary progression-free survival (PFS)on treatment and overall survival (OS) data according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 criteria and modified RECIST criteria by investigator assessment for the whole study and by central assessment for prospective and retrospective analysis.
* To estimate the overall response rate (ORR) and disease control rate (DCR) and PFS on treatment rate at relevant landmark timepoints (24 weeks) for RO6958688 in combination with atezolizumab.

The exploratory objectives for this study are:
* To explore the relationship between exposure, pharmacodynamics, metabolic activity of the tumor and clinical effects of RO6958688 when administered in combination with atezolizumab
* To explore the immunogenicity of RO6958688 when administered in combination with atezolizumab
* To explore the relationship of host and tumor genetic factors with PD or clinical response to therapy
* To investigate tumor mutations, gene expression and other biomarkers related to RO6958688+atezo combination therapy.
* To characterize the natural growth of the tumor using tumor growth kinetics modeling.
* To explore preliminary safety and efficacy in low/moderate and very low CEA expressing tumors

Study design

This is an open-label, multi-center, dose escalation and expansion Phase Ib clinical study of RO6958688 in combination with atezolizumab. Each treatment

cycle will be 21 days in duration and consists of IV infusions of RO6958688 given weekly (QW) (+/-1 day) or every 3 weeks (Q3W) (+/-2 days) in combination with atezolizumab given every 3 weeks (Q3W) (+/-2 days).
Patients will receive atezolizumab (1200 mg fixed dose) IV on Day 1 of each cycle, followed by RO6958688 at least half an hour later, given IV on Day 1, Day 8 and Day 15 of each cycle for the QW regimen and on Day 1 of each cycle for the Q3W regimen. A weekly (QW) step up dosing approach may be considered.
The study will be conducted in two parts (figure 5 protocol, page 65). Part 1 is divided in parts 1A and 1B, and Part II.
Part 1A is a dose escalation part: patients will receive atezo weekly (1200 mg fixed dose) IV on Day 1 of each cycle, followed by RO6958688 3-weekly at least 30 minutes later, given IV on Day 1, Day 8 and Day 15 of each cycle.
Deel 1B is a dose/schedule finding part:
Gedurende de 6 cycli wordt 6 x atezo 1200 mg toegediend middels 250 mL IV infusie (3-wekelijks) in combinatie met RO6958688 waarvan er 4 verschillende doseringsschema's RO6958688 mogelijk zijn:
1.1 Weekly (QW) with a dose of 100 mg RO6958688, or 1.2 every 3 weeks (Q3W) with a dose of 100 mg RO6958688
2. Weekly (QW) with a starting dose of 40 mg RO6958688 and then the RO6958688 dose will be increased each week up to 150 mg after which RO6958688 will be administered every 3 weeks (Q3W).
3. Weekly (QW) with a starting dose of 40 mg RO6958688, and then the RO6958688 dose will be increased each week up to 600 or 1200 g after which RO6958688 will be administered every 3 weeks (Q3W).
4. Weekly (QW) with a starting dose of 100 mg RO6958688, and then the RO6958688 dose will be increased each week up to either 600 mg after which RO6958688 will be administered every 3 weeks (Q3W). The decision to open this dose regimen will be related to the data generated in the previous dose regimens (1 to 3).

Part II is an expansion part to confirm the safety and tolerability of the MTD dose (or OBD) as determined in Part I in order to define an RP2D and schedule of RO6958688 in combination with atezolizumab, and to explore preliminary antitumor activity, pharmacokinetic and pharmacodynamic effects.

Patients will be treated until loss of clinical benefit, unacceptable toxicities, or withdrawal of consent. The treatment period for this protocol is 24 months for both RO6958688 and atezolizumab and may be modified if emerging data supports an alternative duration of therapy. In case one of the treatments is permanently discontinued, treatment with the other drug alone may be continued as long as the patient experiences clinical benefit in the opinion of the investigator or until unacceptable toxicity or symptomatic deterioration develops, which is attributed to
disease progression as determined by the investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, or withdrawal of consent.

For more information regarding the study design, see protocol section3.

Intervention

Patients eligible for participation in the study will be treated with RO6958688 and atezolizumab. Patients will receive RO6958688 every week (QW) or every 3 weeks (Q3W) and atezolizumab every 3 weeks.
For more details concerning IMP administration see protocol section 4.3

Study burden and risks

Sections E2, E3 and E4 describe the assessments and impact the study has on subjects.
In brief:
During 6 cycles the subjects come for 27 visits (weekly schedule) or 23 visits (every 3 weeks schedule). In the Schedule of Assessments (refer to Appendix 1) all assessments are described. Among others: Physical examination, blood withdrawal, IMP infusion, vital functions, lung function, ECG, Biopsies, Scans.

At E9 the possible risk and, side effects and described. For completeness of the possible side effects, please refer to the ICF.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age * 18 years
- Confirmed locally advanced and/or metastatic solid tumor, with at least one tumor lesion of accessible non-critical location to biopsy, in patients who have progressed on a standard therapy, are intolerant to standard therapy, and/or are non-amenable to standard therapy.
- Radiologically measurable and clinically evaluable disease (as per RECIST v1.1 - previously irradiated lesions should not be counted as target lesions)
- Life expectancy of * 12 weeks and LDH levels <=<2.5 ULN
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0*1.
- All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade * 1 or returned to baseline except alopecia (any grade) and Grade 2 peripheral neuropathy
- Adequate haematological, liver and renal function
- Patients with non-colorectal cancer should have confirmed CEA expression in tumor or centrally confirmed CEA expression in tumor tissue. For CRC cancer patients, the CEA assessment should be performed, but result is not required for patient selection. If no archival tumor tissue is available, in this case fresh biopsy is collected.

Exclusion criteria

- Active or untreated central nervous system (CNS) metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for * 2 weeks prior to enrolment
- Leptomeningeal disease
- Patients with paraspinal, paratracheal, and mediastinal pathological lesions larger than 2 cm unless they are previously irradiated.
- Malignancies within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that would

contraindicate the use of an investigational drug
- Known history of autoimmune disease
- patients with bilateral lung lesions and dyspnea and/or SaO2<92% or patients with lobectomy or pneumonectomy with lung metastases in the remaining lung and either dyspnea or SaO2 <92% at baseline.
- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 28 days prior to Cycle 1 Day 1
- Regular immunosuppressive therapy
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Radiotherapy within the last 28 days before Cycle 1 Day 1 with the exception of limited field palliative radiotherapy for bone pain relief
See protocol for Obinutuzumab-specific exclusion criteria.

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):	28-04-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	Obinutuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA

Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	RoActemra
Generic name:	Tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-02-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-03-2016
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:	20-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-11-2016
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:	26-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	21-09-2017
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:	23-11-2017
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:	23-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-08-2018
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:	22-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	09-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-12-2019
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
EudraCT	EUCTR2015-003771-30-NL
CCMO	NL55499.031.15