AN OPEN-LABEL, MULTICENTER, DOSE ESCALATION PHASE I STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND THERAPEUTIC ACTIVITY OF RO6958688, A NOVEL T CELL BISPECIFIC ANTIBODY THAT TARGETS THE HUMAN CARCINOEMBRYONIC ANTIGEN (CEA) ON TUMOR CELLS AND CD3 ON T CELLS, ADMINISTERED INTRAVENOUSLY IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC CEA(+) SOLID TUMORS

Published: 23-10-2014
Last updated: 21-04-2024

Study BP29541 is a first in-human, open-label, multicenter, dose-escalation Phase I clinical study of single-agent RO6958688. The study will be conducted in two parts. Part I of the study is single ascending dose in single patient cohorts to...

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

Summary

ID

NL-OMON46944

Source
ToetsingOnline

Brief title
BP29541 / 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, Intravenously, Solid tumors, T cell bispecific antibody

Outcome measures

Primary outcome

* To assess the safety profile of RO6958688 with/without obinutuzumab

pretreatment

* To determine the maximum-tolerated dose (MTD) and/or the recommended dose and

schedule (optionally with obinutuzumab pretreatment) for further development

* To determine the late cycle maximum tolerated dose (late

cycle MTD)

* To establish the pharmacokinetics of RO6958688 as monotherapy with/without

obinutuzumab pretreatment

* To assess the effect of obinutuzumab pretreatment in decreasing the rate of patients with positive Anti-Drug Antibodies (ADA) titer against RO6958688 at week 8 and/or delaying the time of onset of ADA against RO6958688

Secondary outcome

* To obtain preliminary anti-tumor activity data of RO6958688 with/without obinutuzumab pretreatment on objective overall response rate (ORR), duration of response (DOR), Best overall response (BOR), disease control rate (DCR; defined as response rate [RR] stable disease [SD]) and progression-free survival (PFS) on treatment, defined as the time from C1D1 to the first occurrence of objective disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 criteria or immune related response criteria (irRC), by investigator assessment, or death from any cause. If Sponsor decides, independent central read for computed tomography (CT) or magnetic resonance imaging (MRI) might be performed in this study, both prospectively and retrospectively.
* To characterize pharmacodynamic (PD) effects and duration of PD response for the once per week (QW), for the every 3 weeks (Q3W) regimens and for the step up dosing scheme QW 3x followed by Q3W on the basis of an increase in activated intratumoral T cells

Study description

Background summary

Binding of RO6958688 to CEA and CD3 leads to T-cell activation and tumor cell lysis. The RO6958688-mediated tumor cell lysis is CEA-specific and does not

occur in the absence of CEA expression or in the absence of simultaneous binding (cross-linking) of T cells to CEA-expressing tumor cells (RO6958688 Investigator*s Brochure). In addition to killing, T cells undergo activation followed by tumor lysis as
detected by increase of late and early T-cell activation markers (CD25 and CD69, respectively), cytokine release (interferon * [IFN*], tumor necrosis factor * [TNF*], granzyme B, interleukin [IL]-2, IL-6, IL-10), and proliferation of T cells (RO6958688 Investigator*s Brochure).

See for more background information page 38-46 in the protocol.

Study objective

Study BP29541 is a first in-human, open-label, multicenter, dose-escalation Phase I clinical study of single-agent RO6958688. The study will be conducted in two parts. Part I of the study is single ascending dose in single patient cohorts to evaluate the safety of RO6958688 at the doses that are expected to be below relevant biological effects (starting from a receptor occupancy of 0.11% for the CD3 epsilon chain receptors), and Part II is multiple ascending dose with a dose finding part where RO6958688 is given QW to define the MTD and/or the recommended dose for further development. Sponsor will open, in Part II, parallel multiple ascending dose escalation cohorts of patients receiving obinutuzumab pre-treatment. QW dosing of RO6958688 (± 1 day) will be implemented initially to generate data that can be analyzed to assess whether different dosing schedules are more effective. Sponsor will also open, in Part II, cohorts of patients pretreated with obinutuzumab either with QW flat dose, Q3W flat dose or step up dosing scheme will also be enrolled, in order to assess if obinutuzumab pretreatment would decrease the incidence and/or delay the onset of ADA directed against RO6958688

Study design

This is an open-label, multicenter, dose-escalation Phase I clinical study of single-agent RO6958688. The study will be conducted in two parts. Part I of the study is single ascending dose in single patient cohorts to evaluate the safety of RO6958688 at the doses that are expected to be below relevant biological effects (starting from a receptor occupancy of 0.11% for the CD3 epsilon chain receptors), and Part II is multiple ascending dose with a dose finding part where RO6958688 is given QW to define the MTD and/or the recommended dose for further development. Sponsor will also open, in Part II, cohorts of patients pretreated with obinutuzumab either with QW flat dose, Q3W flat dose or step up dosing scheme, in order to assess if obinutuzumab pretreatment would decrease the incidence and/or delay the onset of ADA directed against RO6958688. Refer to figure 6, page 62 of the protocol with the study scheme/cohorts.

RO6958688 will be administered via intravenous infusion. At the discretion of the investigator and in agreement with the Sponsor, all patients can receive further doses QW at the same dose level or the next available tolerated dose level that has been cleared for dose escalation after they have completed 2 months of treatment at the current dose level. The treatment period for this protocol is 24 months for RO6958688 and may be modified if supported by emerging data. Because of the potential for progression prior to response with immune therapies, patients who exhibit clinical benefit will continue treatment beyond radiographic progression after discussion and agreement with the Sponsor. The study will be conducted in two parts. Part I and Part II of the trial will enroll patients with locally advanced and/or metastatic carcinoembryonic antigen (CEA) positive solid tumors who have progressed on standard treatment, are intolerant to standard of care (SOC), and/or are non amenable to SOC.

For more information see also page 58-66 in the protocol (page 14-15 in the synopsis)

Intervention

Patients eligible for participation in this study are treated with RO6958688, see for administration details, page 89-99 of the protocol.

Study burden and risks

The following problems may be caused by RO6958688 in this study:

Swelling (inflammation) of non-healthy lymph nodes induced by RO6958688 causing obstruction of the airways leading to acute respiratory failure (breathing difficulties) resulting in death, occurred in a patient treated with a dose of 600mg RO6958688 in the dose-escalation part of the single agent BP29541 study. The patient had received the full planned dose and the event started within 24 hours after administration of the first RO6958688 dose.Patients will receive a preventive treatment with corticosteroids for up to 4 days after the first administration of RO6958688 (QW and Q3W regimen). The use of corticosteroids before the infusion of RO6958688 may be considered if indicated.

Infusion related reaction, allergic and hypersensitivity reactions:
Based on experience with monoclonal therapeutic antibodies, reactions to RO6958688 during and/or after the administration of the study drug (so-called infusion-related reactions, allergic or anaphylactic reaction, hypersensitivity reaction) may be experienced.

Infusion-related reactions (IRR): IRRs could occur at the time of, shortly after or within 24 hours after study drug administration (IV infusion). They are more likely to occur at the first infusion with the severity and chance of

them occurring decreasing at future administrations. Symptoms of an IRR include fever, shivering or chills, nausea, vomiting, high blood pressure, disturbed heart rhythm, breathing difficulties, headache, low blood pressure, (tumor) pain, restlessness, diarrhoea, dizziness, sweating, flushing, rapid breathing.When experiencing an infusion related reaction, it may be necessary to give medications to prevent the worsening of this reaction and prevent future reactions.

Allergic reaction: allergic reaction to the study drug may also occur. Allergic reactions can be mild, such as a skin rash or pimples, but can also be severe, such as difficulty breathing or shock. Allergic and IRR appearance can be difficult to tell apart. A severe allergic reaction must be treated, and the patient may have to be admitted to the emergency unit for this. In very rare cases, such a reaction can be fatal.

Development of antibodies to the study drug: When receiving RO6958688, there is a possibility that the immune system might develop antibodies against the drug, so-called anti-drug antibodies (ADA), which may occur after the administration of monoclonal therapeutic antibodies. Therefore, if these special antibodies are developed, it may affect the body*s ability to respond to other drugs of a similar type. At times side effects can occur due to the development of ADA which worsen over time. Usually these side effects are skin rash, joint and muscle pain, fever and tiredness. It is possible to have a transient changed sense of taste or to develop transient peeling of the skin at the palms and soles of their feet. Medicines can be prescibed to decrease the effect of these symptoms. If these side effects are severe or persist for a very long time, it may be necessary to permanently discontinue administration of RO6958688.

If certain side-effects occur due to the drug RO6958688, the doctor will always discuss the options to tolerate the treatment better. If any of the symptoms that are experienced are related to infusion during RO6958688 administration, the infusion may slow down, or temporarily or permanently be stopped. Once the symptoms have responded to any treatment and resolved, the infusion may be continued. To help prevent or reduce the intensity of any reaction related to the infusion, orally or intravenously (in the vein) a drug against fever, such as paracetamol and an antihistamine about 30 minutes before the infusion of RO6958688 can be given. If a severe IRR (infusion-related reaction) is experienced at the time of an infusion, corticosteroid treatment may also be received intravenously. If severe reaction related to the infusion during the previous treatment cycle is experienced, medication against the reaction will be received, such as paracetamol or an antihistamine, or a corticosteroid to prevent the occurrence of similar signs and symptoms at the next cycle of treatment, 30 minutes before infusion. The doctor / study research staff will carefully monitor the patient while given RO6958688 and for a time afterwards. If a severe reaction develops, especially severe breathing difficulties, additional tests on the blood or an x-ray of the chest might be needed. The

infusion will not resume unless the doctor is sure that the patient recovered completely from the reaction. In the event of a severe reaction, the patient may be withdrawn from the study.
Most of these side effects will disappear when appropriately treated or when the treatment with the study drug is delayed and/or stopped.
It is possible that new side effects of RO6958688, unknown at this time, may occur during the study.
Study procedure related risk

Tumor biopsy (Part II)

The most common risks of a biopsy are discomfort during the biopsy procedure, bleeding and infection. With lung biopsies there is also a risk of pneumothorax (lung collapse); often a chest X-ray is done immediately after the biopsy to check if this has happened and if necessary a chest tube may be inserted to re-expand the lung. If you have trouble breathing or your heart rate increases after being discharged from the hospital, it is important to call your study doctor or emergency services immediately. Other risks may exist depending on the location of the tumor being biopsied including puncture of a nearby organ. Your study doctor will discuss these with you. If your study doctor feels you would be at an additional risk from the biopsy after start of treatment then this biopsy would either be postponed or cancelled without affecting your treatment or your participation in the study.

What are the risks of the tumor assessment?

There is a potential risk of radiation exposure from CT scans; however, this risk is considered small. An intravenous (in the vein) contrast dye is usually given with a CT scan. If allergies are experienced already it is more likely to have an allergic reaction to the dye. This reaction may be mild (such as skin rash or hives) to severe (such as breathing difficulties or shock). A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. YMRI: Implanted medical devices that contain metal may malfunction or cause problems during an MRI exam. There is a very slight risk of an allergic reaction if contrast material is injected.
Such reactions usually are mild and easily controlled by medication. If allergic symptoms are experienced, a radiologist or other physician will be available for immediate assistance.

Blood sampling
The risks of blood sampling include slight pain from the needle prick, bruising, discomfort where the blood was taken, and, in rare cases, fainting or infection may occur or anemia may worsen.

Contacts

Public
Roche Nederland B.V.

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Scientific
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Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* For dose escalation, locally advanced and/or metastatic gastrointestinal solid tumor in patients who have progressed on a standard therapy, are intolerant to SOC, and/or are non-amenable to SOC and other solid tumors expressing CEA as per inclusion criterion 14.
* Radiologically measurable disease according to RECIST v1.1
* Life expectancy (in the opinion of the investigator) of >< = 12 weeks and lactate dehydrogenase levels << = 2.5 upper limit of normal
* Eastern Cooperative Oncology Group 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 hematological, liver and renal function
* Patients must agree to be willing to use effective methods of contraception as defined in

the protocol
* Non-gastrointestinal solid tumors (like non-small cell lung cancer or breast cancer patients) should have confirmed CEA expression in tumor tissue ><= 20% of tumor cells staining with at least moderate to high intensity of CEA expression are required (Immunohistochemistry [IHC] 2+ and IHC3+). For CRC patients only, the CEA assessment should be performed but the result is not required to enroll the patient.
* For the biomarker cohort, only patients with moderate/low CEA expression and very low/negative CEA expression or IHCO+ will be enrolled. CEA expression should be determined prior to enrollment.

Exclusion criteria

1.Active or untreated central nervous system (CNS) metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments
2. 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 enrollment.
3. Leptomeningeal disease.
4. patients with paraspinal, paratracheal and mediastinal pathological lesions larger than 2 cm inless they are previously irridiated.
5. Patients with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the investigator to be of low likelihood for recurrence)
6. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or contraindicate the use of an investigational drug, including diabetes mellitus, history of relevant pulmonary disorders, and known autoimmune diseases
7. Patients with bilateral lung lesions and dyspnea and/or with bilateral lung lesions and SaO2 < 92% (at rest, room air) or patients with lobectomy or pneumonectomy with lung metastases in the remaining lung and either dyspnea or SaO2 less than 92% (at rest, room air) at baseline

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):	04-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	obinituzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	not available
Generic name:	unknown
Product type:	Medicine
Brand name:	RoActemra
Generic name:	Tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-10-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-12-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-08-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	10-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	15-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	10-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	13-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	20-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	21-02-2017
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:	28-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-11-2017
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:	24-05-2018
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:	09-10-2018
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:	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:	18-06-2019
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
EudraCT	EUCTR2014-003075-30-NL
CCMO	NL51067.031.14