# AN OPEN-LABEL, MULTICENTRE, DOSE-ESCALATION, PHASE I STUDY WITH AN EXPANSION PHASE, TO EVALUATE SAFETY, PHARMACOKINETICS AND THERAPEUTIC ACTIVITY OF RO6895882, AN IMMUNOCYTOKINE, CONSISTING OF A VARIANT OF INTERLEUKIN-2 (IL-2v) TARGETING CARCINOEMBRYONIC ANTIGEN (CEA) ADMINISTERED INTRAVENOUSLY, IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS.

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* to describe the safety profile for qW, q2W and q3W regimens. * to determine the Maximum Tolerated Dose (MTD), if achieved (all regimens)* to describe the pharmacokinetics (PK) of single-agent RO6895882. Substudy BP28920/IMGThe study is designed to...

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

## Summary

### ID

NL-OMON41678

**Source**
ToetsingOnline

**Brief title**
CEA-IL2v / BP28920

## Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

**Synonym**
advanced and/or metastatic CEA positieve solide tumors/organ tumors

**Health condition**

CEA positieve solide tumoren

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Roche Nederland B.V.
**Source(s) of monetary or material Support:** Roche Nederland B.V.

## Intervention

**Keyword:** CEA positive, Dose escalation, PK/PD, Solid tumors

## Outcome measures

**Primary outcome**

* to describe the safety profile for qW, q2W and q3W regimens.

* to determine the Maximum Tolerated Dose (MTD), if achieved (all regimens)

* to describe the pharmacokinetics (PK) of single-agent RO6895882.

Substudy BP28920/IMG

To investigate the in vivo biodistribution and organ pharmacokinetics of

radioactivity (89Zr) at two doses: 6 mg (or a lower dose should 6 mg not be

considered safe in Part I of the main study BP28920) and at the maximum

tolerated dose (MTD) or a lower dose with equivalent pharmacodynamic (PD) effects as determined for the q2W regimen in Part II of the main study BP28920.

Substudy BP28920/ obinutuzumab:

Proportion of patients without ADA titer at Cycle 4

To evaluate the safety and tolerability of administration of obinutuzumab given prior

to treatment with RO6895882

**Secondary outcome**

Part I (Single Ascending Dose):

* to characterize the pharmacodynamics (PD) of single dose RO6895882 on peripheral blood cells by determining sCD25

Part II and Part III (Dose Escalation Monotherapy and MTD expansion):

* to characterize PD effects (number, proliferation and activation of immune cells) of multiple doses of RO6895882 on peripheral blood cells

* to determine the changes in PD biomarkers (proliferation, activation and infiltration of immune cells and PD-L1 expression) associated with RO6895882 treatment in tumors

* to obtain preliminary anti-tumor activity data of objective overall response rate (ORR), disease control rate (DCR; defined as RR + stable disease [SD]) and progression-free survival (PFS) according to RECIST v1.1 criteria, of single-agent RO6895882.

Exploratory Objectives

* to explore the PD effects and duration of PD response for the qW, q2W and q3W regimens based on an increase in activated CD8+ tumor infiltrating lymphocytes (TIL)

* to explore at different doses the relationship between exposure - PD and clinical effects of RO6895882

* to obtain preliminary anti-tumor activity data of objective overall response rate (ORR), disease control rate (DCR; defined as RR + SD) and progression-free survival (PFS) according to immune-related Response Criteria (irRC), of single-agent RO6895882

* to investigate the correlation between genetic markers from baseline blood samples with response, including but not limited to KIR and HLA genotypes

* to investigate potential predictive PD biomarkers from paired tumour biopsies (including, but not limited to CD3, CD4, CD8)

Substudy BP28920/IMG

1) To describe the relationship between tumor targeting and observed pharmacodynamic effects in the corresponding tumor lesions using:

- changes in PD biomarkers

- dualphase 18F-FDG-PET to measure local RO6895882-induced inflammatory response and anti-neoplastic effects

2) To describe the safety of RO6895882.

Substudy BP28920/ obinutuzumab:

The safety/tolerability outcome measures for this study are as follows:

* Incidence and severity of AEs and IRRs

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

clinical

chemistries, urinalysis)

* Physical examination findings particularly body weight

* Triplicate 12-lead ECGs

* Vital signs

# Study description

**Background summary**

It is increasingly recognized that a low density of infiltrating immune cells in the tumor is associated with a poor prognosis [2] and that the immune cells infiltrating the tumor are not fully functional [3]. Activating the immune system by therapy with cytokines such as IL-2 has therefore been used successfully for the treatment of cancer [4]. IL-2 was consequently approved as a treatment for melanoma and renal cell cancer. The utility of IL-2 is however severely restricted by the widespread occurrence of side effects requiring specialized care and knowledge [5].
RO6895882 was designed to improve on existing cytokine therapy by including the following features and modifications: (i) it is a targeted cytokine that binds to the tumor specific protein CEA (carcinoembryonic antigen). Thereby, it accumulates in the tumor as shown by non-clinical experiments and will have an increased local effect compared to untargeted cytokines. (ii) The IL-2 variant (IL-2v) moiety was modified such that it does not bind to CD25 any longer resulting in (a) reduced pulmumary endothelial activation, (pulmonary endothelial activation was associated with vascular side effects, [6]), and (iii) does not exhibit the preferential activating effect on regulatory T-cells, which have immunosuppressive properties. In conclusion, RO6895882 is a targeted immunocytokine with the potential to enhance antitumor immune responses more efficiently and safely than existing cytokine therapy.

Substudy BP28920/IMG
At the 2 participating Dutch sites, an imaging substudy will be executed with the title: "AN OPEN-LABEL PHASE I IMAGING STUDY OF RO6895882 USING 89Zr-LABELED

RO6895882 AS A TRACER, ADMINISTERED INTRAVENOUSLY, IN PATIENTS WITH ADVANCED AND/OR METASTATIC SOLID TUMORS", in which monotherapy RO6895882 will be combined with zirconium-89-labeled RO6895882.

Substudy BP28920/ obinutuzumab:
In all participating centra an obinutuzumab substudy will be performed wit the titel:A MULTI-CENTER, RANDOMIZED, OPEN-LABEL
PHASE 1 STUDY TO EVALUATE FEASIBILITY, SAFETY AND PHARMACODYNAMIC EFFECT OF PRETREATMENT WITH OBINUTUZUMAB PRIOR TO THERAPY WITH RO6895882, AN IMMUNOCYTOKINE, CONSISTING OF A VARIANT OF INTERLEUKINE-2 (IL-2V) TARGETING CARCINOEMBRYONIC ANTIGEN (CEA), ADMINISTERED INTRAVENOUSLY, IN PATIENTS WITH LOCALLY ADVANCED AND/OR METASTATIC SOLID TUMORS, which will combine a monotherpay with RO6895882 pretreated with RO507259

## Study objective

* to describe the safety profile for qW, q2W and q3W regimens.
* to determine the Maximum Tolerated Dose (MTD), if achieved (all regimens)
* to describe the pharmacokinetics (PK) of single-agent RO6895882.

Substudy BP28920/IMG
The study is designed to evaluate descriptively the tumor targeting and the differences between CEA-positive and CEA-negative tumors, as well as to describe qualitatively the relationship between targeting and PD effects. No formal inferential analysis is foreseen given the limited sample size and the expected variability in study endpoints. The main objective of the study is exploratory.

89Zr- RO6895882 is the radioactively labeled form of RO6895882 for which the radioactive substance zirconium-89 has been linked to RO6895882. 89Zr-RO6895882 will be administered only once during this imaging sub-study. The radioactive dose will be a low dose, making it possible to follow the distribution of RO6895882 throughout the body by imaging (Positron Emission Tomography [PET] scan). Otherwise 89Zr- RO6895882 has the same type of activity as the unlabeled compound (RO6895882).

Substudy BP28920/ Obinutuzumab:
* To assess the the effect of pre-treatment with obinutuzumab on decreasing the proportion of patients with ADA titer at cycle 4
* To evaluate the safety and tolerability of administration of obinutuzumab given prior
to treatment with RO6895882

## Study design

This is a first-in-human, open-label, multicenter, dose-escalation phase I clinical study of single-agent RO6895882 with an expansion phase. The study will be conducted in three parts. Part I is a single ascending dose study in single patient cohorts to evaluate safety of RO6895882 at low doses (* 6 mg). Part II is a dose-escalation part with RO6895882 monotherapy given qW, q2W and q3W. Part III is an expansion phase of the qW, q2W and q3W MTD (as determined in Part II). Part III of the trial will also include at least five patients with CEA-negative tumors of either skin or kidney.
All parts of the trial will enroll patients with CEA-positive solid tumors for whom no standard therapy is available. Part III is an expansion phase of the qW, q2W and q3W MTD (as determined in Part II). Part III of the trial will also include at least five patients with CEA-negative tumors of either skin or kidney.

See protocol section 3 p. 34-36.

Substudy BP28920/IMG
Patients will be recruited in 5 different groups:
the tolerability of an IV bolus will be tested with the standard supply in a pre-imaging (pre-IMG) dose group with two patients.
Group A (CEA positive) and B (CEA negative) will receive low dose 89Zr-RO6895882.
Group C (CEA positive) and D (CEA negative) will receive high dose of 89Zr-RO6895882.
Group E (CEA positive) and F (CEA positive) will receive a 2nd dose of 89Zr-RO6895882 on C4D1 and C3D1 respectively (if tumor targetting is demonstrated by the 89Zr-RO6895882 PET scan at Cycle 1.

The low dose groups (pre-IMG, A, and B) will be recruited once Part I of the main protocol is completed. The high dose groups (C and D) will start enrolment after completion of the q2W MAD in Part II of the main study. In group A-D, per group a minimum of 3 patients will be recruited. New patients will be enrolled into groups E and F only if there is evidence of tumor targetting in patients from group C.

See also protocol section 3 p. 33-35

Add. An 89Zr-PET scan will be included on C1D1 for the first 3 imaging patients to enable more precise radiation dosimetry for the novel 89Zr-RO6895882. The C1D1 scan will replace the C1D9 scan in order not to increase radiation load on these patients. This is a de-risking strategy in the event of unexpected bio-distribution due to the novel format of the antibody-conjugate. The expected dosimetry has now been calculated but must also be measured in vivo to ensure patient safety.

Substudy BP28920/ Obinutuzumab:
In this substudy 20 patients will be treated. Fifteen patients will be

randomized into the obinutuzumab pretreatment arm and five
patients to the control arm without obinutuzumab pretreatment. The patients in the obinutuzumab pretreatment arm will receive 1g of obinutuzumab intravenously on two consecutive days, Day -13 and Day -12 (+/- 2 days) before the Cycle 1 Day 1 (C1D1) RO6895882 administration
See also protocol section 3.1 P 53-55

The patients in the obinutuzumab pretreatment arm will receive 1g of obinutuzumab intravenously on two
consecutive days, Day -13 and Day -12 (+/- 2 days) before the Cycle 1 Day 1 (C1D1)
RO6895882 administration.

**Intervention**

Patients who are eligible will be treated with RO6895882 according the study specific schedule as shown in appendix 1 of the protocol p. 106-118.

Substudy BP28920/IMG
Patients who are eligible will be treated with RO6895882 and 89Zr-RO6895882 according the study specific schedule as shown in appendix 1 of protocol BP28920/IMG on p. 95-98.

Substudy BP28920/ obinutuzumab:
Patients who are eligible will be treated with RO6895882 and RO5072759 according the study specific schedule as shown in appendix 1 of Protocol BP28920/ obinituzumab P126-133

**Study burden and risks**

Targeting CEA overexpressing tumor with IL-2v has the potential to provide substantial anti-tumor immune response with lower associated toxicity compared to untargeted, or unmodified IL-2 therapy and may also enable in the future, a multitude of combinations with other immunotherapies or with established anti-cancer agents. The existing non-clinical data set with RO6895882, in conjunction with the extensive clinical experience with IL-2 provide an acceptable risk-benefit balance for the clinical investigation of RO6895882 in advanced cancer patients for whom no effective standard therapy exists.

See protocol section 1.2, p. 31-33.

Substudy BP28920/IMG
See also protocol BP28920/IMG, page 30-32.

The side effects of the tracer 89Zr-RO6895882 are not yet known, as it has not been administered to humans before. Side effects could occur during or shortly

after the injection of the tracer. The amount of radioactivity that the patient recieved does not have any therapteuric effect. Nonetheless, the patient will be exposed to ionized radioation. The total amount of radiation that the patient will receive as a result of this tracer is 60 mSv, this quantity is accepted as under the current legislation.

SubstudY BP28920/ obinutuzumab:
Side effects of RO6895882 are similuar as in the main study. Possible risks of obinutuzumab are infusion related reaction, alergic reactions and infections. For more side effects see patient informationsheet.

## Contacts

**Public**
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
**Scientific**
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

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

## Inclusion criteria

*Signed informed consent.
*Confirmed advanced and/or metastatic solid tumor, with confirmed progression at baseline, for whom no standard treatment is available.
*Radiologically measurable and clinically evaluable disease.
*Adequate hematological function: neutrophil count of * 1.5 x 109 cells/L, platelet count of * 100,000/µl, Hb * 10 g/dL (6.2 mmol/L), including lymphocytes within normal limits.
*Adequate liver function: Total Bilirubin * 1.5 x ULN (excluding Gilbert*s Syndrome, see below), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) * 2.5 x ULN (in case of liver metastases: * 5 x ULN).
*Adequate renal function: serum creatinine * 1.5 ULN or creatinine clearance by Cockcroft Gault formula [see Appendix X] * 50 mL/min for patients in whom, in the investigator*s judgment, serum creatinine levels do not adequately reflect renal function.
*Locally confirmed CEA expression in tumor tissue (>20% of tumor cells staining with at least moderate intensity);Extra for Imaging substudy:
At least one non-liver tumor lesion that is assessable by PET imaging

## Exclusion criteria

*History or clinical evidence of central nervous system (CNS) primary tumors or metastases including leptomeningeal metastases unless they have been previously treated, are asymptomatic and have had no requirement for steroids or enzyme-inducing anticonvulsants in the last 14 days before screening .
*Patients with a second malignancy in the last 5 years (with the exception of basal cell carcinoma).
*Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders and known autoimmune diseases. ;Extra for Imaging substudy:
Patients who have had a hypersenitivity reaction to 2-[18F]Fluoro-2-deoxyglucose (FDG)

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |

| | |
|---|---|
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 26-02-2014 |
| Enrollment: | 60 |
| 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: | NVT |
| Generic name: | 89Zr-RO6895882 |
| Product type: | Medicine |
| Brand name: | RO6895882 |
| Generic name: | RO6895882 |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 16-10-2013 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

Approved WMO

| | |
|---|---|
| Date: | 13-01-2014 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

Approved WMO

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|---|---|
| Date: | 27-02-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

| | |
|---|---|
| Approved WMO Date: | 13-03-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-05-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-06-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-08-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 23-10-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-10-2014 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 09-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 18-05-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 29-05-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

| | |
|---|---|
| Date: | 02-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 29-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 27-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 26-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-12-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# 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 nummer. |
| EudraCT | EUCTR2013-003041-41-NL |

| Register | ID |
| --- | --- |
| CCMO | NL46386.029.13 |