AN OPEN-LABEL, MULTICENTER, DOSE ESCALATION, PHASE IA/IB STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, AND THERAPEUTIC ACTIVITY OF RO6874281, AN IMMUNOCYTOKINE CONSISTING OF INTERLEUKIN 2 VARIANT (IL-2v) TARGETING FIBROBLAST ACTIVATION PROTEIN-* (FAP), AS A SINGLE AGENT (PART A) OR IN COMBINATION WITH TRASTUZUMAB OR CETUXIMAB

Published: 30-09-2015
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Primary ObjectivesPart A: RO6874281 Dose Escalation as a Single AgentThe primary objectives for this study are as follows:* To describe the safety and tolerability profile of RO6874281 as a single agent* To determine the maximum tolerated dose (MTD...

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

Summary

ID

NL-OMON46970

Source
ToetsingOnline

Brief title
BP29842 / FAP-IL2v

Condition

- Other condition

Synonym
Cancer, solid tumors

Health condition

solide tumoren (part A), Borstkanker (part B), (plaveiselcarcinoom hoofd/hals (partC)

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: FIBROBLAST ACTIVATION PROTEIN, INTERLEUKIN 2, SOLID TUMORS

Outcome measures

Primary outcome

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

* Incidence of DLTs

* Incidence and severity of adverse events and IRRs

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

chemistries,

urinalysis)

* Incidence of anti-antibodies (ADAs)

* Physical examination findings, particularly body weight

* Triplicate 12-lead ECGs

* Chest X-ray (or from computed tomography [CT] scan, if scheduled instead)

*GOLD level classification: forced expiratory volume and forced vital capacity

for the patients with pleural effusion at baseline (X-ray) that fulfill the

eligibility criteria

* Vital signs

* TTE or MUGA scan

EFFICACY OUTCOME MEASURES

The efficacy/activity outcome measures for this study are as follows:

* ORR

* SD

* DCR, defined as RR + SD

* PFS, defined as the time from randomization to the first occurrence of

disease progression

or death from any cause

*OS, if data are mature

Secondary outcome

For the pharmacokinetic and pharmacodynamic outcome measures, see page 117 en

1118 in the study protocol

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study include but are not limited to

the following:

* The density and localization of immune cells will be determined in freshly

obtained biopsy in

order to describe the immune infiltration prior to treatment. When possible,

comparisons

between primary tumor and metastasis will be performed.

* The density and activation status of immune cell subsets in the tumor will be

assessed in

biopsies taken before and during treatment.

* Possible associations of genetic determinants of autoimmunity (e.g., KIR-HLA

mismatch)

with PD response and clinical response will be investigated.

* The baseline values and kinetics of soluble markers of immune cell activation

(such as

sCD25) and tumor markers (such as soluble FAP [sFAP]) will be explored.

Additional

markers may be measured in case a strong scientific rationale for these

analyses develops.

* Assessment of TGK may be explored by comparing on-treatment and post

treatment scans with at least two pretreatment scans not older than 12 weeks

prior to Cycle 1 Day 1, if available. The two pretreatment scans consist of a

pre-study scan and the study baseline scan.

Study description

Background summary

Among other reasons, cancer develops because the immune system fails to survey and
eradicate malignant cells. Cancer immunotherapy differs from traditional chemotherapy,
which primarily targets rapidly dividing cells, and from targeted therapies, which interfere
with key molecular events in tumor cells that drive tumor growth and invasion. Cancer
immunotherapy aims to aid in the recognition of cancer cells as foreign by the immune
system, to alleviate inhibition of the immune system that allows the tolerance of tumor
growth, or to stimulate immune responsiveness and can be applied to a broad spectrum
of malignancies. Fibroblast activation protein-**targeted interleukin 2 variant
immunocytokine (FAP-IL2v), also referred as RO6874281 throughout this protocol, is
designed to augment immune responses within a tumor.

Study objective

Primary Objectives
Part A: RO6874281 Dose Escalation as a Single Agent
The primary objectives for this study are as follows:
* To describe the safety and tolerability profile of RO6874281 as a single agent
* To determine the maximum tolerated dose (MTD), the optimal biological dose (OBS) and/or the recommended dose for further developtment of RO6874281.
* To investigate the single- and multiple-dose pharmacokinetics of RO6874281 as a
single agent

Part B and Part C: RO6874281 Dose-Escalation Phase, in Combination with Trastuzumab or Cetuximab
* To determine the safety profile, the MTD, the OBD, and/or the recommended dose for further development of RO6874281, in combination with trastuzumab (Part B) in patients with metastatic HER2-positive
breast cancer who have progressed on at least two lines of HER2-directed therapies and the
last therapy prior to going on study has to contain a HER2-directed antibody (the period
between the last administration of HER2-directed antibody and first administration of study
treatment should not exceed 6 weeks), and in combination with cetuximab (Part C) in
patients with metastatic squamous cell carcinoma of head and neck who progressed on cetuximab maintenance therapy after cetuximab-containing chemotherapy (the period

between the last administration of cetuximab maintenance therapy and first administration
of study treatment should not exceed 6 weeks).
* To characterize the pharmacokinetics of RO6874281 in combination with trastuzumab (Part B) or in
combination with cetuximab (Part C)

Part B and Part C: Extension Phase
* To describe the safety profile, pharmacokinetics, and therapeutic activity of selected
dose(s) and regimen(s) of RO6874281, in combination with trastuzumab in patients with metastatic or recurrent or locally
advanced HER2-positive breast cancer who have progressed on at least two lines of
HER2-directed therapies and the last therapy prior to going on study has to contain a
HER2-directed antibody (the period between the last administration of HER2-directed
antibody and first administration of study treatment should not exceed 6 weeks) (Part B
extension) and in combination with cetuximab in patients with metastatic squamous cell carcinoma of head and neck who progressed on cetuximab maintenance therapy after cetuximab-containing chemotherapy (the period between the last administration of cetuximab maintenance therapy and first administration of study
treatment should not exceed 6 weeks) (Part C extension). Therapeutic activity is defined as achieving disease control.

Secondary Objectives
The secondary objectives for this study are as follows:

Part A: RO6874281 Dose Escalation as a Single Agent
* To investigate treatment-induced pharmacodynamic (PD) effects (proliferation, activation,
and infiltration of immune cells) of RO6874281 on peripheral blood cells and in tumor
samples. This will include the number of T and NK cells in the peripheral blood and the density (cell/mm2) of CD8+ and CD3* /perforin+ cells in tumor samples.
* To obtain preliminary RO6874281 anti-tumor activity data of objective overall response rate (ORR),
disease control rate (DCR; defined as response rate [RR] + stable disease [SD]), and
progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors
(RECIST) Version 1.1 criteria and immune-related response criteria (irRC)

Part B and C: RO6874281 Dose-Escalation Phase in combination with Trastuzumab

or Cetuximab
* To investigate treatment-induced PD effects (proliferation and infiltration of immune cells) on peripheral blood cells and in tumor samples when RO6874281, administered in combination with trastuzumab (Part B) or in combination with cetuximab (Part C). This will
include the number of T, B, and NK cells in the peripheral blood and the density (cell/mm2) of CD8+, CD20, and CD3*/perforin+ cells in tumor samples.
* To obtain preliminary anti-tumor activity data of RO6874281 in combination with trastuzumab (Part B) and in
combination with cetuximab (Part C). This anti-tumor activity will be measured by ORR, DCR (defined as RR+ SD), and PFS according to RECIST v1.1 criteria and modified RECIST by investigator assessment for the whole study. If therapeutic activity is observed, RECIST v1.1 and modified RECIST may also be independently assessed centrally.

Exploratory Objectives
The exploratory objectives for this study are as follows:
* To explore further PD duration and effects, Inclucing ADCC, based on changes of immune cell numbers and based on functional tests utilizing in
peripheral blood cells and tumor samples
* To explore the relationship between exposure and biomarker parameters and the clinical
effects of RO6874281
* To investigate potential response prediction markers from paired blood and tumor samples
* To investigate the correlation between genotypes in killer-cell immunoglobulin-like receptor
(KIR), human leukocyte antigen (HLA), and potentially other immune factors and clinical
response
* To explore tumor growth kinetics (TGK) if the data are available and the data permit for the analysis.

Study design

This is a first-in-human, open-label, multicenter, Phase IIa/Ib, adaptive, multiple ascending*dose study. The present study consists of three parts, as follows:
* Part A, which assesses the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of RO6874281 as a single agent in adult patients with advanced and/or metastatic solid tumors. In this part, the MTD and/or the OBD and/or the recommended dose for further development of RO6874281 as a single agent will be determined.
* Part B, which assesses the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of RO6874281 in combination with trastuzumab in patients with metastatic or recurrent or locally advanced HER2-positive breast cancer who have progressed on at least

two lines of HER2-directed therapies and the last therapy prior to going on study has to contain a HER2-directed antibody. Further, the period between the last administration of HER2-directed antibody and first administration of study treatment should not exceed 6 weeks. Part B will be followed by an extension cohort. In this part, the MTD and/or the OBD and/or the recommended dose for further development of RO6874281 in combination with trastuzumab will be determined.
* Part C, which assesses the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of RO6874281 in combination with cetuximab in patients with metastatic or recurrent or unresectable squamous cell carcinoma of head and neck who progressed on cetuximab maintenance therapy after cetuximab-containing chemotherapy. Further, the period between the last administration of cetuximab maintenance therapy and first administration of study treatment should not exceed 6 weeks. Part C will be followed by an extension cohort. In this part, the MTD and/or the OBD and/or the recommended dose for further development of RO6874281 in combination with cetuximab will be determined.

Intervention

RO6874281 is considered an investigational medicinal product and will be administered as an
IV infusion. The starting dose regimen of RO6874281 as a single agent will be 5 mg,
administered QW. Different dosing regimens (e.g., Q2W) may be explored in parallel, if
warranted, on the basis of the safety and PK profile of RO6874281

In part B the patients will receive trastuzumab and RO6874281 (first 4 weeks weekly) via IV according a Q2W schedule. At the first infusion of trastuzumab the patient will receive a loading dose of 6mg/kg. The following doses will be 4mg/kg. The starting dose of RO6874281 will be 10 mg. Different dosing regimens (e.g., Q3W) may be explored in parallel, if warranted, on the basis of the safety and PK profile of RO6874281 in combination with trastuzumab.
In part C the patients will receive cetuximab and RO6874281 (first 4 weeks weekly) via IV according a Q2W schedule. At the first infusion of cetuximab the patient will receive a loading dose of 400mg/m2 The following doses will be 250mg/m2. The starting dose of RO6874281 will be 10 mg. Different dosing regimens (e.g., Q3W) may be explored in parallel, if warranted, on the basis of the safety and PK profile of RO6874281 in combination with cetuximab.

Study burden and risks

Zie E9

Contacts

Public
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NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age > 18 years
- Radiologically measurable and clinically evaluable disease
- Life expectancy of 12 weeks
- Confirmed at least one tumor lesion with location accessible to safely biopsy per clinical judgment of the treating physician and the participant*s consented willingness to undergo baseline and on-treatment tumor biopsies for PD biomarker analysis
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
- Patients with unilateral pleural effusion (other than non-small cell lung cancer [NSCLC] indication) should fulfill Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification 0-1 level and New York Health Association (NYHA) classification class 1 criteria for pulmonary and cardiac functions

- Adequate cardiovascular, hematological, liver and renal function
- All acute toxic effects of any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade 1, except alopecia (any grade) and Grade 2 peripheral neuropathy
- Negative serum pregnancy test within 7 days prior to study treatment in premenopausal women and women 12 months after menopause;
- For women who are not postmenopausal and have not undergone surgical sterilization: agreement to remain abstinent or use two adequate non hormonal methods of contraception, including at least one method with a failure rate of 1% per year, during the treatment period and for at least 4 months after the last dose of study drug for RO6874281, and for at least 7 months after the last dose of trastuzumab. For cetuximab, please refer to local prescribing information for cetuximab
- For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm during the treatment period and for at least for at least 2 months after the last dose of study drug or study treatment;
- Patients with Gilbert*s syndrome will be eligible for the study;
- For Part A exclusively (RO6874281 monotherapy), confirmed advanced and/or metastatic solid tumor, with at least one tumor lesion of location accessible to biopsy per clinical judgment of the treating physician, and confirmed progression at baseline; for whom no effective standard therapy that would confer clinical benefit to the patient exists
- For Part B exclusively (RO6874281 in combination with trastuzumab), patients with metastatic or recurrent or locally advanced HER2-positive breast cancer, as defined by the College of American Pathologist HER2 testing guidelines, who have progressed on at least two lines of HER2-directed therapies in the metastatic setting and the last therapy prior to going on study has to contain a HER2-directed antibody.
- Baseline LVEF of ><= 50% (measured by echocardiography) predose on Cycle 1 Day 1
- For Part C exclusively (RO6874281 in combination with cetuximab), Patients with recurrent, unresectable or metastatic squamous cell carcinoma of the head and neck. Patients can have had standard or experimental treatment, including but not limited to radiation therapy, chemotherapy, immunotherapies (excluding IL-2 compounds).

Exclusion criteria

Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.
* Symptomatic or untreated CNS metastases.
* History of treated asymptomatic CNS metastases with any of the following criteria:
o Metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
o History of intracranial hemorrhage or spinal cord hemorrhage
o Lacking radiographic demonstration of improvement upon the completion of CNS-directed therapy and evidence of interim progression between the completion of CNS-directed therapy and the baseline radiographic study
o Ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dosage are allowed

o Stereotactic radiation or whole-brain radiation within 28 days before study treatment administration
o Last CNS radiographic study < 4 weeks since completion of radiotherapy and < 2 weeks since discontinuation of corticosteroids
o CNS metastases treated by neurosurgical resection or brain biopsy performed within 28 days before study treatment administration
- Patients with an active second malignancy
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, and known autoimmune diseases or other disease with ongoing fibrosis
- Patients (all indications) with confirmed bilateral pleural effusion and NSCLC patients with confirmed uni-or bilateral pleural effusion by X-ray are not eligible
- Significant cardiovascular/cerebrovascular vascular disease within 6 months prior to Day 1 of study drug administration
- Active or uncontrolled infections
- Known HIV, HBV, or hepatitis C (HCV) virus infection
- Positive serology for hepatitis B (only for Parts B and C)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection or any major episode of infection requiring treatment with intravenous antibiotics or hospitalization within 4 weeks prior to the start of drug administration
- History of chronic liver disease or evidence of hepatic cirrhosis
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug
- Major surgery or significant traumatic injury < 28 days prior to the first RO6874281 infusion (excluding biopsies) or anticipation of the need for major surgery during study treatment
- Dementia or altered mental status that would prohibit informed consent
- Pregnant or breastfeeding women
- Known hypersensitivity to any of the components of RO6874281
- Concurrent therapy with any other investigational drug
- Immunomodulating agents
- Radiotherapy within the last 4 weeks before start of study drug treatment, with the exception of limited field palliative radiotherapy
- History of progressive multifocal leukoencephalopathy
- Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy
- For Part B, exclusively, known hypersensitivity to any of the components of trastuzumab
- For Part C, exclusively, known hypersensitivity to any of the components of cetuximab
- For Parts A, B, and C, eligibility of patients who require blood transfusion before and after the start of the study treatment should be discussed by the Sponsor and investigator

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):	28-12-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	Cetuximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-09-2015
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	17-12-2015
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	14-07-2016

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-03-2017

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-02-2021

Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-002251-97-NL
CCMO	NL54808.031.15

Study results