A Phase I Multiple Ascending Dose (MAD) Study of RO5458640, a Humanized Monoclonal Antibody Against the TNF-like Weak Inducer of Apoptosis (TWEAK) Ligand, in Patients with Advanced Solid Cancers

Published: 02-05-2011
Last updated: 29-04-2024

RO5458640 is an investigational therapy being studied by Hoffmann La Roche, Inc. and the Dutch Cancer Institute for treating solid tumor cancers. This study is looking for approximately 100 subjects with advanced solid tumors.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38050

Source
ToetsingOnline

Brief title
NP25448, TWEAK inhibitor

Condition

- Other condition

Synonym
cancer, solid tumors

Health condition

geavanceerde en/of gemetastaseerde 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 Inc.

Intervention

Keyword: Advanced, Solid, Tumors, TWEAK

Outcome measures

Primary outcome

To characterize the safety, maximum tolerated dose, dose limiting toxicities, and recommended phase II dose (RP2D) for RO5458640 given intravenously on 3 administration schedules in patients with locally advanced or metastatic solid tumors.

Secondary outcome

Secondary objectives:

1. To characterize RO5458640 pharmacokinetic profile (PK) on two administration schedules.

2. To assess response predictive markers of RO5458640 therapy:

• Plasma TWEAK

• Fn14 receptor expression from archival tissue and/or pre-study biopsy

• Additional tumor characteristics which may be assessed for correlation with RO5458640 response or resistance include Fn14 mutations, Fn14 gene amplification, and constitutive NF*B pathway activation.

3. To describe anti-tumor activity according to RECIST 1.1

4. To evaluate antigenicity in response to RO5458640 treatment (Human anti-human antibody [HAHA] profile)

5. To characterize pharmacodynamic (PD) profiles in peripheral blood and tumor tissue samples in response to treatment with RO5458640. Functional imaging will also be assessed via [18F] - FDG PET/CT Assessments in peripheral blood may include baseline and posttreatment blood sampling for:

• Target modulation: TWEAK ligand (ELISA)

• Downregulation of NF*B transcription products: Cytokines IL-8 and CCL-2

• Investigation of pro-apoptotic MOA: Cleaved cytokeratin 18 and nucleosomal DNA

• Other soluble markers related to TWEAK:Fn14 signaling, including but not limited to IL-6, IL-7 and MMP-9

PD Assessments in Tumor Tissue:

Collection of pre and post treatment paired tumor biopsies are required for all patients. Assessments may include, but are not limited to the following:

• Target modulation: Fn14 expression

• Investigation of pro-apoptotic MOA: cPARP, TUNEL, cleaved caspace 3, cleaved cytokeratin 18

• Antiproliferative effects: pERK and Ki67

• Pathway modulation: TRAF1 (proximal signaling marker)

• Additional markers related to TWEAK:Fn14 signaling may be considered, including but not limited to: CSF2, BIRC3, MMP9, CD68, pAKT , CD31 and gross

vessel morphology (anti-angiogenic effects)

Please see Tables 8, 9 , 10 and 11 in the study protocol for details related to schedule of tumor biopsies.

Imaging:

Uptake and retention of [18F]-FDG will be measured by PET/CT imaging in all patients. (see Section 5.2.5.3.3)

Exploratory Objectives:

The Roche Clinical Repository (RCR) is a centrally administered facility for long term storage of human biological specimens including body fluids, solid tissues and derivatives thereof (e.g. DNA, RNA,proteins/peptides). Specimens stored in the RCR will used to assess any of the following:

• Study associations of biomarkers with efficacy and/or adverse events associated with medicinal products

• Increase knowledge and understanding of disease biology

• Develop biomarker and diagnostic assays and/or establish the performance characteristics of these assays (see Section 2.3)

Study description

Background summary

This is a study concerning RO5458640, an antibody-based therapy directed against the TWEAK (TNF-like Weak Inducer of Apoptosis) protein. It has been show in experiments in animals that blocking the TWEAK protein may reduce tumor growth. The purpose of this first-in-human study is to learn more about how

RO5458640 works in patients with advanced solid tumors.

Study objective

RO5458640 is an investigational therapy being studied by Hoffmann La Roche, Inc. and the Dutch Cancer Institute for treating solid tumor cancers. This study is looking for approximately 100 subjects with advanced solid tumors.

Study design

The study is an open-label, multicenter phase Ia dose escalation of RO5458640 on two schedules. At the commencement of the study groups of 3 to 6 patients will be enrolled in escalating dose levels of RO5458640 administered on a once weekly schedule. A Q 3 weekly schedule will be introduced after two dose levels have been evaluated for PK, PD and safety parameters in the once weekly schedule. For both schedules, treatment cycles will be 3 weeks duration. In amendment C a Q 2 weekly schedule was added to the protocol. The duration of this treatment cycle will be 4 weeks duration (28 days). Cohorts will be enrolled in a 3+3 design with expansions of up to 20 patients conducted for one or both schedules in order to provide additional characterization of safety, PK, PD profiles, and preliminary efficacy at RP2D.

Intervention

Eligible patients will be treated with RO5458640, and will follow the study specific schedule as stated in table 12, 13 en14 (page 58 to 63 of the study protocol).

Study burden and risks

There are risks, discomforts and inconveniences associated with any research study. The following problems may be caused by RO5458640 while while a subject is on this study:

- The study procedures and treatments may have risks and cause discomfort. There is the risk of slight pain or bruising when your blood is drawn. Drawing blood may cause some people to faint.
- Tumor biopsies are to be obtained at two points on this study. There are risks associated with a tumor biopsy, including but not limited to: bruising, bleeding, infection, and side effects from any anesthesia medication that may be administered the patient for the procedure. In very rare cases, these risks may be life-threatening.
- Having an MRI or PET-/CT scan could mean some added discomfort to the patient. In particular, the patient may be bothered by feelings of claustrophobia (a *closed-in* feeling) and the noise during the test.

RO5458640
There have been no previous human studies of RO5458640. Extensive laboratory research has not suggested organ specific side effects with RO5458640 therapy. However, RO5458640 has the potential to react with other tissues in the patients body besides the cancer. It is possible that the patient may experience side effects to RO5458640 that have not been predicted by the preclinical studies. These effects of RO5458640 may be mild, moderate, severe, or in rare cases, life-threatening or even fatal. The patient should be aware that there are groups of side effects common to all antibody-based therapies, therefore potential risks of RO5458640 treatment include:
• An allergic or infusion related reaction to study medication, which may be mild (skin rash, fever, chills, headache, nausea or vomiting) or severe (low blood pressure, rapid heart rate, anxiety, and /or difficulty swallowing or breathing). These side effects most commonly occur during the first few treatments, but may occur with any infusion. The doctor may prescribe medications and other supportive care to lessen the severity of these symptoms. Medications may also be given prior to treatment to prevent these effects. In rare cases these symptoms may be so severe that the patient may need to be permanently withdrawn from study treatments.
• The development of antibodies to the study medication. Occasionally, there may be progressive side effects that occur after exposure to the study treatments over time due to the development of these antibodies. Most commonly, these side effects include rash, joint and muscle aches, fevers, and fatigue. The doctor may prescribe medications to lessen the effect of these symptoms. If these effects are severe or very prolonged, it may be necessary for the patient to be permanently withdrawn from study treatments.
• Potential for cardiovascular effects. The preclinical studies in lab animals have not shown RO5458640 to affect cardiovascular tissue. However, the patient will be closely monitored for any effects during the course of the study, including multiple electrocardiograms before and during the time on study as previously described. In some cases, the doctor may also order additional testing.
• Potential for medication interactions. No studies have currently been conducted to investigate the effect of RO5458640 therapy with other medications. It is possible RO5458640 therapy may reduce or increase the blood levels of another drug during the study treatments. Therefore, the doctor will record the co-medications and monitor the clinical course with blood tests and exams during the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Histologically or cytologically confirmed malignant solid tumors that are refractory or resistant to available therapies, or for which current therapy is not considered to provide benefit.;2) Patients must have measurable and/or evaluable disease;3) Tumor expression of the Fn14 receptor;4) Age >= 18 years;5) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;6) Estimated life expectancy of >= 12 weeks;7) Adequate bone marrow function, defined as ANC >=1.5 x 109/L, platelets > 100 x 109/L, and hemoglobin >=9.0 g/dL (5.6 mmol/L);8) Adequate liver function, defined as total bilirubin <1.5 x ULN, AST and ALT <= 2.5 x ULN (<= 5x ULN with hepatic metastases), and serum bilirubin <= 2.5 mg/dL (43 umol/L);9) Adequate renal function, defined as serum creatinine < 1.5 mg/dL (132 umol/L) or creatinine clearance estimate >=60 mL/min [1.00mL/s/m2] (according to Cockroft-Gault formula, Appendix 5) ;10) Women of childbearing potential and women less than 2 years after menopause must have a negative pregnancy test result within 72 hours prior to receipt of study treatments.;11) Patients must be willing to use effective methods of contraception throughout study participation and for at least 90 days after the last dose of study medication.
Female patients must be postmenopausal, surgically sterile, or agree to use physical barrier method of contraception. Oral or injectable agents must not be the sole method of contraception. Male patients must be surgically sterile or agree to use barrier method of

contraception. ;12) Patients (or legal representative) must be willing and able to provide written informed consent.;13) Patients must be able and willing to comply with protocol requirements as determined by the study investigator. This includes study requirements for clinic visits, safety assessments, and consent for paired tumor biopsies as defined in Section 2.2 of the study protocol.

Exclusion criteria

1) Treatment with any investigational agent within 21 days prior to first dose of study treatment ;2) Prior chemotherapy, radiotherapy, or hormonal therapy for cancer within 3 weeks of first study treatment ;3) Receipt of antibody therapy or other immunotherapy currently or less than 21 days prior to study treatments, including interferons α or β, IL-2, etanercept, infliximab, adalimumab, golimumab, certolizumag pegol, cyclosporine, tacrolimus, and alefacept;4) Current immunosuppressive therapy, including those prescribed for organ transplantation and rheumatologic disease ;5) Corticosteroid therapy except for physiologic replacement dosages;6) Patients who have not recovered (> grade 1 NCI CTCAE severity) from prior adverse events related to any cancer therapy. An exception is made for alopecia. ;7) Pregnant or breast feeding women;8) Surgical procedure or clinically significant trauma within three weeks of study treatments. ;9) Known hypersensitivity to any component of RO5458640 or patients with previous severe hypersensitivity reactions to monoclonal antibody therapy.;10) History of active seizure disorder (event <= 2 months prior to study initiation or seizures not controlled with medication).;11)History of CNS or leptomeningeal metastases, except clinically stable disease characterized by ALL of the following: a) surgical resection or radiotherapy completed >= 3 months prior to first study drug, b) no corticosteroid requirements for >= 4 weeks prior to first study drug, c) stable CNS disease assessed by CT or MRI within 4 weeks of study drug, d) stable neurologic exam (no new focal or global abnormalities) for at least 4 weeks prior to first study drug. To confirm eligibility, a discussion between the Investigator and Sponsor is required for patients with CNS tumor. ;12) Serious cardiovascular illness, including but not limited to a) CVA or MI within 6 months of study initiation, b) CHF >= NYHA Class 2, unstable angina, symptomatic or otherwise uncontrolled arrhythmia requiring medication (does not include stable, lone atrial fibrillation), QTcF > 480 msecs (Fredericia correction method will be the primary evaluation parameter throughout the study), or uncontrolled hypertension;13) Active infection;14) Other uncontrolled, concurrent disease, including diabetes mellitus, pulmonary (clinically significant hypoxia requiring chronic, supplemental oxygen therapy), or altered mental status or psychiatric illness that would limit compliance with study requirements;15) A physical exam or laboratory finding that contra-indicates the use of investigational therapy or otherwise places the patient at excessively high risk for treatment, as determined by the study investigator. A discussion between the Investigator and Sponsor regarding eligibility is encouraged for such cases.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-10-2011
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	02-05-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-06-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	06-06-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-06-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-07-2012
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	EUCTR2010-022933-27-NL
Other	EUDRACT: 2010-022933-27, zo is de studie te vinden op www.rochetrials.com zodra de studie is goedgekeurd
CCMO	NL36450.031.11