A multi-center, open-label, first-in-human, phase I dose-escalation study of single agent RO5503781, a small molecule MDM2 inhibitor, administered orally in patients with advanced malignancies, except leukemia.

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Determine the Maximum Tolerated Dose (MTD) of two different schedules given every 28 days to fasted patients: Schedule A: RO5503781 once weekly x 3 OR Schedule B: RO5503781 daily x 5.

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

Summary

ID

NL-OMON37762

Source
ToetsingOnline

Brief title
NP27872

Condition

- Other condition

Synonym
cancer, malignancies

Health condition

alle gevorderde maligniteiten, behalve leukemie

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: sponsor F.Hoffmann-La Roche

Intervention

Keyword: advanced malignancies, except leukemia, first-in-human, small molecule MDM2 antagonist

Outcome measures

Primary outcome

Determine the Maximum Tolerated Dose (MTD) of two different schedules given

every 28 days to fasted patients.

Characterize the DLTs (dose limited toxicities) and overall safety profile of

escalated dose levels of the compound.

Explore the two dosing regimens for safety and tolerability.

Secondary outcome

Determine the pharmacokinetic (PK) parameters of the compound (and its major

metabolites, if warranted) on two different drug administration schedules.

Assess PD effects (in blood, tumor biopsies and molecular imaging) of the

compound.

Assess any clinical responses.

Expand PK evaluation on the weekly schedule (at a dose level below the MTD) for

food effect evaluation, PD, and safety data in patients.

Study description

Background summary

This is a first-in-human study to investigate the maximum tolerated dose of RO5503781 in patients with advanced malignancies, except leukemia. Preclinical studies have identified that human tumors with over-expression of MDM2, may benefit the most from this novel therapeutic strategy that prevents p53 from MDM2 degradation. MDM2 regulates p53 through a negative feedback loop. Treatment of cancer cells expressing wild-type p53 with RO5503781 stabilizes p53 and activates the p53 pathway leading to activation of p53 target genes, cell cycle arrest, and apoptosis. In view of the existing unmet medical need in advanced cancers with the above molecular signature, RO5503781 is believed to be a promising agent that may offer a new therapeutic option for patients.

Study objective

Determine the Maximum Tolerated Dose (MTD) of two different schedules given every 28 days to fasted patients: Schedule A: RO5503781 once weekly x 3 OR Schedule B: RO5503781 daily x 5.

Study design

A multi-center, open-label, first-in-human, phase I dose-escalation study of single agent RO5503781, administered orally in two different drug administration schedules.

Intervention

Eligible patients will be treated with RO5503781, and will follow the study specific schedule as stated in table 4 (QWx3, page 56 of the study protocol) or table 5 (QDx5, page 58 of the study protocol).

Study burden and risks

This study drug RO5503781 has been shown to be safe in animal studies. However it has never been studied in humans before this research study and its side effects are not fully known. There may be some risks, discomforts and inconveniences associated with current research study. Based on clinical experience with new drug development and the research studies of the study drug RO5503781 in the animal (mice, rat and monkey), patients may experience the following: decreased platelets; low white blood cell counts; liver function abnormalities ; Photosensitivity ; fast heart beat; nausea, vomiting and diarrhea.
In addition, you may experience an allergic reaction to the study drug. These

reactions can sometimes be life-threatening or even fatal if severe.

Procedures
Blood draws: There is the risk of slight pain or bruising when your blood is drawn. Drawing blood may cause some people to faint. You may be asked to have a central venous catheter (CVC) placed in a vein for the required blood drawings. The placement of such a catheter may be associated with an increased risk of infection and/or local discomfort.
ECG: The glue used to keep the electrodes in the place during the ECG may irritate your skin and caused redness.
MRI Scan: 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 you experience allergic symptoms, a radiologist or other physician will be available for immediate assistance.
CT Scan: Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. Every CT scan as part of tumor assessments will expose you to about 5 years* worth of natural radiation.
[18F] FLT-PET/CT Scan (Biomarker Cohorts only):
Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. Every FLT-PET or FLT-PET/CT scan gives your body the equivalent of about 2 extra years' worth of this natural radiation. Every CT scan as part of tumor assessments will expose you to about 5 years* worth of natural radiation. The radiation dose that has been described here is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests.
In order to better see internal structures of your body during the imaging study, you will have an injection of contrast media (*dye*). Infrequently, needle (catheter) may slip out the vein during the injection. The injected contrast media goes into the tissues and may causes local pain. This is usually treated with appropriate compresses.
Some systemic reaction may occur, such as a metallic taste, nausea, vomiting, and hives. This is usually limited. Very infrequently, there is difficulty in breathing, low blood pressure and dizziness that requires appropriate treatment. Severe reactions leading to death are extremely rare. If you have allergies, the possibility of reactions is higher than in patients without allergies. If applicable, and in consultation with your doctor, you may have to pre-medicate to decrease the possibility of these complications.
Tumor Biopsy (Biomarker Cohorts only): Risks include pain, discomfort, soreness, redness, swelling, bleeding, bruising, and/or drainage at the biopsy site, abnormal wound healing, fever, infection, or allergic reaction to the medication used to numb the skin over the biopsy site.

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. Patient must have histologically or cytologically confirmed advanced malignancies, except all forms of leukemia, for which standard curative or palliative measures do not exist, are no longer effective, or are not acceptable to the patient.;2. Measureable disease (by RECIST criteria version 1.1 for solid tumors or by Cheson Criteria for malignant lymphomas or evaluable disease prior to the administration of study drug.;3. Patients must be willing to provide archival tumor tissue for biomarker testing (if available). ;4. Ability to understand and the willingness to sign a written informed consent form and comply with all study requirements.;5. Life expectancy of >=12 weeks.;6. Minimum weight of 35 kg.;7. Age >= 18 years.;8. ECOG performance status of 0 to 1.;9. Female patients with child-bearing potential and post menopausal females with less than two years of amenorrhea must have a negative serum pregnancy test within 72 hours of the study first drug administration. ;10. Patient must be willing to use effective methods of contraception. Female patients must be

postmenopausal (defined as two years of amenorrhea), surgically sterile, or they must agree to use a physical barrier method of contraception. Oral or injectable contraceptive agents cannot be the sole method of contraception. Male patients must be surgically sterile or agree to use acceptable method of contraception.;Country Specific Requirement for France: All patients must be willing to use effective methods of contraception while receiving study treatment and for 10 days after the last dose of RO5503781. Female patients must be postmenopausal (>=2 years of amenorrhea), surgically sterile, or they must agree to use a physical barrier method of contraception. Oral or injectable contraceptive agents can not be the sole method of contraception. Male patients must be surgically sterile or agree to use acceptable method of contraception.;11. There are no limitations on additional, allowable type and amount of prior anti-tumor therapy. Acute toxicities from any prior anti-tumor therapy, surgery, or radiotherapy must have resolved to NCI-CTCAE Grade <= 1. Care should be taken for patients who have developed cytopenias with prior radiotherapy to assure adequate bone marrow recovery prior to study initiation. The last dose of prior therapy must be >= 21 days prior the first administration of study drug RO5503781 (or >=5 x terminal half-life of the therapy for any therapy given less than 21 days previously). ;12. Adequate bone marrow function as defined by:;• ANC of >= 1.5 x 109/L. ;• Platelets count >= lower limit of normal ;• Hemoglobin of >= 9.0 g/dl. ;13. Adequate hepatic function assessed by: ;• Serum total bilirubin <= 2 mg/dl, unless resulting from hemolysis or known Gilbert*s disease.;• AST/ALT <= 2.5 x institutional ULN (or <= 5 x ULN if liver metastases). ;14. Adequate renal function assessed by Serum creatinine within reference lab normal limits OR creatinine clearance >= 50 calculated by Cockcroft Gault (if in the PI judgment, serum creatinine level may not adequately reflect renal function). ;15. Patients with stable CNS metastases (have had therapy or don*t require therapy, are off steroids, have no change on screening CT or MRI and are asymptomatic), are eligible. ;16. Patients with chronic, stable and rate-controlled Atrial Fibrillation are eligible.;17. Biomarker Cohorts and Apoptosis Imaging;Cohort ONLY: Patients in consideration for the;biomarker cohort or apoptosis imaging cohort;(Netherlands Only) must consent and be able to;undergo paired biopsies for tumor biomarker;analyses.;18. Biomarker Cohorts and Apoptosis Imaging;Cohort ONLY: patient*s tumor size must be >= 2;cm and must consent to undergo [18F]-FLT-PET;imaging (biomarker cohort only), or [18F]-FLTPET;imaging and [18F]CP18 imaging (apoptosis;imaging cohort).;19. Apoptosis Imaging Cohort (Netherlands Only):;Patients must consent to provide all CT scans;up to 6 months prior to entering the study, if;available.

Exclusion criteria

1. Patients with history of any form of leukemia except for Stage 0 and 1 chronic lymphocytic leukemia (CLL) not requiring treatment in addition to their underlying solid tumor.;2. Patients who have received hormonal therapy within the 2 weeks prior to the first dose of study medication. Patients with prostate cancer who are not surgically castrated should remain on GnRH analogues. ;3. Patients who are using other investigational agents or who had received investigational drugs <= 4 weeks prior to study treatment start.;4. Patients with pre-existing GI disorders that may interfere with proper absorption of the drug(s), as per investigator discretion.;5. Patients with history of allergic reactions attributed to components of the formulated product.;6. Patients with history of seizure disorders or unstable CNS metastases.

;7. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:;• unstable angina, symptomatic or otherwise uncontrolled arrhythmia requiring medication (does not include stable, lone atrial fibrillation), QTcF > 480 msecs based on the average of 3 screening ECG*s , uncontrolled hypertension., symptomatic congestive heart failure (NYHA II, III, IV), myocardial infarction <= 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia, cerebrovascular accidents <= 6 months before study treatment start.;• any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study. ;• nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study treatment, such as, severe diabetes mellitus that is not controlled with medical management.;8. Patients who must receive CYP2C8 inhibitors, substrates or inducers, strong CYP 3A4 inducers or moderate/strong CYP3A4 inhibitors listed in protocol while on study. Substrates and Inhibitors listed in protocol must be discontinued 7 days prior to start of study medication. Inducers found in protocol must be discontinued 14 days prior to start of study medication.;9. Patients with evidence of electrolyte imbalance such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade >= 2, as per NCI-CTCAE, version 4.03. Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility. ;10. Pregnant or breast feeding patients.;11. Patients with reproductive potential not willing to use effective method of contraception.;Country Specific Requirement for France: Patients with reproductive potential not willing to use effective methods of contraception while receiving study treatment and for 10 days after the last dose of RO5503781.;12. HIV-positive patients who are currently receiving combination anti-retroviral therapy.;13. Patients with known coagulopathy, platelet disorder or history of non-drug induced thrombocytopenia.;14. Patients receiving oral or parenteral anticoagulants/antiplatelet agents (e.g. chronic daily treatment with aspirin (> 325 mg/day), clopidogrel or subcutaneous anticoagulant prophylaxis). Patients may receive anticoagulant flushes for maintenance of indwelling catheters.;15. Patients who refuse to potentially receive blood products and/or have a hypersensitivity to blood products.;16. Patients with known bone marrow disorders which may interfere with bone marrow recovery, (i.e. tumor involvement, fibrosis), or patients with delayed recovery from prior chemoradiotherapy (i.e. after radiation to the pelvis).;17. 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.;18. Biomarker Cohorts and Apoptosis Imaging;Cohorts ONLY: patients who have had a;hypersensitivity reaction to FLT or 18F will be;excluded from having an [18F]-FLT-PET scan.;19. Apoptosis Imaging Cohort ONLY (Netherlands;Only): patients who have had a hypersensitivity;reaction to [18F]CP18 or CP18 will be excluded;from this cohort.

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):	17-02-2012
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	01-09-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-01-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	De studie zal na goedkeuring opgenomen worden op www.rochtrials.com
EudraCT	EUCTR2011-002767-15-NL
CCMO	NL37870.042.11