A phase I, open label, multicenter, dose-escalation study of oral HDM201 in adult patients with advanced solid and hematological tumors characterized by wild-type TP53

Published: 07-07-2014
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Primary objective To determine the MTD and/or to identify the RDE of HDM201 in one or more of the pre-defined regimensSecondary objectives * To characterize the safety and tolerability of HDM201* To characterize the pharmacokinetic (PK) properties…

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

Summary

ID

NL-OMON46915

Source
ToetsingOnline

Brief title
Phase I study of HDM201 in solid and hematological tumors (WT- P53)

Condition

- Leukaemias
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid and hematologic tumors

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutisch Industrie

Intervention

Keyword: HDM201, Phase I, Wild-type TP53

Outcome measures

Primary outcome

To determine the MTD and/or to identify the RDE of HDM201 in one or more of the pre-defined regimens as measured by Incidence of Dose Limiting Toxicities (DLTs) during the first cycle of treatment.

Secondary outcome

* To characterize the safety and tolerability of HDM201 as measured by Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECG, dose interruptions, reductions and dose intensity.
* To characterize the pharmacokinetic (PK) properties of HDM201 and potential metabolites when feasible, measured by Time vs. plasma concentration profiles, PK parameters of HDM201 and potential metabolites when feasible.
* To assess the pharmacodynamics (PD) effect of HDM201 and a potential relationship with clinical outcome as measured by Changes from baseline of PD markers:

o In tumor tissue (e.g. p21, PUMA, HDM2)

o In blood (e.g. GDF-15).

* To assess the preliminary antitumor activity of HDM201 in solid tumors as measured by Tumor response assessed by investigator per RECIST 1.1 (BOR, DOR,

PFS).

* To assess the preliminary antitumor activity of HDM201 in hematological

malignancies as measured by Tumor response assessed by investigator per

clinical benefit: BOR, DOR.

Study description

Background summary

A hallmark of cancer is its ability to continuously proliferate and escape apoptosis. The protein p53 (and its encoding gene TP53) has shown to possess a tumor-suppressing function. Under physiological conditions, the activation of the p53 pathway(s) is tightly controlled. One of the most important negative regulators of p53 is Human Double Minute-2 (HDM2). This protein recognizes p53 as a target and directly binds to it, inhibiting its transactivation. After HDM2 binding to p53, the ability of p53 to function in this role is immediately blocked.
The function of p53 is frequently compromised in tumor cells, where inactivating mutations in TP53 are found in approximately 50% of all human cancers. The frequencies of reported TP53 mutations vary among cancer types, ranging from about 10% in hematopoietic malignancies to 50-70% in colorectal and head and neck cancers, and nearly 100% in high-grade pelvic serous carcinoma, a clinically important subtype of ovarian cancer.
In cancers in which the TP53 gene is not mutated, the function of the p53 pathway is often suppressed owing to perturbation of its associated pathways through mechanisms that affect its stability and activity, with overexpression of HDM2 or silencing of p14ARF being two clinically important mechanisms.

HDM201 is the second-generation HDM2-p53 interaction inhibitor from Novartis, 8 to 10 times more potent than the first generation inhibitor, for which the observed safety profile so far (during dose escalation) has been considered favorable.
The approach taken in this protocol is to pharmacologically activate p53 with HDM201 by increasing its intracellular concentration and thereby to activate downstream effector pathways that decrease cell proliferative events. This mode of action depends crucially on wild-type TP53.

Study objective

Primary objective
To determine the MTD and/or to identify the RDE of HDM201 in one or more of the

pre-defined regimens
Secondary objectives
* To characterize the safety and tolerability of HDM201
* To characterize the pharmacokinetic (PK) properties of HDM201 and potential metabolites when feasible
* To assess the pharmacodynamics (PD) effect of HDM201 and a potential relationship with clinical outcome
* To assess the preliminary antitumor activity of HDM201 in solid tumors
* To assess the preliminary antitumor activity of HDM201 in hematological malignancies

Study design

This is a multi-center, open-label, dose-finding, phase I study of oral single agent HDM201, administered orally in patients with advanced tumors who have progressed despite standard therapy or for whom no standard therapy exists. Two regimens characterized by different dosing frequency and cycle length will be explored in parallel:
* Regimen 1A: once every 3 weeks (3 week cycle)
* Regimen 2A: once daily for two weeks followed by two weeks off treatment (4 week cycle)

Intervention

HDM201 will be administered orally. Two regimens (regimen 1A and regimen 2A) will be investigated in parallel. The starting dose for the first cohort of patients treated with regimen 1A will be 12.5 mg, given once every three weeks. The starting dose for the first cohort of patients treated with regimen 2A will be 1 mg, given daily for two weeks, followed by two weeks off treatment. The subsequent dose levels will be decided based on data generated during the study.

Study burden and risks

Compared to regular treatment, more, and more often, tests and exams will take place. For the patient*s safety more ECGs will be made, more and more often blood will be drawn and the patient will have to visit the hospital more often. Additional heart exams (echocardiogram or MUGA-scan) will be performed. At the start of the study, and during the study, if feasible a tumor biopsy will be performed. To better assess the effect on the tumor, CT- or MRI-scans will be performed more often. Generally, the duration of the visits to the hospital will extend from 1 to 4 hours, because of the extra tests and exams done. On the days extensive blood sampling for pharmacokinetics will take place, a visit will last for about 9 hours. The frequency of the several tests is further described in attachment B1 and B2 of the patient information.
Risks are possible side effects of study medicine, and those from the tests the

patient is asked to do. The risks are further described in attachment C of the patient information.

Contacts

Public
Novartis

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NL
Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- ECOG performance status 0-2
- Locally advanced or metastatic solid malignancy, that has progressed despite standardtherapy, or for which no effective standard therapy exists. Lymphomas are excluded.
- Refractory/relapse non-M3 AML ,
- High and very high risk MDS - IPSS-R (International Prognostic Scoring System) score of > 4.5
- Acute Lymphoblastic Leukemia (B-ALL or T-ALL) including Ph+ ALL, or previously untreated

patients who are considered inappropriate candidates for standard induction therapy
* Tumor of the patient is TP53wt (minimum no mutations in exons 5, 6, 7 and 8)
For solid tumor the TP53 status was obtained from a tumor sample collected no longer than 36 months before screening.
for hematologic tumors the TP53 status was obtained from a bone-marrow aspirate or extra medullary site, collected no longer than 3 months before screening.;* Tumor of the patient is TP53wt (minimum no mutations in exons 5, 6, 7 and 8):
For solid tumor the TP53 status was obtained from a tumor sample collected no longer than 36 months before screening except if HDM2 amplification is documented (irrespectively the date) or EBV positive gastric cancer. ;For hematologic tumors the TP53 status was obtained from a bone-marrow aspirate or extra medullary site, collected no longer than 3 months before screening.

Exclusion criteria

* Prior treatment with compounds with the same mode of action as proposed for HDM201,
* Symptomatic CNS metastasis (NB: Patients with CNS metastases are eligible for thisstudy only if they are asymptomatic, off corticosteroids, and radiographically stable for at least 2 months).
* Concurrent other malignancy. Exceptions to this exclusion criteria include: adequately treated basal cell or squamous cell skin cancer; in situ carcinoma of the cervix
* Patients with significant or uncontrolled cardiovascular disease (e.g. uncontrolled hypertension, peripheral vascular disease, congestive heart failure, cardiac arrhythmia, or acute coronary syndrome) within 6 months of starting study treatment or heart attack within 12 months of starting study treatment
* History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism
* Diagnosis of acute or chronic pancreatitis
* Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral HDM201
* Previous therapy that precludes enrollment < 2 weeks prior tostudy start: for details see protocol section 5.3 exclusion criteria #8.
Patients with hematological tumors
* WBC > 30 x109/L
* Platelets < 25 000/*L = 25 x 109 /L
* Hemoglobin < 8.0 g/dL = 4,96 mmol/L;Specific exclusion criteria for patients receiving eltrombopag
QTc <450msec or <480msec for patients with bundle branch block.

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):	01-10-2014
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	07-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-08-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	25-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2013-003521-28-NL
ClinicalTrials.gov	NCT02143635
CCMO	NL49179.041.14