A Phase I study of IDH305 in patients with advanced malignancies that harbor IDH1R132 mutations (CIDH305X2101)

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The main objective is to estimate the MTD(s) and/or RDE(s) of IDH305 in patients with IDH1R132 mutant malignancies, as measured by the incidence of dose-limiting toxicities.Secondary objectives are characterization of the safety, tolerability, PK...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON43902

Source
ToetsingOnline

Brief title
Phase I study of IDH305 in advanced malignancies with IDH1R132 mutations

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Advanced malignancies that harbor IDH1R132 mutations; IDH1R132 mutated cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: IDH1R132 mutations, IDH305, R-2-Hydroxyglutarate

Outcome measures

Primary outcome

Incidence rate of dose limiting toxicities (DLTs) during the first cycle of

IDH305 treatment.

Secondary outcome

-Safety: Incidence and severity of AEs and SAEs, including changes in

laboratory values, vital signs and ECGs.

-Tolerability: Dose interruptions and reductions.

-Plasma concentration versus time of IDH305 and PK parameters.

-Changes of 2-hydroxyglutarate concentration between pre and post-treatment

tumors and blood samples.

-Overall response rate (ORR) assessed by investigators per RANO for patients

with glioma, per RECIST version 1.1 for patients with cholangiocarcinoma/other

solid tumors, per IWG for patients with AML/MDS along with time-related

efficacy endpoints by disease area (PFS [progression-free survival] or EFS

[event-free survival], TTR [time to response] and DOR [duration of response])

Study description

Background summary

Specific somatic cancer mutations in IDH1 were originally identified in 2008. Cancers with high frequency of IDH1 mutation include: gliomas, cancers of the brain which impact ~ 28,000 patients a year with significant clinical morbidity and mortality; cholangiocarinoma, a cancer of the biliary tract with very poor

prognosis that is increasing in incidence; and AML, an aggressive leukemia from which 10,000 patients die each year. Additionally, IDH1 mutations have been identified at high frequency in chondrosarcoma, a rare cancer, and in low frequency in several common cancers including MDS, melanoma, breast, colon, and prostate cancers.

Since the initial identification of IDH1 mutations, studies have revealed the importance of mutant IDH1 (and subsequently analogous mutants of IDH2) as a cancer driver. Mutation of IDH1 at 132nd amino acid residue (R132*) alters its normal function. When mutated at this position, IDH1 no longer converts *-ketoglutarate to isocitrate, but rather to the metabolite 2-HG. Pre-clinical studies have established that the introduction of mutant IDH and the resultant accumulation of 2-HG levels can block normal cellular differentiation and contribute to tumorigenesis. The clinical relevance of these data has been recently established. Preliminary clinical data was recently reported from a Phase I clinical study of an inhibitor of IDH2, which is a paralog of IDH1 that also initiates cancer via the production of 2-HG. Of 24 evaluable patients with pre-treated IDH2 mutant AML, 14 clinical responses were observed, including 6 complete responses and 3 complete responses with incomplete recoveries. These data emphasize the clinical potential for targeting mutant IDH1-dependent production of 2-HG in advanced malignancies.

IDH305 is an orally available, brain-penetrant, mutant-selective allosteric IDH1 inhibitor that blocks mutant IDH1-dependent production of the *oncometabolite* 2-HG, and inhibits the proliferation of IDH1 mutant preclinical models. The primary purpose of this study is to evaluate the clinical safety profile and PK characteristics of IDH305 in cancer patients. In addition, based on the rationale that the inhibition of IDH1R132 and the subsequent reduction of 2-HG will have anti-proliferative effect, the potential for anti-tumor activity of IDH305 in a patients with IDH1 mutant malignancies will be explored. Results from this study will inform the clinical development of IDH305 in patients with IDH1 mutant cancer.

Study objective

The main objective is to estimate the MTD(s) and/or RDE(s) of IDH305 in patients with IDH1R132 mutant malignancies, as measured by the incidence of dose-limiting toxicities.
Secondary objectives are characterization of the safety, tolerability, PK profile, PD profile of IDH305 and to assess any preliminary anti-tumor activity of IDH305 in patients with glioma, cholangiocarcinoma/other solid tumors and AML/MDS.

Study design

This is an open-label, multi-center Phase I dose escalation followed by a dose

expansion in disease-specific cohorts.

Intervention

Treatment with IDH305.

Study burden and risks

Pre-screening:
Blood collection and/or tumor biopsy/bone marrow aspirate (if an archival tumor sample is not available)

Study:
- Possible toxicity derived from the study treatment. The known adverse events are documented in the informed consent form.
-The study assessments are used in routine practice: blood collection, imaging assessments (CT/MRI and X-ray), ECG, bone marrow aspirates, tumor biopsies. A flowchart with all these assessments can be found in the informed consent form.
-Adequate contraception
-Frequent (and possibly longer) study visits

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

Patients eligible for inclusion in this study have to meet all of the following criteria:
* Subject must be *18 years of age
* Patients with advanced malignancies whose tumors harbor IDHR132 mutations and for whom there are no curative therapy options who have progressed despite standard treatment.
* Availability of a representative tumor specimen (primary or metastatic, archival or newly obtained) for predictive and exploratory biomarker testing (eligibility will not be affected if a sample is not available or medically feasible to obtain).
* ECOG performance
* ECOG performance status * 2
* Measurable disease as per RECIST v1.1 (cholangiocarcinoma/other solid tumors), RANO criteria (glioma), IWG criteria (AML/MDS) in the dose expansion

Exclusion criteria

Exclusion Criteria for Patients with cholangiocarcinoma or other solid tumors and gliomas: Patients eligible for this study must not meet any of the following criteria prior to the first treatment.
* Prior treatment with a mutant-specific IDH1 inhibitor (with the exception of glioma patients)
* Major surgery within the 2 weeks preceding the first dose IDH305
* Patients who require medications that are narrow therapeutic index substrates of CYP3A, CYP2C9, CYP2C19, and CYP2C8 or strong inhibitors and strong inducers of CYP3A
* Rapidly progressing neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Steroid use for management of gliomas or brain metastases is allowed but the dose must be stable for at least 1 week preceding the baseline MRI/CT. If the corticosteroid dose is increased between the date of imaging and the initiation of study treatment, a new baseline MRI/CT is required.
* Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within the prior 2 years; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type
* Patients with corrected QT using the Fridericia correction (QTcF) > 470 msec, or other clinically significant, uncontrolled heart disease, including acute myocardial infarction or unstable angina < 3 months prior to the first dose of IDH305

* Any other medical condition that would, in the investigator*s judgment, prevent the patient*s participation in the clinical study due to safety concerns or compliance with clinical study procedures such as the presence of other clinically significant cardiac, respiratory, gastrointestinal, renal, hepatic or neurological disease
* Patient*s with Gilbert*s syndrome or other heritable disorders of bile processing
* Patients with Acute Promyelocytic Leukemia
* Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment
* Sexually active males must use a condom during intercourse while taking the drug and for 70 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid

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):	30-07-2015
Enrollment:	17
Type:	Actual

Ethics review

Approved WMO

Date:	01-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	12-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-12-2017
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
EudraCT	EUCTR2014-004069-26-NL
ClinicalTrials.gov	NCT02381886
CCMO	NL52665.029.15