A Phase I, multi-center, open label, dose escalation study of LEQ506, an oral Smoothened inhibitor, in patients with advanced solid tumors

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Primary objectiveTo determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities (DLT) of LEQ506 when administered orally on a continuous daily dosing schedule.Secondary objectives* To characterize the safety and…

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

Summary

ID

NL-OMON36627

Source
ToetsingOnline

Brief title
Phase I study with LEQ506, an oral smoothened inhibitor

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid tumors / different types of advanced cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: LEQ506, Phase I, Smoothened inhibitor, Solid tumor

Outcome measures

Primary outcome

Frequency of dose-limiting toxicities (DLTs)

Secondary outcome

* Safety: Adverse drug reactions and serious adverse drug reactions, changes in hematology and chemistry values (specifically those associated with hepatic and renal function), assessment of physical examinations, vital signs and ECG's

* Pharmacokinetics parameters

* Pharmacodynamics: Post-treatment changes in Gli1 mRNA expression in normal skin and tumor samples

* Efficacy: Tumor response using RECIST for patients with solid tumors and using the Neuro-Oncology Criteria of Tumor Response for patients with Medullo Blastoma

Study description

Background summary

LEQ506 is a potent and selective Smo (smoothened) antagonist. Smoothened (Smo) is a Gprotein-coupled receptor (GPCR)-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway.
Activation of the Hedgehog pathway without known mutations has been described for a number of different tumor types. There is evidence of activating

mutations in Hh pathway genes in Medulloblastoma and Basel Cell Carcinoma Growth of tumors driven by Hh signaling in xenograft models has been shown to be inhibited by treatment with Smo antagonist. malignancies. Smo inhibitors may therefore be useful in the treatment of a wide range of human malignancies. The proof of concept for the potential clinical utility of this class of agents has been established in patients with metastatic or locally advanced Basel Cell Carcinoma.

Study objective

Primary objective
To determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities (DLT) of LEQ506 when administered orally on a continuous daily dosing schedule.

Secondary objectives
* To characterize the safety and tolerability of LEQ506
* To characterize the PK of LEQ506 and any relevant metabolites
* To characterize the PD effects of LEQ506 by measuring Gli1 mRNA expression in normal skin and tumor samples
* To characterize any anti-tumor activity associated with LEQ506 treatment

Study design

A phase I, multi-center, open label dose escalation study of LEQ506, administered orally daily on a continuous 21-day dosing schedule.
The study starts with a PK run-in period, with administration of a single dose (SD) of LEQ506 on day 1 followed by serial PK sampling over the subsequent 5 days, will be included in the dose escalation
phase of this trial in order to characterize the SD PK profile of LEQ506.
This will be followed by the dose escalation phase. 3 to 6 patients will be enrolled in each cohort until MTD has been declared.
Individual patients may be considered for treatment at a dose of LEQ506.
After MTD has been declared enrollment to the safety expansion phase will be restricted to patients with tumors that are characterized by Hedgehog pathway activation, such as recurrent or refractory MB or locally advanced BCC.

Intervention

LEQ506, oral dosing, capsules
Starting dose: 80 mg/day

Study burden and risks

Side effects from LEQ506 seen in animal that might happen in human:.
* Abnormal laboratory findings in the kidneys and liver which could potentially

lead to
kidney or liver damage or failure.
* Nausea and vomiting, which can lead to dehydration
* Diarrhea, which can lead to dehydration
* Weakening of hair follicles leading to loss of hair
* Risk of inability to conceive and have children
* Risk of causing malformations in fetuses (unborn babies)
Taking blood and tumorbiopsies may cause pain, bleeding, and/or bruising.

Patients will be exposed to radiation (CT-scan, and X-rays). The radiation exposure will not exceed the maximum ranges that are set within the Netherlands.

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

- Dose escalation phase: patients with a with a histologically or cytologically confirmed solid tumor, who have progressed despite standard therapy or for which no standard therapy exists. Patients with recurrent or refractory Medullo Blastoma (MB) and patients with metastatic or locally advanced Basel Cell Carcinoma (BCC) that cannot be with local therapy.
- Expansion phase: patients with tumors that are characterized by Hedgehog pathway activation, such as recurrent or refractory MB or metastatic or locally advanced BCC
- WHO performance status *2.
- Required baseline laboratory values:
*Absolute Neutrophil Count *1.5x109/L
*Hemoglobin * 9 g/dl <= 5.58 mmol/l
*Platelets * 80x109/L
*AST/SGOT and ALT/SGPT * 2.5 x Upper Limit of Normal (ULN) or * 5.0 x ULN if liver metastases are present
*Serum bilirubin * 1.5 x ULN
*Serum creatinine * 1.5 x ULN or 24-hour clearance * 50 ml/min.
- Patients must have fully recovered from the effects of prior major surgery and from any acute toxic effects of prior chemotherapy and radiotherapy.
- A negative serum pregnancy test * 72 hours before starting study treatment

Exclusion criteria

- History of primary central nervous system tumors or symptomatic brain metastases (except recurrent MB). However, patients with resected brain metastasis with no radiological evidence of disease or with stable brain metastasis with no evidence of progression are eligible. Such patients must have no need for treatment with steroids or anti-epileptic medications.
- Known diagnosis of HIV or Hepatitis C
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LEQ506
- Any unresolved nausea, vomiting, or diarrhea CTCAE grade >1.
- Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
1) Acute myocardial infarction or angina pectoris * 3 months prior to starting study drug
2) QTcF > 450 msec for males and > 470 msec for females on screening ECG
3) Medical history of clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension)
- Any other concurrent severe and/or uncontrolled concomitant medical condition (e.g. uncontrolled diabetes, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection).
- Systemic anti-cancer treatment or radiotherapy < 2 weeks before the first dose of study treatment
(* 4 weeks for monoclonal antibodies).

- Prior treatment with investigational agents * 4 weeks or * 5 x their half-lives (whichever is longer) before the first dose of study treatment.
- Treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5
- Treatment with medications that are known to be substrates of CYP3A4/5 or CYP2C9 and that have low therapeutic indices.

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):	28-10-2010
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	05-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-08-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-10-2010
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-03-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-05-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-10-2013
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	EUCTR2009-017969-30-NL
ClinicalTrials.gov	NCT01106508
CCMO	NL32618.041.10