A Phase II, multi-center, open-label, single-arm study of the efficacy and safety of oral LDE225 in patients with Hh-pathway activated relapsed medulloblastoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON39614

Source
ToetsingOnline

Brief title
LDE225 in patients with Hh+ relapsed medulloblastoma

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Medulloblastoma; malignant brain tumor

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Hedgehog pathway inhibitor, LDE225, Relapsed medulloblastoma, Sonidegib

Outcome measures

Primary outcome

The overall response rate according to an independent review committee, defined as the proportion of patients with best overall response of complete response or partial response, as per tumor response guidelines and criteria for Medulloblastoma.

Secondary outcome

To investiagte the safety and efficacy of LDE225 with respect to ORR and PFS according to local investigator assessment

To assess the efficacy of each treatment on duration of response (DoR) according to both ICR and local investigator assessment

To assess the effect of each treatment on Overall survival (OS)

To further characterize safety and tolerability of each treatment

To further characterize the pharmacokinetics of LDE225 and any relevant metabolites

Study description

Background summary

In the US, between 350 and 500 new cases of pediatric and adult MBs are

diagnosed each year. In general, 30-40% of children with MB will experience recurrence after primary treatment compared with 50-60% of adult patients. There is currently no standard therapy after relapse and most patients will die of the disease. Median survival time after relapse is usually less than 12 months.
Mutations in the Hh pathway have been identified in approximately 20% to 30% of sporadic MBs. Thus, it is expected that LDE225, an oral Hh-pathway inhibitor, would most likely provide clinical benefit only in patients with Hh-pathway activated (Hh+) tumors.

Study objective

The primary objective is to investigate the safety and efficacy of LDE225 with respect to overall response rate according to independent central review (ICR). The key secondary objective is to assess LDE225 with respect to progression-free survival (PFS) according to ICR.

Study design

This study will evaluate the efficacy and safety of LDE225 in adult and pediatric patients with Hh+ relapsed MB, who have relapsed following prior standard-of-care therapy, including radiotherapy. Approximately 20 patients (adults and children combined) with Hh+ relapsed MB, as determined by the 5-gene Hh signature assay, will be included.

Intervention

LDE225 oral suspension (50mg/mL) will be used for both adult and pediatric patients and will be given on a daily basis for 4 weeks.

Study burden and risks

* Study duration in principle until disease progression. Thereafter follow-up for survival.
* The screening phase with extensive assessments. Weekly visits during the first 2 cycles and a monthly visit thereafter.
* Extra blood will be drawn during specific visits for PK-analysis, Coagulation, total CK, pregnancy test (if applicable), bone biomarker, germline genetic status.
* Urine collection for catilage biomarker (<18 years only)
* Full Physical examination during selected visits.
* Capture age at menarche (girls > 10 years)
* Tanner staging (assessment pubertal development; <18 years only))
* ECG at screening and every other week for the first 2 cycles and once during every next cycle and at the end of treatment.
* Neurologic exam during the screening, every 2 cycles thereafter and at the

end of study.
* Knee, wrist and fingers x-ray (<18 years only) at screening and at the end of treatment. Knee x-ray every 8 weeks, and wrist and fingers x-ray every 6 months while on treatment. X-ray hemiskeleton if > 4months and < 12 months, at screening and every 8 weeks.
* Panorex or age appropriate dental x-ray (<18 years only) at screening and at the end of treatment, and yearly while on treatment.
* Dental exam (<18 years only) at screening and at the end of treatment and every 12 weeks while on treatment.
* Echocardiogram at screening.
* Taste Questionnaire (LDE arms and < 18 years only) on day 5 after starting LDE225

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients aged * 4 months
Patients with histologically confirmed diagnosis of MB, who have experienced relapse or progression after standard-of-care therapy including radiotherapy or patients aged >4 months and * 6 years who are RT naive.
Patients currently receiving steroids must have been on a stable (or decreasing) dose for at least 5 days before the brain/spine MRI obtained at screening.
Patients with any number of prior relapses are eligible to enroll provided they have Hh-pathway activated tumors as assessed using the 5-gene Hh signature assay.
Relapsed MB may be defined by imaging tumor biopsy, or evidence of tumor cells in the CSF.
At least one measurable lesion.

Exclusion criteria

Prior treatment with a Smoothened inhibitor
Patients who have neuromuscular disorders that are associated with elevated CK
Patients on concomitant treatment with drugs that are recognized to cause rhabdomyolysis that cannot be discontinued at least 2 weeks before first dose of study treatment. If it is essential that the patient stays on a statin to control hyperlipidemia only pravastatin may be used with extra caution.
Patients receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 or are metabolized by CYP2B6 and CYP2C9, that have narrow therapeutic indices that cannot be discontinued at least 2 weeks before first dose of study treatment and for the duration of the study.
Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms, dose must have been stabilized (or decreasing) for at least 5 days before the brain/spine MRI obtained at screening.
Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 2 weeks before first dose of study treatment, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible.

Study design

Design

Study phase: 2

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-07-2014
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not established
Generic name:	sonidegib

Ethics review

Approved WMO Date:	24-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2014

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2012-003066-40-NL
ClinicalTrials.gov	NCT01708174
CCMO	NL42615.078.13