A phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma

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The purpose of this phase II study is to assess the efficacy and safety of oral treatment with two dose levels of LDE225, as measured by objective response rate (ORR), in patients with locally advanced or metastatic BCC. Additional assessments...

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

Summary

ID

NL-OMON38204

Source
ToetsingOnline

Brief title
BOLT Study

Condition

- Skin neoplasms malignant and unspecified

Synonym
locally advanced and metastatic basal cell carcinoma, skin cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: basal cell carcinoma, hedgehog pathway inhibition, skin cancer

Outcome measures

Primary outcome

To assess the efficacy of LDE225 when administered once daily, as measured by

Objective Response Rate (ORR) in patients with locally advanced or metastatic

BCC.

Secondary outcome

To assess the time to the first documented tumor response (TTR) as complete or

partial response associated with 800 mg and 200 mg dose LDE225 therapy.

To assess duration of overall response, i.e. partial response (PR) or complete

response (CR) associated with 800 mg and 200 mg dose LDE225 therapy.

To assess the effect of LDE225 treatment on progression-free survival (PFS).

To assess overall survival (OS) associated with LDE225 treatment.

Characterize the safety of LDE225 treatment.

To further characterize the pharmacokinetics.

Study description

Background summary

Skin cancers are the most common malignancy in Europe, Australia and North America. Basal-cell carcinomas (BCC) account for about 80%, and the incidence rises in younger individuals. The worldwide incidence is increasing by 10% per

year. It is estimated that 1 in 3 Caucasians will develop BCC in their life-time. Common causes for BCC are genetic predisposition and exposure to ultraviolet radiation.
Although in most cases, BCC is not typically life-threatening, it is associated with considerable morbidity: BCC or its necessary treatment (mainly surgical excision and/or radiotherapy) can destroy the skin and surrounding structures, causing severe disfigurement. In 90 to 95 % of the cases BCC is completely cured. However recurrent, more aggressive, infiltrated or rare cases of metastatic spread BCC are difficult to treat. There are currently no effective systemic treatment options for these patients.
Almost all BCCs are dependent on aberrant Hedgehog (Hh) signaling for growth and survival. Smoothened (Smo) is a receptor molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Normally, the activity of Smo is sufficiently repressed.
The inhibition of the Hh signaling pathway as a therapeutic approach has increasingly become an area of extensive research, with several different compounds currently been tested in labs and clinics. LDE225 is a potent selective and orally bioavailable Smo antagonist from a novel structural class. On the basis of the available data and the understanding of the role of Hh signaling in the pathogenesis of BCC, it is anticipated that LDE225 could offer a viable therapeutic option for this patient population.

Study objective

The purpose of this phase II study is to assess the efficacy and safety of oral treatment with two dose levels of LDE225, as measured by objective response rate (ORR), in patients with locally advanced or metastatic BCC. Additional assessments include safety, pharmacokinetics, other efficacy endpoints and pharmacodynamic biomarkers.

Study design

This is a multi-center, adaptive, randomized double-blind Phase II study. Approximately 120 patients will be needed. All enrolled patients will be initially randomized in a 2:1 fashion to receive LDE225 at either 800 mg or 200 mg on a continuous once daily dosing schedule.
In order to ensure similar patient populations stratification will occur according to the following prognostic factors:
* Stage of disease (locally advanced or metastatic) and
* For locally advanced BCC further stratification of aggressive or non-aggressive
Patients will have tumor assessments with the appropriate radiological imaging modality (CT or MRI) and color clinical photography (where appropriate). Baseline tumor assessments must be performed * 21 days prior to starting study treatment. After baseline (screening assessments), further tumor response evaluations will be performed in week 5, 9 17 and subsequently once every 8

weeks during the first year and once every 12 weeks after the first year until documented disease progression.
An interim analysis (IA) to assess the safety and efficacy of LDE225 will be performed when the first 48 randomized patients have been treated for 16 weeks, discontinued treatment or discontinued the study. The results of this IA determine whether the remaining positions in each treatment arm will be filled or that one or 2 treatment arms are dropped due to futility or poor tolerability.
The primary analysis of study data will be conducted 24 weeks after the last patient is enrolled. A final analysis of safety and efficacy will be performed and the study will be unblinded at 78 weeks (18 months) following enrollment of the last patient. After the final analysis, patients who have not experienced disease progression and are still obtaining benefit from study treatment will continue on the study with reduction in the frequency of the visits and collection of limited efficacy and safety data.
Every effort will be made to obtain archival tumor specimens. 2ml of blood will be collected for Hh pathway mutation analyses from all patients from whom tumor sample are provided.
The study will include clinical and histological assessments (for patients with locally advanced BCCs), assessment of activation of Hh pathway by mutation and gene expression analysis, PK, hematology and blood chemistry laboratory assessments, ECG, pregnancy testing and collection of adverse events. Optional exploratory pharmacogenetic assessments are performed.

Intervention

All enrolled patients will receive LDE225 at either 800 mg or 200 mg.

Study burden and risks

LDE225 is currently undergoing phase I evaluation in a first-in-human clinical trial, to assess the safety, tolerability, PK, PD and potential efficacy of continuous once daily oral administration in patients with malignant solid tumors.
As of October 29, 2010, data were available on 76 patients with cancer who have been treated with LDE225 at different dose levels up to 3000 mg once daily and 750 mg twice daily. Once daily administration of LDE225, up to 800 mg, has been found to be well tolerated.
CTC grade 3 or 4 Adverse Events occurred at higher doses: increases in plasma creatine phosphokinase (CK) associated with muscle pain, increased aspartate amino transferase ,muscular weakness and increased plasma myoglobin. None of the patients experienced impairment of renal function as a result of toxicity. Following discontinuation of LDE225 therapy, resolution of these AEs was observed over a period of up to 4 weeks in 12 patients, and over up to 8 weeks in the remaining two cases.
Commonly (>10%) reported CTCAE grade 1 or 2 adverse events that are suspected

to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms and fatigue. No treatment-related clinically significant changes in the other safety laboratory data (hematology, and urinalysis), vital signs or ECGs have been observed for any of the patients treated in the studies.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patient is male or female * 18 years of age
- Histologically confirmed diagnosis of locally advanced or metastatic BCC with measurable disease
- WHO performance status * 2

- Adequate renal and liver functions

Exclusion criteria

- Patients with concurrent uncontrolled medical conditions that may interfere with their participation in the study or potentially affect the interpretation of the study data.
- Patients who have previously been treated with systemic LDE225 or with other Hh pathway inhibitors.
- Patients who have neuromuscular disorders or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, UNLESS they are using two forms of highly effective contraception
- Fertile males not willing to use condoms throughout the study and for 3 months after

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-10-2011
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	22-07-2011

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-10-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-03-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2010-022629-14-NL
ClinicalTrials.gov	NCT01327053
CCMO	NL37326.091.11