A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase(ALK)

Published: 07-01-2011
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Primary To determine the MTD of LDK378 (oral administration) as a single agent Secondary* Safety and tolerability of LDK378* To characterize single and multiple-dose PK of LDK378.* To assess preliminary anti-tumor activity of LDK378

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

Summary

ID

NL-OMON36240

Source
ToetsingOnline

Brief title
A phase I study with LDK378 in tumors with ALK mutation

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Tumors with genetic abnormality in ALK

Research involving
Human

Sponsors and support

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

Intervention

Keyword: abnormal ALK gene, LDK378, phase I

Outcome measures

Primary outcome

Primary: Incidence rate of Dose Limiting Toxicities (DLT) during the first

cycle including PK run-in.

Secondary outcome

* Adverse drug reactions and serious adverse drug reactions, changes in

hematology and blood chemistry values, assessments of physical examinations,

vital signs and electrocardiograms.

* Plasma concentration of LDK378 and PK parameters.

* Overall response (complete response (CR) or partial response (PR)) rate

defined according to RECIST.

Study description

Background summary

LDK378 is an oral active ALK-inhibitor. The results of studies in animals show that LDK378 can shrink or slow the growth of several
types of cancer when the cancer cells have a genetic abnormality in the ALK gene.
Its greater potency (20-fold) and specificity when compared with crizotinib suggest that it may have a role in the treatment of patients who progress while receiving crizotinib treatment and a more acceptable safety profile.
ALK was detected as oncogen in a small fraction of teh Non-small cell lung cacers, a proportion of primary neuroblastomas and the majority of

inflammatory myofibroblastic tumors. LDK378 could be a new opportunity for the treatment of cancers with an ALK-mutation or translation.

Study objective

Primary
To determine the MTD of LDK378 (oral administration) as a single agent

Secondary
* Safety and tolerability of LDK378
* To characterize single and multiple-dose PK of LDK378.
* To assess preliminary anti-tumor activity of LDK378

Study design

An open-label, phase I, first-in-human, study with an escalation phase and a MTD expansion phase.
The escalation phase will include a PK-run-in period, wherein the patient will be given a single dose (PK run-in day 1) followed by a full PK collection (PK run-in day 1 to day 3). The fourth day of the PK run-in period (cycle 1 day 1) will commence the treatment period in which LDK378 will be given in a continuous daily dosing. It is estimated that 40 patients will be treated during the escalation phase.
The expansion phase will start after the MTD has been estimated. There will be 3 arms in which enrollment will be done in parallel. Each arm will enroll a minimum of 10 patients.
* (Arm 1) NSCLC with ALK-translocation following treatment with an ALK inhibitor,
* (Arm 2) NSCLC with ALK-translocation not previously treated with an ALK-inhibitor
* (Arm 3) ALK-translocated patients with tumor types other than NSCLC
Because of the low overall incidence of cancers with abnormalities in ALK, tumor samples will be pre-screened for ALK translocations or mutations in a central laboratory.

Intervention

Investigational drug: LDK378, available in 25mg, 50 mmg and 100mg capsules.
LDK378 will be administered orally as a continuous daily dosing.
Starting dose will be 50 mg/day.

Study burden and risks

Side effects from LDK378 seen in animals that might happen in human:
- inflammation of the bile duct or pancreas duct,
- phototoxicity

Other side effect may occur as:
nausea, vomiting, diarrhea, elevation of liver enzymes, and inflammation of the lungs (pneumonitis).

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

Raapopseweg 1
6824 DP Arnhem
NL
Scientific
Novartis

Raapopseweg 1
6824 DP Arnhem
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with tumors characterized by abnormalities in ALK (translocation or mutation).
2. ECOG performance status * 2

3. Laboratory:
-Absolute Neutrophil Count *1.5x109/L
- Hemoglobin * 9 g/dl <= 5.58 mmol/l
- Platelets *100x109/L
- Total bilirubin * 1.5 x upper limit of normal (ULN)
- Alkaline phosphatase, AST (SGOT) and ALT (SGPT) * 2.5 x ULN, with liver metastasis *5 x ULN
- Creatinine * 1.5 x ULN or calculated creatinine clearance * 50 mL/min (* 0.835 mL/s)
- Amylase * ULN
- Lipase * ULN
- Fasting plasma glucose * 200 mg/dL (* 11.1 mmol/L)

Exclusion criteria

1. Central nervous system (CNS) metastases which are unstable, symptomatic and require increasing doses of steroids to control the disease.
2. Unresolved nausea, vomiting or diarrhea > CTCAE grade 1
3. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LDK378
4. History of pancreatitis or history of increased amylase or lipase
5. Acute or chronic liver disease. Evidence of previous hepatitis viral infection (testing is not mandatory)
6. Clinically significant cardiac disease including congestive heart failure (New York Heart Association Class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy; or clinically uncontrolled hypertension (blood pressure > 160/110 mmHg)
7. Impaired cardiac function, including:
- Complete left bundle branch block
- Cardiac pacemaker
- Congenital long QT syndrome
- History or presence of ventricular tachyarrhythmia
- Presence of unstable atrial fibrillation (ventricular response > 100 bpm
- Clinically significant resting bradycardia (< 50 bpm)
- Corrected QTcF > 450 msec for males and > 470 msec for females at screening
- PR * 240 msec and QRS * 110 msec
- Right bundle branch block + left anterior hemiblock (bifascicular block)
- Angina pectoris and Acute Myocard Infarction * 3 months prior to starting study drug
8. Other concurrent severe and/or uncontrolled medical conditions
9. Prior treatment with chemotherapy or biologic therapy or other investigational agent < 5x t1/2 or < 2 weeks (whichever is longer) prior to starting study drug . If prior treatment was crizotinib, LDK378 may start 2 weeks after the last dose.
10. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia)
11. Radiotherapy * 3 weeks
12. Major surgery * 2 weeks
13. Strong inhibitors or inducers of CYP3A4/5

14. CYP2C9: warfarin and phenytoin
15. Coumarin-type anticoagulants. Treatment with maximum daily dose of 2 mg of coumarin-type anticoagulants for line patency is permitted. Low molecular weight heparin is permitted.

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):	18-05-2011
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Niet van toepassing
Generic name:	NIet van toepassing

Ethics review

Approved WMO Date:	07-01-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-03-2011
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-05-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-05-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	14-11-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2010-019827-70-NL
CCMO	NL34451.031.10