A Phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-small cell lung cancer (NSCLC) metastatic to the brain and/or to leptomeninges.

Published: 22-07-2015
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47423

Source
ToetsingOnline

Brief title
ASCEND 7 - CLDK378A2205

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, non small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Brain metastases, ceritinib, Lung cancer, NSCLC

Outcome measures

Primary outcome

Overall response rate (ORR), defined as the proportion of patients with a best

overall confirmed response of

complete response (CR) or partial response (PR) in the whole body as assessed

per RECIST 1.1 by the investigator.

Secondary outcome

Disease Control Rate (DCR)

And

1. To evaluate intracranial tumor-response related endpoints (Arms 1-4).

2. To evaluate extracranial tumor-response related endpoints (Arms 1-4).

3. To evaluate whole body tumor-response related endpoints (Arms 1-4).

4. To evaluate overall survival (OS)

5. To evaluate safety

6. To characterize the PK of ceritinib in this patient population

Study description

Background summary

Lung cancer has been among the most common cancers in the world for several decades. In 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers worldwide. It has been the most common cause of death from cancer, with 1.38 million deaths

Ten to 35% of the patients newly diagnosed with NSCLC presents with synchronous BM. It is estimated that 40 to 50% of all patients with NSCLC will develop BM at any stage of the treatment of their disease.

The role of systemic therapies in the treatment of BM remains unclear to date. For decades, systemic chemotherapies were believed to be of limited benefit. Guidelines for the treatment of NSCLC patients with BM, still recommend localized treatment of the brain disease prior to initiating systemic treatment for advanced incurable patients.

ALK rearrangements serve as a key strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases, is the first tyrosine kinase inhibitor to target ALK to have demonstrated a clinical activity and to be approved in the US and EU as treatment of metastatic ALK-positive NSCLC.

Studies with crizotinib in BM showed: Overall Intracranial Response Rate (CR+PR) in a subgroup of 109 patients with untreated BM was 7% (95%CI: 3-14) compared to an extracranial Response Rate of 53% (95% CI: 43-63).

There is a medical need for more effective treatment for patients with ALK-positive NSCLC metastatic to the CNS before and after failure to crizotinib.

Ceritinib is an orally available ALK inhibitor with efficacy seen in the ongoing Phase I and Phase II. The Phase I clinical trial in patients (with and without previous crizotinib therapy) has led to the approval of ceritinib by the FDA and EMA. A total of 14 patients out of the 246 patients included in the 750 mg dose group had brain metastases at baseline considered to be target lesions by the investigator per RECIST 1.0. In these 14 patients, the OIRR was 50% (95% CI: 23.0, 77.0) (1 patient with confirmed CR in the brain and 6 patients with a confirmed PR in the brain).

Additional research is needed in Brain metastases patients to confirm the

efficacy data.

Study objective

The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on whole body overall response rate (ORR), defined as the proportion of patients with a best overall confirmed response of complete response (CR) or partial response (PR) in the whole body as assessed per RECIST 1.1 by the investigator.
The key secondary objective is to evaluate whole body Disease Control Rate (DCR) in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1

Study design

A Phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-small cell lung cancer (NSCLC) metastatic to the brain and/or to leptomeninges
Approximately 125 patients diagnosed with ALK-positive metastatic NSCLC and active lesions in the included in the study, approximately 30 patients in each of the Arms 1 to 4 and approximately 5 patients in Arm 5.
Treatment until disease progression or unacceptable side effects. Patient who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease and all patients will be followed for survival.

Intervention

Drug: LDK378 (ceritinib) 750 mg daily oral intake.

Study burden and risks

Risk: Adverse effects of study drug.
Burden: Cycle of 28 days. 3 visits in cycle 1. 1 visit from cycle 2. usually takes 2 hours. 1 visit is 5- 8 hours.
Physical and neurological examination: course 1: 2 times. cycle 2: 1 time.
Blood tests: (10-15 ml / times): Each visit. PK (9 times): 2 mL extra.
Cerebro-spinal fluid (total 15 patients): 2 x 2mL.
Pregnancy test: 1x per treatment.
Tumor measurements every 2 cycles.
ECG: 3 visits in cycle 1. Up to 10x max
Tumor Biopsy: 0-2 times (1st is required if no archival material available, 2nd optional)

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Female and male patients of 18 years older or older
- Stage IV ALK-positive NSCLC. Pre-treated and treatment naive. See protocol 01 page 45 for details.
- At least one extracranial measurable lesion
- Able to swallow medication and neurological stable within 1 week before first dose.
- WHO performance status 0-2
- Brain metastases or leptomenigeal carcinomatosis

Exclusion criteria

- Patient with a history of treatment with ceritinib

- Patients who need whole brain radiation to control the brain metastases
- In case active brain lesions (single or not) require local treatment
- Patient who has received thoracic radiotherapy to lung fields * 4 weeks prior to starting the study treatment
- Patient with a concurrent malignancy or history of a malignant disease other than NSCLC
- Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event
- Patient has impairment of GI function or GI disease that influence drup uptake
- Concomittent therapy as defined on page 133 of protocol am. 1
- Patient is pregnant or nursing

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):	20-11-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zykadia
Generic name:	ceritinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-07-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	20-11-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-12-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	04-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	12-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	25-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	22-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	12-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-10-2016
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-09-2018

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-09-2018
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
Other	clinicaltrials.gov NCT02336451
EudraCT	EUCTR2014-000578-20-NL
CCMO	NL53760.031.15