A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib

Published: 31-07-2013
Last updated: 22-04-2024

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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-OMON47784

Source
ToetsingOnline

Brief title
ASCEND-5, LDK378 vs chemotherapy in pre-treated ALK + lung cancer patients

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
advanced non-small cell lung cancer, advanced NSCLC

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALK positive, crizotinib pre-treated, LDK378, Lung cancer

Outcome measures

Primary outcome

The primary objective is to compare the antitumor activity of LDK378 versus reference chemotherapy, as measured by progression free survival (PFS).

The key secondary objective is to compare Overall Survival (OS) in patients treated with LDK378 versus reference chemotherapy (pemetrexed or docetaxel). Measured by RECIST 1.1.

Secondary outcome

To assess the antitumor activity of LDK378 versus reference chemotherapy, as measured by overall response rate (ORR), duration of response (DOR), disease control rate (DCR), and time to response (TTR)

To evaluate the safety profile of LDK378 versus reference chemotherapy (physical examination, haematology, biochemistry, urinalysis, sex hormones (males only), coagulation, vital signs, ECG, pregnancy test

To assess the effect of LDK378 versus reference chemotherapy on patient reported outcomes (PRO), including disease related symptoms, functioning, and

health-related quality of life

To characterize the pharmacokinetics (PK) of LDK378

Study description

Background summary

Lung cancer has been among the most common cancers in the world, representing 12.7% of all new cancers worldwide. It was also the most common cause of death from cancer. NSCLC accounts for more than 85% of all lung cancer cases. Overall, current treatments are not considered satisfactory for most NSCLC patients and the prognosis continues to be poor despite chemotherapy treatment, with a 5-year OS rate of only 15%. During the last few years, improved knowledge of NSCLC biology has led to the identification of molecular events crucial for malignant transformation and cancer cell survival and *molecular subsets* of NSCLC patients who may be candidates for targeted therapy. As a result, new targeted treatment options have been developed.
ALK is a receptor tyrosine kinase of the insulin receptor superfamily. ALK gene rearrangements result in aberrant ALK activation, and ALK fusion proteins possess potent oncogenic activity in both in vitro and in vivo models. This activity can be effectively blocked by small-molecule inhibitors that target ALK.
Although ALK gene rearrangement is a relatively uncommon event in NSCLC with a frequency of 2-8%, tumors driven by the EML4 and ALK translocation have been identified as a clinically relevant molecular subset of NSCLC. While crizotinib has impressive activity in patients with ALK-rearranged NSCLC, these cancers invariably progress, typically within 1 year, with the development of resistance to crizotinib. For these patients there is no alternative ALK-targeted therapy. Therefore, the development of ALK TKIs with clinical activity against ALK-positive NSCLC resistant to crizotinib is crucial.
LDK378 is an orally available ALK inhibitor. LDK378 is an approximately 20-fold more potent ALK inhibitor than crizotinib, it is more selective for ALK and does not inhibit MET. In addition, LDK378 shows potent antitumor activity in crizotinib-resistant animal models, and the efficacy seen in the ongoing Phase I clinical trial in patients who failed crizotinib has been extremely encouraging. These features support the hypothesis that LDK378 could be active in NSCLC patients whose disease has progressed on crizotinib.
In conclusion, the rationale for investigating the anti-cancer activity of LDK378 in patients with ALK-rearranged NSCLC with disease progression following treatment with chemotherapy and crizotinib is supported by the following:
* LDK378 is highly active in NSCLC in vitro and in vivo models.
* LDK378 has potent antitumor activity against crizotinib-resistant NSCLC cell lines.

* Preliminary efficacy data demonstrate that LDK378 has clinically important anti-tumor activity in the target population.
* Preliminary efficacy data support the premise that ALK oncogene addiction may continue in NSCLC after crizotinib therapy.
* Preliminary safety data demonstrate that LDK378 is well tolerated by the target population at the 750 mg daily dose.
* There are limited available therapeutic options and no available ALK-targeted treatment options for the target population.

Study objective

The primary objective is to compare the antitumor activity of LDK378 versus reference chemotherapy.
The key secondary objective is to compare Overall Survival (OS) in patients treated with LDK378 versus reference chemotherapy (pemetrexed or docetaxel).

Study design

This is an open-label, randomized, active-controlled, multi-center, phase III study to compare the efficacy and safety of LDK378 to standard, second-line, reference chemotherapy (pemetrexed or docetaxel) in patients with advanced NSCLC harboring a confirmed ALK rearrangement.
Approximately 236 patients will be randomized in a 1:1 ratio to either LDK378 or reference chemotherapy (pemetrexed or docetaxel at the investigator*s discretion). Patients will continue LDK378 or reference chemotherapy treatment until they experience any of the following: disease progression, unacceptable toxicity that precludes further treatment, start of a new anti-cancer therapy, treatment is discontinued at the discretion of the investigator or patient, or death.
Patients in the reference chemotherapy arm will be allowed to crossover to receive LDK378 therapy.

Intervention

Investigational Therapy: LDK378 (750 mg po QD)
Reference chemotherapy based on Investigator*s discretion:
pemetrexed (500 mg/m2 IV q 21 days) or
docetaxel (75 mg/m2 IV q 21 days)

Study burden and risks

There are additional assessments and visits take longer. Some of the tests would be done during regular treatment (CT and / or MRI scans, blood tests). Specifically for this study there will be extra assessments: ECGs, blood draws for PK-sampling, tumor biopsy and filling out questionnaires.
The medication may cause side effects.

The tests to be carried out are generally accepted medical examinations.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically or cytologically confirmed diagnosis of non-squamous NSCLC that is ALK positive
- Stage IIIB or IV NSCLC or relapsed locally advanced or metastatic NSCLC
- At least one measurable lesion as defined by RECIST 1.1.
- 18 years of age or older
- Life expectancy * 12 weeks
- WHO performance status 0-2.
- Patients must have received previous treatment with crizotinib
- Patients must have received one regimen of platinum- doublet, cytotoxic

chemotherapy

Exclusion criteria

- Patients who where previously treated witn ALK-inhibitors (with the exception of crizotinib)
- Patient is currently receiving treatment with coumarin-derivative anticoagulants.
- Patient with symptomatic CNS metastases.
- Patient has received radiotherapy * 2 weeks or * 4 weeks for thoracal radiotherapy prior to starting the study treatment or has not recovered from radiotherapy-related toxicities.
- Patient has had major surgery within 4 weeks prior (2 weeks for resection of brain metastases) to starting study treatment or has not recovered from side effects of such procedure.
- Patient with a concurrent malignancy or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years.
- Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months)
- Patient is pregnant or nursing (lactating) woman

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2014

Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nnb
Generic name:	Ceritinib
Product type:	Medicine
Brand name:	Taxotere
Generic name:	docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-11-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	13-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	02-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-005637-36-NL
ClinicalTrials.gov	NCT01828112

Register	ID
CCMO	NL45183.042.13