A multi-center, open-label study to assess the safety and efficacy of combination ceritinib (LDK378) and nivolumab in adult patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (CLDK378A2120C)

Published: 13-04-2015
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Primary: 1. To determine the MTD and/or RDE of the combination ceritinib and nivolumab. 2. To assess the preliminary antitumor activity of the combination.Secondary: 1: To assess the safety profile of the ceritinib and nivolumab combination. 2: To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON44906

Source
ToetsingOnline

Brief title
CLDK378A2120C

Condition

- Respiratory tract neoplasms

Synonym
non small cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ceritinib, LDK378, nivolumab, NSCLC

Outcome measures

Primary outcome

DLT, objective response rate.

Secondary outcome

Adverse events. DOR, DCR, TR, PFS, OS.

Study description

Background summary

Cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab is standard first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), unless a patient has a known targetable gene mutation or aberration, and is therefore a candidate for a targeted therapy.
Although chemotherapy has led to clinical improvements in patients with locally advanced or metastatic NSCLC, the outcome of treatment in the first-line setting remains poor, with median progression-free survival (PFS) and overall survival (OS) of 5-7 months and 10-16 months, respectively.
A clinically relevant molecular subset of NSCLC is driven by the anaplastic lymphoma kinase (ALK) translocation. It ALK is translocated, mutated, or amplified, it plays a key role in the pathogenesis in several tumor types, including NSCLC.
Metastatic ALK-positive NSCLC remains an incurable disease. Recent studies have demonstrated the efficacy of ALK inhibitors in ALK-positive NSCLC and of immunotherapy with PD-1 antibodies/blocking agents, such as nivolumab, in NSCLC patients.
Ceritinib is an orally available potent ALK inhibitor. Ceritinib shows potent

antitumor activity in animal models. Efficacy was seen in the ongoing phase I clinical trial in patients, which led to the approval of ceritinib by the FDA for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.
Harnessing the immune system to treat patients with NSCLC represents a novel and exciting new treatment approach. The anti-PD-1 antibody Nivolumab has demonstrated response rates of up to 20% in patients with NSCLC and has been safely combined with several small molecules as well as chemotherapies.
The current study will investigate the combination of ceritinib and nivolumab in adult patients with ALK-positive NSCLC. Combination therapy involving targeted agents and immunotherapy may improve PFS and ultimately OS in NSCLC patients. This study is intended to determine the MTD/recommended doses for expansion (RDE) as well as to evaluate the safety and preliminary efficacy of the ceritinib and nivolumab combination.

Study objective

Primary: 1. To determine the MTD and/or RDE of the combination ceritinib and nivolumab. 2. To assess the preliminary antitumor activity of the combination.
Secondary: 1: To assess the safety profile of the ceritinib and nivolumab combination. 2: To assess duration of response (DOR), disease control rate(DCR), time to response(TTR), PFS, OS.

Study design

Multicenter phase IB open-label dose escalation and expansions study.
Starting dose ceritinib 450 mg orally per day and nivolumab IV infusion every 2 weeks (3 mg/kg).
Possible adjustments of ceritinib dose:
* 300 mg daily in case of safety or tolerability issues in first 6 weeks.
* 600 mg daily for next cohort if no safety or tolerability issues in first 6 weeks.
Treatment until disease progression or unacceptable side effects. Patients 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.
Approx. 18 subjects in dose escalation and 60 in expansion phase.

Intervention

Treatment with ceritinib and nivolumab.

Study burden and risks

Risk: Adverse effects of the combination of study drugs.
Burden: Cycles of 4 weeks. Cycle 1: 4 visits, cycle 2: 3 visits, from cycle 3

onwards: 2 visits. Duration mostly 1-4 hours. Some visits up to 8 hours.
2 infusions with nivolumab per cycle (approx. 200 ml).
Low-fat diet.
Physical examination: cycle 1-2: 2 times, from cycle 3 onwards once/cycle.
Blood tests (15 ml/occasion): every visit. PK; up to 12 ml/occasion extra.
Biomarkers: 25 ml/occasion extra.
Pregnancy test: once/cycle.
Tumor measurements: every 8 weeks for the 1st 12 cycles, every 12 weeks thereafter.
ECG: cycle 1-2: twice, from cycle 3 onwards once/cycle.
Tumor biopsy: 1-2 times.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Female and male patients * 18 years of age.
* Relapsed locally advanced or metastatic NSCLC with an ALK-rearrangement.
* Measurable disease.
* Clinically and neurologically stable CNS metastases who have not required increasing doses of steroids or stable doses > 10 mg daily prednisone equivalent within 2 weeks prior to study entry to manage CNS symptoms.
* In the expansion phase, patients must have received prior treatment according to the following: Arm 1: ALK inhibitor-treated, ALK inhibitor: Yes, Chemotherapy: 0 or 1 prior courses, Prior treatment with any ALK inhibitor except ceritinib is allowed.
Arm 2: ALK inhibitor-naïve ALK inhibitor: No, Chemotherapy: 0 or 1 prior courses.
* WHO performance status 0 or 1.

Exclusion criteria

* Severe hypersensitivity reactions to other monoclonal antibodies.
* Prior treatment with anti-PD1/anti-PD-L1 agents.
* Chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted to enroll in the absence of active autoimmune disease.
* Clinically significant, uncontrolled heart disease and/or recent cardiac event. See protocol page 14 for details.
* (History of) interstitial lung disease.
* Comedications listed on page 14 of the protocol.
* Pregnancy, lactation, inadequate contraception (males and females). See protocol page 15 for details.

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):	14-10-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	13-04-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2018
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	EUCTR2014-005054-19-NL
ClinicalTrials.gov	NCT02393625
CCMO	NL52443.078.15