Phase Ib, multicenter, open label study of PDR001 in combination with platinum-doublet chemotherapy in PD-L1 unselected, metastatic NSCLC patients

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Primary: Dose confirmation part: To establish the Maximum Tolerated Dose (MTD) and/or Recommended dose for expansion (RDE) of PDR001 with platinum-doublet chemotherapy in treatment naïve patients with PD-L1 unselected, advanced NSCLC of squamous or…

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45593

Source
ToetsingOnline

Brief title
CPDR001C2101

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Neonatal respiratory disorders

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: advanced, Chemotherapy, NSCLC, PDR001

Outcome measures

Primary outcome

Dose Limiting Toxicities (DLTs). ORR.

Secondary outcome

PFS, Disease control rate (DCR), DOR (Duration of response) and TTR (Time to

Response), OS. Adverse events. PK parameters, Antidrug-antibodies.

Study description

Background summary

Although chemotherapy has led to clinical improvements in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), the outcome of chemotherapy treatment in the first-line setting remains poor.
For patients with NSCLC that does not have EGFR or ALK or ROS1 gene mutation current chemotherapy treatments are not considered satisfactory and the prognosis continues to be poor despite chemotherapy treatment, with a 5-year OS rate of only 15%.
PD-1 inhibitors have provided remarkable clinical benefit for patients with advanced NSCLC. As a result, PD-1 inhibitors have become the preferred option, in first line, for NSCLC that does not have a EGFR or ALK or ROS1 gene mutation but does have PD-L1 expression on greater than 50% of tumor cells, and in second line irrespective of PD-L1 expression but without a *druggable* gene rearrangement, having demonstrated superior overall survival when compared to standard chemotherapy. However, a large fraction of patients do not respond to single agent PD-1 inhibitor. One potential approach to increase response rate is based on the observation that chemotherapy-induced tumor cytotoxicity can result in the release of tumor antigens, which can trigger anti-tumor Tcell immunity. Preclinical studies have confirmed that chemotherapy leads to antigen release in the tumor microenvironment.

Results from other PD1 inhibitors in combination with platinum-doublet chemotherapy in the first line setting in phase Ib/II have shown promising results, including tumor shrinkage in the majority of patients, durable responses, and acceptable safety profiles. Recent data indicate that, in the first-line setting, single agent PD-1 inhibitors are superior to platinum-doublet chemotherapy with respect to PFS and OS in patients with high levels of PD-L1 expression (>50%) on tumor cells. However, the population with high level expression of PD-L1 expression may be relatively small. Preliminary data suggest that even in this population combination with chemotherapy may increase Overall Response Rate (ORR). Taken together these data indicate that further exploration of PD-1 inhibitors in combination with platinum-doublet chemotherapy is warranted in patients with PD-L1 unselected NSCLC.
An unanswered question is the choice of second-line therapy in patients whose disease progresses following first line PD-1 inhibitor therapy. Based on the demonstrated efficacy of platinum-doublet chemotherapy in the first line setting, it can be assumed that platinumdoublet chemotherapy would provide some benefit to this chemotherapy naive population. However, given the preclinical data suggesting that chemotherapy leads to tumor antigen release creating an immunogenic *feedback loop*, the addition of a PD-1 inhibitor may provide improved efficacy over chemotherapy alone.
PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody that blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 shows functional activity in vitro/ex vivo. In the mean time 11 early phase studies with PDR001 as a monotherapy or in combination with LAG525 (an anti-LAG3 antibody) are ongoing. By the end of March 2016, a total of 58 patients had been treated in the first in human study. No patient experienced a dose limiting toxicity and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1.

Study objective

Primary:
Dose confirmation part: To establish the Maximum Tolerated Dose (MTD) and/or Recommended dose for expansion (RDE) of PDR001 with platinum-doublet chemotherapy in treatment naïve patients with PD-L1 unselected, advanced NSCLC of squamous or non-squamous histology, lacking EGFR, ALK or ROS1 gene changes in the first 6 weeks of therapy for groups A, B, C.
Dose expansion part: To assess the antitumor activity (as measured by ORR) of PDR001 with platinum-doublet chemotherapy in treatment naïve patients with PD-L1 unselected, advanced NSCLC of squamous or non-squamous histology, lacking EGFR, ALK or ROS1 gene changes for groups A, B, C.
Secondary:
Antitumor activity in groups A, B, C and D. Safety and tolerability. Pharmacokinetics (PK). Immunogenicity.

Study design

Multicenter phase Ib open-label non-comparative study.
Part I: Dose confirmation part.
Dose escalation of PDR001 (starting dose 300 mg i.v. on day 1 of every course of 3 weeks).
In combination with fixed dose chemotherapy up to first 4 cycles: group A: (squamous): gemcitabine/cisplatin; group B: (non-squamous): pemetrexed/cisplatin; group C: (squamous or non-squamous): paclitaxel/carboplatin.
Part 2: Dose expansion part.
PDR001: MTD or RDE from part 1.
Groups A-C as in part 1.
Group D: (non-squamous): randomization to
* Arm 1: Investigator*s choice pemetrexed/cisplatin or pemetrexed/carboplatin + PDR001 (up to 4 cycles) followed by maintenance with pemetrexed + PDR001.
* Arm 2: Investigator*s choice pemetrexed/cisplatin or pemetrexed/carboplatin (up to 4 cycles) followed by maintenance with pemetrexed alone.
Treatment until progression or unacceptable toxicity.
Follow-up for safety 5 months. Follow-up for survival.
Part 1: up to 60 subjects.
Part 2: 120 subjects.
See also protocol pages 37-38.

Intervention

Treatment with PDR001 and platinum-doublet chemotherapy (see protocol pages 37-38).

Study burden and risks

Risk: Adverse effects of PDR001 plus chemotherapy.
Burden: Cycles of 3 weeks. Visits on day 1, 8, 15 of the first 4 cycles and day 1 of every cycle thereafter. Visit duration mostly 1-4 hours. 2x patient will be admitted to the hospital for 8-9 hour duringPK days.

IV infusions of PDR001 and chemotherapy on day 1 of every cycle (PDR001) or of the first 4 cycles (chemotherapy), in case of gemcitabine also on day 8 of the first 4 cycles. Infusions of 250 mL. Duration of PDR001 infusion standard 0,5 hour (up to 2 hours is accepted).
Physical examination: day 1 of (nearly) every cycle, screening, once during follow-up.
Blood tests (5-50 mL/occasion): day 1, 8, 15 of cycle 1-4, once during every cycle thereafter, screening, once during follow-up.
ECG: every 3rd cycle, screening, once during follow-up.
Echocardiography: twice.
CT-/MRI scan: every 6-12 weeks.
2 tumor biopsies (1st may be replaced by recent archival material).

Optional: tumor biopsy at disease progression.
Optional: extensive PK blood sampling.
Optional: pharmacogenetic blood sample (6 mL).
Optional: biomarker and immunological blood sampling in case of adverse event (2 tubes).
Optional use of the remaining blood and tissue for future research.

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 * 18 years.
* Stage IIIB or stage IV NSCLC or relapsed locally advanced or metastatic NSCLC. See protocol page 42 for more details, incl. criteria for groups A-D.
* Patient who received previous neo-adjuvant or adjuvant systemic therapy will be eligible for

enrollment only if relapse has occurred more than 12 months from the end of this therapy.
* Histologically or cytologically confirmed diagnosis of NSCLC that is EGFR Wild-type, ALK-negative gene changes and ROS1-negative gene changes. See protocol page 42-43 for details.
* ECOG performance status 0-1.
* At least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.

Exclusion criteria

* History of severe hypersensitivity reactions to other monoclonal antibodies which in the opinion of the investigator may pose an increased risk of a serious infusion reaction.
* History of interstitial lung disease or interstitial pneumonitis. See protocol page 44 for details.
* Major surgery in the last 4 weeks. See protocol page 44 for details.
* Thoracic radiotherapy to lung fields in the last 4 weeks. More details on radiotherapy: see protocol page 44.
* Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months). See protocol page 44-45 for details.
* Active, known or suspected autoimmune disease or a documented history of autoimmune disease. See protocol page 45 for details.
* A condition requiring chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within the last 7 days. See protocol page 45 for details.
* Any live vaccines against infectious diseases within the last 4 weeks.
* Pregnancy, lactation, insufficient contraception for females of childbearing potential and males.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-04-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt generiek
Generic name:	carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	nvt generiek
Generic name:	cisplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	nvt generiek
Generic name:	gemcitabin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-04-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-05-2017

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-08-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-07-2019
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: NCT03064854
EudraCT	EUCTR2016-002815-17-NL
CCMO	NL60666.031.17