A Phase Ib, multicenter, open-label dose escalation and expansion platform study of select immunotherapy combinations in adult patients with triple negative breast cancer

Published: 14-02-2019
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Primary: To characterize safety and tolerability of each treatment arm tested and identify recommended doses and regimens for future dosesSecondary:* To characterize the pharmacokinetic profile of each investigational drug within each treatment arm...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON49712

Source
ToetsingOnline

Brief title
CADPT01A12101C

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Triple negative breastcancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: immunotherapy, phase 1, Triple negative breastcancer

Outcome measures

Primary outcome

Incidence and severity of AE*s and SAE*s. DLTs (incidence and nature), dose

interruptions/reductions.

Secondary outcome

Serum/plasma concentrations and PK parameters of individual investigational

drugs within combination treatments

Presence and/or concentration of anti-drug antibodies

Best overall response (BOR) and PFS per RECIST v1.1 and iRECIST

Changes from baseline of PD markers in tumor tissue (e.g.TILs, CD8, PD-L1,

LAG-3

Study description

Background summary

De eerste resultaten van een kleine groep patiënten met TNBC die behandeld werd met spartalizumab (PDR001) in combinatie met LAG525 hebben tekenen van effectiviteit laten zien, waarbij gezien werd dat een behandeling van spartalizumab in combinatie met LAG525 effectiever zou kunnen zijn dan een behandeling met alleen een PD-(L)1 remmer bij de behandeling van TNBC.
Emerging clinical data suggest that combinations of immunotherapy agents with chemotherapy may possess greater anti-tumor activity than single agents.
Preliminary data from a small group of TNBC patients treated with spartalizumab (PDR001) in combination with LAG525 have shown preliminary signs of efficacy

demonstrating that spartalizumab in combination with LAG525 may be more effective than single-agent PD-(L)1 inhibitors in the treatment of TNBC. Nonetheless, most patients did not respond as expected.
Therefore, using spartalizumab + LAG525 as a starting point, the addition of a 3rd agent (such as NIR178, capmatinib, MCS110 or canakinumab), that modulate other mechanisms, may improve the effects of the LAG525 + spartalizumab doublet in patients with TNBC.

Study objective

Primary: To characterize safety and tolerability of each treatment arm tested and identify recommended doses and regimens for future doses

Secondary:

* To characterize the pharmacokinetic profile of each investigational drug within each treatment arm
* To assess immunogenicity of monoclonal antibodies
* To evaluate preliminary anti-tumor activity of each treatment arm
* To assess the pharmacodynamics (PD) effect of each treatment arm

Study design

This is a phase Ib, multi-center, open-label study with multiple treatment arms. The design of this study is adaptive to allow dropping of non-tolerated or ineffective combination treatments and facilitate the introduction of new candidate combinations. The study is comprised of a dose-escalation part and a dose-expansion part.

During the dose-escalation part of each treatment arm, patients will be treated with spartalizumab (fixed dose)+LAG525 (fixed dose) in combination with partner investigational drugs NIR178, capmatinib, MCS110, or canakinumab
Each treatment arm will enroll cohorts of three to six subjects with TNBC treated until the MTD is reached or a lower RDE is established (Figure 3-1). A minimum of 15 subjects are expected to be enrolled in each dose-escalation treatment arm (

There is no requirement for every dose-escalation treatment arms reaching an MTD/RDE to proceed to dose expansion. After the determination of the MTD/RDE for a particular treatment arm, dose expansion may begin in that arm in order to further assess safety, tolerability, PK/PD, and anti-tumor activity of each combination at the MTD/RDE. Approximately 30 subjects
(naive for anti-LAG-3, anti-PD-L1 or anti-PD-L2 therapy) may be enrolled for each treatment arm during dose expansion.

Intervention

Spartalizumab (PDR001) 400mg intravenous administration (infusion) once every 4 weeks
LAG525 intravenous 600mg intravenous administration (infusion) once every 4 weeks

For each treatment arm the following third investigational drug will be added:
- Arm1: NIR178, oral intake BID, starting dose 80mg
- Arm 2: capmatinib, oral intake BID, starting dose 80mg 200mg
- Arm3: MCS110, 5,0 mg/kg intravenous administration (infusion) once every 4 weeks
- Arm 4: canakinumab, subcutaneous injection once every 8 weeks, starting dose 600mg

Study burden and risks

Risks:
- Adverse effects (AE's and SAE's) of Spartalizumab and LAG 525 in combination with either
1) NIR178 or 2) capmatinib or 3) MCS110 or 4) canakinumab
- Risks associated with the assessments as blooddraw, tumor biopsy and imaging

Burden:
Burden: Cycles of 3 or 4 weeks. Cycle 1: 6 visits, cycle 2: 2 visits, thereafter 1 visit per cycle. Duration mostly 1-4 hours.
Physical examination: once per cycle.
Blood tests (15 ml/occasion, during dose escalation part occasionally fasting): every cycle (cycle 1: 4 times). Extra blood draws for PK (in total 50 ml) and biomarkers (in total 50 ml).
Urine testing during screening.
Pregnancy test: every cycle.
ECG: once per cycle (cycle 1: 4 times).
CT-/MRI scan: baseline, every 8 weeks thereafter.

Contacts

Public
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

ECOG Performance Status * 1
Patients with advanced/metastatic TNBC with measurable disease as determined by RECIST version 1.1
Documented disease progression or intolerance to no more than 2 prior lines of chemotherapy for advanced disease. Prior treatment with targeted agents or checkpoint inhibitors will not count as a line of prior therapy unless chemotherapy was administered concurrently.
Patients must have received prior systemic treatment that included taxane-based chemotherapy for neoadjuvant or metastatic disease.
Patients must have a site of disease amenable to core needle biopsy, and be a candidate for tumor biopsy according to the treating institution*s guidelines.
Patients must be willing to undergo a new tumor biopsy at screening, and during therapy on the study.
See for more details protocol section 5.1

Exclusion criteria

Dose expansion arm(s), checkpoint- inhibitor-naive group only: Prior checkpoint inhibitor therapy.
Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within 2 weeks prior to initiating study treatment.

Patients with treated brain metastases should be neurologically stable for at least 4 weeks prior to study entry and off steroids for at least 2 weeks before administration of any study treatment.
Out of range laboratory values:
- Creatinine clearance < 40 mL/min
- Total bilirubin > 1.5 x ULN, except for patients with Gilbert*s syndrome if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
- ALT and AST > 3 x ULN
- Absolute neutrophil count < 1.0 x 109/L
- Platelet count < 75 x 109/L
- Hemoglobin < 9 g/dL
- Potassium, magnesium, calcium or phosphate abnormality > CTCAE grade 1 despite appropriate replacement therapy
Impaired cardiac function or clinically significant cardiac disease
Cardiac Troponin T (cTnT) or Cardiac Troponin I (cTnI) elevation > Grade 1
History or current diagnosis of myocarditis.
Subjects assigned to the canakinumab arm are required to be tested using Interferon-* release assay.
For patients assigned to the the MCS110 arm, active tuberculosis requiring systemic antibiotic
therapy is excluded.
Other exclusion criteria may apply (see protocol section 5.2)

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):	24-06-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	---
Generic name:	---
Product type:	Medicine
Brand name:	---
Generic name:	spartalizumab
Product type:	Medicine
Brand name:	Ilaris
Generic name:	canakinumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-02-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-05-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-07-2019

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)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-07-2020
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-08-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-04-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	25-04-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-04-2021
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	EUCTR2018-002244-82-NL
ClinicalTrials.gov	NCT03742349
CCMO	NL68735.031.19