A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600 mutant melanoma

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* Safety Run inTo determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib for the randomized part (part 3)* Biomarker cohortTo evaluate changes in the immune microenvironment and biomarker modulations upon treatment...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54792

Source
ToetsingOnline

Brief title
CPDR001F2301

Condition

- Miscellaneous and site unspecified neoplasms benign
- Skin neoplasms malignant and unspecified

Synonym

1 - A randomized, double-blind, placebo-controlled, phase III study comparing the co ... 30-05-2025

Melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: dabrafenib, Melanoma, PDR001, trametinib

Outcome measures

Primary outcome

Safety Run in Part

• Incidence of DLTs during the first 8 weeks of treatment for each dose level associated with administration of PDR001 in combination of dabrafenib and trametinib.

Biomarker:

• Descriptive statistics of immune microvenvironment and biomarker modulation values and changes from baseline by visit

Randomized part:

• Investigator assessed PFS (according to RECIST 1.1)

Secondary outcome

part 1

• Safety: Incidence and severity of AEs and SAEs, including changes in

laboratory values, ECOG PS, vital signs, liver and cardiac parameters.

• Tolerability: Dose interruptions, reductions, and dose intensity

• PFS, OS, ORR, DOR, DCR by investigator*s assessment according to RECIST 1.1

Part 2:

none

Part 3

• ORR, DOR and DCR by investigator*s assessment according to RECIST 1.1

• Safety: Incidence and severity of AEs and SAEs, including changes in

laboratory values, ECOG PS, vital signs, liver assessments and cardiac

assessments.

• Tolerability: Dose interruptions, reductions, and dose intensity

• Change from baseline in EORTC QLQ-C30, EQ-5D, and FACT-M melanoma subscale

Study description

Background summary

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. The first in human study is ongoing. By the end of December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg every 2 weeks and 3 and 5 mg/kg every 4 weeks. No patient experienced a dose limiting toxicity and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1. The PK data support the use of flat dosing for PDR001 of 400 mg every 4 weeks.
Agents that enhance anti-tumor immunity are not effective in all cancer types, responses are often not durable, and many patients receive little or no benefit from treatment. Inhibitors of the PD-1/PD-L1 interaction are well tolerated and active across a range of cancer types, and will likely be one component of

combination therapies that increase the response rate and durability of treatment.

Study objective

* Safety Run in
To determine the recommended regimen of PDR001 in combination with dabrafenib and trametinib for the randomized part (part 3)

* Biomarker cohort
To evaluate changes in the immune microenvironment and biomarker modulations upon treatment with PDR001 in combination with dabrafenib and trametinib

* Randomized, placebo-controlled (part 3)
To compare the anti-tumor activity of PDR001 in combination with dabrafenib and trametinib versus placebo plus dabrafenib and trametinib as measured by PFS per investigator*s assessment according to RECIST 1.1

Study design

This study has been designed as a phase III, multi-center study consisting of 3 parts.
• Part 1: Safety run-in part (Figure 4-1)
• Part 2: Biomarker cohort (Figure 4-2)
• Part 3: Double-blind, randomized, placebo-controlled part (Figure 4-3)

Netherlands is not participating in Part 1.

Intervention

All participant will be treated with :

Dabrafenib, oral, 150mg BID
Trametinib, oral, 2 mg QD

Biomarker part
Combination with dabrafenib and trametinib and PDR001 infusion 400mg. Depending of the recommended dose in the safety part, it is expected that this infusion will be either once every 4 weeks, or once every 8 weeks.

randomized part
> Arm 1: PDR001 infusion in combination with trametinib and dabrafenib
> Arm 2: placebo in combination with dabrafenib and trametinib

Study burden and risks

RISK: adverse events of treatment with dabrfenib and trametinib, with placebo or PDR001
Burden: Cycles of 4 weeks, Cycle 1,2,3: 2 visits, from cycle 4 onwards one visit
Infusion with PDR001, approx. 30 minutes
Physical examination: once per cycle.
Blooddraws : at meast once per cycle, on PK days more frequent (max 3)
ECG: every cycle up to cycle 3. Cycle 1 2 12leadECGs, 1 ECG 12lead during cycle 2 and 3 and every 3rd cycle afterwards
MUGA scan during screening, cycle 1 and every 12 weeks afterwards
0-3 tumor biopsies: depending on the studie part. optional additional biopsies are possible.
CT-/MRI-scan: during screening, cycle 4, every 8 weeks during first 6 months and every 12 weeks thereafter.
Skin photographs in case of skin lesions.
Questionnaires EORTC QLQ-C30, EQ-5D-5L, FACT-M : screening, cycle 3, every 8 weeks aferwards during first year, afterwards every 3 months.
ophthamological assessments: on screening and cycle 2 day 1

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)

Inclusion criteria

Part 1: Safety run-in
• Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutation
• Aspartate transaminase (AST) < 2.5× ULN and Alanine transaminase (ALT) < 2.5× ULN
• ECOG performance status <= 1
Part 2: Biomarker cohort
• Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutation
• At least two cutaneous or subcutaneous or nodal lesions for tumor sample collection
• ECOG performance status <= 2
Part 3: Double-blind, randomized, placebo-controlled part
• Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutation
• ECOG performance status <= 2

Exclusion criteria

Part 1: Safety run-in
• Subjects with uveal or mucosal melanoma
• Any history of CNS metastases
• Prior systemic anti-cancer treatment for unresectable or metastatic melanoma
• Prior loco-regional treatment for unresectable or metastatic melanoma in the last 6 month
• Prior neoadjuvant and/or adjuvant therapy for melanoma completed less than 6 months
• Radiation therapy within 4 weeks prior to start of study treatment
• Active, known, suspected or a documented history of autoimmune disease, Parts 2 & 3: Biomarker cohort & double-blind, randomized, placebocontrolled part
• Subjects with uveal or mucosal melanoma
•Clinically active cerebral melanoma metastasis
• Prior systemic anti-cancer treatment for unresectable or metastatic melanoma
• Prior loco-regional treatment for unresectable or metastatic melanoma

in the last 6 month
• Prior neoadjuvant and/or adjuvant therapy for melanoma completed less than 6 months
• Radiation therapy within 4 weeks prior to start of study treatment
• Active, known, suspected or a documented history of autoimmune disease

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-12-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	Trametinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	PDR001
Generic name:	PDR001
Product type:	Medicine

Brand name:	Tafinlar
Generic name:	Dabrafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-12-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-07-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-10-2017

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-07-2018

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-04-2021

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-01-2023

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2016-002794-35-NL
ClinicalTrials.gov	NCT02967692
CCMO	NL59819.028.16