A phase I-Ib/II, open-label, multi-center study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult patients with advanced malignancies

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Primary: Phase I: - To characterize the safety and tolerability of MBG453 as a single agent and in combination with PDR001 and to identify recommended doses for future studies. To further investigate the safety and tolerability of different doses of...

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

Summary

ID

NL-OMON53097

Source
ToetsingOnline

Brief title
CMBG453X2101

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, lungcancer, melanoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: and PDR001, anti PD-1, anti TIM-3, MBG453, Phase I/II

Outcome measures

Primary outcome

Phase I:

Safety: Incidence and severity of (S)AEs, including changes in laboratory parameters, vital signs and ECGs

Tolerability: Dose interruptions, reductions and dose intensity

Incidence of DLTs during the first cycle of treatment with single agent MBG453 and during the first and second cycle of treatment with MBG453 in combination with PDR001.

Phase II: Overall Response Rate (ORR) per RECIST 1.1

Secondary outcome

Phase I: Best Overall response (BOR), Progressive Free Survival (PFS), Duration of Response (DOR) per RECIST 1.1 and Overall Response Rate (ORR) and Progressive Free Survival (PFS) per iRC

Phase II: Safety: Incidence and severity of (S)AEs, including changes in laboratory parameters, vital signs and ECGs

Tolerability: Dose interruptions, reductions and dose intensity

Overall Response Rate (ORR), Best Overall response (BOR), Progressive Free

Survival (PFS), Duration of Response (DOR) per RECIST 1.1 Overall Response Rate

(ORR) and Progressive Free Survival (PFS) per iRC

Study description

Background summary

MBG453 is a high-affinity, ligand-blocking, humanized anti-TIM-3 IgG4 antibody which blocks the binding of TIM-3 to Phosphatidylserine. MBG453 shows functional activity.
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.

This first-in-humans study with MBG453 (alone and in combination with PDR001) will characterize the safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity of MBG453 and MBG453 plus PDR001 administered i.v.
The first-in humans study with PDR001 is ongoing. In the first 6 patients no DLTs, SAEs, dose reductions or dose interruptions during the first cycle of treatment were seen.
The rationale for combining MBG453 with PDR001 is based on scientific evidence in preclinical models. Several reports have shown that the cancer-induced inhibitory modulation of T-cell activation is synergistically promoted by the concurrent blockade of TIM-3 and PD-1.

Study objective

Primary:
Phase I:
- To characterize the safety and tolerability of MBG453 as a single agent and in combination with PDR001 and to identify recommended doses for future studies. To further investigate the safety and tolerability of different doses of MBG453 alone or in combination with PDR001 during the dose ranging part.

Phase II: To estimate the anti-tumor activity of MBG453 alone and in combination with PDR001.

Secondary:
Both phases:
- to evaluate the preliminary anti-tumor activity of MBG453 as single agent and

in combination with PDR001.
- to make an initial comparison for the combination of MBG453 and PDR001 administered on a Q2W and Q4W dosing schedules.

Study design

Multicenter phase I-Ib/II open-label dose escalation study (phase I and Ib) and dose expansion study (phase II) of MBG453 monotherapy (phase I) and MBG453 and PDR001 combination therapy (phase Ib and II).

Phase Ib will commence after at least two cohorts in the dose escalation with single agent have been completed and safety data suggests acceptable toxicity. Once the MTD/RP2D of MBG453 as single agent and/or in combination with PDR001 is achieved, the phase II part will commence with selected indications (melanoma, NSCLC and renal cell cancer).

Following declaration of the MTDs/RP2Ds for single agent and combination, and only if efficacy has already been observed in the dose escalation parts, an optional dose ranging part of the study may be opened. The dose ranging part will only enroll patients not eligible for the phase II part of the study. The dose ranging part may include the testing of different dose levels to better understand the safety, tolerability and PK of MBG453 as single agent and in combination with PDR001.

Should signs of anti-tumor activity be seen in the phase I dose escalation with MBG453 as single agent, a phase II part will be opened in order to further explore single agent efficacy at the recommended dose and schedule. Patients with tumor types that have been shown to respond to single agent MBG453 (maximum of two indications) will be enrolled.

Treatment until disease progression or unacceptable side effects.

Follow-up for survival.

Intervention

MBG453, intravenous every 2 weeks. Starting dose 80mg as single agent, 20mg in combination with PDR001
PDR001, intravenous every 2 weeks. Starting dose 80mg

If necessary a once every 3 or once every 4 weeks schedule might be tested.

Study burden and risks

Risk: Adverse effects of MBG453 with or without PDR001 and potential risks

related to the assesments.

Burden: Cycles of 4 weeks. Cycle 1 and 3: five visits, Cycle 2: two visits, from cycle 4 onwards two visits (in case of a once per 4 weeks dosing schedule: 1 visit per cycle).
Visit duration 1-4 hours.

Physical examination and vital signs: cycle 1: every week, cycle 2 and subsequent cycles: every 2 weeks.
Blood tests for safety: cycle 1: 3 times, cycle 2: 2 times, from cycle 3 onwards: once per cycle. Additional blood draws: for PK, immunology biomarkers: 200 ml in total.
ECG: Screening, Cycles 1, 3 and 6 pre- and post infusion
Fresh tumorbiopsies at baseline, during treatment (cycle 3 and End of Treatment).
CT-/MRIscan: every 2nd cycle until cycle 11. Thereafter every 3rd cycle.
Optional storage and use of the remaining blood and tissue for future research after end of trial.

Contacts

Public
Novartis

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Scientific
Novartis

Haaksbergweg 16
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

* Phase I-Ib part: Advanced/metastatic solid tumors, with (non)-measurable disease, who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists, and who did not receive prior anti-PD1/PD-L1 treatment. Prior therapy with PD-1/PDL-1 inhibitors is allowed provided any toxicity attributed to prior PD-1 or PD-L1-directed therapy did not lead to discontinuation of therapy.
* Phase II single agent part: advanced/metastatic solid tumors in the indication in which signs of
anti-tumor activity (CR, PR or durable SD with tumor shinkrage that does not qualify for PR) were seen during phase I. Patients must have measurable disease, have progressed despite standard therapy or be intolerant to standard therapy.
* Phase II part combination therapy: Advanced/metastatic solid tumors, with at least one measurable lesion, who have received standard therapy or are intolerant of standard therapy, have progressed following their last prior therapy, and fit into one of the following groups: non-small cell lung cancer or melanoma pretreated with anti-PD-1/PD-L1 therapy.
* ECOG performance status 0-1-2.
* Disease amenable to biopsy and a candidate for tumor biopsy according to the treating institution*s guidelines. Patient must be willing to undergo a new tumor biopsy at baseline, and during therapy on this study.

Exclusion criteria

* Symptomatic CNS metastases or CNS metastases that require local CNS-directed therapy or increasing doses of corticosteroids within the prior 2 weeks. Patients with treated brain metastases should be neurologically stable
* Out of range laboratory values.
* Impaired cardiac function or clinically significant cardiac disease.
* HBV or HCV positive patients, with active disease or whose hepatitis is not controlled by therapy are excluded. HIV positive patients are excluded.
* Active autoimmune disease or history of autoimmune disease
* Any condition that requires systemic steroids
* Systemic anti-cancer therapy within 2-4 weeks of the first dose of study treatment.
* Vaccines against infectious diseases within 4 weeks of initiation of study

treatment.
* Major surgery within 2 weeks.
* Radiotherapy within 2 weeks, except for palliative radiotherapy to a limited field.
* Use of hematopietic growth factors (CSF) within 2 weeks.
* Prior participation in an interventional, investigational cancer vaccine or immunotherapy study except for an anti-PD-1/PD-L1 study.
* Participation in another type of interventional study in the last 2 weeks.
For details refer to protocol page 35-36

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):	25-02-2016
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet van toepassing
Generic name:	nog niet van toepassing

Ethics review

Approved WMO

Date:	21-12-2015
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-02-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-09-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-06-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	12-12-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	31-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-07-2018
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-03-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-03-2020
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-01-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	25-06-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2015-002354-12-NL
CCMO	NL55479.058.15