Phase 1b, multi-arm, open-label study of PDR001 and/or MBG453 in combination with decitabine in patients with acute myeloid leukemia or high risk myelodysplastic syndrome (CPDR001X2105)

Published: 24-07-2017
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Primary: To characterize the safety and tolerability of PDR001 and/or MBG453 in combination with decitabine or azacitidine in relapsed/refractory AML patients, de novo AML patients not candidates for standard induction therapy, or high risk or...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55557

Source
ToetsingOnline

Brief title
PDR001 and/or MBG453 in combination with decitabine in AML or MDS

Condition

- Leukaemias

Synonym
bloodcell cancer, bonemarrow cancer. AML: Acute myeloide leukemia, MDS: Myelodysplasia

Research involving

Human

Sponsors and support

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

Intervention

Keyword: AML, decitabine, MBG453, PDR001

Outcome measures

Primary outcome

Adverse events. Dose Limiting Toxicities (DLTs).

Secondary outcome

ORR (Objective response rate), BOR (Best overall response), PFS (Progression free survival), TTP (Time to progression), DOR (Duration of response). PK parameters. Anti-PDR001 and anti-MBG453 antibodies.

Study description

Background summary

The prognosis for patients with de novo AML who cannot tolerate standard therapy and those with relapsed or refractory (R/R) AML and high risk MDS remains extremely poor, and despite the significant unmet medical need, few effective treatment options exist. There is strong evidence and promise for checkpoint inhibition; however, it will be important to determine the ideal checkpoint inhibitor strategy and to consider combination therapies in order to optimize anti-tumor immunity.

Expanding the responses to immunomodulatory therapy is an important focus of current oncology research. Combination therapies using multiple inhibitors of immune function could significantly improve response rates, and efforts to target different steps in the anti-tumor immune response hold the promise of achieving sustained anti-tumor immunity.

The purpose of this study is to combine the standard of care hypomethylating

agent decitabine with inhibitors of either PD-1 or TIM-3, or both in order to identify an optimized checkpoint inhibitor strategy in AML and MDS. Decitabine will be used both for its anti-tumor activity as well as its potential as an immunomodulatory agent allowing for the implementation of focused checkpoint inhibition. Additionaly also MBG453 with or without PDR001
No specific molecular selection will be applied as the data available at present generally do not support excluding patients based on approved molecular diagnostic tests such as PDL1 expression.

Study objective

Primary:
To characterize the safety and tolerability of PDR001 and/or MBG453 in combination with decitabine or azacitidine in relapsed/refractory AML patients, de novo AML patients not candidates for standard induction therapy, or high risk or intermediate risk MDS patients, and to identify recommended doses for future studies.
Secondary:
Preliminary antitumor activity. Pharmacokinetics (PK). Immunogenicity.
See also protocol.

Study design

Multicenter phase Ib open-label multi-arm study.
6 treatment arms:
1. Fixed dose of decitabine in combination with fixed dose PDR001 (Arm 1)
2. Fixed dose of decitabine in combination with escalating dose MBG453 (Arm 2)
3. Fixed dose of decitabine in combination with fixed dose PDR001 and escalating dose MBG453 (Arm 3)
4. Fixed dose of MBG453 , to be confirmed during the course of the trial (Arm 4)
5. fixed dose of PDR001 and Fixed dose of MBG453 , to be confirmed during the course of the trial (Arm 4)
6. Fixed dose of azacitidine in combination with escalating dose MBG453 (Arm 6)

The assignment of a patient to a particular arm or dose level will be coordinated by Novartis and will be based on the dose levels available at the time the patient consents to participation in the study.
Treatment until complete response during treatment or until progression or unacceptable toxicity.
If applicable: follow-up for progression. Follow-up for safety 5 months.
Follow-up for survival.
207 subjects.
See also protocol.

Intervention

Treatment with decitabine in combination with PDR001 and/or MBG453. Treatment with MBG453 with or without PDR001. Treatment with azacitidine in combination with MBG453.

Study burden and risks

Risk: Adverse effects of decitabine in combination with PDR001 and/or MBG453 or azacitidine in combination with MBG453.
Burden: 6-7 cycles of 4 weeks (combination therapy) and 3 optional cycles of decitabine monotherapy. Visits on day 1, 8, 15 and 22 of the first and third cycle and day 1 of every other cycle. Visit duration mostly 1-4 hours.
IV infusions of PDR001 on day 8, MBG453 day 8 and 22, decitabine on the 1st 5 days of every cycle and azacitidine on the first 7 days of every cycle.
Infusions of 250 mL.
Physical examination: day 1 of every cycle and day 8 of cycles 1 and 3, screening, end of treatment.
Blood tests (10-40 mL/occasion): day 1 of every cycle and day 8 of cycles 1 and 3, screening, end of treatment and follow-up for progression. Multiple PK sampling (2-4 times) day 1 and 8 of cycles 1 and 3.
ECG: day 1 and 8 of cycles 1 and 3, screening, end of trial.
CT-/MRI scan: screening, will be repeated if needed.
Bone marrow aspirate and/or 4 times and during follow-up for progression (1st may be replaced by recent archival material).

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female patients * 18 years of age with
ARM 1-2-3 :
* Refractory/relapsed AML following *1 prior therapies
* De novo AML patients who are are suitable for treatment with decitabine (patients who are suitable for standard induction chemotherapy and willing to receive it are excluded)
* Intermediate or high risk MDS or MDS/MPN, including CMML
Arm 4a & 5a:
* Relapsed/refractory AML following *1 prior therapies who have relapsed or exhibited refractory disease (primary failure)
Arm 4b & 5b:
* Intermediate or High risk MDS patients or MDS/MPN, including CMML who have failed hypomethylating agent therapy.
Arm 6a
* Newly diagnosed AML patients who are suitable for treatment with azacitidine
Arm 6b :
* Intermediate or high-risk MDS or MDS/MPN, including CMML
2. ECOG performance status 0-1-2
3. Candidate for serial bone marrow aspirate and/or biopsy according to the institutions guidelines and be willing to undergo the planned bone marrow aspirate and/biopsy according to protocol.

Exclusion criteria

1. Arms 1-2-3 or Arm 6 : Prior decitabine or hypomethylating agent treatment for AML or MDS.
2. Impaired cardiac function or clinically significant cardiac disease. See

protocol page 32 for details.
3. HIV, active hepatitis B, C. See protocol page 32-33 for details.
4. Active, known or suspected autoimmune disease. See protocol page 33 for details.
5. History of, or current drug-induced interstitial lung disease or pneumonitis grade * 2.
6. Patients who discontinued prior PD-1 or PD-L1 directed therapy due to a treatment related toxicity should not be included in the PDR001 containing arms of the study. See protocol page 33 for more details.
7. Patients who discontinued prior TIM-3 directed therapy due to a treatment related toxicity should not be included in the TIM-3 containing arms of the study.
8. Treatment with cytotoxic or targeted antineoplastics within 3 weeks of initiation of study treatment. See protocol page 33 for details.
9. Systemic chronic corticosteroid therapy (* 10 mg/day prednisone or equivalent) or any immunosuppressive therapy within 7 days of first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.
10. Live vaccine against infectious disease within 4 weeks of study treatment.
11. Pregnancy, lactation, insufficient contraception for females of childbearing potential and males.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-02-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dacogen
Generic name:	decitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet van toepassing
Generic name:	nog niet van toepassing
Product type:	Medicine
Brand name:	nog niet van toepassing
Generic name:	spartalizumab
Product type:	Medicine
Brand name:	Vidaza
Generic name:	azacitidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	14-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-005060-33-NL
ClinicalTrials.gov	NCT03066648
CCMO	NL61755.029.17