A randomized, double-blind, placebo-controlled phase III multi-center study of azacitidine with or without MBG453 for the treatment of patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON52708

Source
ToetsingOnline

Brief title
CMBG453B12301 (MDS)

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
bone marrow disorder, myelodysplasia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Azacitidine, Chronic Myelomonocytic, Leukemia-2 (CMML-2), MBG453, myelodysplastic syndrome (MDS)

Outcome measures

Primary outcome

To compare overall survival (OS) in the MBG453 plus azacitidine arm versus

placebo plus azacitidine arm

Secondary outcome

Key secondary objectives

• To compare time to definitive deterioration of fatigue in the MBG453 plus

azacitidine arm versus placebo plus azacitidine arm as measured by FACIT-Fatigue

• To compare RBC transfusion-free intervals in the MBG453 plus azacitidine arm

versus placebo plus azacitidine arm

• To compare improvement of fatigue in the MBG453 plus azacitidine arm versus

placebo plus azacitidine arm using FACIT-Fatigue

• To compare improvement of physical functioning in the MBG453 plus azacitidine

arm versus placebo plus azacitidine arm using EORTC QLQ-C30

• To compare improvement of emotional functioning in the MBG453 plus

azacitidine arm versus placebo plus azacitidine arm using EORTC QLQ-C30

Study description

Background summary

The prognosis is poor and life expectancy is short in patients with medium, high or very high risk myelodysplastic syndrome (MDS) and patients with chronic myelomonocytic leukemia 2 (CMML-2) who are treated with the current standard of care based on hypomethylating agents (HMAs). HMAs represent the standard of care for the vast majority of patients who cannot receive hematopoietic stem cell transplantation (HSCT) or cannot be treated with intensive chemotherapy. Azacitidine is the only HMA that showed a survival gain over conventional care in higher risk MDS and CMML patients. Full remission is reported in a minority of patients treated with azacitidine alone, and the clinical benefits of this drug are often transient and if it fails, second-line treatment options are limited.
The anti-TIM-3 monoclonal antibody MBG453 is a new immunotherapeutic agent with promising activity seen in AML and MDS. The aim of the current study is to assess the clinical effects of MBG453 in combination with azacitidine in adult subjects with MDS with a medium, high or very high risk and CMML-2. In this randomized, placebo-controlled study, MBG453 plus azacitidine or placebo plus azacitidine is compared.

Study objective

The anti-TIM-3 monoclonal antibody MBG453 is a novel immunotherapeutic agent with promising activity seen in AML and MDS. The purpose of the current study is to assess clinical effects of MBG453 in combination with azacitidine in adult subjects with intermediate, high or very high risk MDS, and CMML-2. This randomized, two-arm parallel-group, double-blind, placebo-controlled study will compare MBG453 plus azacitidine or placebo plus azacitidine.

Study design

The trial is a randomized, double-blind, placebo-controlled, multi-center phase III study of MBG453 or placebo added to azacitidine for the treatment of subjects with intermediate, high or very high risk MDS as per IPSS-R or with CMML-2.
Approximately 500 subjects will be randomized in a 1:1 ratio to receive azacitidine 75 mg/m2, intravenous or subcutaneous, with or without MBG453 800 mg IV Q4W in 28-day treatment cycles.
Study treatment consists of cycles of MBG453 or placebo 800 mg IV Q4W

administered on Day 8 of each cycle in combination with azacitidine administered to the subjects on days 1 to 7 (or on days 1 to 5 and days 8 and 9) of each cycle until treatment discontinuation. The planned duration of a cycle is 28 days.

Intervention

Treatment with azacitidine and MBG453/placebo

Study burden and risks

Risk: Side effects of the study medication.

Tax:
Screening 4 weeks.
Therapy:
MBG453 (or placebo): infusion (500ml) 1x per 4 weeks until disease progression.
Azacitidine (same asl standard treatment) 7 days per course of 4 weeks
Physical examination: 2x per course
Blood test: every visit
ECG: 2.
bone marrow biopsies: maximum 5
Questionnaires 10.

Contacts

Public
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

• Signed informed consent must be obtained prior to participation in the study
• Age >= 18 years at the date of signing the informed consent form (ICF)
• Morphologically confirmed diagnosis of myelodysplastic syndrome (MDS) based on WHO 2016 classification (Arber et al 2016) by local investigator assessment with one of the following Prognostic Risk Categories, based on the revised International Prognostic Scoring System (IPSS-R)
Or
Morphologically confirmed diagnosis of Chronic Myelomonocytic Leukemia -2 based on WHO 2016 classification (Arber et al 2016)(persistant PB monocytosis >= 1 x109/L and monocytes accounting for >= 10% of the WBC differential count) by local investigator assessment
• Indication for azacitidine treatment according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions
• Not eligible at time of screening for intensive chemotherapy according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions decisions, including assessment of individual clinical factors such as age, comorbidities and performance status
• Not eligible at time of screening for hematopoietic stem cell transplantation according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions including assessment of individual clinical factors such as age, comorbidities, performance status, and donor availability
• Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
Please refer to protocol for further details and any additional inclusion criteria.

Exclusion criteria

• Prior exposure to TIM-3 directed therapy at any time. Prior therapy with immune checkpoint inhibitors (e.g, anti-CTLA4, anti-PD-1, anti-PD-L1, or

anti-PD-L2), cancer vaccines is allowed except if the drug was administered within 4 months prior to randomization
• Previous first-line treatment for intermediate, high, very high risk myelodysplastic syndromes (based on IPSS-R) or CMML-2 with any antineoplastic agents including for example chemotherapy, lenalidomide and hypomethylating agents (HMAs) such as decitabine or azacitidine. However, previous treatment with hydroxyurea or leukopheresis to reduce WBC count is allowed prior to randomization.
• Investigational treatment received within 4 weeks, or 5 half-lives of this investigational treatment, whatever is longer, prior to randomization. In case of a checkpoint inhibitor: a minimal interval of 4 months prior to randomization is necessary to allow randomization.
• Subjects with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) with revised International Prognostic Scoring System (IPSS-R) <= 3
• Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia, primary or secondary myelofibrosis grade 2 or higher based on WHO 2016 classification (Arber et al 2016). Patients with myelofibrosis grade 1 must not be enrolled if they have symptoms of concurrent myeloproliferative neoplasm
• Diagnosis of therapy related myeloid neoplasms based on WHO 2016 classification
(Arber et al 2016)
• History of organ or allogeneic hematopoietic stem cell transplant
Please refer to protocol for further details and any additional exclusion criteria.

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:	Recruiting
Start date (anticipated):	04-06-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	sabatolumab
Generic name:	sabatolumab
Product type:	Medicine
Brand name:	Vidaza
Generic name:	azacitidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-09-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2024
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2019-002089-11-NL
ClinicalTrials.gov	NCT04266301
CCMO	NL72430.056.20