A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome

Published: 08-03-2021
Last updated: 25-03-2025

Primary (Efficacy):To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R as measured by CR rateTo evaluate the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52320

Source
ToetsingOnline

Brief title
Gilead 5F9009 ENHANCE (3674/0013)

Condition

- Haematological disorders NEC

Synonym
Myelodysplastic Syndrome (a group of bone marrow disorders in which the production of blood cells is seriously disturbed)

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Magrolimab + Azacitidine vs Azacitidine + Placebo, Myelodysplastic Syndrome, Phase 3, Treatment-naïve Patients

Outcome measures

Primary outcome

Endpoints:

* CR rate as assessed by Investigators:

The CR rate is the proportion of participants who reach morphologic CR

(morphological blast of <= 5% and recovery of ANC, platelets, and hemoglobin

from CBS as well as peripheral blast collected on the same day) based on

Investigator assessed IWG 2006 MDS criteria (Cheson 2006) prior to initiation

of any new anticancer therapy for MDS, including SCT (stem cell transplant).

* Overall Survival (OS): The length of OS is measured from randomization to the

date of death from any cause. Those who are not observed to die during the

study will be censored at their last known alive date.

Secondary outcome

See protocol section 3. Objectives and endpoints

Study description

Background summary

Myelodysplastic syndrome (MDS) is a premalignant clonal hematopoietic disorder characterized
by bone marrow failure due to production of dysfunctional, dysplastic bone marrow cells. Low
and very low risk patients, as defined by the Revised International Prognostic Scoring System
(IPSS-R; Greenberg 2012), are often treated with erythroid and myeloid growth factor support
and carry a low risk of leukemic progression. In contrast, intermediate, high, and very high risk
patients with MDS are generally treated with hypomethylating agents and carry an elevated risk
of leukemic progression. Azacitidine (Vidaza®) is standard of care (SOC) for newly diagnosed
MDS patients with specific high risk subtypes. However, complete remission (CR) rates are
low, and overall survival (OS) is only around 18 months (Silverman 2002). Thus, novel
therapies that replace or augment the efficacy of azacitidine are needed to extend survival for patients with MDS.

CD47 is a key molecule mediating cancer cell evasion of phagocytosis by the innate immune
system. CD47 appears to be an indispensable means by which cancer cells, including cancer
stem cells, overcome intrinsic expression of their prophagocytic *eat me* signals (Jaiswal 2009;
Majeti 2009). The progression from normal cell to cancer cell involves changes in genes and
gene expression that trigger programmed cell death and programmed cell removal (Chao 2012).
Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell
death, and the expression of the dominant antiphagocytic signal, CD47, may represent an
important checkpoint (Chao 2012). Increased CD47 expression was identified first on leukemic
stem cells in human acute myeloid leukemia (AML; Majeti 2009), and since then, it has been
found that CD47 expression is increased on the surface of cancer cells from a large number of

diverse human tumor types.

The magrolimab program represents a novel strategy for the treatment of cancer and is the first
therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have
demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon,
leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute
lymphoblastic leukemia, NHL, myeloma, MDS, and others).

For more information see protocol section 2.1 Background

Study objective

Primary (Efficacy):
To evaluate the efficacy of magrolimab + azacitidine compared with that of azacitidine + placebo in previously untreated participants with intermediate/high/very high risk MDS by IPSS-R as measured by CR rate
To evaluate the survival benefit of magrolimab + azacitidine compared with that of azacitidine + placebo

Study design

Patients will be randomized in 1:1 ratio to receive either magrolimab + azacitidine
(experimental arm) or azacitidine + placebo (control arm). Randomization will be stratified by
3 factors: 1) geographic region (US versus ex-US sites); 2) cytogenetic risk status (very
good/good/intermediate versus poor/very poor according to IPSS-R [Greenberg 2012]); and
3) percentage of bone marrow blasts (>= 10% versus < 10% blasts). The primary analysis of CR
rate will be conducted 8 months after 290 patients are randomized.

Patient participation will include screening, treatment, and follow-up. Screening will last up to
30 days before first dose of study treatment, during which time the patient*s eligibility and
baseline characteristics will be determined. Patients will receive study treatment per the dose
schedule in Table 1. No cross-over between arms is allowed. Study treatment may be continued
until disease progression (including treatment failure by International Working

Group [IWG]
2006 criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicities occur. In case patients discontinue the study treatment due to reasons other than disease progression, patients will be followed up for response assessments until documented disease progression occurs. For patients who come off the study treatment to receive an SCT, follow-up for response assessment and collection of SOC bone marrow biopsy/aspirate results will continue until documented disease progression occurs. Then patients will be observed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Treatment with azacitidine as standard of care is recommended for a minimum of 6 cycles.
Therefore, in this study, patients without evidence of disease progression (including treatment failure by IWG 2006 criteria or relapse after PR/CR), loss of clinical benefit, or unacceptable toxicity should continue azacitidine for at least 6 cycles. Patients may be discontinued from the treatment per Investigator*s discretion prior to reaching the recommended minimum cycles for any of these reasons detailed in Section 5.7.

Intervention

Magrolimab + azacitidine, or azacitidine + placebo as follows:

Magrolimab will be dosed intravenously (IV).
• Priming doses of magrolimab: 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11 and 15; and then 30 mg/kg weekly for a total of 5 doses (on Days 22, 29, 36, 43, and 50).
• Maintenance doses of magrolimab: 30 mg/kg on Day 57, and 30 mg/kg every 2 weeks thereafter.

Placebo
• Saline placebo to mirror the magrolimab dosing schedule above.

Azacitidine, 75 mg/m2
Azacitidine will be dosed according to region specific drug labeling, either SC or IV, at the standard clinical dose of 75 mg/m2 on Days 1 to 7 of a 28-day cycle in combination with magrolimab/placebo. Azacitidine may be administered on an alternative schedule of Days 1 to 5, Day 8, and Day 9 of a 28-day cycle

for flexibility and convenience

Study burden and risks

Overall, nonclinical and clinical data to date on magrolimab in combination with azacitidine
show the therapy to have evidence of efficacy in untreated higher risk MDS and show the
therapy to have an acceptable safety profile in this patient population. This encouraging activity
is based on a 92% ORR and 50% CR rate observed with no median DOR reached throughout a
median follow-up of 6.4 months. The safety profile of the combination is acceptable, with no
MTD reached and a treatment discontinuation rate due to AEs of 1.6%. No significant
exacerbation of azacitidine AEs by magrolimab has been observed, as evidenced by the
minimally observed myelosuppression from the combination. The efficacy of magrolimab +
azacitidine compares favorably to azacitidine monotherapy in higher risk MDS. To this point,
based on large historical studies, the ORR for azacitidine monotherapy ranges from 40% to 50%,
and the CR rate ranges from 6% to 17% (azacitidine US package insert, Silverman 2006;
Fenaux 2009). One additional study evaluating azacitidine demonstrated a CR rate of 24%;
however, this study also included lower risk MDS by IPSS-R and chronic myelomonocytic
leukemia participants with the CR rate specifically in higher risk MDS participants not reported
(Sekeres 2017).

Based on the scientific rationale, nonclinical data, and acceptable safety profile and encouraging
clinical activity data obtained for magrolimab in combination with azacitidine, the risk-benefit ratio is acceptable for proceeding forward with this study in untreated higher risk MDS.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Participants with MDS defined according to World Health Organization classification, with an IPSS-R prognostic risk category of intermediate, high, or very high risk. Note: participants who require AML-like therapy are not eligible. Prior and concurrent therapy with hydroxyurea, oral etoposide, erythroid, and/or myeloid growth factors is allowed.
2. White blood cell (WBC) count <= 20 × 10^3/µL prior to randomization. If the participant*s WBC is > 20 × 10^3/µL prior to randomization, the participant can be randomized, assuming all other eligibility criteria are met. Of note, while this does not impact eligibility, please ensure that the WBC is <= 20 × 10^3/µL prior to the first dose of study treatment and prior to each magrolimab/placebo dose for priming doses of magrolimab.
a) Participants can be treated with hydroxyurea (up to 4 g/day) throughout the study or prior to randomization to reduce the WBC to <= 20 × 10^3/µL to enable eligibility and magrolimab dosing. Oral etoposide (up to 200 mg orally per day) may be given as an alternative to hydroxyurea for participants who are intolerant to hydroxyurea or cannot achieve sufficient WBC lowering on hydroxyurea.
3. Participant has provided informed consent.
4. Participant is willing and able to comply with clinic visits and procedures

outlined in the study protocol.
5. Male or female, age >= 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2.
7. Willing to undergo blood transfusions as deemed clinically necessary.
8. Pretreatment blood cross-match including ABO (any of the 4 blood groups A, B, AB, and O comprising the ABO system)/Rh (Rhesus factor), DAT (direct antiglobulin test), and phenotyping or genotyping completed.
9. Biochemical indices within the ranges shown below:
a. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase <= 3× upper limit of normal (ULN)
b. Total bilirubin <= 1.5 × ULN or 3.0 × ULN and primarily unconjugated if participant has a documented history of Gilbert's syndrome or genetic equivalent
c. Serum creatinine <= 1.5 × ULN or calculated glomerular filtration rate (GFR) >= 40 mL/min/1.73 m2
10. All participants must have a documented hemoglobin >=9.0 g/dL within 24 hours prior to the first two doses of magrolimab/placebo infusion. Participants who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet the minimum haemoglobin threshold prior to administering each of the first 2 doses of magrolimab/placebo. Transfusions are allowed in order to meet hemoglobin eligibility.
11. Female participants of childbearing potential must not be nursing or planning to be pregnant and must have a negative urine or serum pregnancy test within 30 days before randomization and within 72 hours before the first administration of study treatment.
12. Male participants and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception as described in protocol Appendix H.
13. Willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines), unless not feasible as determined by the Investigator and discussed with the Sponsor.

Exclusion criteria

1. Prior treatment with CD47 or SIRPα-targeting agents.
2. Prior therapy for the treatment of MDS with an IPSS-R prognostic risk category of intermediate, high or very high risk (excluding hydroxyurea or oral etoposide), prior treatment with hypomethylating agents and/or low dose cytarabine. NOTE: Localized noncentral nervous system (CNS) radiotherapy, erythroid and/or myeloid growth factors, previous hormonal therapy with luteinizing hormone-releasing hormone (LHRH) agonists for prostate cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion. Prior lenalidomide is also not exclusionary.
3.Immediately eligible for an allogeneic SCT, as determined by the

Investigator, with an available donor.
4. Contraindications to azacitidine, including advanced malignant hepatic tumors or known hypersensitivity to azacitidine or mannitol.
5. Known inherited or acquired bleeding disorders.
6. Previous SCT within 6 months prior to randomization, active graft-versus-host disease, or requiring transplant-related immunosuppression.
7. Clinical suspicion of active CNS involvement by MDS.
8. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor, that would substantially increase the risk benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III-IV.
9. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which participants are not on active anticancer therapies and have had no evidence of active malignancy for at least >= 1 year.
10. History of psychiatric illness or substance abuse likely to interfere with the ability to comply with protocol requirements or give informed consent.
11. Pregnancy or active breastfeeding.
12. Known active or chronic hepatitis B or C infection or HIV infection in medical history.
13. Active hepatitis B virus (HBV) and/or active hepatitis C virus (HCV), and/or HIV following testing at screening:
a) Participants who test positive for hepatitis B surface antigen (HBsAg). Participants who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.
b) Participants who test positive for HCV antibody. These participants will require HCV RNA by quantitative PCR for confirmation of active disease.
c) Participants who test positive for HIV antibody.
d) Participants not currently on antiviral therapy and who have an undetectable viral load in the prior 3 months may be eligible for the study.

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:	Completed
Start date (anticipated):	07-01-2022
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Azacitidine
Generic name:	Vidaza
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Magrolimab
Generic name:	-

Ethics review

Approved WMO

Date:	08-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	01-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	27-07-2021
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2022
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	EUCTR2020-004287-26-NL
ClinicalTrials.gov	NCT04313881
CCMO	NL75750.056.21

Study results

Date completed: 17-08-2022

Results posted: 30-04-2024

First publication
01-02-2024

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File