A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

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Primary:• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in patients with previously untreated acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy as measured by...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54256

Source
ToetsingOnline

Brief title
ENHANCE-3 (GS-US-590-6154)

Condition

- Leukaemias
- Leukaemias

Synonym
AML; Leukemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Acute Meyloid Leukemia, GS-US-590-6154, Magrolimab versus Placebo, Phase 3

Outcome measures

Primary outcome

The primary endpoint is OS. Two interim OS analyses will be conducted, the first one after 121 deaths (40% of the expected 303 deaths), and the second one after 227 deaths (75% of the expected 303 deaths) are observed among all patients; the primary OS analysis will be conducted after 303 deaths have occurred.

Secondary outcome

• Rate of CR + CRh within 6 cycles of treatment

• Rate of CR within 6 cycles of treatment

• EFS

• Duration of CR + CRh in patients who achieved CR or CRh within 6 cycles of treatment

• DCR in patients who achieved CR within 6 cycles of treatment

• Rate of CR/CRhMRD- within 6 cycles of treatment

• Rate of CRMRD- within 6 cycles of treatment

• Transfusion independence conversion rate

• TTD on the GHS/QoL and the physical functioning scales of the EORTC QLQ-C30

• Incidence of treatment-emergent adverse events (AEs) and clinical laboratory abnormalities during the study

• Magrolimab serum concentrations over time

• Incidence/prevalence rate and magnitude of anti-magrolimab antibodies in serum

Exploratory study parameters/outcome of the study:

• Transfusion independence maintenance rate

• TTD on the EORTC QLQ-C30 pain, fatigue, role functioning, emotional functioning, social functioning, and cognitive functioning scales and single items

• Mean change from baseline on the EORTC QLQ-C30 domains, the EQ-VAS, and PGIS scale

• Descriptive summaries on the EQ-5D-5L descriptive system and PGIS/PGIC scales

• ORR within 6 cycles of treatment

• Rate of CR/CRiMRD- within 6 cycles of treatment

• Rate of CR + CRi within 6 cycles of treatment

• EFS (including CR and CRh)

• Rate of hematological improvement

• DOR in patients who achieved response within 6 cycles of treatment

• Duration of CR + CRi achieved within 6 cycles of treatment

• Rate of MRD negativity in patients with CR + CRi

• Rate of MRD negativity in patients with CR + CRh

• Rate of MRD negativity in patients with CR + CRi

• Rate of MRD negativity by flow cytometry and NGS, and concordance between methods

• Rate of SCT

• 30- and 60-day mortality rate

• Changes and percentage changes from baseline of biomarkers including biomarkers of immune cell recruitment or of immune cell signaling

• Biomarkers related to resistance, including mutational profile of leukemic clones, and immune profile of tumor microenvironment

Study description

Background summary

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Magrolimab versus Placebo in Combination with Venetoclax and Azacitidine in Newly Diagnosed, Previously Untreated Patients with Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

Study objective

Primary:
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine in patients with previously untreated acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy as measured by overall survival (OS)

Secondary:
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of complete remission (CR) + complete remission with partial hematologic recovery (CRh) within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by the rate of CR within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus

placebo + venetoclax + azacitidine as measured by event-free survival (EFS)
• To evaluate the duration of CR + CRh in patients whoachieved CR or CRh within 6 cycles of treatment
• To evaluate the duration of complete remission (DCR) in patients who achieved CR within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRh without minimal residual disease (MRD-) within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR without minimal residual disease (CRMRD-) within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by conversion rate of transfusion dependence to transfusion independence
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by time to first deterioration (TTD) on the global health status/quality of life (GHS/QoL) and the physical functioning scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
• To assess the safety and tolerability of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine
• To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab

Exploratory:
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by maintenance rate of transfusion independence
• To evaluate the health-related quality of life (HRQoL) of patients as measured by the EORTC QLQ-C30, EuroQol (5 dimensions, 5 levels) (EQ-5D-5L), and Patient Global Impression of Severity (PGIS)/Patient Global Impression of Change (PGIC)
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by objective response rate (ORR) and rate of CR + complete remission with incomplete hematologic recovery (CRi) achieved within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by rate of CR + CRi without minimal residual disease (MRD-) within 6 cycles of treatment
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by EFS (including CR and CRh)
• To compare the efficacy of magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine as measured by hematological improvement
• To evaluate the duration of response (DOR) and the duration of CR + CRi achieved within 6 cycles of treatment
• To evaluate minimal residual disease (MRD) negativity in patients with CR + CRh
• To evaluate minimal residual disease (MRD) negativity in patients with CR +

CRi
• To evaluate minimal MRD negativity by flow cytometry and next generation sequencing (NGS)
• To compare the rate of stem cell transplant (SCT) between magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine
• To evaluate 30- and 60-day mortality in patients treated with magrolimab + venetoclax + azacitidine versus placebo + venetoclax + azacitidine
• To assess biomarkers of immune cell recruitment and immune cell signaling
• To assess the mechanism of intrinsic and acquired resistance to magrolimab + venetoclax + azacitidine

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of magrolimab versus placebo in combination with venetoclax and azacitidine in newly diagnosed, previously untreated patients with AML who are ineligible for intensive chemotherapy. Approximately 432 patients will be randomized in 1:1 ratio to receive either magrolimab + venetoclax + azacitidine (experimental arm) or placebo
+ venetoclax + azacitidine (control arm). Randomization will be stratified by 3 factors:
•age (< 75 years, >= 75 years)
•genetic risk group (favorable/intermediate, adverse, unknown)
•geographic region (United States [US], outside the US)

The primary endpoint is OS. Two interim OS analyses will be conducted, the first one after 121 deaths (40% of the expected 303 deaths), and the second one after 227 deaths (75% of the expected 303 deaths) are observed among all patients; the primary OS analysis will be conducted after 303 deaths have occurred.

Number of Patients Planned: Approximately 432 patients in total

Intervention

Magrolimab 1 mg/kg intravenous (IV)
Magrolimab 15 mg/kg IV
Magrolimab 30 mg/kg IV
In combination with:
Venetoclax 10 mg oral
Venetoclax 50 mg oral
Venetoclax 100 mg oral
Venetoclax 200 mg oral
Venetoclax 400 mg oral
In combination with:
Azacitidine 75 mg/m2 IV or SC

Placebo for Magrolimab IV
In combination with:
Venetoclax 10 mg oral
Venetoclax 50 mg oral
Venetoclax 100 mg oral
Venetoclax 200 mg oral
Venetoclax 400 mg oral
In combination with:
Azacitidine 75 mg/m2 IV or SC

Duration of Treatment: Cycle length is 28 days and all patients will continue on study treatment unless they meet study treatment discontinuation criteria.

Study burden and risks

see ICF Secition 6 Appendix D

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Previously untreated patients with histological confirmation of AML by 2016 World Health Organization criteria who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to age, or comorbidity. Patients must be considered ineligible for intensive chemotherapy, defined by the following:
a)>= 75 years of age;
Or
b)>= 18 to 74 years of age with at least 1 of the following comorbidities:
i) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3
ii)Diffusing capacity of the lung of carbon monoxide <= 65% or forced expiratory volume in 1 second <= 65%
iii)Left ventricular ejection fraction <= 50%
iv)Baseline creatinine clearance >= 30 mL/min to < 45 mL/min calculated by the Cockcroft Gault formula or measured by 24-hour urine collection
v) Hepatic disorder with total bilirubin > 1.5 ** upper limit of normal (ULN)
vi) Any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy that must be approved by the sponsor*s medical monitor before study enrollment
2) ECOG performance status:
a)Of 0 to 2 for subjects >= 75 years of age
Or
b)Of 0 to 3 for subjects >= 18 to 74 years of age
3)Patients with white blood cell (WBC) count <= 20x10*3/µL prior to randomization. If the patient*s WBC is > 20x10*3/µL prior to randomization, the patient can be enrolled, assuming all other eligibility criteria are met.
However, the WBC should be <= 20x10*3/µL prior to the first dose of study treatment and prior to each magrolimab/placebo dose during Cycle 1.
NOTE: Patients can be treated with hydroxyurea and/or leukapheresis prior to randomization and throughout the study to reduce the WBC to <= 20x10*3/µL to enable eligibility for study drug dosing.
4)Hemoglobin must be >= 9 g/dL prior to initial dose of study treatment based on complete
blood count result.
NOTE: Transfusions are allowed to meet hemoglobin eligibility.
5) Patient has provided informed consent.
6) Patient is willing and able to comply with clinic visits and procedures outlined in the study
protocol.
7) Male or female, >= 18 years of age
8) Patients must have adequate renal function as demonstrated by a creatinine

clearance >= 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-hour urine collection.
9) Adequate liver function as demonstrated by:
a)aspartate aminotransferase <= 3.0xULN
b)alanine aminotransferase <= 3.0xULN
c) total bilirubin <= 1.5xULN, or primary unconjugated bilirubin <= 3.0xULN if patient has a documented history of Gilbert*s syndrome or genetic equivalent
d)Patients >= 18 to 74 years of age may have total bilirubin <= 3.0xULN
10) Pretreatment RBC phenotype or genotype completed
11) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.
12) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow assessments (aspirate and trephines).

Exclusion criteria

1) Positive serum pregnancy test
2) Breastfeeding female
3) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient.
4) Patients receiving any live vaccine within 4 weeks prior to initiation of study treatments.
5) Prior treatment with any of the following:
a) CD47 or signal regulatory protein alpha-targeting agents
b) Antileukemic therapy for the treatment of AML (eg, hypomethylating agents (HMAs), low-dose cytarabine, and/or venetoclax), excluding hydroxyurea
NOTE: Patients with prior myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) who have not received prior HMAs or venetoclax or chemotherapeutic agents for MDS/MPN may be enrolled in the study. Prior treatment with MDS/MPN therapies including, but not limited to lenalidomide, erythroid-stimulating agents, or similar red blood cell (RBC-), WBC-, or platelet-direct therapies or growth factors is allowed for these patients.
6) Current participation in another interventional clinical study
7) Known inherited or acquired bleeding disorders
8) Patients who have received treatment with strong and/or moderate CYP3A inducers (eg, preparations containing St. John*s wort) within 7 days prior to the initiation of study treatments
9) Patients who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment and are unwilling to discontinue consumption of these throughout the receipt of study drug
10) Patients who have malabsorption syndrome or other conditions that preclude enteral route of administration
11) Clinical suspicion of or documented active central nervous system (CNS)

involvement with AML
12) Patients who have acute promyelocytic leukemia
13) Significant disease or medical conditions, as assessed by the investigator 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 uncontrolled infection, and congestive heart failure New York Heart Association Class III to IV.
14) Known history, diagnosis, or suspicion of Hemophagocytic Lymphohistiocytosis (HLH) syndrome.
15) Second malignancy (except MDS) treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti- cancer therapies and have had no evidence of active malignancy for at least 1 year
NOTE: Patients on maintenance therapy alone who have no evidence of active malignancy
for at least >= 1 year are eligible.
NOTE: Localized non-CNS radiotherapy, erythroid and/or myeloid growth factors, hormonal therapy for prostate cancer, hormonal therapy or maintenance for breast cancer, and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are also not criteria for exclusion.
16) Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or HIV infection in medical history within 3 months of study entry.
17) Active HBV, and/or active HCV, and/or HIV following testing at screening:
a) Patients who test positive for hepatitis B surface antigen and patients who test positive for hepatitis B core antibody will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.
b) Patients who test positive for HCV antibody will require HCV RNA quantitative PCR for confirmation of active disease.
c) Patients who test positive for HIV antibody will require viral load testing: those 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:	Recruiting
Start date (anticipated):	20-04-2023
Enrollment:	33
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	N/A
Generic name:	Magrolimab
Product type:	Medicine
Brand name:	Venclyxto
Generic name:	Venetoclax
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vidaza
Generic name:	Azacitidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	25-01-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	30-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	19-02-2024
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	EUCTR2021-003434-36-NL
ClinicalTrials.gov	NCT05079230
CCMO	NL79260.029.22

Study results

Results posted: 23-10-2024

First publication
12-09-2024