A phase 3, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy.

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This study has been transitioned to CTIS with ID 2022-502832-37-00 check the CTIS register for the current data. To assess efficacy and safety of ivosidenib/enasidenib vs. placebo in combination with induction therapy and consolidation therapy...

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

Summary

ID

NL-OMON52917

Source
ToetsingOnline

Brief title
HOVON 150 / AMLSG 29-18

Condition

- Leukaemias

Synonym
AML, leukemia, MDS

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Celgene Corporation,HOVON;en firma's Celgene en I.R.I.S.,Institut de Recherches Internationales Servier I.R.I.S

Intervention

Keyword: AML/MDS, Enasidenib, IDH1/IDH2 mutation, Ivosidenib

Outcome measures

Primary outcome

- Event-free survival (EFS)

Secondary outcome

Key secondary endpoint:

- Overall survival (OS)

Other secondary endpoints:

- Relapse-free survival (RFS) after CR/CRi

- Cumulative incidence of relapse (CIR) after CR/CRi

- Cumulative incidence of death (CID) after CR/CRi

- Complete remission without minimal residual disease (CRMRD*) rate after

induction cycle 2

- Frequency and severity of adverse events according to CTCAE version 5.0

- CR/CRi rates after induction cycle 1 and 2

- CR/CRi rate after remission induction (i.e., CR or CRi as best response

during or at completion of induction therapy)

- Time to hematopoietic recovery after each chemotherapy treatment cycle

- Quality of life as assessed by EQ-5D-5L visual analogue scale (VAS) and EQ-5D

domains.

- Quality of life as assessed byEORTC-QLQ-C30 global health status/QoL scale

and other QLQ-C30 subdomains.

Study description

Background summary

Mutations in isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) are observed in approximately 20% of patients with newly diagnosed AML (cumulative percentage for both mutations). The rationale of the current study is that addition of drugs specifically designed to target leukemias harboring these mutations may improve treatment outcome in newly diagnosed patients when combined with standard induction and consolidation therapy and when given as maintenance therapy thereafter. The drugs investigated in this study are ivosidenib (AG-120) and enasidenib (AG-221), which are potent inhibitors of the IDH1 and IDH2 mutant proteins, respectively.

Study objective

This study has been transitioned to CTIS with ID 2022-502832-37-00 check the CTIS register for the current data.

To assess efficacy and safety of ivosidenib/enasidenib vs. placebo in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) with excess blasts-2 (EB2), with an IDH1 or IDH2 mutation, eligible for intensive chemotherapy.

Study design

Prospective, multicenter, double-blinded, randomized, placebo-controlled phase 3 clinical study.

Intervention

Based on the assessment of IDH1 or IDH2 mutations, patients will be randomized to receive one of the investigational drugs, ivosidenib or enasidenib, or a placebo in combination with standard induction and consolidation treatment. After completing induction and consolidation treatment, patients will receive maintenance therapy with the investigational drug or placebo according to the initial randomization.

Study burden and risks

Treatment outcomes for patients with AML or MDS-EB2 with IDH1 or IDH2 mutations treated with current standard of care including intensive chemotherapy are unsatisfactory. The selective oral IDH inhibitors ivosidenib and enasidenib have shown promising anti-leukemic activity in phase 1/2 clinical trials in patients with IDH1 or IDH2 mutations, respectively. When added to current treatment regimens, these inhibitors can potentially prevent relapse and improve long term outcome. The potential undesirable effects of ivosidenib and enasidenib in humans based on recent clinical studies are summarized in Section 9.7 and 9.8. Patients will have adequate and appropriate monitoring during the study to monitor for AEs and to minimize risk. The independent Data Safety Monitoring Board (DSMB) will perform review of the data as documented in the protocol and DSMB Charter.
The potential risks identified from non-clinical and clinical studies are judged to be acceptable in light of the potential benefits. Strict adherence to the eligibility criteria is essential to ensure that appropriate patients are selected for participation. Equally important is strict adherence to the schedule of safety assessments to ensure that patients are appropriately monitored.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Age >=18 years
• Newly diagnosed AML or MDS-EB2 defined according to WHO criteria, with a documented IDH1 or IDH2 gene mutation (as determined by the clinical trial assay) at a specific site (IDH1 R132, IDH2 R140, IDH2 R172). AML may be secondary to prior hematological disorders, including MDS, and/or therapy-related . Patients may have had previous treatment with hypomethylating agents (HMAs) for MDS. HMAs have to be stopped at least four weeks before registration
• Patients with dual mutant FLT3 and IDH1 or IDH2 mutations may be enrolled only if, for medical or other reasons, treatment with a FLT3 inhibitor is not considered.
• Considered to be eligible for intensive chemotherapy.
• ECOG/WHO performance status <= 2
• Adequate hepatic function as evidenced by:
o Serum total bilirubin <= 2.5 × upper limit of normal (ULN) unless considered due to Gilbert*s disease (e.g. a mutation in UGT1A1) (only for patients in IDH2 cohort), or leukemic involvement of the liver - following written approval by the (Co)Principal Investigator.
o Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) <= 3.0 × ULN, unless considered due to leukemic involvement of the liver, following written approval by the Principal Investigator.
• Adequate renal function as evidenced by creatinine clearance > 40 mL/min based on the Cockroft-Gault formula for glomerular filtration rate (GFR).

• Able to understand and willing to sign an informed consent form (ICF).
• Written informed consent
• Female patient must either:
o Be of nonchildbearing potential:
* Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
* Documented surgically sterile or status posthysterectomy (at least 1 month prior to screening)
o Or, if of childbearing potential,
* Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
* And have a negative urine or serum pregnancy test at screening
* And, if heterosexually active, agree to consistently use highly effective* contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after the final study drug administration.
*Highly effective forms of birth control include:
• Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
• Established intrauterine device (IUD) or intrauterine system (IUS),
• Bilateral tubal occlusion,
• Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
• Male is sterile due to a bilateral orchiectomy.
• Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual activity during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
*List is not all inclusive. Prior to enrollment, the investigator is responsible for confirming patient will utilize highly effective forms of birth control per the requirements of the CTFG Guidance document *Recommendations related to contraception and pregnancy testing in clinical trials', September 2014 (and any updates thereof) during the protocol defined period.
o Female patient must agree not to breastfeed starting at screening and throughout the study period, and for 2 months and 1 week after the final study drug administration.
o Female patient must not donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.
• Male patient and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 4 months and 1 week after the final study drug administration
• Male patient must not donate sperm starting at screening and throughout the study period and for 4 months and 1 week after the final study drug

administration.
.• Subject agrees not to participate in another interventional study while on treatment

Exclusion criteria

• Prior chemotherapy for AML or MDS-EB2 (with the exception of HMA). Hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis (e.g., white blood cell [WBC] counts > 30x109/L).
• Dual IDH1 and IDH2 mutations.
• Acute promyelocytic leukemia (APL) with PML-RARA or one of the other pathognomonic variant fusion genes/chromosome translocations.
• Blast crisis after chronic myeloid leukemia (CML).
• Known allergy or suspected hypersensitivity to Ivosidenib or Enasidenib and/or any exipients.
• Taking medications with narrow therapeutic windows with potential interaction with investigational medication unless the patient can be transferred to other medications prior to enrolling or unless the medications can be properly monitored during the study.
• Taking P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporter-sensitive substrate medications unless the patient can be transferred to other medications within >= 5 half-lives prior to administration of ivosidenib or enasidenib, or unless the medications can be properly monitored during the study.
• Breast feeding at the start of study treatment.
• Active infection, including hepatitis B or C or HIV infection that is uncontrolled at randomization. An infection controlled with an approved or closely monitored antibiotic/antifungal treatment is allowed.
• Patients with a currently active second malignancy. Patients are not considered to have a currently active malignancy if they have completed therapy and are considered by their physician to be at < 30% risk of relapse within one year. However, patients with the following history/concurrent conditions are allowed:
o Basal or squamous cell carcinoma of the skin
o Carcinoma in situ of the cervix
o Carcinoma in situ of the breast
o Incidental histologic finding of prostate cancer
• Significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure ;
myocardial infarction, unstable angina and/or stroke; or left ventricular ejection fraction (LVEF) < 40% by ultrasound or MUGA scan obtained within 28 days prior to the start of study treatment.
• QTc interval using Fridericia*s formula (QTcF) >= 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart

failure, family history of long QT interval syndrome). Prolonged QTc interval associated with bundle branch block or pacemaking is permitted with written approval of the (co)Principal Investigator.
• Taking medications that are known to prolong the QT interval (see Appendix K), unless deemed critical and without a suitable alternative. In those cases, they may be administered, but with proper monitoring (see section 10.2, Table 13)
• Dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of orally administered drugs.
• Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid (CSF) during screening is only required if there is a clinical suspicion of CNS involvement by leukemia during screening.
• A known medical history of progressive multifocal leukoencephalopathy (PML)
• Immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or severe disseminated intravascular coagulation
• Any other medical condition deemed by the Investigator to be likely to interfere with a patient*s ability to give informed consent or participate in the study.
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

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):	19-06-2019

Enrollment:	196
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	onbekend
Generic name:	Enasidenib
Product type:	Medicine
Brand name:	onbekend
Generic name:	Ivosidenib

Ethics review

Approved WMO Date:	18-10-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	21-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2024
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
EU-CTR	CTIS2022-502832-37-00
EudraCT	EUCTR2018-000451-41-NL
CCMO	NL66002.029.18