A phase 3, multicenter, open-label, randomized, study of gilteritinib versus midostaurin in combination with induction and consolidation therapy followed by one-year maintenance in patients with newly diagnosed Acute Myeloid Leukemia (AML) or Myelodysplastic syndromes with excess blasts-2 (MDS-EB2) with FLT3 mutations eligible for intensive chemotherapy

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This study has been transitioned to CTIS with ID 2022-502478-18-00 check the CTIS register for the current data. To compare OS between gilteritinib and midostaurin in combination with induction therapy and consolidation therapy followed by one-year...

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

Summary

ID

NL-OMON54682

Source
ToetsingOnline

Brief title
HOVON 156 AML / AMLSG 28-18

Condition

- Leukaemias
- Leukaemias

Synonym
Acute myeloid leukemia, AML, MDS-EB2

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Astellas Pharma,HOVON

Intervention

Keyword: AML, FLT3, Gilteritinib, Midostaurin

Outcome measures

Primary outcome

Overall survival (OS)

Secondary outcome

- Event-free survival (EFS)

- Complete remission (CR) rate after induction (i.e., CR as best response

during or at completion of induction)

- Prolongation of EFS with a modified CR by 60 days after initiation of the

last induction cycle (mEFS)

- CR and CRi rates after induction cycle 1 and after induction cycle 2

- Relapse-free survival (RFS) after CR

- Cumulative incidence of relapse (CIR) after CR

- Cumulative incidence of death (CID) after CR

- Complete remission and CR/CRi without minimal residual disease (CRmrd* and

CR/CRi mrd-) rate

- Frequency and severity of adverse events according to CTCAE

- Time to hematopoietic recovery after each chemotherapy treatment cycle

Study description

Background summary

AML and MDS-EB2 are malignant diseases of the bone marrow. The standard treatment for these diseases is chemotherapy. A specific type of these diseases consists of an error in DNA in the blasts. This is the FLT3 mutation, which leads to a change of a certain protein (FLT3) on the blasts. This altered protein plays an important role in the development of leukemia and the survival of leukemic cells.

FLT3 can be inhibited by the drug midostaurin. Adding midostaurin to chemotherapy leads to better treatment results in patients with AML. Therefore, the standard treatment for AML or MDS-EB2 with a FLT3 mutation (FLT3-AML) is a combination of chemotherapy and midostaurin.

Gilteritinib is also a medication that inhibits FLT3. In laboratory studies, gilteritinib was found to be significantly more specific and potent than midostaurin in inhibiting FLT3.
Gilteritinib has subsequently been studied in patients with AML, who relapsed after previous treatment with chemotherapy. This resulted in a much larger number of complete remission than previously seen when comparable patients were treated with midostaurin. Because gilteritinib is more focused on FLT3 compared to midostaurin, we hope that this will also lead to fewer side effects.

Study objective

This study has been transitioned to CTIS with ID 2022-502478-18-00 check the CTIS register for the current data.

To compare OS between gilteritinib and midostaurin in combination with induction therapy and consolidation therapy followed by one-year maintenance therapy in patients with newly diagnosed AML with a FLT3 gene mutation eligible for intensive chemotherapy.

Study design

Prospective, multicenter, open-label, randomized, phase 3 clinical study.

Intervention

Patients with FLT3 mutation will be randomized to receive either the investigational drug gilteritinib (120 mg QD PO) or midostaurin (50 mg BID) given sequentially to standard induction and consolidation chemotherapy. After completing induction and consolidation treatment, patients who achieve CR/CRi/MLFS will receive maintenance therapy with gilteritinib or midostaurin

Study burden and risks

Investigations (e.g. bone marrow and blood assessments) of patients in this trial will largely follow routine standard-of-care that would also be provided to patients not included in a clinical trial. It is therefore anticipated that the additional burden of trial-related risks will be limited.

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 with excess of blasts-2 (EB2) defined according to WHO criteria (appendix A), with centrally documented FLT3 gene mutation (either TKD or ITD or both). AML may be secondary to prior hematological disorders, including MDS, and/or therapy-related. Patients may have had previous treatment with erythropoiesis stimulating agents (ESA) for MDS. ESA have to be stopped at least four weeks before registration
• FLT3 mutation as assessed by DNA fragment analysis PCR for FLT3-ITD and FLT3-TKD mutation. Positivity is defined as a FLT3-ITD or FLT3-TKD / FLT3-WT ratio of >= 0.05 (5%).
• Considered to be eligible for intensive chemotherapy
• Patient is suitable for oral administration of study drug
• WHO/ECOG performance status <= 2
• Adequate hepatic function as evidenced by
o Serum total bilirubin <= 2.5 × upper limit of normal (ULN) unless considered due to leukemic involvement 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 following written approval by the (co) Principal Investigator
• Adequate renal function as defined by creatinine clearance > 40 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR)
• Written informed consent
• Patient is capable of giving 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.
• Patient agrees not to participate in another interventional study while on treatment

Exclusion criteria

• Prior chemotherapy for AML or MDS-EB2, including prior treatment with hypomethylating agents. Hydroxyurea is allowed for the control of peripheral leukemic blasts in patients with leukocytosis (e.g., white blood cell [WBC] counts > 30 x 10^9/L)
• Acute promyelocytic leukemia (APL) with PML-RARA or one of the other pathognomonic variant fusion genes/chromosome translocations
• Blast crisis after CML
• Known or suspected hypersensitivity to midostaurin or gilteritinib and/or any excipients
• Patient requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A
• Breast feeding at 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/antiviral/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 less than 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:
o New York Heart Association (NYHA) Class III or IV congestive heart failure;
o Myocardial infarction;
o Unstable angina and/or stroke;
o Left ventricular ejection fraction (LVEF) < 40% by ECHO or MUGA scan obtained within 28 days prior to the start of study treatment
• QTc interval using Fridericia*s formula (QTcF) >= 450 msec (average of triplicate determinations) 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.
• Patient with hypokalemia and/or hypomagnesemia before registration (defined as values below LLN) Note: electrolyte suppletion is allowed to correct LLN values before registration.
• 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
• Immediate life-threatening, severe complications of leukemia such as uncontrolled bleeding and/or disseminated intravascular coagulation
• Any other medical or psychological 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:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-12-2019
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ASP2215
Generic name:	Gilteritinib
Product type:	Medicine
Brand name:	Rydapt
Generic name:	Midostaurin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2019
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
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:	15-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2023
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:	24-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2024
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
EU-CTR	CTIS2022-502478-18-00
EudraCT	EUCTR2018-000624-33-NL
ClinicalTrials.gov	NCT04027309
CCMO	NL66038.029.18