A phase Ib feasibility study of the combination of panobinostat and midostaurin in recipients of allogeneic stem cell transplantation with FLT3-ITD AML

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Primary objective:To asses the safety and feasibility of post-transplant panobinostat combined with midostaurin in patients with adverse risk AML/RAEB with FLT3-ITD with high allelic ratio in terms of dose limiting toxicity.Secondary objectives:To...

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

Summary

ID

NL-OMON48580

Source
ToetsingOnline

Brief title
HOVON 148 AML

Condition

- Leukaemias

Synonym
Acute myeloid leukemia, AML, MDS

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: AML, FLT3-ITD, Midostaurin, Panobinostat

Outcome measures

Primary outcome

Feasibility of protocol treatment as defined by the number of dose limiting toxicities (DLTs) during the first cycle of PNB/MST.

Secondary outcome

• Number of PNB/MST cycles given.

• Complete hematological remission (with full peripheral blood recovery) rate at 3, 6 and 12 months post alloHSCT

• MRD after PNB/MST cycle 3, or at 6 months post alloHSCT if patient goes off protocol treatment early.

• Relapse/progression rate as assessed after cycle 1, 3, 5 and 7 and at 12 months post alloHSCT, or at approx. 3, 6 and 12 months post alloHSCT in case of early termination of protocol treatment.at 3, 6, and 12 months post alloHSCT

• OS defined as the time from alloHSCT to death from any cause

• PFS from alloHSCT with relapse (for patients in CR) and progression (for patients in PR) and death from any cause as events

• Engraftment and chimerism at 3, 6, and 12 months post alloHSCT

• (Serious) adverse events

• The incidence and severity of acute and chronic GvHD up to 12 months post

alloHSCT

• NRM up to 12 months post alloHSCT

• Number and percentage of registered patients starting protocol treatment)

• Number and percentage of patients receiving post-transplant epigenetic

therapy after alloHSCT and the duration of epigenetic treatment in patients who

discontinue study treatment prematurely

Study description

Background summary

The hypothesis of this study is that a combination of panobinostat with midostaurin may be effective for preventing relapse of patients with a high allelic ratio FLT3-ITD positive AML after hematopoietic stem cell transplantation (HSCT). We have previously demonstrated that panobinostat as post-HSCT maintenance therapy for high-risk AML and MDS is feasible and associated with a favourable outcome, presumably through modulation of the allogeneic anti-leukemic immune response. Midostaurin has been shown by the RATIFY trial to be effective in FLT3-ITD-positive AML. Patients with a high allelic ratio of FLT3-ITD are at high risk of relapse after an allogeneic HSCT. Therefore, we reason that FLT3 inhibition in addition to panobinostat-mediated immunomodulation may be more effective to prevent relapse than either therapy alone. Furthermore, the combination seems rational, since panobinostat is known to induce proteasomal degradation of FLT3-ITD and might therefore add antileukemic activity to midostaurin. Also, FLT3-ITD inhibition alone runs the risk of secondary resistance due to resistance mutations or due to the activation of redundant signalling pathways.
Here, we therefore plan to select patients with high allelic ratio of FLT3-ITD (>0.5) prior to allogeneic HSCT to be treated after HSCT with the combination of panobinostat and midostaurin with the aim to:
- Administer antileukemic activity and at the same time to
- Modulate the immune system to enhance the graft-versus-leukemia (GvL) effect.

Study objective

Primary objective:
To asses the safety and feasibility of post-transplant panobinostat combined with midostaurin in patients with adverse risk AML/RAEB with FLT3-ITD with high allelic ratio in terms of dose limiting toxicity.

Secondary objectives:
To assess feasibility in terms of completion of the protocol treatment
To assess efficacy in terms of complete hematological remission rate with full peripheral blood recovery, residual disease response rate, overall and progression free survival, chimerism, immune recovery, and toxicities.

Study design

Multicenter, prospective phase Ib trial

Intervention

This is a dose-escalation study of midostaurin (MST) in combination with a fixed dose panobinostat in high allelic ratio FLT3-ITD positive AML. Patients will receive panobinostat (PNB) at a starting dose of 20 mg once a day three times a week every other week for each cycle of 4 weeks. Midostaurin treatment will start at a daily dose of 50 mg and escalated in successive cohorts of 5-10 patients to 75 mg (50-25 mg) and 100 mg (50 mg bid) which is the maximum target dose. No intrapatient dose escalation is allowed. Treatment will be continued for a maximum of one year as from transplantation in the absence of relapse or unacceptable toxicity.

Study burden and risks

Although alloHSCT is standard care in adverse risk AML/RAEB with FLT3-ITD, the incidence of relapse after alloHSCT is high, especially if the allelic ratio > 0.5.
We recently showed that PNB post-transplant may prevent relapse, although very-poor risk patients and/or patients with MRD are at greater risk for relapse. It is hypothesized that the addition of midostaurin to PNB may further reduce the risk of relapse and thereby improve outcome. The risks associated with this procedure are opportunistic infections associated with neutropenia and lymphopenia, that may occur after PNB/MST, as compared to standard alloHSCT.

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

• Adult patients (18-70 years of age);
• AML (except acute promyelocytic leukemia, AML M3 and bcr/abl positive AML) according to WHO 2016 classification or RAEB with IPSS-R > 4.5 with high mutant to wild-type allelic ratio of FLT3-ITD;
• Newly diagnosed or in first relapse having obtained remission after induction chemotherapy;
• First allogeneic HSCT scheduled within the next 2 months upon having achieved hematological remission (<5% blasts at the bone marrow level);
• Matched sibling or matched unrelated donor (i.e. 10/10 or 9/10 HLA-matched) or haploidentical donor;
• Using one of the following conditioning regimens:
-Fludarabine/Cyclophosphamide/TBI 2 Gy in combination with post-Tx cyclophosphamide (PT-CY) only;
-Fludarabine/Busulfan or Melphalan/Fludarabine/TBI or fludarabin/TBI 8 Gy with post-transplant cyclophosphamide;
or one of the alternative regimen in the protocol;
• No history of significant cardiac disease and absence of active symptoms, otherwise documented left ventricular EF> 40%;
• Negative serum pregnancy test for female patients of childbearing potential, at registration;
• Female patients of childbearing potential and all men must be willing and able to use an effective contraceptive method during the study and for a minimum of 6 months after study treatment;

• Written informed consent.

Exclusion criteria

• Known HIV or HCV positivity;
• History of active malignancy during the past 2 years with the exception of basal carcinoma of the skin or carcinoma *in situ* of the cervix or breast;
• Pregnant or breast-feeding female patients;
• Psychiatric disorder that interferes with ability to understand the study and give informed consent, and/or impacts study participation or follow-up;

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-08-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farydak
Generic name:	panobinostat
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Rydapt
Generic name:	midostaurin

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2017-002335-42-NL
CCMO	NL62303.078.17