European Intergroup Trial on panobinostat maintenance after HSCT for high-risk AML and MDS - A randomized, multicenter phase III study to assess the efficacy of panobinostat maintenance therapy vs. standard of care following allogeneic stem cell transplantation in patients with high-risk AML or MDS (ETAL-4 / HOVON-145)

Published: 09-07-2018
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Primary objective* To determine the efficacy of panobinostat maintenance therapy versus standard of care administered to patients with high-risk MDS or AML in complete hematologic remission after an allogeneic hematologic stem cell transplantation (...

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

Summary

ID

NL-OMON55887

Source
ToetsingOnline

Brief title
HOVON 145 AML / ETAL-4

Condition

- Leukaemias

Synonym
acute myeoloid leukemia, myelodysplasia

Research involving
Human

Sponsors and support

Primary sponsor: Goethe Unversität, Frankfurt, Main, Germany
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: AML, HSCT, maintenance, MDS

Outcome measures

Primary outcome

Overall survival

Secondary outcome

- Event-free survival (EFS)

- Disease-free survival (DFS)

- Cumulative incidence of hematologic relapse

- Cumulative incidence, time and cause of non-relapse mortality

- Cumulative incidence of new onset or aggravation of acute GvHD grade III-IV

- Cumulative incidence and maximal grade of severity of chronic GvHD requiring

systemic treatment within one year after HSCT

- Percentage of patients who are free of systemic immunosuppressive therapy at

one and two years after HSCT

- Percentage of patients completing the one year study treatment and duration

of panobinostat administration in patients who discontinue study treatment

prematurely

- Percentage of patients with MRD conversion from baseline to 6 months after

HSCT

- Patient-reported HRQoL during panobinostat maintenance therapy

Study description

Background summary

Collectively, the PANOBEST and HOVON-116 studies provide the rationale for a European prospective randomized trial of panobinostat as post-transplant intervention with the aim to determine the definite role of DACi maintenance for high-risk myeloid malignancies (Table 7). Together with available data from clinical trials of post-transplant HMA, they support a prophylactic versus a pre-emptive strategy, particularly given the limited availability of highly sensitive and clinically validated MRD markers and the lower clinical burden in the MRD negative setting. Following HSCT, a timely initiation of panobinostat treatment is needed to make the potentially beneficial therapy accessible to patients with aggressive diseases, but the panobinostat dose must be chosen carefully, taking into account the vulnerability of the hematopoietic and immune reconstitution in the early post-transplant period.

Study objective

Primary objective
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To determine the efficacy of panobinostat maintenance therapy versus standard of care administered to patients with high-risk MDS or AML in complete hematologic remission after an allogeneic hematologic stem cell transplantation (HSCT)

Secondary objectives

- To assess the safety and tolerability of panobinostat maintenance therapy after HSCT compared with standard of care
- To evaluate HRQoL of patients under panobinostat maintenance therapy after HSCT
- To study the treatment effect in subgroups of patients defined by treatment approach (i.e. HOVON-approach vs. RIC vs MAC conditioning), donor type

(HLA-compatible versus haploidentical) and molecular distinct subgroups of AML/MDS

Study design

Multicenter, randomized phase III trial

Intervention

Patients will receive panobinostat at a starting dose of 20 mg, once a day, three days per week, every other week. Study treatment will be started within 7 days after randomization and continued for a maximum of one year after HSCT in the absence of relapse or unacceptable toxicity.

Study burden and risks

Although alloHSCT is standard care in high risk AML or MDS, the incidence of relapse after alloHSCT is high. We recently showed that treatment with panobinostat post transplant may prevent relapse. The risk associated with panobinostat treatment are opportunistic infections, associated with neutropenia and lymphopenia.

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 with PML-RARA and AML with BCR-ABL1) according to WHO 2016 classification with high-risk features defined as one or more of the following criteria:
- refractory to or relapsed after at least one cycle of standard chemotherapy
- > 10% bone marrow blasts at day 14-21 of the first induction cycle
- adverse risk according to ELN 2017 risk stratification by genetics regardless of
stage
- secondary to MDS or radio-/chemotherapy
- MRD positive before HSCT based on flow cytometry or PCR
or, - MDS with excess blasts (MDS-EB) according to the WHO 2016 classification, or high-risk or very high-risk according to IPSS-R

Exclusion criteria

- Active acute GvHD grade III-IV according to modified Glucksberg criteria
- Active acute GvHD grade II or chronic GvHD moderate/severe according to NIH criteria requiring systemic corticosteroids > 0.5 mg/kg body weight of methylprednisolone equivalent or combination immunosuppressive treatment
- Uncontrolled or significant heart disease, including recent myocardiac infarction, cardiac failure (NYHA II-IV), unstable angina pectoris, or clinically significant bradycardia
- Long QT syndrome
- QTcF >=*480 msec on screening ECG to be performed within 14 days prior to enrollment
- Concurrent use of medications that have a relative risk of prolonging QT interval or of inducing Torsade de Pointes, if such treatment cannot be discontinued or switched to a different medication prior to the first dose of study drug.

- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, chronic obstructive or chronic restrictive pulmonary disease including dyspnoea at rest from any cause) or history of serious organ dysfunction or disease involving the heart, kidney, or liver and/or seropositive HIV or HCV .
- Serious active infection
- CMV reactivation, which is not responsive to first-line valganciclovir or ganciclovir
- Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral panobinostat (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, obstruction, or stomach and/or small bowel resection).
- Pregnancy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-02-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2021
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	EUCTR2017-0007640-1-NL
CCMO	NL63857.078.17