Randomized study with a run-in dose-selection phase to assess the added value of lenalidomide in combination with standard remission-induction chemotherapy and post-remission treatment in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or high risk myelodysplasia (MDS) (IPSS-R risk score > 4.5)

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20903

Source
Nationaal Trial Register

Brief title
HOVON 132 AML

Health condition

Acute Myeloid Leukemia (AML), myelodysplasia (MDS), Lenalidomide

Sponsors and support

Primary sponsor: HOVON Data Center
Source(s) of monetary or material Support: Genzyme Corporation, KWF kanker bestrijding, HOVON

Intervention

Outcome measures

Primary outcome

Part A-run-in: Lenalidomide dose level selection
DLT and duration of myelosuppression of induction treatment with or without lenalidomide for each of the distinct predefined dose levels

Part A: Induction - Efficacy
EFS after induction treatment with or without lenalidomide (i.e., time from registration to induction failure, death from any cause or relapse whichever occurs first)

Part B: Maintenance - Efficacy
Cumulative incidence of relapse (CIR) after second randomization (maintenance treatment with lenalidomide or observation only)

Secondary outcome

Part A Run-in : Lenalidomide dose level selection
Response (CR and CRi) after induction therapy cycles I and II

Part A: Induction- Efficacy
1. EFS in the distinct prognostic subsets (AML good-risk vs. AML intermediate-risk vs. AML poor-risk vs. AML-very poor-risk) and cytogenetically and molecularly defined subgroups of AML
2. Response (CR and CRi) after induction therapy cycles I and II
3. Disease-free survival (DFS, measured from time of CR/CRi to day of relapse or death from any cause, whichever occurs first)
4. OS measured from the time of registration
5. Outcome of induction treatments in relation to MRD measurements
6. Evaluation of molecular prognostic markers and gene expression profiles for and overexpression of defined genes (e.g. EVI1, cereblon) for outcome in relation to induction and post induction treatments
7. Toxicities
8. Evaluation of MRD after induction and post-induction treatments
9. Time to hematopoietic recovery (ANC 0.5 and 1.0 x 109/L; platelets 50 and 100 x 109/L) after each treatment cycle
10. Number of platelet transfusions and last day of platelet transfusion after each cycle

11. Impact of the use of lenalidomide on the effectiveness of stem cell mobilization

Part B: Maintenance - efficacy
1. OS and DFS measured from 2nd randomization, and also in the distinct prognostic subsets (AML good-risk vs. AML intermediate-risk vs. AML poor-risk vs. AML very poor-risk) and cytogenetically and molecularly defined subgroups of AML
2. Toxicities
3. Number of platelet transfusions and last day of platelet transfusion after each cycle
4. Number of RBC transfusions in relation to maintenance or no maintenance treatment
5. Evaluation of MRD after 2nd randomization
6. Time to hematopoietic recovery (ANC 0.5 and 1.0x109/L; platelets 50 and 100x109/L) after each treatment cycle

Study description

Background summary

Study design
Phase III randomized trial for remission
induction as well as for the maintenance starting with a dose selection run-in phase.

Patient population
Patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or myelodysplasia (MDS) with IPSS-R > 4.5.

Intervention
First, we will establish in a randomized run-in study the dose level of lenalidomide in addition to the standard induction treatment of idarubicin/cytarabine (cycle I) and daunorubicine/cytarabine (cycle II) (part A-run-in).
Following the dose-selection phase the study will continue as a randomized study for induction therapy (part A).
Subsequently, we will also investigate the effect of lenalidomide maintenance treatment (10 mg/day) by randomization to be administered in first CR.

Duration of treatment
Patients will receive an induction treatment of 2-3 months. If eligible for the second part of the study, patients in the maintenance arm will receive maintenance therapy for 7 to 8 months.
Subsequently, patients will be followed until 10 years after registration for the phase III trial.

Study objective

The hypothesis to be tested is that arm B is tolerable and that the outcome in arm B is better than in arm A.

Study design

1. At entry
2. After each induction cycle
3. After cycle III, autoSCT of alloSCT
4. Before start each maintenance cycle or every 5 weeks
5. During follow up: every 6 months

Intervention

1. A randomized run-in study to establish the dose level of lenalidomide in addition to the standard induction treatment of idarubicin/cytarabine (cycle I) and daunorubicine/cytarabine (cycle II) (part A-run-in).
2. Following the dose-selection phase the study will continue as a randomized study for induction therapy (part A).
3. Subsequently, the effect of lenalidomide maintenance treatment (10 mg/day) by randomization to be administered in first CR will be investigated.

Contacts

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Eligibility criteria

Inclusion criteria

First randomization:
1. Age 18-65 years, inclusive

2. Patients with
a. A diagnosis of AML and related precursor neoplasms according to WHO 2008 classification (excluding acute promyelocytic leukemia) including secondary AML (after an antecedent hematological disease (e.g. MDS) and therapy-related AML), or
b. Acute leukemia's of ambiguous lineage according to WHO 2008 or
c. A diagnosis of refractory anemia with excess of blasts (MDS) and IPSS-R score > 4.5
3. WHO performance status 0, 1 or 2
4. Sampled bone marrow and/ blood cells at diagnosis for centralized molecular analysis, MRD evaluation and biobanking, unless in case of a dry marrow tap with no possibility to collect marrow cells. In cases of marrow tap failure only blood cells will be sampled.
5. Adequate renal and hepatic functions unless clearly disease related as indicated by the following laboratory values:
a. Serum creatinine ≤1.0 mg/dL (≤88.7 µmol/L); if serum creatinine >1.0 mg/dL (>88.7 µmol/L), then the estimated glomerular filtration rate (GFR) must be >60 mL/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m2) = 186 x (Serum Creatinine in mg/dL)-1.154 x (age in years)-0.203 x (0.742 if patient is female) x (1.212 if patient is black). NOTE: if serum creatinine is measured in umol/L, recalculate it in mg/dL according to the equation: 1 mg/dL = 88.7 umol/L) and use above mentioned formula.
b. Serum bilirubin ≤2.5 x upper limit of normal (ULN)
c. Aspartate transaminase (AST) ≤ 2.5 x ULN
d. Alanine transaminase (ALT) ≤ 2.5 x ULN
e. Alkaline phosphatase ≤ 2.5 x ULN
6. Written informed consent
7. Ability and willingess to adhere to the lenalidomide Pregnancy Prevention Program

Second randomization:
1. CR or CRi
2. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
3. Platelet count ≥ 75 x 10^9/L
4. Serum creatinine clearance ≥ 30 ml/min or estimated glomerular filtration rate (GFR) >60mL/min/1.73 m2
5. Total bilirubin ≤ 2.5 x ULN
6. AST ≤ 2.5 x ULN
7. ALT ≤ 2.5 x ULN

Exclusion criteria

First randomization:
1. Previous therapy with lenalidomide
2. Acute promyelocytic leukemia
3. Myeloproliferative neoplasia
4. Previous treatment for AML or high risk MDS (IPSS-R > 4.5), except hydroxyurea
5. Concurrent history of active malignancy in two past years prior to diagnosis except for:
a. Basal and squamous cell carcinoma of the skin

b. In situ carcinoma of the cervix
6. Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera)
7. Cardiac dysfunction as defined by:
a. Myocardial infarction within the last 6 months of study entry, or
b. Reduced left ventricular function with an ejection fraction < 50% as measured by MUG scan or echocardiogram or
c. Unstable angina, or
d. Unstable cardiac arrhythmias
8. Pregnant or lactating females
9. Unwilling or not capable to use effective means of birth control
10. Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Second randomization:
1. Severe cardiac dysfunction (NYHA classification II-IV, see appendix G)
2. Severe pulmonary dysfunction (CTCAE grade III-IV, see appendix F)
3. Severe neurological or psychiatric disease
4. Serious active infections
5. Previous serious toxicities related to the use of lenalidomide
6. CMV reactivation, which is not responsive to first line valganciclovir

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2014
Enrollment:	972
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	14-01-2014
Application type:	First submission

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
NTR-new	NL4231
NTR-old	NTR4376
Other	2013-002843-26 : HO132 AML

Study results

Summary results
N/A