HOVON 132 AML / SAKK 30/13, 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)

Published: 13-11-2013
Last updated: 22-04-2024

See above

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

Summary

ID

NL-OMON55471

Source
ToetsingOnline

Brief title
HOVON 132 AML/ SAKK 30/13

Condition

- Leukaemias
- Leukaemias

Synonym
Acute Myeloid Leukemia, Myelodysplasia

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: KWF;HOVON,Celgene Corporation

Intervention

Keyword: AML, Lenalidomide, Leukemia, MDS

Outcome measures

Primary outcome

Primary endpoint 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

Primary endpoint 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)

Primary endpoint Part B: Maintenance - Efficacy

- Cumulative incidence of relapse (CIR) after second randomization (maintenance

treatment with lenalidomide or observation only)

Secondary outcome

Secondary endpoints Part A Run-in : Lenalidomide dose level selection

- Response (CR and CRi) after induction therapy cycles I and II

Secondary endpoints Part A: Induction- Efficacy

- 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
- Response (CR and CRi) after induction therapy cycles I and II
- Disease-free survival (DFS, measured from time of CR/CRi to day of relapse or death from any cause, whichever occurs first)
- OS measured from the time of registration
- Outcome of induction treatments in relation to MRD measurements

-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

-Toxicities

-Evaluation of MRD after induction and post-induction treatments

-Time to hematopoietic recovery (ANC 0.5 and 1.0 x 10^9/L; platelets 50 and 100 x 10^9/L) after each treatment cycle

-Number of platelet transfusions and last day of platelet transfusion after each cycle

-Impact of the use of lenalidomide on the effectiveness of stem cell

mobilization

Secondary endpoints Part B: Maintenance - efficacy

- 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

- Toxicities

- Number of platelet transfusions and last day of platelet transfusion after each cycle

- Number of RBC transfusions in relation to maintenance or no maintenance treatment

- Evaluation of MRD after 2nd randomization

- Time to hematopoietic recovery (ANC 0.5 and 1.0x10 ^ 9/L; platelets 50 and 100x10^9/L) after each treatment cycle

Study description

Background summary

AML in adults continues to have a fatal prognosis in a great majority of patients. The medical need for new therapies in this important patient group has remained considerable. The study is a randomized Phase II in patients aged 18-65 years with newly diagnosed AML. In single arm studies the addition of lenalidomide to chemotherapy has shown encouraging clinical response rates with acceptable side effects in AML. Lenalidomide appears a highly active anti-AML drug that has mainly been examined in relapsed AML and in patients of older age, but not yet in the frontline in patients of younger age. A regimen of lenalidomide combined with standard remission induction chemotherapy which is potentially clinically valuable (as regards CR and CR duration, overall and in

prognostic subsets), has not yet been critically evaluated as regards feasibility and efficacy, nor in induction nor in a combination of induction treatment and nor in maintenance treatment. The latter questions represent the investigational objectives of the current study.

Study objective

See above

Study design

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

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.

Study burden and risks

In Part A of the study, all patients receive the standard treatment. Patients who receive study treatment will receive by randomisation the additional drug lenalidome in addition to standard treatment. In part B patients will receive as happens in the current default situation, no further treatment after the closing own stem cell transplantation or the last chemotherapy cycle. If they draw for research arm they will be treated with six concluding cycles of lenalidomide. The addition of this last maintenance treatment involves extra blood controls and possible additional likelihood of side effects with respect to the current standard.

Patients randomized for the lenalidomide arms may experience side effects.

Contacts

Public
HOVON

HOVON Centraal Bureau, VUMC, De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
HOVON

HOVON Centraal Bureau, VUMC, De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Part A:
1. Age 18-65 years, inclusive
2. Patients with
- 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
- acute leukemia*s of ambiguous lineage according to WHO 2008 or
- 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 for centralized molecular analysis and MRD evaluation, 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 as indicated by the following laboratory values:
- 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 m^2 as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m^2) = 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.
- Serum bilirubin <=2.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) <= 2.5 x ULN
- Alanine transaminase (ALT) <= 2.5 x ULN
- Alkaline phosphatase <= 2.5 x ULN
6. Written informed consent
7. Ability and willingness to adhere to the lenalidomide Pregnancy Prevention Program, Part B:
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/1.73^2
5. Total bilirubin <= 2.5 x ULN
6. AST <= 2.5 x ULN
7. ALT <= 2.5 x ULN

Exclusion criteria

Part A:
1. Previous therapy with lenalidomide
2. Acute promyelocytic leukemia
3. Previous treatment for AML or high risk MDS (IPSS-R > 4.5), except hydroxyurea
4. Concurrent history of active malignancy in two past years prior to diagnosis except for:
- basal and squamous cell carcinoma of the skin
- in situ carcinoma of the cervix
5. Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera)
6. Cardiac dysfunction as defined by:
- Myocardial infarction within the last 6 months of study entry, or
- Reduced left ventricular function with an ejection fraction < 50% as measured by MUGA scan or echocardiogram or
- Unstable angina, or
- Unstable cardiac arrhythmias
Hypersensitivity to the active substance or to any of the excipients of the drug product
7. Pregnant or lactating females

8. Unwilling or not capable to use effective means of birth control
9. Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule, Part B:
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 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:	Recruiting
Start date (anticipated):	24-04-2014
Enrollment:	395
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revlimid
Generic name:	lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-11-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2021
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	EUCTR2013-002843-26-NL
CCMO	NL45528.078.13