A randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral lenalidomide to standard induction therapy in AML and RAEB >= 66 years and very poor risk AML >= 18 years

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Primary objectivesPart A of the study (if applicable):1. To assess the safety and tolerability of Lenalidomide added to standard induction chemotherapy for AML and select the feasible dose level for part B of the study2. To assess in a randomized...

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

Summary

ID

NL-OMON39429

Source
ToetsingOnline

Brief title
HOVON 103 AML Lenalidomide

Condition

- Leukaemias
- Leukaemias

Synonym
Acute myeloid leukemia, leukemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Acute myeloid leukemia, RAEB, very poor risk AML

Outcome measures

Primary outcome

Part A:

DLT of Lenalidomide at three dose levels (10mg, 15mg and 20mg) added to

standard chemotherapy

DLT is defined as: Death within 31 days of start cycle I

Part B:

To assess in a randomized comparison the effect of the in Part A selected dose

of Lenalidomide on the CR rate.

Secondary outcome

Part B

- Overall survival (time from registration till the death of the patient.)

- Event free survival (i.e., time from registration to induction failure (i.e.

no CR on induction), death or relapse whichever occurs first)

- Disease free survival (time from CR on protocol treatment until relapse or

death, whichever comes first)

- Prognostic value of molecular markers and gene expression profiles of the

leukemia assessed at diagnosis

- Prognostic value of minimal residual disease (MRD) measurements following

therapy by standardized sampling of marrow/blood

Study description

Background summary

HOVON/SAKK Cooperative groups concentrate their developmental therapeutic efforts for the 66+ yrs age segment of AML patients and very poor risk AML of any age, on developing effective treatments for these patients, for whom current treatment in spite of active clinical research has remained highly unsatisfactory. Therefore new treatment modalities are introduced and evaluated in combination with standard chemotherapy. For this an approach is chosen with multiple parallel randomized phase II studies that will be conducted within the frame of a master protocol.
This will allow for introducing and evaluating new treatment modalities in combination with standard chemotherapy.
In this randomized Phase II study Lenalidomide is added to the standard chemotherapy for remission induction therapy of adults of age 66 years or older with acute myeloid leukaemia(AML), refractory anemia with excess of blasts(RAEB) with International Prognostic Score System (IPSS)>+ 1.5 or patients< 66 year with very poor risk AML. The aim of this study is to examine whether the addition of Lenalidomide to standard chemotherapy is feasible and whether the percentage of patients achieving a Complete Remission is promising enough as compared to the control arm to start a Phase III study. Lenalidomide is given orally in addition to daunorubicin and cytosin-arabinoside in cycle I and to cytosin-arabinoside in Cycle II during day 1-21. In the first part A of the study the feasibility of three dose levels (10,15,20mg) will be compared to the treatment without Lenalidomide in a randomized design. In the second part of the study the assigned dose will be tested compared to the control arm with CR as primary endpoint.

Study objective

Primary objectives
Part A of the study (if applicable):
1. To assess the safety and tolerability of Lenalidomide added to standard induction chemotherapy for AML and select the feasible dose level for part B of the study
2. To assess in a randomized comparison the effect of Lenalidomide on the CR rate.

Part B of the study:
1. To assess the safety and tolerability of Lenalidomide added to standard induction chemotherapy for AML as regards the selected dose level of Lenalidomide
2. To assess in a randomized comparison the effect of the in Part A selected dose of Lenalidomide on the CR rate.

Secondary objectives
For part B:
1. To determine the efficacy profile (event free survival and disease free survival and overall survival) associated with the two therapy regimens.
2. To measure MRD by immunophenotyping in relation to clinical response parameters.
3. To identify potential biomarkers predictive of response, event free survival and disease free survival.by exploratory genomic analysis (microarray, gene mutations)

Study design

This is a prospective, open label, multicenter study that is conducted in the frame of a masterprotocol with multiple parallel randomized phase II studies. The scheme of this design consists of one arm with the standard treatment for AML as compared to various arms with experimental treatments. Patients in this study are treated with standard induction chemotherapy with or without lenalidomide. During the first part A of the studies the feasibility of combining lenalidomide with DNR/Ara-C will be evaluated and the dose of lenalidomide will be selected. Decisions regarding dose escalation, continuation with starting dose level or stopping, are based on the incidence of DLT (dose limiting toxicity: death within 31 days of start cycle I and before start cycle II .) During part B of the study that will be conducted with the selected dose of the added new drug, the CR rate (primary endpoint) and secondary endpoints (EFS, DFS, OS, as well as MRD and genomic profiling) will be assessed.

Intervention

In the experimental arm Lenalidomide will be added to the standard daunorubicin -cytarabin-arabinoside in cycle I and to cytarabine-arabinoside in cycle II
The study starts at dose level 10mg orally day 1-21 in both cycles and if possible escalated to 20mg. At each dose level the decision to stop or escalate will be made on the basis of the incidence of DLT defined as Death within 31 days of start cycle I and before start cycle II.

Study burden and risks

The addition of Lenalidomide can increase the possibilities of toxicities.

Lenalidomide has been given as monotherapy and also in combination with chemotherapy but not with this peticular antileukemic standard chemotherapy regimen. So unexpected toxicities are possible.
Lenalidomide is associated with myelosuppression and other toxicities like nausea, vomiting, diarrhea thrombosis and infections. At time of the normal bone marrow punctions a limited amount of extra bone
marrow will be collected via the same needle. This is abouth 30 ml at start and 10 ml at follow up .

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

· Patients eligible for standard chemotherapy.
· Patients >= 66 years with a cytopathologically confirmed diagnosis according WHO

classification of
o AML (not APL) or
o refractory anemia with excess of blasts (RAEB) with
an IPSS score >= 1.5
OR
Patients of any age >= 18 years with a cytopathologically confirmed diagnosis according WHO classification of
o AML with very poor risk AML
· Subjects with secondary AML progressing from antecedent (at least 4 months duration) myelodysplasia are also eligible.
· SGOT (AST) and SGPT (ALT) <= 1.5 x the upper limit of the normal range (ULN) at the laboratory where the analyses were performed.
· Total serum bilirubin level <= 1.5 x the ULN at the laboratory where the analysis was performed.
· Serum creatinine concentration <= 1.5 x the ULN at the laboratory where the analysis was performed.
· WHO performance status <= 2
· Written informed consent.
· Female patients of childbearing potential must have a negative serum pregnancy test within 2 weeks prior to enrollment.
· Male and female patients must use an effective contraceptive method during the study and for a minimum of 6 months after study treatment.(see protocol appendix J for more information and specific requirements)

Exclusion criteria

· Acute promyelocytic leukemia
· Patients previously treated for AML (any antileukemic therapy including investigational agents), a short treatment period (< 2 weeks) with Hydroxyurea is allowed
· Past or current history (within the last 2 years prior to randomization) of malignancies except for the indication under this study and curatively treated:
* Basal and squamous cell carcinoma of the skin
* in situ carcinoma of the cervix
· Blast crisis of chronic myeloid leukemia
· Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents (<= 6 months prior to randomization), myocardial infarction (<= 6 months prior to randomization), unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure
· Patients with a history of non-compliance to medical regimens or who are considered unreliable with respect to compliance
· Patients with any serious concomitant medical condition which could, in the opinion of the investigator, compromise participation in the study.
· Patients who have senile dementia, mental impairment or any other psychiatric disorder that prohibits the patient from understanding and giving informed

consent.
· Pregnant or lactating patients.
· Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol.

Study design

Design

Study phase:	2
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):	01-06-2010
Enrollment:	168
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:	19-08-2009

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2013
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	EUCTR2009-013094-17-NL
CCMO	NL29253.078.09