A randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral tosedostat to standard induction therapy in AML and RAEB >= 66 years and very poor risk AML >= 18 years.;A study in the frame of the masterprotocol of parallel randomized phase II studies in elderly AML

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Primary objectivesPart A of the study (if applicable):1. To assess the safety and tolerability of tosedostat added to standard induction chemotherapy for AMLand 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-OMON39280

Source
ToetsingOnline

Brief title
HOVON 103 AML Tosedostat

Condition

- Leukaemias
- Leukaemias

Synonym
Acute myeloid leukemia, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Chroma Therapeutics Ltd,HOVON

Intervention

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

Outcome measures

Primary outcome

Part A:

DLT of tosedostat at three dose levels (120mg, 180mg and 240mg) 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 tosedostat 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 tosedostat 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 tosedostat 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. Tosedostat 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 tosedostat 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 tosedostat 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 tosedostat on the CR rate.
Part B of the study:
1. To assess the safety and tolerability of tosedostat added to standard induction chemotherapy for AML
as regards the selected dose level of tosedostat
2. To assess in a randomized comparison the effect of the in Part A selected dose of tosedostat 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 tosedostat 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 120mg orally days 1-21 in cycle I and on days 1-56 in cycle II. If possible the dose will be escalated to 240mg. 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 tosedostat can increase the possibilities of toxicities. Tosedostat has been given as
monotherapy and not with this peticular antileukemic standard chemotherapy regimen. So unexpected toxicities are possible.
Tosedostat is associated with myelosuppression and other toxicities like fatigue, diarhea en peripheral edema. Besides these toxicities, skin rash, nausea, infections en other complaints are described that are probably more related to the underlying disease than the medication, like cardiac arrhythmias, fever and dizziness.

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 .

With regards to the patients that participate in the pharmacokinetic studies:

For measuring the concentration of tosedostat daunorubicine and cytarabine in blood, extra blood will be collected on
days 1, 2, 3, 22 and 23 of cycle 1 via a special infusion needle at several timepoints. The total amount of blood to be
collected is about 280 ml.

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

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):	13-09-2010
Enrollment:	168
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	unknown
Generic name:	tosedostat

Ethics review

Approved WMO

Date:	28-12-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	16-08-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2011
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:	05-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2014
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	EUCTR2009-014455-68-NL
CCMO	NL30483.078.09