A randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral selinexor (KPT-330) to standard induction chemotherapy in AML and high risk myelodysplasia (MDS) (IPSS-R > 4.5) in patients aged >= 66 years .

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Primary objectivesPart A of the study (if applicable):1. To assess the safety and tolerability of selinexor 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-OMON44963

Source
ToetsingOnline

Brief title
HOVON 103 AML Selinexor

Condition

- Leukaemias
- Leukaemias

Synonym

acute myeloid leukemia, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: HOVON,Karyopharm Therapeutics Inc

Intervention

Keyword: Acute Myeloid Leukemia, High Risk Myelodysplasia

Outcome measures

Primary outcome

Part A:

DLT of selienxor at two dose levels (60 and 80 mg) 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 selinexor 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 high risk myelodysplasia, 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 selinexor is added to the standard chemotherapy for remission
induction therapy of adults of age 66 years or older with acute myeloid leukaemia(AML),
or high risk myelodysplasia (MDS) (IPSS-R risk score > 4.5).
The aim of this study is to examine whether the addition of selinexor 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. Selinexor is
given twice a week orally in addition to daunorubicin and cytosin-arabinoside during day 1-24 in cycle I and II.

In the first part A of the study the feasibility of two dose levels (60 and 80 mg) will be compared to the treatment without selinexor 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 selinexor 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 selinexor on the CR rate.
Part B of the study:
1. To assess the safety and tolerability of selinexor added to standard induction chemotherapy for AML
as regards the selected dose level of selinexor
2. To assess in a randomized comparison the effect of the in Part A selected dose of selinexor 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 selinexor. During the first part
A of the studies the feasibility of combining selinexor with DNR/Ara-C will be evaluated and the dose of
selinexor 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 selinexor 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 60 mg twice weekly orally days 1-24 in cycle I and II. If possible the dose will be
escalated to 80 mg. 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 selinexor can increase the possibilities of toxicities.
Selinexor has been given as
monotherapy and not with this peticular antileukemic standard chemotherapy regimen. So unexpected toxicities are
possible.
Selinexor is associated with toxicities like nausea, loss of appetite, fatigue, vomiting, weight loss and diarhea. Besides
these toxicities, change in taste, changes in vision, low platelets, decrease in red blood cells and low sodium without symptomps are described less common.
Worsening of existing cataract, elevated levels of bilirubin and elevated levels of liver enzymes are rare.
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

Public
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Scientific

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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 and older
• Patients with:
o 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
o acute leukemia*s of ambiguous lineage according to WHO 2008 or
o a diagnosis of refractory anemia with excess of blasts (MDS) and IPSS-R > 4.5
• Adequate renal and hepatic functions unless clearly disease related as indicated by the following laboratory
values:
o 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 the 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 µmol/L, recalculate it in mg/dL according to the equation: 1 mg/dL =

88.7 µmol/L and use the above mentioned formula.
o Serum bilirubin <= 2.5 x upper limit of normal (ULN)
o Aspartate transaminase (AST) <= 2.5 x ULN
o Alanine transaminase (ALT) <= 2.5 x ULN
o Alkaline phosphatase <= 2.5 x ULN
• WHO performance status 0, 1 or 2 (see Appendix F)
• Written informed consent.
• 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
• Concurrent history of active malignancy in the two past years prior to diagnosis except for:
o Basal and squamous cell carcinoma of the skin
o in situ carcinoma of the cervix
• Blast crisis of chronic myeloid leukemia
• Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension,
pulmonary disease etcetera)
• Cardiac dysfunction as defined by:
o Myocardial infarction within the last 6 months of study entry, or
o Reduced left ventricular function with an ejection fraction < 50% ad measured by MUG scan or echocardiogram
or
o Unstable angina or
o New York Heart Association (NYHA) grade II or greater congestive heart failure (see Appendix I) or
o Unstable cardiac arrthythmias
• 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.
• Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol.
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

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):	27-06-2017
Enrollment:	140
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	27-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2018
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	EUCTR2014-001876-75-NL
CCMO	NL49953.078.15