A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE III STUDY OF IDASANUTLIN, AN MDM2 ANTAGONIST, WITH CYTARABINE VERSUS CYTARABINE PLUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (AML).

Published: 04-01-2016
Last updated: 19-04-2024

The primary objective for this study is as follows:Within the TP53 wild-type populationTo compare overall survival (OS) in patients with relapsed or refractory AML who havebeen randomized to idasanutlin in combination with cytarabine versus those...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON47508

Source
ToetsingOnline

Brief title
WO29519, MIRROS

Condition

- Leukaemias

Synonym
leukemia, Relapsed or Refractory acute myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Idasanutlin, MDM2 antagonist, phase III, R/R Acute Myeloid Leukemia

Outcome measures

Primary outcome

The efficacy outcome measures for this study are:

* Overall survival (OS)

* Event-free survival (EFS)

* Leukemia-free survival (LFS)

* Complete remission (CR)

* Complete remission with incomplete platelet recovery (CRp)

* Complete remission with incomplete blood count recovery (CRi)

* Overall remission rate (ORR) (CR, CRp, and CRi)

* Proportion of allogeneic HSCT following response

In this study CR and CRp will need to be confirmed for the purpose of the

interim

analysis. Confirmed CR is defined as CR, CRp with a duration of at least 28

days after

hematologic malignancy response assessment (HMRA) at the end of Cycle 1. For all

patients in remission not proceeding to Cycle 2 an additional HMRA is scheduled

30 (±3)

days following End-of-Cycle 1 HMRA. In case a patient proceeds directly to HSCT

in

aplasia after Cycle 1, or prior to HMRA, this will be considered confirmed CR

unless

HSCT was clearly performed in disease progression/relapse.

Secondary outcome

Safety Outcome Measures

The safety outcome measures for this study are:

* Incidence and severity of adverse events and serious adverse events

* Incidence of clinically significant laboratory abnormalities

* ECGs

* Vital signs

* 30- and 60-day mortality rates

Pharmacodynamic/Biomarker Outcome Measures

The pharmacodynamic/biomarker outcome measures for this study are:

* p53 mutation analysis by next generation sequencing

* Serum MIC-1 profile (raw and/or adjusted from baseline as percentage of

change)

* MDM2 expression by qRT-PCR and flow cytometry as well as gene signatures by

qRT-PCR and/or RNA sequencing

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are:

* Apparent clearance (CL/F) and apparent volume of distribution (Vd/F) as well as Cmax, steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration [Ctrough]), area under the concentration*time curve during one dosing interval (AUC0-*), AUC24h, and t1/2 of idasanutlin (and M4 metabolite RO6802287)

* Total clearance (CL) and volume of distribution (Vd) of cytarabine

* Effect of idasanutlin on cytarabine PK

* Effect of cytarabine on idasanutlin PK

Patient-Reported Outcome Measures

The Patient-Reported Outcome (PRO) measures for this study are:

* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

* EuroQol 5 Dimension 5-Level (EQ-5D-5L) Questionnaire

Study description

Background summary

The yearly incidence of acute myeloblastic leukaemia (AML) in European adults is five to eight cases per 100 000 individuals with a steep increase in the population aged over 70 years where the incidence reaches 15*25/100 000 per annum (Fey 2013).
Approximately 20,000 patients will be diagnosed with AML with greater than 10,000 AML patient deaths in the United States during 2015 (American Cancer Society 2015). By intensive initial treatment of acute myeloid leukemia (AML), using cytarabine and anthracycline*based chemotherapy induction regimens,

complete remission (CR) proportions ranging from 50% to 80% can be achieved. Nonetheless, the majority of
responding patients under the age of 60 relapse (60%*70%), and results are poorer in older patients, with fewer than 20% of elderly patients being long-term survivors (Burnett et al. 2011).

Prognostic factors for AML include age, white blood cell count, percentage of CD34-positive blasts, cytogenetic and molecular risk factors, and secondary or therapy-related AML. Improvements have been made in prognostic subclassification of patients*including those with normal cytogenetics*by testing for molecular abnormalities (i.e., FLT3, NPM1, CEBPalpha, MLL, WT1, and EVI1) to allow early identification of patients at high risk of relapse who should be treated with more intensive therapies (i.e. hematopoietic stem cell transplant (HSCT), or for whom
experimental therapies are warranted. Patients who do not respond to standard therapy or who relapse within a year of initial treatment have median survival measured in months (Breems et al. 2005). No standard regimen exists for the treatment of patients with relapsed or refractory AML, particularly in patients with a remission duration of less than 1 year in response to their initial induction regimen. These patients are
candidates for novel therapeutic interventions with the goal of disease remission, making potentially curative transplant options available for appropriate patients (Forman 2005). This will be the population studied in this clinical trial.

Study objective

The primary objective for this study is as follows:
Within the TP53 wild-type population
To compare overall survival (OS) in patients with relapsed or refractory AML who have
been randomized to idasanutlin in combination with cytarabine versus those who have
been randomized to cytarabine and placebo

For secundairy and exploratory objectives please see protocol paragraph 2.2 and 2.3

Study design

This is a Phase III multicenter, double-blind, randomized, placebo-controlled study of idasanutlin in combination with cytarabine compared with cytarabine and placebo.

A total of 440 patients with AML who have relapsed following, or are refractory to cytarabine*containing standard induction chemotherapy after at least 1 and

no more than 2 prior cytarabine*containing induction chemotherapy regimen(s) are planned to be enrolled. Relapsed patients are defined as patients with first or second relapse; however patients who are young and had had a good response to initial therapy (i.e. age < 60 years with first CR (CR1) duration > 1 year) are excluded. Refractory patients are defined as patients with persistent leukemia after 1 or 2 induction cycles, or patients with CR1 duration of < 90 days. Patients may have received prior HSCT in remission. Note that patients with prior allogenic HSCT within 90 days prior to randomization will not be eligible for this study. The TP53 wild-type population will consist of patients with wild-type TP53, established centrally.

Intervention

The patient receives additional to the standard treatment on the first 5 days of the cycle two times daily an oral dose of Idasanutlin / placebo. The patients are asked to fill out two QoL questionnaires multiple times per cycle using an electronic device. After treatment, the patient will return for a follow-up visit and blood sample will be collected monthly and bone marrow aspirate will be taken three monthly to assess the status of the leukemia.

Study burden and risks

The number of times the patient will visit the hospital, the number of blood tests and other study-related activities is dependent on the duration of a cycle and the number of cycles that the patient will stay in the study. Study Specific actions include: ICF, QoL questionnaires, oral dose of Idasanutlin / placebo. In addition, the patient can give separate consent to blood sampling for RCR

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age * 18 years,
- Documented/confirmed 1st/2nd refractory/relapsed AML using World Health Organization classification, except acute promyelocytic leukemia and first relapsed AML patients with a CR1 duration of >1 year AND age <60 years. ,
- No more than 2 prior induction regimens (excl. prior HSCT) in their first line treatment and one must have included cytarabine with an anthracycline (or anthracenedione).,
- Eastern Cooperative Oncology Group performance status of 0 * 2
- Adequate hepatic function assessed by the following: Serum total bilirubin * 1.5 x institutional upper limit of normal (ULN), unless resulting from hemolysis, Gilbert*s syndrome, or liver infiltration with leukemia. AST/ALT * 3 x institutional ULN (or * 5 x upper limit of institutional laboratory reference range if liver infiltration with leukemia)
- Adequate renal function assessed by serum creatinine within reference laboratory ranges OR creatinine clearance (by Cockcroft Gault formula) * 50 mL/min.,
- WBC count at randomization of *50.000/mm3
Note: When treatment is not started immediately upon randomization, the WBC count at the start of induction therapy (C1) must remain at *50.000/mm3. The use of hydroxyurea (HU) or leukapheresis to meet eligibility is allowed. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for up to 6 months after the last dose of study drug. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and established, proper use of

hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Barrier methods must always be supplemented with the use of a spermicide., - For men unless permanently sterile by bilateral orchidectomy: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for up to 6 months after the last dose of study drug. Men must refrain from donating sperm during this same period.
The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient., - Ability to understand and willingness to sign a written informed consent form and comply with all study requirements including completion of PRO measures.

Exclusion criteria

- First relapsed patients with CR1 duration of >1 year AND age <60 years,
- Patients with prior documented AHD including the following: myelodysplastic syndrome, myeloproliferative disease (i.e., chronic myelomonocytic leukemia, polycythemia vera, primary myelofibrosis, and essential thrombocythemia), and aplastic anemia,
- AML secondary to any prior chemotherapy unrelated to leukemia,
- Patients who are either refractory to or have relapsed within 90 days of receiving a regimen containing a cumulative dose of * 18 g/m2 cytarabine,
- Patients who have received allogeneic HSCT within 90 days prior to randomization. HSCT should have been performed in remission and not used for salvage (patients who have received autologous HSCT as consolidation in CR1 are eligible).,
- Patients who have received immunosuppressive therapy for graft versus host disease (GvHD) or for engraftment syndrome after autologous stem cell transplantation within 2 weeks prior to randomization
- Prior treatment with a Murine Double Minute 2 (MDM2) antagonist,
- Patients with clinically relevant QTc prolongation (QTcF> 480 ms), a family history of long QT syndrome, or who are currently receiving treatment with medications that are known to prolong the QT interval,
- Patients receiving any other investigational or commercial agents or therapies administered with the intention to treat their malignancy within 30 days (or 5 half-lives) from first receipt of study drug. Note: The exception is

HU or leukapheresis in patients who need to continue this therapy to maintain a WBC count * 50,000/mm3. HU or leukapheresis must be discontinued at least 24 hours prior to the initiation of study medication,
- Patients with acute toxicities from any prior anti-leukemia therapy which have not resolved to Grade * 2 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.,
- Patients with a history of other malignancy within 5 years prior to screening except for malignancy that has been in remission without treatment for at least 2 years prior to randomization,
- Patients unable to temporarily interrupt treatment with moderate to strong CYP2C8 inducers and inhibitors (including gemfibrozil, which is also an inhibitor of UGT1A3), CYP2C8 or OATP1B1/3 substrates, or strong CYP3A4 inducers as defined inTable 3, Table 4, and Table 5 of the protocol during the treatment phase. These agents must be discontinued 7*14 days prior to the start of study medication.,
- Patients unable to temporarily interrupt treatment with oral or parenteral anticoagulants/anti-platelet agents (e.g., warfarin, chronic daily treatment with aspirin [> 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban) during the treatment phase. These agents must be discontinued 7 days (or 5 half-lives) prior to the start of study medication.
Note: treatment with or switch to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is allowed, according to local practice. However, platelet levels need to be closely monitored in these patients (see protocol).
- Patients with history of systemic hypersensitivity reactions * grade 2 attributed to cytarabine or components of the formulated product,
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, impair the ability of the investigator to evaluate the patient, or impair the patient*s ability to complete the study (for examples see protocol),
- Infection considered by the investigator to be clinically uncontrolled or of unacceptable risk to the patient upon the induction of neutropenia, that is patients who are or should be on anti-microbial agents for treatment of active infection (for examples see protocol),
- Patients with a history of active or chronic infectious hepatitis unless serology demonstrates clearance of infection, - Patients who have a history of clinically significant liver cirrhosis.,
- Patients with clinically significant electrolyte abnormalities such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade > 1 per NCI CTCAE v4.03. Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility,
- Patients with extramedullary AML with no evidence of systemic involvement,
- Patients with active CNS leukemia,
- Pregnant or breastfeeding patients., - HIV-positive patients,
- Patients who might refuse to receive blood products and/or have a hypersensitivity to blood products.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-11-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	Cytarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	Idasanutlin

Ethics review

Approved WMO

Date:	04-01-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	18-05-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-12-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-07-2017
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-02-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	27-08-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2014-003065-15-NL
ClinicalTrials.gov	NCT02545283
CCMO	NL54789.068.15