A Phase III, International, Randomized, Controlled Study of Rigosertib versus Physician*s Choice of Treatment in Patients with Myelodysplastic Syndrome after Failure of a Hypomethylating Agent

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Primary:• To compare the overall survival (OS) of patients in the rigosertib group vs the Physician*s Choice group, in all patients and in a subgroup of patients with IPSS-R very high riskSecondary efficacy• To compare rigosertib to Physician*s...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON47424

Source
ToetsingOnline

Brief title
04-30

Condition

- Haematological disorders NEC

Synonym
ineffective production of blood cells, Myelodysplastic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Onconova Therapeutics, Inc.
Source(s) of monetary or material Support: sponsor: Onconova Therapeutics;Inc.

Intervention

Keyword: MDS, Physician□s Choice, Rigosertib

Outcome measures

Primary outcome

Study Endpoints:

Efficacy endpoints: The primary efficacy endpoints are overall survival of all randomized patients (ITT population), and overall survival of patients scored as IPSS-R very high risk.

Secondary outcome

The other efficacy endpoints, in hierarchical order, are overall survival of patients with monosomy 7 and/or trisomy 8 chromosomal aberrations; overall response rate according to 2006 IWG criteria; quality-of-life scores using the EuroQol EQ-5D Questionnaire; bone marrow blast response rate according to 2006 IWG criteria; and hematologic improvement (erythroid, platelet or neutrophil response) according to 2006 IWG criteria.

Pharmacokinetics: Blood samples for measurement of rigosertib will be taken in rigosertib patients at Cycle 1 (Week 1) and Cycle 2 (Week 3), on Day 1 of the infusion, 1 hr after its start, and on Day 2 of the infusion, 6 hr after its start.

Safety endpoints: Adverse events (AEs); deaths, other serious AEs; AEs resulting in discontinuation of study treatment; clinical laboratory

abnormalities.

Study description

Background summary

Patients with higher-risk MDS failing HMA treatment have no approved alternative therapy and a short life expectancy (approximately 4-6 months). We propose to enroll patients with MDS who have excess blasts (5% to 30% BM blasts), and have progressed during, failed to respond to, are intolerant of, or relapsed after AZA or DAC treatment. Patients* MDS must be classified as RAEB-1 and RAEB-2 by World Health Organization (WHO) criteria or refractory anemia with excess blasts in transformation (RAEB-t) based on the French-American-British (FAB) classification.
Rigosertib will be administered at a dose of 1800 mg/24 hr as 72-hr CIV infusions on Days 1, 2, and 3 of a 2-week cycle for the first 8 cycles, and on Days 1, 2, and 3 of a 4-week cycle thereafter.
The rationale for the proposed dose regimen is as follows:
1. Overall, in the 6 MDS/AML studies conducted to date, patients receiving 3-day infusions of rigosertib every other week (Q2W) achieved better BMBL responses than patients receiving 2-day infusions weekly for 3 weeks of a 4-week cycle. Extending infusion duration beyond 3 days did not result in further improvements of the rate of BMBL responses. In addition, initial BMBL response was highly correlated to survival benefit in these patients.
2. The selected dose of 1800 mg/24 hr rigosertib administered as 72-hr CIV infusions Q2W has been the most frequently administered dose in our studies conducted to date, including in the Phase III Study 04-21 in 299 patients with MDS; 199 of whom received rigosertib. No improvement in efficacy was noted in the patients receiving higher doses of rigosertib compared to those who received the selected dose for this study and no increased safety risk was observed at the 1800 mg/24 hr dose.

Study objective

Primary:
• To compare the overall survival (OS) of patients in the rigosertib group vs the Physician*s Choice group, in all patients and in a subgroup of patients with IPSS-R very high risk
Secondary efficacy
• To compare rigosertib to Physician*s Choice with regard to the following:
o Overall survival of patients with monosomy 7 chromosomal aberrations
o Overall survival of patients with trisomy 8 chromosomal aberrations
o Overall response according to 2006 International Working Group (IWG) criteria
o Quality-of-life (QoL) scores using the EuroQol EQ-5D Questionnaire

o Overall bone marrow blast response according to 2006 IWG criteria
o Hematologic improvement (HI) (erythroid, platelet or neutrophil response) according to 2006 IWG criteria
Exploratory: Evaluation of the following:
• Bone marrow genomic mutational status
• Transformation time to AML (defined as a bone marrow or peripheral blood blast percentage >30%)
Safety objectives: Evaluation of the following:
• Safety and tolerability of rigosertib administered as 72-hour CIV infusions versus PC.
• Rigosertib population pharmacokinetics (PK)

Study design

Design: Phase III, open-label, randomized (2:1), controlled, international study
Patient population: Patients with MDS classified as RAEB-1, RAEB-2 or RAEB-t after failure of treatment with azacitidine (AZA) or decitabine (DAC)
Treatment regimens:
• Rigosertib 1800 mg/24 hr administered as a 72-hr CIV infusion on Days 1, 2, and 3 of a 2-week cycle (N ~150 patients) for the first eight 2-week cycles, then on Days 1, 2, and 3 of a 4-week cycle thereafter
• Physician*s choice of alternative treatment (N ~75 patients), which may include any approved or standard-of-care therapy, based on frequently used treatment for MDS after failure of treatment with HMAs. Experimental therapies are not allowed.
If a patient requires a change to a different PC treatment, that patient must be discontinued from the study treatment, with AEs followed for 30 days after discontinuation of the initial study treatment.
Stratified prior to random assignment by IPSS-R classification of very high risk (VHR) vs non-VHR, and by geographic region (North America vs Europe vs Asia) (for the purpose of this study, Australia, New Zealand and Israel will be included in the Europe group).
Duration of treatment: Until disease progression per 2006 IWG criteria (ie, 50% increase of BM blasts or worsening of cytopenias) or onset of an unacceptable toxicity or intolerance. All patients will be followed for survival until death.
Concomitant therapy allowed in both treatment groups: Red blood cell (RBC) and platelet transfusions, growth factors (erythropoietin, granulocyte colony-stimulating factor [G-CSF], thrombopoietin [TPO]). Once a patient*s MDS has progressed and the patient has discontinued from study treatment on either arm, other therapies (except for rigosertib) are allowed at the discretion of the investigator.
Data Monitoring Committee (DMC): An independent DMC will be established for the purpose of reviewing patient safety and the results of the interim analysis.
The DMC will review the interim analysis results and may recommend stopping the study for futility, or continuing the trial as initially planned. The DMC may also recommend increasing the sample size using an adaptive design algorithm.

Intervention

Study Treatments, Dose and Mode of Administration:
• Rigosertib sodium is supplied by Onconova Therapeutics, Inc., as a sterile concentrated solution that must be stored between 2°C and 8°C, and should be diluted in 0.9% sodium chloride for injection just prior to dosing.
Reconstituted rigosertib must be kept at room temperature and administration must start within 6 hr of reconstitution, through a port or central line using an infusion pump with an in-line filter. Infusion bags must be changed every 24 hours.
• Rigosertib dose: 1800 mg/24 hr as 72-hr CIV infusion every other week for the first eight 2-week cycles (ie, 16 weeks, if no dose delays), then every 4 weeks afterward.
• Dosing adjustments of rigosertib are based on hematologic and non-hematologic toxicities.
• Physician*s Choice of treatment (approved or standard-of-care therapy, based on frequently used regimens for MDS treatment after receipt of HMAs).The drugs used in the Physician's Choice arm should be used according to the recommendations, if clinically appropriate (eg, dosing regimen and administration scheme) provided in the corresponding Summary of Product Characteristics (SmPC) and Prescribing Information of these drugs. Experimental therapies are not allowed.
• All patients will receive, as clinically indicated, transfusions of RBC and/or platelets and growth factors.

Study burden and risks

This study places additional burdens on patients as they will be required to attend visits more frequently than they would for standard of care. This is required in order for the participants to be closely monitored. The study drug will also be given over 72 hours via a catheter and the participants will be required to either stay each time in the clinic for 72 hours or go home but come in to the study centre after each 24 hour period of the 3 day infusion to change the bag. Participants will also be exposed to risks and side effects that they perhaps wouldn't normally be exposed to following standard treatment. Although additional risks and burdens are being placed on participants, patients with higher risk MDS failing hypomethylating agent treatments have no approved alternative therapy and have a short life expectancy (46 months). Information on the risks associated with the investigational drug is provided in the Investigator*s Brochure version 21.1 . Also, risks and discomforts associated with the investigational drug and study procedures are described in the ICF. Risk-benefit analysis is described in the document *Summary/Update Risk Benefit Profile*.
The potential risks identified in association with rigosertib are considered justified by the anticipated benefits that may be afforded to patients with myelodysplastic syndrome or hematologic malignancies and patients with advanced

cancer and solid tumors. Continued close monitoring to determine whether there is an increase in frequency and or severity of these events and to detect other potential safety signals will help to monitor patient safety and minimize the risk to patients participating in ongoing and future studies.

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

a. 18-81 years of age;
b. Disease classification and cytogenetics confirmed within 8 weeks prior to or during screening as follows:
• RAEB-1 per World Health Organization (WHO) MDS criteria (5% to <10% BM blasts)
• RAEB-2 per WHO MDS criteria (10% to <20% BM blasts)
• RAEB-t per modified French-American-British (FAB) classification (20% to 30% BM blasts)

c. At least one cytopenia (ANC < 1800/µL or platelet count < 100,000/µL or hemoglobin [Hgb] < 10 g/dL)
d. Progression (according to 2006 IWG criteria) at any time after initiation of AZA or DAC treatment or
Failure to achieve complete or partial response or hematological improvement (HI) (according to 2006 IWG) after at least six 4-week cycles of AZA or either four 4-week or four 6-week cycles of DAC administered or Relapse after initial complete or partial response or HI (according to 2006 IWG criteria) or Intolerance to AZA or DAC
e. Total duration of prior HMA therapy <= 9 months and/or total <= 9 cycles of prior HMA therapy in <= 12 months
f. Last dose of AZA or DAC within 6 months before the planned date of randomization; however, must be off these treatments for >= 4 weeks before randomization
g. Has failed to respond to, relapsed following, not eligible for, or opted not to participate in allogeneic stem cell transplantation
h. Off all treatments for MDS (including AZA and DAC) for >= 4 weeks before randomization; growth factors (G-CSF, erythropoietin and TPO) and transfusions are allowed before and during the study as clinically indicated
i. Patients with 5q- syndrome should have failed to respond to or progressed on treatment with lenalidomide, where available and indicated
j. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
k. Willing to adhere to the prohibitions and restrictions specified in this protocol
l. Patient must sign an Informed Consent Form indicating that the patient understands the purpose of and procedures required for the study and is willing to participate in the study.In case a patient is incapable of giving consent, the patient;*s legally authorized representative (as defined by local regulation) must give consent. However, should the patient in any manner indicate the will not to participate this takes precedence and must be respected [This requirement is not applicable for the Netherlands, as only patients who are able to give consent can participate in the study there].

Exclusion criteria

a. Previous participation in a clinical study of IV or oral rigosertib; patients who failed screening for other rigosertib studies may be screened for participation in this study
b. Eligible to receive induction chemotherapy, such as 7-10 days of cytosine arabinoside plus 2-3 days of an anthracycline, or high-dose cytarabine (HDAC)
c. Patient previously diagnosed with AML (defined as a bone marrow or peripheral blood blast percentage >30%)
d. Suitable candidate to receive allogeneic stem cell transplantation; patient is eligible for study if a suitable candidate refuses to undergo an allogeneic stem cell transplant or a suitable donor cannot be found.
e. Any active malignancy within the past year, except basal cell or squamous cell skin cancer or carcinoma in situ of the cervix or breast
f. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure or unstable angina pectoris
g. Active infection not adequately responding to appropriate therapy

h. Total bilirubin >=1.5 mg/dL not related to hemolysis or Gilbert*s disease
i. Alanine transaminase (ALT)/aspartate transaminase (AST) >=2.5 x upper limit of normal (ULN)
j. Serum creatinine >=2.0 mg/dL or eGFR (estimated Glomerular Filtration Rate) <40 mL/min.
k. Known active HIV, hepatitis B or hepatitis C, where active is defined as follows:
a. HIV or Hepatitis C - presence of viral load
b. Hepatitis B - antigen positive
l. Uncorrected hyponatremia (defined as serum sodium value of <130 mEq/L)
m. Female patients of child-bearing potential (pre-menopausal and not surgically sterilized) who are breast-feeding or have a positive blood beta-human chorionic gonadotropin (βHCG) pregnancy test at Screening
n. Female patients of child-bearing potential and male patients with sexual partners of child-bearing potential who are unwilling to follow strict contraception requirements before entry and throughout the study, up to and including the 30-day non-treatment follow-up period
Examples of acceptable contraception methods include:
* estrogen-gestagen based contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal),
* gestagen-only based contraceptives associated with inhibition of ovulation (oral, injectable, implantable),
* intra-uterine devices (IUDs),
* intra-uterine hormone-releasing systems (IUSs),
* bilateral tubal occlusion
* vasectomized partner
* sexual abstinence in accordance with an individual*s lifestyle
o. Major surgery without full recovery or major surgery within 3 weeks before planned randomization
p. Uncontrolled hypertension
q. New onset seizures (within 3 months before planned randomization) or poorly controlled seizures
r. Any other concurrent investigational agent or chemotherapy, radiotherapy, immunotherapy, or corticosteroids (prednisone up to 20 mg/day or its equivalent is permitted for chronic conditions)
s. Treatment with cytarabine at any dose, lenalidomide, or any other therapy targeted to the treatment of MDS (other than growth factors and other supportive care measures) within 4 weeks of planned randomization
t. Investigational therapy within 4 weeks of planned randomization
u. Psychiatric illness or social situation that would limit the patient*s ability to tolerate and/or comply with study requirements.

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:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Physician's Choice of treatment
Generic name:	Physician's Choice of treatment
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rigosertib
Generic name:	Rigosertib sodium

Ethics review

Approved WMO Date:	10-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-001476-22-NL

Register	ID
ClinicalTrials.gov	NCT02562443
CCMO	NL57704.029.16