INSPIRE - Onconova 04-30 (dernière mise à jour : 03/09/2019)

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Informations générales

Titre de l'étude : 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

Traitement :

Type d'étude : Hors ciblage moléculaire

Phase : III **Stade** : NA **Ligne(s)** :

Schéma : This is a Phase III, open-label, randomized, controlled, international study. Approximately 360 patients < 82 years of age with MDS classified as RAEB-1, RAEB-2, or RAEB-t who received AZA or DAC for ? 9 months and/or ? 9 cycles over 12 months and had their last dose of AZA or DAC within 6 months prior to screening will be stratified by:
* Very high risk (VHR) vs non-VHR per IPSS-R, and
* Geographic region (North America vs Europe vs Asia; because approved products and standard of care may vary by region), and randomly assigned in a 2:1 ratio to one of the following 2 treatment groups:
* Rigosertib 1800 mg/24 hr administered as a 72 hr CIV infusion 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 (N = approximately 240 patients);
* Physician's Choice of alternative treatment, which may include any approved or standard-of-care therapy that the patient has not shown to be hypersensitive to, based on frequently used treatment for MDS, as per institutional guidelines, after receipt of HMAs (N = approximately 120 patients). The drugs used in the Physician's Choice arm should be used according to the recommendations, if clinically appropriate, provided in the corresponding Summary of Product Characteristics (SmPC) and Prescribing Information of these drugs. Experimental therapies are not allowed on the PC arm.

Patients will be treated until 2006 IWG progression criteria are met (ie, 50% increase of BM blasts or worsening of cytopenias) or until an unacceptable toxicity or intolerance.

For all randomized patients who discontinue study treatment, subsequent therapies with their start and end dates, as well as survival time after treatment discontinuation, will be documented at least monthly until death.

Patients in the PC group who progress will not be allowed to cross over to rigosertib.

All patients in both treatment groups will be allowed, as medically justified, access to RBC and platelet transfusions and to growth factors (granulocyte colony-stimulating factor (G-CSF), erythropoietin, and thrombopoietin).

Study arms:
- Experimental: rigosertib + best supportive care (BSC)
Interventions:
Drug: rigosertib. Patients will receive intravenous rigosertib 1800 mg/24 hr for 3 days every 2 weeks for first 8 cycles, then every 4 weeks thereafter.
Drug: best supportive care (BSC)
- Active Comparator: Physician's Choice (PC) + best supportive care (BSC)
Interventions:
Drug: Any approved or standard-of-care therapy
Drug: best supportive care (BSC)

Current primary outcome:
Overall survival of all randomized patients and overall survival of patients scored as IPSS-R very high risk. [Time Frame: Up to 30 Months]

Current secondary outcomes:
- Overall survival of patients with monosomy 7 chromosomal aberrations. [Time Frame: Up to 30 Months]

Evaluate OS of patients with monosomy 7 chromosomal aberrations in the rigosertib vs PC group. Overall survival is the time (months) from date of randomization to date of death or date last known to be alive at the time of date cut-off.
- Overall survival of patients with trisomy 8 chromosomal aberrations. [Time Frame: Up to 30 Months]
Evaluate OS of patients with trisomy 8 chromosomal aberrations in the rigosertib vs PC group. Overall survival is the time (months) from date of randomization to date of death or date last known to be alive at the time of date cut-off.
- Percent of patients with response according to 2006 IWG criteria. [Time Frame: Up to 30 Months]
Responses of complete remission (CR), partial remission (PR), mCR, SD, failure, and PD will be determined by 2006 IWG criteria. The number and percent of patients with CR, PR, mCR, SD, Failure, or PD will be summarized by treatment group.
- Scores of Quality of Life Questionnaire. [Time Frame: At Baseline, at Week 4, Every 4 Weeks thereafter, and at the End-of-treatment.]
Compare rigosertib vs PC in regard to the the scores of the EuroQol EQ-5D-5L Questionnaire. The EuroQol EQ-5D-5L Questionnaire includes five levels of severity in each of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and a visual analogue scale.
- Percent of patients with bone marrow blast response rate according to 2006 IWG criteria. [Time Frame: Up to 30 Months]
Compare rigosertib vs PC in regard to the bone marrow blast responses of marrow complete response (mCR ? 50% decrease of BMBL vs pretreatment values to a value ? 5%), marrow partial response (mPR, ? 50% decrease of BMBL vs pretreatment values to a value > 5%), stable disease (SD, no mCR or mPR, but no progressive disease (PD), and PD (? 50% BMBL increase relative to baseline or nadir) will be assessed. The number and percent of patients with mCR, mPR, SD, or PD will be summarized by treatment group. Responses of complete remission (CR), partial remission (PR), mCR, SD, failure, and PD will be determined by 2006 International Working Group (IWG) criteria.
- Percent of patients with hematologic improvement (HI) (erythroid, platelet and neutrophil responses) according to 2006 IWG criteria. [Time Frame: Up to 30 Months]
Compare rigosertib vs PC in regard to the number and percent of patients who meet the 2006 IWG criteria.

Spécialités / Localisations

Spécialité n°1 : Tissus lymphoïde, hématopoïétique et apparentés

CIM10 - Localisation n°1 : **C96** - Tumeurs malignes des tissus lymphoïde, hématopoïétique et apparentés, autres et non précisées

Critères

Critères d'inclusion : - MDS classified 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 French-American-British (FAB) classification (20% to 30% BM blasts)
- At least one cytopenia (ANC < 1800/µL or platelet count < 100,000/µL or hemoglobin [Hgb] < 10 g/dL)
- 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)
- Duration of prior HMA therapy <= 9 months and/or total <= 9 cycles of prior HMA therapy in <= 12 months
- 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
- Has failed to respond to, relapsed following, not eligible for, or opted not to participate in allogeneic stem cell transplantation
- Off all treatments for MDS (including AZA and DAC) for >= 4 weeks before randomization; growth factors (G-CSF, erythropoietin and thrombopoietin) and transfusions are allowed before and during the study as clinically indicated
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
- Willing to adhere to protocol prohibitions and restrictions
- Patient must sign informed consent form to indicate patient's understanding study's purpose and procedures and willingness to participate. Should patient be incapable of giving consent, the patient's legally authorized representative (as defined by local regulation) must give consent. However, should patient, in any manner, choose not to participate this takes precedence and will

be respected.
- Patients with 5q- syndrome should have failed to respond to or progressed on treatment with lenalidomide, where available and indicated

Critères de non-inclusion : - Previous participation in a clinical study of IV or oral rigosertib; patients who failed screening for other rigosertib studies may be screened for participation
- Eligible to receive induction chemotherapy, such as 7-10 days of cytosine arabinoside plus 2-3 days of an anthracycline, or high-dose cytarabine
- 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
- Any active malignancy within the past year, except basal cell or squamous cell skin cancer or carcinoma in situ that is unlikely to progress in two years
- Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure or unstable angina pectoris
- Active infection not adequately responding to appropriate therapy
- Total bilirubin >=1.5 mg/dL not related to hemolysis or Gilbert's disease
- Alanine transaminase (ALT)/aspartate transaminase (AST) >=2.5 x upper limit of normal (ULN)
- Serum creatinine >=2.0 mg/dL or eGFR (estimated Glomerular Filtration Rate) < 40 mL/min.
- Known active HIV, hepatitis B or hepatitis C, where active is defined as follows:
* HIV or hepatitis C - presence of viral load
* Hepatitis B - antigen positive
- Uncorrected hyponatremia (defined as serum sodium value of <130 mEq/L)
- 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
- 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 pregnancy test at Screening
- Major surgery without full recovery or within 3 weeks before planned randomization;
- Uncontrolled hypertension
- New onset seizures (within 3 months before planned randomization) or poorly controlled seizures
- 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)
- 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
- Investigational therapy within 4 weeks of planned randomization
- Psychiatric illness or social situation that would limit the patient's ability to tolerate and/or comply with study requirements.
- Patient previously diagnosed with AML (defined as a bone marrow or peripheral blood blast percentage of >30%).

Informations promoteur

Nom du promoteur : ONCONOVA Therapeutics

Type de promoteur : Industriel

Adresse : 375 Pheasant Run Newtown, PA 18940, USA - 00000 HORS FRANCE

Coordonnateur : - *Mail :* - *Tél :*

Informations centre investigateur n°1

Nom du centre : Centre Hospitalier Universitaire de Lille

Adresse : 2 Avenue Oscar Lambret 59000 LILLE

Investigateur : Professeur Bruno QUESNEL

TEC / ARC / IDE : Secrétariat de recherche - *Mail :* fanny.miquel@chru-lille.fr - *Tél :* 03.20.44.57.13

Ouverture de l'essai : OUVERT

Liens utiles

ClinicalTrials (anglais) : https://clinicaltrials.gov/ct2/show/record/NCT02562443?term=NCT02562443&rank=1