Clinical Trial Summary for Laypersons.

Clinical Trial: 04-30

Sponsor: Onconova Therapeutics, Inc.

1. Study Name

1.1. Study Title:

1.1.1. Short title: Rigosertib compared to physician's choice of treatment in high-risk Myelodysplastic Syndrome (MDS)

1.1.2. Full study title: 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

1.2. Protocol Number: 04-30

1.3. NCT number: NCT02562443

1.4. EudraCT number: 2015-001476-22

1.5. Abstract: The purpose of the study was to assess whether rigosertib provided benefit in terms of extending life compared to other treatment options for high-risk MDS participants after failure of a hypomethylating agent such as azacitidine or decitabine. Some of the participants received rigosertib, while others were assigned the treatment recommended by their doctor. Three hundred and seventy-two participants, including males and females, from 25 countries took part in the study. The study showed that there was no survival benefit for those participants that received rigosertib as compared to those that received other treatments. Rigosertib was generally well tolerated by the participants.

2. Who Sponsored this Study?

2.1. The study was sponsored by Onconova Therapeutics, Inc.

2.1.1. Telephone: +1 267-759-3680

2.1.2. E-mail: info@onconova.us

3. General Information About the Clinical Trial

3.1. The study took place in the 25 countries. See section 4.2 for details.

3.2. The first participant started the study 03 December 2015 and the last participant visit was 26 July 2021. When the study data was reviewed it showed that there was no benefit to rigosertib treatment, so the study was stopped, and participants were taken off study.

3.3. The purpose of the trial was to see whether rigosertib allowed MDS patients that had failed on standard treatment (hypomethylating agents) to live longer than other treatments used in this patient group. As there is no standard medication for such patients, doctors were able to give participants any acceptable treatment option if they were not assigned to receive rigosertib. This was a phase 3 study and participants who met the criteria to join the study were entered into either the rigosertib group or physician's choice group according to chance (randomization).

3.4. The study data was reviewed at the time anticipated by the protocol, but as the study failed to show benefit for rigosertib, it was stopped at that time.

4. Population of Subjects

4.1. The participants in this study had high-risk MDS and had already received the standard of care treatment of either azacitidine or decitabine and had either not gained benefit from that treatment or their disease had become worse despite the treatment.

4.2. Three hundred and seventy-two participants took part in the study from the following countries: See Table 1.

Table 1: Enrollment by Country

Country	Participants Enrolled
Australia	7
Austria	5
Belgium	8
Brazil	4
Bulgaria	7
Canada	11
Croatia	2
Czechia	21
Estonia	2
France	22
Germany	9
Great Britain	1
Hungary	8
India	4
Ireland	3
Israel	8
Italy	22
Japan	50
Poland	25
Russia	11
Spain	37
Sweden	1
Switzerland	2
Turkey	4
United States of America	98

4.3. Of the participants, 121 (32.5%) were female and 251 (67.5%) were male. The average (median) age was 73 years old (ages were from 40 to 85), with the majority (234, 62.9%) being less than 75 years old.

4.4. Key inclusion criteria (required to be a participant)

- 4.4.1. At least 18 years old
- 4.4.2. Confirmed myelodysplastic syndrome
- 4.4.3. Low neutrophils, platelets, or hemoglobin
- 4.4.4. Failure of hypomethylating agent (HMA) treatment (progression of MDS, failure to achieve a response on HMA treatment, worsening of MDS after an initial response, or intolerance to HMA treatment)

4.4.5. Failed to respond to, relapsed following, not eligible for, or opted not to participate in allogenic stem cell transplantation

4.5. Key exclusion criteria (any of these prevents a participant from joining the study)

4.5.1. Previously received rigosertib in another clinical study

4.5.2. Eligible for induction chemotherapy

4.5.3. Previously diagnosed with acute myeloid leukemia (AML)

4.5.4. Suitable for allogenic stem cell transplant

4.5.5. Other infection or illness that might impact the safety of the participant and/or the results of the study

4.5.6. Insufficient liver or kidney function as assessed by lab results

5. Investigational Medicinal Product Used

5.1. The study drug was rigosertib. Multiple alternative treatments were used in the comparator arm of the study, as determined by the availability of treatments in each country and the preference of the treating doctor and the participant.

5.2. The study was randomized, which means that each participant was assigned to receive either rigosertib or physician's choice by chance. Of every 3 participants, two were randomized to receive rigosertib and 1 was randomized to receive physician's choice of treatment.

6. Description of Adverse Reactions and Their Frequency

6.1. The average (median) amount of time that participants received rigosertib treatment was 13 weeks, this ranged from 2 weeks to 166 weeks.

6.2. One hundred and fifty-eight (66.7%) of the rigosertib participants experienced side effects that were thought to be related to rigosertib. Side effects are unwanted medical events (such as headache) that happen during the study and which the doctor thinks may be because of the study treatment. Serious 'side effects' are life threatening, require the participant to be hospitalized, or are otherwise medically serious.

6.2.1. Fifty-four (22.8%) of the rigosertib participants experienced serious side effects that were considered by the treating doctor to be at least possibly related to rigosertib, the most common were: fever associated with low neutrophil counts in 9 participants (3.8%), fever in 7 participants (3%), pneumonia in 6 participants (2.5%), confusion in 3 participants (1.3%) and low neutrophils in 3 participants (1.3%).

6.2.2. The most commonly reported non-serious side effects that were considered by the treating doctor to be at least possibly related to rigosertib were: nausea (32 participants [13.5%]), diarrhea (28 participants [11.8%]), and anemia (low red blood cell counts) (22 participants [9.3%]).

7. Overall Results of the Clinical Trial

7.1. The characteristics of the two groups prior to starting treatment were generally equivalent.

7.2. The primary endpoint of the study was overall survival, which is an estimate of how long participants will live until half of them have died. This endpoint is very commonly used in cancer studies. The average (median) overall survival in the rigosertib group was 6.5 months, while that of the physicians' choice group was 6.3 months, but this difference (6 days) was not statistically significant (it could have occurred by chance and may not be real).

7.3. There is a statistical term that measures how reliable the average (median) overall survival number is based on all the survival data of all the participants. That term is the 95% confidence interval, which is expressed as a range. We can be 95% sure that the real or true median survival is within that range. For the rigosertib group, that range was 5.8 to 7.8 months and for the physicians' choice group, it was 5.2 to 9.9 months. The large overlap of these ranges suggests that there is not a real difference between the treatment effects.

7.4. Hazard ratio is a statistical tool associated with overall survival that measures whether one treatment is better than the other. If the hazard ratio is less than 1.0, then the study arm (rigosertib) is better (the lower the number the more benefit there is of the study treatment). In this study the hazard ratio was more than 1.0 (it was 1.155), showing that rigosertib was not more beneficial than physician's choice of treatment.

7.5. This overall survival analysis was also performed in certain pre-planned sub-groups of the study participants. The result was consistent in those sub-groups.

7.6. Four participants in the rigosertib group and 1 in the physician's choice group achieved a complete remission of their MDS. Five participants in the rigosertib group and 8 in the physician's choice group achieved a partial remission of their MDS.

7.7. Once the outcome of the primary endpoint was confirmed, the study was stopped.

8. Comments on the Outcome of the Clinical Trial

8.1. As a result of this study outcome, it was decided to stop development of rigosertib for MDS.

8.2. As part of this study, genomic (DNA) analysis related to MDS associated genes was performed for many of the participants before they started study treatment. This genomic information provides a better understanding of the genomic profile and specific gene mutations of MDS patients that have failed on prior hypomethylating therapy. This is useful information to the MDS scientific community.

9. Indication Whether Follow Up Clinical Trials are Foreseen

9.1. No further studies of rigosertib in MDS are planned.

9.2. Studies of rigosertib in some other cancer indications are ongoing.

10. Indication of Where Additional Information Can be Found

10.1. Additional information about this study and other clinical trials can be found on the www.clinicaltrials.gov website.

10.2. General information about clinical trials can be found here: https://www.clinicaltrials.gov/ct2/about-studies/learn