Abstract

Rigosertib (ON 01910.Na) is a non-ATP competitive multi-kinase inhibitor which inhibits polo-like kinase and PI-3 kinase pathways. Rigosertib has shown in preclinical models and clinical trials an eradication of cells with dysregulation of Cyclin-D1 and Akt phosphorylation. Some clinical trials in advanced solid tumors as well as in a randomized phase I trial [1] showed a manageable toxicity profile. Based on the preclinical data and Phase I results of the ongoing trials, a Phase I/2 study evaluating the safety, tolerability, and clinical activity of rigosertib in patients (pts) with relapsed or refractory acute leukemia and myelodysplastic syndromes was designed. Treatment was given in a 2 cycle (2-week) schedule with a continuous IV infusion of rigosertib at a dose of 2400 mg/day either for 72 hrs or 120 hrs every other week using a standard 3 day or 5 day schedule. Eligibility criteria included pts ≥18 years with AML-MDS, AML-MPN, MDS, or MDS-AML. AML-MDS: Acute Myeloid Leukemia evolved from MDS, AML-MPN: AML evolved from myeloproliferative neoplasms (MPN). Pts were given rigosertib by continuous IV infusions over 24 hours. Rigosertib is rapidly metabolized to a single hydrolyzable metabolite with a non-linear relationship between the dose and plasma concentration of rigosertib. The study was conducted under Institutional Review Board and patient’s consent. Rigosertib showed early evidence of clinical activity. Therefore, we initiated a study in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) and acute leukemia reported a favorable toxicity profile and showed early evidence of clinical activity. Therefore, we initiated a study in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) and acute leukemia reported a favorable toxicity profile and early evidence of clinical activity.

Study Design

- Single center, open label, phase 1/2 study
- Accrue to 24 patients

Phase 1: Dose escalation done using “3+3” rule.

Phase 2: Accrual started after completing phase 1

All patients treated at the MTD during the Phase 1 can be included in the Phase 2

Total study duration is 30 weeks = 2-week screening phase + 24-week dosing phase + 4-week follow-up phase.

Treatment Plan

Rigosertib 2400 mg continuous IV infusion for 24 hours for 72 or 120 consecutive hours every 2 weeks for the first 4 weeks.

Per amendment: From week 5 drug given as oral parts of the trial.

Eligibility

- Patients ≥18 years of age
- Relapsed or refractory acute leukemia
- Bone marrow blasts ≥10%
- Adequate organ function
- Declined or not candidates for stem cell transplant or other chemotherapy known to induce disease of Cyclin-D1 and Akt phosphorylation
- Clinical studies in advanced solid tumors, myelodysplastic syndrome (MDS) and acute leukemia have reported favorable toxicity profile and early evidence of clinical activity.

Objectives

- Define the toxicities of ON 01910.Na
- Define the Maximum Tolerated Dose (MTD)
- Determine the clinical response rate

Common Adverse Events (AE) & DLT

- Eosinophils
- Anemia
- Hemorrhage
- Hypokalemia
- Hypertension
- Transient altered mental status
- Confusion
- Sepsis

Common Adverse Events & DLT

- Fever
- Hyperlactatemia
- Increase transaminases
- Increase bilirubin
- Intracranial bleed
- None considered drug-related

Phase1/2 Single Arm Study of Rigosertib (ON 01910.Na) In Patients (Pts) with Relapsed or Refractory Acute Leukemia or Myelodysplasic Neoplasms

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Conclusions

- Rigosertib has favorable toxicity profile
- Main adverse event is transient altered mental status
- Therapy with single agent results in stable disease in some patients.
- Combination therapy with Rigosertib is being explored.