**BACKGROUND**

- Azacitidine (AZA) is first-line therapy for patients (pts) with higher-risk MDS.
- Rigosertib is a Ras-mimetic that inhibits the PI3K pathway by binding directly to RAS-binding domain found in Ras effector proteins.
- In vitro, the combination of rigosertib with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent manner (rigosertib administered prior to AZA) (Skidan, AACR 2006).
- The combination of oral rigosertib and AZA has been administered to 40 pts with MDS. Further exploration of this combination is warranted in defined MDS populations.

**OBJECTIVES**

- To investigate the safety and toxicity of the combination of oral rigosertib and AZA in pts with MDS.
- To evaluate the activity of the combination of oral rigosertib and AZA with respect to IWG response and hematologic improvement.

**METHODS**

- Oral rigosertib was administered twice daily on Days 1-21 of a 28-day cycle.
- Dose was escalated to the recommended Phase II dose.
- Azacitidine 75 mg/m² SC or IV was administered for 7 days on Day 8.
- A CBC was performed weekly and a bone marrow aspirate and/or biopsy was done at baseline, on Day 29, and every 4 weeks thereafter.

**RESULTS**

**CONCLUSIONS**

- A novel and important observation is that oral rigosertib in combination with AZA showed an overall response rate of 77% in pts with MDS, including an 84% response rate among pts who had not previously been treated with an HMA, and a 64% response rate among pts with prior HMA failure.
- Importantly, 90% of pts with very high risk per IPSS-R showed a response to the combination.
- The combination was well-tolerated in pts with MDS; repetitive cycles of the combination can be safely administered without evidence of cumulative toxicity.

**REFERENCES**


