Background

• Novel treatments as well as innovative trial designs are needed to expeditiously address the high unmet medical needs of patients with HMA failure HMD-S.
• Higher Risk (HR) MDS represents approximately 30% of all MDS cases.
• Hypomethylating agents (HMAs), such as azacitidine and Decitabine are the standard of care for patients with HR-myelodysplastic syndrome (MDS).
• However, only around 50% of patients respond to these agents.
• Responses tend to be transient, with loss of response typically occurring within 2 years and being associated with very poor prognosis and limited therapeutic options.
• All patients ultimately fail HMA treatment with a median OS of 4-6 months.
• Currently, there are no approved treatments for HMA failure HR MDS and treatment guidelines generally recommend that patients participate in a clinical trial.
• Rigosertib is a Ras-mimetic that inhibits PI3K and PLK signaling pathways by binding directly to the Ras-binding Domain (RBD) present in several RAS effector proteins.
• INSPIRE is an ongoing innovative phase 3 trial that employs an adaptive design to evaluate rigosertib efficacy in HR MDS following HMA failure; Summary of INSPIRE Trial

• Open label multicenter trial;
• 2:1 Rigosertib:Physician’s Choice randomization to the following treatment arms;
• Rigosertib 1800 mg/24 hr – Infusion on Days 1, 2, and 3 of each 2-week cycle for the first 8 cycles, and on Days 1, 2, and 3 of each 4-week cycle thereafter;
• Treatment until progression or death
• Physician’s Choice of Treatment – Experimental therapies are not allowed on the PC arm as first therapeutic option
• Primary endpoint is median OS in both the ITT population and the IPSS-R VHR cohort;
• OS was defined as time between randomization and death from any cause;
• A single IA for the primary endpoint was planned after both 88 survival events in the ITT population and 42 events in the VHR cohort;

Pre-planned Revision to INSPIRE Trial Design

Following Initial Analysis

- The IA indicated that futility was successfully passed and that the trial was underpowered. An increase in enrollment was recommended by IDMC with a change in the required number of survival events (176 to 288).
- There was no change in trial IA criteria following IA.

Advantages of Adaptive Trial Design

• Minimizes risk of an underpowered phase 3 trial which contributes to reduced success in oncology studies [approximate 70% success rate];
• Sample size can be adjusted in real time when there is high variance in estimating the true treatment effect of the trial drug under investigation;
• Re-estimation of sample size is data-driven based on the results of an un-blinded IA and can be performed without jeopardizing the integrity of the trial;
• Increase in sample size is pre-planned if a re-estimation is recommended by IDMC;
• Provides IDMC with increased number of options to recommend following IA;
• Investigators and sponsor are blinded to the IA results and the trial integrity and data validity remain intact;

Sample Size Re-estimation (SSRE) for INSPIRE

- SSRE is an appropriate mitigation strategy against an underpowered trial;
- Given the high unmet medical need in HR MDS following HMA failure and the limited studies in this patient population this approach seems reasonable;
- Because an increase in sample size may influence investigator interest and behavior in trial participation and enrollment, the rationale, benefits and outcomes of the adaptive trial design need to be clearly communicated to trial investigators at the beginning of the trial as well as following the IA.

References