UTILITY OF ADAPTIVE TRIAL DESIGN IN HIGHER-RISK MYELODYSPLASTIC SYNDROMES (HR-MDS): REVISE INSPIRE STUDY DESIGN FOLLOWING ADAPTIVE ANALYSIS

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BACKGROUND: Patients with HR-MDS have a dismal prognosis after failure of hypomethylating agents HMA, with median overall survival (OS) of 6 months. Rigosertib, a Ras-targeted therapy with novel mechanism of action as well as innovative study designs are needed to address and alleviate the unmet medical needs in HMA refractory HR-MDS. Rigosertib is a Ras-mimetics that inhibits the PI3K and PLK cellular signaling pathways binding directly to the Ras-binding Domain in flavin protein kinases.

METHODS: INSPIRE (NCT02562443), is a Phase 3 trial in MDS patients after HMA failure. Patients are randomized to rigosertib or treatment based on physician choice. Key inclusion criteria: age <82 years; MDS classified as RAEB-1, RAEB-2 or 5q-syndrome; refractory or progression on HMA; duration of prior HMA ≥6 cycles within 12 months; last dose of HMA ≥6 months before enrollment; and ECOG score 0-2. The primary endpoint of OS will be tested in the ITT population and in the VHR subgroup. Secondary endpoints include OS in patients with monosomy 7 or trisomy 8, overall response, quality-of-life, and hematologic improvement. The initial sample size was 223 patients with a pre-planned interim analysis after 88 events. INSPIRE featured an adaptive trial design with Sample Size Re-estimation (SSRE) process. This adaptive design is advantageous as it allows study sample size to be adjusted when there is high variance in estimating the true effect of the drug under investigation. The INSPIRE had several options following the interim analysis, including continual unplanned, discontinued for futility or safety, trial expansion using pre-planned sample size re-estimation, and continuation for only the pre-defined VHR subgroup.

RESULTS: Based on the results of interim analysis, the IDMC recommended continued continuation of the trial based on OS result in “Promising zone” with a one-time expansion in enrollment, using a pre-planned sample size re-estimation. As recommended by the IDMC, the expanded INSPIRE will study an increased sample size of 360 randomized patients with eligibility as defined based on the original trial criteria. Adapted design utilizes data collection to decide how to modify aspects of the trial without undermining the validity and integrity, while preserving type-I error. The investigators remain blinded to the specific interim analysis results. The trial is ongoing with final data expected 2019. Clinical trial information: NCT02562443.

RATIONAL FOR INSPIRE STUDY ADAPTIVE DESIGN

- Post hoc analyses from ONTIME were key in identifying the most appropriate patient population for INSPIRE and the development of the final protocol.
- Identification of a specific patient subset from a previous study may be included in a subsequent phase 3 study either as the sole population or as a subset in a broader population. This has been recognized by the FDA as an acceptable enrollment strategy for clinical trials.
- Post hoc analyses can be associated with limitations in estimating the true treatment effect which may lead to impression in estimating sample size.
- To maximize the risk of underestimating sample size in INSPIRE, an adaptive study design with the following innovative features was incorporated into the study design:
  - Continuation of median OS for the ITT population and the VHR subgroup:
    - Pre-planned Sample Size Re-estimation (SSRE) following an un-blinded interim analysis (IA) by IDMC. This was a pre-specified and allowed, as a one-time increase in the enrollment number of events;

SUMMARY OF INSPIRE STUDY

- Open label multicenter study;
- 2:1 randomization to the following treatment arms:
  - Physician’s Choice of Treatment + Best Supportive Care (BSC) alone
  - Rigosertib (1,800 mg) – Infusion on Days 1, 3, and 5 of each 2 week cycle
  - Rigosertib and oral supportive care (BSC) for the phase 3;8

IDMC OPTIONS FOLLOWING IA

- Based on an interim analysis, for adaptive SSRE for an ongoing 2 arm study, the results for each population (ITT, VHR) were categorized into 3 zones (Unfavorable, Promising, Favorable) with pre-specified boundaries for results, if either population fell into the “Promising” zone, the study is considered to be an underpowered study and a re-estimated sample size may be recommended.

The following options were available to IDMC as recommendations following IA:
- Continue INSPIRE as originally planned;
- Stop for futility or safety;
- INSPIRE expansion using pre-planned sample size re-estimation;
- Continue INSPIRE enrollment only for the VHR subgroup with or without a sample size adjustment.

ADVANTAGES OF ADAPTIVE STUDY DESIGN

- Minimizes risk of an underpowered phase 3 study which contributes to reduced success in oncology studies (40% success rate);
- Allows for may be recommended when there is high variance in estimating the true treatment effect of the study drug under investigation.
- Re-estimation of sample size is data-driven based on the results of an un-blinded IA by IDMC and can be done without jeopardizing the study;
- Maximum increase in sample size is pre-planned and fixed if a re-estimation is recommended by IDMC;
- Provides IDMC with increased number of recommendations following IA;
- Investigators remain blinded to the specific IA results and the study validity and integrity remain intact;

POTENTIAL PERCEPTION OF SAMPLE SIZE RE-ESTIMATION (SSRE) FOR INSPIRE

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

SUMMARY

- Novel treatments as well as innovative study designs are both important in expeditiously and effectively addressing the unmet medical needs of patients with HMA failure HR-MDS.
- Utilization of an adaptive study design with appropriate such as sample size re-estimation is an innovative and advantageous approach to reduce the risk of underpowered studies and missing the clinical benefit of novel treatments.
- There are other hematological malignancies with a similar unmet medical need to HR MDS and where novel therapies are being evaluated in which the treatment setting unusual and sample size determination difficult. Implementation of a sample size re-estimation, such as was done in INSPIRE, may be an useful approach in clinical trials for these diseases.

REFERENCES/ACKNOWLEDGEMENTS

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