UTILITY OF ADAPTIVE TRIAL DESIGN IN A HIGHER-RISK MYELODYSPLASTIC (HR-MDS) SYNDROMES PHASE 3 TRIAL OF INTRAVENOUS RIGOSERTIB: INSPIRE TRIAL

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ABSTRACT

Background: Patients with HR-MDS have a dismal prognosis after failure of hypomethylating agents HMAs,[9] with median overall survival (OS) of 6 months (Prebet 2011) and no approved second-line therapy. [5] Target therapy with novel mechanism of action as well as innovative study designs are needed to expedite and address the unmet medical needs in HMA refractory HR-MDS. Rigosertib is a Ras-mimetic that inhibits the PI3K and PLK cellular signaling pathways binding directly to the Ras-binding Domain found in Ras effector proteins.[1]

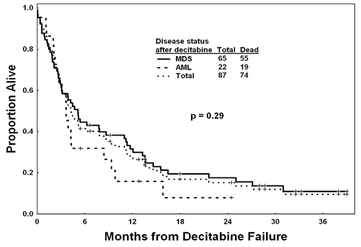
Methods: INSPIRE (NCT02562443), is a Phase 3 trial in MDS patients after HMA failure. Patients are randomized to rigosertib or treatment based on physician's choice. Key inclusion criteria: age <82 years; MDS classified as RAEB-1, RAEB-2 or RAEB-t; ≥1 cytopenia; refractory or progression on prior HMA; duration of prior HMA ≤9 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 the IPSS-R very high risk (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 225 patients with a pre-planned interim analysis after 88 deaths. INSPIRE featured an adaptive trial design with Sample Size Re-estimation. 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 IDMC had several options following the interim analysis, including continuation as initially planned, discontinuation for futility or safety, trial expansion using pre-planned sample size re-estimation, and continuation for only the pre-defined VHR subgroup.

Conclusions: Based on the results of interim analysis, the IDMC recommended continuation of the trial based on ITT result in "Promising zone" (04-30 SAP 2016) with a one-time expansion in enrollment, using a pre-planned sample size re-estimation. As recommended by the IDMC, the expanded INSPIRE study will have an increased sample size to 360 randomized patients with eligibility as defined based on the original trial criteria. Adaptive Design uses accumulating data to decide how to modify aspects of the trial without undermining the validity and integrity, while preserving type-1 error. The investigators remain blinded to the specific interim analysis results. The trial is ongoing with topline data expected 2H19. Clinical trial information: (NCT02562443).[11]

BACKGROUND

- HR MDS represents approximately 30% of all MDS cases;
- Azacitidine or Decitabine (Hypomethylating agents) are approved for frontline HR-MDS patients with clinical responses observed in 45-50%[8] (CR rate 7-24%);
- All patients ultimately fail HMA treatment with a median OS of 4-6 months[6], currently there are no approved treatments for HMA failure HR MDS and it is recommended that patients participate in a clinical trial;
- Novel treatments as well as innovative study designs are needed to expeditiously address the unmet medical needs of patients with HMA failure HR-MDS;
- 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[1] INSPIRE is an ongoing innovative phase 3 study that employs an adaptive design

THE HIGH UNMET MEDICAL NEED IN HR MDS POST HMA FAILURE

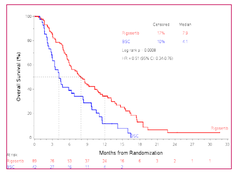


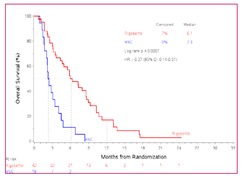
RATIONALE FROM ONTIME DATA SUPPORTING INSPIRE DESIGN

- ONTIME was the first phase 3 multicenter study in HMA failure HR MDS (n=299). The primary endpoint was an improvement in median overall survival (OS). The study assumed that a total of 223 deaths in 270 enrolled patients would result in a significant and clinically meaningful difference (> 13 weeks) in median OS (HR 0.57) with rigosertib vs best supportive care (BSC);
- Rigosertib did ***not*** significantly improve OS for the entire study population. The median OS in the rigosertib arm was 8·2 mos (95% CI 6·1–10·1) vs 5·9 mos (4·1–9·3) in the BSC arm (HR 0·87, 95% CI 0·67–1·14; p=0·33);
- Post hoc analyses of subgroups suggested that rigosertib might provide a survival benefit in certain patients, specifically those with the following characteristics:
  - Age < 82 years;
  - Duration of prior HMA ≤ 9 months and/or ≤ 9 cycles of prior HMA in ≤ 12 months;
  - Time from last dose of prior HMA to random assignment ≤ 6 months;
- Applying the above criteria, post hoc analyses of the ITT and the VHR (IPSS-R) cohort suggested potential clinical benefit (Figure 1A and 1B);[12]

- Post-hoc analysis of ONTIME patients (N=299) using INSPIRE enrollment criteria of ≤ 9 HMA DoT and < 82 years:
  - Entire ITT population if new criteria were applied for patient selection
  - Very High Risk (VHR) subgroup using new criteria

ONTIME POST HOC ANALYSIS USING INSPIRE CRITERIA





HR = 0.53; P 0.0008 HR = 0.27; P 0.0001 [12]

INSPIRE Trial Hypothesis: HR 0.625: P 0.04 for ITT; P 0.01 for VHR

REVISION TO INSPIRE STUDY DESIGN
FOLLOWING INTERIM ANALYSIS

SSRE following IA

INSPIRE Study Design	Total patients (N)	Events needed	Proportion of VHR enrolled
Pre-planned IA	225 (80% power)	176 (final) 88 (IA)	45% (anticipated)
Revisions by IDMC Post IA	360 (90% power)	288 ITT 139 VHR	>70% (actual)

The IA indicated that futility was successfully passed and that the study 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 study I/E criteria following IA;

RATIONALE 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 primary endpoint;
- 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 enrichment strategy for clinical trials;
- Post hoc analysis can be associated with limitations in estimating the true treatment effect which may lead to imprecision in estimating sample size;
- To minimize the risk of underestimating sample size in INSPIRE, an adaptive study design with the following innovative features was incorporated into the study design:
  - Co-primary endpoints 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 as a pre-specified and allowed, as a one-time increase in the enrollment and number of events; [4,7]

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
  - Experimental therapies are not allowed on the PC arm as first therapeutic option
- Rigosertib 1,800 mg/24 hr
  - Infusion on Days 1, 2, and 3 of each 2 week cycle
  - Treatment until progression or death
- Primary endpoint is median OS in both the IIT population and the IPSS-R VHR cohort;
- Overall survival was defined as time between randomization and death from any cause;
- An IA for the primary endpoint was planned after 88 survival events in the ITT population and 42 events in the VHR cohort;

IDMC OPTIONS FOLLOWING IA

- Based on published methodology 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. If results for either population fell into the "Promising" zone, the study is considered to be underpowered and a re-estimation of 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; [2]

ADVANTAGES OF ADAPTIVE STUDY DESIGN

- Minimizes risk of an underpowered phase 3 study which contributes to reduced success in oncology studies (40% success rate);
- Sample size can be re-adjusted 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;
- Given 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 approaches 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 effect is unclear 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.

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The authors gratefully appreciate the contributions of clinical investigators, study personnel, and, above all, the patients who participated in the trial.

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