The INSPIRE study in Higher Risk Myelodysplastic Syndrome (HR-MDS): A Novel Phase 3 Study Adaptive Design for Hematological Malignancies in Adults

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Submitted Abstract

Background
Patients with HR-MDS have a dismal prognosis after failure of hypomethylating agents (HMAs) (Zeidan 2014), with median overall survival (OS) of less than 6 months (Prebet 2011) and currently no approved second-line therapy (Garcia-Manero 2016). Targeted therapies with novel mechanisms of action, combination strategies, as well as innovative study designs, are all needed to expedite and address the high unmet medical need in patients with HMA refractory HR-MDS. Rigosertib is a unique targeted therapy that inhibits PI3K and PLK signaling pathways by binding directly to the Ras-binding domain (Athuluri-Divakar 2016) and in vitro cytotoxicity studies have demonstrated synergy with azacitidine (Cosenza 2015). INSPIRE study is an example of a study with a novel compound and unique mechanism of action as well as an innovative study design.

Methods
INSPIRE (NCT02562443) is a global randomized Phase 3 trial in patients with HR-MDS after HMA failure. Patients are randomized in a 2:1 fashion to rigosertib or physician's choice of treatment. Key inclusion criteria: age <82 years; MDS classified as RAEB-1, RAEB-2 or RAEB-t; ≥1 cytopenia; patient must demonstrate one of the following: progression any time after initiation of HMA treatment, intolerance to HMA, failure to achieve complete remission (CR), partial remission (PR), or hematologic improvement (HI) after six 4-week cycles of aza or either four 4-week or four 6-week cycles of DAC, or relapse after initial CR, PR or HI; 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 overall survival (OS) will be tested in a sequential fashion in the intention to treat (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 HI. The initial sample size was 225 patients with a pre-planned interim analysis (IA) after 88 deaths. INSPIRE featured an adaptive trial design with a pre-planned Sample Size Re-estimation (Cui 1999) to 360 patients and 288 OS events as one option that the Independent Data Monitoring Committee (IDMC) could implement at IA. The adaptive sample size modification of an on-going two-arm, group sequential clinical trial is used to categorize the results for each population into three zones of Unfavorable, Promising, and Favorable. 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 which could otherwise result in underpowering of the study. The IDMC had several options following the interim analysis, including continuation of the study 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. The investigators remain blinded to the specific interim analysis results. Enrollment in the trial is ongoing with topline data expected in 2020.

Conclusions
Based on the results of interim analysis, the IDMC recommended continuation of the trial based on ITT result in promising zone with one-time expansion in enrollment, using a pre-planned sample size re-estimation, the sample size for the study was increased from 225 to 360 with unchanged eligibility criteria. The Adaptive Design used real time data from the IA to modify sample size and mitigate the risk of underpowering without undermining its validity and integrity, while preserving type-1 error. The study design used in INSPIRE may be advantageous for other novel agents in rare hematological diseases during the transition from phase 2 to phase 3 studies. Clinical trial information: (NCT02562443).

Background

- Novel treatments as well as innovative trial designs are needed to expeditiously address the high unmet medical needs of patients with HMA failure HR-MDS;
- Higher Risk (HR) MDS represents approximately 30% of all MDS cases;[1]
- 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;[8]
- All patients ultimately fail HMA treatment with a median OS of 4-6 months[2]. 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.[4]
- INSPIRE is an ongoing innovative phase 3 trial that employs an adaptive design to evaluate rigosertib efficacy in HR MDS following HMA failure;

Rationale from ONTIME supporting INSPIRE design

- ONTIME was the first phase 3 multicenter trial in HMA failure HR MDS (n=299). The primary endpoint was an improvement in median OS. The trial 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 + best supportive care (BSC) vs BSC alone;
- Rigosertib did ***not*** significantly improve OS for the entire trial 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 may provide a survival benefit in a subset 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 in select patient subsets following rigosertib treatment (Figure 1a/1b);[9]

ONTIME STUDY (04-21): Proposed Patient Population for INSPIRE (04-30)

Figure 1a

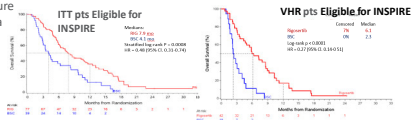
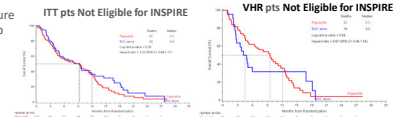


Figure 1b



Post-hoc analysis of ONTIME patients (N=299) using that the following characteristics identified a subset of patients who seemed to clinically benefit from rigosertib treatment;

- Age < 82 years;
- Duration of prior HMA ≤ 9 cycles of prior HMA in ≤ 12 months;
- Time from last dose of prior HMA to random assignment ≤ 6 months;

The above clinical features were used as key I/E criteria to enrich for a responsive patient population in the INSPIRE study.

Rationale for INSPIRE Adaptive Trial Design

- Post hoc analyses from ONTIME were key in identifying and enriching for a potential responsive and more homogenous patient population for INSPIRE and the development of the primary endpoint;
- Identification of a specific patient subset from a previous trial may be included in a subsequent phase 3 trial 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; [10,11]
- Post-hoc analysis can be associated with a 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 trial design with the following innovative features was incorporated into the trial design:
  - Sequential endpoints of median OS for both the ITT population and the VHR subgroup;
  - Pre-planned Sample Size Re-estimation (SSRE) following an interim analysis (IA) by the IDMC which resulted in a one-time, approved, and pre-defined increase in the enrollment number and number of events.

Summary of INSPIRE Trial

- Open label multicenter trial;
- 2:1 Rigosertib:Physician's Choice randomization to the following treatment arms;
- Rigosertib 1,800 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 a 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

INSPIRE Trial 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 (80% power)	288 ITT 139 VHR	>70% (actual)

SSRE following IA

Following Interim 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 I/E criteria following IA;

IDMC Options following IA

- Based on published methodology for adaptive SSRE for an ongoing 2 arm trial, the results for each population (ITT, VHR) were categorized into 3 zones (Unfavorable, Promising, Favorable) with pre-specified boundaries. If results for either population fall into the "Promising" zone, the trial is considered to be underpowered and a re-estimation of sample size may be recommended. [12]
- The following options were available to IDMC as recommendations following IA:
  - Unfavorable results would lead to trial discontinuation for futility or safety
  - Promising results would lead to either:
    - INSPIRE expansion using pre-planned SSRE
    - Continue INSPIRE enrollment only for the VHR subgroup with or without a sample size adjustment
  - Favorable results would lead to continuation of INSPIRE as originally planned

Advantages of Adaptive Trial Design

- Minimizes risk of an underpowered phase 3 trial which contributes to reduced success in oncology studies (approximately 40% 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 by IDMC and can be performed without jeopardizing the integrity of the trial;
- Increase in sample size is pre-planned and fixed 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;

Summary

- Post hoc analysis of the ONTIME trial demonstrated clinical characteristics that potentially predict for longer survival with rigosertib treatment. This facilitates the enrichment of a homogeneous population of patients anticipated to benefit from rigosertib treatment in future clinical trials.
- Novel treatments as well as innovative trial designs are both important in expeditiously and effectively addressing the unmet medical needs of patients with HMA failure HR MDS. [13]
- Utilization of an adaptive trial design with approaches such as sample size re-estimation (SSRE) is an innovative and advantageous approach to reduce the risk of underpowered studies and missing the clinical benefit of novel treatments.
- Adoption of adaptive trial design, similar to that of INSPIRE, may be a useful approach in clinical trials for diseases such as HR MDS with unmet medical need.
- An increase in sample size may influence investigator interest and behavior regarding trial participation and enrollment, therefore the rationale, integrity 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.

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