**Phase 2/3, Multi-Center, International, Randomized, Double-Blind, Placebo Controlled Study of Oral Rigosertib + Injectable Azacitidine (aza) Versus Injectable Azacitidine in Treatment-Naive Patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS)**

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**Background**

- **Evidence supports** a single arm phase 1/2 study (09-153) in which rigosertib binds directly to the Ras-Binding Domain (RBD) found in RAS effector proteins and inhibits the RAS-Raf-AKt-Erk & the PI3K pathway (Afoluso 2014; Del Carpio 2016) by TCGA. In vitro, the combination of rigosertib with aza synergistically inhibits growth & induces apoptosis of leukemic cells in a sequence-dependent fashion (Skidmore K 2006; Silverman EHA 2010).
- **In a single arm phase 1/2 study (09-153), oral rigosertib at daily doses of 400 mg or 1120 mg administered in combination with standard dose aza both demonstrated favorable efficacy and safety in HMAs-MDS pts with an ORR of 90% and a CR/PR rate of 36% (Navada et al 2020).
- **To evaluate the clinical benefit of novel treatments like rigosertib and improve the efficiency of randomized clinical trials, a variety of adaptive trial designs are increasingly being used in oncology (Sato 2018; Bhattacharyya 2017).** We propose an adaptive seamless phase 2/3 study design to confirm the optimal dose of oral rigosertib for combination with standard dose aza and demonstrate efficacy and safety of this combination therapy in patients with HMA naïve MDS (Eisenhauer 2017).

**Conventional Phase 3 Design for HMA-naive HR MDS**

- **Eligibility:**
  - No prior therapy
  - <20% blasts
  - IFP/Ficarra > 3
  - Stratification: ~75% ≤ 75 yrs of age; ~30% ≤ 60 yrs vs ≥ 60 yrs
  - Europe vs ROW

- **Primary endpoint:** Improvement (SR vs PR)

**Adaptive Phase 2/3 Study Design for Oral Rigosertib and Aza**

(Final study design will require HA review and approval)

**Table 1: Summary of clinical benefit of rigosertib/aza in pts w HMA-naive HR MDS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination Treatment (ITT) *</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selkere et al 2017 (Adaptive phase 2/3)</td>
<td>aza monotherapy, n=92</td>
<td>36</td>
</tr>
<tr>
<td>Ades et al 2018 (Randomized phase 2)</td>
<td>aza + lenalidomide, n=93</td>
<td>34</td>
</tr>
<tr>
<td>Navada et al 2019 (Single arm phase 1/2)</td>
<td>aza + rigosertib, n=39</td>
<td>59.7</td>
</tr>
</tbody>
</table>

*ITT population will be used for analyses from studies intended for risk submission, mlR is currently not considered a regulatory endpoint.*

**Summary of Seamless Adaptive Phase 2/3 design to evaluate rigosertib and azacitidine combination in HR MDS**

- **Objectives:**
  - Identify optimal rigosertib/aza combination and confirm RR and safety in the phase 3 evaluation as standard dose aza monotherapy.
  - Confirm the efficacy (HR) for the combination of rigosertib/aza compared to standard dose aza.
  - Demonstrate an improvement in OS with rigosertib/aza combination.

- **Adverse event study:**
  - Confirm optimal rigosertib dose to be used.
  - Adenote blinded sample size from single arm in phase 2 study (90).
  - Include aza monotherapy as control arm.
  - Rigosertib administered by oral or intravenous route as phase 2/3 phase 1.

- **Potential limitations of design:**
  - Data from the phase 2 and phase 3 randomizations may not be homogeneous.
  - HR response is limited compared to conventional phase 3 study designs.

**Study conduct and Efficacy analyses**

- **Phase 2 part of study:**
  - Interim analysis to be conducted by IDMC for RR (CR/PR) after all 225 patients have been enrolled into the three arms of the phase 2 study and have completed six weeks cycles or are withdrawn from study. RR from each of the rigosertib/aza arms will be compared to the aza arm.
  - Criteria for selection of optimal rigosertib dose would be established apriori and include both efficacy and safety. The IDMC may recommend one of two options:
    - **Phase 3 part of study:**
      - Primary endpoint: RR will occur after a total of at least 400 patients have completed six cycles weeks or are withdrawn from study. The primary analysis of all efficacy endpoints will be the ITT population and RR will be conducted using WGS 2006 criteria.
      - Key secondary endpoint: final analysis of OS will occur after a total of 300 deaths on both arms are observed.

- **Dosing**
  - Ph 2/3, multi-center, international, randomized, double-blind, placebo-controlled study to be conducted in patients with treatment-naive HR MDS who will receive oral rigosertib or placebo in combination with aza at 75 mg/m2 daily (SC or IV).
  - The following two doses of oral rigosertib will be studied in the phase 2 part of the study in combination with aza: 1120 mg/m2 (560 mg every 560 mg every 60 mg dose;)
  - 840 mg/day (560 mg morning & 280 mg afternoon);
  - Patients will receive rigosertib/placebo on days 1-21 of a 28-day cycle and starting on day 8, aza will be administered by oral or intravenous infusion or at a 75 mg/m2 daily dose for 7 days of a 28-day cycle according to the approved label;
  - Treatment will continue to disease progression as defined by WGS 2006 or unacceptable toxicity, after which pts will be followed for survival every 2 months until death or 3 years, whichever occurs first;

- **Conclusions**
  - Clinical benefit with oral rigosertib at doses ≤ 840 mg/m2 in combination with standard dose aza for patients with treatment-naive HR MDS has been reported from a single arm phase 2/3 study (09-08) (ASH abstract # 566).
  - Phase 3 part of the study is intended to confirm clinical benefit as measured by RR and OS in a well powered study (n=400).
  - It is anticipated that an adaptive phase 2/3 study design will compress study timelines and reduce total number of patients required (n=475), compared to separate phase 2 and 3 studies conducted sequentially (n=750).

**References**

- Shyamala C. Navada, MD, PhD; Chien-Chao C. Navada, MD; Pierre Fenaux, MD, PhD; Patrick S. Zhouwski, MBA; Alessio Romeo Addeo, MD; Nasser Asaazim, PHD; Steven M. Fruchtman, MD; Laura S. Silverman, MD; MD Anderson Cancer Center, Houston, TX; Tisch Cancer Institute, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Hospital Sant Pau, Parc Francament, Hospitalets Thraciae Therapeutics, Inc., Newington, PA.

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