**Abstract (submitted 8/8/13)**

**Background and Methods:**

Rigosertib is a bi-daily, oral, microtubule polymerizing agent which induces differentiation and apoptosis in myeloid malignancies via inhibition of the mitotic Exit Kinase (MEX-1) kinase. In prior trials, dosing regimens of 560 mg BID with 280 mg PM dose were selected to minimize nocturnal symptoms of urinary urgency. This study assesses the efficacy of a new intermittent dosing regimen with 560 mg AM dose and 280 mg PM dose in patients with advanced refractory MDS. The prior analysis of 36 evaluable patients treated with intermittent dosing was a single-arm, open-label phase II study that evaluated the efficacy and safety of intermittent dosing (21 day cycle) of rigosertib with 560 mg AM dose and 280 mg PM dose treating patients who did not tolerate or respond to prior dose of 8 weeks (range: 1–12 weeks). Only one patient so far developed grade 2 urinary toxicity (urinary tract infection).

**Conclusions:**

Based on the prior interim analysis, 560 mg AM dose and 280 mg PM dose was selected for further study. In the current study, 11/26 patients (42%) had a response to this regimen, with a median duration of response of 11 weeks (range: 1–26 weeks).

**Methods:**

- **Study Design of Oral Rigosertib in Lower Risk MDS:**
  - No patients enrolled as of 4/20/13.
  - Only 5 patients randomized to continuous dosing (11/20/12).
  - Protocol amended to enroll patients as an intermittent dosing (4/20/12).

- **Rigosertib Efficacy:**
  - **Patient Demographics:**
    - Median Age 74 (66-89) yrs.
    - Male/Female 32/12.
    - Median years from MDS diagnosis (range) 3 (0-12) yrs.
  - **Rigosertib Induces Transfusion Independence (TI) Alone or Combined with ESA:**
    - **Phase II Dosing:**
      - Grade 1/2 hemorrhagic urinaturia
      - None
      - Grade 1/2 urinaturia
      - None
      - Grade 3-4 urinaturia
      - None
    - **Phase III Dosing:**
      - Grade 1/2 hemorrhagic urinaturia
      - None
      - Grade 1/2 urinaturia
      - None
      - Grade 3-4 urinaturia
      - None

**Study Design of Oral Rigosertib in Lower Risk MDS Transfusion Independence - Primary MDS Patients:**

- **All patients randomized to TI:**
  - **Patient Demographics:**
    - Median Age 74 (66-89) yrs.
    - Male/Female 32/12.
    - Median years from MDS diagnosis (range) 3 (0-12) yrs.
  - **Rigosertib Induces Transfusion Independence (TI) Alone or Combined with ESA:**
    - **Phase II Dosing:**
      - Grade 1/2 hemorrhagic urinaturia
      - None
      - Grade 1/2 urinaturia
      - None
      - Grade 3-4 urinaturia
      - None
    - **Phase III Dosing:**
      - Grade 1/2 hemorrhagic urinaturia
      - None
      - Grade 1/2 urinaturia
      - None
      - Grade 3-4 urinaturia
      - None

**Patient Demographics:**

- **Median Age:** 74 (66-89) yrs.
- **Male/Female:** 32/12.
- **Median years from MDS diagnosis (range):** 3 (0-12) yrs.

**Rigosertib Tolerability:**

- **BID Dosing**
  - **No. of Patients:**
    - Grade 1
    - Grade 2
    - Grade 3
    - Grade 4
  - **Incidence of All Urinary Events:**
    - Grade 2
    - Grade 3
    - Grade 4
  - **Incidence of All Urinary Toxicity:**
    - Grade 2
    - Grade 3
    - Grade 4

**Conclusions:**

- **Rigosertib active in inducing transfusion independence**
  - As a single agent,
  - When combined with ESA
- **Combined response rate (TI + HI + BMCR):** 33% in 11/26 patients treated with combined ESA.
- **Transfusion independence better tolerated than continuous dosing:**
  - Bladder toxicity best managed by hydration, hypotension and strict drip.

**Identification of genomic methylations**

- **Combined cohort of 26 patients were enrolled**
- **Potential of patient selection after further confirmation.**