**BACKGROUND**

Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in ~3% of patients with myelodysplastic syndrome (MDS) and are thought to result in the metabolic shunting of alpha-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (2-HG), which results in epigenetic dysregulation and impaired cellular differentiation.1-3 Ivosidenib (AG-120) is a first-in-class, orally available, small-molecule inhibitor of the IDH1 enzyme.4-7

- **Goals:**
  - To report safety and efficacy data from patients with R/R MDS enrolled in the first-in-human phase 1 study of ivosidenib in patients with IDH1-mutated refractory anemia with excess blasts (R/R aEBM).
  - To assess the durability of responses.

**OBJECTIVE**

- To report safety and efficacy data from patients with R/R MDS enrolled in the first-in-human phase 1 study of ivosidenib in patients with IDH1-mutated refractory anemia with excess blasts (R/R aEBM).

**METHODS**

- Single-arm, open-label, phase 1, multicenter trial (NCT02074839) in patients with R/R MDS (median age, 72.6 years) with IDH1 point mutations. Dose-escalation (n=180) was based on safety and responses.

- Patients with R/R MDS were eligible for study treatment.

- The objective response rate (ORR) for MDS was defined as complete remission (CR) + partial remission (PR) + marrow transplantation (MTX), see the International Working Group (IWG) 2006 MDS response criteria.

- Baseline co-occurring mutations were assessed using a targeted next-generation sequencing panel that detects common variants in known cancer genes.

- Dose-escalation (n=180) was based on safety and responses.

- Patients with R/R MDS were eligible for study treatment.

**RESULTS**

- **Safety and Efficacy:**
  - Safety and efficacy data are presented for patients with R/R MDS enrolled in the first-in-human phase 1 study of ivosidenib.
  - There were no dose-limiting toxicities reported in the dose escalation phase.
  - The most frequent co-occurring mutations and mutational burden were shown in the results (Figures 3 and 5).
  - Duration of response was 21.4 months (range, 2.3–NE).

- **Efficacy:**
  - ORR 92%, median duration 21.4 months.
  - CR 4 (33.3)
  - SD on treatment
  - NE [2.8, NE]
  - PD: 1 (8.3)

- **AEs:**
  - The majority of adverse events (AEs) were grade 1–2.
  - The data cutoff date for this analysis was May 11, 2018.

- **Conclusion:**
  - In this molecularly defined mIDH1 R/R MDS patient population, ivosidenib induced durable responses:
    - ORR 92%, median duration not estimable.
    - CR 45%.
    - No patients discontinued treatment due to progressive disease.

**CONCLUSIONS**

- In this molecularly defined mIDH1 R/R MDS patient population, ivosidenib induced durable responses: ORR 92%, median duration not estimable.

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