Ivosidenib (AG-120) induces durable remissions and transфusion independence in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome in a phase 1 dose escalation and expansion study


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BACKGROUND

• Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in >25% of patients with myelodysplastic syndrome (MDS) and have been linked with increased transformation to acute myeloid leukemia (AML)."14

• The mutant IDH1 (mIDH1) enzyme catalyzes the reduction of α-ketoglutarate to the nonmetabolizable 2-Hydroxyglutarate (2-HG), and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation.15,16

• Ivosidenib (AG-120) is a first-in-class, oral, potent, targeted, prodrug of 2HG, whose starting dose was 500 mg QD (n=3).

• Ivosidenib suppresses the production of 2-HG, leading to clinical responses via differentiation of malignant cells.

• Ivosidenib is approved in the US for the treatment of AML with IDH1-R132G or IDH2-R1408 mutations as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥70 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy and in adults with relapsed or refractory (R/R) AML.

METHODS

• 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 mIDH1 advanced hematologic malignancies.

RESULTS

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 CR (mCR), per 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 hematologic malignancies.

• mIDH1 variant alleles frequency (VAF) in bone marrow mononuclear cells was detected using BEAMing Digital PCR (Symanis Biologic, lower limit of detection for mIDH1, 0.02–0.04%).

• The data cutoff date for this analysis was November 2, 2018.

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