Ivosidenib (IVO) in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome (R/R MDS): Updated enrollment of a phase 1 dose escalation and expansion study

Courtney D DiNardo1, James M Foran2, Justin M Watts3, Eytan M Stein4, Stéphane de Botton5, Amir T Fathi6, Gabrielle T ... S Stein8, Richard M Stone9, Prapti A Patel10, Gail J Roboz11, Martha L Arellano12, Harry P Erba13, Arnaud Pigneux14,

BACKGROUND

- Somatic mutations in the isocitrate dehydrogenase 1 (IDH1) gene occur in ~3% of patients with myelodysplastic syndrome (MDS) and have been associated with increased transformation to acute myeloid leukemia (AML).1
- The mutant IDH1 (15R) enzyme catalyzes the irreversible oxidation of L-2-hydroxyglutarate to the nonmetabolizable D-2-hydroxyglutarate (2-HG), and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation4-6
- Ivosidenib (IVO; AG-120) is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme7
- IVO suppresses the production of 2-HG, leading to clinical responses via the reduction of 2-HG, which is a potent oncometabolite D-2-hydroxyglutarate (2-HG),3 and the resulting 2-HG accumulation leads to epigenetic dysregulation and impaired cellular differentiation4-6

SUB-STUDY DESIGN

This is a sub-study of the phase 1 dose escalation and expansion study, enrolling patients with IDH1 R/R MDS (Figure 4)
- In the expansion cohort of patients with IDH1 R/R MDS, the objectives of this study are:
  - Primary: to assess clinical activity, tolerability, and clinical activity of IVO 500 mg
  - Secondary: to characterize the pharmacokinetics of IVO and to evaluate the pharmacokinetic-pharmacodynamic relationship of IVO and 2-HG
- To further assess the pharmacodynamic effects of IVO

SUMMARY AND CURRENT STATUS

Summary

- The favorable efficacy and safety of IVO in the small population of patients with mIDH1 R/R MDS in the phase 1 clinical study of patients with mIDH1 hematologic malignancies supports further evaluation in this sub-study
- This sub-study will evaluate the safety and efficacy of IVO in ~20 patients with mIDH1 R/R MDS
- Further information is available at https://clinicaltrials.gov/ct2/show/NCT02107485 (study status)
- Patients are being recruited from 22 sites in the US and Europe