A phase 1, multicenter, randomized, open-label, perioperative study of AG-120 (ivosidenib) and AG-881 in patients with recurrent, nonenhancing, IDH1-mutant, low-grade glioma

Ingo K Mellinghoff1, Elizabeth A Maher2, Patrick Y Wen3, Timothy F Cloughesy4, Katherine B Peters4, Isabel Arrillaga-Romany5, Changho Choi6, Benjamin M Ellingson7, Alexander P Lin7, Yan Li8, Brian J Soher9, Robert J Young1, Lori Steelman1, Kha Le1, Feng Yin1, Bin Wu1, Min Lu1, Yanwei Zhang1, Brandon Nicolay1, Steven Schoenfeld1, Katharine Yen1, Shuchi S Pandya7, Jennifer Clarke1

Memorial Sloan Kettering Cancer Center, New York, NY, USA; The University of Texas Southwestern Medical Center, Dallas, TX, USA; Dana-Farber Cancer Institute, Boston, MA, USA; University of California Los Angeles, Los Angeles, CA, USA; Duke University Medical Center, Durham, NC, USA; Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; University of California San Francisco, San Francisco, CA, USA; Agios Pharmaceuticals, Inc., Cambridge, MA, USA

BACKGROUND

• Somatic mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and 2 occur in many human cancers.
• IDH1 mutations are common in lower-grade gliomas (LGG; WHO grade 2/3), occurring in ~80% of LGGs.1 IDH2 mutations occur in ~4% of LGGs.2
• The mutant IDH (mIDH) proteins have a gain-of-function enzyme activity catalyzing the reduction of alpha-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (2-HG).3
• 2-HG accumulation results in metabolic dysregulation and inhibition of α-KG-dependent enzymes, which causes epigenetic dysregulation and impaired cellular differentiation, promoting oncogenesis.4
• Inhibitors of mIDH enzymes block 2-HG production and restore cellular differentiation and maturation.

Ivosidenib (AG-120)

• Ivosidenib is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme5 that is approved for the treatment of adults with mIDH1-related or refractory acute myeloid leukemia, respectively.

AG-881

• AG-881 is an oral, potent, reversible, brain-penetrant inhibitor of the mIDH1 and mIDH2 enzymes.
• In an orthotopic mouse xenograft model of human grade 3 mIDH1-R132H glioma, ivosidenib treatment inhibited 2-HG production by up to 85% in brain tumor samples.6
• In an ongoing phase 1 study of ivosidenib in patients with advanced mIDH1 solid tumors (NCT02073994), including 56 patients with gliomas, ivosidenib treatment was associated with a favorable safety profile.7
• Among 35 patients with nonenhancing glioma in this phase 1 study, ivosidenib treatment resulted in a minor response in 6% and stable disease in 83% of patients, with a median treatment duration of 16 months and median progression-free survival of 13 months.8

AG-881

• AG-881 is an oral, potent, reversible, brain-penetrant inhibitor of the mIDH1 and mIDH2 enzymes.
• In an orthotopic mouse xenograft model of human grade 3 mIDH1-R132H glioma, AG-881 reduced 2-HG levels in brain tumors by 90% and impeded glioma growth.9
• In an ongoing phase 1 study of AG-881 in patients with advanced mIDH1 solid tumors (NCT02481154), including 52 patients with gliomas, AG-881 was associated with a favorable safety profile at doses <100 mg once daily (QD).10
• Among 22 patients with nonenhancing glioma in this phase 1 study, AG-881 was associated with an objective response rate of 9.1%, including one partial response and one minor response, and stable disease in 82% of patients. The median treatment duration was 15 months with 59% of these patients continuing in the study at the time of the data cut-off.

KEY PRIMARY OBJECTIVES

• The primary objective of this perioperative study is to determine the 2-HG concentration in tumors resected following presurgical treatment with ivosidenib or AG-881 compared with untreated control tumors in patients with recurrent, nonenhancing, mIDH1-R132H LGG.
• The secondary objectives of the study are to evaluate the plasma pharmacodynamics (PD; 2-HG concentration pre- and posttreatment compared with untreated controls), pharmacokinetics (PK; in plasma and tumor tissue), safety, and preliminary clinical activity of ivosidenib and AG-881.

REFERENCES


TRIAL DESIGN

• This perioperative study is a phase 1, multicenter, open-label study of ivosidenib and AG-881 in patients with recurrent, nonenhancing, mIDH1-R132H LGG for whom surgical resection is indicated.

• ClinicalTrials.gov NCT03343197.
• Based on the safety, tolerability, and PK/PD data from the ongoing phase 1 studies, ivosidenib 500 mg QD and AG-881 50 mg QD will be tested in cohort 1.
• An alternative dose regimen of ivosidenib and AG-881 may be tested in cohort 2.

• Patients will receive 4 weeks of ivosidenib, 4 weeks of AG-881, or no treatment prior to surgical resection. All patients will have the option to receive ivosidenib or AG-881 following surgery.

• Concentrations of 2-HG and ivosidenib or AG-881 will be measured in tumor, plasma, and cerebrospinal fluid (CSF). 2-HG concentration in treated tumors will be compared with untreated and reference controls.

• The study design is shown in Figure 1.

SUMMARY AND CURRENT STATUS

Summary

• Ivosidenib and AG-881 have shown favorable safety profiles and preliminary clinical activity in patients with nonenhancing LGG in phase 1 studies.
• This is a phase 1, multicenter, open-label, perioperative study of ivosidenib and AG-881 in patients with recurrent, nonenhancing, mIDH1-mutant LGG eligible for resection.
• This study will evaluate CNS penetration and PK/PD activity of ivosidenib and AG-881 by measuring the concentrations of 2-HG and ivosidenib or AG-881 in resected brain tumor tissue following ivosidenib or AG-881 administration.

Study status

• This perioperative study of ivosidenib and AG-881 in patients with mIDH1 LGG is currently enrolling patients at participating sites in the USA.

Figure 1. Perioperative study design

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Disclosures

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