RBTT-03

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 Mellinghoff[1], Elizabeth A Maher[2], Patrick Y Wen[3], Timothy F Cloughesy[4], Katherine B Peters[5], Isabel Arrillaga-Romany[6], Changho Choi[2], Benjamin M Ellingson[4], Alexander P Lin[3], Yan Li[7], Brian J Soher[5], Robert J Young[1], Lori Steelman[8], Kha Le[8], Feng Yin[8], Bin Wu[8], Min Lu[8], Yanwei Zhang[8], Brandon Nicolay[8], Steven Schoenfeld[8], Katharine Yen[8], Shuchi S Pandya[8], Jennifer Clarke[7]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]The University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]University of California Los Angeles, Los Angeles, CA, USA; [5]Duke University Medical Center, Durham, NC, USA; [6]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [7]University of California San Francisco, San Francisco, CA, USA; [8]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.[1,2] IDH2 mutations occur in ~4% of LGGs.[1,2]
- 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).[3,4]
- 2-HG accumulation results in metabolic dysregulation and inhibition of α-KG–dependent enzymes, which causes epigenetic dysregulation and impaired cellular differentiation, promoting oncogenesis.[5-7]
- Inhibitors of mIDH enzymes block 2-HG production and restore cellular differentiation and maturation.
  - TIBSOVO® (ivosidenib) and IDHIFA® (enasidenib) are approved by the US FDA for mIDH1 and mIDH2 relapsed or refractory acute myeloid leukemia, respectively.

Ivosidenib (AG-120)

- Ivosidenib is a first-in-class, oral, potent, targeted, small-molecule inhibitor of the mIDH1 enzyme[8] that is approved for the treatment of adults with mIDH1 relapsed or refractory acute myeloid leukemia and is being tested in various solid tumors, including glioma.
- 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.[9]
- In an ongoing phase 1 study of ivosidenib in patients with advanced mIDH1 solid tumors (NCT02073994), including 66 patients with gliomas, ivosidenib treatment was associated with a favorable safety profile.[10,11]
  - 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.[11]

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 98% and impeded glioma growth.[12]
- In an ongoing phase 1 study of AG-881 in patients with advanced mIDH solid tumors (NCT02481154), including 52 patients with gliomas, AG-881 was associated with a favorable safety profile at doses <100 mg once daily (QD).
  - 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.
    - See SNO 2018 oral presentation ACTR-31 by Mellinghoff et al. (November 16, 1:30–1:40 pm).

KEY STUDY 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.

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 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.
- Further information is available at https://clinicaltrials.gov/ct2/show/NCT03343197.

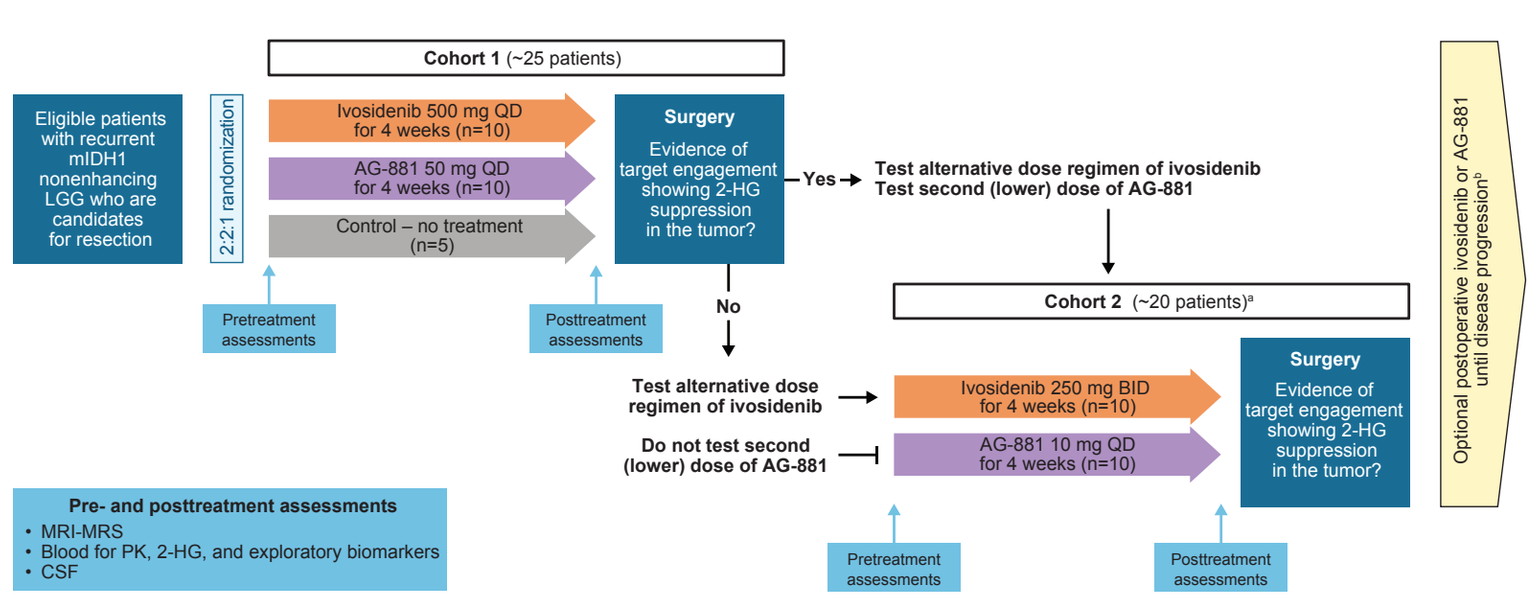
Study status

- 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

Key inclusion criteria
- Patients with recurrent WHO 2016 grade 2 or 3 oligodendroglioma or astrocytoma who are candidates for clinical resection (but for whom surgery is not urgently indicated)
- ≥18 years of age
- Centrally confirmed primarily nonenhancing disease by T2 FLAIR MRI
- Documented IDH1-R132H mutation and known 1p19q or ATRX mutation status by local laboratory testing
- Karnofsky Performance Status score ≥60
- ALT/AST within normal limits
- Expected survival time of ≥12 months

Key exclusion criteria
- Prior systemic anticancer therapy within 1 month of the first dose of ivosidenib or AG-881
- Receipt of an investigational agent <14 days (or <5 half-lives of the investigational agent) prior to the first dose of ivosidenib or AG-881
- Prior radiation therapy within 6 months of the first dose of ivosidenib or AG-881
- Prior treatment with an IDH inhibitor
- Prior treatment with bevacizumab
- Heart-rate corrected QTc interval (Fridericia's formula) of ≥450 ms or other factors that increase the risk of QTc prolongation or arrhythmic events



Primary endpoint: 2-HG concentration in surgically resected tumors

Secondary endpoints
- Safety[c]
- Change from baseline in concentration of 2-HG in plasma
- Ivosidenib or AG-881 concentration in surgically resected tumors
- Plasma-concentration time profiles and PK parameters of ivosidenib or AG-881
- Preliminary clinical activity of ivosidenib or AG-881 monotherapy in the residual disease setting as assessed by modified RANO-LGG criteria[d]

Exploratory endpoints
- Change from baseline in concentration of 2-HG in CSF
- Ivosidenib or AG-881 concentration in CSF
- Change in signal in 2-HG MRS
- Changes in molecular and cellular markers associated with the mechanism of action of ivosidenib and AG-881, when feasible, in blood, archived tumor tissue, and surgically resected tumors

[a]Second doses of ivosidenib and/or AG-881 may be tested in cohort 2. In the event that both are tested, patients will be randomized 1:1 to either ivosidenib or AG-881
[b]Patients in the control group can opt to be randomized to either ivosidenib or AG-881 postoperatively
[c]Includes adverse events, safety laboratory parameters, physical examination findings, vital signs, 12-lead electrocardiography, left ventricular ejection fraction, and Karnofsky Performance Status
[d]Based on investigator assessment
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; RANO-LGG = Response Assessment in Neuro-oncology for LGG; T2 FLAIR MRI = T2-weighted fluid-attenuated inversion recovery; WHO = World Health Organization

References

1. Yan H et al. *N Engl J Med* 2009;360:765-73.
2. The Cancer Genome Atlas Research Network. *N Engl J Med* 2015;372:2481-98.
3. Dang L et al. *Nature* 2009;462:739-44.
4. Ward PS et al. *Cancer Cell* 2010;17:225-34.
5. Lu C et al. *Nature* 2012;483:474-8.
6. Saha SK et al. *Nature* 2014;513:110-4.
7. Xu W et al. *Cancer Cell* 2011;19:17-30.
8. Popovici-Muller J et al. *ACS Med Chem Lett* 2018;9:300-5.
9. Nicolay B et al. *Neuro-Oncology* 2017;19(Suppl 6):EXTH-59.
10. Mellinghoff IK et al. *SNO Annual Scientific Meeting* 2016: Oral presentation ACTR-46.
11. Mellinghoff IK et al. *SNO Annual Scientific Meeting* 2017: Oral presentation ACTR-46.
12. Nicolay B et al. *Neuro-Oncology* 2017;19(Suppl 6):EXTH-34.

Acknowledgments

We would like to thank the patients taking part in this study.

Disclosures

This study is funded by Agios Pharmaceuticals, Inc.
Editorial assistance was provided by Susanne Vidot, PhD, CMMP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

Scan code to receive PDF file of the poster or visit http://bit.ly/2y2PJtQ

Presented at the 23rd Annual Scientific Meeting and Education Day of the Society for Neuro-oncology (SNO), November 15–18, 2018, New Orleans, LA, USA