The IDH1 mutant inhibitor AG-120 shows strong inhibition of 2-HG production in an orthotopic IDH1 mutant glioma model in vivo

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BACKGROUND

- Somatic mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and 2 confer neomorphic enzymatic activity, which results in the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG).1,2
- 2-HG drives multiple oncogenic processes, including increased histone and DNA methylation, leading to a block in cellular differentiation.3,4
- The threshold of inhibition of 2-HG production required for antitumor activity remains to be defined.
- IDH1/2 mutations occur in >70% of diffuse low-grade gliomas (LGG).5
- Standard of care treatment for patients with diffuse LGG involves combined modality approaches, including surgery, radiation, and chemotherapy.6
- Previously reported data suggested that 2-HG production by the mutant IDH1 (mIDH1) protein radiosensitizes glioma cells7,8 and that inhibition of mIDH1 resulted in a loss of radiosensitivity in vitro.9
- AG-120 (ivosidenib) is an orally available, potent, targeted inhibitor of the IDH1 protein that is currently being assessed in two clinical trials in solid tumors: ClinicalTrials.gov NCT02073994 and NCT02989857.
- Clinical data from the subset of patients with nonenhancing glioma were reported in oral presentation ACTR-46.

OBJECTIVES

- Validate that AG-120 crosses the blood-brain barrier and inhibits 2-HG production in an orthotopic mouse xenograft model of a human IDH1-R132H glioma.
- Determine whether AG-120 treatment antagonizes the efficacy of radiation therapy (RT) in vivo.

METHODS

Orthotopic mouse xenograft model of human grade 3 mIDH1-R132H glioma

- TS603 glioma cells with an endogeneous heterozygous IDH1-R132H mutation (5×10⁶ cells) were intracranially implanted into female CB17 SCID mice on Day 0.10
- The TS603 cell line was derived from a patient with grade 3 anaplastic oligodendroglioma, and also harbors a co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q).11
- Assessment of pharmacokinetics (PK) and pharmacodynamics (PD) (Figure 1A):
  - Following tumor engraftment for 40 days, mice were randomized to receive either vehicle (n=12) or AG-120 50, 150, or 450 mg/kg orally (PO) twice daily (BID) (n=16 each) for 4 days.
  - At 1, 4, 12, and 24 hr after the last dose of AG-120, three mice in the vehicle group and four mice in each AG-120 dose group were sacrificed, and plasma, brain, and brain tumor samples were analyzed for AG-120 and 2-HG.
  - Evaluation of AG-120 in combination with RT (Figure 1B):
    - Following tumor engraftment for 36 days, 60 mice were randomized into five treatment groups (n=12 each) and treated with either vehicle, RT (2 Gy focal radiation once daily [QD]), and/or AG-120 (150 mg/kg PO BID) as indicated for 21 days (Days 37–57).12
    - Tumor volume was measured by magnetic resonance imaging (MRI) on Day 36 and every 3–5 days during dosing, and survival was assessed from Day 0 to Day 85.
Subcutaneous mouse xenograft model of human grade 3 mIDH1-R132H glioma

- Male ICR SCID mice were injected subcutaneously with 10⁵ TS603 glioma cells (Figure 1C).
- Following tumor engraftment for 43 days, 24 mice were randomized to receive either vehicle (n=12) or AG-120 (150 mg/kg PO BID, n=12) for 21 days.
- Tumor volume was assessed every 3–4 days during dosing.

RESULTS

Validation of 2-HG inhibition by AG-120 in orthotopic grade 3 mIDH1 glioma

- AG-120 strongly inhibited 2-HG production in human mIDH1 brain tumor xenografts in mice dosed at 50, 150, or 450 mg/kg PO BID (Figure 2).
- AG-120 was detectable in the brain and brain tumor tissues of the mice, although at much lower exposures than in the plasma (Table 1).
- AG-120 treatment did not antagonize RT efficacy in orthotopic grade 3 mIDH1 glioma
  - AG-120 dosed at 150 mg/kg PO BID, which inhibits tumor 2-HG production by 77–79% (Figure 2), did not have an antagonistic effect on the antitumor activity of RT, but did not confer monotherapy benefit in this model (Figure 3).
  - Likewise, AG-120 (150 mg/kg PO BID) exhibited 2-HG production by >80% and reduced in vivo growth of a subcutaneous grade 3 mIDH1 glioma by 52% (Figure 4).
- AG-120 treatment reduced in vivo growth of a subcutaneous grade 3 mIDH1 glioma
  - AG-120 (150 mg/kg PO BID) exhibited 2-HG production by >80% and reduced in vivo growth of a subcutaneous grade 3 mIDH1 glioma by 52% (Figure 5).

CONCLUSIONS

- In mice engrafted with orthotopic human grade 3 mIDH1-R132H gliomas:
  - AG-120 had very low brain penetration following oral administration, but sufficient AG-120 brain exposure was achieved to confer a dose-dependent reduction in 2-HG levels in brain tumors, with 85% maximal inhibition achieved.
  - Inhibition of 2-HG by 79% did not confer an antitumor effect in this model.
  - The combination of AG-120 + RT demonstrated no antagonism of RT efficacy.
  - In a subcutaneous human grade 3 mIDH1-R132H glioma mouse model, mIDH1 inhibition by AG-120 impeded tumor growth and, after achieving >84% 2-HG production inhibition.
  - These observations support the clinical investigation of AG-120 in patients with mIDH1-driven gliomas.
  - Our findings do not support previous in vitro nonclinical work13 that suggested a potential antagonism between mIDH1 inhibition and RT.

Figure 1. Human grade 3 mIDH1-R132H glioma mouse xenograft model development and in vivo study designs

Figure 2. AG-120 concentration in plasma and 2-HG concentration in orthotopic grade 3 mIDH1 glioma after eight oral doses

Figure 3. No antagonistic effect of AG-120 treatment on RT efficacy in orthotrophic grade 3 mIDH1 glioma

Figure 4. No antagonistic effect of AG-120 treatment on RT survival benefit in orthotrophic grade 3 mIDH1 glioma

Figure 5. Inhibition of 2-HG production and tumor growth by AG-120 in a subcutaneous grade 3 mIDH1 glioma

Table 1. Brain penetration of AG-120

Table: 2-HG inhibition by AG-120 in orthotopic grade 3 mIDH1 glioma

Table: Brain penetration of AG-120

50 mg/kg BID 150 mg/kg BID 450 mg/kg BID

Brain AUC0–12 (hr·ng/g)
727 1480 3550
Plasma AUC0–12 (hr·ng/mL)
19.200 37.400 99.400
Brain-to-tumor ratio
0.037 0.039 0.035
% 2-HG inhibition (AUC0–12)
71 79 85

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References