

# Combined use of the pan-IDH mutant inhibitor AG-881 with radiation therapy shows added benefit in an orthotopic IDH1 mutant glioma model *in vivo*

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## BACKGROUND

- Somatic mutations in isocitrate dehydrogenase (IDH) 1 or 2 confer neomorphic enzyme activity, producing the oncometabolite 2-hydroxyglutarate (2-HG).<sup>1,2</sup>
- Accumulation of 2-HG facilitates tumorigenesis through DNA hypermethylation, increased repressive histone methylation, and inhibition of differentiation processes.<sup>3,4</sup>
- Over 70% of diffuse low-grade gliomas (LGG) harbor IDH1/2 mutations.<sup>5</sup>
- Standard of care treatment for patients with diffuse LGG involves combined modality approaches, including surgery, radiation, and chemotherapy.<sup>6</sup>
- Studies performed with an early tool compound, AGI-5198, which is active against the mutant IDH1 protein (mIDH1) but not mIDH2, have demonstrated that mIDH1 inhibition can repress growth of mIDH1-driven gliomas in some models but not others.<sup>7,8</sup>
- Furthermore, recent *in vitro* studies using AGI-5198 in mIDH1 glioma models have suggested that 2-HG production by mIDH1 may radiosensitize glioma cells<sup>9-12</sup> and that mIDH1 inhibition may result in a loss of radiosensitivity.<sup>12</sup>
- mIDH1-driven LGGs have been found to be particularly sensitive to temozolomide (TMZ) treatment, presumably due to hypermethylation of the MGMT promoter.<sup>13-15</sup>
  - There is potential for antagonism between mIDH1 inhibition and TMZ treatment, owing to the possibility of high levels of 2-HG leading to and/or enforcing hypermethylation of the MGMT promoter.
- AG-881 is a novel, potent inhibitor of both the mIDH1 and mIDH2 proteins that is currently in phase 1 clinical development in patients with advanced mIDH1 or mIDH2 solid tumors, including gliomas (ClinicalTrials.gov NCT02481154) and hematologic malignancies (ClinicalTrials.gov NCT02492737).
  - As demonstrated previously, AG-881 is highly brain penetrant.<sup>16</sup>

## OBJECTIVES

- In a mouse xenograft model of a human mIDH1-R132H grade 3 oligodendroglioma, we assessed the potential for antagonism between 2-HG suppression using the pan-IDH mutant inhibitor AG-881 and:
  - Radiation therapy (RT)
  - TMZ treatment.

## METHODS

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

- TS603 glioma cells with an endogenous heterozygous IDH1-R132H mutation ( $5 \times 10^4$  cells) were intracranially implanted into female CB17 SCID mice.<sup>7</sup>
- 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).<sup>7</sup>
- Following tumor engraftment (tumor size 5–20 mm<sup>3</sup>), animals were treated with vehicle, AG-881, RT, or AG-881 in combination with RT (AG-881 + RT), and pharmacokinetics (PK), pharmacodynamics (PD), tumor volume, and survival were assessed, as shown in **Figure 1A**.

### Subcutaneous mouse xenograft model of human grade 3 mIDH1-R132H glioma

- Male ICR SCID mice were injected subcutaneously with  $10^6$  TS603 glioma cells.
- Following tumor engraftment for 34–44 days, animals were treated with vehicle, AG-881, TMZ, or AG-881 + TMZ and assessed for tumor volume as shown in **Figure 1B**.

## RESULTS

### Orthotopic grade 3 mIDH1 glioma model

- AG-881 readily crossed the blood-brain barrier and strongly inhibited 2-HG production in mIDH1 brain tumor xenografts (**Figure 2**).
- mIDH1 inhibition with AG-881 modestly impeded glioma growth *in vivo*. The combination of AG-881 + RT produced significantly greater inhibition of tumor growth than either of the monotherapies (**Figure 3**).
  - AG-881 did not antagonize the survival benefit conferred by RT (**Figure 4**).

### Subcutaneous grade 3 mIDH1 glioma model

- AG-881 treatment impeded *in vivo* tumor growth (**Figure 5**).
- AG-881 treatment did not antagonize TMZ efficacy (**Figure 6**).
- 2-HG concentrations were reduced to baseline levels in terminal tumor samples from animals treated with AG-881 alone or in combination with TMZ, but remained elevated in mice treated with TMZ alone (**Figure 7**).

Figure 1. Study designs

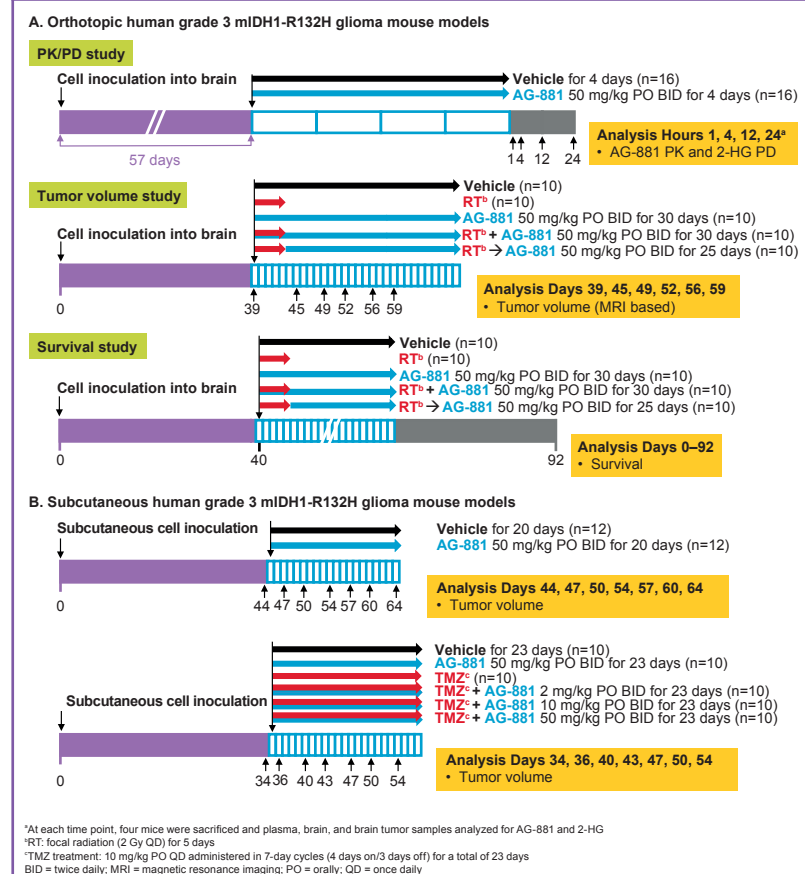


Figure 2. AG-881 inhibited 2-HG in an orthotopic grade 3 mIDH1 glioma model

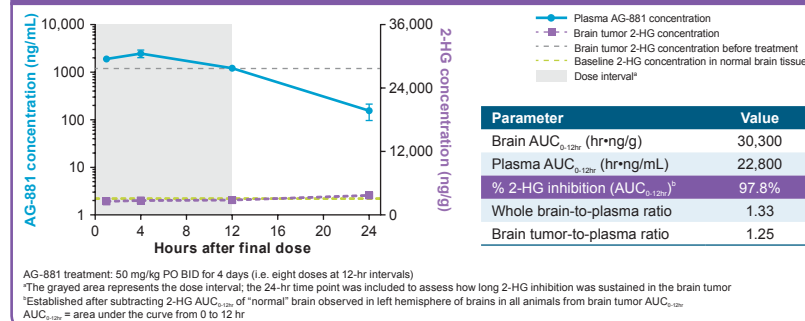


Figure 3. No antagonistic effect of AG-881 on RT efficacy in an orthotopic grade 3 mIDH1 glioma model

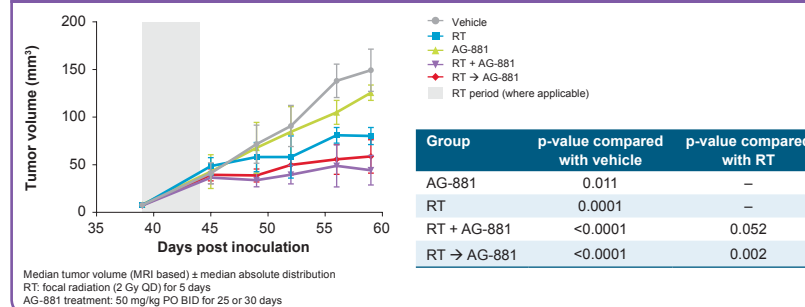


Figure 4. No antagonistic effect of AG-881 on RT survival in an orthotopic grade 3 mIDH1 glioma model

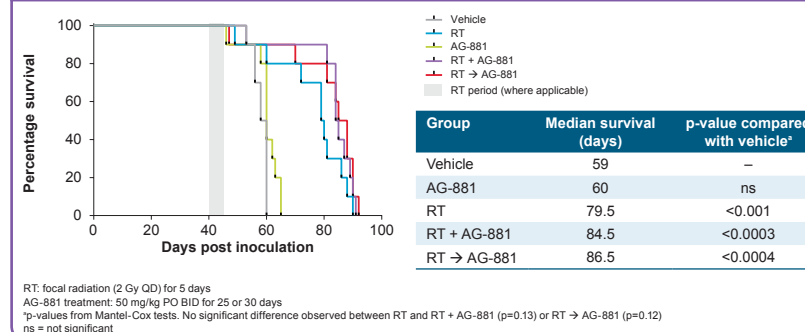


Figure 5. AG-881 impeded *in vivo* tumor growth in a subcutaneous grade 3 mIDH1 glioma model

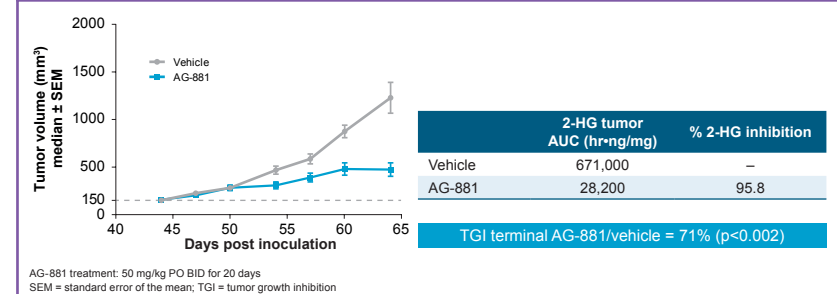


Figure 6. No antagonistic effect of AG-881 on TMZ efficacy in a subcutaneous grade 3 mIDH1 glioma model

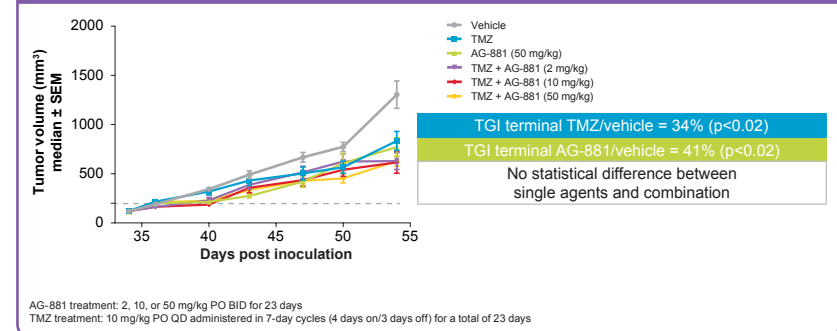
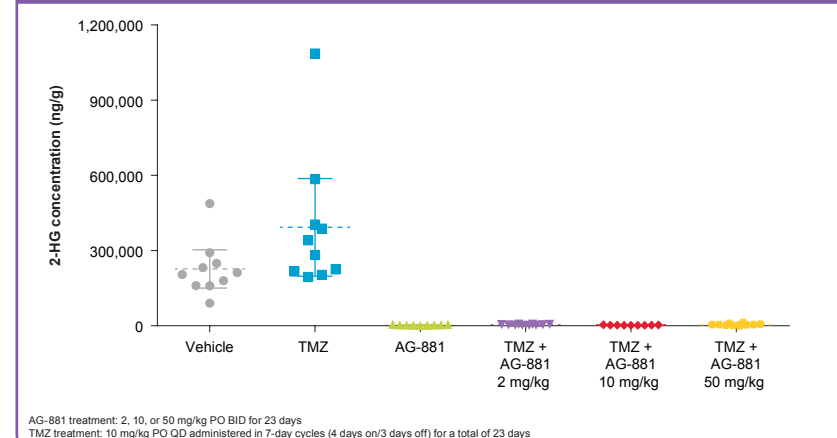


Figure 7. AG-881 reduced 2-HG concentrations to baseline level in a subcutaneous grade 3 mIDH1 glioma model



## CONCLUSIONS

- In an orthotopic human grade 3 mIDH1-R132H glioma mouse model:
  - Treatment with the highly brain penetrant mIDH1/2 inhibitor AG-881 resulted in >98% inhibition of 2-HG levels in brain tumor xenografts.
  - mIDH1 inhibition by AG-881 impeded glioma growth *in vivo*.
  - The combination of AG-881 + RT produced a significantly greater inhibitory effect on tumor growth than each single-modality treatment.
- In a subcutaneous human grade 3 mIDH1-R132H glioma mouse model:
  - AG-881 treatment resulted in inhibition of 2-HG to baseline levels in tumors.
  - AG-881 had an inhibitory effect on glioma growth.
  - No antagonism with TMZ was observed.
- These observations support the clinical investigation of AG-881 in patients with mIDH1-driven gliomas.
- Our findings do not support previous *in vitro* nonclinical work<sup>12</sup> that suggested a potential antagonism between mIDH1 inhibition and RT.

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