The use of DNA demethylating agent in combination with retinoids shows promise, but further optimization and preclinical studies are required for the treatment of intracranial IDH-mutant gliomas [1) 2)].

Human IDH1 WT and IDH1R132H cell lines and patient-derived xenografts (PDX) were used to evaluate the FDA-approved DNA demethylating agent 5-Azacytidine (5-Aza). Cell growth, protein and gene expression, chromatin immunoprecipitation, and nucleosome position assays were performed in 5-Aza treated cells. To evaluate antitumor activity in vivo, 5-Aza was administered alone and in combination with Temozolomide (TMZ) in a patient-derived xenograft (PDX) glioma models harboring IDH1R132H mutation.

5-Aza treatment has been found to reduce cell growth and increase Glial Fibrillary Acid Protein expression. Chromatin immunoprecipitation and nucleosome position assay showed that the mechanism of increased GFAP expression induction is associated with histone modification and nucleosome repositioning of the GFAP promoter, respectively. In vivo, 5-Aza treatment extended survival in IDH1R132H mutant, but not in an IDH1 WT glioma model. Additionally, 5-Aza enhances the therapeutic effect of DNA damaging agent TMZ in both subcutaneous and orthotopic PDX models of IDH1R132H mutant glioma [3)].

1)
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3)
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