Inhibiting IDH mutations in low-grade glioma alters cellular function and the immune environment

Min Lu1, Ingo K Mellinghoff, Aaron Diaz2, Jennie W Taylor3, Sung Choe1, Ania Tissiari4, Dongwei Zhu1, Kha Le,1, Feng Tai5, Islam Hassan5, Shuchi S Pandora1, Lori Steelman4, Bin Wu5

1Agios Pharmaceuticals, Inc., Cambridge, MA, USA; 2Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3University of California San Francisco, San Francisco, CA, USA

BACKGROUND
Isocitrate dehydrogenase (IDH) mutations in cancer:
- Somatic mutations in the enzyme IDH1 that converts isocitrate to alpha-ketoglutarate (α-KG) occur in many cancers.
- Mutations in IDH1 and IDH2 are somatic in most cancers, with a prevalence of 5% to 50%.
- IDH1 and IDH2 mutations are associated with immune evasion in glioma.
- IDH1 and IDH2 mutations are associated with hypoxia and tumorigenesis.

METHODS
- Staining and assays:
  - Serial sections of brain tissue were stained for IDH1, IDH2, and HIF1A using standard procedures.
  - CD8+ T cells were stained using standard immunohistochemistry (IHC) procedures.
  - PD-L1 expression was assessed using standard IHC procedures.
- Multiplex IHC for CD68, CD163, and HLA-DR was carried out at Akoya Biosciences.
- T-cell receptor (TCR) sequencing was performed at Life Technologies Clinical Services Lab.
- Multiplex TCR sequencing was performed to assess T-cell clonality and diversity.
- Tol2 transgenic mice were employed to assess tumor growth and T-cell infiltration.
- Overall, these findings suggest that both tumor-intrinsic and tumor-extrinsic mechanisms contribute to the immune response.

RESULTS
- IDH1 inhibition increased the expression of tumor-associated macrophage markers and improved the immune response.
- IDH1 inhibition decreased the expression of tumor-associated macrophage markers and improved the immune response.
- Multiplex TCR sequencing revealed increased T-cell infiltration, clonality, and diversity.

CONCLUSIONS
- Overall, these findings suggest that both tumor-intrinsic and tumor-extrinsic mechanisms contribute to the immune response.
- IDH1 inhibition lead to an increase in the immune response.