Review Nat Rev Neurol. 2024 May 17. doi: 10.1038/s41582-024-00967-7. Online ahead of print.

IDH inhibition in gliomas: from preclinical models to clinical trials

Roberta Rudà [1], Craig Horbinski [2 3], Martin van den Bent [4], Matthias Preusser [5], Riccardo Soffietti [6]

Affiliations

PMID: 38760442 DOI: 10.1038/s41582-024-00967-7

Abstract

Gliomas are the most common malignant primary brain tumours in adults and cannot usually be cured with standard cancer treatments. Gliomas show intratumoural and intertumoural heterogeneity at the histological and molecular levels, and they frequently contain mutations in the isocitrate dehydrogenase 1 (IDH1) or IDH2 gene. IDH-mutant adult-type diffuse gliomas are subdivided into grade 2, 3 or 4 IDH-mutant astrocytomas and grade 2 or 3 IDH-mutant, 1p19q-codeleted oligodendrogliomas. The product of the mutated IDH genes, D-2-hydroxyglutarate (D-2-HG), induces global DNA hypermethylation and interferes with immunity, leading to stimulation of tumour growth. Selective inhibitors of mutant IDH, such as ivosidenib and vorasidenib, have been shown to reduce D-2-HG levels and induce cellular differentiation in preclinical models and to induce MRI-detectable responses in early clinical trials. The phase III INDIGO trial has demonstrated superiority of vorasidenib, a brain-penetrant pan-mutant IDH inhibitor, over placebo in people with non-enhancing grade 2 IDH-mutant gliomas following surgery. In this Review, we describe the pathway of development of IDH inhibitors in IDH-mutant low-grade gliomas from preclinical models to clinical trials. We discuss the practice-changing implications of the INDIGO trial and consider new avenues of investigation in the field of IDH-mutant gliomas.