Review J Clin Oncol. 2024 Jun 4:JCO2302195. doi: 10.1200/JCO.23.02195. Online ahead of print.

Multidisciplinary Management of Isocitrate Dehydrogenase-Mutated Gliomas in a Contemporary Molecularly Defined Era

Rupesh Kotecha [1], David Schiff [2], Arnab Chakravarti [3], Jessica L Fleming [3], Paul D Brown [4], Vinay K Puduvalli [5], Michael A Vogelbaum [6], Vinai Gondi [7], Marco Gallus [8], Hideho Okada [8], Minesh P Mehta [1]

Affiliations

PMID: 38833641 DOI: 10.1200/JCO.23.02195

Abstract

Mutations in isocitrate dehydrogenase (IDH) genes, an early step in the ontogeny of lower-grade gliomas, induce global epigenetic changes characterized by a hypermethylation phenotype and are critical to tumor classification, treatment decision making, and estimation of patient prognosis. The introduction of IDH inhibitors to block the oncogenic neomorphic function of the mutated protein has resulted in new therapeutic options for these patients. To appreciate the implications of these recent IDH inhibitor results, it is important to juxtapose historical outcomes with chemoradiotherapy. Herein, we rationally evaluate recent IDH inhibitor data within historical precedents to guide contemporary decisions regarding the role of observation, maximal safe resection, adjuvant therapies, and the import of patient and tumor variables. The biological underpinnings of the IDH pathway and the mechanisms, impact, and limitations of IDH inhibitors, the actual magnitude of tumor regression and patient benefit, and emergence of resistance pathways are presented to guide future trial development. Management in the current, molecularly defined era will require careful patient selection and risk factor assessment, followed by an open dialog about the results of studies such as INDIGO, as well as mature data from legacy trials, and a discussion about risk-versus-benefit for the choice of treatment, with multidisciplinary decision making as an absolute prerequisite.