Review CNS Drugs. 2025 Nov 7. doi: 10.1007/s40263-025-01238-9. Online ahead of print.

New and Emerging Therapies for Patients with Low-Grade Glioma

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PMID: 41201564 DOI: 10.1007/s40263-025-01238-9

Abstract

Both pediatric and adult patients can develop low-grade glioma (World Health Organization [WHO] grade 2), a type of primary brain tumor that can impact neurologic function and limit one's ability to thrive and survive. Traditionally, the treatment of low-grade gliomas mirrored recommendations for patients with higher-grade gliomas, such as glioblastoma. The diagnosis and categorization of primary brain tumors, including low-grade gliomas, were transformed in 2021 with an update of the World Health Organization classification system for pediatric and adult diffuse gliomas. In the pediatric population, there is recognition that a majority of low-grade gliomas have alterations in the mitogen-activated protein kinase (MAPK) pathway (BRAF mutations and rearrangements and other alterations in genes in this pathway); whereas in the adult population, mutations in isocitrate dehydrogenase (IDH), a key enzyme of the Krebs cycle, define diffuse low-grade glioma, namely oligodendroglioma and astrocytoma. Parallel to the advancements in diagnosis and tumor classification, the treatment has advanced to develop targeted therapies for patients with diffuse low-grade glioma. This review will highlight the molecular and genetic underpinnings of these tumors and how targeted therapeutic strategies led to the US Food and Drug Administration's approvals of combination therapy with dabrafenib and trametinib for pediatric patients with BRAF V600E mutant low-grade glioma; tovorafenib, a pan-RAF inhibitor, for pediatric BRAF mutant glioma; and vorasidenib, an inhibitor of mutant IDH1/2 enzymes, for patients with mutant IDH low-grade glioma. Integration of these targeted therapies into currently accepted treatment paradigms remains to be fully understood, along with the long-term impact on patient quality of life and prognosis.