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Immunotherapy and targeted therapy for high grade gliomas: current and future directions

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Abstract in English, French

Background: High grade gliomas are aggressive intrinsic brain tumors with limited treatment options and a universally poor prognosis. In recent years, significant progress has been made in understanding the genetic and molecular underpinnings of high grade gliomas and their interactions with the tumor microenvironment, including vasculature, immune cells, neurons, and glia, and, consequently, in the development of novel molecularly targeted therapies and immunotherapies.

Methods: Here, we review ongoing work in the clinical development of new therapeutic strategies for high grade gliomas, discuss ongoing challenges, and highlight emerging opportunities for targeted intervention, with particular focus on molecularly targeted and immunotherapy in recent and ongoing clinical trials.

Results: We discuss relevant molecular targets in high grade glioma, including IDH, VEGF, RTK signaling (EGFR, PI3K/Akt, Ras/Raf/MEK), p53, CDKN2A/B, CDK4/6, MGMT, PARP, TERT, and ATRX, as well as contemporary immunotherapeutic strategies including immune checkpoint inhibition (including classical and emerging targets), cell-based immunotherapy (CAR-T cells, TCR therapy, TIL therapy, and other engineered cell therapies), cancer vaccines, oncolytic viruses, as well as emerging mechanisms including cancer neuroscience-based therapies.

Conclusions: High grade glioma is a networked disease, involving numerous interconnected molecular and microenvironmental phenomena from tumor-intrinsic pathways and antigenicity to immune recognition and attack to neuronal modulation of both tumor and immune signaling. Emerging therapies harness several of these intersectional mechanisms, often simultaneously, and together offer hope for the future of clinical treatment of these devastating cancers.

Keywords: Clinical trials; Glioblastoma; Glioma; Immunotherapy; Molecular therapy; Targeted therapy; Tumor microenvironment.