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Immune checkpoint inhibitors for glioblastoma: emerging science, clinical advances, and future directions

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Abstract

Glioblastoma (GBM), the most common and aggressive primary central nervous system (CNS) tumor in adults, continues to have a dismal prognosis. Across hundreds of clinical trials, few novel approaches have translated to clinical practice while survival has improved by only a few months over the past three decades. Randomized controlled trials of immune checkpoint inhibitors (ICIs), which have seen impressive success for advanced or metastatic extracranial solid tumors, have so far failed to demonstrate a clinical benefit for patients with GBM. This has been secondary to GBM heterogeneity, the unique immunosuppressive CNS microenvironment, immune-evasive strategies by cancer cells, and the rapid evolution of tumor on therapy. This review aims to summarize findings from major clinical trials of ICIs for GBM, review historic failures, and describe currently promising avenues of investigation. We explore the biological mechanisms driving ICI responses, focusing on the role of the tumor microenvironment, immune evasion, and molecular biomarkers. Beyond conventional monotherapy approaches targeting PD-1, PD-L1, CTLA-4, we describe emerging approaches for GBM, such as dual-agent ICIs, and combination of ICIs with oncolytic virotherapy, antigenic peptide vaccines, chimeric antigenic receptor (CAR) T-cell therapy, along with nanoparticle-based delivery systems to enhance ICI efficacy. We highlight potential strategies for improving patient selection and treatment personalization, along with real-time, longitudinal monitoring of therapeutic responses through advanced imaging and liquid biopsy techniques. Integrated radiomics, tissue, and plasma-based analyses, may potentially uncover immunotherapeutic response signatures, enabling early, adaptive therapeutic adjustments. By specifically targeting current therapeutic challenges, outcomes for GBM patients may potentially be improved.

Keywords: Brain malignancy; Durvalumab; Immune exhaustion; Immunotherapy; Ipilimumab; Nivolumab; Pembrolizumab.