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Treatment strategies and innovation for recurrent high-grade glioma

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Abstract

Background: Recurrent high-grade glioma (HGG)-including glioblastoma-remains lethal, with median survival of approximately 6-10 months after first progression, although patients with IDH mutant tumors often have better survival. Recent ASCO/SNO data and expanding trial data are reshaping available treatment strategies.

Methods: We review evidence for alkylators and anti-angiogenic therapy; summarize targeted options for rare, actionable alterations; review immuno-oncology combinations and cellular therapies; highlight DNA damage response (DDR)/radiosensitization strategies and discuss advances in blood-brain barrier modulation and locoregional delivery. We propose a patient-centered algorithm that prioritizes trial enrollment, biomarker-guided approaches, steroid stewardship, and quality of life.

Results: Lomustine, temozolomide rechallenge, and bevacizumab remain commonly used but provide modest benefit. Targeted agents show meaningful activity only in select subsets (BRAF V600E, NTRK). DDR-directed agents such as ATM/ATR inhibitors show early promise. Immunotherapy advances center on rationale combinations, oncolytic viruses, and locoregionally delivered CAR-T/TCR platforms. Blood-Brain-Barrier (BBB) modulation strategies and adaptive trials are broadening access to innovative therapies. The 2025 landscape features meaningful, if incremental, options-alongside the first ever FDA-approved therapy for H3K27M-mutant diffuse midline glioma at relapse-and a pipeline of rational combinatorial approaches poised to refine outcomes for selected patients. This article concentrates on medical options and intentionally omits extended discussions of surgery and radiation beyond their integration with systemic therapies at recurrence.

Conclusions: Despite poor overall outcomes, incremental progress across targeted, immune, and delivery-based approaches supports a patient centered strategy emphasizing clinical-trial enrollment, molecular profiling and symptom focused care.

Keywords: Biomarkers; Glioblastoma; IDH; Immunotherapy; MGMT.