CANCER NEUROSCIENCE

Glioblastoma: Overcoming fundamental biological and delivery barriers to therapy

Genaro R. Villa[1,2,3]†, Ashish D. Patel[2,4,5]†, David A. Reardon[2,4]*, E. Antonio Chiocca[1,2,3]*

Glioblastoma remains the most aggressive primary malignant brain tumor in adults, with survival largely unchanged despite advances in molecular diagnostics and supportive care. Therapeutic failure reflects fundamental biological and anatomical barriers, including intratumoral heterogeneity, an immunosuppressive tumor microenvironment, and restricted drug delivery across the blood-brain barrier. In this Review, we summarize the current standard of care and critically examine emerging strategies aimed at overcoming these constraints, including locoregional delivery technologies, immunotherapy, biomarker-defined precision approaches, and adaptive clinical trial designs. We highlight key translational and clinical studies shaping the field and discuss principles for developing more effective, integrated therapeutic paradigms.

INTRODUCTION

Glioblastoma (GBM) remains the most common and aggressive primary malignant brain tumor in adults. In trial-eligible patients treated with standard therapy, median overall survival (OS) ranges from ~15 months in tumors with an unmethylated *O*6-methylguanine–DNA methyltransferase (*MGMT*) promoter to nearly 22 months in *MGMT*-methylated disease (*1*), whereas population-level survival in the United States remains closer to 8 to 9 months (*2*), with international population-based studies likewise demonstrating persistently poor GBM outcomes worldwide (*3*). Standard treatment consists of maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide (*4*, *5*).

Recent updates to the World Health Organization (WHO) classification of central nervous system (CNS) tumors have refined the molecular definition of GBM, distinguishing isocitrate dehydrogenase (IDH)–wild-type disease from other diffuse gliomas and emphasizing the importance of integrated pathological assessment (*6*). Contemporary diagnostic approaches increasingly incorporate next-generation sequencing, copy number profiling, DNA methylation analysis, and fusion detection to improve diagnostic precision and identify potentially actionable alterations. Despite these advances, molecular stratification alone has not translated into durable therapeutic success for patients with GBM. In contrast, for other high-grade gliomas now recognized as biologically distinct entities, such as H3K27M-mutant diffuse midline glioma and IDH-mutant astrocytoma, molecular insights have led to US Food and Drug Administration (FDA)–approved therapies targeting defining driver alterations (*7*, *8*).

Several biological and pharmacologic constraints continue to limit progress, including intratumoral heterogeneity and tumor cell plasticity, an immunosuppressive microenvironment, and restricted therapeutic penetration imposed by the blood-brain barrier (BBB) (*9*–*12*). This heterogeneity is reflected in the ability of GBM cell populations to transition between multiple transcriptional states, contributing to therapeutic resistance and disease progression (*9*).

At the same time, there has been renewed momentum in the field driven by advances in locoregional drug delivery, immunotherapy, precision medicine, and adaptive clinical trial design. Strategies such as focused ultrasound–mediated BBB disruption, convection-enhanced delivery (CED), cellular and chimeric antigen receptor (CAR) T cell immunotherapies, oncolytic virotherapy, and biomarker-defined precision approaches targeting molecularly stratified subgroups, as well as rational combination approaches, are beginning to generate clinical signals that warrant careful synthesis and contextualization. Here, we summarize the current standard of care and critically examine emerging therapeutic strategies designed to overcome long-standing biological and anatomical barriers to effective treatment, highlighting key clinical trials shaping the field.

CURRENT STANDARD OF CARE

Medical management and supportive care

Optimal medical management of patients with GBM extends beyond antitumor therapy and encompasses seizure control, corticosteroid stewardship, venous thromboembolism (VTE) prophylaxis and treatment, and proactive management of treatment-related toxicities. These supportive measures can help preserve neurologic function, maintain functional independence, and enable patient participation in standard oncologic treatments and investigational trials.

Brain tumor–related epilepsy affects ~30 to 60% of patients with GBM and can impair quality of life (*13*). Current Society for Neuro-Oncology consensus guidelines recommend against routine primary anticonvulsant prophylaxis in seizure-free patients, given that randomized data have not demonstrated benefit (*14*, *15*). For patients who present with seizures, levetiracetam remains the most used first-line agent because of its favorable pharmacokinetic profile and lack of hepatic cytochrome P450 enzyme induction, which is important in patients receiving concurrent temozolomide or targeted therapies. Lacosamide is an increasingly used alternative with similarly low interaction potential. Conversely, enzyme-inducing antiseizure medications such as fosphenytoin and carbamazepine are generally avoided because of their potential for detrimental drug-drug interactions. Cases of refractory brain tumor–related epilepsy should prompt clinicians to reevaluate patients for tumor progression and treatment modification (*16*).

[1]Harvey Cushing Neuro-Oncology Laboratories, Department of Neurosurgery, Mass General Brigham, Boston, MA, USA. [2]Harvard Medical School, Boston, MA, USA. [3]Center for Tumors of the Nervous System, Mass General Brigham Cancer Institute, Boston, MA, USA. [4]Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. [5]Pappas Center for Neuro-Oncology, Massachusetts General Hospital, Boston, MA, USA.
†These authors contributed equally to this work.
*Corresponding author. Email: David_Reardon@DFCI.Harvard.edu (D.A.R.); eachiocca@mgb.org (E.A.C.)

Corticosteroids, specifically dexamethasone, have remained a mainstay for managing tumor-associated vasogenic edema and mass effect. However, prolonged and even short-term corticosteroid use carries well-documented adverse effects including immunosuppression, myopathy, hyperglycemia, osteoporosis, hypothalamic-pituitary-adrenal axis suppression, and psychiatric disturbance. Emerging evidence further suggests that corticosteroids may impair antitumor immune responses and adversely affect survival, underscoring the importance of early discontinuation or aggressive tapering to the lowest effective dose (*17*, *18*). Judicious corticosteroid management is particularly important in the context of immunotherapy, because corticosteroid use above defined thresholds frequently can serve as an exclusion criterion for clinical trial enrollment, yet the minimum dose that avoids clinically meaningful immunologic compromise remains undefined. Instead, bevacizumab can serve as a steroid-sparing agent in selected circumstances. Small retrospective series have explored boswellic acid, an over-the-counter nutraceutical with anti-inflammatory properties, as a potential corticosteroid-sparing option for radiation-induced cerebral edema and necrosis; however, the available evidence remains limited and lacks prospective validation (*19*).

VTE is among the most common medical complications in GBM, with an incidence of about 20 to 30% over the disease course (*20*). Once VTE is diagnosed, therapeutic anticoagulation with direct oral anticoagulants is increasingly used, with retrospective data supporting acceptable safety even in the setting of intracranial tumors (*21*). Emerging data further suggest that VTE occurrence is associated with worse clinical outcomes in patients with GBM, highlighting the systemic prothrombotic state driven by tumor biology and inflammation (*22*). The question of primary thromboprophylaxis remains unresolved, however. The ongoing Venous Thromboembolism Prevention in Outpatients With Glioma (VTE-POG) trial (NCT05683808) is prospectively evaluating this uncertainty by assessing whether prophylactic apixaban in patients with ambulatory glioma is safe and effective in preventing VTE.

Surgical management

Maximal safe surgical resection remains the cornerstone of initial GBM management and serves multiple critical roles, including cytoreduction, histopathologic and molecular diagnosis, and facilitation of subsequent adjuvant therapies. Surgical cytoreduction can also ameliorate symptoms by reducing intracranial pressure, decreasing corticosteroid dependence and associated toxicities, and improving seizure control. Greater extent of resection, particularly of contrast-enhancing disease, has been consistently associated with improved progression-free survival (PFS) and OS (*23*, *24*). Subsequent multi-institutional molecularly annotated analyses have extended this framework, demonstrating that resection of both contrast-enhancing and selected non–contrast-enhancing tumor correlates with survival across subgroups and that, in appropriately selected patients, supramaximal resection into surrounding fluid-attenuated inversion recovery (FLAIR) abnormality may confer additional benefit (*25*–*27*). Importantly, these benefits appear age dependent, underscoring the need for individualized, risk-adapted surgical strategy rather than rigid volumetric targets (*28*).

Advances in functional mapping and intraoperative adjuncts have improved the reproducibility of achieving maximal safe resection, particularly for tumors involving eloquent cortical regions responsible for critical functions such as language, motor control, and sensation (Fig. 1). Among these techniques, fluorescence-guided resection using 5-aminolevulinic acid (5-ALA) has the strongest randomized evidence base. In a multicenter phase 3 trial, 5-ALA–guided surgery improved extent of resection and PFS compared with white-light resection in patients with malignant glioma, establishing fluorescence guidance as a validated surgical adjunct in the appropriate patients (*29*). Intraoperative ultrasound has also been adopted as a real-time imaging adjunct to mitigate brain shift and update intraoperative anatomy; contemporary implementations, including navigated and three-dimensional ultrasound, can improve tumor visualization and support maximal safe resection in selected settings (*30*, *31*).

For tumors that are deep-seated, located in the eloquent cortex, or otherwise not amenable to conventional open craniotomy, magnetic resonance imaging (MRI)–guided laser interstitial thermal therapy (LITT) has emerged as a minimally invasive cytoreductive alternative. LITT delivers stereotactically targeted thermal ablation under real-time MRI thermometry, enabling controlled tumor destruction while minimizing collateral normal tissue injury. Early-phase and prospective registry data suggest that, when followed by standard chemoradiation, outcomes in selected newly diagnosed patients with GBM may approximate those observed with conventional resection (*32*, *33*). Beyond cytoreduction, LITT transiently disrupts the peritumoral BBB, generating interest in its use as a strategy to enhance local drug delivery and combination approaches (*34*).

The surgical cavity provides a platform for direct local therapeutic delivery, including focal chemotherapy and radiation strategies, given that most GBM recurrences arise at or near the resection margin. Carmustine-impregnated biodegradable wafers (Gliadel, Azurity Pharmaceuticals) were approved by the FDA in 2003 for newly diagnosed high-grade glioma and for patients with recurrent GBM as an adjunct to surgical resection. A pivotal phase 3 trial demonstrated a modest but statistically significant OS benefit of 2.3 months in newly diagnosed malignant glioma (*35*). Despite remaining the only FDA-approved local chemotherapy for GBM, adoption has been limited by concerns regarding wound complications, cerebrospinal fluid leakage, intracranial hypertension, and uncertain incremental benefits in the temozolomide era.

GammaTile (GT Medical Technologies), FDA-approved initially in 2018 for recurrent brain tumors and in 2020 for newly diagnosed malignant tumors, consists of bioresorbable collagen tiles embedded with cesium-131 sources and implanted into the resection cavity. These implants deliver immediate, localized radiation to eliminate residual tumor cells. Early clinical experience in recurrent GBM suggests favorable local control rates with a safety profile comparable to resection alone (*36*, *37*). A planned randomized trial [Postoperative Adjuvant Therapy w/wo GammaTile + Systemic Therapy (PATHWAyS); NCT05900908] evaluating GammaTile plus surgery versus surgery alone in recurrent GBM was withdrawn in favor of a revised study schema, underscoring the ongoing evolution of prospective validation efforts (*38*). Together, surgical management in GBM is best viewed as foundational rather than definitive, reducing tumor burden, enabling integrated molecular diagnosis, and creating a therapeutic window for radiotherapy, systemic therapy, and emerging combination strategies.

Radiation therapy

Radiation therapy has been another cornerstone of GBM treatment. The standard approach for patients with adequate performance status (Karnofsky performance status $\geq$ 60 to 70) consists of fractionated focal radiation delivered over 6 weeks to a total dose of 60 Gy (gray) in 30 fractions, typically administered concurrently with temozolomide

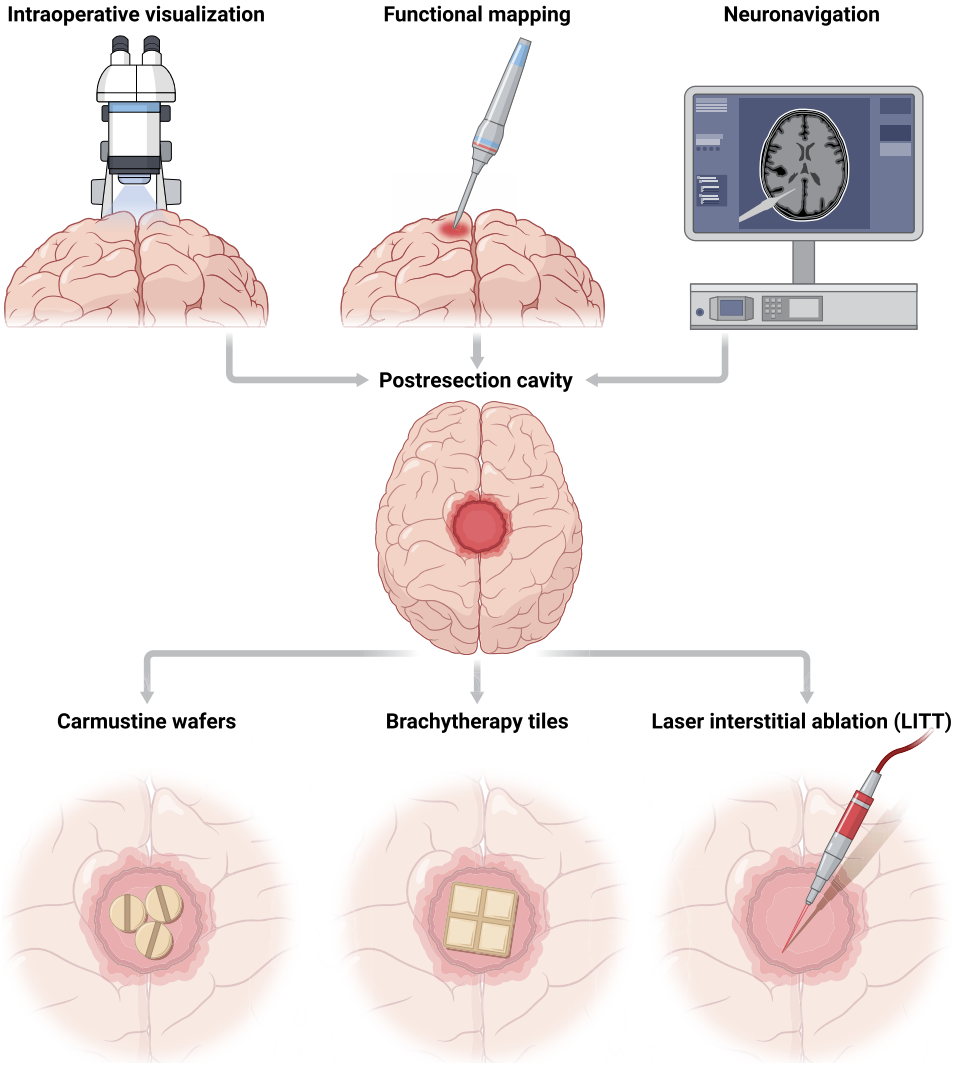

Fig. 1. Surgical guidance and locoregional therapies for GBM. Maximal safe tumor resection increasingly integrates complementary intraoperative technologies that improve tumor visualization, maintain spatial accuracy, and preserve neurologic function. Intraoperative visualization approaches, including fluorescence-guided surgery (e.g., 5-ALA or fluorescein), aid in identifying tumor margins. Functional mapping defines eloquent cortical and subcortical regions, whereas neuronavigation provides spatial guidance during resection. The resulting postresection cavity can also serve as a platform for locoregional therapeutic strategies, including carmustine wafer implantation, intracavitary brachytherapy tiles, and LITT, which aim to enhance local disease control.

as established by the landmark European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) trial (*4*). The clinical target volume generally encompasses the resection cavity or residual tumor with a 1- to 2-cm margin to include microscopic disease extension. Treatment planning relies on fusion of preoperative and postoperative MRI with computed tomography simulation to optimize conformality while minimizing radiation to nearby critical structures such as the optic apparatus, brainstem, and hippocampi.

For elderly patients (typically >65 to 70 years) and those with poor performance status, hypofractionated radiation regimens have demonstrated noninferior outcomes compared with the standard 6-week course and offer the advantage of reduced treatment duration. The Nordic trial and the Perry *et al.* (*39*, *40*) randomized study established that hypofractionated radiation (40 Gy in 15 fractions over 3 weeks) combined with concurrent and adjuvant temozolomide provides a survival benefit over hypofractionated radiation alone in elderly patients. Even shorter courses of 25 Gy in five fractions have been evaluated and shown to be noninferior to 40 Gy in 15 fractions in elderly or frail patients (*41*). These abbreviated schedules improve treatment completion rates and preserve quality of life in a vulnerable population.

Reirradiation at the time of recurrence is an option for selected patients with favorable prognostic features, including good performance status, a long interval from initial radiation (6 to 12 months), and a circumscribed recurrence pattern amenable to focal radiation. Techniques including single-session stereotactic radiosurgery and fractionated stereotactic radiotherapy over several sessions are commonly used. Although randomized evidence remains limited, retrospective and single-arm prospective data suggest that reirradiation can provide local control and modestly prolong PFS in well-selected patients (*42*, *43*). The LEGATO (EORTC-2227-BTG) phase 3 trial (NCT05904119) is now recruiting to evaluate the efficacy of adding reirradiation to lomustine chemotherapy in patients with first progression of GBM.

Management of radiation-related toxicity is an increasingly recognized component of comprehensive care of patients with GBM. Treatment-related cognitive decline is unfortunately common and can substantially affect quality of life. Hippocampal-avoidant radiation techniques, where anatomically feasible, may help mitigate memory impairment. Donepezil, an acetylcholinesterase inhibitor, has shown improvement in cognitive function and quality of life in patients with irradiated brain tumor in randomized controlled data (*44*, *45*) and is considered for patients at risk of postradiation cognitive decline. Radiation-induced necrosis, a late complication that can mimic tumor recurrence on standard MRI, is managed with corticosteroids and, in refractory cases, bevacizumab, which has demonstrated high response rates for symptomatic radiation necrosis in a small but randomized trial (*46*).

Proton beam therapy has emerged as a modality of growing interest in GBM. By virtue of the Bragg peak phenomenon, proton therapy enables a sharp dose fall-off beyond the disease target, potentially reducing integral dose to normal tissue. This dosimetric advantage may translate to reduced neurocognitive toxicity, which is

particularly relevant to the quality of life of patients with longer expected survival (*47*). Prospective studies evaluating proton therapy in newly diagnosed GBM are ongoing, and initial reports suggest feasibility and safety with comparable disease control (*48*). Definitive evidence of clinical superiority over modern photon techniques awaits larger randomized trial results, however.

Systemic therapy

The Stupp protocol, which includes radiation with concurrent temozolomide followed by adjuvant temozolomide, has been a standard systemic treatment for newly diagnosed patients with GBM for the past 20 years (*4*). This regimen improved median OS from 12.1 to 14.6 months and established a new benchmark for the field. The survival benefit is most pronounced in patients whose tumors harbor epigenetic silencing of the *MGMT* gene by promoter methylation. *MGMT*, located on chromosome 10q26, encodes a DNA repair protein that stoichiometrically removes alkyl groups from the O6 position of guanine, which is an important site of DNA alkylation. When the promoter is methylated and thus silenced, unrepaired O6-methylguanine lesions induced by temozolomide persist, triggering cytotoxicity and apoptosis. In the EORTC-NCIC trial, *MGMT*-methylated patients treated with temozolomide and radiation achieved a median OS of 21.7 months compared with 15.3 months for those with unmethylated tumors (*1*). Whether temozolomide should be omitted in favor of alternative strategies for patients with unmethylated *MGMT* promoter status remains an area of active investigation and clinical debate (*14*).

Tumor treating fields (TTFields; Optune) represent a device-based modality that delivers low-intensity, intermediate-frequency (200 kHz) alternating electric fields to the tumor bed via transducer arrays affixed to the scalp. The pivotal EF-14 trial demonstrated that the addition of TTFields to adjuvant temozolomide significantly improved both PFS (6.7 versus 4.0 months) and OS (20.9 versus 16.0 months) compared with temozolomide alone (*49*). Compliance-dependent benefit was observed, with patients wearing the device more than 18 hours per day deriving the greatest survival advantage. Despite FDA approval in 2011 and guideline inclusion, uptake has varied because of device cost, practical burden, and questions regarding quality-of-life impact; however, patient-reported outcomes from EF-14 did not demonstrate detrimental effects on quality of life (*50*). Building on these findings, an ongoing randomized, placebo-controlled phase 3 trial is evaluating adjuvant temozolomide and TTFields combined with either pembrolizumab or placebo in newly diagnosed GBM (NCT06556563) to test whether immune checkpoint inhibition may enhance therapeutic efficacy. Recent regulatory approvals of tumor-treating fields in additional solid tumors further suggest that this biophysical antimitotic mechanism may have broader applicability, supporting continued investigation of rational combination strategies across malignancies (*51*, *52*).

The CeTeG/NOA-09 [CeeNU (lomustine) and temozolomide in glioblastoma/Neuro-Oncology Working Group trial 09] trial evaluated the combination of lomustine [a nitrosurea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea or CCNU] plus temozolomide with radiation in newly diagnosed patients with GBM with MGMT promoter methylation. This phase 3 trial reported a significant improvement in OS with the combination [48.1 versus 31.4 months; hazard ratio (HR), 0.60] compared with temozolomide alone in the MGMT-methylated subgroup (*53*). Although the trial was relatively small ($n = 129$) and the results have not been independently replicated, the lomustine-temozolomide combination has been adopted in some European centers for MGMT-methylated patients. Increased hematologic toxicity associated with this regimen, particularly thrombocytopenia, requires careful monitoring.

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has been widely used to treat GBM despite the absence of an OS benefit in the newly diagnosed setting. Two large, randomized trials, RTOG 0825 and AVAglio, demonstrated improvements in PFS but not OS when bevacizumab was added to standard chemoradiation (*54*, *55*). In the recurrent setting, bevacizumab received accelerated FDA approval on the basis of objective response rates and is valued primarily for its antipermeability effect, which can rapidly reduce peritumoral edema and ameliorate associated neurologic deficits, often enabling corticosteroid dose reduction or discontinuation and thereby improving quality of life. Bevacizumab is commonly combined with lomustine for recurrent disease, based on the EORTC 26101 trial, which showed improved PFS but no OS benefit versus lomustine alone (*56*).

At recurrence, treatment options remain limited, and no regimen has demonstrated a definitive OS benefit in a randomized trial. Current approaches include enrollment in clinical trials, which is preferred for eligible patients and a category 1 National Comprehensive Cancer Network guideline recommendation, lomustine or the lomustine-bevacizumab combination, temozolomide rechallenge (particularly for MGMT-methylated tumors with a long treatment-free interval), and repeat surgery where feasible. There is no established standard of care for second-line systemic therapy, underscoring the urgent need for effective new treatments.

Special considerations apply to elderly patients and those with poor performance status. In the elderly, temozolomide monotherapy (without radiation) or short-course hypofractionated radiation represents evidence-based options for patients unable to tolerate the full Stupp protocol (*39*, *57*). The combination of hypofractionated radiation with temozolomide, as demonstrated by Perry *et al.* (*40*), offers a practical and effective approach. Treatment decisions must carefully balance expected benefit with treatment burden, considering comorbidities, cognitive reserve, and caregiver support. Palliative care consultation should be integrated early and throughout the disease trajectory.

EMERGING THERAPEUTIC STRATEGIES

Drug delivery and locoregional therapies

The BBB remains a central obstacle to effective GBM therapy, limiting penetration of many cytotoxic, targeted, and immune-modulating agents into both contrast-enhancing tumor and infiltrative margins (*12*, *58*–*60*). Although regions of enhancement often demonstrate BBB disruption, the resulting blood-tumor barrier, a variably permeable tumor-associated vascular interface, remains heterogeneous and incompletely permissive to many systemic therapies (*12*). Moreover, infiltrative tumor frequently extends beyond areas of radiographic enhancement and remains protected by an intact or only partially disrupted BBB, further contributing to heterogeneous and frequently subtherapeutic drug exposure after systemic administration. As a result, agents with promising preclinical activity may fail clinically not because of insufficient biological potency, but because effective intratumoral concentrations are not consistently achieved (*60*). This has prompted development of locoregional and BBB-modulating strategies aimed at improving intratumoral drug delivery while limiting systemic toxicity (*59*).

CED represents a prototypical approach to directing intraparenchymal drug administration. By using positive-pressure infusion through stereotactically placed catheters, CED enables bulk flow of therapeutic agents through the extracellular space, theoretically achieving homogeneous distribution over large tissue volumes independent of molecular weight (*61*, *62*). This modality has been explored for a wide range of locally administered macromolecular payloads, including chemotherapeutics, targeted toxins, radiolabeled agents, and other biologic therapeutics (*63*). Whereas technical challenges related to catheter design, backflow, and variability in distribution have historically limited reproducibility, advances in reflux-resistant catheters and real-time imaging of infusate distribution have improved the reliability of contemporary CED platforms (*64*–*66*). The phase 3 PRECISE trial did not demonstrate an OS benefit for CED of cintredekin besudotox compared to carmustine wafers in recurrent GBM, underscoring the importance of distribution fidelity and procedural standardization in focal delivery strategies (*67*).

Additional locoregional approaches include intratumoral and intraventricular delivery strategies, which are particularly relevant for agents with limited BBB permeability or short systemic half-lives. Reservoir-based systems enable repeated administration without repeated surgery and may facilitate sustained or iterative exposure in select contexts (*68*). Similarly, biodegradable polymers and drug-eluting wafers have demonstrated the feasibility of sustained local drug release in the resection cavity, although their clinical utility has been constrained by limited penetration beyond the surgical margin and challenges integrating with systemic therapies (*35*, *69*).

More recently, focused ultrasound–mediated BBB disruption has emerged as a noninvasive strategy to transiently and spatially modulate vascular permeability. When combined with systemically administered microbubbles, low-intensity focused ultrasound can reversibly increase BBB permeability in targeted regions without permanent vascular injury, enabling enhanced delivery of circulating agents (*70*–*73*). Unlike focal intratumoral delivery approaches, BBB modulation has the potential to scale across broader tumor volumes and repeated treatment sessions, positioning it as a delivery-enabling approach rather than a standalone therapy (*12*, *59*). Early first-in-human studies established the safety and reproducibility of transient BBB opening in patients with glioma (*72*, *73*). Subsequent phase 1/2 studies paired BBB opening with systemic agents such as carboplatin and nab-paclitaxel in recurrent GBM (*74*, *75*), whereas the multicenter BT008NA study demonstrated that repeated, transcranial BBB opening could be reproducibly integrated into the adjuvant temozolomide window after chemoradiotherapy, supporting scalability across institutions (*76*). Collectively, these studies position focused ultrasound as a delivery-enabling platform rather than a standalone intervention.

Together, these approaches reflect a broader conceptual shift in GBM therapeutics: Rather than relying exclusively on increasingly potent drugs, therapeutic failure may arise as much from inadequate delivery as from insufficient biological activity. As a result, locoregional and BBB-modulating strategies are increasingly viewed as enabling technologies that may be essential for realizing the full potential of systemic, targeted, and immune-based therapies (*12*, *60*). Notably, many agents deemed ineffective in GBM may never have been adequately tested at the site of disease, complicating post hoc interpretations of biological failure.

Immunotherapy

Despite transformative successes in several solid tumors, immunotherapy has produced limited durable clinical benefit in GBM, reflecting fundamental biological and anatomical constraints (*10*, *77*). GBM is characterized by low tumor mutational burden, extensive intratumoral heterogeneity (*9*), and a profoundly immunosuppressive microenvironment enriched by myeloid-derived populations (*10*, *78*, *79*). These features, compounded by corticosteroid exposure and restricted immune trafficking, limit effective cytotoxic T cell engagement in infiltrative tumor regions.

Immune checkpoint blockade

Immune checkpoint blockade has a strong biological rationale in GBM given evidence of T cell infiltration and programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) expression in the tumor microenvironment. However, randomized phase 3 trials have not demonstrated an OS benefit in either recurrent or newly diagnosed disease. In recurrent GBM, nivolumab failed to improve survival compared to bevacizumab in CheckMate 143 (*80*). In newly diagnosed MGMT-methylated and MGMT-unmethylated GBM, the addition of nivolumab to standard chemoradiotherapy did not improve OS (*81*, *82*). Although immune checkpoint inhibition can induce measurable immune activation, translational analyses suggest that T cell infiltration is frequently spatially restricted and functionally exhausted in a myeloid-dominant tumor microenvironment (*82*, *83*). These findings underscore a central challenge in GBM immunotherapy: Immune activation alone is insufficient in the absence of effective intratumoral access and reversal of local immunosuppression. As a result, current strategies increasingly emphasize rational combinations, optimized timing, and biomarker-informed trial design rather than checkpoint monotherapy.

Adoptive cellular therapy

Adoptive cellular therapies, including CAR T cells, have been pursued to overcome limitations in endogenous T cell priming and trafficking in GBM. Early phase 1 trials targeting epidermal growth factor receptor variant III (EGFRvIII), a constitutively active truncated receptor expressed on ~25 to 30% of GBM tumors but absent from normal tissue, and interleukin-13 receptor alpha 2 (IL13Rα2), a high-affinity decoy receptor overexpressed in GBM, established the feasibility and safety of CAR T cell therapy and generated some of the most compelling radiographic responses reported in recurrent GBM (*84*, *85*). However, these studies also highlighted fundamental barriers to durability, including antigen heterogeneity, treatment-associated antigen loss, limited T cell persistence, and adaptive resistance in the tumor microenvironment (*84*–*86*).

Recent advances have focused on strategies to address these constraints. In a first-in-human phase 1 study, intraventricular administration of CARv3-TEAM-E T cells combined EGFRvIII-directed CAR T cells with local secretion of a bispecific T cell–engaging antibody targeting wild-type epidermal growth factor receptor (EGFR), resulting in rapid radiographic tumor regression despite limited durability (*87*). Notably, antitumor activity was observed even in a patient lacking detectable EGFRvIII expression, supporting the biological rationale for broader antigen coverage in heterogeneous tumors. Similarly, a phase 1 trial of intrathecally delivered bivalent CAR T cells targeting EGFR and IL13Rα2 demonstrated the safety and feasibility of multiantigen targeting via the cerebrospinal fluid compartment and induced early radiographic changes, although sustained objective responses remained uncommon (*88*).

Collectively, these studies demonstrate that adoptive cellular therapies can achieve meaningful cytoreduction in GBM. Importantly, however, locoregionally delivered CAR T cells are associated with

clinically significant treatment-related neurotoxicity. In the phase 1 trial of intrathecal bivalent EGFR/IL13Rα2-targeting CAR T cells, all six patients experienced moderate-severe neurotoxicity with elements of both immune effector cell–associated neurotoxicity syndrome and tumor inflammation–associated neurotoxicity (*86*). Similarly, approximately one-third of patients in the phase 1 locoregional IL-13Rα2 CAR T cell trial experienced grade 3 or higher treatment-related toxicities (*84*). These safety signals highlight that optimizing the therapeutic index of locoregionally administered cellular therapies including dose scheduling, supportive management algorithms, and patient selection will be essential alongside efforts to improve efficacy. Achieving durable clinical benefit, therefore, will likely require improved persistence, multiantigen engagement, optimized locoregional delivery, management of treatment-related neurotoxicity, and integration with strategies that remodel the immunosuppressive tumor microenvironment.

Therapeutic vaccines

Therapeutic cancer vaccines have been explored as a means of inducing tumor-specific immune responses with favorable safety profiles. Dendritic cell–based and personalized neoantigen vaccines can elicit measurable systemic and intratumoral immune responses in GBM (*89*, *90*). However, therapeutic benefit has been variable, likely reflecting constraints shared across GBM immunotherapy, including antigen heterogeneity, limited effector trafficking into infiltrative tumor, and microenvironmental suppression. Concomitant corticosteroid exposure can further blunt vaccine-driven immunity, underscoring the importance of treatment context and combination strategies when interpreting vaccine trial outcomes (*18*). These observations suggest that vaccines may be most effective when integrated with strategies that enhance antigen presentation and relieve local immune suppression.

Viral and gene-based immunotherapies

Oncolytic and gene-based viral therapies occupy a distinct conceptual space in GBM immunotherapy by combining direct tumor cell lysis with in situ immune priming and amplification of endogenous tumor-reactive T cell responses. These platforms promote antigen release, interferon signaling, and immune cell recruitment within the tumor microenvironment, with the potential to convert immunologically "cold" tumors into more inflamed states (*91*–*93*).

Clinical studies demonstrate that these biological effects are measurable in patients and may correlate with outcome. In a first-in-human phase 1 trial of the conditionally replicating oncolytic herpes simplex virus CAN-3110, virus-induced intratumoral immune activation, rather than radiographic response alone, was associated with prolonged survival (*93*). Integrated spatial and multiomic analyses further showed persistent infiltration and expansion of preexisting tumor-infiltrating cytotoxic T cell clonotypes associated with clinical benefit (*94*), providing in situ evidence of ongoing T cell–mediated tumor cytotoxicity in treated tumors at late time points in human GBM. However, spatial gradients of T cell exclusion in hypoxic and mesenchymal tumor regions highlight biologically organized resistance niches that may limit durable tumor control despite persistent immune activation (Fig. 2).

Consistent signals have emerged across viral platforms. Intratumoral DNX-2401 produced objective responses and long-term survivors in recurrent high-grade glioma (*91*), and combination with pembrolizumab yielded encouraging survival signals (*95*). Poliovirus (Sabin)–rhinovirus internal ribosome entry site–poliovirus open reading frame (PVSRIPO) similarly demonstrated a subset of long-term survivors compared with historical controls (*92*). Nonetheless, benefit remains heterogeneous and likely reflects limitations in viral distribution, spatial and metabolic constraints in hypoxic tumor niches, relative skewing of adaptive responses toward antiviral rather than tumor antigens, and tumor-intrinsic resistance mechanisms, including suppressive myeloid populations in the GBM microenvironment (*79*, *96*). These insights are motivating rational combination strategies aimed at enhancing distribution, modulating hypoxia and angiogenesis, and sustaining adaptive immune engagement. Collectively, these constraints are shifting the field away from immunotherapy monotherapy and toward rational combination strategies that integrate immune activation with approaches to improve delivery, remodel the tumor microenvironment, and address antigen heterogeneity—recognizing that context, timing, and intratumoral access may be as important as the choice of immunotherapy agent itself (Fig. 2).

Biomarker-defined and emerging targeted therapies

Precision oncology in diffuse gliomas has diverged into two distinct trajectories (Fig. 3). In molecularly defined subtypes, IDH-mutant, H3 K27M–mutant diffuse midline glioma, B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E–mutant glioma, and rare neurotrophic tyrosine receptor kinase (NTRK)–fusion tumors, biomarker-directed inhibition has achieved regulatory approval. In contrast, IDH–wild-type GBM, shaped by intratumoral heterogeneity and the absence of uniform truncal drivers, has shown limited durable benefit from targeted monotherapies. These contrasting outcomes underscore both the importance of molecular stratification and the need to broaden precision strategies beyond static genomic alterations toward functional and microenvironmental dependencies (Table 1).

IDH inhibitors

Although IDH-mutant astrocytomas are now classified separately from IDH–wild-type GBM under the WHO 2021 framework, the development of IDH inhibitors represents one of the most notable recent advances in neuro-oncology. The phase 3 Investigating Vorasidenib in Glioma (INDIGO) trial demonstrated that vorasidenib, a dual IDH1/2 inhibitor with CNS penetration, significantly improved PFS compared with placebo in patients with residual or recurrent IDH-mutant grade 2 astrocytoma or oligodendroglioma (*7*). The FDA approved vorasidenib in 2024, establishing the first targeted therapy for IDH-mutant gliomas, with subsequent regulatory endorsement by the European Medicines Agency in 2025.

BRAF/MEK inhibitors

BRAF V600E mutations occur in ~1 to 3% of adult GBMs but at higher frequencies in pleomorphic xanthoastrocytoma and pediatric low-grade gliomas. The combination of dabrafenib and trametinib has shown activity in BRAF V600E-mutant gliomas, with an overall response rate of 29% in recurrent GBM in the Rare Oncology Agnostic Research (ROAR) basket trial (*97*). Tumor-agnostic FDA approval for *BRAFV600E*-mutant solid tumors makes these agents immediately available for patients with molecularly confirmed glioma, highlighting the importance of comprehensive molecular profiling to identify rare actionable subgroups in GBM.

ONC201/dordaviprone

Dordaviprone, a first-in-class imipridone and dopamine receptor D2/D3 (DRD2/3) antagonist and caseinolytic protease proteolytic (ClpP) subunit agonist, has demonstrated notable activity in H3

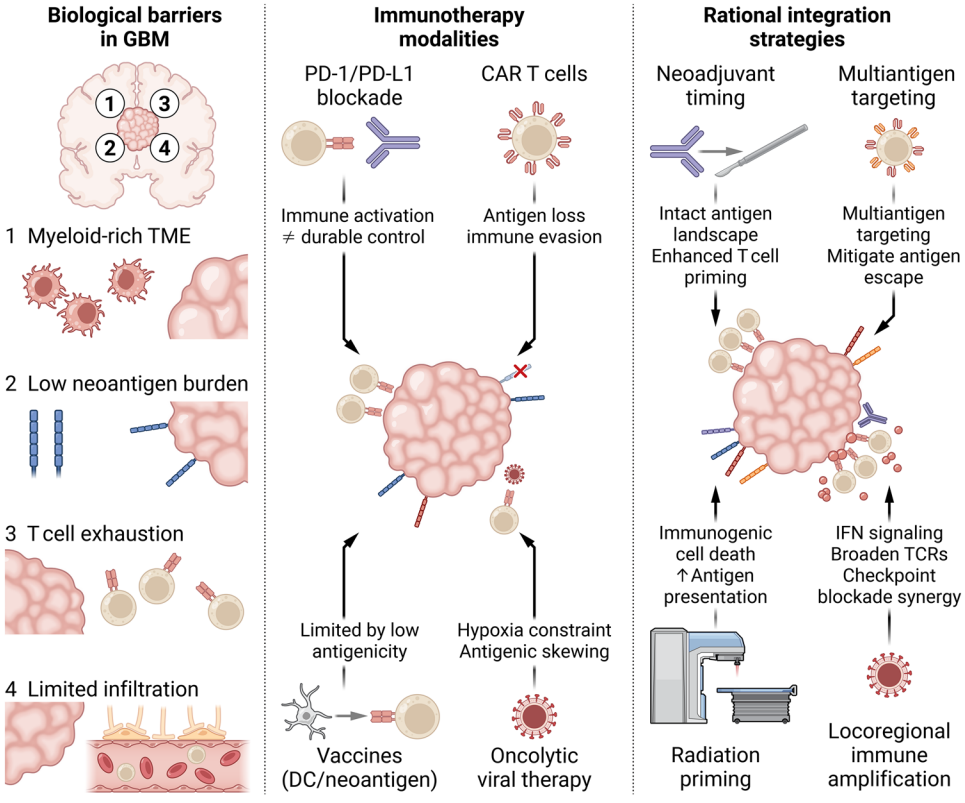

Fig. 2. Biological barriers to immunotherapy in GBM and rational integration strategies. GBM (**left**) is characterized by low neoantigen burden, myeloid-dominant immunosuppression, T cell exhaustion, and limited immune infiltration, creating a tumor microenvironment constrained by insufficient antigenicity and impaired immune engagement. Immunotherapy strategies (**middle**), including checkpoint blockade using anti–PD-1 or PD-L1, adoptive cellular therapy using CAR T cells, neoantigen or dendritic cell (DC) vaccination, and oncolytic viral therapy, can induce intratumoral immune activation; however, efficacy is limited by failure to achieve durable immune control, antigen heterogeneity and loss, insufficient antigenicity limiting immune priming, and hypoxic and mesenchymal resistance states associated with antigenic skewing. Rational integration approaches (**right**) aim to overcome these barriers through optimized neoadjuvant timing to preserve antigen landscape and enhance T cell priming, multiantigen targeting to mitigate antigen escape, radiation-induced immunogenic cell death to increase antigen presentation, and locoregional immune amplification to enhance interferon (IFN) signaling, broaden tumor-directed T cell responses, and promote checkpoint blockade synergy and more durable immune control. TCRs, T cell receptors; TME, tumor microenvironment.

K27M-mutant diffuse midline glioma. In a pooled analysis of five clinical trials, dordaviprone monotherapy achieved a 20% objective response rate by Response Assessment in Neuro-Oncology–high-grade glioma (HGG) criteria with a median duration of response of 11.2 months in recurrent disease (*8*). In August 2025, the FDA granted accelerated approval to dordaviprone for adult and pediatric patients aged 1 year and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease after prior therapy, making it the first approved therapy for this disease.

Rare molecular subsets

Larotrectinib and entrectinib have received tumor-agnostic FDA approval for the rare patients with GBM harboring an *NTRK*-fusion, although such alterations account for only a small fraction of cases (*98*).

Neurotransmitter-targeting approaches

The emerging field of cancer neuroscience has revealed that GBM cells integrate into neuronal networks through functional synapses and exploit neurotransmitter signaling, including glutamate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and monoaminergic pathways, to promote tumor growth and invasion (*99*, *100*). These discoveries have opened a therapeutic frontier by enabling the repurposing of agents already approved for other neurological or psychiatric indications. Perampanel, a noncompetitive AMPA receptor antagonist approved for epilepsy, is being evaluated for potential antitumor effects in GBM (*101*). Troriluzole, a glutamate-modulating prodrug of riluzole, is under investigation in recurrent GBM (NCT06552260). Preclinical evidence also suggests that certain antidepressants such as vortioxetine may modulate tumor-neuron interactions (*102*). Gabapentinoids, FDA-approved agents for seizures and neuropathic pain, target the α2δ calcium channel subunit bound by thrombospondin-1 (TSP-1), a prosynaptogenic factor secreted by functionally connected GBM subpopulations that may promote aberrant neuron-glioma synapse formation. In a recent multiinstitutional retrospective analysis, postoperative gabapentin use was associated with improved OS in multivariable models and reduced serum TSP-1 levels in newly diagnosed GBM; prospective validation will be required to determine whether this reflects a causal therapeutic effect (*103*). Recent work further extends this paradigm by demonstrating that tumor–astrocyte signaling networks can actively suppress antitumor immunity through interleukin-11–signal transducer and activator of transcription 3–dependent induction of tumor necrosis factor–related apoptosis-inducing ligand, linking nonmalignant stromal elements to immune evasion and therapeutic resistance (*104*).

INNOVATIVE CLINICAL TRIAL DESIGN AND TRANSLATIONAL STRATEGY IN GBM

Increasingly, progress in GBM depends not only on novel therapeutics but also on innovative clinical trial designs capable of interrogating biological activity, accelerating decision-making, and adapting to tumor heterogeneity. In contrast with traditional two-arm randomized studies, contemporary GBM trials increasingly incorporate adaptive platform infrastructure, longitudinal molecular profiling, neoadjuvant pharmacodynamic interrogation, biomarker-enriched enrollment, and rational combination strategies. Together, these approaches aim to overcome the historical disconnect between biological signal and clinical outcome.

Adaptive and platform trials

GBM AGILE (GBM Adaptive, Global, Innovative Learning Environment; NCT03970447) represents a paradigm shift in clinical trial

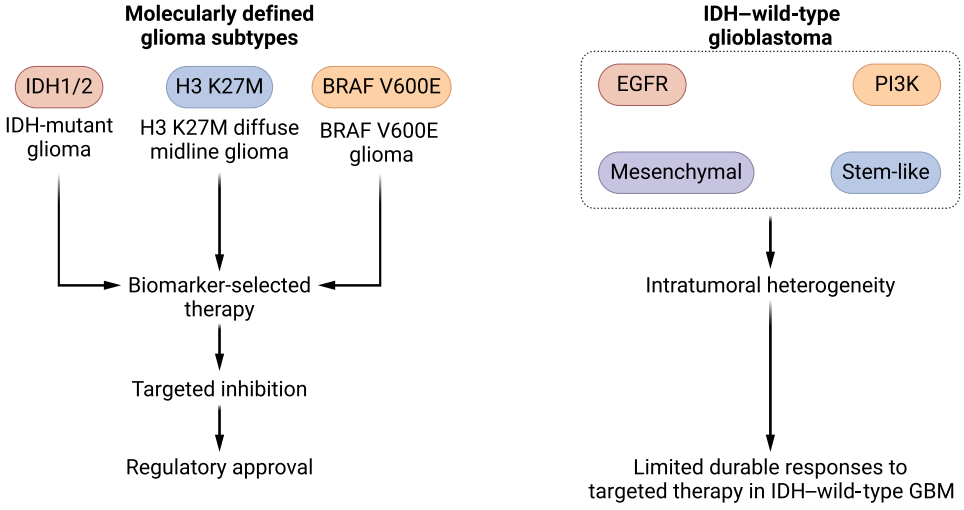

Fig. 3. Divergent trajectories of precision oncology for molecularly defined gliomas and IDH–wild-type GBM. Molecular classification has enabled biomarker-directed therapy in glioma subsets harboring dominant driver alterations, including IDH1/2 mutations, H3 K27M mutations, BRAF V600E mutations, and NTRK fusions, leading to regulatory approvals in defined contexts (**left**). In contrast, IDH–wild-type GBM (**right**) is characterized by marked intratumoral heterogeneity and coexisting genetic and transcriptional states in a single tumor. This biological complexity has limited the durability of single-agent targeted therapies and has thus far precluded the establishment of a broadly effective molecularly targeted standard of care. PI3K, phosphatidylinositol 3-kinase.

design. This international, biomarker-based, multiarm, seamless phase 2/3 platform trial uses Bayesian adaptive randomization to simultaneously evaluate multiple investigational therapies against a shared control arm. The adaptive design allows arms to be added or dropped on the basis of emerging efficacy and futility signals, substantially improving efficiency. Approximately 25% of patients with GBM enrolling in clinical trials in the United States participate in GBM AGILE, reflecting its central role (*14*, *105*). GBM AGILE has reported results from its first completed experimental arm: regorafenib, which did not demonstrate benefit over control in recurrent or newly diagnosed unmethylated GBM (*106*). More encouragingly, a prespecified secondary analysis of the paxalisib arm showed a clinically meaningful improvement in median OS (15.5 versus 11.9 months) in newly diagnosed patients with unmethylated GBM. Multiple additional experimental arms continue to enroll in the AGILE infrastructure, complemented by multiarm institutional and consortium-based programs including the German NOA (Neuro-Oncology Working Group) cooperative group trials and parallel efforts at major academic centers.

Longitudinal and translational sampling

An emerging clinical trial paradigm in GBM incorporates longitudinal sampling during experimental therapy, with prospectively timed serial multisector tumor biopsies accompanied by cerebrospinal fluid and peripheral blood mononuclear cell analyses. Integrated multiomic profiling enables interrogation of the temporal and spatial evolution of the tumor and its microenvironment in response to therapeutic perturbation, addressing the limitations of single–time point "window-of-opportunity" designs in a biologically heterogeneous disease (*107*).

In a recent proof-of-concept study using repeated intratumoral dosing of an oncolytic immunotherapy, serial multisector biopsies demonstrated longitudinal reshaping of the tumor microenvironment and expansion of antitumor T cell clonotypes, biological responses not apparent on conventional imaging (*108*). Comprehensive transcriptomic, proteomic, and immune profiling performed at defined injection time points (days 0, 15, 30, 60, 90, and 120) revealed that durable clinical benefit was associated with sustained interferon signaling, enhanced antigen presentation, and adaptive immune engagement, even in the absence of early radiographic response. These findings highlight a critical limitation of imaging-based end points in GBM immunotherapy and illustrate how longitudinal human profiling can define target engagement, uncover adaptive resistance mechanisms, and inform rational therapeutic refinement.

Neoadjuvant immune checkpoint inhibition

Neoadjuvant administration of immune checkpoint inhibitors has been explored as a strategy to enhance antitumor immune priming by exposing an intact tumor antigenic landscape before surgical resection. In a randomized study of recurrent GBM, a single dose of pembrolizumab administered before surgery followed by adjuvant therapy was associated with a survival advantage and demonstrated increased interferon-γ signaling, T cell clonal expansion, and enhanced antigen presentation in resected tumors (*109*).

Subsequent expansion cohorts and independent studies confirmed reproducible on-target immune remodeling after neoadjuvant PD-1 blockade but did not demonstrate a survival benefit in recurrent GBM (*110*, *111*). These findings highlight a critical distinction between immune activation and effective tumor control, reinforcing the need for biomarker-enriched enrollment and rational combination strategies to overcome adaptive resistance and immune exclusion.

These studies demonstrate that although diverse immunotherapeutic platforms can induce measurable biological activity, including immune infiltration, antigen-specific targeting, and transient radiographic responses, durable survival extension has not yet been consistently demonstrated. The recurring challenges of antigen heterogeneity, treatment-induced adaptation, and incomplete intratumoral coverage argue for combination strategies that integrate immune activation with delivery optimization and microenvironmental modulation.

Precision medicine and targeted trials

Whereas currently approved targeted therapies primarily apply to non-GBM glioma entities or rare tumor-agnostic genomic subsets, a growing number of clinical trials are evaluating molecularly targeted agents in IDH–wild-type GBM that have not yet received FDA approval for CNS tumors (Table 2). These trials represent a shift from empiric treatment toward biomarker-enriched and pathway-directed therapies.

PARP inhibitors and DDR-targeting agents

The DNA damage response (DDR) pathway, which encompasses the cellular machinery responsible for detecting, signaling, and repairing

Table 1. Approved and repurposed targeted therapeutic approaches in gliomas. AMPA-R, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; DMG, diffuse midline glioma; ORR, objective response rate.

Molecular target/pathway	Agent(s)	Tumor type	Status/phase	Key findings
		FDA-approved agents		
IDH1/2 mutation	Vorasidenib	IDH-mutant glioma (grade 2)	FDA-approved (2024)	Phase 3 INDIGO: improved PFS versus placebo (*6*)
BRAF V600E mutation	Dabrafenib + trametinib	BRAF-mutant glioma	FDA-approved (tumor-agnostic; 2023)	ORR 29% in recurrent GBM; ROAR basket trial (*25*)
NTRK fusions	Larotrectinib, entrectinib	NTRK-fusion glioma	FDA-approved (tumor-agnostic; 2018, 2023)	Responses in NTRK-fusion CNS tumors; rare in GBM (*96*)
DRD2/ClpP (imipridone)	Dordaviprone (ONC201)	H3K27M-mutant glioma	FDA-approved (2025)	Accelerated approval; ORR 20% in recurrent DMG; phase 3 ACTION ongoing (*7*)
		Repurposed and mechanism-based approaches in GBM		
Neurotransmitter pathways (AMPA-R)	Perampanel	GBM	Approved for epilepsy; repurposed early phase	Cancer neuroscience rationale; antitumor evaluation ongoing (*97*)
Neurotransmitter pathways (glutamate)	Troriluzole	GBM	Phase 2	Glutamate modulation; recurrent GBM trial underway (NCT06552260)
Neurotransmitter pathways (serotonin)	Vortioxetine	GBM	Approved for depression; preclinical	Preclinical evidence of tumor-neuron modulation (*98*)
Neurotransmitter pathways (synaptogenesis/TSP-1)	Gabapentinoids (gabapentin, pregabalin)	GBM	Retrospective	Multi-institutional retrospective study ($n = 1072$): postop gabapentin associated with improved OS (HR 0.65); reduced serum TSP-1 (*101*)

DNA lesions including single- and double-strand breaks, is of particular interest in GBM given the mechanism of action of temozolomide and radiation. Poly(ADP-ribose) polymerase (PARP) enzymes play a critical role in this pathway by catalyzing the addition of poly(ADP-ribose) chains to target proteins at sites of DNA damage, facilitating the recruitment of repair factors and maintenance of genomic integrity. Pharmacologic PARP inhibition exploits these dependencies, trapping PARP at damage sites and converting repairable single-strand breaks into lethal double-strand breaks, a mechanism that may synergize with the DNA-damaging effects of temozolomide and ionizing radiation (*112*). Phase 0/2 "trigger" trials have demonstrated that niraparib achieves sufficient CNS concentrations to inhibit PARP activity in tumor tissue (*113*). The randomized ABTC 1801 trial demonstrated that veliparib added to temozolomide and radiation did not improve outcomes in *MGMT*-methylated newly diagnosed GBM (*114*), highlighting that not all PARP inhibitors are equivalent in terms of brain penetration and target engagement. A phase 3 niraparib trial is now evaluating the agent versus temozolomide specifically in *MGMT*-unmethylated newly diagnosed GBM, seeking to define a new standard for this underserved population where conventional alkylating chemotherapy offers minimal benefit. Beyond PARP, AZD1390, a brain-penetrant ataxia telangiectasia mutated (ATM) kinase inhibitor, is under phase 1 evaluation in combination with radiation therapy (*115*), broadening the DDR-targeting strategy to additional nodes in the pathway.

CDK4/6 inhibitors

The cyclin D–cyclin–dependent kinase 4/6 (CDK4/6)–retinoblastoma (Rb) protein cell cycle regulatory pathway is frequently altered in GBM, with homozygous cyclin-dependent kinase inhibitor 2A/B deletion present in ~50 to 60% of tumors. CDK4/6 inhibitors such as abemaciclib and ribociclib have demonstrated CNS penetration and are under clinical evaluation in Rb-intact GBM populations (*116*). Early-phase trials are examining these agents both as monotherapy and in combination with temozolomide or radiation.

Antibody-drug conjugates

Antibody-drug conjugates (ADCs) leverage monoclonal antibodies to selectively deliver cytotoxic payloads to tumor cells expressing a surface antigen, concentrating chemotherapeutic exposure at the tumor while limiting systemic toxicity. Depatuxizumab mafodotin (ABT-414), targeting EGFR-amplified tumors, was evaluated in two large, randomized trials. The Intellance 1 trial in newly diagnosed EGFR-amplified GBM did not meet its primary OS end point (*117*), whereas Intellance 2 in recurrent disease suggested possible activity but was limited by significant ocular toxicity (*118*). Next-generation ADCs with improved therapeutic windows and novel payloads are under development.

Rare molecular subsets

Trials targeting additional rare molecular subsets, such as fibroblast growth factor receptor fusions, are ongoing or planned, although the low frequency of many of these alterations necessitates collaborative multi-institutional efforts (*119*). The success of basket and umbrella trial designs in identifying responses in rare molecular subgroups has accelerated this approach across neuro-oncology (*97*, *98*).

COMBINATION AND SEQUENCING APPROACHES

Given the multifaceted nature of GBM resistance, combination strategies that integrate radiation, immunotherapy, and targeted agents

Table 2. Investigational molecularly targeted strategies in IDH–wild-type GBM. FGFR, fibroblast growth factor receptor; RT, radiation therapy; TMZ, temozolomide.

Molecular target/pathway	Agent(s)	Tumor type	Status/phase	Key findings
PARP/DDR pathway	Niraparib	GBM (MGMT-unmethylated)	Phase 3	CNS penetration confirmed; versus TMZ in unmethylated GBM (*110*)
PARP/DDR pathway	Veliparib	GBM (MGMT-methylated)	Phase 3 (negative)	ABTC 1801: no benefit added to TMZ/RT (*111*)
ATM/DDR pathway	AZD1390	GBM	Phase 1	Brain-penetrant ATM inhibitor; RT combination (*112*)
CDK4/6 pathway	Abemaciclib, ribociclib	RB-intact GBM	Phase 0/1	CNS penetration demonstrated (*113*)
EGFR (ADC)	Depatuxizumab mafodotin (ABT-414)	EGFR-amplified GBM	Phase 3 (negative)	Intellance 1: no OS benefit; ocular toxicity (*114*)
FGFR fusions	Various	FGFR-altered glioma	Phase 1/2	Basket trials ongoing; rare molecular subgroup (*116*)

are increasingly being evaluated. Radiation therapy, in addition to its direct cytotoxic effects, can promote immunogenic cell death, enhance tumor antigen presentation, and transiently alter vascular permeability, creating a potential therapeutic window for immune-based and targeted therapies. These biological effects have motivated increasing interest in treatment timing and sequencing, particularly in relation to surgical intervention.

Window-of-opportunity trial designs allow administration of an investigational agent for a defined preoperative period, with pharmacodynamic and pharmacokinetic endpoints assessed in the resected specimen (*120*, *121*). These designs are particularly valuable in GBM, where tissue access is otherwise limited. Analyses performed at surgery can quantify intratumoral drug concentrations, target engagement, and immune microenvironment changes, parameters that are often inaccessible in conventional postoperative trials. Importantly, they also can compare these parameters in the nonenhancing leading edge of the tumor where the BBB is relatively intact with those in the enhancing core where the BBB is deficient. As a result, window-of-opportunity studies can inform rational combination strategies and enable rapid go/no-go decisions based on biological activity rather than radiographic response alone (*122*). Multiple institutions have adopted these designs to accelerate translational progress (*14*).

Rational sequencing of therapies from initial diagnosis through recurrence remains an underexplored area. The optimal timing and integration of immunotherapy relative to radiation and chemotherapy remain a critical question. Radiation may prime the immune microenvironment for subsequent immunotherapy, whereas alkylating chemotherapy may be immunosuppressive. Future trial designs should incorporate longitudinal molecular and immune profiling to understand how sequential therapies reshape the tumor and its microenvironment.

CONCLUSION AND OUTLOOK

Despite 2 decades of intensive investigation since the establishment of the Stupp protocol, the prognosis for patients with GBM remains modest. Nonetheless, several avenues offer genuine near-term promise. Recent approvals in molecularly defined glioma subtypes demonstrate that biomarker-directed therapy can yield meaningful benefit, reinforcing the importance of rigorous molecular stratification and target engagement. Innovations in drug delivery, including focused ultrasound–mediated BBB opening, CED, and local depot strategies, are beginning to address longstanding pharmacologic barriers that have historically confounded the interpretation of systemic therapeutic failure. CAR T cell therapies and oncolytic virotherapies have produced compelling early biological and radiographic responses, and ongoing refinement, including locoregional delivery, armored constructs (engineered CAR T cells equipped with additional transgenes encoding proinflammatory cytokines, checkpoint resistance modules, or other modifications designed to enhance persistence and overcome the immunosuppressive microenvironment), and rational combination strategies, may be required to achieve durable clinical benefit. The cancer neuroscience paradigm offers an entirely new class of therapeutic targets based on the recognition that GBM cells parasitize neuronal circuitry.

Adaptive platform trials such as GBM AGILE represent a transformative advance in clinical trial efficiency by enabling continuous learning in a disease characterized by high biological heterogeneity and frequent single-agent failure. Longitudinal sampling of GBM during clinical trials can be performed safely and adds to window-of-opportunity trials to understand complex and long-term effects of the investigational agent. Liquid biopsy, including cell-free DNA analysis, and minimal residual disease monitoring may soon enable earlier detection of recurrence and real-time assessment of treatment response. The integration of advanced molecular diagnostics, including comprehensive next-generation sequencing, methylation profiling, and single-cell analyses, into routine clinical practice will be essential for identifying actionable targets and appropriately matching patients to emerging therapies.

Looking ahead, the next decade in GBM treatment will likely be defined by the convergence of four paradigms: precision medicine guided by comprehensive molecular and epigenomic profiling; enhanced drug delivery to overcome the BBB; reinvigoration of the antitumor immune response through combination immunotherapy and cellular therapy strategies; and novel cancer neuroscience–informed interventions targeting tumor-neuron interactions. Meaningful progress will require not only scientific innovation but also sustained

investment in collaborative clinical trial infrastructure, equitable access to emerging therapies, and the routine integration of translational end points into clinical studies. Only through such a coordinated, multidisciplinary approach can the trajectory of GBM outcomes begin to change.

REFERENCES AND NOTES

1. M. E. Hegi, A.-C. Diserens, T. Gorlia, M.-F. Hamou, N. de Tribolet, M. Weller, J. M. Kros, J. A. Hainfellner, W. Mason, L. Mariani, J. E. C. Bromberg, P. Hau, R. O. Mirimanoff, J. G. Cairncross, R. C. Janzer, R. Stupp, MGMT gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* **352**, 997–1003 (2005).
2. Q. T. Ostrom, M. Price, C. Neff, G. Cioffi, K. A. Waite, C. Kruchko, J. S. Barnholtz-Sloan, CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016—2020. *Neuro Oncol.* **25**, iv1–iv99 (2023).
3. F. Girardi, M. Matz, C. Stiller, H. You, R. Marcos Gragera, M. Y. Valkov, J.-L. Bulliard, P. De, D. Morrison, M. Wanner, D. K. O'Brian, N. Saint-Jacques, M. P. Coleman, C. Allemani, CONCORD Working Group, Global survival trends for brain tumors, by histology: Analysis of individual records for 556,237 adults diagnosed in 59 countries during 2000-2014 (CONCORD-3). *Neuro Oncol.* **25**, 580–592 (2023).
4. R. Stupp, W. P. Mason, M. J. van den Bent, M. Weller, B. Fisher, M. J. B. Taphoorn, K. Belanger, A. A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R. C. Janzer, S. K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J. G. Cairncross, E. Eisenhauer, R. O. Mirimanoff, European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* **352**, 987–996 (2005).
5. M. Weller, M. van den Bent, M. Preusser, E. Le Rhun, J. C. Tonn, G. Minniti, M. Bendszus, C. Balana, O. Chinot, L. Dirven, P. French, M. E. Hegi, A. S. Jakola, M. Platten, P. Roth, R. Rudà, S. Short, M. Smits, M. J. B. Taphoorn, A. von Deimling, M. Westphal, R. Soffietti, G. Reifenberger, W. Wick, EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat. Rev. Clin. Oncol.* **18**, 170–186 (2021).
6. D. N. Louis, A. Perry, P. Wesseling, D. J. Brat, I. A. Cree, D. Figarella-Branger, C. Hawkins, H. K. Ng, S. M. Pfister, G. Reifenberger, R. Soffietti, A. von Deimling, D. W. Ellison, The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol.* **23**, 1231–1251 (2021).
7. I. K. Mellinghoff, M. J. van den Bent, D. T. Blumenthal, M. Touat, K. B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W. P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A. F. Hottinger, Y. Arakawa, J. M. Sepulveda, W. Wick, R. Soffietti, J. R. Perry, P. Giglio, M. de la Fuente, E. A. Maher, S. Schoenfeld, D. Zhao, S. S. Pandya, L. Steelman, I. Hassan, P. Y. Wen, T. F. Cloughesy, INDIGO Trial Investigators, Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N. Engl. J. Med.* **389**, 589–601 (2023).
8. I. Arrillaga-Romany, S. L. Gardner, Y. Odia, D. Aguilera, J. E. Allen, T. Batchelor, N. Butowski, C. Chen, T. Cloughesy, A. Cluster, J. de Groot, K. S. Dixit, J. J. Graber, A. M. Haggiagi, R. A. Harrison, A. Kheradpour, L. B. Kilburn, S. C. Kurz, G. Lu, T. J. MacDonald, M. Mehta, A. S. Melemed, P. L. Nghiemphu, S. C. Ramage, N. Shonka, A. Sumrall, R. S. Tarapore, L. Taylor, Y. Umemura, P. Y. Wen, ONC201 (Dordaviprone) in recurrent H3 K27M-mutant diffuse midline glioma. *J. Clin. Oncol.* **42**, 1542–1552 (2024).
9. C. Neftel, J. Laffy, M. G. Filbin, T. Hara, M. E. Shore, G. J. Rahme, A. R. Richman, D. Silverbush, M. L. Shaw, C. M. Hebert, J. Dewitt, S. Gritsch, E. M. Perez, L. N. G. Castro, X. Lan, N. Druck, C. Rodman, D. Dionne, A. Kaplan, M. S. Bertalan, J. Small, K. Pelton, S. Becker, D. Bonal, Q.-D. Nguyen, R. L. Servis, J. M. Fung, R. Mylvaganam, L. Mayr, J. Gojo, C. Haberler, R. Geyeregger, T. Czech, I. Slavc, B. V. Nahed, W. T. Curry, B. S. Carter, H. Wakimoto, P. K. Brastianos, T. T. Batchelor, A. Stemmer-Rachamimov, M. Martinez-Lage, M. P. Frosch, I. Stamenkovic, N. Riggi, E. Rheinbay, M. Monje, O. Rozenblatt-Rosen, D. P. Cahill, A. P. Patel, T. Hunter, I. M. Verma, K. L. Ligon, D. N. Louis, A. Regev, B. E. Bernstein, I. Tirosh, M. L. Suvà, An integrative model of cellular states, plasticity and genetics for glioblastoma. *Cell* **178**, 835–849.e21 (2019).
10. D. F. Quail, J. A. Joyce, The microenvironmental landscape of brain tumors. *Cancer Cell* **31**, 326–341 (2017).
11. C. W. Brennan, R. G. W. Verhaak, A. McKenna, B. Campos, H. Noushmehr, S. R. Salama, S. Zheng, D. Chakravarty, J. Z. Sanborn, S. H. Berman, R. Beroukhim, B. Bernard, C.-J. Wu, G. Genovese, I. Shmulevich, J. Barnholtz-Sloan, L. Zou, R. Vegesna, S. A. Shukla, G. Ciriello, W. Yung, W. Zhang, C. Sougnez, T. Mikkelsen, K. Aldape, D. D. Bigner, E. G. Van Meir, M. Prados, A. Sloan, K. L. Black, J. Eschbacher, G. Finocchiaro, W. Friedman, D. W. Andrews, A. Guha, M. Iacocca, B. P. O'Neill, G. Foltz, J. Myers, D. J. Weisenberger, R. Penny, R. Kucherlapati, C. M. Perou, D. N. Hayes, R. Gibbs, M. Marra, G. B. Mills, E. Lander, P. Spellman, R. Wilson, C. Sander, J. Weinstein, M. Meyerson, S. Gabriel, P. W. Laird, D. Haussler, G. Getz, L. Chin, TCGA Research Network, The somatic genomic landscape of glioblastoma. *Cell* **155**, 462–477 (2013).
12. C. D. Arvanitis, G. B. Ferraro, R. K. Jain, The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nat. Rev. Cancer* **20**, 26–41 (2020).
13. M. Maschio, Brain tumor-related epilepsy. *Curr. Neuropharmacol.* **10**, 124–133 (2012).
14. P. Y. Wen, M. Weller, E. Q. Lee, M. Touat, M. Khasraw, R. Rahman, M. Platten, M. Lim, F. Winkler, C. Horbinski, R. G. W. Verhaak, R. Y. Huang, M. S. Ahluwalia, N. L. Albert, J.-C. Tonn, D. Schiff, J. S. Barnholtz-Sloan, Q. Ostrom, K. D. Aldape, T. T. Batchelor, R. S. Bindra, E. A. Chiocca, T. F. Cloughesy, J. F. DeGroot, P. French, E. Galanis, N. Galldiks, M. R. Gilbert, M. E. Hegi, A. B. Lassman, E. Le Rhun, M. P. Mehta, I. K. Mellinghoff, G. Minniti, P. Roth, M. Sanson, M. J. B. Taphoorn Andreas, v. D. T. Weiss, W. Wick, G. Zadeh, D. A. Reardon, S. M. Chang, S. C. Short, M. J. van den Bent, M. Preusser, Glioblastoma in adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol.* **27**, 2751–2788 (2025).
15. M. J. Glantz, B. F. Cole, P. A. Forsyth, L. D. Recht, P. Y. Wen, M. C. Chamberlain, S. A. Grossman, J. G. Cairncross, Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors [RETIRED]. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **54**, 1886–1893 (2000).
16. E. K. Avila, S. Tobochnik, S. K. Inati, J. A. F. Koekkoek, G. M. McKhann, J. J. Riviello, R. Rudà, D. Schiff, W. O. Tatum, J. W. Templer, M. Weller, P. Y. Wen, Brain tumor-related epilepsy management: A Society for Neuro-oncology (SNO) consensus review on current management. *Neuro Oncol.* **26**, 7–24 (2024).
17. K. L. Pitter, I. Tamagno, K. Alikhanyan, A. Hosni-Ahmed, S. S. Pattwell, S. Donnola, C. Dai, T. Ozawa, M. Chang, T. A. Chan, K. Beal, A. J. Bishop, C. A. Barker, T. S. Jones, B. Hentschel, T. Gorlia, U. Schlegel, R. Stupp, M. Weller, E. C. Holland, D. Hambardzumyan, Corticosteroids compromise survival in glioblastoma. *Brain* **139**, 1458–1471 (2016).
18. J. B. Iorgulescu, P. C. Gokhale, M. C. Speranza, B. K. Eschle, M. J. Poitras, M. K. Wilkens, K. M. Soroko, C. Chhoeu, A. Knott, Y. Gao, M. J. Lim-Fat, G. J. Baker, D. M. Bonal, Q.-D. Nguyen, G. R. L. Grant, K. L. Ligon, P. K. Sorger, E. A. Chiocca, A. C. Anderson, P. T. Kirschmeier, A. H. Sharpe, G. J. Freeman, D. A. Reardon, Concurrent dexamethasone limits the clinical benefit of immune checkpoint blockade in glioblastoma. *Clin. Cancer Res.* **27**, 276–287 (2021).
19. C. S. Dejonckheere, D. Scafa, L. Käsmann, T. Zeyen, A.-L. Potthoff, N. Schäfer, J. Weller, U. Herrlinger, M. Schneider, H. Vatter, A.-L. Grosu, S. Brehmer, F. A. Giordano, G. R. Sarria, E. Gkika, J. P. Layer, Boswellia serrata for the management of radiation-induced cerebral edema and necrosis: A systematic meta-narrative review of clinical evidence. *Adv. Radiat. Oncol.* **10**, 101732 (2025).
20. J. T. Jo, D. Schiff, J. R. Perry, Thrombosis in brain tumors. *Semin. Thromb. Hemost.* **40**, 325–331 (2014).
21. B. J. Carney, E. J. Uhlmann, M. Puligandla, C. Mantia, G. M. Weber, D. S. Neuberg, J. I. Zwicker, Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J. Thromb. Haemost.* **17**, 72–76 (2019).
22. A. R. Sloan, A. J. Gordillo, A. Kennemer, A. A. Khorana, C. Horbinski, D. C. Kaelber, S. J. Cameron, J. D. Lathia, Venous thromboembolism incidence shortens survival in isocitrate dehydrogenase wild-type glioblastoma. *Neurooncol. Adv.* **7**, vdaf018 (2025).
23. M. Lacroix, D. Abi-Said, D. R. Fourney, Z. L. Gokaslan, W. Shi, F. DeMonte, F. F. Lang, I. E. McCutcheon, S. J. Hassenbusch, E. Holland, K. Hess, C. Michael, D. Miller, R. Sawaya, A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. *J. Neurosurg.* **95**, 190–198 (2001).
24. N. Sanai, M.-Y. Polley, M. W. McDermott, A. T. Parsa, M. S. Berger, An extent of resection threshold for newly diagnosed glioblastomas. *J. Neurosurg.* **115**, 3–8 (2011).
25. A. M. Molinaro, S. Hervey-Jumper, R. A. Morshed, J. Young, S. J. Han, P. Chunduru, Y. Zhang, J. J. Phillips, A. Shai, M. Lafontaine, J. Crane, A. Chandra, P. Flanigan, A. Jahangiri, G. Cioffi, Q. Ostrom, J. E. Anderson, C. Badve, J. Barnholtz-Sloan, A. E. Sloan, B. J. Erickson, P. A. Decker, M. L. Kosel, D. LaChance, J. Eckel-Passow, R. Jenkins, J. Villanueva-Meyer, T. Rice, M. Wrensch, J. K. Wiencke, N. A. Oberheim Bush, J. Taylor, N. Butowski, M. Prados, J. Clarke, S. Chang, E. Chang, M. Aghi, P. Theodosopoulos, M. McDermott, M. S. Berger, Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. *JAMA Oncol.* **6**, 495–503 (2020).
26. Y. M. Li, D. Suki, K. Hess, R. Sawaya, The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? *J. Neurosurg.* **124**, 977–988 (2016).
27. P. Karschnia, J. S. Young, A. Dono, L. Häni, T. Sciortino, F. Bruno, S. T. Juenger, N. Teske, R. A. Morshed, A. F. Haddad, Y. Zhang, S. Stoecklein, M. Weller, M. A. Vogelbaum, J. Beck, N. Tandon, S. Hervey-Jumper, A. M. Molinaro, R. Rudà, L. Bello, O. Schnell, Y. Esquenazi, M. I. Ruge, S. J. Grau, M. S. Berger, S. M. Chang, M. van den Bent, J.-C. Tonn, Prognostic validation of a new classification system for extent of resection in glioblastoma: A report of the RANO resect group. *Neuro Oncol.* **25**, 940–954 (2023).
28. N. Teske, A. Dono, J. S. Young, S. T. Juenger, G. C. Youssef, L. Häni, T. Sciortino, F. Bruno, J. Dietrich, C. Y. Mau, M. Weller, J. Beck, S. Hervey-Jumper, A. M. Molinaro, S. M. Chang, M. van den Bent, M. A. Vogelbaum, M. I. Ruge, D. P. Cahill, R. Rudà, L. Bello, S. J. Grau, O. Schnell, R. Y. Huang, P. Y. Wen, N. Tandon, M. S. Berger, J.-C. Tonn, Y. Esquenazi, P. Karschnia, Associations of supramaximal resection with outcome in glioblastoma across age groups: A report of the RANO *resect* group. *Neuro Oncol.* **28**, 470–484 (2026).

29. W. Stummer, U. Pichlmeier, T. Meinel, O. D. Wiestler, F. Zanella, H.-J. Reulen, ALA-Glioma Study Group, Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. *Lancet Oncol.* **7**, 392–401 (2006).
30. R. Sastry, W. L. Bi, S. Pieper, S. Frisken, T. Kapur, W. Wells, A. J. Golby, Applications of ultrasound in the resection of brain tumors. *J. Neuroimaging* **27**, 5–15 (2017).
31. L. B. Palavani, M. Y. Ferreira, P. G. L. B. Borges, L. Bandeira, G. da Silva Semione, M. V. Almeida, G. Verly, A. D. Polverini, F. F. Andreão, R. Camerotte, C. C. Ferreira, W. Paiva, R. Bertani, J. Boockvar, Ultrasound-guided resection of high-grade gliomas: A single-arm meta-analysis. *World Neurosurg.* **186**, 17–26 (2024).
32. A. E. Sloan, M. S. Ahluwalia, J. Valerio-Pascua, S. Manjila, M. G. Torchia, S. E. Jones, J. L. Sunshine, M. Phillips, M. A. Griswold, M. Clampitt, C. Brewer, J. Jochum, M. V. McGraw, D. Diorio, G. Ditz, G. H. Barnett, Results of the NeuroBlate system first-in-humans phase I clinical trial for recurrent glioblastoma: Clinical article. *J. Neurosurg.* **118**, 1202–1219 (2013).
33. J. F. de Groot, A. H. Kim, S. Prabhu, G. Rao, A. W. Laxton, P. E. Fecci, B. J. O'Brien, A. Sloan, V. Chiang, S. B. Tatter, A. M. Mohammadi, D. G. Placantonakis, R. E. Strowd, C. Chen, C. Hadjipanayis, M. Khasraw, D. Sun, D. Piccioni, K. D. Sinicrope, J. L. Campian, S. C. Kurz, B. Williams, K. Smith, Z. Tovar-Spinoza, E. C. Leuthardt, Efficacy of laser interstitial thermal therapy (LITT) for newly diagnosed and recurrent *IDH* wild-type glioblastoma. *Neurooncol. Adv.* **4**, vdac040 (2022).
34. O. H. Butt, A. Y. Zhou, J. Huang, W. A. Leidig, A. E. Silberstein, M. G. Chheda, T. M. Johanns, G. Ansstas, J. Liu, G. Talcott, R. Nakiwala, J. S. Shimony, A. H. Kim, E. C. Leuthardt, D. D. Tran, J. L. Campian, A phase II study of laser interstitial thermal therapy combined with doxorubicin in patients with recurrent glioblastoma. *Neurooncol. Adv.* **3**, vdab164 (2021).
35. M. Westphal, D. C. Hilt, E. Bortey, P. Delavault, R. Olivares, P. C. Warnke, I. R. Whittle, J. Jääskeläinen, Z. Ram, A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol.* **5**, 79–88 (2003).
36. D. J. Gessler, E. C. Neil, R. Shah, J. Levine, J. Shanks, C. Wilke, M. Reynolds, S. Zhang, C. Özütemiz, M. Gencturk, M. Folkertsma, W. R. Bell, L. Chen, C. Ferreira, K. Dusenbery, C. C. Chen, GammaTile® brachytherapy in the treatment of recurrent glioblastomas. *Neurooncol. Adv.* **4**, vdab185 (2022).
37. K. Smith, P. Nakaji, T. Thomas, D. Pinnaduwage, G. Wallstrom, M. Choi, J. Zabramski, C. Chen, D. Brachman, Safety and patterns of survivorship in recurrent GBM following resection and surgically targeted radiation therapy: Results from a prospective trial. *Neuro Oncol.* **24**, S4–S15 (2022).
38. M. A. Garcia, A. Turner, D. G. Brachman, The role of GammaTile in the treatment of brain tumors: A technical and clinical overview. *J. Neurooncol.* **166**, 203–212 (2024).
39. A. Malmström, B. H. Grønberg, C. Marosi, R. Stupp, D. Frappaz, H. Schultz, U. Abacioglu, B. Tavelin, B. Lhermitte, M. E. Hegi, J. Rosell, R. Henriksson, Nordic Clinical Brain Tumour Study Group (NCBTSG), Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. *Lancet Oncol.* **13**, 916–926 (2012).
40. J. R. Perry, N. Laperriere, C. J. O'Callaghan, A. A. Brandes, J. Menten, C. Phillips, M. Fay, R. Nishikawa, J. G. Cairncross, W. Roa, D. Osoba, J. P. Rossiter, A. Sahgal, H. Hirte, F. Laigle-Donadey, E. Franceschi, O. Chinot, V. Golfinopoulos, L. Fariselli, A. Wick, L. Feuvret, M. Back, M. Tills, C. Winch, B. G. Baumert, W. Wick, K. Ding, W. P. Mason, Trial Investigators, Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N. Engl. J. Med.* **376**, 1027–1037 (2017).
41. W. Roa, L. Kepka, N. Kumar, V. Sinaika, J. Matiello, D. Lomidze, D. Hentati, D. Guedes de Castro, K. Dyttus-Cebulok, S. Drodge, S. Ghosh, B. Jeremić, E. Rosenblatt, E. Fidarova, International atomic energy agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. *J. Clin. Oncol.* **33**, 4145–4150 (2015).
42. S. E. Combs, C. Thilmann, L. Edler, J. Debus, D. Schulz-Ertner, Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: Long-term results in 172 patients treated in a single institution. *J. Clin. Oncol.* **23**, 8863–8869 (2005).
43. G. Minniti, M. Niyazi, F. Alongi, P. Navarria, C. Belka, Current status and recent advances in reirradiation of glioblastoma. *Radiat. Oncol.* **16**, 36 (2021).
44. E. G. Shaw, R. Rosdhal, R. B. D'Agostino, J. Lovato, M. J. Naughton, M. E. Robbins, S. R. Rapp, Phase II study of donepezil in irradiated brain tumor patients: Effect on cognitive function, mood, and quality of life. *J. Clin. Oncol.* **24**, 1415–1420 (2006).
45. S. R. Rapp, L. D. Case, A. Peiffer, M. M. Naughton, M. D. Chan, V. W. Stieber, D. F. Moore, S. C. Falchuk, J. V. Piephoff, W. J. Edenfield, J. K. Giguere, M. E. Loghin, E. G. Shaw, Donepezil for irradiated brain tumor survivors: A phase III randomized placebo-controlled clinical trial. *J. Clin. Oncol.* **33**, 1653–1659 (2015).
46. V. A. Levin, L. Bidaut, P. Hou, A. J. Kumar, J. S. Wefel, B. N. Bekele, J. Grewal, S. Prabhu, M. Loghin, M. R. Gilbert, E. F. Jackson, Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int. J. Radiat. Oncol. Biol. Phys.* **79**, 1487–1495 (2011).
47. D. B. P. Eekers, C. M. L. Zegers, K. A. Ahmed, D. Amelio, T. Gupta, S. B. Harrabi, T. Kazda, D. Scartoni, C. Seidel, H. A. Shih, G. Minniti, Controversies in neuro-oncology: Focal proton versus photon radiation therapy for adult brain tumors. *Neurooncol. Pract.* **11**, 369–382 (2024).
48. P. D. Brown, C. Chung, D. D. Liu, S. McAvoy, D. Grosshans, K. Al Feghali, A. Mahajan, J. Li, S. L. McGovern, M.-F. McAleer, A. J. Ghia, E. P. Sulman, M. Penas-Prado, J. F. de Groot, A. B. Heimberger, J. Wang, T. S. Armstrong, M. R. Gilbert, N. Guha-Thakurta, J. S. Wefel, A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. *Neuro Oncol.* **23**, 1337–1347 (2021).
49. R. Stupp, S. Taillibert, A. Kanner, W. Read, D. Steinberg, B. Lhermitte, S. Toms, A. Idbaih, M. S. Ahluwalia, K. Fink, F. Di Meco, F. Lieberman, J.-J. Zhu, G. Stragliotto, D. Tran, S. Brem, A. Hottinger, E. D. Kirson, G. Lavy-Shahaf, U. Weinberg, C.-Y. Kim, S.-H. Paek, G. Nicholas, J. Bruna, H. Hirte, M. Weller, Y. Palti, M. E. Hegi, Z. Ram, Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA* **318**, 2306–2316 (2017).
50. M. J. B. Taphoorn, L. Dirven, A. A. Kanner, G. Lavy-Shahaf, U. Weinberg, S. Taillibert, S. A. Toms, J. Honnorat, T. C. Chen, J. Sroubek, C. David, A. Idbaih, J. C. Easaw, C.-Y. Kim, J. Bruna, A. F. Hottinger, Y. Kew, P. Roth, R. Desai, J. L. Villano, E. D. Kirson, Z. Ram, R. Stupp, Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: A secondary analysis of a randomized clinical trial. *JAMA Oncol.* **4**, 495–504 (2018).
51. T. Leal, R. Kotecha, R. Ramlau, L. Zhang, J. Milanowski, M. Cobo, J. Roubec, L. Petruzelka, L. Havel, S. Kalmadi, J. Ward, Z. Andric, T. Berghmans, D. E. Gerber, G. Kloecker, R. Panikkar, J. Aerts, A. Delmonte, M. Pless, R. Greil, C. Rolfo, W. Akerley, M. Eaton, M. Iqbal, C. Langer, LUNAR Study Investigators, Tumor treating fields therapy with standard systemic therapy versus standard systemic therapy alone in metastatic non-small-cell lung cancer following progression on or after platinum-based therapy (LUNAR): A randomised, open-label, pivotal phase 3 study. *Lancet Oncol.* **24**, 1002–1017 (2023).
52. H. M. Babiker, V. Picozzi, S. R. Chandana, B. Melichar, A. Kasi, J. Gang, J. Gallego, A. Bullock, H. Chunyi, L. Wyrwicz, E. Hitre, A. Osipov, C. de la Fouchardiere, I. Ales, T. Dragovich, W. Lee, K. Feeney, P. Philip, M. Ueno, E. Van Cutsem, T. Seufferlein, T. Macarulla, PANOVA-3 Study Investigators, Tumor treating fields with gemcitabine and Nab-paclitaxel for locally advanced pancreatic adenocarcinoma: Randomized, open-label, pivotal phase III PANOVA-3 study. *J. Clin. Oncol.* **43**, 2350–2360 (2025).
53. U. Herrlinger, T. Tzaridis, F. Mack, J. P. Steinbach, U. Schlegel, M. Sabel, P. Hau, R.-D. Kortmann, D. Krex, O. Grauer, R. Goldbrunner, O. Schnell, O. Bähr, M. Uhl, C. Seidel, G. Tabatabai, T. Kowalski, F. Ringel, F. Schmidt-Graf, B. Suchorska, S. Brehmer, A. Weyerbrock, M. Renovanz, L. Bullinger, N. Galldiks, P. Vajkoczy, M. Misch, H. Vatter, M. Stuplich, N. Schäfer, S. Kebir, J. Weller, C. Schaub, W. Stummer, J.-C. Tonn, M. Simon, V. C. Keil, M. Nelles, H. Urbach, M. Coenen, W. Wick, M. Weller, R. Fimmers, M. Schmid, E. Hattingen, T. Pietsch, C. Coch, M. Glas, Neurooncology Working Group of the German Cancer Society, Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): A randomised, open-label, phase 3 trial. *Lancet* **393**, 678–688 (2019).
54. M. R. Gilbert, J. J. Dignam, T. S. Armstrong, J. S. Wefel, D. T. Blumenthal, M. A. Vogelbaum, H. Colman, A. Chakravarti, S. Pugh, M. Won, R. Jeraj, P. D. Brown, K. A. Jaeckle, D. Schiff, V. W. Stieber, D. G. Brachman, M. Werner-Wasik, I. W. Tremont-Lukats, E. P. Sulman, K. D. Aldape, W. J. Curran Jr., M. P. Mehta, A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N. Engl. J. Med.* **370**, 699–708 (2014).
55. O. L. Chinot, W. Wick, W. Mason, R. Henriksson, F. Saran, R. Nishikawa, A. F. Carpentier, K. Hoang-Xuan, P. Kavan, D. Cernea, A. A. Brandes, M. Hilton, L. Abrey, T. Cloughesy, Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N. Engl. J. Med.* **370**, 709–722 (2014).
56. W. Wick, T. Gorlia, M. Bendszus, M. Taphoorn, F. Sahm, I. Harting, A. A. Brandes, W. Taal, J. Domont, A. Idbaih, M. Campone, P. M. Clement, R. Stupp, M. Fabbro, E. Le Rhun, F. Dubois, M. Weller, A. von Deimling, V. Golfinopoulos, J. C. Bromberg, M. Platten, M. Klein, M. J. van den Bent, Lomustine and bevacizumab in progressive glioblastoma. *N. Engl. J. Med.* **377**, 1954–1963 (2017).
57. W. Wick, M. Platten, C. Meisner, J. Felsberg, G. Tabatabai, M. Simon, G. Nikkhah, K. Papsdorf, J. P. Steinbach, M. Sabel, S. E. Combs, J. Vesper, C. Braun, J. Meixensberger, R. Ketter, R. Mayer-Steinacker, G. Reifenberger, M. Weller, NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society, Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. *Lancet Oncol.* **13**, 707–715 (2012).
58. N. J. Abbott, A. A. K. Patabendige, D. E. M. Dolman, S. R. Yusof, D. J. Begley, Structure and function of the blood-brain barrier. *Neurobiol. Dis.* **37**, 13–25 (2010).
59. O. van Tellingen, B. Yetkin-Arik, M. C. de Gooijer, P. Wesseling, T. Wurdinger, H. E. de Vries, Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. *Drug Resist. Updat.* **19**, 1–12 (2015).

60. J. N. Sarkaria, L. S. Hu, I. F. Parney, D. H. Pafundi, D. H. Brinkmann, N. N. Laack, C. Giannini, T. C. Burns, S. H. Kizilbash, J. K. Laramy, K. R. Swanson, T. J. Kaufmann, P. D. Brown, N. Y. R. Agar, E. Galanis, J. C. Buckner, W. F. Elmquist, Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. *Neuro Oncol.* **20**, 184–191 (2018).
61. R. H. Bobo, D. W. Laske, A. Akbasak, P. F. Morrison, R. L. Dedrick, E. H. Oldfield, Convection-enhanced delivery of macromolecules in the brain. *Proc. Natl. Acad. Sci. U.S.A.* **91**, 2076–2080 (1994).
62. R. R. Lonser, M. Sarntinoranont, P. F. Morrison, E. H. Oldfield, Convection-enhanced delivery to the central nervous system. *J. Neurosurg.* **122**, 697–706 (2015).
63. A. I. Mehta, B. D. Choi, D. Ajay, R. Raghavan, M. Brady, A. H. Friedman, I. Pastan, D. D. Bigner, J. H. Sampson, Convection enhanced delivery of macromolecules for brain tumors. *Curr. Drug Discov. Technol.* **9**, 305–310 (2012).
64. M. L. Brady, R. Raghavan, D. Singh, P. J. Anand, A. S. Fleisher, J. Mata, W. C. Broaddus, W. L. Olbricht, In vivo performance of a microfabricated catheter for intraparenchymal delivery. *J. Neurosci. Methods* **229**, 76–83 (2014).
65. M. S. Fiandaca, J. R. Forsayeth, P. J. Dickinson, K. S. Bankiewicz, Image-guided convection-enhanced delivery platform in the treatment of neurological diseases. *Neurotherapeutics* **5**, 123–127 (2008).
66. A. M. Mehta, A. M. Sonabend, J. N. Bruce, Convection-enhanced delivery. *Neurotherapeutics* **14**, 358–371 (2017).
67. S. Kunwar, S. Chang, M. Westphal, M. Vogelbaum, J. Sampson, G. Barnett, M. Shaffrey, Z. Ram, J. Piepmeier, M. Prados, D. Croteau, C. Pedain, P. Leland, S. R. Husain, B. H. Joshi, R. K. Puri, PRECISE Study Group, Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. *Neuro Oncol.* **12**, 871–881 (2010).
68. G. Frosina, Advances in drug delivery to high grade gliomas. *Brain Pathol.* **26**, 689–700 (2016).
69. H. Brem, S. Piantadosi, P. C. Burger, M. Walker, R. Selker, N. A. Vick, K. Black, M. Sisti, S. Brem, G. Mohr, P. Muller, R. Morawetz, S. C. Schold, Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* **345**, 1008–1012 (1995).
70. K. Hynynen, N. McDannold, N. Vykhodtseva, F. A. Jolesz, Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. *Radiology* **220**, 640–646 (2001).
71. M. Aryal, C. D. Arvanitis, P. M. Alexander, N. McDannold, Ultrasound-mediated blood-brain barrier disruption for targeted drug delivery in the central nervous system. *Adv. Drug Deliv. Rev.* **72**, 94–109 (2014).
72. A. Carpentier, M. Canney, A. Vignot, V. Reina, K. Beccaria, C. Horodyckid, C. Karachi, D. Leclercq, C. Lafon, J.-Y. Chapelon, L. Capelle, P. Cornu, M. Sanson, K. Hoang-Xuan, J.-Y. Delattre, A. Idbaih, Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci. Transl. Med.* **8**, 343re2 (2016).
73. T. Mainprize, N. Lipsman, Y. Huang, Y. Meng, A. Bethune, S. Ironside, C. Heyn, R. Alkins, M. Trudeau, A. Sahgal, J. Perry, K. Hynynen, Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: A clinical safety and feasibility study. *Sci. Rep.* **9**, 321 (2019).
74. A. M. Sonabend, A. Gould, C. Amidei, R. Ward, K. A. Schmidt, D. Y. Zhang, C. Gomez, J. F. Bebawy, B. P. Liu, G. Bouchoux, C. Desseaux, I. B. Helenowski, R. V. Lukas, K. Dixit, P. Kumthekar, V. A. Arrieta, M. S. Lesniak, A. Carpentier, H. Zhang, M. Muzzio, M. Canney, R. Stupp, Repeated blood-brain barrier opening with an implantable ultrasound device for delivery of albumin-bound paclitaxel in patients with recurrent glioblastoma: A phase 1 trial. *Lancet Oncol.* **24**, 509–522 (2023).
75. A. Carpentier, R. Stupp, A. M. Sonabend, H. Dufour, O. Chinot, B. Mathon, F. Ducray, J. Guyotat, N. Baize, P. Menei, J. de Groot, J. S. Weinberg, B. P. Liu, E. Guemas, C. Desseaux, C. Schmitt, G. Bouchoux, M. Canney, A. Idbaih, Repeated blood-brain barrier opening with a nine-emitter implantable ultrasound device in combination with carboplatin in recurrent glioblastoma: A phase I/II clinical trial. *Nat. Commun.* **15**, 1650 (2024).
76. G. F. Woodworth, P. Anastasiadis, A. Ozair, J. Chabros, C. Bettegowda, C. Chen, J. V. E. Gerstl, C. Douville, R. A. Mekary, T. R. Smith, Y. Meng, C. Hawkins, C. B. Pople, A. Abrahao, M. Llinas, C. Heyn, A. Bunevicius, A. R. Rezai, A. J. S. Ball, K. Henry, A. Sahgal, E. Torio, H. Ren, H. Ahmad, H. Arora, H. Eisenberg, J. Perry, J. S. Carpenter, K. Hynynen, L. C. Pham, M. B. Anketell, M. J. Lim-Fat, Z. Xu, C. P. Cifarelli, J. P. Sheehan, N. J. McDannold, D. Gandhi, A. J. Golby, N. Lipsman, Microbubble-enhanced transcranial focused ultrasound with temozolomide for patients with high-grade glioma (BT008NA): A multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* **26**, 1651–1664 (2025).
77. E. K. Nduom, M. Weller, A. B. Heimberger, Immunosuppressive mechanisms in glioblastoma. *Neuro Oncol.* **17** (Suppl. 7), vii9–vii14 (2015).
78. K. Gabrusiewicz, B. Rodriguez, J. Wei, Y. Hashimoto, L. M. Healy, S. N. Maiti, G. Thomas, S. Zhou, Q. Wang, A. Elakkad, B. D. Liebelt, N. K. Yaghi, R. Ezhilarasan, N. Huang, J. S. Weinberg, S. S. Prabhu, G. Rao, R. Sawaya, L. A. Langford, J. M. Bruner, G. N. Fuller, A. Bar-Or, W. Li, R. R. Colen, M. A. Curran, K. P. Bhat, J. P. Antel, L. J. Cooper, E. P. Sulman, A. B. Heimberger, Glioblastoma-infiltrated innate immune cells resemble M0 macrophage phenotype. *JCI Insight* **1**, 85841 (2016).
79. T. E. Miller, C. A. El Farran, C. P. Couturier, Z. Chen, J. P. D'Antonio, J. Verga, M. A. Villanueva, L. N. Gonzalez Castro, Y. E. Tong, T. A. Saadi, A. N. Chiocca, Y. Zhang, D. S. Fischer, D. H. Heiland, J. L. Guerriero, K. Petrecca, M. L. Suva, A. K. Shalek, B. E. Bernstein, Programs, origins and immunomodulatory functions of myeloid cells in glioma. *Nature* **640**, 1072–1082 (2025).
80. D. A. Reardon, A. A. Brandes, A. Omuro, P. Mulholland, M. Lim, A. Wick, J. Baehring, M. S. Ahluwalia, P. Roth, O. Bähr, S. Phuphanich, J. M. Sepulveda, P. De Souza, S. Sahebjam, M. Carleton, K. Tatsuoka, C. Taitt, R. Zwirtes, J. Sampson, M. Weller, Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: The CheckMate 143 phase 3 randomized clinical trial. *JAMA Oncol.* **6**, 1003–1010 (2020).
81. M. Lim, M. Weller, A. Idbaih, J. Steinbach, G. Finocchiaro, R. R. Raval, G. Ansstas, J. Baehring, J. W. Taylor, J. Honnorat, K. Petrecca, F. De Vos, A. Wick, A. Sumrall, S. Sahebjam, I. K. Mellinghoff, M. Kinoshita, M. Roberts, R. Slepetis, D. Warad, D. Leung, M. Lee, D. A. Reardon, A. Omuro, Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. *Neuro Oncol.* **24**, 1935–1949 (2022).
82. K. Woroniecka, P. Chongsathidkiet, K. Rhodin, H. Kemeny, C. Dechant, S. H. Farber, A. A. Elsamadicy, X. Cui, S. Koyama, C. Jackson, L. J. Hansen, T. M. Johanns, L. Sanchez-Perez, V. Chandramohan, Y.-R. A. Yu, D. D. Bigner, A. Giles, P. Healy, G. Dranoff, K. J. Weinhold, G. P. Dunn, P. E. Fecci, T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. *Clin. Cancer Res.* **24**, 4175–4186 (2018).
83. E. Friebel, K. Kapolou, S. Unger, N. G. Núñez, S. Utz, E. J. Rushing, L. Regli, M. Weller, M. Greter, S. Tugues, M. C. Neidert, B. Becher, Single-cell mapping of human brain cancer reveals tumor-specific instruction of tissue-invading leukocytes. *Cell* **181**, 1626–1642.e20 (2020).
84. C. E. Brown, D. Alizadeh, R. Starr, L. Weng, J. R. Wagner, A. Naranjo, J. R. Ostberg, M. S. Blanchard, J. Kilpatrick, J. Simpson, A. Kurien, S. J. Priceman, X. Wang, T. L. Harshbarger, M. D'Apuzzo, J. A. Ressler, M. C. Jensen, M. E. Barish, M. Chen, J. Portnow, S. J. Forman, B. Badie, Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N. Engl. J. Med.* **375**, 2561–2569 (2016).
85. D. M. O'Rourke, M. P. Nasrallah, A. Desai, J. J. Melenhorst, K. Mansfield, J. J. D. Morrissette, M. Martinez-Lage, S. Brem, E. Maloney, A. Shen, R. Isaacs, S. Mohan, G. Plesa, S. F. Lacey, J.-M. Navenot, Z. Zheng, B. L. Levine, H. Okada, C. H. June, J. L. Brogdon, M. V. Maus, A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci. Transl. Med.* **9**, eaaa0984 (2017).
86. C. E. Brown, J. C. Hibbard, D. Alizadeh, M. S. Blanchard, H. M. Natri, D. Wang, J. R. Ostberg, B. Aguilar, J. R. Wagner, J. A. Paul, R. Starr, R. A. Wong, W. Chen, N. Shulkin, M. Aftabizadeh, A. Filippov, A. Chaudhry, J. A. Ressler, J. Kilpatrick, P. Myers-McNamara, M. Chen, L. D. Wang, R. C. Rockne, J. Georges, J. Portnow, M. E. Barish, M. D'Apuzzo, N. E. Banovich, S. J. Forman, B. Badie, Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: A phase 1 trial. *Nat. Med.* **30**, 1001–1012 (2024).
87. B. D. Choi, E. R. Gerstner, M. J. Frigault, M. B. Leick, C. W. Mount, L. Balaj, S. Nikiforow, B. S. Carter, W. T. Curry, K. Gallagher, M. V. Maus, Intraventricular CARv3-TEAM-E T cells in recurrent glioblastoma. *N. Engl. J. Med.* **390**, 1290–1298 (2024).
88. S. J. Bagley, M. Logun, J. A. Fraietta, X. Wang, A. S. Desai, L. J. Bagley, A. Nabavizadeh, D. Jarocha, R. Martins, E. Maloney, L. Lledo, C. Stein, A. Marshall, R. Leskowitz, J. K. Jadlowsky, S. Christensen, B. S. Oner, G. Plesa, A. Brennan, V. Gonzalez, F. Chen, Y. Sun, W. Gladney, D. Barrett, M. P. Nasrallah, W.-T. Hwang, G.-L. Ming, H. Song, D. L. Siegel, C. H. June, E. O. Hexner, Z. A. Binder, D. M. O'Rourke, Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: Phase 1 trial interim results. *Nat. Med.* **30**, 1320–1329 (2024).
89. D. B. Keskin, A. J. Anandappa, J. Sun, I. Tirosh, N. D. Mathewson, S. Li, G. Oliveira, A. Giobbie-Hurder, K. Felt, E. Gjini, S. A. Shukla, Z. Hu, L. Li, P. M. Le, R. L. Allesøe, A. R. Richman, M. S. Kowalczyk, S. Abdelrahman, J. E. Geduldig, S. Charbonneau, K. Pelton, J. B. Iorgulescu, L. Elagina, W. Zhang, O. Olive, C. McCluskey, L. R. Olsen, J. Stevens, W. J. Lane, A. M. Salazar, H. Daley, P. Y. Wen, E. A. Chiocca, M. Harden, N. J. Lennon, S. Gabriel, G. Getz, E. S. Lander, A. Regev, J. Ritz, D. Neuberg, S. J. Rodig, K. L. Ligon, M. L. Suvà, K. W. Wucherpfennig, N. Hacohen, E. F. Fritsch, K. J. Livak, P. A. Ott, C. J. Wu, D. A. Reardon, Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature* **565**, 234–239 (2019).
90. N. Hilf, S. Kuttruff-Coqui, K. Frenzel, V. Bukur, S. Stevanović, C. Gouttefangeas, M. Platten, G. Tabatabai, V. Dutoit, S. H. van der Burg, P. T. Straten, F. Martínez-Ricarte, B. Ponsati, H. Okada, U. Lassen, A. Admon, C. H. Ottensmeier, A. Ulges, S. Kreiter, A. von Deimling, M. Skardelly, D. Migliorini, J. R. Kroep, M. Idorn, J. Rodon, J. Piró, H. S. Poulsen, B. Shraibman, K. McCann, R. Mendrzyk, M. Löwer, M. Stieglbauer, C. M. Britten, D. Capper, M. J. P. Welters, J. Sahuquillo, K. Kiesel, E. Derhovanessian, E. Rusch, L. Bunse, C. Song, S. Heesch, C. Wagner, A. Kemmer-Brück, J. Ludwig, J. C. Castle, O. Schoor, A. D. Tadmor, E. Green, J. Fritsche, M. Meyer, N. Pawlowski, S. Dorner, F. Hoffgaard, B. Rössler, D. Maurer, T. Weinschenk, C. Reinhardt, C. Huber, H.-G. Rammensee, H. Singh-Jasuja, U. Sahin, P.-Y. Dietrich, W. Wick, Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature* **565**, 240–245 (2019).
91. F. F. Lang, C. Conrad, C. Gomez-Manzano, W. K. A. Yung, R. Sawaya, J. S. Weinberg, S. S. Prabhu, G. Rao, G. N. Fuller, K. D. Aldape, J. Gumin, L. M. Vence, I. Wistuba,

J. Rodriguez-Canales, P. A. Villalobos, C. M. F. Dirven, S. Tejada, R. D. Valle, M. M. Alonso, B. Ewald, J. J. Peterkin, F. Tufaro, J. Fueyo, Phase I study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: Replication and immunotherapeutic effects in recurrent malignant glioma. *J. Clin. Oncol.* **36**, 1419–1427 (2018).

92. A. Desjardins, M. Gromeier, J. E. Herndon, N. Beaubier, D. P. Bolognesi, A. H. Friedman, H. S. Friedman, F. McSherry, A. M. Muscat, S. Nair, K. B. Peters, D. Randazzo, J. H. Sampson, G. Vlahovic, W. T. Harrison, R. E. McLendon, D. Ashley, D. D. Bigner, Recurrent glioblastoma treated with recombinant poliovirus. *N. Engl. J. Med.* **379**, 150–161 (2018).
93. A. L. Ling, I. H. Solomon, A. M. Landivar, H. Nakashima, J. K. Woods, A. Santos, N. Masud, G. Fell, X. Mo, A. S. Yilmaz, J. Grant, A. Zhang, J. D. Bernstock, E. Torio, H. Ito, J. Liu, N. Shono, M. O. Nowicki, D. Triggs, P. Halloran, R. Piranlioglu, H. Soni, B. Stopa, W. L. Bi, P. Peruzzi, E. Chen, S. W. Malinowski, M. C. Prabhu, Y. Zeng, A. Carlisle, S. J. Rodig, P. Y. Wen, E. Q. Lee, L. Nayak, U. Chukwueke, L. N. Gonzalez Castro, S. D. Dumont, T. Batchelor, K. Kittelberger, E. Tikhonova, N. Miheecheva, D. Tabakov, N. Shin, A. Gorbacheva, A. Shumskiy, F. Frenkel, E. Aguilar-Cordova, L. K. Aguilar, D. Krisky, J. Wechuck, A. Manzanera, C. Matheny, P. P. Tak, F. Barone, D. Kovarsky, I. Tirosh, M. L. Suvà, K. W. Wucherpfennig, K. Ligon, D. A. Reardon, E. A. Chiocca, Clinical trial links oncolytic immunoactivation to survival in glioblastoma. *Nature* **623**, 157–166 (2023).
94. M. Meylan, Y. Tian, L. Wu, A. L. Ling, D. Kovarsky, G. L. Barlow, L. D. Nguyen, J. Pyrdol, S. Marx, L. Westphal, J. Michel, L. N. Gonzalez Castro, S. Dumont, A. Santos, I. Tirosh, M. L. Suvà, E. A. Chiocca, K. W. Wucherpfennig, Persistent T cell activation and cytotoxicity against glioblastoma following single oncolytic virus treatment in a clinical trial. *Cell* **189**, 1287–1304.e18 (2026).
95. F. Nassiri, V. Patil, L. S. Yefet, O. Singh, J. Liu, R. M. A. Dang, T. N. Yamaguchi, M. Daras, T. F. Cloughesy, H. Colman, P. U. Kumthekar, C. C. Chen, R. Aiken, M. D. Groves, S. S. Ong, R. Ramakrishna, M. A. Vogelbaum, S. Khagi, T. Kaley, J. M. Melear, D. M. Peereboom, A. Rodriguez, M. Yankelevich, S. G. Nair, V. K. Puduvalli, K. Aldape, A. Gao, Á. López-Janeiro, C. E. de Andrea, M. M. Alonso, P. Boutros, J. Robbins, W. P. Mason, A. M. Sonabend, R. Stupp, J. Fueyo, C. Gomez-Manzano, F. F. Lang, G. Zadeh, Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: A phase 1/2 trial. *Nat. Med.* **29**, 1370–1378 (2023).
96. F. Khan, L. Pang, M. Dunterman, M. S. Lesniak, A. B. Heimberger, P. Chen, Macrophages and microglia in glioblastoma: Heterogeneity, plasticity, and therapy. *J. Clin. Invest.* **133**, e163446 (2023).
97. P. Y. Wen, A. Stein, M. van den Bent, J. De Greve, A. Wick, F. Y. F. L. de Vos, N. von Bubnoff, M. E. van Linde, A. Lai, G. W. Prager, M. Campone, A. Fasolo, J. A. Lopez-Martin, T. M. Kim, W. P. Mason, R.-D. Hofheinz, J.-Y. Blay, D. C. Cho, A. Gazzah, D. Pouessel, J. Yachnin, A. Boran, P. Burgess, P. Ilankumaran, E. Gasal, V. Subbiah, Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): A multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol.* **23**, 53–64 (2022).
98. S. Thavaneswaran, H.-W. Sim, J. Grady, D. Espinoza, M. L. Huang, F. Lin, M. McGrath, J. Desai, M. Charakidis, M. Brown, M. Kansara, J. Simes, D. Thomas, A phase II trial of larotrectinib in tumors with NTRK fusions or extremes of NTRK mRNA overexpression identified by comprehensive genomic profiling. *Oncologist* **30**, oyae339 (2025).
99. V. Venkataramani, D. I. Tanev, C. Strahle, A. Studier-Fischer, L. Fankhauser, T. Kessler, C. Körber, M. Kardorff, M. Ratliff, R. Xie, H. Horstmann, M. Messer, S. P. Paik, J. Knabbe, F. Sahm, F. T. Kurz, A. A. Acikgöz, F. Herrmannsdörfer, A. Agarwal, D. E. Bergles, A. Chalmers, H. Miletic, S. Turcan, C. Mawrin, D. Hänggi, H.-K. Liu, W. Wick, F. Winkler, T. Kuner, Glutamatergic synaptic input to glioma cells drives brain tumour progression. *Nature* **573**, 532–538 (2019).
100. H. S. Venkatesh, W. Morishita, A. C. Geraghty, D. Silverbush, S. M. Gillespie, M. Arzt, L. T. Tam, C. Espenel, A. Ponnuswami, L. Ni, P. J. Woo, K. R. Taylor, A. Agarwal, A. Regev, D. Brang, H. Vogel, S. Hervey-Jumper, D. E. Bergles, M. L. Suvà, R. C. Malenka, M. Monje, Electrical and synaptic integration of glioma into neural circuits. *Nature* **573**, 539–545 (2019).
101. S. Heuer, I. Burghaus, M. Gose, T. Kessler, F. Sahm, P. Vollmuth, V. Venkataramani, D. Hoffmann, M. Schlesner, M. Ratliff, C. Hopf, U. Herrlinger, F. Ricklefs, M. Bendszus, S. M. Krieg, A. Wick, W. Wick, F. Winkler, PerSurge (NOA-30) phase II trial of perampanel treatment around surgery in patients with progressive glioblastoma. *BMC Cancer* **24**, 135 (2024).
102. S. Lee, T. Weiss, M. Bühler, J. Mena, Z. Lottenbach, R. Wegmann, M. Sun, M. Bihl, B. Augustynek, S. P. Baumann, S. Goetze, A. van Drogen, P. G. A. Pedrioli, D. Penton, Y. Festl, A. Buck, D. Kirschenbaum, A. M. Zeitlberger, M. C. Neidert, F. Vasella, E. J. Rushing, B. Wollscheid, M. A. Hediger, M. Weller, B. Snijder, High-throughput identification of repurposable neuroactive drugs with potent anti-glioblastoma activity. *Nat. Med.* **30**, 3196–3208 (2024).
103. J. D. Bernstock, M. Mehari, J. V. E. Gerstl, D. M. Meredith, P. A. Valdes, P. Heesen, V. S. Ambati, S. Krishna, J. A. Chen, H. Arora, B. R. Johnston, M. Negussie, K. Grieco, C. Nava Gonzales, A. Dada, A. B. Lebouille-Veldman, A. Kabir, L. Spanehl, J. Kaur, S. Oten, Y. E. Sibih, R. A. Mekary, A. Daniel, J. F. de Groot, S. Izzy, F. A. Gessler, S. Stone, O. Arnaout, Y. Lu, B. D. Choi, M. D. Hall, M. P. Mehta, Y. Odia, G. K. Friedman, E. A. Chiocca, P. P. Peruzzi, T. R. Smith, S. L. Hervey-Jumper, Gabapentinoids confer survival benefit in human glioblastoma. *Nat. Commun.* **16**, 4483 (2025).
104. C. Faust Akl, B. M. Andersen, Z. Li, F. Giovannoni, M. Diebold, L. M. Sanmarco, M. Kilian, L. Fehrenbacher, F. Pernin, J. M. Rone, H.-G. Lee, G. Piester, J. E. Kenison, J.-H. Lee, T. Illouz, C. M. Polonio, L. Srun, J. Martinez, E. N. Chung, A. Schüle, A. Plasencia, L. Li, K. Ferrara, M. Lewandrowski, C. A. Strathdee, L. Lerner, C. Quéva, I. C. Clark, B. Deneen, J. Lieberman, D. H. Sherr, J. P. Antel, M. A. Wheeler, K. L. Ligon, E. A. Chiocca, M. Prinz, D. A. Reardon, F. J. Quintana, Glioblastoma-instructed astrocytes suppress tumour-specific T cell immunity. *Nature* **643**, 219–229 (2025).
105. B. M. Alexander, S. Ba, M. S. Berger, D. A. Berry, W. K. Cavenee, S. M. Chang, T. F. Cloughesy, T. Jiang, M. Khasraw, W. Li, R. Mittman, G. H. Poste, P. Y. Wen, W. K. A. Yung, A. D. Barker, GBM AGILE Network, Adaptive global innovative learning environment for glioblastoma: GBM AGILE. *Clin. Cancer Res.* **24**, 737–743 (2018).
106. P. Wen, B. Alexander, D. Berry, M. Buxton, W. Cavenee, H. Colman, J. de Groot, B. Ellingson, G. Gordon, E. Hyddmark, M. Khasraw, M. Lim, I. Mellinghoff, T. Mikkelsen, J. Perry, A. Powell, E. Sulman, K. Tanner, M. Weller, W. K. A. Yung, N. Blondin, A. Brenner, O. Butt, M. de la Fuente, J. Drappatz, F. Iwamoto, L. Kim, E. Lee, M. Mantica, B. Nabors, H. Newton, D. Schiff, T. Walbert, S.-P. Weathers, T. Cloughesy, A. Lassman, CTNI-85. GBM agile platform trial for newly diagnosed and recurrent GBM: Results of first experimental arm, regorafenib. *Neuro. Oncol.* **25**, v97–v98 (2023).
107. E. Chen, A. L. Ling, D. A. Reardon, E. A. Chiocca, Lessons learned from phase 3 trials of immunotherapy for glioblastoma: Time for longitudinal sampling? *Neuro Oncol.* **26**, 211–225 (2024).
108. A. L. Ling, J. Gantchev, M. C. Prabhu, S. Basu, R. Ahn, A. D'Souza, N. Masud, A. Ball, O. Nikas, G. R. Villa, M. S. Regan, G. Baquer, G. Ayoub, C. A. Whittaker, Z. Abou-Mrad, A. Santos, C. P. Couturier, D. Elharouni, J. Vogelzang, K. K. H. Yu, H. Chen, Z. He, W. Jiang, C. H. Lucas, H. E. Sax, F. F. Lang, V. K. Puduvalli, V. Tabar, C. W. Brennan, A. Boire, M. Holdhoff, C. Bettegowda, M. Cima, I. H. Solomon, Y. Yuan, P. P. Tak, Accelerating GBM Therapies TeamLab, P. Sharma, F. M. White, K. L. Ligon, N. Y. R. Agar, D. A. Reardon, G. Oliveira, E. A. Chiocca, Serial multiomics uncovers anti-glioblastoma responses not evident by routine clinical analyses. *Sci. Transl. Med.* **17**, eadv2881 (2025).
109. T. F. Cloughesy, A. Y. Mochizuki, J. R. Orpilla, W. Hugo, A. H. Lee, T. B. Davidson, A. C. Wang, B. M. Ellingson, J. A. Rytlewski, C. M. Sanders, E. S. Kawaguchi, L. Du, G. Li, W. H. Yong, S. C. Gaffey, A. L. Cohen, I. K. Mellinghoff, E. Q. Lee, D. A. Reardon, B. J. O'Brien, N. A. Butowski, P. L. Nghiemphu, J. L. Clarke, I. C. Arrillaga-Romany, H. Colman, T. J. Kaley, J. F. de Groot, L. M. Liau, P. Y. Wen, R. M. Prins, Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat. Med.* **25**, 477–486 (2019).
110. K. A. Schalper, M. E. Rodriguez-Ruiz, R. Diez-Valle, A. López-Janeiro, A. Porciuncula, M. A. Idoate, S. Inogés, C. de Andrea, A. López-Diaz de Cerio, S. Tejada, P. Berraondo, F. Villarroel-Espindola, J. Choi, A. Gúrpide, M. Giraldez, I. Goicoechea, J. Gallego Perez-Larraya, M. F. Sanmamed, J. L. Perez-Gracia, I. Melero, Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. *Nat. Med.* **25**, 470–476 (2019).
111. J. R. McFaline-Figueroa, L. Sun, G. C. Youssef, R. Huang, G. Li, J. Kim, E. Q. Lee, L. Nayak, U. Chukwueke, R. Beroukhim, T. T. Batchelor, E. A. Chiocca, R. G. Everson, L. Doherty, J. Stefanik, K. Partridge, A. Spearman, A. Myers, C. Westergaard, A. Russ, M. Lavallee, A. Smokovich, C. LaForest-Roys, R. Garcia Fox, C. McCluskey, W. L. Bi, O. Arnaout, P. Peruzzi, G. R. Cosgrove, K. L. Ligon, I. Arrillaga-Romany, J. L. Clarke, D. A. Reardon, T. F. Cloughesy, R. M. Prins, P. Y. Wen, Neoadjuvant anti-PD1 immunotherapy for surgically accessible recurrent glioblastoma: Clinical and molecular outcomes of a stage 2 single-arm expansion cohort. *Nat. Commun.* **15**, 10757 (2024).
112. C. J. Lord, A. Ashworth, PARP inhibitors: The first synthetic lethal targeted therapy. *Science* **355**, 1152–1158 (2017).
113. N. Sanai, Y. Umemura, T. Margaryan, J. Molloy, H. Zhang, W. Knight, J. Harmon, A. Hong, J. Wanebo, K. Braun, W. Kennedy, M. Garcia, I. Barani, W. Yoo, A. Tien, A. Tovmasyan, S. Mehta, P18.31.A niraparib efficacy in patients with newly-diagnosed glioblastoma: Clinical readout of a phase 0/2 'TRIGGER' trial. *Neuro Oncol.* **26**, v104 (2024).
114. J. N. Sarkaria, K. V. Ballman, S. H. Kizilbash, E. P. Sulman, C. Giannini, B. B. Friday, N. A. Butowski, N. A. Mohile, D. E. Piccioni, J. D. Battiste, J. Drappatz, J. L. Campian, S. Mashru, K. A. Jaeckle, B. J. O'Brien, J. G. Dixon, B. F. Kabat, N. L. Laack, L. S. Hu, T. Kaufmann, P. Kumthekar, B. M. Ellingson, S. K. Anderson, E. Galanis, Efficacy of adding veliparib to temozolomide for patients with MGMT-methylated glioblastoma: A randomized clinical trial. *JAMA Oncol.* **10**, 1637–1644 (2024).
115. P. Wen, J. T. Yang, B. S. Imber, J. Drappatz, R. Jena, D. Forst, A. Zukas, S. C. Short, C. Fan, W. Trigg, A. Milner, U. M. Polanska, C. Glover, C. Stavraka, D. Dalal, D. Karanovic, A. J. Chalmers, CTIM-16. Safety and preliminary efficacy of AZD1390 + radiation therapy for glioblastoma. *Neuro Oncol.* **26**, viii88 (2024).
116. A.-C. Tien, J. Li, X. Bao, A. Derogatis, S. Kim, S. Mehta, N. Sanai, A phase 0 trial of ribociclib in recurrent glioblastoma patients incorporating a tumor pharmacodynamic- and pharmacokinetic-guided expansion cohort. *Clin. Cancer Res.* **25**, 5777–5786 (2019).

117. A. B. Lassman, M. J. van den Bent, H. K. Gan, D. A. Reardon, P. Kumthekar, N. Butowski, Z. Lwin, T. Mikkelsen, L. B. Nabors, K. P. Papadopoulos, M. Penas-Prado, J. Simes, H. Wheeler, T. Walbert, A. M. Scott, E. Gomez, H.-J. Lee, L. Roberts-Rapp, H. Xiong, P. J. Ansell, E. Bain, K. D. Holen, D. Maag, R. Merrell, Safety and efficacy of depatuxizumab mafodotin + temozolomide in patients with EGFR-amplified, recurrent glioblastoma: Results from an international phase I multicenter trial. *Neuro Oncol.* **21**, 106–114 (2019).
118. M. Van Den Bent, M. Eoli, J. M. Sepulveda, M. Smits, A. Walenkamp, J.-S. Frenel, E. Franceschi, P. M. Clement, O. Chinot, F. De Vos, N. Whenham, P. Sanghera, M. Weller, H. J. Dubbink, P. French, J. Looman, J. Dey, S. Krause, P. Ansell, S. Nuyens, M. Spruyt, J. Brilhante, C. Coens, T. Gorlia, V. Golfinopoulos, INTELLANCE 2/EORTC 1410 randomized phase II study of Depatux-M alone and with temozolomide vs temozolomide or lomustine in recurrent EGFR amplified glioblastoma. *Neuro Oncol.* **22**, 684–693 (2020).
119. A. B. Lassman, J. M. Sepúlveda-Sánchez, T. F. Cloughesy, M. J. Gil-Gil, V. K. Puduvalli, J. J. Raizer, F. Y. F. De Vos, P. Y. Wen, N. A. Butowski, P. M. J. Clement, M. D. Groves, C. Belda-Iniesta, P. Giglio, H. S. Soifer, S. Rowsey, C. Xu, F. Avogadri, G. Wei, S. Moran, P. Roth, Infigratinib in patients with recurrent gliomas and FGFR alterations: A multicenter phase II study. *Clin. Cancer Res.* **28**, 2270–2277 (2022).
120. G. R. Harsh, T. S. Deisboeck, D. N. Louis, J. Hilton, M. Colvin, J. S. Silver, N. H. Qureshi, J. Kracher, D. Finkelstein, E. A. Chiocca, F. H. Hochberg, Thymidine kinase activation of ganciclovir in recurrent malignant gliomas: A gene-marking and neuropathological study. *J. Neurosurg.* **92**, 804–811 (2000).
121. S. Jiang, C. Zhong, Glioma drug development benefits from emerging phase 0 and window-of-opportunity trial paradigm. *Cell Commun. Signal* **23**, 399 (2025).
122. M. A. Vogelbaum, D. Krivosheya, H. Borghei-Razavi, N. Sanai, M. Weller, W. Wick, R. Soffietti, D. A. Reardon, M. K. Aghi, E. Galanis, P. Y. Wen, M. van den Bent, S. Chang, Phase 0 and window of opportunity clinical trial design in neuro-oncology: A RANO review. *Neuro Oncol.* **22**, 1568–1579 (2020).

Acknowledgments
Funding: E.A.C. is supported by grants from the National Institute of Neurological Disorders and Stroke (R01 NS134723-01A1) and the National Cancer Institute (P01 CA236749 and P01 CA163205). D.A.R. receives research support (paid to Dana-Farber Cancer Institute) from Agenus Inc., Ashvattha Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Corbus Pharma, EMD Serono, Enterome, Invios, Medicenna Therapeutics, Mogling Bio, NeoTx Ltd., Numiera Therapeutics, Sapience Therapeutics, SphereBio, and Vaccinex. **Author contributions:** G.R.V., A.D.P., D.A.R., and E.A.C. contributed to the conceptual development and design of the manuscript. G.R.V. and A.D.P. wrote the original manuscript draft and performed literature synthesis. G.R.V., A.D.P., D.A.R., and E.A.C. contributed to manuscript revision, interpretation of the literature, and critical revision of the intellectual content. All authors reviewed and approved the final manuscript. **Competing interests:** E.A.C. is currently an adviser to Bionaut Labs, Seneca Therapeutics, and Reignite Therapeutics. He has equity options in Bionaut Laboratories, Seneca Therapeutics, Ternalys Therapeutics, and RElgnite Therapeutics. He is cofounder and on the board of directors of Ternalys Therapeutics. He receives research support from NIH and Alliance for Cancer Gene Therapy. He also is a named inventor on patents related to oncolytic HSV1 and noncoding RNAs, owned by Mass General Brigham who has licensed these to third parties. He also provides or has provided (in the past 3 years) unpaid scientific and clinical advice to Amacathera, Alpheus Medical, Bio TTT, Brave Bio, Calidi Biotherapeutics, Candel Therapeutics, Carthera Sonocloud, Diakonos, Genenta, Iconovir, Incephalo Therapeutics, Insightec Inc., Lumicell, Ovie Therapeutics, Rocket Science, RZnomics, and Targtex. He is a named inventor on patents related to oncolytic HSV1, including patents owned by Brigham and Women's Hospital on CAN-3110 and other oHSV technologies that are now licensed to Candel Therapeutics Inc. (patent no. US10,806,761 B2, date: 20 October 2020; patent no. 6,897,057, date 24 May 2005; patent no. 7,214,515, date: 4 January 2002) that provides milestone and royalty payments to BWH. D.A.R. consults for or is part of the advisory boards of AnHeart Pharmaceuticals, BlueRock Therapeutics LP, CeCaVaGmbH & Co.KG, Chimeric Therapeutics, Enterome, Genenta Sciences, Jupiter Life Sciences Consulting LLC, Kintara, Miltenyi Biomedicine GmbH, Neuvogen, Servier, WebMD, Paradigm Medical Communications, and Putnam Inizii Associates LLC; is on the data safety monitoring boards of ImVax and CeCaVaGmbH; and holds stock in AnHeart Therapeutics and Bionaut Labs.

Submitted 2 March 2026
Accepted 24 June 2026
Published 29 July 2026
10.1126/scitranslmed.aeg8772

Science Translational Medicine

Glioblastoma: Overcoming fundamental biological and delivery barriers to therapy

Genaro R. Villa, Ashish D. Patel, David A. Reardon, and E. Antonio Chiocca

Sci. Transl. Med. **18** (860), eaeg8772. DOI: 10.1126/scitranslmed.aeg8772

Science Translational Medicine (ISSN 1946-6242) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science Translational Medicine* is a registered trademark of AAAS.