

Emerging pharmacological agents for glioblastoma multiforme: An update on active clinical trials (2025–2026)

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive primary brain tumour in adults, with a median overall survival of approximately 15 months despite maximal safe resection, radiotherapy, and temozolomide as defined by the Stupp protocol. The persistence of this poor prognosis has driven an unprecedented wave of investigational drug development now entering pivotal clinical evaluation. This narrative review synthesises agents in active clinical trials during 2025–2026, grouped into four mechanism-defined domains. First, molecular-targeted agents include central nervous system-penetrant EGFR antibody-drug conjugates such as ABBV-155, the CDK4/6 inhibitor abemaciclib, the multikinase inhibitor regorafenib evaluated in the REGOMA programme, and emerging RAS/MAPK and BRAF pathway inhibitors. Second, immunotherapeutic strategies span autologous dendritic cell vaccines (DCVax-L, DOC1021), nucleic acid vaccines (INO-5401/INO-9012 with cemiplimab), and adoptive cell therapies including bivalent EGFR/IL-13Rα2 CAR T-cells and engineered tumour-infiltrating lymphocytes. The third category of oncolytic and gene-therapy platforms includes retroviral replicating vectors (DB107-RRV/DB107-FC) and tumour-selective transgene delivery systems. The fourth group of agents targets cancer metabolism and microenvironment through their effects on mitochondrial bioenergetics and fatty acid synthase and tumour hypoxia. The medical field now requires patient screening through IDH mutation testing and MGMT promoter methylation and EGFR amplification to achieve successful treatment results. Forthcoming Phase II/III data will clarify which platforms merit regulatory prioritisation. Key limitations of current trials include heterogeneous endpoints, limited blood-brain barrier penetration of many agents, and the persistent immunosuppressive tumour microenvironment that constrains immunotherapy response.

INTRODUCTION

Glioblastoma multiforme (GBM; WHO Grade IV diffuse glioma) represents approximately 48% of all primary malignant intracranial tumors and confers five-year survival rates below 10% [1]. Since 2005, the Stupp protocol, comprising maximal safe surgical resection followed by concurrent radiotherapy with temozolomide and subsequent adjuvant temozolomide, has remained

the uncontested standard of care, with few meaningful advances challenging this paradigm in the two intervening decades [2]. Patients who receive multimodal treatment experience disease return at a high rate because their overall survival remains below expectations during their initial and subsequent GBM diagnosis stages [3].

The current therapeutic deadlock exists because three fundamental biological obstacles prevent progress: (i) The tumor shows extreme internal diversity

because glioblastoma stem-like cells and evolving cancer clones create complex patterns; (ii) The tumor microenvironment contains strong immunosuppressive conditions because of tumor-associated macrophages, myeloid-derived suppressor cells and regulatory T cells; and (iii) The blood-brain barrier limits systemic drug levels to maintain therapeutic concentrations which become available at the tumor location [4]. GBM tumors experience hypoxia which activates HIF-1 α signaling to create multiple obstacles through its effects on mesenchymal transformation and blood vessel formation and therapeutic resistance to radiation and standard cancer treatments [5].

These persistent barriers have nonetheless spurred an unprecedented wave of investigational drug development spanning molecular targeting, cancer immunology, oncolytic virology, gene therapy, and metabolic oncology [6]. The present perspective provides a concise, mechanism-oriented synthesis of the most clinically significant agents currently undergoing active evaluation in GBM clinical trials during 2025–2026, with emphasis on post-2020 evidence and biomarker-guided patient selection.

MOLECULAR-TARGETED AGENTS

EGFR-targeting combinations

Epidermal growth factor receptor (EGFR) amplification or mutation, most commonly the truncated EGFRvIII variant - occurs in approximately 57% of GBM cases and constitutes one of the most recurrent oncogenic drivers in this disease [7]. Single-agent treatments with first- and second-generation EGFR inhibitors have failed to show effective results in unselected patients because of multiple resistance mechanisms and poor brain penetration of these drugs. The present clinical trial network conducts studies on ABBV-155 with KTM-101 by using a window-based research method to treat patients who experience GBM relapse. ABBV-155 (mirzotamab clezutoclast) is a first-in-class antibody-drug conjugate targeting the cell-surface antigen B7-H3 (CD276) and delivering a selective BCL-XL inhibitor payload, thereby overcoming the anti-apoptotic block that limits cytotoxic chemotherapy and radiation in GBM. KTM-101 concurrently targets complementary resistance escape pathways. The window-of-opportunity design allows pharmacodynamic tumor sampling between study drug administration and surgical resection, enabling direct assessment of target engagement within the tumor parenchyma.

CDK4/6 inhibitors

Loss of the CDKN2A/RB axis, occurring in the vast majority of IDH-wild-type GBM tumors, renders cyclin-dependent kinase (CDK) 4/6-mediated cell cycle progression a mechanistically compelling target. The

third-generation CDK4/6 inhibitor abemaciclib which received breast cancer approval demonstrates superior brain penetration compared to its predecessor drugs. Research data from animal studies together with initial human pharmacokinetic studies demonstrated that abemaciclib achieves brain tumor tissue concentrations to match plasma levels better than palbociclib does [8]. In GBM, abemaciclib is being investigated in combination with the ERK inhibitor LY3214996 (NCT04391595) in a Phase 0/II window-of-opportunity and expansion cohort design at the Ivy Brain Tumor Center. The dual-kinase approach targets the G₁/S checkpoint to prevent cell cycle progression and blocks ERK from activating the RAS-MAPK pathway through phosphorylation which causes resistance to CDK4/6 inhibitors when used alone. The INSIGHT adaptive platform trial (NCT02977780) which Dana-Farber Cancer Institute leads includes an abemaciclib treatment group for patients who received their MGMT-unmethylated GBM diagnosis. The first findings indicate that abemaciclib treatment produces longer progression-free survival than the standard control arm.

RAS/MAPK-pathway inhibitors

Aberrant RAS/MAPK signaling represents a convergent oncogenic node in GBM, participating in proliferation, invasion, and resistance to both targeted therapies and immunotherapy [4]. The small-molecule modulators MB-101, JIN-001, and CT-179 are advancing through Phase I evaluation as CNS-penetrant agents targeting oncogenic RAS signaling. A key prerequisite for clinical activity in GBM is demonstrable BBB permeability, and each of these agents has demonstrated favorable CNS exposure in preclinical pharmacokinetic models. Tumor molecular profiling for KRAS, NRAS, and BRAF alterations is being integrated as an enrollment biomarker in several of these trials.

BRAF pathway inhibitors

BRAF activating alterations occur in a small but clinically actionable subset of GBM, with somatic BRAF V600E mutations identified in approximately 1–2% of adult GBM and at higher frequency (5–15%) in epithelioid glioblastoma and paediatric high-grade glioma. KRAS and NRAS hotspot mutations are uncommon in adult IDH-wildtype GBM, but RAS/MAPK pathway activation by other mechanisms (NF1 loss, receptor tyrosine kinase amplification) is recurrent. The selective BRAF V600 inhibitor vemurafenib has been evaluated in BRAF-mutant gliomas, with case-series and early-phase trial evidence demonstrating radiographic responses in BRAF V600E-mutant high-grade glioma [9]; combination BRAF/MEK inhibition with dabrafenib plus trametinib has subsequently demonstrated clinically meaningful activity in the ROAR phase 2 basket trial of BRAF V600E-mutant

high-grade glioma [10] and is being further evaluated in ongoing basket and umbrella protocols, including NCI-MATCH and several investigator-initiated GBM-specific cohorts. Routine BRAF V600E testing is therefore recommended in molecular diagnostic workflows for newly diagnosed GBM to identify candidates for genotype-directed therapy.

Multikinase inhibitors: Regorafenib

Tyrosine kinase inhibitors targeting angiogenic and proliferative pathways have emerged as a clinically relevant class in recurrent GBM. Regorafenib, an oral multikinase inhibitor of VEGFR1-3, TIE2, PDGFR, FGFR and several intracellular kinases, was evaluated against lomustine in the REGOMA trial, an Italian multicentre, open-label, randomised Phase 2 study in patients with relapsed GBM [11]. Regorafenib improved median overall survival (7.4 vs. 5.6 months; hazard ratio 0.50, 95% CI 0.33–0.75; $P = 0.0009$) at the cost of increased grade 3–4 adverse events, establishing it as a referenced second-line option. Subsequent trials, including REGOMA-OSS and confirmatory European cohorts coordinated by national neuro-oncology groups, have continued to refine the role of regorafenib and explore biomarker enrichment.

IDH1/2 inhibitors

Although IDH-mutant astrocytomas were reclassified as a separate entity from IDH-wildtype glioblastoma in the WHO 2021 CNS tumour classification, the IDH-mutant astrocytoma CNS WHO grade 4 subgroup retains historical overlap with the GBM literature and is an active focus of targeted drug development. The oral IDH1 inhibitor ivosidenib and the dual IDH1/2 inhibitor vorasidenib have demonstrated activity in IDH-mutant glioma. The INDIGO Phase 3 trial demonstrated that vorasidenib improved progression-free survival and decreased tumor expansion in patients with residual or recurrent grade 2 IDH-mutant glioma [12]. The current studies investigate these drugs for treatment of advanced IDH-mutant astrocytoma which includes the WHO grade 4 subset of IDH-mutant CNS tumors. Their inclusion reinforces the WHO 2021 emphasis on molecularly defined patient selection.

Nationally coordinated trial networks

Several national neuro-oncology consortia coordinate investigator-initiated GBM trials that complement industry-sponsored programmes. In Germany, the Neuroonkologische Arbeitsgemeinschaft (NOA) of the German Cancer Society leads multicentre trials including studies of bevacizumab, lomustine combinations, immunotherapy and reirradiation strategies, with patient enrolment across academic centres. Comparable networks

include the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group, the Adult Brain Tumor Consortium (ABTC) in the United States, and the Canadian Brain Tumour Consortium. These networks provide essential infrastructure for evaluating agents with limited commercial sponsorship and for biomarker-stratified randomised trials in defined molecular subgroups.

IMMUNOTHERAPIES AND THERAPEUTIC VACCINES

Dendritic cell vaccines

Immunotherapeutic strategies in GBM must contend with a distinctive central nervous system immune environment and a profoundly immunosuppressive tumour microenvironment that have constrained progress to date [13]. Dendritic cell (DC)-based vaccination represents one of the most mature active immunotherapy approaches in GBM. The strategy involves *ex-vivo* loading of patient-derived antigen-presenting cells with autologous tumor lysate or defined tumor-associated peptides, followed by intradermal or intranodal reinfusion to elicit antigen-specific cytotoxic T-lymphocyte responses [14]. DCVax-L, the most clinically advanced DC platform, completed a Phase 3 prospective externally controlled cohort trial enrolling 331 patients with newly diagnosed or recurrent GBM [15]. With approximately 90% of the intent-to-treat population ultimately receiving DCVax-L under the crossover design, median OS from randomization was 19.3 months in the DCVax-L group versus 16.5 months in the external control population (HR 0.80; 98% CI 0.00–0.94; $P = 0.002$). Patients with methylated MGMT promoter derived the greatest benefit, achieving a median OS of 30.2 months from randomization (approximately 33 months from surgery), with substantially improved long-term survival relative to the matched external control [15]. An updated meta-analysis incorporating the DCVax-L Phase 3 data confirmed an OS benefit associated with DC vaccination across GBM trials and determined that the required sample size threshold for a definitive conclusion had been reached by trial sequential analysis [14]. The second-generation platform DOC1021 follows a similar immunological rationale and is currently in ongoing evaluation.

Beyond DCVax-L, the broader DC vaccination landscape includes oncolytic virus-pulsed DC platforms and combination strategies. Van Gool and colleagues have reviewed multiphase combined treatment paradigms in which DC vaccines are integrated with Newcastle disease virus or other oncolytic viral preparations to enhance antigen presentation, prime cytotoxic T-cell responses, and modulate the immunosuppressive tumour microenvironment in GBM patients [16, 17].

Compassionate-use and individual-patient experiences with this paradigm have reported prolonged survival in selected GBM cases and have informed the design of subsequent prospective evaluations. Critical methodological considerations for DC vaccine trials include standardisation of antigen-loading protocols, validation of DC maturation markers, route of administration (intradermal vs. intranodal), schedule optimisation, and integration with checkpoint blockade or radiation to overcome local immunosuppression. The choice of antigen source, autologous tumour lysate versus defined tumour-associated peptides versus neoantigen-directed pulsing, remains a central design variable that influences both immunogenicity and feasibility in multicentre settings.

mRNA and plasmid DNA vaccine platforms

Nucleic acid vaccines deliver mRNA or plasmid DNA encoding tumour-associated antigens directly to antigen-presenting cells, where the encoded protein is expressed, processed and presented on MHC class I and II to prime CD8⁺ cytotoxic and CD4⁺ helper T-cell responses. In GBM, candidate epitopes include tumour-restricted antigens (EGFRvIII), cancer-testis antigens, telomerase reverse transcriptase (hTERT), Wilms tumour 1 (WT-1), prostate-specific membrane antigen (PSMA, expressed on tumour vasculature), and patient-specific neoantigens identified by tumour exome sequencing. The immunological rationale is to generate polyclonal T-cell responses against multiple antigens simultaneously, mitigating antigen-loss escape and exploiting the modest but real neoantigen burden present in GBM despite its lower mutational load than many other adult solid tumours. *In vivo* electroporation enhances plasmid DNA uptake and increases the magnitude and durability of vaccine-induced responses, while lipid nanoparticle-formulated mRNA platforms enable rapid manufacturing of personalised neoantigen vaccines on clinically actionable timescales.

Nucleic acid vaccine platforms have gained significant momentum following their clinical validation in infectious disease, and several GBM-directed programs are now in active clinical evaluation. The plasmid DNA-based combination INO-5401/INO-9012, encoding shared GBM-associated antigens (hTERT, WT-1, PSMA) delivered by electroporation, is under Phase I/II assessment in combination with the PD-1 checkpoint inhibitor cemiplimab for newly diagnosed GBM. This platform exploits synthetic antigen delivery to prime durable CD8⁺ cytotoxic T lymphocyte responses against multiple tumor antigens simultaneously, theoretically mitigating antigen-loss escape that has undermined single-target approaches [18]. The concurrent PD-1 blockade is intended to overcome the chronic T-cell exhaustion phenotype that prevails within the GBM

TME and is mechanistically consistent with preclinical data demonstrating that checkpoint inhibition augments vaccine-primed anti-tumor immunity [18].

CAR T-cell and tumor-infiltrating lymphocyte therapies

Adoptive cellular therapy together with chimeric antigen receptor (CAR) T-cell therapy has become the leading clinical interest in GBM immunotherapy since the last three years. The active evaluation of CAR targets includes multiple antigens which consist of EGFRvIII (found in about 30% of primary GBM cases), IL-13R α 2 and GD2 and HER2 which show different expression patterns in various GBM subtypes [19]. All CAR T-cell programs for GBM encounter their primary obstacle because tumor cells reduce their target antigen expression which drives the development of bivalent and multivalent CAR construct approaches. The Nature Medicine (2025) published a groundbreaking Phase 1 clinical trial which studied ICV administration of bivalent CAR T-cells that targeted EGFR (epitope 806) and IL-13R α 2 (CART-EGFR-IL13R α 2) in patients with EGFR-amplified, multifocal recurrent GBM [19, 20]. ICV administration was feasible and well tolerated; the maximum tolerated dose was identified, with one patient achieving a partial radiographic response and one patient demonstrating durable stable disease. The Phase I clinical trials now test engineered TILs which produce anti-PD-1 antibodies inside tumors to create a self-sufficient checkpoint blockade system through adoptive cell transfer [19].

Beyond bivalent CAR T-cells, several additional adoptive cell therapy approaches are advancing in GBM. Trivalent and tandem CAR constructs targeting EGFRvIII, IL-13R α 2, and HER2 simultaneously are designed to overcome antigen heterogeneity and antigen-loss relapse. Armoured CAR T-cells engineered to secrete cytokines such as IL-7, IL-15 or IL-18 within the tumour aim to sustain T-cell proliferation in the hostile GBM microenvironment. Tumour-infiltrating lymphocyte (TIL) therapy, established as a registered treatment in metastatic melanoma, is being adapted for GBM with autologous TIL expansion from resected tumour combined with checkpoint inhibition and lymphodepleting conditioning. Key translational challenges include preventing cytokine release syndrome and immune effector cell-associated neurotoxicity in the constrained intracranial compartment, optimising delivery route (intraventricular vs. intratumoural vs. systemic), and combining cell therapy with measures to reverse the immunosuppressive myeloid-cell infiltrate that dominates the GBM microenvironment. The chronic T-cell exhaustion characteristic of GBM-infiltrating lymphocytes additionally motivates combination with checkpoint blockade and metabolic modulators.

ONCOLYTIC VIRUSES AND GENE THERAPIES

Retroviral replicating vector platforms

Oncolytic viral therapy uses viruses which multiply preferentially in cancer cells to produce selective cell death while releasing tumor-associated antigens and damage-associated molecular patterns which trigger both innate and adaptive immune responses against tumors [8]. The upcoming retroviral replicating vector (RRV) platforms named DB107-RRV and DB107-FC were created to replace the previous Toca 511/Toca FC program [21]. The agents contain cytosine deaminase (CD) which functions as a prodrug activating enzyme to transform 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU) inside tumors which produces targeted toxicity against tumor cells that are dividing while protecting brain tissue that is not actively growing [22]. The RRV method enables continuous viral reproduction which spreads through tumors before prodrug activation thus creating immune stimulation within the tumor environment. The current research phase for DB107-RRV and DB107-FC involves Phase I/II trials which test these treatments together with standard chemoradiation for patients with newly discovered high-grade glioma.

Selective gene therapy: Trogenix program

Trogenix Ltd. has developed a new gene-therapy system which combines tumor-specific oncolytic virus action with transgene delivery to activate immune responses. The program uses a transcription-based method to activate therapeutic genes only in GBM cells by using tumor-specific regulatory elements which enable the treatment to kill cancer cells while generating pro-inflammatory signals to break down the immunosuppressive tumor microenvironment [8]. The treatment works through two different biological pathways which overcome the weak performance of cytolytic therapies because they fail to treat GBM effectively due to its non-responsive immune microenvironment. The first human patient will receive this treatment during the first part of 2026.

METABOLIC AND TUMOR MICROENVIRONMENT-TARGETING AGENTS

GBM cells experience significant metabolic changes including their transition to aerobic glycolysis (Warburg effect), their increased ability to produce lipids, their rising need for glutamine and their modified acetate metabolism [5]. The increased activity of HIF-1 α -driven glycolytic genes produces negative clinical results in GBM patient groups, making their metabolic system a target for medical

treatment [5]. BPM31510 is a ubidecarenone (CoQ10)-based formulation targeting mitochondrial bioenergetics and redox homeostasis; by disrupting the metabolic flexibility that allows GBM cells to switch between oxidative phosphorylation and glycolysis under varying microenvironmental conditions, it aims to narrow tumor survival options. ASC40 is a selective oral inhibitor of fatty acid synthase (FASN), a rate-limiting enzyme of *de novo* lipid synthesis that is overexpressed in GBM, associated with tumor growth and resistance to alkylating chemotherapy [23]. Both agents are under Phase I/II evaluation as monotherapy and in combination with temozolomide.

OTHER NOTABLE PIPELINE AGENTS

Several mechanistically distinct agents are advancing through early-phase GBM trials and are summarized alongside all discussed agents in Table 1. Enzastaurin, an oral protein kinase C β (PKC β)/PI3K-pathway inhibitor, suppresses intracellular survival and proliferative signaling and is under evaluation with biomarker-enrichment in patients with DGM1 genetic alterations who may derive preferential benefit [24]. Asunercept (APG101), a CD95L (FasL) inhibitor, disrupts an apoptosis-resistance mechanism exploited by GBM cells that overexpress CD95L to evade immune surveillance. Azeliragon targets the receptor for advanced glycation end-products (RAGE), which mediates inflammatory signaling in the TME. Marizomib, a pan-proteasome inhibitor derived from a marine microorganism, uniquely crosses the BBB, distinguishing it from bortezomib and carfilzomib, which are excluded from the CNS [24]. Despite promising Phase I safety data, the EORTC 26122 Phase II/III trial of marizomib in newly diagnosed GBM did not meet its primary endpoint for OS, underscoring the persistent translational challenge in this disease. Berubicin, the first anthracycline analog demonstrated to cross the BBB, exploits intercalation into double-stranded DNA as its primary cytotoxic mechanism and is in Phase II evaluation for recurrent GBM [24].

DISCUSSION

The GBM treatment environment of 2025–2026 will experience a complete transformation because it now bases its treatment decisions on biological mechanisms instead of historical cancer-killing methods. The four therapeutic domains presented in this review show distinct biological understanding of GBM disease progression (Figure 1). The molecular targeting approach uses recurring driver mutations which affect EGFR and CDK4/6 and the RAS/MAPK signaling pathway. The immunotherapy approach works to activate anti-tumor immunity which has become inactive by using either antigen-specific priming or adoptive cell transfer methods. The primary goal of gene

Table 1: Summary of selected emerging investigational agents for glioblastoma multiforme (2025–2026)

Agent	Class	Setting	Phase	Status	Selected References
ABBV-155 + KTM-101	B7-H3 ADC + complementary kinase inhibitor (combo)	Recurrent GBM	Early phase (WoO)	Active, recruiting	Trial in progress
Abemaciclib + LY3214996	CDK4/6 + ERK1/2 inhibitor	Recurrent GBM	Phase 0/II	Active, recruiting	NCT04391595
MB-101/JIN-001/CT-179	RAS/MAPK pathway modulators	GBM	Phase I	Active, recruiting	Trials in progress
Vemurafenib	BRAF V600E inhibitor (monotherapy)	BRAF V600E-mutant GBM/HGG	Phase II (basket)	Completed	Kaley et al., 2018 [20]
Dabrafenib + Trametinib	BRAF + MEK inhibitor combination	BRAF V600E-mutant HGG	Phase II (basket)	Active, not recruiting	Wen et al., ROAR, 2022 [22]
Regorafenib	Oral multikinase inhibitor (VEGFR, TIE2, PDGFR, FGFR)	Recurrent GBM	Phase II (REGOMA)	Completed	Lombardi et al., 2019 [15]
Ivosidenib	IDH1 inhibitor	IDH1-mutant glioma	Phase I/II	Active, recruiting	Trial in progress
Vorasidenib	Dual IDH1/2 inhibitor	Residual/recurrent IDH-mutant grade 2 glioma; HGG ongoing	Phase III (INDIGO)	Completed; further trials active	Mellinghoff et al., 2023 [18]
DCVax-L/DOC1021	Autologous dendritic cell vaccine	Newly diagnosed and recurrent GBM	Phase II/III	Completed (DCVax-L); active (DOC1021)	Liau et al., 2023 [8]
INO-5401 + INO-9012 + cemiplimab	Plasmid DNA vaccine + electroporation + PD-1 inhibitor	Newly diagnosed GBM	Phase I/II	Active, not recruiting	NCT03491683 [9]
CART-EGFR-IL13Rα2 (bivalent)	Bivalent CAR T-cell, intracerebroventricular delivery	Recurrent multifocal EGFR-amplified GBM	Phase I	Active, recruiting	Bagley et al., 2024 [21]
PD-1-secreting TILs	Engineered TIL secreting anti-PD-1	GBM	Phase I	Active, recruiting	Trial in progress
DB107-RRV/DB107-FC	Retroviral replicating vector + 5-FC prodrug	Recurrent high-grade glioma	Phase I/II	Active, recruiting	NCT06264388; Cloughesy et al., 2020 [24] (legacy Toca 5)
Trogenix gene therapy	Selective oncolytic gene therapy	GBM	Phase I (FIH 2026)	Preclinical/planned first-in-human	Investigational
BPM31510	Ubidecarenone (CoQ10)/mitochondrial bioenergetics modulator	Newly diagnosed GBM	Phase II (2b)	Active, recruiting	NCT04752813
ASC40 (TVB-2640)	Fatty acid synthase (FASN) inhibitor	Recurrent GBM	Phase II	Active, recruiting	NCT05118776
Enzastaurin	PKCβ/PI3K inhibitor (biomarker-enriched, DGM1+)	GBM (DGM1+)	Phase II/III	Active, not recruiting	NCT03776071
Asunercept (APG101)	CD95L (FasL) inhibitor	Recurrent GBM	Phase II	Completed	NCT01071837
Marizomib	Pan-proteasome inhibitor (CNS-penetrant)	Newly diagnosed GBM	Phase II/III (EORTC 26122)	Completed; primary OS endpoint not met	EORTC 26122
Berubicin	CNS-penetrant anthracycline (DNA intercalator)	Recurrent GBM	Phase II	Active, not recruiting	NCT02429453

Abbreviations: ADC: antibody-drug conjugate; CAR: chimeric antigen receptor; CDK: cyclin-dependent kinase; CNS: central nervous system; DC: dendritic cell; ERK: extracellular signal-regulated kinase; FASN: fatty acid synthase; 5-FC: 5-fluorocytosine; FGFR: fibroblast growth factor receptor; FIH: first-in-human; GBM: glioblastoma multiforme; HGG: high-grade glioma; ICV: intracerebroventricular; IDH: isocitrate dehydrogenase; IL-13Rα2: interleukin-13 receptor alpha 2; MEK: mitogen-activated protein kinase kinase; OS: overall survival; PD-1: programmed cell death protein 1; PDGFR: platelet-derived growth factor receptor; PI3K: phosphoinositide 3-kinase; PKCβ: protein kinase C beta; RAS/MAPK: rat sarcoma/mitogen-activated protein kinase; RRV: retroviral replicating vector; TIE2: tunica intima endothelial kinase 2; TIL: tumor-infiltrating lymphocyte; VEGFR: vascular endothelial growth factor receptor; WoO: window-of-opportunity. Trial status reflects publicly available information from ClinicalTrials.gov and published reports at the time of writing (May 2026).

therapy and oncolytic virology consist of delivering cytotoxic and immune-stimulatory payloads which target cancer cells. The metabolic intervention strategy focuses on GBM cells because they have developed energy-sensing weaknesses which resulted from their exposure to low oxygen levels and restricted access to essential nutrients.

Several cross-cutting challenges are evident across these modalities. First, intratumoral heterogeneity means that agents targeting a single molecular marker, EGFRvIII, for instance, are subject to antigen-loss resistance in the subset of tumor cells not expressing the target, motivating bivalent or combination strategies. Second, the immunosuppressive TME remains a formidable barrier for all immunotherapeutic approaches, potentially explaining the modest single-agent CAR T-cell and checkpoint inhibitor activity observed to date in unselected GBM populations. Third, BBB penetration is a prerequisite for systemic agents and is frequently underestimated as a design criterion; the relative success of CNS-penetrant agents such as abemaciclib and temozolomide underscores this requirement.

From a patient selection perspective, MGMT promoter methylation status-already predictive for temozolomide benefit, has emerged as a key stratification variable in multiple immunotherapy trials, with methylated patients demonstrating the greatest survival gains in the DCVax-L Phase 3 data [15]. IDH mutation

status distinguishes a biologically and prognostically distinct subgroup in which several targeted agents are under separate investigation. The WHO 2021 classification requires clinical studies to select patients through molecular testing instead of using traditional tissue analysis according to its new guidelines for GBM diagnosis [24].

The unequal advantage which appears in MGMT promoter-methylated tumors results from multiple factors that work together in their mechanism. First, methylated MGMT silences O6-methylguanine-DNA methyltransferase expression, preventing repair of temozolomide-induced O6-methylguanine adducts and resulting in more extensive DNA damage, mismatch repair-driven futile cycles, and ultimately apoptosis or senescence [25]. Second, the increased neoantigen burden generated by temozolomide-induced hypermutation in MGMT-deficient tumours enhances the pool of tumour-specific peptides available for presentation, potentially augmenting the immunogenicity of co-administered vaccines such as DCVax-L. Third, MGMT methylation correlates with a less aggressive baseline biology and slower tumour kinetics, providing more time for adaptive immune responses to develop. Conversely, MGMT-unmethylated tumours remain refractory to temozolomide-driven apoptosis, motivating the parallel evaluation of MGMT-independent mechanisms such as CDK4/6 inhibition (abemaciclib in the INSIGHt trial) specifically in this subgroup.

Four Mechanism-Based Therapeutic Domains in GBM

Narrative Review (2025–2026) • Biomarker-guided strategies targeting distinct GBM vulnerabilities

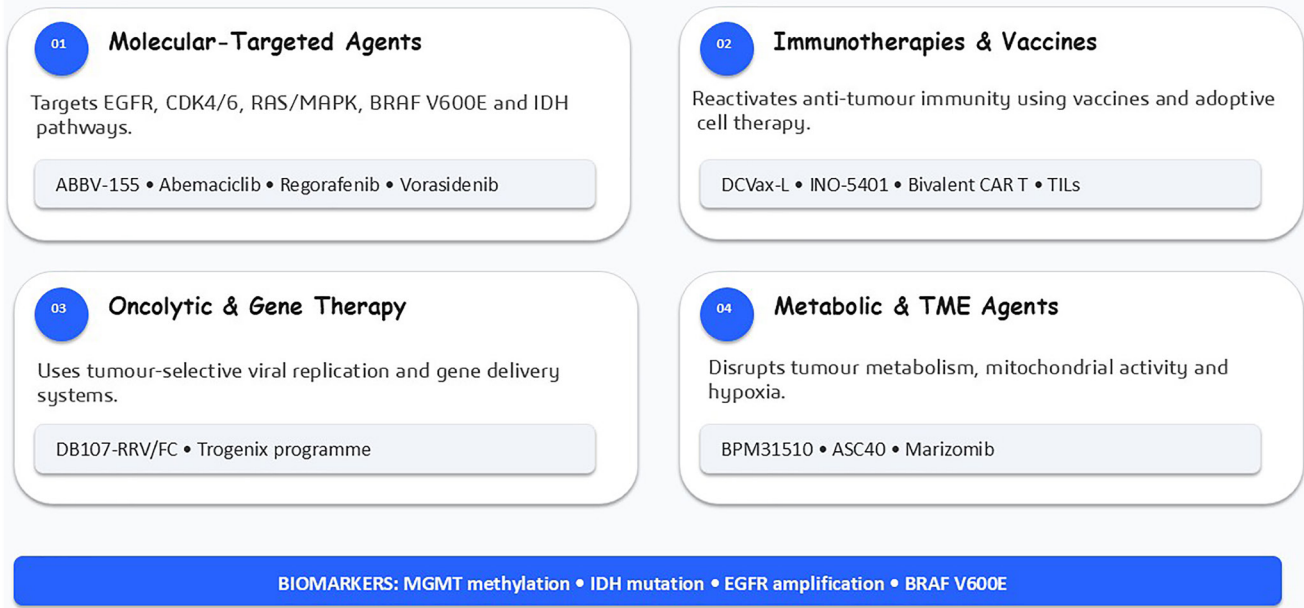


Figure 1: The four mechanism-based therapeutic domains of the 2025–2026 glioblastoma multiforme (GBM) pipeline: molecular-targeted agents (EGFR, CDK4/6, RAS/MAPK, BRAF V600E, IDH), immunotherapies and vaccines, oncolytic and gene therapy, and metabolic/tumour microenvironment agents, with representative investigational drugs. Patient selection across all domains is guided by MGMT methylation, IDH mutation, EGFR amplification and BRAF V600E status.

Key findings

Three principal findings emerge from this synthesis. First, the GBM investigational pipeline has shifted decisively from empirical cytotoxic agents toward mechanism-defined, biomarker-guided strategies, with the most advanced programmes (DCVax-L, bivalent CAR T-cells, abemaciclib in MGMT-unmethylated tumours, regorafenib in recurrent disease) each anchored in a defined biological hypothesis. Second, central nervous system penetration is now an explicit design criterion, and agents such as abemaciclib, regorafenib and marizomib achieve therapeutic tumour concentrations that earlier-generation drugs did not. Third, molecular stratification by MGMT promoter methylation, IDH mutation status, EGFR amplification, and BRAF V600E is increasingly being embedded in trial design, consistent with the WHO 2021 classification, and is expected to be a prerequisite for regulatory approval of next-generation GBM therapeutics.

Limitations of current therapies

Important limitations apply across the modalities reviewed. Molecular-targeted agents face intratumoural heterogeneity and the rapid emergence of bypass resistance pathways, particularly in unselected populations where the target alteration is present in only a fraction of tumour cells. Immunotherapeutic platforms, including DC vaccines, nucleic acid vaccines, CAR T-cell therapy and checkpoint inhibitors, contend with the profoundly immunosuppressive GBM microenvironment dominated by tumour-associated macrophages, myeloid-derived suppressor cells, regulatory T-cells, and chronic T-cell exhaustion. Oncolytic virus and gene therapy approaches are limited by intratumoural delivery logistics, neutralising antiviral immunity, and the need for specialised neurosurgical infrastructure. Metabolic and microenvironment-targeting agents must overcome the metabolic plasticity of GBM cells, which can switch between glycolytic and oxidative phosphorylation programmes under selective pressure. Across all classes, trial heterogeneity in eligibility criteria, endpoints, imaging response assessment, and corticosteroid use complicates cross-trial comparisons and meta-analysis, an issue highlighted in current EANO management guidance [26].

Comparison with temozolomide-based standard of care

Several investigational agents have demonstrated activity in subpopulations that historically derive limited benefit from temozolomide. Abemaciclib in MGMT-unmethylated newly diagnosed GBM addresses precisely the subgroup with poor temozolomide response. Regorafenib in REGOMA demonstrated a survival benefit over lomustine in recurrent GBM, a setting where

temozolomide is typically exhausted. DCVax-L extended median overall survival by approximately three months in the intent-to-treat newly diagnosed population on top of standard temozolomide and offered substantially greater long-term survival in the MGMT-methylated subgroup. Importantly, none of these agents has yet displaced temozolomide; rather, the emerging clinical paradigm is biomarker-directed combination therapy in which temozolomide remains the chemotherapy backbone while targeted, immunotherapeutic, or metabolic agents are added in molecularly defined subgroups.

Future directions

The next phase of GBM therapeutic development will likely be defined by three trends. First, increasing use of adaptive platform trials (such as INSIGHt and GBM AGILE) that evaluate multiple agents and biomarker-defined subgroups in parallel will accelerate the identification of effective therapies and minimise patient exposure to inactive treatments. Second, rational combination therapy, integrating targeted agents with immunotherapy, oncolytic virology, or metabolic modulation, is expected to outperform single-agent approaches given the multi-axial biology of GBM. Third, personalised neoantigen vaccines manufactured on actionable clinical timescales, advances in blood-brain barrier-penetrant delivery systems (focused ultrasound, convection-enhanced delivery, engineered nanoparticles), and integration of liquid biopsy and imaging biomarkers for response assessment [27]. This will collectively shape the field between 2026 and 2030. Readouts from ongoing Phase II/III trials of DCVax-L long-term follow-up, bivalent CAR T-cell expansion cohorts, INSIGHt abemaciclib data, and IDH inhibitor trials are anticipated to define the next regulatory inflection points.

Evolution of untreated glioblastoma

A small minority of patients diagnosed with GBM decline disease-modifying treatment, either because of personal or cultural preference, frailty, concurrent comorbidity precluding standard care, or geographical and economic barriers to access. The natural history of untreated GBM is dismal: median overall survival from diagnosis without any disease-directed therapy is approximately three to four months, with rapid neurological deterioration driven by tumour expansion, peritumoural oedema, mass effect, and intracranial hypertension. Patients receiving best supportive care only may benefit from corticosteroids for symptomatic oedema, anticonvulsants for seizure control, analgesia, and early integration of palliative and hospice services. Recognition of the untreated trajectory provides essential context for shared decision-making in patients considering treatment intensity, and highlights the importance of clear communication regarding prognosis, quality of life

implications, and goals-of-care discussions at the point of diagnosis. Investigational therapies should be framed against this natural history when discussing potential benefits and burdens with patients and families.

MATERIALS AND METHODS

This narrative review synthesises the GBM investigational pharmacotherapy landscape during 2025–2026. Searches were conducted in PubMed, Embase, and ClinicalTrials.gov between 1 January 2020 and 9 May 2026 using combinations of the terms “glioblastoma”, “clinical trial”, “phase I/II/III”, and the names of investigational agents. Conference proceedings from the American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Society for Medical Oncology (ESMO), and Society for Neuro-Oncology (SNO) annual meetings from 2022–2025 were screened for late-breaking abstracts. Trials were included if (i) the indication was newly diagnosed or recurrent GBM or IDH-mutant astrocytoma CNS WHO grade 4, (ii) recruitment was active or completed with results reported during the search window, and (iii) the agent represented a distinct pharmacological class or mechanistic advance. Trials limited to paediatric populations or to other CNS tumours were excluded unless directly informative for adult GBM. Tumour terminology follows the WHO 2021 classification of CNS tumours, which separates IDH-wildtype glioblastoma from IDH-mutant astrocytoma CNS WHO grade 4 [28].

CONCLUSIONS

The GBM investigational pipeline in 2025–2026 is characterized by mechanistic breadth and increasing biological sophistication. The Stupp protocol remains the only method which has demonstrated population-level survival improvement but new clinical trial findings indicate that DCVax-L and bivalent CAR T-cell therapy show promise for treating specific GBM patient groups through immunotherapy. The combination of precision molecular targeting with new immune activation methods and CNS-based drug delivery and metabolic interference establishes a foundation for developing combination therapies which should use proven predictive biomarkers for maximum effectiveness. The results from Phase II/III research between 2026 and 2028 will determine which platforms will proceed to regulatory submission.

AUTHOR CONTRIBUTIONS

Conceptualization: M.R. and M.J.H.; Literature Search and Data Acquisition: M.R., M.Z.I., and F.I.; Writing – Original Draft Preparation: M.R.; Writing – Review and Editing: M.J.H., M.Z.I., and F.I.; Supervision:

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CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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