# Frontier therapeutic strategies and molecular mechanisms of glioblastoma (Review)

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**Abstract.** The present study critically summarizes recent progress in therapeutic strategies and molecular mechanisms of glioblastoma (GBM) from 2020 to 2025, appraise the strength of evidence underlying emerging treatments, and provide practical references for individualized clinical decision-making. Relevant studies were retrieved from PubMed, Embase and Web of Science using predefined search strings combining 'glioblastoma', 'molecular classification', 'targeted therapy', 'immunotherapy' and 'drug resistance'. After duplicate removal and independent two-reviewer screening, 86 studies were included and synthesized, and the evidence was graded according to study design (randomized trials vs. single-arm early-phase trials vs. preclinical studies). The results demonstrated that molecular classification centered on IDH mutation and MGMT promoter methylation has become the basis of GBM treatment decision-making, although the WHO CNS5 classification now integrates additional diagnostic and prognostic biomarkers (for example, CDKN2A/B homozygous deletion, EGFR amplification, TERT promoter mutation, chromosome 7 gain/10 loss). 5-aminolevulinic acid fluorescence-guided surgery improves the extent of resection, and tumor treating fields provide an additional survival benefit in newly diagnosed GBM. Emerging approaches, including dual-target CAR-T cells, mRNA vaccines and metabolic inhibitors, have shown preliminary signals of activity in recurrent GBM, but most remain investigational and are supported by early-phase trials with small sample sizes. GBM treatment resistance arises from interconnected DNA repair, epigenetic, metabolic, tumor microenvironment and glioblastoma stem cell networks. In conclusion, GBM management is transitioning from empirical therapy toward molecularly guided precision therapy, but the translational gap between promising preclinical findings and proven clinical benefit remains substantial. Multimodal strategies integrating refined molecular classification, blood-brain barrier-penetrant drug delivery and rationally combined, rigorously tested therapies represent the most realistic path to improving GBM outcomes.

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## 1. Introduction

Glioblastoma (GBM), a WHO grade 4 diffuse glioma defined in the 2021 WHO Classification of Tumors of the Central Nervous System (1), is the most common and most aggressive primary malignant brain tumor in adults, accounting for ~57% of all gliomas and more than 50% of adult intracranial malignant tumors (2). The global annual incidence is ~3.2 per 100,000 population, with a predilection for adults aged 45-70 years, and the incidence is ~1.6-fold higher in men than in women (3). Despite advances in neurosurgery, radiotherapy and chemotherapy, prognosis remains poor: Maximal safe resection plus concurrent temozolomide (TMZ) chemoradiotherapy followed by adjuvant TMZ yields a median overall survival (mOS) of only 14-16 months and a 5-year survival rate below 5% (4).

The poor prognosis reflects two core biological features: Diffuse invasive growth and extreme molecular heterogeneity. GBM cells secrete matrix metalloproteinases (MMP2 and MMP9) that degrade the extracellular matrix, allowing tumor cells to infiltrate surrounding brain parenchyma and even cross the midline, so that complete resection is rarely possible and scattered residual micro-infiltration drives

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recurrence (recurrence exceeds 90%, with a median time of 7-9 months) (5). GBM also shows marked spatiotemporal heterogeneity: Distinct regions of the same tumor harbor different genomic and transcriptomic profiles, and the molecular phenotype evolves dynamically under chemoradiotherapy pressure through epigenetic reprogramming (6). A single lesion may contain both IDH-mutant and IDH-wildtype cell populations, or both MGMT promoter-methylated and unmethylated clones, thus no single agent can cover all tumor cells (5).

In parallel, advances in single-cell sequencing and liquid biopsy have shifted the field from histology-based subtyping toward molecularly guided precision therapy (7,8). The 2021 WHO classification incorporated molecular biomarkers (IDH mutation, MGMT promoter methylation, TERT promoter mutation, EGFR amplification, chromosome 7 gain/10 loss, H3 K27M mutation) into the diagnostic framework (1,9). It is important, however, to distinguish three biomarker classes that are frequently conflated: Diagnostic markers (for example, IDH mutation, TERT promoter mutation, EGFR amplification, chromosome 7 gain/10 loss), which establish the tumor type; prognostic markers (for example, IDH status, CDKN2A/B homozygous deletion), which predict outcome independent of treatment; and predictive markers (for example, MGMT promoter methylation), which predict response to a specific therapy (9). This distinction is emphasized throughout the present review.

Several reviews published between 2023 and 2025 have summarized individual aspects of GBM therapy, such as immunotherapy, targeted agents or specific resistance pathways. The present review differs in three respects. First, it integrates molecular classification, optimization of conventional therapy, emerging therapies and resistance mechanisms within a single framework. Second, it explicitly grades the level of evidence behind each therapeutic claim, distinguishing randomized trials from early-phase and preclinical studies. Third, it emphasizes the interconnected, network-like nature of GBM resistance rather than treating resistance pathways in isolation. The aim is to provide clinicians and researchers with a critical, balanced and translational overview of the 2020-2025 literature, and to identify the barriers that must be overcome before emerging therapies can enter routine practice.

## 2. Molecular pathological characteristics and subtyping advances

*Clinical translation of molecular subtyping.* The 2021 WHO (CNS5) classification defines adult-type diffuse gliomas primarily by IDH status. IDH-wildtype GBM (~90% of cases) is diagnosed when a diffuse astrocytic glioma harbors TERT promoter mutation, EGFR amplification, or combined chromosome 7 gain and chromosome 10 loss, even in the absence of microvascular proliferation or necrosis (1,10). IDH-mutant astrocytoma is graded as CNS WHO grade 4 in the presence of CDKN2A/B homozygous deletion, necrosis, or microvascular proliferation (1,10). H3 K27M-mutant diffuse midline glioma is a distinct, highly aggressive entity occurring mainly in children and adolescents (10). These criteria illustrate that molecular classification is no longer determined solely by IDH mutation and MGMT methylation, but by a combination of diagnostic, prognostic and predictive markers (10).

MGMT promoter methylation is a predictive biomarker rather than a diagnostic one: It identifies patients most likely to benefit from TMZ, and methylated patients show a mOS ~4-6 months longer than unmethylated patients (11,12). IDH mutation is both diagnostic and prognostic: IDH-mutant tumors carry a mOS 6-8 months longer than IDH-wildtype GBM and may respond to IDH1/2 inhibitors (13,14). A 2023 multicenter cohort study reported that patients with IDH-wildtype GBM with MGMT promoter methylation treated with TMZ plus immunotherapy achieved a mOS of 18.5 months vs. 14.3 months in unmethylated patients (11). In addition, circ-SETDB1 was recently identified as an independent prognostic factor in IDH-wildtype GBM (12).

*Molecular mechanisms of tumor heterogeneity.* Single-cell RNA sequencing has revealed that GBM is composed of transcriptionally plastic cellular states rather than fixed subtypes. The landmark integrative analysis identified four recurrent states, neural progenitor cell-like, oligodendrocyte progenitor cell-like, astrocyte (AC)-like and mesenchymal (MES)-like, that coexist within individual tumors and interconvert dynamically (7,15). The MES-like state is enriched in hypoxic and necrotic regions, upregulates TGF-β pathway genes, suppresses $CD8^+$ T-cell activation, enhances invasion and reduces chemo-radiosensitivity (15). Recent spatial transcriptomics and single-cell multi-omics studies further show that lineage plasticity and cellular-state transitions are key drivers of treatment resistance and represent one of the most active areas of GBM research (16,17).

Temporal heterogeneity is equally important. A 2025 longitudinal study showed that GBM cells undergo epigenetic reprogramming under TMZ pressure, leading to MGMT promoter demethylation and upregulation of MGMT expression, converting TMZ-sensitive cells into TMZ-resistant cells and driving early progression after an initially effective response (16,18).

## 3. Optimization of traditional treatment strategies

Maximal safe resection combined with TMZ-based chemoradiotherapy remains the first-line standard of care. Recent optimization has focused on precision surgery, individualized chemoradiotherapy, and the addition of tumor treating fields (TTFields).

*Precision surgical technology.* 5-aminolevulinic acid (5-ALA) fluorescence-guided surgery is the most mature precision technique. A 2023 meta-analysis of 12 randomized controlled trials reported that 5-ALA increased the gross total resection rate by 32% and extended mOS by 2.1 months compared with conventional surgery (19-21). Nevertheless, the benefit is limited to patients in whom complete resection of the enhancing tumor is achievable, and fluorescence-guided surgery does not address the diffuse infiltrative component. Intraoperative rapid molecular testing has also advanced: A 2024 study described an intraoperative MGMT promoter methylation assay completed within 30 min that can guide postoperative chemoradiotherapy planning (22).

*Individualized chemoradiotherapy*. Whether to extend adjuvant TMZ beyond six cycles remains controversial. A 2022 phase III trial reported that extending adjuvant TMZ from 6 to 12 cycles in MGMT-methylated GBM prolonged median progression-free survival (PFS) from 6.4 to 10.2 months (23); however, this finding has not been consistently reproduced, and prolonged TMZ increases toxicity and cost without a universal overall survival benefit. Extended adjuvant TMZ should therefore be regarded as an individualized option rather than a new standard. Hyperbaric oxygen therapy combined with chemoradiotherapy has been reported to improve the objective response rate (ORR) by 15% by increasing tumor oxygenation and TMZ cytotoxicity (24), but the supporting evidence is limited and preliminary, and this approach should be interpreted cautiously.

*TTFields*. TTFields deliver low-intensity, intermediate-frequency alternating electric fields that disrupt mitosis. In the pivotal EF-14 randomized trial, adding TTFields to maintenance TMZ in newly diagnosed GBM extended mOS from 16.0 to 20.9 months (25), and TTFields are now incorporated into major management guidelines for eligible patients. Real-world data from 2020-2025 generally support the feasibility of TTFields in routine practice, although adherence, scalp toxicity and cost remain practical limitations (25).

## 4. Emerging therapeutic strategies

Emerging approaches, immunotherapy, targeted therapy and oncolytic viruses, have generated substantial interest, but most supporting evidence derives from phase I/II trials or preclinical models, and these findings should be regarded as preliminary rather than definitive. The main clinical trial results are summarized in Table I.

*Immunotherapy: Rationale and remaining barriers*. Immune checkpoint inhibitors have transformed several solid tumors but have largely failed in GBM. The randomized CheckMate 143 trial found no survival benefit of nivolumab over bevacizumab in recurrent GBM (26), and this negative result is now understood to reflect profound immune suppression, T-cell exhaustion, antigen heterogeneity, corticosteroid-induced immunosuppression and poor T-cell infiltration in the GBM microenvironment (27,28). Combination strategies aim to overcome these barriers: A 2024 phase II trial reported that nivolumab plus bevacizumab achieved an ORR of 22% and a mOS of 9.8 months in recurrent GBM [vs. 6.2 months for monotherapy (29)], but confirmatory phase III data are still lacking.

CAR-T cell therapy: Intracranial delivery is used to bypass the BBB. A 2025 phase I trial of intracranial EGFRvIII-directed CAR-T cells in 12 patients with recurrent GBM reported partial responses in 4 patients and a median PFS of 5.3 months (30). Dual-target (EGFRvIII + IL13Rα2) CAR-T cells may reduce antigen-escape resistance (31,32). However, CAR-T therapy in GBM faces major challenges, including antigen escape, limited T-cell persistence, neurotoxicity and delivery limitations, and efficacy remains unproven in randomized trials.

Tumor vaccines: A 2023 phase III trial reported that a dendritic cell vaccine added to standard therapy extended mOS to 19.3 months in IDH-wildtype GBM (33), and a 2025

Table I. Clinical trial results of emerging therapies for GBM (2020-2025).

| First author(s), year | Therapy/Drug | Target/Mechanism | Phase | Population | Efficacy | (Refs.) |
|---|---|---|---|---|---|---|
| Kreatsoulas *et al*, 2022 | Nivolumab + bevacizumab | PD-1 + VEGF inhibition | II | Recurrent GBM | ORR 22%, mOS 9.8 months | (29) |
| Zhang *et al*, 2026 | EGFRvIII-targeted CAR-T | EGFRvIII-specific elimination | I | Recurrent GBM | PR 4/12, mPFS 5.3 months | (30) |
| Mitchell *et al*, 2015 | DC vaccine + standard therapy | Induction of antitumor immunity | III | Newly diagnosed IDH-wildtype GBM | mOS 19.3 months | (33) |
| Van Den Bent *et al*, 2018 | Depatuxizumab mafodotin + TMZ | EGFRvIII ADC + chemotherapy | II | EGFRvIII-positive GBM | ORR 18% | (36) |
| Singh *et al*, 2025 | OMO-103 + TMZ | HK2 inhibition + chemotherapy | I | MGMT-unmethylated GBM | mPFS extended by 2.9 months | (23) |
| Todo *et al*, 2022 | Oncolytic HSV-1 + radiotherapy | Tumor lysis + immune induction | II | Newly diagnosed GBM | mOS 17.6 months | (41) |
| Nassiri *et al*, 2023 | Oncolytic adenovirus (PD-L1 inhibitor) | Tumor lysis + PD-L1 inhibition | I | Recurrent GBM | ORR 25% | (42) |

ORR, objective response rate; mOS, median overall survival; mPFS, median progression-free survival; ADC, antibody-drug conjugate; HK2, hexokinase 2; CAR-T, chimeric antigen receptor T cell; DC, dendritic cell; GBM, glioblastoma; PD-L1, programmed cell death ligand-1.

Table II. Summary of included studies (2020-2025).

| First author/s, year | Study (topic) | Study type | Population | Main finding | (Refs.) |
|---|---|---|---|---|---|
| A. Molecular classification and heterogeneity | | | | | |
| Neftel *et al*, 2019 | Cellular states and plasticity | Single-cell RNA-seq | Human GBM | Four plastic cellular states (NPC-, OPC-, AC-, MES-like) | (7) |
| McMahon *et al*, 2022 | ctDNA in glioma | Systematic review/ meta-analysis | Glioma | ctDNA biomarker performance | (8) |
| LeBlanc *et al*, 2022 | Single-cell landscapes | Single-cell | Primary GBM | Variable inter-/intratumor heterogeneity retention | (16) |
| Migliozzi *et al*, 2025 | Spatial plasticity restraint | Single-cell/spatial | GBM | Homotypic clustering restrains plasticity | (17) |
| Hamed *et al*, 2025 | Gliomagenesis injury response | Single-cell | Glioma | Neural crest-like cells orchestrate gliomagenesis | (18) |
| B. Standard therapy and optimization | | | | | |
| Qazi *et al*, 2017 | TMZ + radiotherapy | Phase III RCT | Newly diagnosed GBM | Established TMZ chemoradiotherapy standard | (5) |
| Hegi *et al*, 2005 | MGMT methylation and TMZ | RCT (biomarker analysis) | GBM | MGMT methylation predicts TMZ benefit | (11) |
| Barault *et al*, 2015 | MGMT digital PCR | Cohort | GBM/CRC | Digital PCR refines MGMT-based prediction | (12) |
| Stummer *et al*, 2006 | 5-ALA fluorescence surgery | Phase III RCT | Malignant glioma | Improved complete resection rate | (19) |
| Coty-Fattal *et al*, 2025 | Intraoperative MGMT assay | Proof-of-concept | GBM | 30-min intraoperative MGMT assay | (22) |
| Arienti *et al*, 2021 | Hyperbaric oxygen | Preclinical/ translational | GBM cells | HBO rewires glucose metabolism | (24) |
| Stupp *et al*, 2017 | TTFields EF-14 | Phase III RCT | Newly diagnosed GBM | mOS 20.9 vs. 16.0 months | (25) |
| Mellinghoff *et al*, 2023 | Vorasidenib | Phase III RCT | IDH-mutant low-grade glioma | Vorasidenib efficacy in IDH-mutant glioma | (14) |
| C. Immunotherapy | | | | | |
| Reardon *et al*, 2020 | CheckMate 143 | Phase III RCT | Recurrent GBM | No survival benefit of nivolumab | (26) |
| Schalper *et al*, 2019 | Neoadjuvant nivolumab | Phase II | Resectable GBM | Nivolumab modifies TME | (27) |
| Zhao *et al*, 2019 | Anti-PD-1 correlates | Cohort | GBM | Immune/genomic correlates of response | (28) |
| Zhang *et al*, 2026 | B7-H3 CAR-T | Phase I | Recurrent GBM | Intracranial B7-H3 CAR-T delivery | (30) |
| Clubb *et al*, 2026 | Armored CAR-T | Preclinical | GBM | Targets antigen-heterogeneous glioma | (31) |
| Kong *et al*, 2012 | IL13R CAR-T | Preclinical | Glioma xenografts | IL13Rα2 CAR-T suppression | (32) |
| Mitchell *et al*, 2015 | DC vaccine | Clinical trial | GBM | DC vaccine + tetanus/CCL3 improves survival | (33) |

Table II. Continued.

| First author/s, year | Study (topic) | Study type | Population | Main finding | (Refs.) |
|---|---|---|---|---|---|
| C. Immunotherapy | | | | | |
| Berneman *et al*, 2025 | WT1 mRNA DC vaccine | Phase I | GBM/solid tumors | WT1-mRNA DC vaccination responses | (34) |
| Garfinkle *et al*, 2026 | Neoantigen DNA vaccine | Phase I | MGMT-unmethylated GBM | Personalized multivalent vaccination | (35) |
| D. Targeted therapy/ADC | | | | | |
| Van Den Bent *et al*, 2018 | Depatux-M (INTELLANCE 2) | Phase II RCT | Recurrent EGFR-amplified GBM | Depatux-M + TMZ results | (36) |
| Padovan *et al*, 2020 | Depatux-M real-world | Cohort | Recurrent GBM | Real-world Depatux-M + TMZ experience | (37) |
| E. Oncolytic viruses | | | | | |
| Todo *et al*, 2022 | G47Δ HSV-1 | Phase II | Residual/recurrent GBM | Intratumoral G47Δ survival | (41) |
| Nassiri *et al*, 2023 | DNX-2401 + pembro | Phase I/II | Recurrent GBM | Oncolytic adenovirus + pembrolizumab | (42) |
| Desjardins *et al*, 2018 | Recombinant poliovirus | Phase I | Recurrent GBM | PVSRIPO survival | (43) |
| F. Resistance mechanisms | | | | | |
| Suvà *et al*, 2009 | EZH2 in GSC | Preclinical | GBM stem cells | EZH2 essential for GSC maintenance | (44) |
| Jin *et al*, 2017 | BMI1/EZH2 inhibition | Preclinical | GBM stem cells | Combined BMI1 + EZH2 targeting | (45) |
| Stefan *et al*, 2025 | Olaparib + TMZ | Phase I | GBM | PARP inhibitor + TMZ safety/activity | (46) |
| Natsume *et al*, 2013 | PRC2 plasticity | Preclinical | GBM | PRC2 regulates epigenetic plasticity | (47) |
| Minami *et al*, 2023 | CDKN2A lipid | Preclinical | GBM | CDKN2A deletion primes ferroptosis | (48) |
| Duman *et al*, 2019 | ACBP FAO | Preclinical | GBM | ACBP sustains fatty acid oxidation | (49) |
| Masui *et al*, 2013 | mTORC2 glycolysis | Preclinical | GBM | mTORC2-FoxO-c-Myc glycolysis | (50) |
| Ye *et al*, 2023 | Microglial rewiring | Preclinical | GBM | Microglial metabolic rewiring + ICB | (51) |
| Polania *et al*, 2025 | TAM exhaustion | Preclinical | GBM | TAM antigen presentation drives exhaustion | (52) |
| Wang *et al*, 2024 | Hypoxic macrophages | Preclinical | GBM | Hypoxic macrophage vascular normalization | (53) |
| Sattiraju *et al*, 2023 | Hypoxic niche | Preclinical | GBM | Hypoxic niches reprogram TAM/T-cells | (54) |
| Jeon *et al*, 2023 | Tissue factor RT | Preclinical | GBM | Tissue factor regulates RT remodeling | (55) |
| Hoogstrate *et al*, 2023 | TME transcriptome | Preclinical | GBM | TME transcriptomic changes | (56) |

Table II. Continued.

| First author/s, year | Study (topic) | Study type | Population | Main finding | (Refs.) |
|---|---|---|---|---|---|
| F. Resistance mechanisms | | | | | |
| Man *et al*, 2018 | Notch1 GSC | Preclinical | GSC | Hypoxic Notch1 turnover maintains GSC | (57) |
| Li *et al*, 2009 | Hypoxia-inducible factor GSC | Preclinical | GSC | Hypoxia-inducible factor regulates GSC tumorigenic capacity | (58) |
| Bao *et al*, 2006 | GSC radioresistance | Preclinical | GSC | GSC preferential DNA damage response | (59) |
| G. Background reviews and consensus papers | | | | | |
| Louis *et al*, 2021 | WHO CNS5 classification | Consensus/ classification | CNS tumors | Molecular diagnostic framework | (1) |
| van den Bent *et al*, 2023 | Primary brain tumors | Review | Adult brain tumors | Diagnostic and therapeutic overview | (2) |
| Tan *et al*, 2020 | GBM management | Review | GBM | State-of-the-art management | (3) |
| Qazi *et al*, 2017 | Intratumoral heterogeneity | Review | GBM | Heterogeneity drives resistance | (5) |
| Weller *et al*, 2024 | Glioma (Primers) | Review | Glioma | Comprehensive overview | (6) |
| Horbinski *et al*, 2024 | Molecular testing | Review | CNS tumors | Molecular testing framework | (9) |
| Wen *et al*, 2021 | WHO 2021 implications | Review | Adult gliomas | Clinical translation | (10) |
| Reardon *et al*, 2023 | IDH-mutant therapy | Review | IDH-mutant glioma | Targeting mutant IDH | (13) |
| Mukherjee *et al*, 2024 | Transcriptional plasticity | Review | GBM | Phenotypic plasticity mechanisms | (15) |
| Moiyadi *et al*, 2014 | Fluorescence surgery review | Review | Malignant glioma | 5-ALA paradigm | (20) |
| McCracken *et al*, 2022 | 5-ALA story | Review | Brain tumor | 5-ALA evolution | (21) |
| Singh *et al*, 2025 | GBM crossroads | Review | GBM | Therapeutic horizons | (23) |
| Kreatsoulas *et al*, 2022 | Immunotherapy landscape | Review | GBM | Translational immunotherapy | (29) |
| Mair *et al*, 2023 | ADC brain tumors | Review | Brain tumors | ADC activity | (38) |
| Gan *et al*, 2017 | ADC GBM | Review | GBM | ADC design | (39) |
| Furnari *et al*, 2015 | EGFR heterogeneity | Review | GBM | EGFR signaling heterogeneity | (40) |
| Wu *et al*, 2023 | Radiotherapy resistance | Review | Tumors | Molecular resistance mechanisms | (60) |

GBM, glioblastoma; TMZ, temozolomide; ADC, antibody-drug conjugate; 5-ALA, 5-aminolevulinic acid; CNS, central nervous system; TME, tumor microenvironment; RCT, randomized controlled trial; TAM, tumor-associated macrophage.

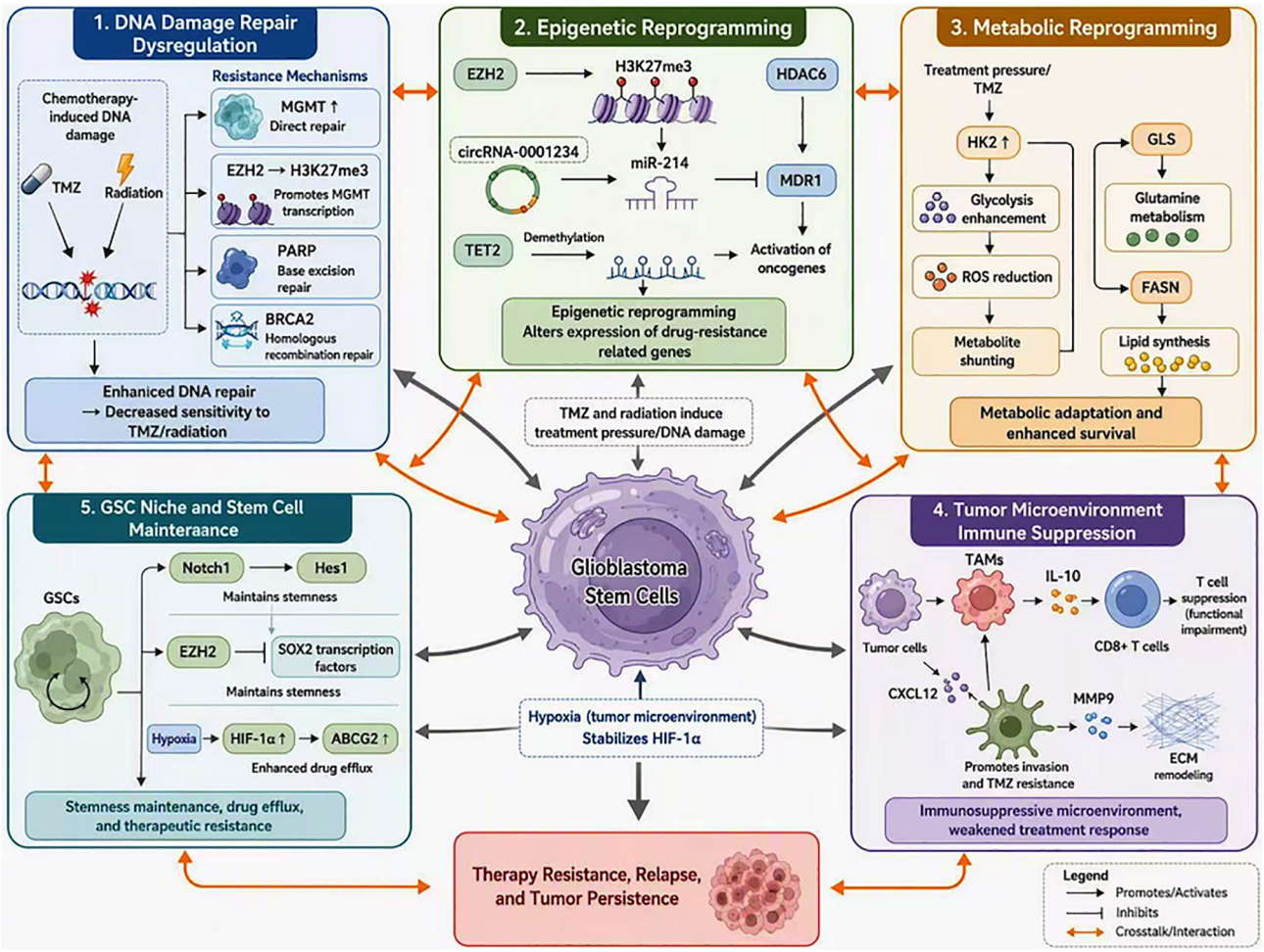



Figure 1. Interconnected network of glioblastoma therapy resistance mechanisms. DNA repair, epigenetic reprogramming, metabolic reprogramming, tumor microenvironment immunosuppression and GSC stemness are mutually reinforcing; orange arrows indicate crosstalk. miR, microRNA; HIF-1α, hypoxia-inducible factor 1α; TMZ, temozolomide; ECM, extracellular matrix; GLS, glutaminase; FASN, fatty acid synthase; miR, microRNA; TAMs, tumor-associated macrophages; MMP9, matrix metalloproteinase 9; ROS, reactive oxygen species; GSCs, glioblastoma stem cell.

phase I trial of an mRNA vaccine targeting GBM-specific mutations reported induction of tumor-specific immune responses with acceptable safety (34,35). These results are encouraging but require independent confirmation.

*Targeted therapy: New targets, persistent barriers*. Targeted therapy has shifted from conventional signal-pathway inhibition toward metabolic inhibition and antibody-drug conjugates (ADCs). Depatuxizumab mafodotin, an EGFRvIII-directed ADC, achieved an ORR of 18% in EGFRvIII-positive GBM in a phase II trial (36,37). However, EGFR-targeted therapies have generally been disappointing in GBM despite frequent EGFR alterations, largely because of inadequate BBB penetration, pharmacokinetic limitations and redundant signaling pathways (38-40). A 2025 phase I trial of the hexokinase 2 (HK2) inhibitor OMO-103 plus TMZ in MGMT-unmethylated GBM extended median PFS by 2.9 months (23); again, this is an early-phase signal requiring confirmation.

*Oncolytic virus therapy*. Oncolytic viruses both lyse tumor cells and stimulate antitumor immunity and are increasingly combined with radiotherapy or immunotherapy. A 2024 phase II trial of oncolytic HSV-1 (T-VEC) plus radiotherapy in newly diagnosed GBM reported a mOS of 17.6 months (41), and a 2025 phase I trial of an oncolytic adenovirus expressing a PD-L1 inhibitor achieved an ORR of 25% in recurrent GBM (42,43). These agents remain investigational.

## 5. Mechanisms of treatment resistance and intervention strategies

GBM treatment resistance results from multiple interacting mechanisms. Importantly, these mechanisms do not operate in isolation; hypoxia, DNA repair, metabolic reprogramming, TME immunosuppression and glioblastoma stem cell (GSC) stemness form an interconnected network (Fig. 1). Throughout this section, preclinical findings are distinguished from observations validated in human clinical studies.

*Abnormal DNA damage repair*. TMZ cytotoxicity depends on DNA alkylation, and enhanced DNA repair is a major resistance mechanism. MGMT-mediated direct repair: IDH-wildtype GBM upregulates MGMT transcription through EZH2-mediated H3K27me3 modification after TMZ exposure (44); the EZH2 inhibitor tazemetostat plus TMZ increased apoptosis of MGMT-high GBM cells by 42% in

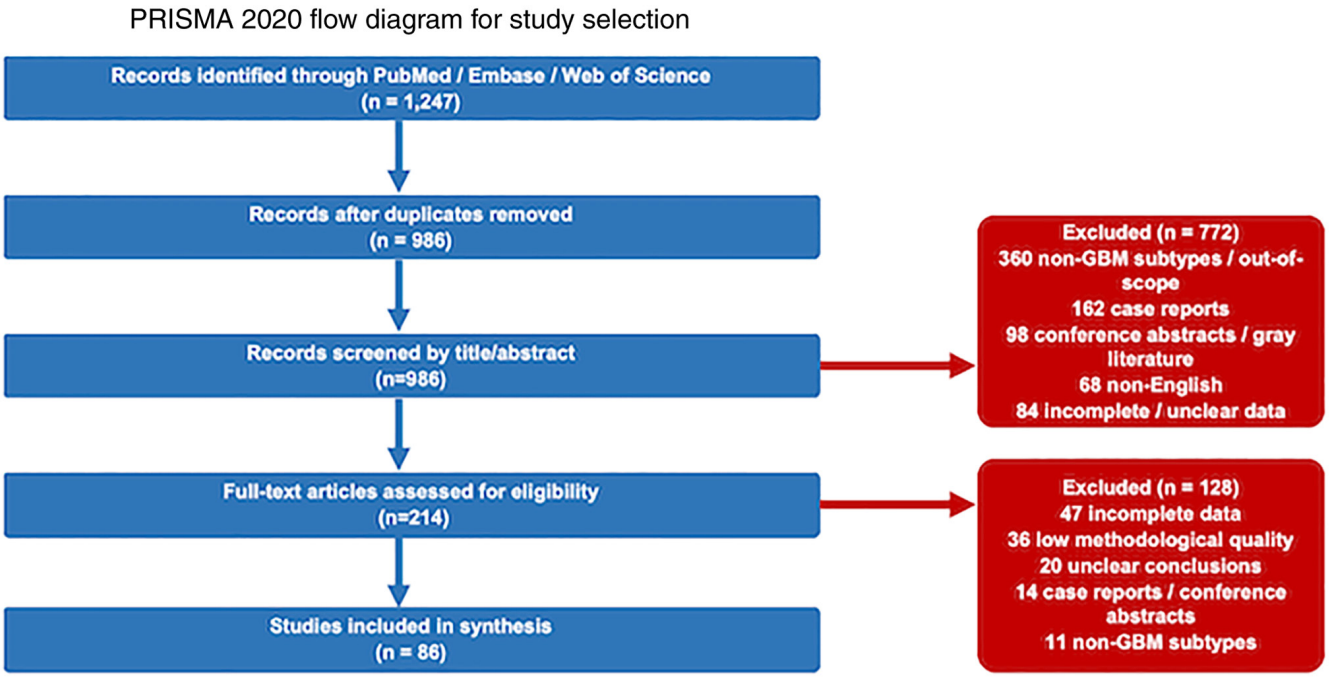



Figure 2. PRISMA-style literature selection flowchart. The 772 records excluded at title/abstract screening comprised 360 non-GBM/out-of-scope records, 162 case reports, 98 conference abstracts or gray-literature items, 68 non-English records and 84 records with incomplete or unclear data. The 128 records excluded at full-text assessment comprised 47 with incomplete data, 36 with low methodological quality, 20 with unclear conclusions, 14 case reports/conference abstracts and 11 non-GBM glioma subtypes. GBM, glioblastoma.

preclinical models (44,45). PARP-mediated base excision repair: a 2025 phase I trial reported that the PARP inhibitor olaparib plus TMZ extended median PFS to 7.1 months (vs. 4.2 months in controls) in MGMT-unmethylated GBM (46). ~30% of recurrent GBM harbor BRCA2 mutations, which activate homologous recombination and may predict response to PARP inhibitors (46).

*Epigenetic regulation*. Histone modification, non-coding RNA regulation and DNA methylation dynamics all contribute to acquired resistance. GBM upregulates HDAC6 after radiotherapy, stabilizing DNA repair proteins; the HDAC6 inhibitor ricolinostat plus radiotherapy extended survival in tumor-bearing mice (47). The circular RNA circRNA-0001234 upregulates MDR1 by sponging miR-214 in drug-resistant GBM (18). In IDH-mutant GBM, TET2 silencing induces global hypomethylation and activates invasion-related genes (18). These are predominantly preclinical observations.

*Metabolic reprogramming*. GBM cells adapt metabolically to therapeutic pressure. TMZ upregulates HK2 by 2.3-fold, enhancing glycolysis and reducing reactive oxygen species to evade apoptosis; the HK2 inhibitor 2-DG plus TMZ reduced GBM cell survival by 60% *in vitro* (48,50). Recurrent GBM overexpresses glutaminase (GLS), which maintains GSC stemness; the GLS inhibitor CB-839 plus CAR-T cells increased GSC clearance in preclinical models (51). Radiotherapy activates fatty acid synthase (FASN); the FASN inhibitor orlistat plus radiotherapy reduced tumor volume in animal models (49).

*TME immunosuppression*. Tumor-associated macrophages dominate the GBM TME and secrete IL-10, inducing $CD8^+$ T-cell exhaustion; anti-IL-10 plus anti-PD-1 increased the ORR to 28% in a phase I study of recurrent GBM (52,53). GBM-induced ACs secrete CXCL12, promoting invasion and TMZ resistance; the CXCR4 inhibitor plerixafor plus TMZ extended survival in mice (54). GBM-secreted MMP9 remodels the extracellular matrix; the MMP9 inhibitor marimastat may enhance oncolytic virus penetration (55,56).

*GSC stemness maintenance*. GSCs are self-renewing, multidrug-resistant cells central to recurrence. Notch1 signaling maintains stemness through Hes1; the Notch inhibitor DAPT plus radiotherapy reduced GSC proportion by 80% in preclinical models (57). EZH2 maintains stemness by repressing SOX2 negative regulators; tazemetostat plus CD133-ADC eliminated 90% of GSCs *in vitro* and *in vivo* (44). Hypoxia-inducible factor 1α (HIF-1α) upregulates ABCG2 in hypoxic GSCs, enhancing drug efflux; the HIF-1α inhibitor belzutifan plus TMZ increased GSC drug sensitivity in preclinical studies (58,59).

*An interconnected resistance network*. A key emerging concept is that these mechanisms are mutually reinforcing. Hypoxia stabilizes HIF-1α, which simultaneously drives metabolic reprogramming (glycolysis), GSC stemness (ABCG2 upregulation) and TME immunosuppression (TGF-β, IL-10), while DNA damage from TMZ and radiotherapy feeds back to activate epigenetic and metabolic adaptations (23,60). A schematic summary is provided in Fig. 1. Targeting single nodes of this network is therefore unlikely to be curative, and rational combination strategies that simultaneously address DNA repair, metabolism, immunosuppression and stemness are more likely to succeed.

## 6. Conclusions and perspectives

Over the past five years, GBM research has progressed from empirical multimodal therapy toward molecularly guided precision therapy. The 2021 WHO classification has established the clinical value of molecular biomarkers, enabling stratified treatment: MGMT-methylated patients may benefit from extended TMZ, and IDH-mutant patients may respond to metabolic-pathway inhibitors. Precision surgery (5-ALA, intraoperative molecular testing) has improved resection and decision-making, and TTFields have added a meaningful, guideline-endorsed survival benefit (4,19,25). Emerging therapies, including dual-target CAR-T cells, mRNA vaccines and metabolic inhibitors, have produced preliminary signals of activity in recurrent GBM.

However, substantial translational barriers remain. The BBB severely limits drug penetration; spatiotemporal heterogeneity leads to failure of single-agent therapy; the interconnected resistance network is difficult to reverse; and the immunosuppressive TME reduces the efficiency of immunotherapy (23). At present, most emerging therapies have not been validated in adequately powered randomized trials, and none can yet be described as curative. The most realistic path forward is multimodal, molecularly stratified therapy that combines refined single-cell and liquid-biopsy-based classification, BBB-penetrant delivery systems, and rationally designed combinations targeting the interconnected resistance network, all tested in rigorous, controlled clinical trials. Significant additional work is required before these strategies can become standard practice, and any expectation of cure for a broad GBM population remains premature (6,23).

## 7. Literature search methods

*Databases and search strategy*. PubMed, Embase and Web of Science were searched on 15 December 2025 for records published between 1 January 2020 and 15 December 2025. The following search string was adapted for each database: (‘glioblastoma’ OR ‘GBM’) AND (‘molecular classification’ OR ‘molecular subtyping’ OR ‘IDH’ OR ‘MGMT’) AND (‘targeted therapy’ OR ‘immunotherapy’ OR ‘tumor treating fields’ OR ‘drug resistance’ OR ‘tumor microenvironment’). No language restriction was applied at retrieval; non-English records were excluded after screening because of data-integrity concerns.

*Study selection*. After duplicate removal, two reviewers (L.S. and S.S.) independently screened titles and abstracts, and then full texts, against predefined inclusion and exclusion criteria. Disagreements were resolved by discussion or by a third reviewer (Y.G.). Inclusion criteria were: i) Original research, clinical trials or high-quality reviews published in authoritative oncology/neuro-oncology journals; ii) studies with clear experimental or clinical data on GBM molecular pathology, therapy or resistance; and iii) trials reporting phase, population and efficacy endpoints. Exclusion criteria were: i) case reports, conference abstracts and unpublished gray literature; ii) studies with incomplete data, unclear conclusions or low methodological quality; and iii) studies focused on non-GBM glioma subtypes.

*Screening results and quality assessment*. The search identified 1,247 records, of which 261 duplicates were removed, leaving 986 records for screening. Of these, 68 non-English records were excluded after title/abstract screening because of data-integrity concerns. The 772 records excluded at the title/abstract stage comprised 360 records on non-GBM glioma subtypes or out-of-scope topics, 162 case reports, 98 conference abstracts or gray-literature items, and 84 records with incomplete or unclear data. A further 128 records were excluded at the full-text stage, comprising 47 with incomplete data, 36 with low methodological quality, 20 with unclear conclusions, 14 case reports/conference abstracts confirmed on full text, and 11 non-GBM glioma subtypes. The remaining 86 studies were synthesized (Fig. 2). Inter-reviewer agreement was substantial (Cohen's $\kappa$=0.82). Methodological quality was assessed by study design, sample size and endpoint definition; findings from randomized trials were weighted above single-arm early-phase trials, which were in turn weighted above preclinical studies. The main clinical and pre-clinical studies included in this review are summarized in Table II.

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## Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

## Authors' contributions

LS and YG conceptualized and designed the study. LS, SS and LY conducted literature acquisition and analysis. LS drafted the manuscript. JY and JY critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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