Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

p53 Pathway-Targeted Therapeutic Strategies in Glioblastoma: A CNS-Specific Framework Integrating Therapeutic Resistance, Molecular Stratification, CNS Pharmacology, and Clinical Translation

Fan Bu[1], Shulin Zeng[2,*], Chao Ma[3,*], Mingbo Zhang[3]

[1]Department of Neurology, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing, People's Republic of China; [2]Department of General Surgery, Qidong Hospital of Traditional Chinese Medicine, Qidong, Jiangsu, People's Republic of China; [3]Department of Oncology, Pingyang Hospital of Traditional Chinese Medicine, Zhejiang Chinese Medical University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mingbo Zhang, Email zhangmingbo257@163.com

Abstract: Glioblastoma (GBM) remains one of the most difficult therapeutic problems in adult neuro-oncology. Its resistance to treatment reflects not only malignant cellular biology but also central nervous system-specific constraints, including blood-brain barrier and blood-tumor barrier heterogeneity, diffuse infiltrative growth, uncertain target-site exposure, treatment-induced evolution, and the need to preserve neurological function. The tumor suppressor p53, encoded by TP53, is highly relevant to glioblastoma because it regulates cell-cycle arrest, DNA repair, apoptosis, senescence, genomic stability, and cellular responses to radiotherapy and temozolomide. However, p53 pathway-targeted therapy in glioblastoma cannot be translated by simply extrapolating from extracranial solid tumors. This narrative review develops a CNS-specific translational framework for p53 pathway-targeted therapy in GBM. The framework integrates molecular dependency, unbound brain exposure and intratumoral distribution, pharmacodynamic confirmation, molecular stratification, and neuro-oncology-specific clinical endpoints. We discuss how distinct p53 pathway states, including TP53 mutation, MDM2/MDM4-mediated suppression, and downstream apoptotic competence, influence therapeutic vulnerability and biomarker-guided clinical development. Among current strategies, MDM2-axis inhibition in TP53-wild-type glioblastoma appears to be one of the most mechanistically tractable approaches, with emerging GBM-specific translational evidence, although clinical efficacy remains to be established. Other mutant p53-directed, network-based, gene-, immune-, and combination strategies remain less mature and require stronger glioblastoma-specific evidence. Future progress will depend on aligning target biology with CNS drug delivery, tissue pharmacokinetics/pharmacodynamics, biomarker-enriched trial design, and clinically meaningful neurological outcomes.

Keywords: glioblastoma, p53, MDM2, blood-brain barrier, CNS pharmacology, molecular stratification

Introduction

Glioblastoma remains one of the most difficult therapeutic problems in adult neuro-oncology because biological aggressiveness, diffuse invasion, molecular heterogeneity, blood-brain barrier (BBB) constraints, treatment-induced evolution, and neurological vulnerability converge in the same disease. These features make GBM fundamentally different from extracranial solid tumors as a platform for targeted therapy.[1,2] A molecularly active drug may still fail if it does not reach relevant intracranial compartments, engage its target in tumor tissue, or preserve neurological function at clinically tolerable doses.

The tumor suppressor p53, encoded by the TP53 gene, is a central regulator of genome stability and cellular responses to stress.[3] By controlling transcriptional programs involved in cell-cycle arrest, apoptosis, DNA repair, and senescence,

https://doi.org/10.2147/DDDT.S509447
Received: 16 May 2026
Accepted: 25 July 2026
Published: 14 August 2026

p53 helps determine whether damaged cells undergo repair, durable arrest, or elimination. In GBM, this pathway is especially relevant because radiotherapy and temozolomide, the major DNA damage-based components of standard treatment, directly depend on how tumor cells interpret and respond to genotoxic stress.[4]

Therapeutic strategies directed at the p53 pathway have expanded from simple wild-type p53 activation or mutant p53 restoration to include MDM2/MDM4 antagonism, mutant p53 reactivation or degradation, gene- and immune-based approaches, and rational combinations.[5,6] In GBM, however, these strategies cannot be evaluated by extrapolating from extracranial cancers. p53 dysfunction in GBM is better understood as a network state rather than a single-gene abnormality. TP53 mutation is only one mechanism of pathway disruption; in TP53-wild-type tumors, p53 activity may be restrained by MDM2 or MDM4 dysregulation, CDKN2A/ARF alteration, PTEN/AKT pathway activation, or impaired downstream apoptotic competence. Conversely, TP53-mutant tumors may involve loss-of-function, dominant-negative, or gain-of-function biology, each with different therapeutic implications.

The limited clinical translation of p53-targeted therapy in glioblastoma should therefore not be interpreted as failure of p53 as a therapeutic target. Rather, previous strategies may have underestimated the importance of CNS-specific pharmacology, including brain exposure, intratumoral distribution, and pharmacodynamic confirmation. Plasma exposure alone does not guarantee effective target-site exposure, and drug activity observed in extracranial tumors may not predict intracranial efficacy.

The MDM2-p53 axis illustrates this translational challenge. Glioblastoma-focused studies of BI-907828 (brigimadlin), a potent MDM2 inhibitor, demonstrated measurable CNS and tumor exposure, activation of p53 target genes, reduced viability of TP53-wild-type glioblastoma brain tumor stem cell models, decreased tumor burden, and prolonged survival in orthotopic xenograft models.[7] These findings illustrate the type of evidence required for successful p53-directed therapeutic translation in GBM: molecularly appropriate patient selection, CNS exposure, pharmacodynamic confirmation, and intracranial efficacy.[8]

Rather than evaluating p53 targeting solely from a molecular oncology perspective, this narrative review develops a CNS-specific framework for evaluating p53 pathway-targeted therapy in GBM.

The central argument is that p53-directed strategies should be judged by the alignment of tumor biological dependency, CNS-relevant drug exposure, pharmacodynamic evidence of pathway modulation, and neuro-oncology-specific clinical benefit. Accordingly, the review emphasizes therapeutic resistance, molecular stratification, CNS pharmacology, biomarker-guided patient selection, and clinically meaningful neurological outcomes.

Methods

This article was designed as a narrative review rather than a systematic review or meta-analysis. The aim was to develop a CNS-specific translational framework for p53 pathway-targeted therapy in glioblastoma by integrating evidence from molecular biology, drug development, CNS pharmacology, and clinical translation. Relevant literature was selectively identified through targeted searches of PubMed, Web of Science, Scopus, and Google Scholar from database inception to June 2026. Search terms included combinations of glioblastoma, GBM, p53, TP53, mutant p53, MDM2, MDM4, USP7, WIP1, blood-brain barrier, CNS pharmacokinetics, unbound brain exposure, temozolomide resistance, radiotherapy resistance, glioma stem cells, and clinical trial design.

Priority was given to glioblastoma-specific original studies, CNS pharmacokinetic/pharmacodynamic investigations, molecularly annotated preclinical studies, early-phase clinical trials, and high-quality reviews directly relevant to p53 pathway biology and therapeutic translation. Seminal earlier studies were retained when they provided foundational evidence that could not be replaced by more recent publications.

Because this was a narrative review, formal risk-of-bias assessment, systematic screening, and meta-analysis were not performed. Study selection was guided by relevance to the predefined translational questions rather than by formal systematic-review eligibility criteria. The literature was synthesized around predefined translational questions: which p53 pathway states may be therapeutically actionable, whether candidate agents can achieve CNS-relevant exposure, how pathway modulation should be pharmacodynamically confirmed, and which clinical endpoints are meaningful in GBM.

Molecular Landscape of the p53 Pathway in Glioblastoma

Molecular Context of p53 Dysfunction in Glioblastoma

The molecular landscape of glioblastoma provides the biological context required for interpreting p53 pathway dysfunction and therapeutic vulnerability. In the WHO CNS5 era, glioblastoma diagnosis increasingly relies on integrated molecular and histological classification rather than morphology alone.[9,10] This transition is particularly relevant for targeted therapy because tumors with the same histological diagnosis may differ substantially in genetic alterations, pathway dependencies, and treatment responses.[11]

For p53 pathway-targeted therapy, molecular classification should not be viewed as a descriptive framework but as a tool for identifying biologically meaningful therapeutic subgroups. Key molecular features, including IDH status, TERT promoter mutation, EGFR alteration, chromosome 7 gain/chromosome 10 loss, MGMT promoter methylation, CDKN2A/B status, PTEN alteration, and TP53 status, define distinct biological states that may influence the response to p53 modulation.[12] However, these markers should be interpreted within the context of pathway function rather than as isolated abnormalities.[13]

TP53 alteration represents one important mechanism of p53 pathway disruption in glioblastoma, but it does not fully define therapeutic sensitivity. TP53-wild-type tumors may exhibit functional p53 suppression through increased MDM2 or MDM4 activity, altered upstream regulation, or impaired downstream apoptotic signaling. Conversely, TP53-mutant tumors may display different biological behaviors depending on whether mutations result in loss-of-function, dominant-negative effects, or gain-of-function phenotypes. Therefore, TP53 status should be considered a starting point for molecular stratification rather than a standalone therapeutic decision marker.

A clinically relevant framework for p53-targeted therapy should therefore define the functional state of the p53 network, including upstream regulation, downstream response capacity, DNA damage response status, and survival pathway activation. This approach shifts p53 pathway-targeted therapy from a mutation-centered strategy toward a context-dependent precision oncology model in which treatment selection is guided by functional pathway dependency rather than TP53 status alone.[14]

TP53 Alterations and Their Functional Consequences

TP53 alterations are biologically important in glioblastoma, but their therapeutic implications depend on the functional consequences of individual alterations rather than mutation status alone. TP53 mutations may result in loss of tumor suppressive activity, dominant-negative inhibition of residual wild-type p53 function, or gain-of-function phenotypes that actively promote malignant behaviors. These distinct biological outcomes create different therapeutic challenges and opportunities.[15]

Loss-of-function TP53 alterations impair canonical p53-mediated responses, including cell-cycle arrest, apoptosis, and DNA damage control. In this setting, therapeutic restoration is challenging because effective treatment would need either to restore functional p53 signaling or to exploit vulnerabilities created by p53 loss. Dominant-negative mutant p53 proteins can further suppress remaining wild-type p53 activity by interfering with p53 tetramer formation or transcriptional function, potentially increasing treatment resistance.[16]

Gain-of-function mutant p53 represents a more complex therapeutic scenario. Certain mutant p53 variants may acquire oncogenic properties that promote proliferation, invasion, stem-like characteristics, and resistance to therapy. In glioblastoma, specific mutant p53 contexts have been associated with altered responses to temozolomide and radiotherapy, suggesting that mutant p53 biology may contribute directly to aggressive tumor phenotypes rather than simply representing loss of tumor suppression.

However, TP53 mutation alone remains insufficient as a predictive biomarker for p53-targeted therapy in glioblastoma. The therapeutic relevance of a specific TP53 alteration depends on mutation type, mutant protein stability, cellular state, DNA damage response capacity, and the availability of downstream apoptotic pathways. Consistent with this complexity, clinical and genomic studies have shown variable associations between TP53 alterations and glioblastoma outcomes, indicating that TP53 status should be interpreted within a broader molecular framework rather than as an isolated determinant of prognosis or treatment response.[17]

Therapeutically, TP53-mutant GBM should be distinguished from TP53-wild-type disease. Potential strategies include mutant p53 reactivation, mutant protein degradation, and synthetic-lethal approaches, but these remain less mature than MDM2-axis inhibition because of mutation heterogeneity, uncertain pharmacodynamic markers, and the requirement for effective CNS exposure.[18]

Regulatory Networks Shaping p53 Therapeutic Vulnerability: MDM2/MDM4, CDKN2A/ARF, PTEN/AKT, and DNA Damage Response

The therapeutic relevance of p53 in glioblastoma is determined not only by TP53 status but also by regulatory networks that control p53 stability, transcriptional activity, and cellular responses to stress. Among these regulators, MDM2-mediated suppression represents the most clinically tractable mechanism for pharmacological p53 reactivation in TP53-wild-type tumors, whereas MDM4-mediated suppression remains biologically relevant but less clinically developed.

MDM2 promotes p53 degradation through ubiquitin-mediated regulation, whereas MDM4 primarily suppresses p53 transcriptional activity. In glioblastomas retaining wild-type TP53, increased MDM2 or MDM4 activity may functionally inactivate p53 despite preservation of the TP53 gene. This provides a strong rationale for MDM2-axis inhibition as a strategy to restore endogenous p53 activity. However, MDM2 amplification or overexpression alone may not be sufficient to predict therapeutic response because effective p53 reactivation also requires intact downstream apoptotic machinery and appropriate CNS drug exposure.[15]

Other components of the p53 regulatory network further influence therapeutic vulnerability. CDKN2A/ARF alterations can disrupt the regulatory relationship between cell-cycle control and the MDM2-p53 pathway, potentially reducing the effectiveness of p53 activation.[19] Similarly, PTEN loss or PI3K/AKT pathway activation may increase survival signaling and raise the threshold required for p53-induced apoptosis. In such tumors, p53 stabilization may lead primarily to cell-cycle arrest or senescence rather than durable tumor elimination, suggesting the need for rational combination strategies.[20]

The DNA damage response (DDR) context also determines how glioblastoma cells interpret therapeutic stress. Because radiotherapy and temozolomide rely on DNA damage induction, alterations in DNA repair capacity, replication stress responses, and checkpoint regulation may influence whether p53 activation results in apoptosis, senescence, repair, or survival. Therefore, p53-targeted therapy should be considered within the broader framework of cellular stress response rather than as an isolated pathway intervention.[21]

Taken together, these regulatory contexts suggest that the most immediately actionable p53 pathway state in GBM is not TP53 mutation itself, but functional suppression of otherwise intact p53 signaling. TP53-wild-type tumors with MDM2-driven p53 suppression provide the clearest current rationale for pharmacological p53 reactivation. MDM4-mediated suppression may define an additional biologically plausible subgroup, but its therapeutic tractability and predictive value remain less established. Therapeutic sensitivity requires not only wild-type TP53 and an upstream inhibitory mechanism, but also preserved downstream response capacity and sufficient CNS tumor exposure. Therefore, MDM2 and MDM4 alterations should be interpreted as components of a broader functional pathway state rather than as standalone eligibility markers.

CDKN2A/ARF, PTEN/AKT signaling, and DNA damage response programs further modify whether p53 activation produces apoptosis, durable arrest, senescence, repair, or adaptive survival. CDKN2A/ARF links cell-cycle control to the MDM2-p53 axis, whereas PTEN loss or PI3K/AKT activation may raise the apoptotic threshold even when upstream p53 signaling is restored.[14,15] DNA repair context is also relevant because MGMT promoter methylation, mismatch repair status, replication stress, and checkpoint dependence influence how GBM cells interpret radiotherapy- or temozolomide-induced injury. These interacting pathways explain why p53 activation may require combination strategies rather than single-agent pathway modulation in selected tumors.

p53 Pathway Dysregulation and Therapeutic Resistance in GBM

p53 Dysfunction in DNA Damage-Induced Therapeutic Resistance

Radiotherapy and temozolomide (TMZ) remain central components of glioblastoma treatment because they induce DNA damage and activate cellular stress responses. The p53 pathway is a key determinant of how tumor cells interpret such

stress, regulating cell-cycle arrest, DNA repair, apoptosis, senescence, and survival. In GBM, however, p53 pathway dysfunction may shift treatment-induced damage from irreversible cell death toward temporary arrest, senescence, repair-mediated survival, or adaptive resistance.[22]

Radiation-induced DNA damage activates checkpoint signaling, but the final cellular outcome depends on the balance between repair capacity, apoptotic competence, and long-term cell-state adaptation. In tumors with impaired p53-mediated apoptosis, radiation exposure may induce reversible growth arrest or senescence rather than durable tumor elimination. Radiation-induced senescent cells may also contribute to recurrence through senescence-associated secretory phenotype signaling, suggesting that p53 activation is not uniformly beneficial unless it drives a durable antitumor cell fate.[23,24]

TMZ resistance is similarly shaped by the interaction between DNA repair mechanisms, p53 signaling, and survival pathways.[25] MGMT-mediated repair, mismatch repair status, replication stress, and adaptive DNA repair programs influence whether TMZ-induced lesions become lethal. USP7 has also been implicated in TMZ resistance through regulation of MGMT stability, linking DNA repair resistance to the broader p53-MDM2 regulatory network.[26]

These observations have a direct implication for p53 pathway-targeted therapy: p53 activation alone may be insufficient if DNA damage is efficiently repaired, if apoptotic machinery is defective, or if survival pathways remain dominant. Combination strategies should therefore be selected according to the resistance mechanism present in a given tumor rather than added empirically. Examples include pairing p53 activation with DNA repair inhibition, apoptosis-sensitizing approaches, or pathway-directed therapies that lower the threshold for p53-mediated tumor cell death.

p53 Pathway and Glioma Stem-Like States

Glioma stem-like cells (GSCs) represent a critical component of GBM therapeutic resistance and recurrence. These cells exhibit self-renewal capacity, phenotypic plasticity, enhanced DNA repair activity, relative quiescence, and adaptation to hypoxic or inflammatory microenvironments. The persistence of stem-like and treatment-tolerant populations after standard therapy may partly explain why reduction of tumor bulk does not necessarily translate into durable disease control.[27,28]

The relationship between p53 signaling and GSC biology is context dependent. Because p53 regulates cell-cycle control, differentiation, genomic stability, and stress responses, p53 pathway alterations may influence whether GSCs undergo elimination, differentiation, arrest, senescence, or survival after therapeutic stress. Importantly, p53 activation in stem-like populations may not uniformly produce apoptosis; depending on cellular state and downstream pathway competence, it may instead induce reversible growth suppression or senescence.

This heterogeneity has practical implications for therapeutic evaluation. Multiregional sampling has further shown that glioma stem-like populations derived from the same tumor may differ in molecular programs and therapeutic responses, reinforcing the need for models that preserve spatial and functional heterogeneity.[29] Conventional tumor cell lines may not adequately represent the vulnerability of stem-like compartments. Therefore, p53-directed agents should be tested in patient-derived GSC models, organoids, orthotopic systems, and BBB-relevant platforms that better preserve tumor heterogeneity and clinically relevant cell states. From a translational perspective, TP53 status alone is insufficient; candidate p53-directed therapies should also be evaluated for activity against stem-like and treatment-tolerant compartments rather than only against bulk tumor cells.

Mutant p53 and Aggressive Tumor Phenotypes

Gain-of-function (GOF) mutant p53 represents a distinct therapeutic challenge because mutant p53 proteins may actively contribute to tumor progression rather than simply reflect loss of tumor suppressive activity. Depending on mutation type, protein stability, and cellular context, mutant p53 may promote proliferation, invasion, genomic instability, stem-like properties, or resistance to therapeutic stress, although these effects should not be generalized across all TP53-mutant GBMs. In GBM, the biological consequences of mutant p53 appear highly context dependent.[30] Specific mutant p53 variants or isoform-specific alterations have been associated with increased proliferation and invasion, reduced apoptosis, and altered responses to TMZ and radiotherapy, suggesting that mutant p53 may contribute directly to aggressive tumor

phenotypes in selected molecular settings.[31] Their biological and therapeutic significance remains dependent on mutation type, mutant protein accumulation, cellular state, and cooperating genomic alterations.

The therapeutic implication is that TP53-mutant GBM should not be treated as a single category. Mutant p53-directed strategies may be relevant only when a defined mutant protein state, pathway dependency, and pharmacodynamic marker can be demonstrated. At present, this makes mutant p53 biology an important precision oncology opportunity, but not yet an established therapeutic class in GBM.

CNS Pharmacology: The Central Barrier to p53 Pathway-Targeted Therapy in GBM

BBB/BTB Heterogeneity and Tumor Compartmentalization

The blood-brain barrier (BBB) represents a major determinant of therapeutic success in GBM. However, the BBB in GBM is not a uniform structure but a spatially heterogeneous interface shaped by tumor location, vascular remodeling, treatment status, and disease progression. The enhancing tumor core, peritumoral region, and non-enhancing infiltrative margin represent distinct pharmacological compartments with different degrees of barrier disruption and drug accessibility.[32]

This heterogeneity is directly relevant to p53 pathway-targeted therapy. Drug exposure measured in enhancing tumor regions may not reflect exposure in infiltrative tumor cells that survive standard therapy and contribute to recurrence. Therefore, preclinical and clinical evaluation should determine whether therapeutically meaningful concentrations can be achieved in recurrence-relevant compartments, not only in the contrast-enhancing tumor mass. BBB-relevant models, including advanced in vitro barrier systems and orthotopic models, are increasingly important because conventional tumor models may overestimate drug accessibility.[33,34]

Brain Exposure and Target Engagement Rather Than Plasma Exposure

A major challenge in CNS drug development is that systemic exposure does not necessarily represent pharmacologically active drug exposure within brain tumors. For CNS-directed therapies, unbound brain exposure is more informative than total plasma or total brain concentration because only free drug is available for target interaction and downstream biological effects. The unbound brain-to-plasma concentration ratio (Kp, uu, brain) provides a useful measure of effective brain penetration.[35]

This concept is particularly relevant for p53-targeted agents. A compound with high biochemical potency may still fail clinically if sufficient free drug concentrations cannot be achieved at the tumor site. Conversely, limited total brain penetration does not necessarily indicate failure if potent target engagement occurs at relevant concentrations. Therefore, the critical question is not simply whether a drug enters the brain, but whether unbound drug exposure at the relevant tumor site is sufficient to engage the intended target and modulate the p53 pathway.

The Delivery–Potency–Efficacy Framework for p53-Targeted Therapy

The relationship between delivery, potency, and efficacy provides a practical framework for evaluating p53-targeted therapies in glioblastoma. This framework addresses three sequential questions: whether the drug reaches relevant CNS tumor compartments, whether exposure exceeds the threshold required for target modulation, and whether pathway modulation produces meaningful biological and clinical effects.

BI-907828 provides an illustrative example of this principle. Its glioblastoma-focused evidence suggests that a compound with limited or incomplete BBB penetration may still produce intracranial activity when potency, target engagement, and pathway activation are sufficient in the relevant tumor compartment.[36] The broader lesson is not that BBB penetration is unimportant, but that CNS translation should be judged by the integrated relationship among unbound exposure, pharmacodynamic modulation, and intracranial efficacy.

Accordingly, CNS drug development for p53-targeted therapy should prioritize pharmacokinetic/pharmacodynamic integration. Demonstrating molecular target modulation within tumor tissue may be more informative than relying solely on systemic pharmacokinetic measurements or radiographic response.

CNS Pharmacology Requirements Across p53-Targeted Strategies

Different p53-targeted strategies require different CNS pharmacological considerations. MDM2 inhibitors require sufficient exposure to stabilize wild-type p53 and induce downstream transcriptional responses, including CDKN1A/p21, PUMA, BAX, and MDM2 feedback. MDM2/MDM4 dual inhibitors require additional attention to selectivity and tolerability because broader pathway modulation may increase toxicity. For mutant p53-directed therapies, mutation-specific engagement, protein-level modulation, and adequate tumor exposure are essential. Strategies targeting regulatory proteins such as USP7 or WIP1 require particular caution because these proteins regulate multiple biological pathways beyond p53. Drug delivery technologies may improve CNS accessibility for selected agents, but improved delivery alone does not establish therapeutic validity. Any delivery strategy must still demonstrate tumor-relevant exposure, pharmacodynamic pathway modulation, meaningful antitumor activity, and acceptable neurological safety.[37] Clinical studies using implantable ultrasound devices further indicate that repeated, localized BBB opening can be incorporated into drug-delivery protocols for recurrent GBM. However, successful delivery of one therapeutic agent cannot be assumed to establish adequate exposure or efficacy for p53-directed compounds.[38]

Therapeutic Strategies Targeting the p53 Pathway in GBM

MDM2/MDM4 Axis Inhibition: The Most Clinically Tractable Strategy

Among p53-targeted strategies in GBM, inhibition of the MDM2-p53 axis currently appears to be the most biologically and pharmacologically tractable approach, particularly in tumors retaining wild-type TP53. Unlike mutant p53-directed therapies, which require restoration or elimination of altered proteins, MDM2 inhibition aims to reactivate endogenous wild-type p53 by disrupting negative regulation. MDM2 promotes p53 degradation through interaction with the p53 transactivation domain, whereas MDM4 suppresses p53 transcriptional activity. Pharmacological inhibition of these regulatory interactions can stabilize p53 and activate downstream transcriptional programs involving CDKN1A/p21, PUMA, BAX, and other mediators of cell-cycle arrest or apoptosis.

Several MDM2 inhibitors and MDM2-p53 interaction-directed strategies have been developed, including idasanutlin, navtemadlin (KRT-232), BI-907828 (brigimadlin), and peptide-based or transcriptome-informed approaches targeting the MDM2-p53 interaction.[39,40] Their relevance to GBM should not be inferred only from systemic oncology activity, because CNS exposure and tumor-tissue pharmacodynamics are decisive. BI-907828 provides one of the clearest GBM-specific preclinical examples because available evidence supports pharmacologically meaningful CNS and tumor exposure, p53 pathway activation, and intracranial antitumor activity despite limited BBB penetration in TP53-wild-type models. Navtemadlin is important from a translational design perspective because surgical window-of-opportunity studies can directly assess tumor drug concentration and pharmacodynamic response rather than relying on plasma pharmacokinetics alone.[41] By contrast, MDM2 inhibitors with limited GBM-specific CNS PK/PD evidence should be considered mechanistically plausible but less mature for neuro-oncology translation.

However, MDM2 inhibition should not be considered a universal strategy for all GBMs. Therapeutic sensitivity is expected to require wild-type TP53, demonstrable upstream pathway suppression—most clearly involving MDM2—preserved downstream response capacity, and sufficient CNS tumor exposure. MDM2 overexpression alone is therefore insufficient as a selection biomarker. Future development should integrate TP53 status, MDM2/MDM4 regulation, apoptotic competence, CNS PK/PD confirmation, and toxicity monitoring. MDM4 adds a further challenge because it suppresses p53 transcriptional activity independently of MDM2-mediated degradation and may also participate in broader regulatory functions beyond the canonical MDM2-p53 axis.[42] Dual MDM2/MDM4 inhibition may therefore be rational in selected tumors, but its clinical development remains limited by pharmacological complexity and tolerability concerns. Sulanemadlin, a stabilized cell-permeating α-helical peptide designed to inhibit both MDM2 and MDM4, illustrates an alternative dual-targeting strategy, although its development outside GBM does not establish CNS exposure or efficacy in glioblastoma.[43] Emerging MDM2-directed degradation strategies, including PROTAC-based approaches, may further expand this therapeutic space, but their relevance to GBM will require CNS exposure and tumor-tissue pharmacodynamic validation.[44]

Mutant p53 Reactivation and Degradation Strategies

Mutant p53 pathway-targeted therapy represents an attractive precision oncology strategy because selected TP53 mutations may create tumor-specific vulnerabilities.[18] Unlike MDM2 inhibition, which reactivates endogenous wild-type p53, mutant p53 approaches aim to restore tumor-suppressive function, eliminate oncogenic mutant proteins, or exploit dependencies created by mutant p53 biology. APR-246 (eprenetapopt) is among the most extensively studied compounds developed to restore or exploit mutant p53-associated vulnerabilities in oncology, but its relevance to GBM remains uncertain because GBM-specific CNS exposure, mutation-level patient selection, and tumor-tissue pharmacodynamic evidence are limited.[45] Mutant p53 degradation strategies provide a different rationale by targeting mutant p53 stabilization or accumulation rather than attempting to restore wild-type function.[46,47] More recent induced-proximity approaches suggest that accumulated mutant p53 proteins may be selectively targetable, although their applicability to GBM will depend on mutation prevalence, mutant protein accumulation, CNS penetration, and reliable markers of target engagement.[48]

Targeting the Broader p53 Regulatory Network

Beyond direct targeting of p53 or MDM2, broader regulatory nodes may influence p53 stability, DNA damage signaling, and cellular survival. USP7/HAUSP regulates substrates within and beyond the p53–MDM2 axis and has also been linked to MGMT-associated temozolomide resistance in GBM.[49] WIP1/PPM1D negatively regulates stress-response and DNA damage checkpoint signaling, providing a general mechanistic rationale for therapeutic investigation. However, current intervention evidence is derived predominantly from non-GBM tumor models, and GBM-specific therapeutic relevance remains unestablished.[50] PTEN loss or PI3K/AKT activation may further reduce the likelihood that upstream p53 stabilization will produce apoptosis, supporting context-dependent combination strategies rather than isolated pathway activation.

These network-level targets remain substantially less mature than selective MDM2 inhibition in GBM. Because USP7, WIP1/PPM1D, and PI3K/AKT regulate multiple p53-dependent and p53-independent processes, responses cannot be interpreted as evidence of p53 pathway modulation without appropriate pharmacodynamic controls.[51] Their most plausible near-term role is therefore in biomarker-guided combination studies supported by evidence of pathway dependency, CNS exposure, tumor-tissue target engagement, and acceptable neurological safety.

Gene-, Immune-, and Combination-Based Approaches

Gene- and immune-based approaches provide additional opportunities for p53 pathway modulation but remain less clinically mature in GBM than small-molecule MDM2-axis strategies. p53 gene therapy aims to restore functional p53 expression through viral or nanoparticle-based delivery,[52] whereas immune-based strategies attempt to exploit mutant p53-derived antigens or enhance antitumor immune recognition.[53] In GBM, however, CNS delivery limitations, tumor heterogeneity, immunosuppressive microenvironments, corticosteroid exposure, and neuroinflammatory risks remain major barriers to immune-, gene-, and virotherapy-based strategies.[54] Early clinical evaluation of the oncolytic adenovirus DNX-2401 combined with pembrolizumab supports the feasibility of viro-immunotherapy in recurrent GBM, although this evidence reflects a therapeutic platform rather than direct validation of p53-specific immune therapy.[55] Recent locally delivered, multi-antigen CAR-T studies further illustrate both the feasibility of intracranial immune therapy and the persistent challenges of antigen heterogeneity and response durability in recurrent GBM.[56,57]

Intratumoral G47Δ oncolytic herpesvirus has also reached Phase 2 evaluation in residual or recurrent GBM, demonstrating that locally delivered virotherapy has progressed beyond exclusively preclinical investigation.[58] These virotherapy studies do not validate p53-specific treatment; their relevance to the present framework is limited to demonstrating the clinical feasibility and translational constraints of locally delivered viral platforms in GBM.[59]

Given the complexity of GBM, combination therapy is likely to be more realistic than broad unselected monotherapy. Potential combinations include MDM2 inhibitors with radiotherapy or TMZ in TP53-wild-type tumors, mutant p53-directed approaches with DNA damage response inhibitors, and p53 pathway modulation combined with survival-pathway inhibition or immune-based approaches.[60] These combinations should not be justified by the simple

accumulation of mechanisms. They should be selected according to molecular dependency, CNS pharmacology, pharmacodynamic validation, and neuro-oncology-specific safety.

Representative p53 pathway-targeted agents, their molecular contexts, current developmental status, major translational challenges, and key supporting references are summarized in Table 1.

Table 1 Major p53 Pathway-Targeted Therapeutic Strategies in Glioblastoma and Their Translational Maturity

Therapeutic Strategy	Representative Agents or Approaches	Most Rational Molecular Context	CNS-Specific Evidence and Key Translational Limitation	Current Translational Maturity in GBM
MDM2 inhibition	BI-907828 (brigimadlin); navtemadlin (KRT-232); idasanutlin; peptide-based MDM2-p53 inhibitors	TP53-wild-type GBM with evidence of MDM2-driven p53 suppression and preserved downstream apoptotic competence	Requires tumor-relevant unbound exposure and tumor-tissue pharmacodynamic confirmation. BI-907828 demonstrates intracranial activity despite limited BBB penetration, whereas navtemadlin provides a perioperative PK/PD model.	The most mechanistically and pharmacologically tractable p53-directed strategy in GBM. GBM-specific preclinical and window-of-opportunity evidence is emerging, but clinical efficacy remains unestablished.[7,8,36,39–41]
Dual MDM2/MDM4 targeting	Sulanemadlin (ALRN-6924); dual MDM2/MDM4 antagonism; combined blockade	TP53-wild-type GBM with evidence of MDM4-dominant suppression or incomplete pathway activation after selective MDM2 inhibition	Dual targeting may restore transcriptional activity when MDM4 limits p53 output, but increases requirements for selectivity, CNS exposure, tolerability, and pharmacodynamic attribution.	Biologically plausible but less clinically developed than selective MDM2 inhibition; predictive selection criteria and GBM-specific CNS efficacy remain unvalidated.[42,43]
USP7/HAUSP or WIP1/PPM1D targeting	USP7 inhibitors; WIP1 inhibitors; biomarker-guided network combinations	Context-dependent p53-network dysregulation involving p53-MDM2 stability, DNA-damage signaling, MGMT-associated resistance, or checkpoint adaptation	Pleiotropic p53-dependent and p53-independent functions complicate target attribution, biomarker selection, and toxicity interpretation. CNS exposure and GBM-specific target engagement remain poorly characterized.	Early/preclinical. Most rational as a biomarker-guided combination strategy rather than an unselected monotherapy.[26,49–51]
Mutant p53 reactivation	APR-246 (eprenetapopt); mutation-directed conformational rescue; redox- or vulnerability-based approaches	Selected TP53-mutant tumors with a defined rescuable mutant state, demonstrable mutant-p53 dependency, and measurable pharmacodynamic markers	Activity is mutation- and context-dependent. Mutant-protein abundance, CNS exposure, restored transcriptional output, and tumor-tissue pharmacodynamics must be demonstrated.	Established as an oncology concept but immature in GBM; no validated mutation-specific selection framework or clinical efficacy.[18,45,46]
Mutant p53 degradation	Mutant-p53 stabilization targeting; induced-proximity degraders; protein-depletion strategies	Tumors with accumulated or stabilized oncogenic mutant p53 protein and demonstrable dependence on that protein state	Requires protein-level confirmation of mutant-p53 accumulation and depletion, mutation-informed selection, adequate CNS tumor exposure, and evidence that depletion produces antitumor activity.	Highly experimental and predominantly preclinical in GBM.[46–48]
Gene-, immune-, and virotherapy-based approaches	Viral or nanoparticle p53 delivery; mutant-p53 antigen-directed immunotherapy; oncolytic or vector-based platforms	Selected vector-deliverable, antigen-defined, or immune-responsive settings	Major barriers include heterogeneous delivery, immunosuppressive microenvironments, corticosteroid exposure, neuroinflammation, antigen heterogeneity, and neurological safety. Existing GBM virotherapy and CAR-T studies demonstrate platform feasibility rather than p53-specific efficacy.	Highly investigational for p53-directed GBM therapy; no validated treatment-selection framework or established clinical benefit.[52–59]
Biomarker-guided combination strategies	MDM2 inhibitor plus radiotherapy or TMZ; p53 modulation plus DDR, PI3K/AKT, apoptosis-sensitizing, or immune-directed therapy	Molecularly defined tumors in which p53 activation alone is unlikely to produce durable apoptosis because of DNA-repair capacity, survival signaling, or treatment-evolved states	Combination selection must be driven by a defined resistance mechanism and supported by CNS PK/PD, tumor-tissue target engagement, overlapping-toxicity assessment, and neurological safety.	Mechanistically attractive but not clinically validated as a class in GBM; should be tested in biomarker-enriched, mechanism-specific studies rather than empirically.[20–26,60]

Notes: Translational maturity refers specifically to GBM and does not imply validated routine treatment selection or established clinical efficacy.

Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; DDR, DNA damage response; GBM, glioblastoma; HAUSP, herpesvirus-associated ubiquitin-specific protease; MDM2, mouse double minute 2 homolog; MDM4, mouse double minute 4 homolog; PD, pharmacodynamics; PK, pharmacokinetics; TMZ, temozolomide; TP53, tumor protein p53; USP7, ubiquitin-specific protease 7; WIP1, wild-type p53-induced phosphatase 1.

Molecular Stratification and Patient Selection for p53 Pathway-Targeted Therapy in Glioblastoma

TP53 Status as the Entry Point, Not a Treatment Rule

TP53 status is an essential entry point for selecting p53-directed therapies in GBM, but it should not be used as an independent treatment rule. The distinction between TP53-wild-type and TP53-mutant tumors is therapeutically meaningful because it separates strategies aimed at reactivating endogenous wild-type p53 from those aimed at mutant p53 reactivation, mutant protein degradation, or synthetic lethality.

In TP53-wild-type GBM, p53 remains genetically intact and may be pharmacologically reactivated if it is functionally suppressed by MDM2, MDM4, or related upstream regulatory mechanisms. This setting currently provides the strongest rationale for MDM2-axis inhibition, provided that upstream p53 suppression and preserved downstream response capacity can be demonstrated. However, TP53-wild-type status alone is insufficient because downstream apoptotic competence, DNA damage response status, survival signaling, CNS drug exposure, and intratumoral molecular heterogeneity all influence whether p53 activation produces apoptosis, senescence, or adaptive survival.

In TP53-mutant GBM, mutation presence alone is also insufficient because therapeutic relevance depends on mutation type, mutant protein accumulation, cellular context, and the availability of measurable target engagement. Different TP53 alterations may produce loss-of-function, dominant-negative, or gain-of-function biology, and treatment strategies will likely require mutation-level characterization, evidence of mutant protein accumulation or dependency, and pharmacodynamic markers of target engagement.[61]

Functional Pathway Stratification Beyond TP53

Beyond TP53 genotype, the functional state of the p53 regulatory network provides a more clinically meaningful framework for patient selection. In TP53-wild-type GBM, MDM2 amplification or overexpression provides the clearest current molecular rationale for pharmacological p53 reactivation, whereas MDM4-mediated suppression remains a less clinically developed context. Rare MDM2-related genomic events, such as MDM2::PDGFRA fusion, may define additional investigational contexts, but their predictive and therapeutic relevance cannot currently be generalized to broader GBM populations.[62] However, effective p53 pathway activation requires more than removal of upstream inhibition. The transcriptional consequences of p53 stabilization may also depend on chromatin accessibility and the availability of appropriate transcriptional cofactors, providing an additional reason why TP53-wild-type status alone cannot define therapeutic sensitivity.[63] Tumors with impaired apoptotic machinery, PTEN loss or AKT activation, altered DNA damage response, or stem-like cell-state features may show reduced sensitivity even when p53 is stabilized.

A clinically relevant stratification approach should therefore integrate multiple layers of biological information, including TP53 mutation status and mutation type, MDM2/MDM4 regulation, downstream apoptotic competence, DNA repair context, survival pathway activation, and tumor cell-state features. This integrated approach is more likely to identify therapeutic vulnerability than any single marker alone and moves p53 pathway-targeted therapy toward functional precision oncology. The major p53 pathway-related molecular contexts, their biological meanings, potential therapeutic implications, current limitations, and key supporting references are summarized in Table 2.

A Biopsy-Based Selection Framework for Future Clinical Development

Based on current biological evidence and CNS pharmacological constraints, p53 pathway-targeted therapy in GBM is unlikely to succeed as an unselected universal strategy. It should instead be developed through biomarker-enriched patient selection. The most clinically tractable investigational subgroup currently appears to be TP53-wild-type GBM with evidence of MDM2-driven p53 suppression and preserved downstream response capacity. MDM4-dominant tumors represent a biologically plausible but less clinically developed subgroup. In this subgroup, the p53 pathway is genetically intact but functionally restrained, providing a rational context for MDM2- or MDM2/MDM4-directed therapy.[64]

For TP53-mutant GBM, treatment selection should be guided by mutation-specific functional consequences rather than mutation status alone. Selected tumors with demonstrable mutant p53 dependency may eventually be candidates for mutant p53 reactivation, degradation, or synthetic-lethal strategies, although these approaches remain less clinically

Table 2 p53 Pathway-Related Molecular Contexts in Glioblastoma and Their Translational Implications

Biomarker or Pathway State	Biological Meaning	Potential Therapeutic Implication	Key Limitation and Current Evidence
TP53 wild-type	p53 may remain structurally intact but can be functionally restrained by upstream negative regulators or an unfavorable downstream pathway context.	An entry criterion for MDM2-axis investigation when an upstream suppressive mechanism and preserved downstream response capacity are demonstrated.	Wild-type TP53 alone does not establish pathway dependency, apoptotic competence, or treatment sensitivity. Its predictive value remains context dependent.[7,8,15,39–41]
TP53 mutant	May represent loss-of-function, dominant-negative, or gain-of-function biology, with variable mutant-protein stability, accumulation, and dependency.	May support mutation-specific reactivation, mutant-p53 degradation, or synthetic-lethal strategies in selected tumors.	Mutation heterogeneity, functional classification, protein accumulation, pharmacodynamic markers, and CNS exposure remain unresolved; TP53-mutant GBM is not a single therapeutic category.[15–18,31,45–48,61]
MDM2-driven p53 suppression	Promotes degradation of otherwise wild-type p53 and limits stress-induced tumor-suppressive signaling.	Currently the clearest enrichment context for pharmacological p53 reactivation in TP53-wild-type GBM.	Amplification or overexpression alone is insufficient; tumor-tissue pathway activation, downstream response capacity, and CNS exposure must be confirmed.[7,8,36,39–41]
MDM4-mediated p53 suppression	Restrains p53 transcriptional activity independently of, or in addition to, MDM2-mediated degradation.	May justify dual MDM2/MDM4 targeting when selective MDM2 inhibition does not produce adequate pathway activation.	Less clinically developed than MDM2-driven suppression; predictive thresholds, CNS pharmacology, and GBM-specific efficacy are unvalidated.[42,43]
Downstream apoptotic competence	Determines whether p53 stabilization produces apoptosis rather than reversible arrest, senescence, repair, or adaptive survival.	A critical functional modifier for selecting p53-directed monotherapy versus apoptosis-sensitizing or other rational combinations.	No single validated clinical assay exists. Composite molecular and functional biomarkers and tumor-tissue pharmacodynamic readouts will likely be required.[15,23,24,41,63]
CDKN2A/ARF alteration	Disrupts cell-cycle control and the regulatory balance linking ARF, MDM2, RB, and p53 signaling.	May modify whether p53 activation produces arrest, senescence, apoptosis, repair, or adaptive survival and may influence combination selection.	Frequently co-occurs with other pathway alterations, making its independent predictive value difficult to establish.[14,15,19]
PTEN loss or PI3K/AKT activation	Enhances survival signaling and raises the apoptotic threshold despite restoration of upstream p53 signaling.	Supports biomarker-guided combinations with survival-pathway, apoptosis-sensitizing, or DNA-damage-response inhibitors rather than unselected p53 monotherapy.	Pathway redundancy, combination toxicity, CNS tolerability, and lack of prospective predictive validation remain major limitations.[20,22]
MGMT/MMR and DNA-repair context	Determines how GBM cells process temozolomide-induced DNA damage, alkylation stress, replication stress, and checkpoint activation.	May guide whether p53 activation should be combined with TMZ or with alternative DNA-repair/checkpoint-directed strategies.	Repair status can evolve after treatment, especially at recurrence or in hypermutated disease; serial reassessment may be required.[21,23–26]
Stem-like, spatially heterogeneous, or treatment-evolved state	Reflects cellular plasticity, enhanced repair capacity, quiescence, microenvironmental adaptation, regional heterogeneity, and therapy-driven evolution.	May identify tumors requiring multiregional assessment, re-stratification, resistant-compartment testing, or rational combinations rather than genotype-only selection.	No standardized clinical assay defines p53 dependency across spatial or temporal cell states; evidence remains largely preclinical and sampling dependent.[27–31,64–66]

Notes: These molecular contexts are proposed for biomarker enrichment and prospective clinical evaluation. They should not be interpreted as validated routine treatment-selection criteria.

Abbreviations: AKT, protein kinase B; CDKN2A/ARF, cyclin-dependent kinase inhibitor 2A/alternative reading frame; CNS, central nervous system; DDR, DNA damage response; GBM, glioblastoma; MDM2, mouse double minute 2 homolog; MDM4, mouse double minute 4 homolog; MGMT, O6-methylguanine-DNA methyltransferase; MMR, mismatch repair; PTEN, phosphatase and tensin homolog; RB, retinoblastoma protein; TMZ, temozolomide; TP53, tumor protein p53.

https://doi.org/10.2147/DDDT.S509447

mature than MDM2-axis inhibition. Tumors with PTEN/AKT activation, defective apoptosis, enhanced DNA repair, or stem-like states may require rational combinations rather than single-agent p53 modulation.

A practical future selection framework should combine tissue-based molecular profiling with pharmacodynamic assessment. Diagnostic or recurrent biopsy specimens may be used to assess TP53 status, MDM2/MDM4 alterations, DNA repair context, survival pathway activation, and treatment-relevant cellular states. Spatially resolved profiling demonstrates that molecular and microenvironmental states may vary across different regions of glioblastoma. Future biomarker-driven studies should therefore document sampling location and, where feasible, incorporate spatially resolved or multiregional tissue assessment.[67] Downstream apoptotic competence will likely require composite molecular or functional biomarkers rather than a single routine tissue marker. These molecular data should be interpreted together with evidence of CNS drug exposure and intratumoral target engagement. In this way, p53 pathway-targeted therapy can be developed for defined functional GBM subgroups rather than applied as a broad molecular concept.

However, most components of this framework have not yet been prospectively validated as predictive biomarkers in GBM. It should therefore be regarded as a trial-enrichment framework rather than a routine clinical treatment algorithm.

Clinical Translation Framework: From Target Engagement to Patient Benefit

Biomarker-Driven Clinical Trial Design

Clinical translation of p53-targeted therapy in GBM cannot be built by simply importing evidence from extracranial tumors. A compound may show acceptable systemic pharmacokinetics, target modulation, or antitumor activity in non-CNS malignancies, yet still fail in GBM because the therapeutic problem is spatially and clinically different. The drug must cross or bypass CNS barriers, reach infiltrative tumor regions, produce measurable p53 pathway modulation in tumor tissue, and preserve neurological function at tolerable doses. Correcting this development paradigm requires early designs that can determine whether failure reflects target biology, inadequate CNS exposure, insufficient pharmacodynamic modulation, or poor patient selection.[68]

This distinction is particularly important for p53-directed agents. In extracranial tumors, blood-based pharmacokinetics and accessible biopsies may provide relatively direct evidence of exposure and target engagement. In GBM, plasma exposure does not ensure tumor exposure, and imaging response may be confounded by edema, pseudoprogression, corticosteroid use, and treatment-related changes. Therefore, a p53-targeted agent should not be considered ready for GBM development solely because it is active in another cancer type. Figure 1 summarizes the proposed framework linking functional pathway dependency, CNS-relevant exposure, intratumoral pharmacodynamic confirmation, tumor cell-fate response, and clinically meaningful benefit.

Window-of-Opportunity Trials for PK/PD Validation

Window-of-opportunity trials are especially valuable for p53 pathway-targeted therapy because they can directly test two central translational assumptions: whether the drug reaches GBM tissue and whether it modulates the intended pathway. Early Phase 0, window-of-opportunity, and adaptive trial designs can link exposure, biological effect, and patient selection before larger efficacy trials are attempted.[69]

The most relevant model is perioperative drug administration before planned resection, followed by measurement of drug concentration and pharmacodynamic biomarkers in surgical tissue. A surgical window-of-opportunity trial of the MDM2 inhibitor navtemadlin in TP53-wild-type recurrent GBM was designed to determine achievable tumor drug concentrations and mechanisms of response and resistance.[41] This type of design is instructive because it allows investigators to measure tumor tissue exposure, assess p53 stabilization, evaluate biomarkers such as p21, PUMA, BAX, MDM2 feedback, cleaved PARP, apoptosis, or senescence, and identify resistance mechanisms.

Two testable research priorities follow from this framework. First, a perioperative PK/PD study could evaluate recurrent, resectable, TP53-wild-type GBM enriched for MDM2-mediated p53 suppression. The primary objective would be to determine whether sufficient unbound drug exposure and p53 pathway activation can be demonstrated in tumor tissue, including, where feasible, both enhancing tumor and infiltrative regions. Second, biomarker-guided studies could evaluate p53-directed combinations according to apoptotic competence, DNA repair context, and PTEN/AKT pathway

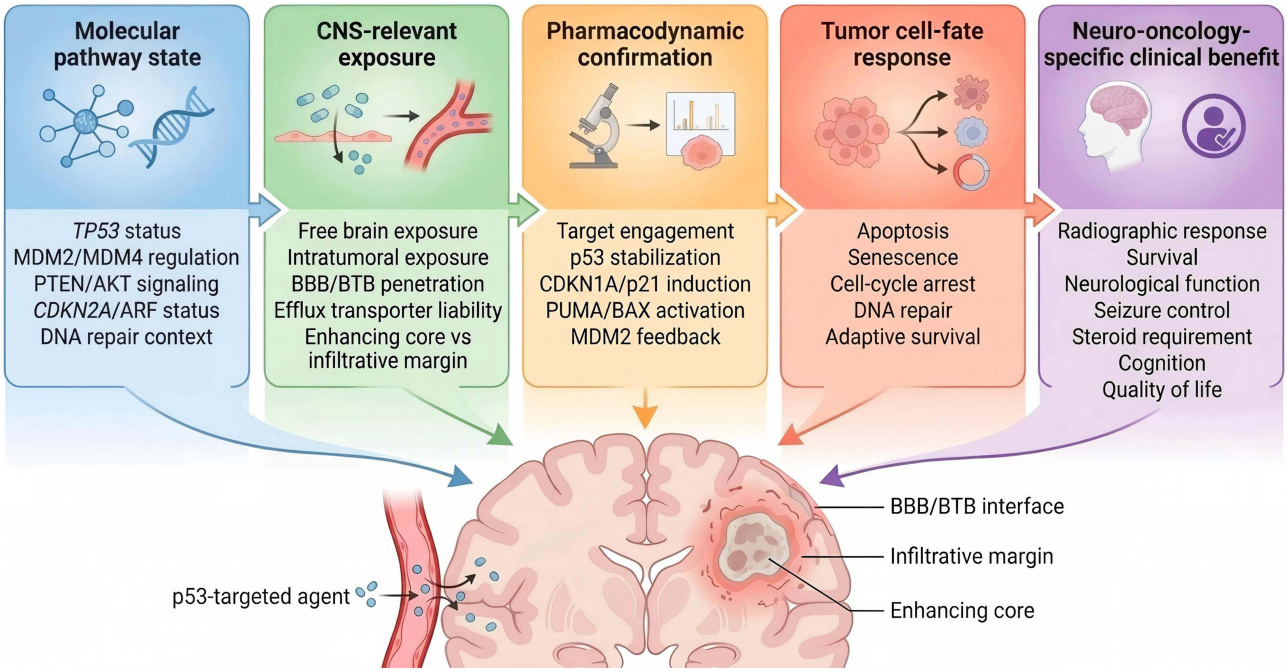

Figure 1 CNS-specific framework for p53 pathway-targeted therapy in glioblastoma. The proposed framework links molecular pathway state, CNS-relevant exposure, pharmacodynamic confirmation, tumor cell-fate response, and neuro-oncology-specific clinical benefit. TP53 status, MDM2/MDM4 regulation, PTEN/AKT signaling, CDKN2A/ARF status, DNA repair context, and downstream apoptotic competence collectively define therapeutic plausibility. Unbound brain exposure and intratumoral distribution determine whether a p53-targeted agent reaches the enhancing tumor core, the BBB/BTB interface, and the infiltrative margin. Pharmacodynamic markers establish whether pathway modulation occurs in tumor tissue and whether it results in apoptosis, senescence, cell-cycle arrest, DNA repair, or adaptive survival. Clinical translation should incorporate radiographic response, survival, neurological function, seizure control, corticosteroid requirement, cognition, and quality of life.

activation. Figure 2 presents the integrated translational pipeline for p53-targeted therapy, encompassing target biology, molecular stratification, CNS drug design, unbound brain exposure and intratumoral distribution assessment, tissue PK/PD validation, disease-relevant orthotopic and BBB-relevant models, window-of-opportunity trials, biomarker-enriched Phase II studies, rational combination strategies, and neuro-oncology-specific clinical outcomes.

Trial Settings: Newly Diagnosed versus Recurrent GBM

The optimal clinical setting for p53-targeted therapy depends on the intended mechanism. Newly diagnosed GBM offers the opportunity to combine p53 pathway agents with radiotherapy or TMZ, where p53 activation may intensify DNA damage-induced apoptosis or senescence. However, this setting introduces interpretive and safety challenges, including overlapping myelosuppression with TMZ, radiation-related edema or necrosis, corticosteroid effects, and difficulty separating the contribution of the investigational agent from standard therapy.

Recurrent GBM offers a different opportunity. It may be more suitable for early signal detection, re-biopsy, molecular re-stratification, and window-of-opportunity designs. For p53 pathway-targeted therapy, recurrent disease may be particularly valuable when the goal is to test CNS exposure, tumor-tissue pharmacodynamics, and resistance mechanisms after prior treatment.[70] However, recurrent tumors are more heterogeneous, treatment-evolved, and clinically fragile. Trial setting should therefore be selected according to the translational question being asked, rather than by assuming that one setting is universally preferable.

Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers should bridge drug exposure and clinical interpretation. For MDM2-axis therapy, candidate biomarkers include p53 stabilization, CDKN1A/p21 induction, PUMA and BAX activation, MDM2 feedback induction, cleaved PARP, and markers of apoptosis or senescence. For mutant p53-directed strategies, pharmacodynamic assessment may require mutant protein depletion, restored transcriptional activity, conformational change, or correction

https://doi.org/10.2147/DDDT.S509447

Figure 2 Integrated translational pipeline for p53 pathway-targeted therapy in glioblastoma. The pipeline is organized into three stages: preclinical validation, CNS PK/PD translation, and clinical trial development. It begins with target biology and molecular stratification, followed by CNS drug design, assessment of unbound brain exposure and intratumoral distribution, tissue PK/PD validation, testing in disease-relevant orthotopic and BBB-relevant models, window-of--opportunity trials, biomarker-enriched phase II studies incorporating molecular selection and rational combination strategies, and evaluation of neuro-oncology-specific clinical outcomes. Progression is guided by four decision checkpoints: confirmation of an actionable biological target, demonstration of sufficient CNS exposure, confirmation of tumor pharmacodynamic modulation, and justification for clinical translation. The feedback loop emphasizes iterative refinement of biomarkers, CNS pharmacology, model systems, and clinical endpoints.

https://doi.org/10.2147/DDDTS509447

of downstream pathway activity. For broader regulatory targets such as USP7 or WIP1, biomarkers must be selected carefully because pathway effects may not be p53-specific.

Clinical experience with MDM2 inhibitors outside GBM shows that pharmacodynamic biomarkers, dosing schedule, and toxicity management are closely linked.[71,72] This is relevant because p53 activation can produce systemic toxicities, especially hematologic toxicity, while also requiring CNS exposure. A useful biomarker is not merely one that changes after drug administration; it should help determine whether the intended pathway is modulated in the relevant tissue at a tolerable dose. In GBM, peripheral blood pharmacodynamics should be regarded as supportive rather than definitive evidence unless paired with tumor-tissue exposure, intratumoral pathway modulation, or another CNS-relevant measure.

Neuro-Oncology-Specific Safety and Endpoints

In neuro-oncology, clinical benefit cannot be defined only by tumor shrinkage. Updated response assessment work in glioma emphasizes the need for standardized criteria that account for imaging complexity, treatment-related changes, and clinical status.[73,74] For p53-targeted therapy, radiographic response, progression-free survival, and overall survival should be interpreted together with neurological function, seizure control, cerebral edema, steroid requirement, cognition, fatigue, quality of life, and treatment-related imaging changes.

These endpoints are not secondary considerations. A drug that modestly delays progression but worsens cognition, increases edema, or requires prolonged corticosteroid exposure may provide limited meaningful benefit. Conversely, a therapy that stabilizes disease while preserving neurological function may be clinically valuable even without dramatic tumor shrinkage. For GBM, p53 pathway-targeted trials should therefore incorporate neuro-oncology-specific endpoints from the beginning rather than adding them as exploratory outcomes.

Challenges and Future Directions

Future development should prioritize prospective validation of biomarkers that distinguish effective p53-mediated apoptosis from transient arrest, senescence, repair, or adaptive survival. The key challenge is no longer simply to define genomic p53 pathway subgroups, but to determine whether functional pathway states can predict tumor-tissue target engagement and clinically meaningful benefit across newly diagnosed and recurrent GBM.

CNS pharmacokinetics and pharmacodynamics should become early gatekeepers for p53 pathway-targeted therapy. Biochemical potency or systemic exposure should not justify GBM clinical development unless accompanied by evidence of CNS-relevant exposure, target engagement, and pathway modulation.[75] The minimum translational package should include unbound brain exposure and intratumoral distribution, efflux transporter liability, pharmacodynamic activation or inhibition of the intended p53 pathway node, and activity in orthotopic or BBB-relevant models. Without these data, failed trials may remain uninterpretable because they cannot distinguish true target failure from pharmacological underexposure.

More faithful preclinical and translational models are also needed. Conventional monolayer cell lines and subcutaneous xenografts are insufficient for evaluating CNS exposure, tumor-BBB interactions, infiltrative growth, and cell-state heterogeneity. Advanced BBB/BTB models, patient-derived GSC systems, organoids, microfluidic platforms, and orthotopic models may improve the assessment of p53 pathway modulation in clinically relevant compartments.[76,77] Longitudinal stratification is equally important because a single diagnostic biopsy may not define the p53 therapeutic opportunity across the disease course. Reoperation tissue, liquid biopsy approaches, spatial profiling, and single-cell technologies may help determine whether TP53 status, MDM2/MDM4 regulation, DNA repair state, apoptotic competence, and tumor microenvironmental features change at recurrence.[65,66]

The most important future direction is integration within the broader landscape of next-generation molecularly targeted and translational strategies for GBM.[78] p53 pathway-targeted therapy in GBM should follow a translational pipeline that connects target biology, molecular stratification, CNS PK/PD validation, orthotopic or BBB-relevant efficacy modeling, window-of-opportunity testing, biomarker-enriched trials, rational combinations, and neuro-oncology-specific endpoints. This framework prevents premature clinical translation based only on target enthusiasm and may also prevent promising agents from being abandoned before adequate exposure and pathway modulation have been demonstrated.

Conclusion

The p53 pathway remains a compelling therapeutic axis in GBM, but its clinical value depends on context rather than pathway relevance alone. p53 pathway-targeted therapy should be developed as a functional, CNS-specific precision strategy in which TP53 status, MDM2/MDM4 regulation, DNA repair context, apoptotic competence, survival signaling, stem-like cell states, and treatment-induced evolution are interpreted together.

Among current approaches, MDM2-axis inhibition in TP53-wild-type GBM with functional p53 suppression appears to be the most tractable strategy, but it remains clinically unproven and requires molecular selection, CNS PK/PD confirmation, and neuro-oncology-specific safety assessment. Mutant p53 reactivation, mutant p53 degradation, broader network targeting, gene- or immune-based strategies, and rational combinations remain important but require stronger GBM-specific evidence.

Future progress will depend on aligning tumor biology with brain-relevant exposure, intratumoral pharmacodynamic validation, biomarker-enriched trial design, faithful GBM models, and clinically meaningful neurological endpoints. This integrated approach may help distinguish true p53 target failure from inadequate CNS exposure, poor patient selection, or insufficient translational design.

Abbreviations

AKT, protein kinase B; BAX, BCL2-associated X protein; BBB, blood-brain barrier; BTB, blood-tumor barrier; CAR-T, chimeric antigen receptor T-cell; CDKN1A/p21, cyclin-dependent kinase inhibitor 1A; CDKN2A/ARF, cyclin-dependent kinase inhibitor 2A/alternative reading frame; CNS, central nervous system; DDR, DNA damage response; EGFR, epidermal growth factor receptor; GBM, glioblastoma; GOF, gain-of-function; GSCs, glioma stem-like cells; HAUSP, herpesvirus-associated ubiquitin-specific protease; IDH, isocitrate dehydrogenase; Kp,uu,brain, unbound brain-to-plasma concentration ratio; MDM2, mouse double minute 2 homolog; MDM4, mouse double minute 4 homolog; MDMX, mouse double minute X; MGMT, O6-methylguanine-DNA methyltransferase; MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase; PD, pharmacodynamics; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetics; PPM1D, protein phosphatase, Mg2+/Mn2+-dependent 1D; PROTAC, proteolysis-targeting chimera; PTEN, phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; RB, retinoblastoma protein; TERT, telomerase reverse transcriptase; TMZ, temozolomide; TP53, tumor protein p53; USP7, ubiquitin-specific peptidase 7; WHO CNS5, fifth edition of the World Health Organization Classification of Tumours of the Central Nervous System; WIP1, wild-type p53-induced phosphatase 1.

Data Sharing Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed. All data discussed are from previously published studies cited in the references.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Scientific Research Project of Zhejiang Chinese Medical University (Grant No. 2024FSYYZY51).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Wen PY, Weller M, Lee EQ. et al. 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*. 2020;22(8):1073–1113. doi:10.1093/neuonc/noaa106
2. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. 2021;18(3):170–186. doi:10.1038/s41571-020-00447-z
3. Narsinh KH, Perez E, Haddad AF, et al. Strategies to improve drug delivery across the blood–brain barrier for glioblastoma. *Curr Neurol Neurosci Rep*. 2024;24(5):123–139. doi:10.1007/s11910-024-01338-x
4. Peuget S, Zhou X, Selivanova G. Translating p53-based therapies for cancer into the clinic. *Nat Rev Cancer*. 2024;24(3):192–215. doi:10.1038/s41568-023-00658-3
5. Wang W, Liu X, Liu H, et al. p53: from understanding its structure to advances in therapeutic targeting. *Signal Transduct Target Ther*. 2026;11(1):121. doi:10.1038/s41392-025-02549-5
6. Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. *Nat Rev Drug Discov*. 2023;22(2):127–144. doi:10.1038/s41573-022-00571-8
7. Hao X, Bahia RK, Cseh O, et al. BI-907828, a novel potent MDM2 inhibitor, inhibits glioblastoma brain tumor stem cells in vitro and prolongs survival in orthotopic xenograft mouse models. *Neuro Oncol*. 2023;25(5):913–926. doi:10.1093/neuonc/noac271
8. Pellot Ortiz KI, Rechberger JS, Nonnenbroich LF, Daniels DJ, Sarkaria JN. MDM2 inhibition in the treatment of glioblastoma: from concept to clinical investigation. *Biomedicines*. 2023;11(7):1879. doi:10.3390/biomedicines11071879
9. Ocampo-Navia MI, Navas FM, Agudelo-Arrieta M, Taub-Krivoy A, Lee OHF. Molecular markers in gliomas: a practical review and algorithm proposal. *Interdiscip Neurosurg*. 2025;41:102062. doi:10.1016/j.inat.2025.102062
10. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23(8):1231–1251. doi:10.1093/neuonc/noab106
11. Melhem JM, Detsky J, Lim-Fat MJ, Perry JR. Updates in IDH-wildtype glioblastoma. *Neurotherapeutics*. 2022;19(6):1705–1723. doi:10.1007/s13311-022-01251-6
12. Lan Z, Li X, Zhang X. Glioblastoma: an update in pathology, molecular mechanisms and biomarkers. *Int J Mol Sci*. 2024;25(5):3040. doi:10.3390/ijms25053040
13. Sareen H, Ma Y, Becker TM, Roberts TL, de Souza P, Powter B. Molecular biomarkers in glioblastoma: a systematic review and meta-analysis. *Int J Mol Sci*. 2022;23(16):8835. doi:10.3390/ijms23168835
14. Koh L, Novera W, Lim SW, et al. Integrative multi-omics approach to targeted therapy for glioblastoma. *Pharmacol Res*. 2022;182:106308. doi:10.1016/j.phrs.2022.106308
15. Liu Y, Su Z, Tavana O, Gu W. Understanding the complexity of p53 in a new era of tumor suppression. *Cancer Cell*. 2024;42(6):946–967. doi:10.1016/j.ccell.2024.04.009
16. Mantovani F, Collavin L, Del Sal G. Mutant p53 as a guardian of the cancer cell. *Cell Death Differ*. 2019;26(2):199–212. doi:10.1038/s41418-018-0246-9
17. Esperante D, Galicia KD, Rivas-Cuervo KG, et al. TP53 oncogenic variants as prognostic factors in individuals with glioblastoma: a systematic review and meta-analysis. *Front Neurol*. 2024;15:1490246. doi:10.3389/fneur.2024.1490246
18. Andrysik Z, Espinosa JM. Harnessing p53 for targeted cancer therapy: new advances and future directions. *Transcription*. 2025;16(1):3–46. doi:10.1080/21541264.2025.2452711
19. Engeland K. Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ*. 2022;29(5):946–960. doi:10.1038/s41418-022-00988-z
20. Colardo M, Segatto M, Di Bartolomeo S. Targeting RTK-PI3K-mTOR axis in gliomas: an update. *Int J Mol Sci*. 2021;22(9):4899. doi:10.3390/ijms22094899
21. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461(7267):1071–1078. doi:10.1038/nature08467
22. Du L, Zhang Q, Li Y, et al. Research progress on the role of PTEN deletion or mutation in the immune microenvironment of glioblastoma. *Front Oncol*. 2024;14:1409519. doi:10.3389/fonc.2024.1409519
23. Dehghan N, Mousavikia SN, Qasempour Y, Azimian H. Radiation-induced senescence in glioblastoma: an overview of the mechanisms and eradication strategies. *Life Sci*. 2024;359:123218. doi:10.1016/j.lfs.2024.123218
24. Berezovsky A, Nuga O, Datta I, et al. Impact of developmental state, p53 status, and interferon signaling on glioblastoma cell response to radiation and temozolomide treatment. *PLoS One*. 2025;20(2):e0315171. doi:10.1371/journal.pone.0315171
25. Pu J, Yuan K, Tao J, et al. Glioblastoma multiforme: an updated overview of temozolomide resistance mechanisms and strategies to overcome resistance. *Discov Oncol*. 2025;16(1):731. doi:10.1007/s12672-025-02567-3
26. Li J, Feng X, Liu Z, et al. USP7 promotes temozolomide resistance by stabilizing MGMT in glioblastoma. *Cell Death Dis*. 2025;16(1):631. doi:10.1038/s41419-025-07969-3
27. He J, Yan X, Hu S. Glioma stem cells: drivers of tumor progression and recurrence. *Stem Cell Res Ther*. 2025;16(1):293. doi:10.1186/s13287-025-04352-z
28. Eckerdt F, Platanias LC. Emerging role of glioma stem cells in mechanisms of therapy resistance. *Cancers*. 2023;15(13):3458. doi:10.3390/cancers15133458
29. Brynjulvsen M, Solli E, Walewska M, et al. Functional and molecular heterogeneity in glioma stem cells derived from multiregional sampling. *Cancers*. 2023;15(24):5826. doi:10.3390/cancers15245826
30. Bernstock JD, Mooney JH, Ilyas A, et al. Molecular and cellular intratumoral heterogeneity in primary glioblastoma: clinical and translational implications. *J Neurosurg*. 2020;133(3):655–663. doi:10.3171/2019.5.JNS19364
31. Joruiz SM, Von Muhlinen N, Horikawa I, Gilbert MR, Harris CC. Distinct functions of wild-type and R273H mutant Δ133p53α differentially regulate glioblastoma aggressiveness and therapy-induced senescence. *Cell Death Dis*. 2024;15(6):454. doi:10.1038/s41419-024-06769-5
32. Abikenari M, Sjoholm MA, Liu J, et al. Molecular and biophysical remodeling of the blood–brain barrier in glioblastoma: mechanistic drivers of tumor–neurovascular crosstalk. *Front Phys*. 2025;13:1723329. doi:10.3389/fphy.2025.1723329
33. Mathew-Schmitt S, Peindl M, Neundorf P, et al. Blood-tumor barrier in focus-investigation of glioblastoma-induced effects on the blood-brain barrier. *J Neurooncol*. 2024;170(1):67–77. doi:10.1007/s11060-024-04760-w

34. Ter Linden E, Abels ER, van Solinge TS, Neefjes J, Broekman ML. Overcoming barriers in glioblastoma—advances in drug delivery strategies. *Cells*. 2024;13(12):998. doi:10.3390/cells13120998
35. Zou L, Chien H-C, Pade D, et al. Considerations in Kp,uu,brain-based strategy for selecting CNS-targeted drug candidates with sufficient target coverage and substantial pharmacodynamic effect. *AAPS j*. 2025;27(2):52. doi:10.1208/s12248-025-01035-8
36. Zhang W, Vaubel RA, Oh J-H, et al. Delivery versus potency in treating brain tumors: BI-907828, a MDM2-p53 antagonist with limited BBB penetration but significant in vivo efficacy in glioblastoma. *Mol Cancer Ther*. 2024;23(1):47–55. doi:10.1158/1535-7163.MCT-23-0217
37. Duan M, Cao R, Yang Y, et al. Blood–brain barrier conquest in glioblastoma nanomedicine: strategies, clinical advances, and emerging challenges. *Cancers*. 2024;16(19):3300. doi:10.3390/cancers16193300
38. Sonabend AM, Gould A, Amidei C, et al. 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*. 2023;24(5):509–522. doi:10.1016/S1470-2045(23)00112-2
39. Han M, Kakar M, Li W, et al. Targeting MDM2-p53 interaction in glioblastoma: transcriptomic analysis and peptide-based inhibition strategy. *Bioorg Chem*. 2024;150:107620. doi:10.1016/j.bioorg.2024.107620
40. Wang W, Albadari N, Du Y, et al. MDM2 inhibitors for cancer therapy: the past, present, and future. *Pharmacol Rev*. 2024;76(3):414–453. doi:10.1124/pharmrev.123.001026
41. Rendo V, Lee EQ, Bossi C, et al. A window-of-opportunity trial reveals mechanisms of response and resistance to navtemadlin in patients with recurrent glioblastoma. *Sci Transl Med*. 2025;17(786):eadn6274. doi:10.1126/scitranslmed.adn6274
42. Thapa D, St John A, Parrales A, Ranjan A, Iwakuma T. MDM4 at the crossroads: beyond p53 and MDM2. *Cancers*. 2026;18(7):1059. doi:10.3390/cancers18071059
43. Guerlavais V, Sawyer TK, Carvajal L, et al. Discovery of sulanemadlin (ALRN-6924), the first cell-permeating, stabilized α-helical peptide in clinical development. *J Med Chem*. 2023;66(14):9401–9417. doi:10.1021/acs.jmedchem.3c00623
44. Li H, Cai X, Yang X, Zhang X. An overview of PROTACs targeting MDM2 as a novel approach for cancer therapy. *Eur J Med Chem*. 2024;272:116506. doi:10.1016/j.ejmech.2024.116506
45. Wang Z, Zhang S, Irakoze LM, Zhao Y. Targeting p53 activation: recent therapeutic advances in cancer and diabetic macular edema. *Eur J Med Chem*. 2025;297:117909. doi:10.1016/j.ejmech.2025.117909
46. Zhang N, Jing Z, Song J, et al. Discovery of drugs targeting mutant p53 and progress in nano-enabled therapeutic strategy for p53-mutated cancers. *Biomolecules*. 2025;15(6):763. doi:10.3390/biom15060763
47. Wang J, Liu W, Zhang L, Zhang J. Targeting mutant p53 stabilization for cancer therapy. *Front Pharmacol*. 2023;14:1215995. doi:10.3389/fphar.2023.1215995
48. Sadagopan A, Carson M, Zamurs EJ, et al. Mutant p53 protein accumulation is selectively targetable by proximity-inducing drugs. *Nat Chem Biol*. 2026;22(5):783–792. doi:10.1038/s41589-025-02051-7
49. Zhou J, Wang J, Chen C, Yuan H, Wen X, Sun H. USP7: target validation and drug discovery for cancer therapy. *Med Chem*. 2018;14(1):3–18. doi:10.2174/1573406413666171020115539
50. Chen L, Chen M, Yuan S, et al. Targeting WIP1 reprograms immunosuppressive tumor microenvironment to potentiate immunotherapy response in colorectal cancer. *Cell Death Differ*. 2026;2026:1.
51. Carreira LD, Oliveira RI, Moreira VM, Salvador JA. Ubiquitin-specific protease 7 (USP7): an emerging drug target for cancer treatment. *Expert Opin Ther Targets*. 2023;27(11):1043–1058. doi:10.1080/14728222.2023.2266571
52. Peng Y, Bai J, Li W, Su Z, Cheng X. Advancements in p53-based anti-tumor gene therapy research. *Molecules*. 2024;29(22):5315. doi:10.3390/molecules29225315
53. Carlsen L, Zhang S, Tian X, et al. The role of p53 in anti-tumor immunity and response to immunotherapy. *Front Mol Biosci*. 2023;10:1148389. doi:10.3389/fmolb.2023.1148389
54. Liu Y, Zhou F, Ali H, Lathia JD, Chen P. Immunotherapy for glioblastoma: current state, challenges, and future perspectives. *Cell Mol Immunol*. 2024;21(12):1354–1375. doi:10.1038/s41423-024-01226-x
55. Nassiri F, Patil V, Yefet LS, et al. Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial. *Nat Med*. 2023;29(6):1370–1378. doi:10.1038/s41591-023-02347-y
56. Choi BD, Gerstner ER, Frigault MJ, et al. Intraventricular CARv3-TEAM-E T cells in recurrent glioblastoma. *N Engl J Med*. 2024;390(14):1290–1298. doi:10.1056/NEJMoa2314390
57. Bagley SJ, Logun M, Fraietta JA, et al. Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results. *Nat Med*. 2024;30(5):1320–1329. doi:10.1038/s41591-024-02893-z
58. Todo T, Ito H, Ino Y, et al. Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial. *Nat Med*. 2022;28(8):1630–1639. doi:10.1038/s41591-022-01897-x
59. Nizamutdinov D, Sentmanat A, Tong J, et al. The emerging role of oncolytic virotherapy in glioblastoma management. *Cancers*. 2025;17(21):3465. doi:10.3390/cancers17213465
60. Alaseem AM. Advancements in MDM2 inhibition: clinical and pre-clinical investigations of combination therapeutic regimens. *Saudi Pharm J*. 2023;31(10):101790. doi:10.1016/j.jsps.2023.101790
61. Bykov VJ, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. *Nat Rev Cancer*. 2018;18(2):89–102. doi:10.1038/nrc.2017.109
62. Beach CZ, Febres-Aldana CA, Marti JLG, et al. Clinical and preclinical insights into a novel MDM2::PDGFRA fusion in recurrent glioblastoma. *NPJ Precis Oncol*. 2025;9(1):289. doi:10.1038/s41698-025-01076-4
63. Isbel L, Iskar M, Durdu S, et al. Readout of histone methylation by Trim24 locally restricts chromatin opening by p53. *Nat Struct Mol Biol*. 2023;30(7):948–957. doi:10.1038/s41594-023-01021-8
64. Wang L, Wang H, D'Angelo F, et al. Quantifying intra-tumoral genetic heterogeneity of glioblastoma toward precision medicine using MRI and a data-inclusive machine learning algorithm. *PLoS One*. 2024;19(4):e0299267. doi:10.1371/journal.pone.0299267
65. Wang L, Jung J, Babikir H, et al. A single-cell atlas of glioblastoma evolution under therapy reveals cell-intrinsic and cell-extrinsic therapeutic targets. *Nat Cancer*. 2022;3(12):1534–1552. doi:10.1038/s43018-022-00475-x
66. Spitzer A, Johnson KC, Nomura M, et al. Deciphering the longitudinal trajectories of glioblastoma ecosystems by integrative single-cell genomics. *Nat Genet*. 2025;57(5):1168–1178. doi:10.1038/s41588-025-02168-4

67. Ravi VM, Will P, Kueckelhaus J, et al. Spatially resolved multi-omics deciphers bidirectional tumor-host interdependence in glioblastoma. *Cancer Cell*. 2022;40(6):639–655.e13. doi:10.1016/j.ccell.2022.05.009
68. Singh K, Hotchkiss KM, Parney IF, et al. Correcting the drug development paradigm for glioblastoma requires serial tissue sampling. *Nat Med*. 2023;29(10):2402–2405. doi:10.1038/s41591-023-02464-8
69. Cho NS, Wong WK, Nghiemphu PL, Cloughesy TF, Ellingson BM. The future glioblastoma clinical trials landscape: early phase 0, window of opportunity, and adaptive Phase I–III studies. *Curr Oncol Rep*. 2023;25(9):1047–1055. doi:10.1007/s11912-023-01433-1
70. Fukushima CM, de Groot J. Updates for newly diagnosed and recurrent glioblastoma: a review of recent clinical trials. *Curr Opin Neurol*. 2024;37(6):666–671. doi:10.1097/WCO.0000000000001320
71. Vaubel RA, Zhang W, Oh J-H, et al. Preclinical modeling of navtemadlin pharmacokinetics, pharmacodynamics, and efficacy in IDH-wild-type glioblastoma. *Clin Cancer Res*. 2025;31(17):3771–3786. doi:10.1158/1078-0432.CCR-25-0244
72. Al-Ali HK, Heidel ST, Palandri F, Heidel FH. MDM2 inhibitors in myeloid cancers: from basic biology to clinical use in myeloproliferative neoplasms. *Leukemia*. 2026;40(6):1111–1121. doi:10.1038/s41375-026-02975-6
73. Youssef G, Wen PY. Updated response assessment in neuro-oncology (RANO) for gliomas. *Curr Neurol Neurosci Rep*. 2024;24(2):17–25. doi:10.1007/s11910-023-01329-4
74. Wen PY, van den Bent M, Youssef G, et al. RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. *J Clin Oncol*. 2023;41(33):5187–5199. doi:10.1200/JCO.23.01059
75. Bartusik-Aebisher D, Tylutki J, Tylutki M, Leś D, Aebisher D. Navigating the central nervous system (CNS): a pharmacokinetic approach to the treatment of CNS tumors, glioblastoma multiforme (GBM), in particular. *Int J Mol Sci*. 2025;26(19):9418. doi:10.3390/ijms26199418
76. Ferreira C, Sarmento B, Martins C. In vitro models of the interplay between glioblastoma and blood-brain barrier for stratifying drug efficacy. *Adv Drug Deliv Rev*. 2025;227:115702. doi:10.1016/j.addr.2025.115702
77. Wu M, Wang T, Ji N, et al. Multi-omics and pharmacological characterization of patient-derived glioma cell lines. *Nat Commun*. 2024;15(1):6740. doi:10.1038/s41467-024-51214-y
78. Rizwani F, Patil P, Jain K. Unlocking glioblastoma: breakthroughs in molecular mechanisms and next-generation therapies. *Med Oncol*. 2025;42(7):276. doi:10.1007/s12032-025-02830-1