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Abstract

Human glioblastoma (GBM) is the most lethal type of brain tumor. Current therapies struggle to effectively target the tumor, leading to high recurrence rates and poor survival outcomes. Chimeric antigen receptor T-cell (CAR-T) therapy, although new and evolving, has shown success in hematological malignancies such as leukemia and lymphoma, and is currently being adapted for GBM. This review discusses emerging clinical and preclinical studies that serve as evidence for both the advancements and limitations of CAR-T therapy for GBM treatment. While prior reviews have addressed individual aspects of CAR-T therapy for GBM, this review explores how antigen selection, delivery strategy, and the tumor microenvironment collectively influence therapeutic outcomes. Tumor antigens have been used as therapeutic targets, each exhibiting differential expression patterns and distinct anti-tumor activity. Next-generation multivalent CAR-T constructs, which simultaneously engage multiple antigens or pathways, have shown promise in addressing GBM's heterogeneity and treatment resistance. Beyond antigen targets, delivery methods have also been found to play a crucial role in determining the success of this treatment. Cerebrospinal fluid and locoregional delivery show superior tumor penetration compared to typical intravenous delivery. Still, successful CAR-T engraftment faces major challenges, such as the immunosuppressive nature of the GBM microenvironment, the transient effects of CAR-T cells, and antigen loss. It is important to note that many findings discussed in this review are derived from small-scale Phase I clinical trials, which may limit the generalizability of the conclusions. Collectively, evidence indicates that CAR-T immunotherapy represents a promising, yet evolving, treatment with the potential to improve outcomes for patients with this malignant disease.

Keywords: glioblastoma, CAR-T cell therapy, immunotherapy, cancer, limitations, advancements

1. Introduction

Glioblastoma (GBM) is an extremely aggressive Grade IV astrocytoma that most commonly arises in the cerebral hemispheres.[1] Its highly infiltrative growth allows tumor cells to migrate into surrounding healthy brain tissue, making complete surgical resection nearly impossible. Although relatively rare, GBM accounts for 54% of all gliomas and 16% of all primary brain tumors in the United States, with an incidence of approximately 3.2 per 100,000 people annually.[1] GBM resides within the blood-brain barrier (BBB), rendering many forms of

chemotherapy useless, as they are unable to reach the tumor. The BBB is a highly selective membrane formed by specialized endothelial cells lining brain blood vessels. Its tight junctions act as a protective filter, preventing pathogens and most foreign substances from entering the brain. While this is essential for neurological protection, it also means that most chemotherapy drugs, which must enter the bloodstream to travel to the brain, are blocked from reaching the tumor. Additionally, no standard therapies at relapse have shown any survival benefit in clinical trials.[2] Together, infiltrative growth, BBB restriction, and rapid molecular adaptation make GBM highly resistant to conventional therapies and contribute to its high recurrence rate.[3] Despite multimodal treatment such as surgery, radiation, and chemotherapy, prognosis remains poor, with median survival under 15 months.[4] However, emerging immunotherapies show promise for glioblastoma treatment. Immunotherapies seek to change the immune response by using the patient's own immune system to recognize and kill cancer cells. Recently, a promising immunotherapy, CAR-T cell therapy, has been explored for GBM treatment. CAR-T cells are generated by genetically engineering a patient's T cells to express synthetic receptors that enhance antigen recognition, activate cytotoxic signaling pathways, and promote targeted tumor cell elimination. The therapy has shown great success in blood cancers such as leukemia and lymphoma, and is now expanding to solid tumors, including glioblastoma.

However, translating CAR-T therapy to GBM presents challenges not encountered in blood cancers. Circulating tumor cells in leukemia and lymphoma are readily accessible to infused CAR-T cells, whereas GBM resides behind the BB and within a hostile tumor microenvironment (TME). The TME is immunosuppressive and can inhibit CAR-T cell function through multiple mechanisms, thereby contributing to tumor resistance to therapy. These barriers limit CAR-T trafficking and functional activity. Additionally, GBM exhibits substantial intratumoral heterogeneity, which enables antigen-negative tumor cells to evade monospecific CAR-T constructs and cause relapse. Clonal evolution, the process by which tumor cells acquire new mutations over time, further contributes to this heterogeneity by allowing antigen-negative variants to gain a survival advantage and selectively proliferate. To address these obstacles, recent preclinical and early-phase clinical studies have explored multivalent CAR designs, new antigen targets, and locoregional delivery strategies such as intratumoral, intracerebroventricular, and intrathecal administration. These approaches aim to reduce antigen escape and enhance CAR-T cell function within the TME.

This review synthesizes emerging evidence from early-phase clinical and preclinical studies to evaluate how antigen selection, delivery methods, and constructs that influence the microenvironment can collectively shape the current trajectory for GBM treatment.

2. Antigen Targets and Multivalent/Multi-Pathway CAR-T Designs

2.1 IL-13Rα2 Targeting

Interleukin-13 receptor alpha-2 (IL-13Rα2)-directed CAR-T cell therapy represents a targeted immunotherapeutic approach for GBM, exploiting the tumor's overexpression of IL-13Rα2 to achieve antitumor activity while minimizing off-target effects on healthy brain tissue. Brown et al. (2022) marked a meaningful advance in IL-13Rα2-targeted CAR-T cells for glioblastoma by engineering a steroid-resistant, allogeneic product, GRm13Z40-2.[5] Using zinc-finger nucleases to disrupt the glucocorticoid receptor, donor-derived CAR-T cells were created that retained their effector function. This product was designed to be manufacturable as an "off-the-shelf" therapy,

meaning it can be produced in advance from donor cells and stored for use in any patient, rather than requiring individualized manufacturing from each patient's own cells. This distinction is clinically significant because personalized manufacturing is costly, time-consuming, and not always feasible for patients with rapidly progressing disease. Their first human Phase I Trial (n = 6) demonstrated that intracranial delivery of GRm13Z40-2 was safe, exhibiting no signs of alloreactivity, and showed transient antitumor activity despite ongoing steroid therapy, including tumor necrosis at infusion sites. While promising, the extremely small sample size of 6 patients limits the conclusions that can be drawn from this study. However, the study proved the feasibility of a therapy that is both manufacturable as "off-the-shelf" and functionally resilient in an immunosuppressive tumor environment.[5] This is a significant discovery given the steroid sensitivity of many previous CAR-T cell therapies.

Building on the progress of the 2022 study, Brown et al. (2024) published the findings of a Phase I trial with 65 patients experiencing recurrent high-grade glioma.[6] In this trial, locoregional delivery, the administration of a treatment directly to the tumor or specific area of the body, of IL-13Rα2-targeted CAR-T cells proved to be safe and feasible (Brown et al., 2024). No dose-limiting toxicities were observed, and a clinical maximum feasible dose of 200×10^6 CAR-T cells per infusion cycle was reached. In approximately 50% of evaluable patients, the disease stabilized or improved, including two partial responses and two complete responses. Moreover, patients in the optimized dual intratumoral/ intraventricular CAR-T cell delivery group experienced a median overall survival of 10.2 months, exceeding the 7.7-month median for the overall cohort.[6] These findings establish that IL-13Rα2 is a viable antigen target in human glioma, and that the locoregional delivery method can prevent some of the toxicity and delivery challenges.

Together, these studies demonstrate progressive advances in IL-13Rα2 CAR-T development by establishing steroid-resistant, off-the-shelf feasibility and confirming safety and early signs of clinical activity in a larger patient cohort. IL-13Rα2 CAR-T development exemplifies how advances in antigen targeting and CAR-T cell engineering can work in tandem to improve the feasibility, safety, and efficacy of CAR-T cell therapies in human glioblastomas. However, the transient nature of responses in both studies highlights the continued need for further research and clinical trials to establish long-term efficacy and nontoxicity.

2.2 EGFR / EGFRvIII Targeting

Epidermal Growth Factor Receptor variant III (EGFRvIII) is a promising therapeutic tumor-specific target antigen for GBM treatment by CAR-T cell technology. EGFRvIII is expressed in approximately 40% of GBM cases, producing a tumor-specific, oncogenic, and immunogenic epitope.[7,8] Being entirely absent from healthy tissue, EGFRvIII offers a unique opportunity for potent antitumor activity without the risk of off-target toxicity. First in-human clinical trials confirm that EGFRvIII-directed CAR-T cells are safe and feasible, typically avoiding severe cytokine release syndrome and off-target effects.[7] The lack of side effects associated with this therapy demonstrates the selective nature of the EGFRvIII target. Nonetheless, the therapeutic impact of this treatment is limited by antigen escape, driven by the clonal evolution characteristic of GBM. EGFRvIII expression frequently occurs in a mosaic against non-mutated EGFR amplification, allowing antigen-negative cells to evade T-cell detection and driving disease recurrence.[8] Once refined to account for clonal evolution, researchers can leverage this specificity to initiate more durable and effective tumor clearance.

To overcome GBM intratumoral heterogeneity, researchers have developed more advanced CAR-T designs. While first- through third-generation CAR-T cells mainly focused on improving T-cell activation, fourth-generation "armored" CAR-T cells are engineered to secrete immune-modulating proteins such as signal regulatory protein gamma-related protein (SGRP). EGFRvIII-directed CAR-T cells secreting SGRP trigger phagocytosis in both antigen-positive and antigen-negative tumor cells, overcoming the inherent heterogeneity of GBM.[8] Phagocytosis is the result of immune modulation via SGRP, which shifts the typically immunosuppressive tumor microenvironment to immunostimulatory by utilizing EGFRvIII recognition to kill antigen-positive cells and SGRP secretion to kill bystander cells. Administration of this treatment resulted in nearly complete eradication of EGFRvIII-mosaic GBM, highlighting the clinical potential of reprogramming the immunosuppressive TME to facilitate comprehensive tumor regression.[8] Consequently, SGRP-secreting EGFRvIII CAR-T cells address the limitations of monovalent EGFRvIII therapies by providing a strategy that achieves a sustained therapeutic response against heterogeneous GBM. Together, these advances reaffirm the potential for EGFRvIII as a clinically viable and safe target antigen for GBM, but still require next-generation designs such as SGRP-secreting constructs to achieve durable responses. Coupled with immune-modulatory designs such as SGRP secretion, EGFRvIII-directed CAR-T cells can overcome antigen escape and drive comprehensive and sustained tumor regression in heterogeneous GBM.

2.3 GD2 Targeting

GD2-antigen CAR is a relatively new and developing therapy, and current studies are only preclinical. GD2 is a disialoganglioside normally expressed at low levels in healthy tissues but highly upregulated in several solid tumors, including glioblastoma. Its restricted expression pattern and association with aggressive tumor behavior offer potential for selective tumor recognition. A pre-clinical study conducted by Prapa et al. investigated GD2-targeting CAR-T cells, which demonstrated strong antitumor activity in both two-dimensional and three-dimensional glioblastoma models. The study tested cells from 12 patient-derived samples, with 7 of 12 showing GD2 positivity greater than 80%.[4] Most importantly, the GD2 CAR-T cells produced dramatic anticancer effects with clusters of activated cytotoxic lymphocytes. In this study, TGF-β1 served as a test of whether the immunosuppressive tumor microenvironment could impair GD2 CAR-T cell function. TGF-β1 is an immunosuppressive cytokine abundantly secreted by glioblastoma cells and tumor-associated cells. These proteins usually pose a challenge to CAR-T efficacy, contributing to immunosuppression and preventing the CAR-T cells from killing tumor cells. However, in the Prapa et al. study, TGF-β1 did not have an impact on the treatment's antitumor activity.[4] TGF-β1 was consistently expressed in all culture conditions at both 48 hours and 7 days.

Despite this immunosuppressive environment, GD2-directed CAR-T cells maintained significant killing activity, a finding that Prapa et al. suggest may reflect the inherently strong activation profile of GD2 CAR-T cells and their ability to sustain cytotoxic signaling even in the presence of TGF-β. This resistance may also relate to the high levels of granzyme B and pro-inflammatory cytokines produced by the GD2 CAR-T cells, which can counteract TGF-β–mediated suppression.[4] Across studies, multivalent designs consistently outperform monovalent constructs in preventing antigen escape, suggesting that multi-targeting is becoming a foundational requirement for GBM CAR-T therapy. GD2 targeting remains at the pre-clinical stage and has not yet entered formal clinical trials in GBM patients; clinical translation will require safety and

toxicity testing in early-phase human trials before broader use can be considered.

2.4 Bivalent and Multivalent CAR Constructs

There have been recent critical advancements regarding the number of antigens a CAR-T cell targets, with both bivalent (targeting two antigens) and multivalent (targeting more than two antigens) constructs showing promising results in early phase studies. Bagley et al. showcase a bivalent CAR construct in which the two antigens previously discussed in Sections 2.1 and 2.2 are targeted simultaneously by a single CAR-T cell.[9] Beyond enhancing targeting efficacy, the study's findings suggest that the bivalent design facilitated wider CAR-T cell expansion and distribution, as evidenced by their presence in the CSF and peripheral blood in addition to the injection site. Most notably, the impact of these constructs on the development of CAR-T cell therapy is their ability to overcome the challenge of antigen loss.

2.5 dnTGFβRII Suppression Prevention

Unlike bivalent or multivalent constructs that expand antigen recognition, CART-EGFR-IL13Rα2 cells use a dominant-negative TGF-β receptor II (dnTGFβRII) domain to resist TGF-β–driven immunosuppression, allowing the CAR-T cells to remain active in the GBM microenvironment. The study reported by Li et al. shows potential solutions to barriers caused by TGF-β. A dominant-negative TGF-β receptor II (dnTGFβRII) domain was incorporated into the CART-EGFR-IL13Rα2 construct.[10] This modification does not expand antigen targeting; instead, it blocks TGF-β signaling, preventing CAR-T cells from receiving suppressive signals within the tumor microenvironment. Li et al. reported enhanced tumor killing along with increased effector cytokine production and improved T-cell proliferation, indicating that with dnTGFβRII, the CAR-T cells remained active despite high TGF-β levels.[10] This demonstrates how CAR-T-EGFR-IL13Rα2 cells with dnTGFβRII can overcome immunosuppression, highlighting the potential of multivalent CAR constructs.

3. Delivery Methods and Their Impact on Efficacy

3.1 Intravenous Delivery

Intravenous (IV) administration is the most clinically practical and used delivery route for CAR-T therapy. A first-in-human study by O'Rourke et al. demonstrated that IV delivery of EGFRvIII-directed CAR-T cells in ten recurrent glioblastoma patients was safe and feasible, with no evidence of off-tumor toxicity or cytokine release syndrome.[7] The study confirmed successful penetration of the BBB and local expansion within GBM. However, even though all patients infused with the CAR-T therapy had detectable CART-EGFRvIII cell engraftment, several significant limitations emerged. CART-EGFRvIII cells engrafted approximately 50-fold less than CD19-specific CAR-T cells for leukemia and other blood cancers using the same manufacturing process.[7] This reflects the challenge of target antigens being confined to brain tissue rather than circulating throughout the blood and lymphoid organs. Second, CAR-T trafficking to the tumor was limited, with relatively low numbers of cells detected in peripheral blood and cerebrospinal fluid compared to expectations from systemic CAR-T therapies. Finally, post-infusion tumor specimens showed increased expression of immunosuppressive molecules and reduced CAR-T cell persistence, along with decreased EGFRvIII expression after 30 days; this is an indication of both microenvironment-mediated suppression and antigen loss.[7] These findings highlight how IV delivery faces challenges of limited rapid trafficking to target tumor areas and tumor microenvironment resistance.

3.2 Locoregional Delivery: Intracerebroventricular (ICV), Intrathecal (IT), Intracranial (IC)

Recent clinical trials have shown that CSF-based delivery routes such as intracerebroventricular (ICV), intrathecal (IT), and intracranial (IC) administration offer promising advantages for GBM treatment in comparison to IV routes. Brown et al. (2024) conducted a Phase I clinical trial with IL-13Rα2-targeted CAR-T cells for recurrent high-grade GBM with locoregional CAR-T delivery testing intratumoral (ICT), ICV, and dual delivery.[6] ICT delivery is the direct injection of CAR-T cells into the tumor site through a catheter placed during surgery. This can maximize local concentration of CAR-T cells at the primary tumor site and minimize systemic exposure; however, it may not effectively target tumor cells that have migrated away from the primary site. ICV application delivers CAR-T cells into the cerebral ventricles, allowing the cells to circulate throughout the CSF, providing broader coverage of the central nervous system. However, using ICV treatment alone can cause large intraparenchymal tumors deep within the brain tissue to continue to progress while just eliminating small subpial lesions.[6]

Because ICT was beneficial for eradicating unifocal (single-location) tumors and ICV was more beneficial for multifocal (multiple-location) tumors, the dual approach was administered to overcome individual limitations by getting cells to both large, deep, and multifocal tumors. After the administration of the dual therapy, CAR-T cells were detected in CSF and tumor cavity fluid for the majority of patients for more than 7 days post-infusion, which is significant since CSF volume turns over approximately four times.[6]

The efficacy of locoregional delivery was also demonstrated in Bagley et al.'s intrathecal bivalent CAR-T trial, which administered the CAR-T cells directly into the CSF. Peaks of CAR-T cells in CSF showed similar levels to those in hematologic cancers treated with CD19 CAR-T cells.[9] Additionally, reductions in tumor enhancement and size were observed in all six patients on early MRI, with tumor shrinkage of at least 30% in three of six patients. Neurotoxicity side effects did arise, but were controllable with high-dose dexamethasone and anakinra.[9]

Chan et al.'s systematic review of 13 trials covering 128 patients with IV, ICV, ICT, and intracavitary deliveries confirmed this safety profile: the direct methods of CAR-T therapies were well tolerated with low dose-limiting toxicities. The review also highlighted advantages of the direct delivery method with CAR-T cells in blood being consistently lower (0%-2% concentration) than in CSF (~70% concentration) after intraventricular injection.[11] This is in comparison to the intravenous-only study that detected little to no CAR-T cells in the brain. However, one notable limitation is discussed in a study by Choi et al., which tested CARv3-TEAM-E, a therapy that targets two types of EGFR: the tumor-specific variant and the normal protein. With direct CSF application, there was a report of the development of anti-CARv3-TEAM-E antibodies in the CSF, which increased with each reinfusion, leading to immunogenicity barriers.[12] However, these results may only be attributed to that specific CAR-T therapy and associated antigens.

In summation, these findings establish a growing foundation that locoregional delivery significantly improves tumor-site CAR-T concentration while maintaining manageable toxicity. This leads to a pattern in which CSF-based routes become the preferred approaches for GBM CAR-T therapy over IV delivery, which is limited by trafficking inefficiency. A comparative overview of IV, ICV, and ICT/IT delivery routes is summarized in Table 1, which highlights key differences in BBB penetration, tumor-site exposure, toxicity profiles, and CAR-T persistence.

Table 1. Comparative Characteristics of Intravenous, Intraventricular, and Intratumoral/Intrathecal CAR-T Delivery Routes for GBM

Parameter	IV (intravenous)	ICV (intraventricular)	ICT/IT (intratumoral/intrathecal)
BBB Penetration	Poor Blocked by BBB; limited entry	Good Bypasses BBB via ventricles	Excellent Direct CNS/tumor placement)
Tumor-Site Concentration	~0-2% in CSF 50x less than blood cancer IV CAR-T	~70% in CSF High CSF levels post-injection	Maximized locally Comparable to CD19 CAR-T (IT)
Coverage Scope	Systemic Whole body; poor CNS targeting	Broad CNS Multifocal; may miss post-injection	Focal/Broad CNS ICT focal; IT broad CSF coverage
Adverse Effects	Low (no CRS observed) Limited CAR-T expansion	Higher (grade 3+ reported)	Low-Moderate CRS grade 1-2; no dose-limiting toxicities
CAR-T Persistence	Transient Undetectable in blood after 30 days	Moderate CSF detection varies by case	Good (>7 days in CSF) Detected beyond injection site (ICT)
Clinical Suitability	Limited use in GBM; poor CNS penetration	Best for multifocal/disseminated disease; combine with ICT	Preferred route; dual ICT+ICV approach improves Overall survival to 10.2 months

Sources: Brown et al. (2024); O'Rourke et al. (2017); Bagley et. al (2024); Chan et al (2025); Choi et al. (2025)

4. Safety Considerations

4.1 Cytokine Release Syndrome (CRS) and Neurotoxicity

Two major adverse effects of CAR-T cell therapy in patients are cytokine release syndrome (CRS) and neurotoxicity. Notably, in a pilot study by Bagley et al., all 6 patients enrolled in the Phase I trial developed CRS, and all the cases were classified as low-grade based on the American Society for Transplantation and Cellular Therapy criteria.[9] The patients who received a lower dosage exhibited grade 1 CRS, while the patients who received a higher dosage exhibited both grade 1 and grade 2 CRS. Unfortunately, all 6 patients also developed moderate-severe neurotoxicity, graded using a modified Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) severity scale. Dose variations, however, did not result in any meaningful differences in the severity of the neurotoxicity developed. This study utilized an intrathecal method of delivery: administration of the therapy into the CSF (as opposed to the bloodstream) means there is limited circulation of the CAR-T cells. A reduced exposure decreases the likelihood of CRS in peripheral blood. Ultimately, this highlights how the route of delivery can greatly influence the adverse events experienced by the

patients.[9] In another study by O'Rourke et al., patients did not develop systemic CRS or EGFR-directed toxicity.[7] Because this trial used intravenous delivery, the absence of toxicity cannot be attributed solely to the route of administration. Instead, the low toxicity is more likely explained by the biology of the target and the behavior of the CAR-T cells. EGFRvIII is expressed only on tumor cells, not on normal tissues, and the CAR-T cells in this study showed limited expansion. Together, these factors reduce the likelihood of off-tumor toxicity.

4.2 Off-Target Effects and Toxicity Profiles

In an analysis of 13 Phase I trials by Chan et al., where CAR-T cell therapy was administered in patients with GBM, dose-limiting toxicities were noted at relatively higher doses from 1×10^7 to 1×10^{10} cells.[11] This is further illustrated by how six out of the seven studies reporting adverse effects of grade three or higher used dose orders of 1×10^7 and above. Regarding delivery methods of the CAR T cell therapy, Chan et al. concluded that the most adverse effects observed per patient (beyond CRS and neurotoxicity) were therapies involving an intraventricular injection of CAR-T cells targeted at the EGFR and IL-13 antigens.[11] On the contrary, a study by Brown et al. concluded that there were no dose-limiting toxicities observed with a locoregional delivery of CAR-T cells.[6] Similarly, a study by Barish et al. also found that there were no limiting toxicities observed with Chlorotoxin-directed CAR-T cell therapy, as well as no development of antibodies to the treatment.[13]

5. Summary: Overall Clinical Progress

Selectively overexpressed surface antigens such as IL-13Rα2, EGFRvIII, and GD2 have emerged as promising targets for CAR-T cell therapy for GBM, demonstrating significant clinical efficacy in early-stage clinical trials. Among these, IL-13Rα2 stands out due to its demonstrated clinical feasibility, including off-the-shelf potential, steroid resistance, and compatibility with a locoregional delivery approach.[5,6] EGFRvIII remains a highly specific tumor-restricted target, and next-generation constructs engineered to secrete SGRP have shown enhanced activity against heterogeneous tumors.[8] GD2, while still in pre-clinical development, is consistently expressed on aggressive glioma cells and has demonstrated potent antitumor activity even under TGF-β–rich conditions.[4] Together, these antigens are complementary strategies for targeting both bulk and resistant tumors. A persistent challenge across all antigen-specific approaches is antigen loss and escape, which limits the durability of mono-specific CAR-T responses. Strategies such as SGRP secretion, multivalent targeting, and constructs resistant to TGF-β–mediated suppression can counteract this problem by enabling CAR-T cells to eliminate both antigen-positive and antigen-negative tumor cells.[8] Despite these advances, long-term persistence remains limited, with evidence of T-cell exhaustion and reduced proliferation over time.[6]

To address GBM's cellular heterogeneity, bivalent and multivalent CAR-T constructs have shown improved efficacy over monovalent designs by simultaneously recognizing multiple antigens.[9] These constructs demonstrate broader tumor coverage and improved resistance to antigen escape. Delivery route is also another critical determinant of therapeutic success. IV administration, while clinically convenient, is hindered by the BBB, limited trafficking, and microenvironment-mediated suppression.[7] In contrast, locoregional delivery such as ICT, ICV, and IT routes achieve higher local CAR-T concentration, reduced systemic toxicity, and improved persistence.[14] Optimizing delivery strategies is an essential step in translating CAR-T potency into more clinical trials.

Across studies, a major barrier to progress is the lack of standardized patient cohorts and reporting formats. Variability in eligibility criteria, dosing schedules, and outcome reporting complicates cross-trial comparisons and limits the ability to draw reliable conclusions.[10,11] Greater standardization to reduce confounding variables and improve interpretability. In terms of clinical translation, IL-13Rα2-targeted CAR-T cells are the most advanced, now progressing toward Phase II evaluation. EGFRvIII constructs, particularly SGRP-secreting variants, are entering later-stage testing, while GD2- and dnTGFβRII-based therapies remain in pre-clinical development. If Phase II trials confirm safety and early efficacy, regulatory approval for next-generation constructs could be feasible within the next 5–10 years; though this is contingent on consistent outcomes and scalable manufacturing. Overall, the field is moving toward integrating multi-mechanism CAR-T strategies that simultaneously address antigen heterogeneity, microenvironment suppression, and delivery barriers. This approach appears most likely to yield stronger clinical responses for GBM.

6. Conclusion

Recent clinical and preclinical studies demonstrate that CAR-T therapy for GBM is progressing toward more effective and durable strategies through advancements in antigen targeting, delivery optimization, and anti-suppressive microenvironment designs. Early trials involving IL-13Rα2, EGFRvIII, GD2, and multivalent constructs show that CAR-T cells can safely target GBM through overcoming the challenges posed by the BBB and the immunosuppressive tumor microenvironment. Moving forward, the most promising progress will come from integrated approaches that combine multi-antigen recognition, enhanced persistence and capacity mechanisms, and resistance to microenvironmental suppression. More clinical trials using locoregional delivery methods is essential for maximizing tumor exposure while minimizing systemic toxicity. Equally important is the need for standardized clinical trial designs, which will enable clearer comparisons across studies and accelerate the path toward regulatory approval.

Although challenges remain, including antigen escape, limited persistence, and risks such as cytokine release syndrome and neurotoxicity, emerging evidence supports CAR-T therapy as an increasingly viable option for GBM. By combining antigen selection, delivery strategy, and microenvironment engineering into one cohesive treatment, next-generation CAR-T constructs hold significant potential to improve outcomes for patients with this malignant and treatment-resistant disease.

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