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Perspective

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CAR-T cell therapy for the treatment of adult high-grade gliomas

Sangwoo Park[1], Marcela V. Maus[1] & Bryan D. Choi[1,2]

Treatment for malignant primary brain tumors, including glioblastoma, remains a significant challenge despite advances in therapy. CAR-T cell immunotherapy represents a promising alternative to conventional treatments. This review discusses the landscape of clinical trials for CAR-T cell therapy targeting brain tumors, highlighting key advancements like novel target antigens and combinatorial strategies designed to address tumor heterogeneity and immunosuppression, with the goal of improving outcomes for patients with these aggressive cancers.

Gliomas comprise a diverse group of brain tumors that arise from glial cells and span a wide range of grades, from less aggressive forms to highly malignant tumors such as glioblastoma (GBM). GBM accounts for more than half of all malignant central nervous system (CNS) tumors, with a five-year survival rate of less than 10%[1]. The current standard-of-care for GBM consists of surgical resection followed by radiation and temozolomide chemotherapy. When these tumors invariably recur, even fewer options are available for treatment; although anti-angiogenic agents such as bevacizumab are often used, they have not been shown to improve overall survival compared to best supportive care. Depending on their location, gliomas can also drastically impair or disrupt vital functions. In children, these tumors can develop in midline structures like the brainstem (e.g., diffuse intrinsic pontine gliomas or DIPG), and due to their anatomic location, they are often unresectable and associated with significant morbidity.

Immune-based strategies, particularly the use of adoptive T-cell therapy with chimeric antigen receptor (CAR) T cells, have rapidly emerged as a promising approach to treating brain tumors. This is due to their theoretical capacity to specifically target cancer cells while bypassing the need for endogenous tumor-specific T-cell responses, which are often absent or impaired in the context of glioma. CAR-T cells are T cells engineered to express molecules that allow them to identify and eliminate cells expressing specific surface targets of interest. Since their first approval by the U.S. Food and Drug Administration in 2017, several CAR-T cell products have been successfully implemented for various hematologic cancers (Table 1). However, translating these therapies for solid tumors has been limited. The challenges to effective CAR-T cell therapy for solid tumors are under active investigation and include the identification of ideal target antigens and antigenic heterogeneity, subsequent tumor antigen escape, T-cell trafficking to and within solid tumors, and the immunosuppressive tumor microenvironment (TME)[2,3].

In this review, we provide an overview of the current landscape of clinical trials and the development of novel strategies aimed at optimizing CAR-T cell therapy for brain tumors. This discussion highlights key advancements, such as the identification and characterization of novel target antigens and innovative combinatorial approaches designed to enhance efficacy in the context of tumor heterogeneity and associated immunosuppression.

Adoptive T-cell therapy for solid tumors

To bypass the need for endogenous T-cell priming, adoptive cell strategies can be employed to produce large numbers of tumor-specific T-cells for therapeutic purposes. One approach is the use of tumor-infiltrating lymphocytes (TILs), which entails the isolation and expansion of a subgroup of intratumoral lymphocytes followed by reinfusion. Promising results have been reported with TIL therapy in solid tumors, including those for cervical carcinoma[4,5], colorectal cancer[6], cholangiocarcinoma[7], non-small cell lung cancer[8], breast cancer[9], and nasopharyngeal cancer[10]. However, TILs in glioma are often limited in quantity, dysfunctional, or difficult to isolate due to structural characteristics.

As a result, the adoptive transfer of T cells engineered to express transgenic T cell receptors (TCRs) has been developed as a potential method for artificially generating tumor-specific T cells. TCR-T cells have demonstrated efficacy in treating melanoma[11–13] and metastatic colorectal cancer[14]. However, several cancers, such as GBM, downregulate the expression of major histocompatibility complex (MHC) class I and II molecules as a mechanism of immune cell escape[15,16], thereby impeding the efficacy of strategies that rely on the presentation of antigens in the context of MHC.

Unlike endogenous TILs or transgenic TCRs, CAR-T cells can be activated through interaction with specific targets independently of antigen presentation by MHC[17,18]. The use of CAR-T cell therapy targeting solid tumors outside of the CNS has shown promising results in clinical studies. For example, Claudin18.2-redirected CAR-T cells have been utilized in the

[1]Cellular Immunotherapy Program, Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [2]Brain Tumor Immunotherapy Lab, Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. e-mail: bchoi@mgh.harvard.edu

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Table 1 | FDA Approved CAR-T cell therapy

Name	Target antigen	FDA approval	Year
Kymriah® (tisagenlecleucel)	CD19	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	2017
		Relapsed or refractory large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy	2018
		Relapsed or refractory follicular lymphoma (FL) after ≥2 lines of systemic therapy	2022
Yescarta® (axicabtagene ciloleucel)	CD19	Relapsed or refractory large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy	2017
		Relapsed or refractory follicular lymphoma (FL) after ≥2 lines of systemic therapy	2021
		Large B-cell lymphoma (LBCL) refractory to first-line chemoimmunotherapy or relapses < 12 months of first-line chemoimmunotherapy	2022
Tecartus® (brexucabtagene autoleucal)	CD19	Relapsed or refractory mantle cell lymphoma (MCL)	2020
		Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	2021
Breyanzi® (lisocabtagene maraleucel)	CD19	Relapsed or refractory large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy	2021
		Large B-cell lymphoma (LBCL) refractory to first-line chemoimmunotherapy or relapses < 12 months of first-line chemoimmunotherapy and not eligible for hematopoietic stem cell transplantation (HSCT)	2022
		Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥2 lines of systemic therapy	2024
Abecma® (idecabtagene vicleucel)	BCMA	Relapsed or refractory multiple myeloma after ≥4 prior lines of therapy (2021)	2021
Carvykti® (ciltacabtagene autoleucel)	BCMA	Relapsed or refractory multiple myeloma after ≥4 prior lines of therapy (2022)	2022

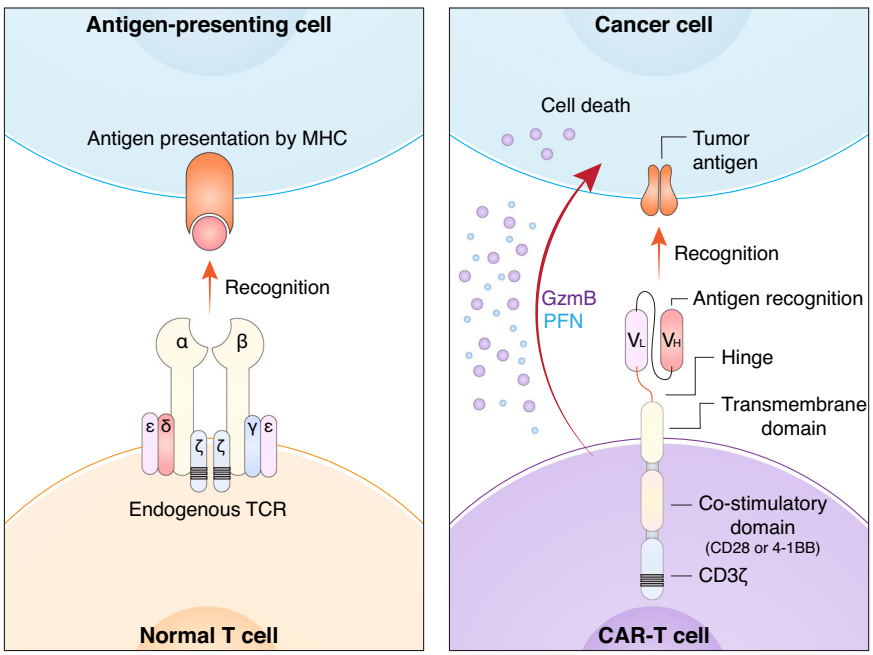

Fig. 1 | Structure of CAR-T cell. The CAR structure includes antigen-binding domains, hinges, transmembrane domains, and signaling domains. This structural framework collectively influences the specificity, activation, and function of CAR-T cells. MHC major histocompatibility complex, TCR T cell receptors.

setting of digestive system cancers, wherein the overall response rate was 48.6%, and the 6-month overall survival rate was 81.2%, as reported in phase 1 interim results (NCT03874897)[19]. In addition, GD2-CART01, a third-generation gene-edited autologous CAR-T cell therapy targeting GD2 in patients with high-risk neuroblastoma, was tested in 27 patients, 17 of whom achieved at least a partial response, resulting in an overall response rate of 63%. Patients receiving the recommended phase 2 dose of GD2-CART01 had a 3-year overall survival rate of 60% and a 3-year event-free survival rate of 36%[20].

CAR-T cell structure and function

CAR molecules consist of an antigen-binding domain and intracellular activation domains derived from T-cell signaling components (Fig. 1). The ectodomain typically comprises an extracellular single-chain antibody fragment (scFv), which, in some cases, has been optimized for binding affinity or to minimize nonspecific toxicity against non-tumor tissues. This process is also streamlined by carefully selecting tumor-specific targets.

The hinge region within CAR molecules serves as a bridge between the antigen-recognition domain and T-cell membrane, providing a degree of flexibility to accommodate spatial and steric constraints. This region also regulates the intermembrane space between a T cell and target cancer cells[21]. Tailoring the hinge region has been shown to be relevant for several CAR-T cells targeting both solid and hematologic cancers[21–27]. In addition to altering the size of the hinge region, biochemical aspects of this domain (e.g., dimerization capacity, FcγR interactions) can also heavily influence T-cell activation, proliferation, and anti-tumor efficacy[28].

The transmembrane domain assists in positioning the CAR molecule on the T-cell surface and facilitates the connection between the extracellular and intracellular domains, enabling the intracellular transmission of ligand recognition via the signaling endodomain. First-generation CARs employed an intracellular domain derived from CD3ζ; however, this approach was

limited by poor long-term T-cell activity and function[29]. Over time numerous modifications have been made to the original CAR structure, with the most substantial changes occurring in the choice or combination of signaling endodomains, giving rise to the so-called "second- and third-generation" CARs. Although various co-stimulatory signals have been tested[30–33], CD28 and 4-1BB remain the most commonly utilized endodomains in clinical trials to date.

Challenges in glioma immunotherapy

Tumor heterogeneity

One of the primary challenges in CAR-T cell therapy for glioma is the relative dearth of surface target antigens that are frequently and specifically expressed. Moreover, gliomas exhibit significant cellular and molecular heterogeneity, which can lead to partial or complete loss of antigen expression and, ultimately, tumor recurrence (Fig. 2). This has been observed after CD19 CAR-T cell therapy, where decreased CD19 expression and disease recurrence has been reported in 30–70% of patients[34,35]. Similar occurrences can also be noted, albeit less frequently, after treatment with BCMA CAR-T cells for multiple myeloma[36–38]. This mechanism of resistance has also been observed in the context of GBM, where recurrent tumors have displayed reduced cognate target antigen expression following treatment with either interleukin-13 receptor α chain variant 2 (IL-13Rα2) or epidermal growth factor receptor variant III (EGFRvIII) CAR-T cell therapy[39,40].

Immunosuppressive microenvironment

The TME is a complex and dynamic space that surrounds and interacts with solid tumors, potentiating counterproductive cellular infiltrates consisting of regulatory T cells, myeloid-derived suppressor cells, and other populations that work together to actively impede anti-tumor immune responses[41,42]. The milieu also drives the production of tumor-signaling molecules, growth factors, cytokines, chemokines, and immunomodulatory factors such as transforming growth factor β (TGF-β), interleukin 10 (IL-10), indoleamine 2,3-dioxygenase (IDO), macrophage migration inhibitory factor (MIF), and prostaglandin E-2 (PGE2)[43–49] (Fig. 2). Tumor cells utilize critical immune checkpoint molecules and signaling axes, such as those mediated through programmed death ligand 1 (PD-1) or cytotoxic T lymphocyte-associated protein 4 (CTLA-4), to enhance the inhibitory pathways of T cells, thereby further abrogating effective anti-tumor immune responses[50]. Finally, intratumoral hypoxia associated with the TME in gliomas may additionally drive tumor-associated impairment of immune cell function, particularly through increased expression of hypoxia-inducible factor 1-α (HIF1-α)[51].

CNS immune privilege

Immunotherapies targeting intracerebral tumors face unique challenges related to the phenomenon of immune privilege in the CNS. The concept of limited immune surveillance in the CNS was first introduced by Sir Peter Medawar in 1947[52], and since then, investigators have further refined these observations, highlighting unique characteristics that are now generally associated with the CNS, including the presence of a specialized blood–brain barrier (BBB), the absence of conventional draining lymph nodes, and the dearth of professional antigen-presenting cells within the brain[53–55].

The BBB plays a key role in protecting the brain from harmful toxins and chemicals, as well as fine-tuning brain homeostasis, given its unique ability to tightly regulate the movement of ionic substances and large molecules, as well as immune cells, into the CNS[56–58]. In addition to the BBB, another structure referred to as the blood–cerebrospinal fluid (CSF) barrier is formed by the choroid plexus epithelium and also plays a role in limiting communication between these respective anatomical compartments[59]. Evolving data suggest that the CNS, especially in the context of tumors, may not be as isolated from the immune system as once believed. In particular, immune cells are known to migrate to and throughout the brain relatively frequently despite the presence of the BBB[60–65]. When activated, T cells appear to readily cross the capillary tight junctions of the BBB[66,67]. How these mechanisms might be exploited to ultimately inform adoptive T-cell strategies is under active investigation.

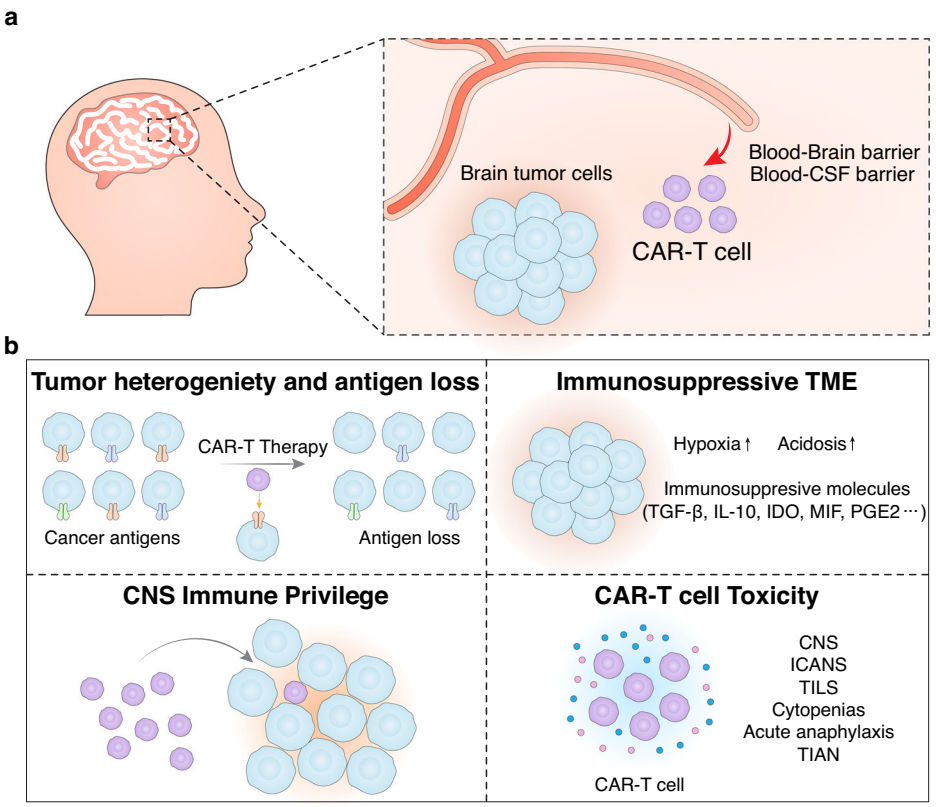

Fig. 2 | CAR-T cell therapies in brain tumors and their limitations. a and **b** CAR-T cell therapy targeting brain tumors face multiple challenges, including tumor heterogeneity, antigen loss, immunosuppressive tumor microenvironment, blood–brain barrier, limited trafficking, and CAR-T cell-associated cell toxicity. CNS cytokine release syndrome, ICANS immune effector cell-associated neurotoxicity syndrome, TLS tumor lysis syndrome, TIAN tumor inflammation-associated neurotoxicity.

CAR-T cell toxicity

Common toxicities observed after CAR-T cell therapy include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), tumor lysis syndrome (TLS), and acute anaphylaxis[68,69] (Fig. 2). CRS and ICANS are well-characterized phenomena in the treatment of hematological cancers and often occur in the absence of CNS tumor involvement. CRS is the most common type of toxicity after CAR-T cell therapy and is characterized by fever, hypotension, tachycardia, hypoxia, and, in severe cases, multiorgan dysfunction. It typically occurs within hours to days following CAR-T cell administration, although there have been reports of late onset[70–73]. The release of inflammatory cytokines such as interleukin-6 (IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) contribute to its pathogenesis.

The second most common toxicity related to CAR-T cell administration is ICANS, which affects ~40% of CAR-T cell recipients[74]. ICANS involves a complex interplay of mechanisms, including blood-brain barrier disruption, microangiopathy, thrombotic microangiopathy, and amplification of the inflammatory response. The integrity of the BBB is compromised by cytokine-induced activation of brain endothelial cells, leading to increased permeability and neuroinflammation. Disruption of the BBB and subsequent cerebral edema through systemic CAR-T cell-induced cytokine release appear to be key features of ICANS[73,75]. Additionally, thrombotic microangiopathy and inflammatory response amplification contribute to the pathophysiology of ICANS. Clinical manifestations include confusion, delirium, aphasia, seizures, and, in severe cases, cerebral edema and elevation of intracranial pressure. These symptoms are mediated by elevated levels of cytokines such as IL-6 and IFN-γ, which induce neuroinflammation and endothelial damage.

The mechanisms underlying CAR-T cell-associated neurotoxicity are not yet fully understood. However, in the CNS, upon infusion into patients, CAR-T cells encounter target cancer cells and subsequently release inflammatory cytokines such as TNF-α and IFN-γ. These cytokines then activate monocytes and macrophages to secrete additional cytokines, including IL-1, IL-6, and inducible nitric oxide synthase (iNOS). Elevated levels of IL-6 have been observed in patients experiencing CRS. Additionally, IL-1β, which is released earlier than other major cytokines, promotes IL-6 production and has been implicated in the pathogenesis of CRS and ICANS[76,77].

In the setting of tumors in the CNS, a potential emerging syndrome of neurotoxicity has been reported, which is thought to be related to localized tumor-associated inflammation (i.e., tumor inflammation-associated neurotoxicity or TIAN). The manifestations of TIAN tend to depend on the neuroanatomical location of the tumor and its proximity to eloquent regions of the brain[78]. Two subtypes of TIAN have been proposed[78]; Type 1 TIAN consists of inflammation-induced mechanical aspects of neurotoxicity, which may manifest as symptoms such as headache, focal neurological deficits, or changes in consciousness. Type 2 TIAN is characterized by inflammation-induced electrophysiological changes, potentially resulting in symptoms such as seizures, confusion, or altered mental status. These two subtypes can occur simultaneously within days to weeks of receiving therapy and may not be mutually exclusive, with symptoms often consistent with concurrent cytokine release syndrome (CRS) and elevated inflammatory markers. However, clinical and radiographic markers of TIAN may be subtle, vary from patient to patient, and may evolve rapidly, underscoring the need for additional investigation and characterization.

CAR-T cells for glioma: clinical studies

CAR-T cell therapy for brain tumors represents a promising and rapidly growing area of research; however, successful translation remains a challenge due to the aforementioned low mutational burden associated with brain tumors and the relative dearth of feasible tumor-specific target antigens[3,79]. Ongoing clinical trials exploring potential antigens for glioma include those targeting B7-H3, EGFRvIII, CD70, chlorotoxin, human epidermal growth factor receptor 2 (HER2), IL-13Rα2, interleukin-7Rα (IL-7Rα), GD2, MMP-2, and NKG2D. Here, we provide a brief review of these antigens that are currently in clinical trials and have been published ("Published Clinical Trials"), as well as those that are in clinical trials but have not yet been published ("Unpublished Clinical Trials") for CAR-T cells in glioma (Table 2 and Supplementary Table 1).

Published clinical trials

B7-H3. B7 homolog 3 protein (B7-H3; also known as CD276) is a member of the B7 family of molecules, consisting of type I transmembrane immune checkpoint proteins encoded by human chromosome 15[80,81]. B7-H3 is significantly overexpressed in gliomas compared to normal brain tissue. It is also found in several primary GBM cells isolated from clinical samples and associated cell lines[80,82]. Several CARs have been designed to target B7-H3 and these have shown promising results in preclinical studies[80,83]. B7-H3 CAR-T cells are currently being studied in patients with malignant glioma, including two clinical trials specifically for DIPG (Supplementary Table 1).

In a recent Phase I trial with B7-H3 CAR-T cells, three children with recurrent/refractory CNS tumors and DIPG were administered with repeated locoregional B7-H3 CAR-T cells[84]. No dose-limiting toxic effects were reported after 40 infusions in the first three DIPG patients. The patients showed evidence of a correlation between B7-H3 CAR T cells and local immune activation, as well as the persistence of CAR T cells in the cerebrospinal fluid (CSF) (NCT04185038).

EGFRvIII. EGFRvIII is a tumor-specific variant of EGFR present in approximately 30% of newly diagnosed GBM cases, making it the second most frequent EGFR variant in these tumors after wild-type EGFR amplification. Because EGFRvIII is specifically expressed in GBM and not expressed in any healthy tissues[85], this antigen has been extensively studied as a possible target for antibody-redirected T cell therapy, among other immunotherapeutic strategies[55,86–94].

A first-in-human study with intravenous delivery of EGFRvIII-specific CAR-T cells was conducted on 10 recurrent GBM patients. The CAR-T cells showed active localization to tumors in the brain, where they mediated on-target effects[40] (NCT02209376). A follow-up trial investigated a combination of EGFRvIII CAR-T cell therapy with pembrolizumab on patients with recurrent glioblastoma. This approach was also shown to be safe without dose-limiting toxicity[95], but it did not demonstrate clinical efficacy, which may be partly due to the limitations of targeting a single antigen in a heterogeneous disease (NCT03726515). To address this barrier to translation, EGFRvIII CAR-T cells have been engineered to secrete T-cell-engaging antibody molecules (TEAMs) against EGFR[90]. These TEAMs enhance the functionality of CAR-T cells by promoting the engagement of endogenous T cells with tumor cells, thereby increasing the overall anti-tumor immune response. In a clinical trial with the use of EGFRvIII CAR-T-secreting TEAMs, three patients with recurrent glioblastoma received a single intraventricular infusion of the engineered CAR-T cells. The treatment led to dramatic and rapid radiographic tumor regression, although responses were transient in two participants. Adverse events were minimal, with no grade 3 or dose-limiting toxic effects reported (NCT05660369)[96].

EphA2. The EphA2 receptor is a member of the Eph receptor family of tyrosine kinase receptors. This family consists of fifteen members, classified into classes A and B according to the degree of homology of their extracellular domains[97]. Typically, these domains include a globular NH2-terminal ligand-binding domain, followed by a cysteine-rich domain and two fibronectin type III repeats. EphA2 plays a critical role in modulating signal transduction pathways, including those that regulate migration, differentiation, and growth[98]. Approximately 90% of GBM tissues and cell lines overexpress EphA2, while relatively low levels are present in normal brain tissue[99].

In a recent clinical trial involving three EphA2-postive recurrent GBM patients, EphA2-redirected CAR-T cells were administered intravenously[100]. Two patients experienced grade 2 cytokine release syndrome with pulmonary edema; otherwise, there were no other organ

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Table 2 | Published clinical trials using CAR-T cell therapies for Glioma

Target antigen	ID	Phase	# Patient	Title	Generation	Results	Sponsor	Route	Ref.
B7-H3	NCT04185038	I	3	Study of B7-H3-specific CAR T cell locoregional immunotherapy for diffuse intrinsic pontine glioma/ diffuse midline glioma and recurrent or refractory pediatric central nervous system tumors	2 (BBζ)	* 3 patients with DIPG * One patient had sustained clinical and radiographic improvement through 12 months of study	Seattle Children's Hospital, WA, USA	ICT	84
EGFRvIII	NCT01454596	I, II	18	CAR T cell receptor immunotherapy targeting EGFRvIII for patients with malignant gliomas expressing EGFRvIII	3(28BBζ)	2 PR Median OS: 6.9 months Median PFS: 1.3 months	National Cancer Institute, MD, USA	IV	173
	NCT02209376	I	10	Increased expression of inhibitory molecules and loss of EGFRvIII expression following therapy; Patients with residual or reccurent EGFRvIII+ glioma	2 (BBζ)	5 SD Median OS: 251 days	University of Pennsylvania, PA, USA	IV	40
	NCT03726515	I	7	CART-EGFRvIII + pembrolizumab in GBM	2 (BBζ)	Median OS: 11.8 months Median PFS: 5.2 months	University of Pennsylvania, PA, USA	IV	95
	NCT05660369	I	3	CARv3-TEAM-E T cells in glioblastoma	2 (BBζ)	2 PR	Massachusetts General Hospital, MA, USA	ICV	96
EphA2	NCT03423992	I	3	Personalized chimeric antigen receptor T cell immunotherapy for patients with recurrent malignant gliomas	3(8BBζ)	1 SD & 2 PD OS: 86–181 days	Fuda Cancer Hospital, Guangdong, China	IV	100
GD2	NCT03170141	I	8	Immunogene-modified T (IgT) cells against glioblastoma multiforme	4 (28BBζ & inducible suicide caspase 9 gene)	5 PR & SD Median OS: 10 months	Shenzhen Geno-Immune Medical Institute, Guangdong, China	IV or ICT	108
HER2	NCT01109095	I	17	CMV-specific cytotoxic T lymphocytes expressing CAR targeting HER2 in patients with GBM	3(28BBζ)	1 PR & 7 SD Median OS: 11.1 months Median PFS: 2.5 months	Baylor College of Medicine, TX, USA	IV	110
	NCT03500991	I	3	HER2-specific CAR T cell locoregional immunotherapy for HER2-positive recurrent/refractory pediatric CNS tumors	2 (BBζ)	no dose-limiting toxicity	Seattle Children's Hospital, WA, USA	ICT	112
IL-13Rα2	NCT00730613	I	3	Cellular adoptive immunotherapy using genetically modified T-lymphocytes in treating patients with recurrent or refractory high-grade malignant glioma	1 (ζ)	1 PR Median OS: 10.3 months	City of Hope Medical Center, CA, USA	ICT	114
	NCT01082926	I	6	Phase I study of cellular immunotherapy for recurrent/ refractory malignant glioma using intratumoral infusions of GRm13Z40-2, an allogeneic CD8+ cytolitic T-cell line genetically modified to express the IL 13-zetakine and HyTK and to be resistant to glucocorticoids, in combination with Interleukin-2	N/A	Median OS: 2.9 months	City of Hope Medical Center, CA, USA	ICT	174
	NCT02208362	I	1	Genetically modified T-cells in treating patients with recurrent or refractory malignant glioma	2 (BBζ)	1 CR Median OS: 7.5 months	City of Hope Medical Center, CA, USA	ICT or ICV	39
		I	65	Genetically modified T-cells in treating patients with recurrent or refractory malignant glioma	2 (BBζ)	29 SD & 2 PR Median OS: 8 months	City of Hope Medical Center, CA, USA	ICT or ICV	115
IL-13Rα2 & EGFR	NCT05168423	I	6	CART-EGFR-IL13Ra2 in EGFR amplified recurrent GBM	N/A	Tumor shrinkage >30% 3 SD	University of Pennsylvania, PA, USA	ICT	175

Information obtained from ClinicalTrials.gov using keywords "CAR-T" AND "Glioblastoma" or "Glioma", accessed on 1 October 2024. The antigens are arranged alphabetically.

ICT intratumoral/intracavitary, *ICV* intracerebroventricular, *IV* intravenous, CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

toxicities, including neurotoxicity. In one patient, a transient reduction in tumor size was observed. Among these three patients, one reported stable disease, while two exhibited progressive disease, with overall survival durations ranging from 86 to 181 days (NCT 03423992).

GD2. Gangliosides are molecules composed of glycosphingolipids coated with sugar chains that are widely expressed in normal tissues. However, the disialoganglioside GD2 is present in several tumor types, including GBM[101,102], while its expression in normal tissue is primarily limited to the CNS and peripheral nerve tissues, accounting for less than 4% of all gangliosides[103–105]. In preclinical trials, GD2-targeting CAR-T cells have successfully demonstrated potent cytotoxicity against GBM and DIPG in both in vitro and murine models[102,106,107]. Several ongoing clinical trials are in Phase I, three of which are designed for DIPG.

In a recent clinical trial, eight patients with GD2-positive GBM received autologous fourth-generation GD2-specific CAR-T cells (4SCAR), which were designed with safety in mind and included CD28 transmembrane and cytoplasmic domains, the co-stimulatory 4-1BB intracellular TRAF binding domain, the CD3ζ chain intracellular domain, and an inducible suicide caspase-9 gene, allowing for controlled elimination of CAR-T cells if necessary. Among the eight patients, four experienced a partial response lasting between 3 and 24 months, three showed progressive disease with durations of 6–23 months, and one had stable disease for 4 months. The median overall survival was 10 months from the infusion. Importantly, there were no severe adverse events reported, including neurotoxicity or off-target effects. This approach has been associated with the loss of GD2 antigen and an activated immune response within the TME[108] (NCT03170141).

HER2. HER2 is a receptor tyrosine kinase that is normally expressed at low levels in epidermal tissue but is overexpressed in a variety of cancers. In GBM, HER2 levels are upregulated in up to 80% of tumors[109]. One clinical trial studying a second-generation HER2 CAR-T cell therapy on patients with GBM showed that the approach was safe and did not result in dose-limiting toxicities[110]. However, targeting HER2 with CAR-T cells has also been reported to mediate fatal toxicity and multiorgan system failure in a patient with colon cancer metastatic to the lungs and liver[111]. The unique characteristics of CAR-T cell therapies, such as their design and targeting mechanisms, as well as the conditions surrounding cell infusion, may be critical contributing factors.

In a recent clinical trial, three young adults aged 19–26 who had gliomas were given repeated, localized doses of these HER2 CAR-T cells for four weeks[112]. Two patients were treated intrathecally, and one was treated intracerebroventricularly without first undergoing lymphocyte reduction. None of the patients experienced dose-limiting toxicity, except for headache, pain at the metastatic site, and neurologic impairment (NCT03500991).

IL-13Rα2. In the immune system, IL-13 typically works in conjunction with its homolog, IL-4, to regulate immune responses through shared receptors present in many normal tissues. Notably, the IL-13 receptor is associated with the IL-13Rα2 protein chain, which is highly expressed in 50–80% of GBMs[113] but, unlike IL-4, is rarely detectable in normal tissues. To date, several IL-13Rα2-specific CARs have differed structurally from traditional CARs in that they co-opt the natural IL-13 ligand as the antigen-recognition domain instead of using an antibody-based fragment. Early clinical trials studying intracranial infusion of IL-13Rα2 CAR-T cells for recurrent GBM were safe[114], with one patient demonstrating a remarkable response in the setting of multifocal glioblastoma, but only after serial intraventricular infusions. In this case, the disease had spread along the leptomeninges, which may have made the tumor tissue more susceptible to treatment[39]. Recently, Phase 1 trials involving locoregional delivery of IL-13Rα2 CAR-T cells for recurrent GBM patients were published[115]. In this clinical trial, 50% of participants achieved stable disease or better. Additionally, 22% of patients maintained confirmed stable disease or better for at least 90 days, with two patients exhibiting a partial response, although these responses were limited to IDH-mutant glioma. This trial indicates that a significant proportion of patients experienced either stable disease or an improvement in their disease status following treatment with IL-13Rα2-targeted CAR-T cells (NCT02208362). Furthermore, IL-13Rα2 CAR-T cells have also been engineered to simultaneously target EGFR through bicistronic constructs for six patients with multifocal, treatment-refractory GBM (NCT05168423). In this trial, half of the patients showed at least 30% tumor shrinkage and 75% of patients showed stable disease at least 2 months after CAR-T cell therapy[95].

Unpublished clinical trials

CD44 and CD133. CD44 is a hyaluronan receptor expressed in both low-grade glioma and GBM[116]. CD133, a pentaspan membrane glycoprotein, has been used as a marker for cancer stem cells in GBM[117]. Co-expression of CD133 and CD44 has been linked to certain GBM subtypes and clinical outcomes, as revealed by gene expression profiles obtained from large patient datasets[118]. Clinical studies of CAR-T cells targeting both CD44 and CD133 are currently underway, in some cases with the introduction of a truncated IL-7 receptor α chain (IL-7Rα) within the intracellular signaling domain. IL-7 receptor regulates survival, proliferation, and differentiation of T cells[119]. In the GBM microenvironment, IL-7 signaling is reduced by methylation of *IL7/IL7R* genes, which in turn affects T cells function and survival[120]. A phase 1 clinical trial involving 10 patients with recurrent glioblastoma is currently underway (NCT05577091).

CD70. As a member of the tumor necrosis factor superfamily, CD70 mediates tumor progression and immune escape by recruiting immunosuppressive regulatory T cells and inducing T-cell exhaustion. CD70 exhibits aberrant, constitutive expression in a variety of cancers, including GBM[121–123]. Although CD70 expression in normal tissue is limited, it is present on the cell surface of mature dendritic cells (DCs) and antigen-activated T and B lymphocytes[124]. A phase 1 clinical trial with CD70 CAR-T cell therapy for recurrent GBM cases is underway (NCT05353530).

CD147. CD147 is a glycoprotein that is involved in tumor growth, invasion, and metastasis. It is known as an inducer of extracellular matrix metalloproteinases (MMPs), which trigger the degradation of the extracellular matrix[125]. CD147 is overexpressed in various cancers, including gliomas, and is associated with tumor grade and prognosis[126,127]. A phase 1 clinical trial is currently investigating the use of CD147-targeted CAR-T cells to treat recurrent malignant glioma. However, CD147 is also expressed in several normal tissues, including those of the CNS, which may lead to off-target effects[128,129]. To minimize this on-target/off-tumor toxicity, CD147-CAR-T cells have been incorporated into the synNotch-inducible system, a synthetic receptor system that only activates CAR-T cells in the presence of a specific antigen, thereby improving targeting precision. This system has shown promising preclinical results[130]. Currently, a phase 1 clinical trial with CD147 CAR-T cells is underway (NCT04045847).

MMP-2. Matrix metalloproteinase 2 (MMP-2) is part of a family of proteolytic enzymes that degrade various components of the extracellular matrix. Overexpression of MMP-2 has been associated with intrinsic glial malignancies and has also been shown to play a role in metastasis formation[131]. Chlorotoxin (CLTX), a naturally occurring small peptide found in the venom of the deathstalker scorpion *Leiurus quinquestriatus*[132], binds to MMP-2 expressed on the surface of glioma cells. This binding is rarely detectable in normal brain tissue, as well as many other normal human tissues, including skin, kidneys, and lungs[133–136]. Due to its binding specificity, CAR-T cells have been engineered to incorporate CLTX as an antigen recognition domain.

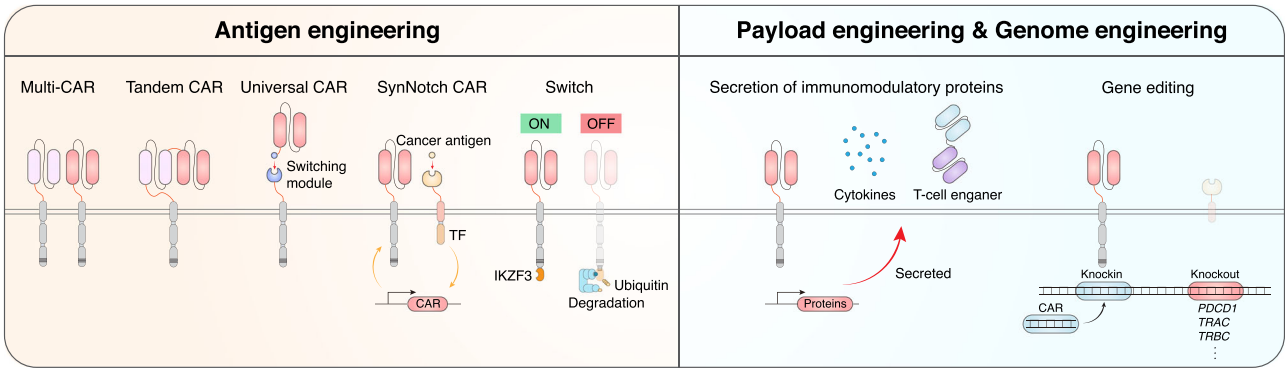

Fig. 3 | Engineering approaches for GBM. Next-generation CAR-T cell therapies integrate antigen receptor engineering, genome engineering, and payload delivery. Antigen receptor engineering includes multiple CAR constructs (Dual CAR), tandem CARs with two different scFvs, universal CARs for versatile scFv switching, SynNotch CARs that detect target antigens and trigger T-cell signaling, and logic gate approaches. Payload engineering enables CAR-T cells to secrete enzymes, cytokines, and antibodies, such as T-cell engagers. In addition, CAR-T cells utilize CRISPR-Cas9-based gene editing to target negative regulators of T-cell function to optimize treatment outcomes.

Two phase 1 clinical trials studying CLTX-CAR-T in MMP-2 positive recurrent glioblastoma are currently underway (NCT04214392 and NCT05627323).

Muc1. Muc1 is a member of the transmembrane mucin family, consisting of highly glycosylated tandem repeats. The survival and prognosis of patients with lung, stomach, colorectal, and pancreatic cancer are associated with elevated expression of Muc1[137–139]. A specific glycosylation pattern on membrane proteins, including Muc1, has been shown to be a marker for tumorigenesis and metastasis[140–143]. The most prevalent glycosylation patterns include Tn (GalNAcα1-O-Ser/Thr) and sialyl-Tn (STn) (NeuAcα2-6-GalNAcα1-O-Ser/Thr) glycoforms[144], which are present in many types of cancer, including GBM[145–147]. Glycosylation and elevated expression of Muc1 have been shown to form nanoscale physical barriers against immune cells, thereby reducing immune cell killing by CAR-T cells[148]. Tn-Muc1 targeting CAR-T cells have shown promise in the preclinical setting for Muc1-positive solid tumors[149]. One clinical trial with CAR-T cells targeting Muc1 is currently underway (NCT02617134).

NKG2D. NKG2D is a C-type lectin-like receptor in the NKG2 family, involved in the activation and regulation of natural killer (NK) cells. This receptor plays an essential role in NK cell-mediated cytotoxicity by binding to the homolog of the stress-inducible MHC class I chain-related protein A and B (MICA, MICB)[150]. NKG2D ligands are typically not expressed in normal cells but are upregulated in malignantly transformed or infected cells[151]. GBMs are known to express NKG2D ligands; however, immunosuppressive changes in the TME can lead to reduced expression, which may ultimately impair the effectiveness of NK cells or other therapeutic modalities targeting this receptor[152]. CAR-T cell approaches targeting NKG2D are currently being tested in patients with GBM and other solid tumors (NCT04270461, NCT04717999, NCT05131763)[153].

PD-L1. Programmed death-ligand 1 (PD-L1) is a type 1 transmembrane protein that acts as a pro-tumorigenic factor in cancer cells and can modulate the induction of T cell-mediated immune tolerance. Interaction between PD-L1 and PD-1 on the surface of activated T cells leads to tumor immune escape and tumor growth[154]. PD-L1 is highly expressed in glioblastoma multiforme[155] and other malignancies. While checkpoint therapy has emerged as a proven strategy for cancer immunotherapy, its effectiveness in brain tumors, including glioblastoma, has been limited[156]. In a phase III clinical trial for patients with recurrent GBM, there was no discernible improvement in survival benefit attributed to nivolumab[156]. Using the interaction between PD-L1 and PD-1, the extracellular domain of PD-1 is fused to the transmembrane and cytoplasmic domains of CD28 in CAR molecules. The CAR molecule containing the extracellular domain of PD-1 can recognize PD-L1-expressing tumor cells and transduce signals to activate T cells. With this structure, a clinical trial is ongoing for patients with recurrent GBM (NCT02937844).

Next-generation CAR-T cell targeting GBM

A variety of strategies have emerged to enhance the anti-tumor activity and durability of response in CAR-T cell treatment for GBM. These approaches build on lessons learned from early clinical experiences and pave the way for the next generation of cell therapies currently being investigated in the preclinical setting. These innovations can be grouped into three main categories: antigen receptor engineering, genome engineering, and payload delivery[157] (Fig. 3).

Antigen receptor engineering for GBM

CAR-T cell therapies have historically targeted single antigens, but the antigenic heterogeneity of GBM presents a challenge for long-term efficacy. Recent studies have focused on engineering CAR constructs that target multiple antigens simultaneously to mitigate this issue. Specifically, several engineered CARs, including tandem, bispecific, and universal CARs, may offer enhanced fine-tuning for specific anti-tumor effects[158–161]. Tandem CARs targeting IL-13Rα2 and HER2 or EGFRvIII have demonstrated superior anti-tumor responses and reduced antigen escape compared to single-targeted therapies in preclinical glioblastoma models[92,162]. A phase 1 trial is currently testing a bicistronic CAR targeting both IL-13Rα2 and EGFR in GBM patients (NCT04661384).

Many target antigens expressed on the surface of tumor cells, especially brain tumors, are also expressed on healthy cells, thus limiting the potential for safe, tumor-specific treatment. To address this challenge, several synthetic biology strategies are being employed, often incorporating multiple antigen-specific Boolean logic gates[163,164]. The Synthetic Notch (SynNotch), an engineered receptor system that functions as a molecular switch to control gene expression in response to specific antigens, has been used to address the tumor heterogeneity, persistence, and specificity issues associated with glioblastoma[165,166]. In the context of CAR-T cell therapy, SynNotch receptors are used to trigger the expression of CAR molecules targeting solid tumor antigens in a Boolean AND-gate fashion when SynNotch recognizes its corresponding antigen[166–168]. This SynNotch CAR-T technology is currently being tested in patients with EGFRvIII-positive glioblastoma in a phase I clinical trial by inducing anti-IL-13Rα2 and EphA2 CAR molecules through the anti-EGFRvIII SynNotch receptor (NCT06186401).

Engineering CAR-T cells to overcome the brain tumor microenvironment

One of the main challenges in treating brain tumors is the immune-suppressive nature of the tumor microenvironment. Several approaches are being developed to enable the delivery of immune-modulating factors, such as cytokines, directly to the TME. For example, CAR-T cells engineered to secrete cytokines IL-12 and IL-18 have shown increased activation of surrounding immune cells, such as NK, NKT, and γδ T cells[169]. Similarly, CAR-T cells designed to secrete IL-15 have exhibited improved effector functions, elevated levels of the anti-apoptotic protein Bcl-2, decreased expression of PD-1, and superior tumor control and persistence in preclinical GBM models[170].

Additionally, CRISPR-Cas9 genome editing techniques have been used to engineer CAR-T cells that resist TGF-β-mediated immunosuppression, a common feature of the GBM tumor microenvironment[171]. Also, CAR-T cells have been engineered to prevent the expression of immune checkpoint molecules such as PD-1, which are often upregulated in the TME of GBM and contribute to T cell exhaustion. By knocking out these checkpoint molecules, CAR-T cells can resist the suppressive signals in the TME, improving their persistence and anti-tumor efficacy[172].

Concluding remarks

Advances in gene and protein engineering continue to drive the development of translationally relevant CAR-T cell therapies. As the field progresses, integrating innovative strategies and ongoing research efforts will lead to safer, more precise, and potent CAR-T cell therapies for brain tumors. This review highlights early clinical experience for CAR-T cell therapy in patients with brain malignancies. Efforts are underway to address the challenges impacting the efficacy of CAR-T cell therapy in this context, including tumor heterogeneity, the tumor microenvironment, the structural complexities of the brain that hinder immune cell infiltration, and the limited understanding of post-CAR-T therapy toxicities affecting the CNS. Strategies to overcome these obstacles include the development of engineered CAR constructs and the exploration of novel cancer-associated antigens. As our experience with these approaches expands, collaborative efforts across multiple disciplines, including engineering, immunology, and patient clinical care, will be critical to fully realizing the potential of CAR-T cell therapy for aggressive brain tumors where the need for effective treatments is great.

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Author contributions

S.P. and B.D.C. searched for the relevant literature and wrote the manuscript. S.P., M.V.M., and B.D.C. reviewed and/or edited the manuscript before submission. All authors made a significant contribution to the discussion.

Competing interests

M.V.M. is an inventor on patents related to adoptive cell therapies held by Massachusetts General Hospital (some licensed to Promab) and the University of Pennsylvania (some licensed to Novartis). M.V.M. holds equity in 2SeventyBio, Century Therapeutics, Neximmune, Oncternal, and TCR2, and has served as a consultant for multiple companies involved in cell therapies. M.V.M. is a member of the Board of Directors of 2SeventyBio. B.D.C. is an inventor of patents and patent applications relating to T-cell engineering approaches.

Additional information

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Correspondence and requests for materials should be addressed to Bryan D. Choi.