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SYSTEMATIC REVIEW

Chimeric Antigen Receptor-T Cell Therapy for Pediatric and Young Adult Primary Central Nervous System Tumors: A Systematic Review of Early Phase Clinical Trials with a Focus on Diffuse Midline Glioma

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Abstract

Background Chimeric antigen receptor (CAR)-T cell therapy has demonstrated substantial efficacy in hematologic malignancies; however, its application in pediatric and young adult primary central nervous system (CNS) tumors, particularly pediatric diffuse midline glioma (DMG), remains investigational. Several early phase trials have recently reported clinical experiences with CNS-directed CAR-T cell therapies, necessitating a systematic distillation to better understand the state of the field.

Objective The aim of the study was to systematically review early phase clinical evidence evaluating the safety, feasibility, and preliminary efficacy of CAR-T cell therapy in pediatric and young adult patients with primary CNS tumors.

Patients and Methods A systematic review was conducted on early phase clinical studies assessing CAR-T cell therapies in pediatric and young adult patients diagnosed with primary brain tumors. Data collected included information on antigen targets, route of administration, dosing strategies, patient characteristics, prior therapies, toxicity profiles, anti-inflammatory management, radiographic and clinical outcomes, biologic correlates, and survival.

Results The search identified eight early phase trials involving 74 pediatric and young adult patients. Of the cohort, 63 received CAR-T cell infusion, targeting B7-H3, GD2, HER2, EGFR806, and PSMA-GD2 via intraventricular, intravenous, or combined routes. All patients had heavily pretreated, recurrent, or refractory disease, with all DMG cohorts receiving prior radiation. CAR-T cell therapy was feasible, with no treatment-related mortality. Immune toxicities, including cytokine release syndrome and CNS neurotoxicity, were common but reversible with corticosteroids and cytokine therapies. Among response-evaluable patients, 65% achieved disease control (stable disease or partial response), while 35% had progressive disease. Objective responses were rare, but many had disease stabilization, especially in DMG cohorts. Post-infusion, immune activation was evident, with CAR-T cell trafficking to CNS and increased cytokines in cerebrospinal fluid and plasma. Median survival ranged from 13 to over 30 months, with some patients exceeding expectations.

Conclusions Preliminary clinical experience indicates that CAR-T cell therapy for pediatric and young adult CNS tumors is biologically active and clinically feasible, exhibiting a distinct yet manageable toxicity profile. Although durable objective responses are currently limited, the frequent occurrence of disease stabilization and extended survival in certain patients substantiate ongoing research and the refinement of CAR-T cell strategies for CNS malignancies.

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Key Points

Early clinical trials suggest that CAR-T cell therapy for brain tumors in children and young adults is feasible and can be safely delivered, although side effects related to immune activation are common but usually manageable.

While clear tumor shrinkage is uncommon, many patients experience stabilization of their disease, and some show longer-than-expected survival compared with historical outcomes.

These findings support continued research, particularly to refine how and when CAR-T cell therapy is used to improve its effectiveness in brain tumors.

1 Introduction

Primary malignant brain tumors in children and young adults, particularly diffuse midline glioma (DMG), continue to be highly lethal [1, 2]. Despite ongoing research, the survival rates for DMG, including diffuse intrinsic pontine glioma (DIPG), remain low, with a median survival of less than 1 year [1–4]. Conventional radiotherapy provides only temporary disease control, and systemic therapies have not demonstrated long-term benefits, highlighting an unmet clinical need [5–8]. Historically, the central nervous system (CNS) has been regarded as a challenging target for immunotherapy owing to perceived immune privilege, limited lymphatic drainage, and the blood–brain barrier [9, 10]. However, recent insights into CNS immune surveillance, meningeal lymphatics, and tumor immune interactions have transformed this perspective, establishing the brain as an immunologically active organ [9–14]. These developments have rekindled interest in cellular immunotherapies, such as chimeric antigen receptor (CAR)-T cell therapy, which has demonstrated efficacy in hematologic malignancies [15, 16].

The translation of CAR-T cell therapy to solid tumors, particularly primary CNS malignancies, encounters several challenges, including the blood–brain barrier, limited space for immune infiltration and swelling, antigen heterogeneity, an immunosuppressive microenvironment, limited T cell trafficking, and concerns regarding toxicity [17–20]. Within the CNS, associated risks such as cerebral edema and intracranial pressure necessitate meticulous selection of target antigens, administration routes, and strategies to mitigate toxicity [17, 18, 21]. Nonetheless, pediatric brain tumors such as DIPG frequently express targets, including disialoganglioside (GD2), B7 homolog 3 protein (B7-H3), human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor (EGFR) variants, rendering them suitable candidates for CAR-T cell therapy [17, 21–27]. The spectrum of antigen targets examined across various studies is summarized in Fig. 1, which depicts representative tumor-associated antigens and the downstream effector mechanisms of CAR-T cells.

Over the past several years, multiple early phase clinical trials have reported first-in-human experiences with CAR-T cell therapy in pediatric and young adult CNS tumors [17, 21–27]. These studies have employed innovative strategies, including locoregional delivery via intraventricular or intratumoral routes, intra-patient dose escalation, and cytokine-enhanced CAR constructs, to overcome barriers to efficacy while preserving safety [17, 21–27]. Collectively, these trials have begun to define a CNS-specific CAR-T cell toxicity phenotype, including tumor inflammation-associated neurotoxicity (TIAN), that is distinct from systemic immune effector cell-associated toxicities observed in hematologic malignancies [17, 21, 28, 29].

While objective radiographic responses have been modest, emerging data suggest consistent biologic activity, evidenced by CAR-T cell trafficking to the CNS, robust cytokine induction in cerebrospinal fluid, and prolonged disease stabilization in select patients [18, 24, 30]. Importantly, several studies have reported survival durations exceeding historical benchmarks in DMG, raising critical methodological questions about how efficacy should be measured in this population. These include: (1) whether traditional endpoints such as progression-free survival adequately capture treatment benefit in the context of immunotherapy-related inflammation and pseudoprogression; (2) how radiographic response should be defined when tumor enlargement may reflect immune infiltration rather than true progression; (3) whether neurologic function, steroid dependence, or quality-of-life measures should be incorporated as co-primary endpoints; and (4) how early phase dose-escalation designs can be adapted for locoregional CAR-T cell delivery strategies [17, 21, 23, 31, 32]. However, the rapidly evolving and heterogeneous nature of these early phase trials has limited cross-study comparisons and impeded consensus on standardized response criteria and optimal trial design.

In this context, a systematic synthesis of early clinical experience with CAR-T cell therapy in pediatric and young adult CNS tumors is needed to better understand the current investigative landscape to treat these difficult diseases. Such an analysis offers the opportunity to integrate neuro-oncologic and immunologic perspectives, delineate patterns of safety and toxicity, evaluate signals of clinical and biologic

efficacy, and identify key design principles to guide future trials. Here, we systematically review early phase CAR-T cell clinical studies in primary CNS tumors, focusing on antigen targets, delivery strategies, immune-mediated toxicities, biologic correlates of response, and survival outcomes, with the goal of informing the next generation of CAR-T cell immunotherapy for CNS malignancies.

2 Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Given the exploratory and early phase nature of the available evidence, this study was designed as a qualitative systematic review, and no quantitative meta-analysis was performed. The review protocol was developed a priori but was not registered, as the primary objective was descriptive synthesis of early clinical experience rather than effect estimation. Data from this study are available from the corresponding author upon reasonable request.

2.1 Search Strategy and Eligibility Criteria

A comprehensive literature search was conducted using PubMed (MEDLINE), Embase, and Scopus from the inception of the databases through January 2026 to identify clinical studies assessing CAR-T cell therapy in pediatric and young adult patients with primary CNS tumors. The search terms integrated controlled vocabulary and free-text keywords pertaining to CAR-T cell therapy, cellular immunotherapy, brain tumors, diffuse midline glioma, and pediatric CNS malignancies. The complete search strategy is detailed in Supplementary Table S1.

Studies qualified for inclusion if they satisfied the following criteria: (1) reporting clinical outcomes from prospective or retrospective early phase (phase I or first-in-human) trials; (2) evaluating CAR-T cell therapy administered either

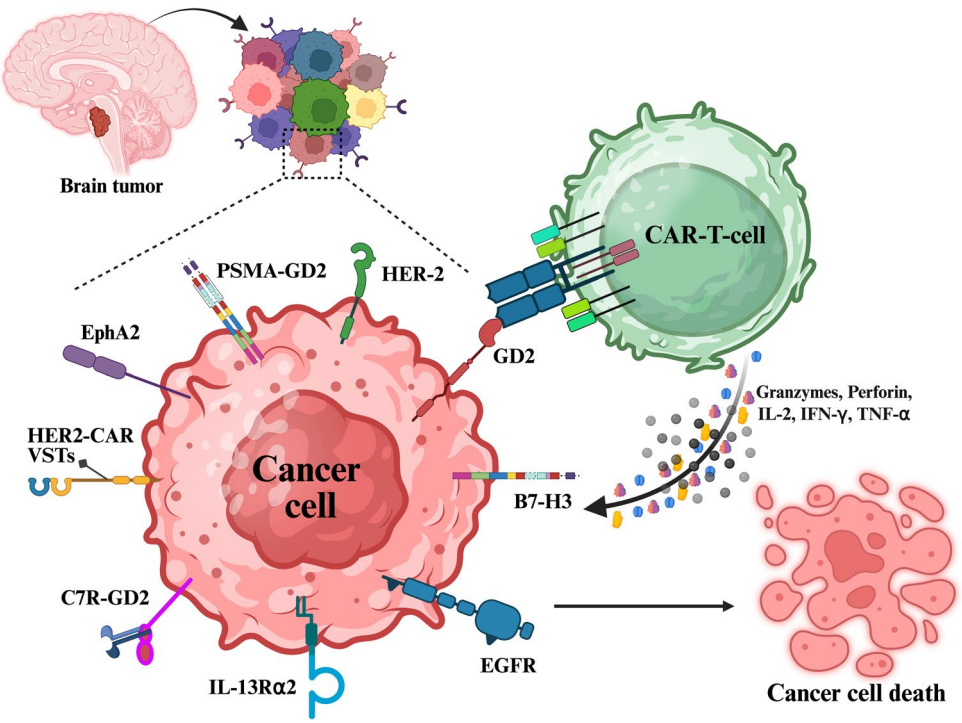
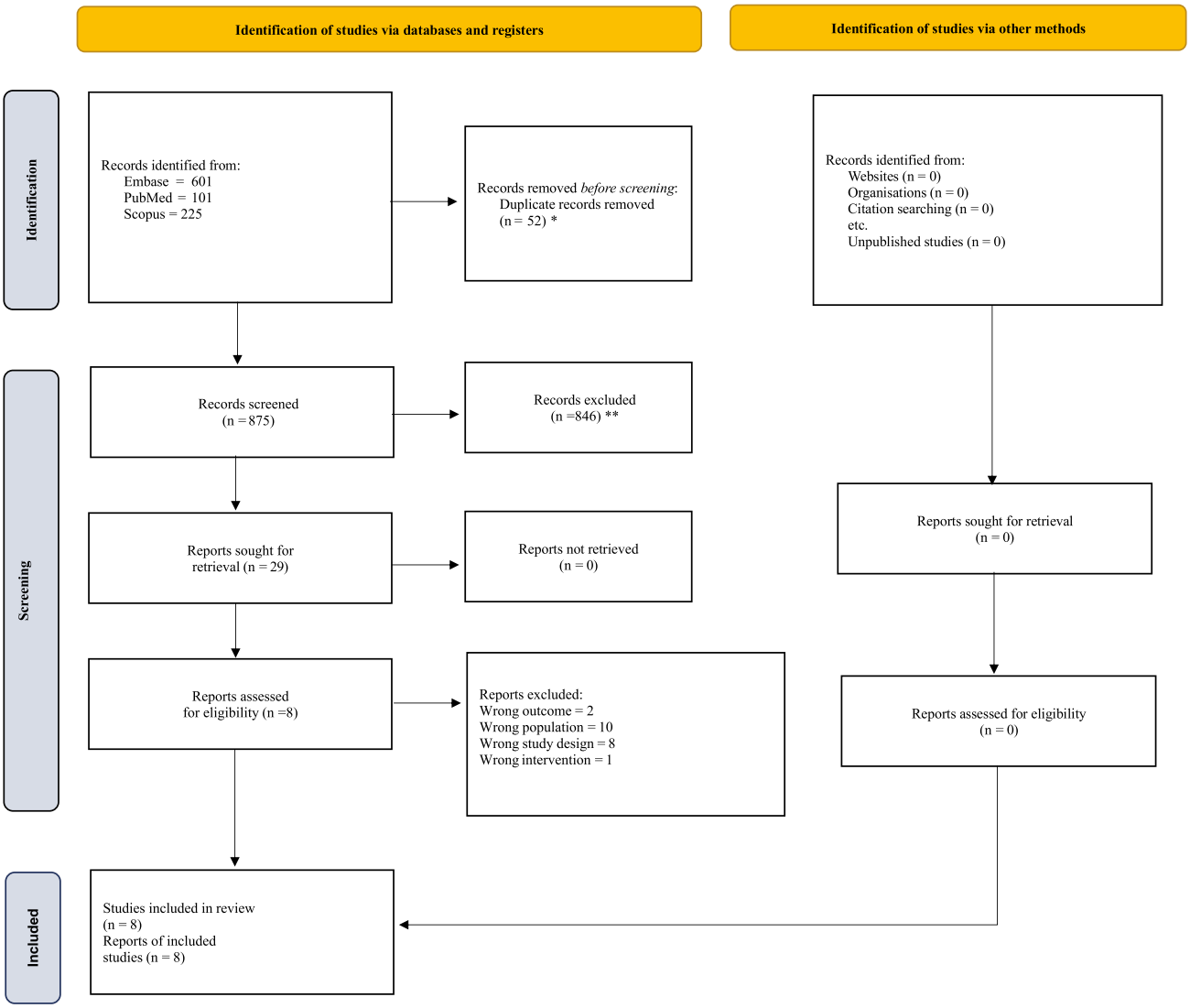


Fig. 1 Antigen targets and mechanisms of CAR T-cell therapy in central nervous system tumors. Schematic illustration of chimeric antigen receptor (CAR) T-cell therapy targeting primary central nervous system (CNS) tumors. Tumor cells express a heterogeneous array of surface antigens, including B7-H3, GD2, HER2, EGFR, IL-13Rα2, EphA2, and PSMA-GD2, which are recognized by engineered CAR T cells or CAR-modified virus-specific T cells. Following antigen engagement, CAR T cells become activated through intracellular signaling domains, resulting in T-cell cytotoxicity, release of granules (perforin and granzymes), and secretion of pro-inflammatory cytokines such as interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). These effector mechanisms promote tumor cell killing and immune-mediated tumor control. Advanced CAR designs, including cytokine-augmented constructs (e.g., C7R-GD2), aim to enhance T-cell persistence and function within the immunosuppressive CNS tumor microenvironment. *GD2* disialoganglioside GD2, *HER2* human epidermal growth factor receptor 2, *EGFR* epidermal growth factor receptor, *IL-13Rα2* interleukin-13 receptor alpha-2, *EphA2* ephrin type-A receptor 2, *PSMA* prostate-specific membrane antigen, *B7-H3* B7 homolog 3 (CD276), *VSTs* virus-specific T cells, *C7R* constitutively active interleukin-7 receptor

systemically or through locoregional CNS delivery; (3) involving pediatric and/or young adult patients with primary CNS tumors; and (4) reporting at least one of the following outcomes: safety/toxicity, clinical or radiographic response, biologic or immunologic correlates, or survival outcomes. Studies were excluded if they were preclinical or animal-only investigations, review articles, editorials, conference abstracts lacking primary clinical data, or studies assessing non-CAR-T cell cellular therapies. Trials exclusively focused on metastatic CNS disease were also excluded. When multiple publications reported overlapping patient cohorts, the most comprehensive or most recent report was incorporated to prevent duplication. A detailed summary of the inclusion and exclusion criteria is provided in Supplementary Table S2.

2.2 Study Selection and Data Collection

The process of study selection was conducted in accordance with PRISMA 2020 guidelines. All records obtained from database searches were imported into EndNote X9, where duplicate entries were identified and eliminated. The deduplicated dataset was subsequently exported in RIS format and uploaded to the Rayyan systematic review platform (https://www.rayyan.ai/) for screening.



* With automation tool; ** Without automation tool.

Fig. 2 PRISMA flowchart of study selection. *With automation tool; **without automation tool

Two independent reviewers (S.S. and B.D.) examined titles and abstracts for relevance, followed by a comprehensive review of full texts of studies deemed potentially eligible. Any discrepancies identified at various stages were resolved through consensus, with adjudication by senior investigators (A.N.S. and V.M.L.) when needed. Reference lists of all included studies and pertinent review articles were manually screened to ensure completeness. The entire study selection process is summarized in the PRISMA flow diagram (Fig. 2).

2.3 Data Extraction

Data extraction was performed independently by two reviewers using a standardized data collection form. Extracted variables included: (1) study characteristics (author, year, country, and trial identifier); (2) CAR-T cell construct and antigen target; (3) route of administration and dosing strategy; (4) patient demographics and tumor histology; (5) disease status at enrollment and prior therapies; (6) toxicity profiles, including cytokine release syndrome (CRS) and neurologic adverse events; (7) anti-inflammatory and supportive interventions; (8) clinical and radiographic response outcomes; (9) reported biologic or immunologic correlates; and (10) survival outcomes where available. All outcomes were recorded as reported in the original publications. Given heterogeneity in response definitions and reporting frameworks, no attempt was made to harmonize outcomes using uniform response criteria.

2.4 Outcomes of Interest

The outcomes of interest were the following:

Safety and toxicity, with particular attention to immune-mediated and CNS-specific adverse events.
Clinical and radiographic outcomes, including objective response and disease stabilization.
Biologic activity, defined by evidence of CAR-T cell trafficking or immune activation.
Survival outcomes, including overall survival from diagnosis or CAR-T cell infusion.

3 Results

3.1 Study Selection and Trial Characteristics

After an initial screening of 927 studies, titles, and abstracts, 29 full-text articles were evaluated for eligibility. A total of eight early phase clinical trials evaluating CAR-T cell therapy for primary brain tumors met the inclusion criteria [17, 21–27]. These studies enrolled 74 patients, of whom 63 received CAR-T cell infusion. All studies were phase I or first-in-human investigations, with sample sizes ranging from 2 to 23 patients. Most trials were conducted in the USA, with one study reported from China. Among the eight included studies, three (37.5%) were DMG-specific [17, 21, 23], three (37.5%) included mixed CNS tumor populations (including DMG) [22, 26, 27], and two (25%) focused on non-DMG histologies [24, 25] such as glioblastoma and ependymoma. Target antigens included B7-H3, GD2, HER2, EGFR806, and PSMA-GD2. CAR-T cell delivery strategies varied and included intraventricular (ICV), intravenous (IV), or combined IV/ICV administration. All studies employed dose-escalation designs, with administered doses ranging from 1×10^6 to 1×10^8 CAR-T cells/kg, or equivalent fixed-dose regimens. Full details of the studies included are detailed in Table 1. A notable and recurring observation across locoregional trials and GD2-directed CAR-T cell trials was the association between post-infusion cerebrospinal fluid (CSF) cytokine elevation (including CXCL10, IFN-γ, and IL-2) and radiographic disease stabilization [17, 21]. While preliminary, this pattern suggests that biologic immune activation may serve as an early biomarker of therapeutic engagement, potentially preceding or complementing radiographic response criteria.

3.2 Patient and Disease Characteristics

The patient population primarily comprised pediatric and young adult individuals, with reported ages spanning from 2 to 30 years. Female representation varied from 33 to 75% across the studies. DMG, including DIPG, accounted for the majority of treated tumors, followed by glioblastoma, with smaller incidences of ependymoma, anaplastic astrocytoma, medulloblastoma, and atypical teratoid rhabdoid tumor. Across studies, approximately 75% of patients were treated in the recurrent or progressive setting at the time of enrollment, although several diffuse midline glioma trials included patients earlier in the disease course following completion of radiotherapy, reflecting evolving interest in earlier therapeutic intervention. Prior radiation therapy was reported in the majority of DMG cohorts, and the majority of patients had undergone multiple previous tumor-directed therapies, including surgical interventions and chemotherapy. The reported median durations from diagnosis to trial enrollment ranged from 3.1 to 22.5 months. While prior radiotherapy was consistently reported in DMG cohorts, reporting across other histologies was variable, although most patients were heavily pretreated with multimodal therapy. Data regarding re-irradiation were not uniformly available across studies. Furthermore, although some studies reported the time from diagnosis to CAR-T cell infusion, the interval between the

Table 1 Characteristics and outcomes of early phase clinical trials of car-T cell therapy in pediatric and young adult central nervous system tumors

Study	Country	Trial identifier	Transduction method	Antigen target	ROA	Dosing	Patients enrolled (patients treated)	Age group, years	Female	Cancer type
Vitanza et al., 2025	USA	NCT04185038	Lentiviral	B7-H3	ICV	4 dose regimens. DR1, 3 (1×10^7) CAR-T cells per dose. DR2, DR3, and DR4 used intra-patient dose escalation. DR2, 6 (up to 2.5×10^7) CAR-T cells per dose; in DR3, 3 (up to 5×10^7) CAR-T cells per dose and, in DR4, 6 (up to 10×10^7) CAR-T cells per dose	23 (21)	(2–22)	14 (61%)	DIPG (diagnosed radiographically or via histopathologic confirmation of high-grade glioma or diffuse midline glioma H3K27M-altered [DMG])
Majzner et al., 2022	USA	NCT04196413	Retroviral	GD-2	IV/ICV	Dose escalation, weight-based strategy	4 (4)	(4–24)	3 (75%)	3 participants with DIPG and 1 participant with spinal cord DMG (all with H3K27M mutation)
Vitanza et al., 2021	USA	NCT03500991	Lentiviral	HER2	ICV	Dose escalation (1×10^7 to 2.5×10^7)	3 (3)	(16–26)	1 (33%)	2 Ependymoma (66.6%), 1 anaplastic astrocytoma (33.3%)
Ahmed et al., 2017	USA	NCT01109095	Retroviral	HER2-CAR VSTs	IV	Dose escalation 1×10^6 /m^2; 3×10^6/m^2; 1×10^7/m^2; $3\ 10^7$/m^2; and 1×10^8/m^2	7 (7)	(10–17)	3 (42.8%)	7 Glioblastoma (100%)
Monje et al., 2024	USA	NCT04196413	Retroviral	GD-2	IV / ICV	DL1, 1×10^6/kg; DL2, 3×10^6/ kg	13 (11)	(2–30)	6 (54.5%)	9 (81.8%) participants with DIPG and 2 (18.2%) participants with spinal DMG (all with H3K27M mutation)

Table 1 (continued)

Study	Country	Trial identifier	Transduction method	Antigen target	ROA	Dosing	Patients enrolled (patients treated)	Age group, years	Female	Cancer type
Lin et al., 2023	USA	NCT04099797	Retroviral	GD-2; 3, GD2-directed CAR-T cells (GD2 CAR-Ts); 8 with a constitutively active interleukin (IL)-7 receptor (C7R-GD2 CAR-Ts)	IV	Dose escalation (1×10^7 to 3.5×10^7)	11 (11)	(4–17)	5 (45.5%)	8 (72.2%) with DMG and 2 (18.2%) with medulloblastoma, and 1 (9.1%) with atypical teratoid rhabdoid tumor
Gu et al., 2025	China	NA	Lentiviral	PSMA-GD2	IV	$1–5 \times 10^6$ cells/kg	2 (2)	12 and 16	0 (0%)	1 (50%) GBM, 1 (50%) DGM
Gust et al., 2025	USA	NCT03638167	Lentiviral	EGFR806	ICV	$1–2.5 \times 10^7$ cells/kg	11 (4)	(7–17)	2 (50%)	3 (75%) GBM, 1 (25%) atypical teratoid rhabdoid tumor

Study	DMG	Study population	Pre-adjuvant therapies	Median time from diagnosis to enrollment	Anti-inflammatory interventions	Adverse effects and toxicities	Clinical results	Biologic results	Survival results
Vitanza et al., 2025	23	Previous progression, 12 (52%); no previous progression, 11 (48%)	Radiation therapy, 23 (100%)	6 (3–22)	Dexamethasone ($\leq 2.5\,mg/m^2$/day)	Headache (17 patients, 81%), nausea or vomiting (17 patients, 81%), fatigue (13 patients, 62%), and fever (12 patients, 57%)	A total of 18 patients received sufficient CAR-T cell infusions to be evaluable for neuroimaging assessment. On MRI, 1 PR (6%), 15 SD, (83%) and 2 PD (11%)	CSF cytokine profiling showed post-infusion increases in CXCL10, IFNγ, GM-CSF, and TARC, with sustained CXCL10/IFNγ elevations across infusions, consistent with locoregional CAR-T cell activation and cytotoxic immune activity	The median survival from their initial CAR-T cell infusion was 10.7 months (range: 0.6–45.8 months), and the median time from diagnosis to death (or last contact for survivors) was 19.8 months with 3 patients still alive 44.6, 45.6, and 52.5 months from diagnosis (range: 6.5–52.5 months)

Table 1 (continued)

Study	DMG	Study population	Pre-adjuvant therapies	Median time from diagnosis to enrollment	Anti-inflammatory interventions	Adverse effects and toxicities	Clinical results	Biologic results	Survival results
Majzner et al., 2022	4	Previous progression, 3 (75%); no previous progression, 1 (25%)	Radiation therapy, 4 (100%)	3.1 (1.4–12.4)	Tocilizumab, dexamethasone, methylprednisolone, anakinra (no dosage information)	CRS occurred in 2 patients (50%; grade ≥ 3 in 1/4 [25%]), and neuroinflammatory toxicity with edema/ICP elevation occurred in 2 patients (50%), all reversible; no on-target off-tumor toxicity was observed (0%)	All 4 patients received CAR-T cell infusions and were evaluable for clinical and radiographic response; 3 (75%) patients demonstrated clinical and/or radiographic improvement, including tumor volume reduction or decreased T2/FLAIR signal, while 1 (25%) patient showed PD	Post-infusion analyses demonstrated increased inflammatory cytokines in CSF and plasma, with evidence of CAR-T cell trafficking and immune activation, supporting on-target locoregional CAR-T cell activity	Survival from CAR-T cell infusion ranged from 3 to 11 months, with overall survival from diagnosis ranging from 13 to 26 months across the 4 patients
Vitanza et al., 2021	0	Refractory or recurrent	3 (100%) or more tumor-directed surgical procedures and had received at least 1 prior irradiation and at least 1 prior chemotherapy regimen	NA	Dexamethasone: 1 (33.3%) was on long-standing before enrollment and continued throughout; 2 (66.6%) received only at select timepoints	Systemic CRP elevations occurred in all 3 patients (3/3, 100%)	End of course 2 imaging: PD in 2/3 (66.7%) and SD in 1/3 (33.3%)	All 3 showed local CNS inflammatory responses after infusion; CSF/serum signals highlighted CXCL10 and CCL2.	NA

Table 1 (continued)

Study	DMG	Study population	Pre-adjuvant therapies	Median time from diagnosis to enrollment	Anti-inflammatory interventions	Adverse effects and toxicities	Clinical results	Biologic results	Survival results
Ahmed et al., 2017	0	Refractory or recurrent	7 (100%) underwent surgery and chemotherapy	7.3 (5.9–16.7)	NA	NA	1 (14.3%) patient showed partial response, 2 (28.6%) stable disease[17], and 4 (57.1%) progressive disease	NA	1 patient had non-progressive disease. Median time to progression in remaining 6 patients from time of infusion was 2 months (1.1–9.2). At the time of study completion, 1 patient was alive; among 6 patients, median time of survival from first dose of infusion was 7.1 months (2.7–26.9), and from diagnosis 19.9 months (8.9–34.2)
Monje et al., 2024	11	NA	Radiation therapy, 11 (100%)	5 (3.9–11.6)	CRS was managed according to established guidelines using tocilizumab, anakinra, corticosteroids (dexamethasone and methylprednisolone), fluid resuscitation, and supportive care	CRS occurred in all 11 (100%) patients at least once, immune effector cell acute neurotoxicity syndrome (ICANS) in 5 (45.4%), 10 (90.9%) with tumor inflammation-associated neurotoxicity (TIAN)	3 (27.3%) progressive disease, 8 (72.7%) stable disease or partial response	No differences in the CD4:CD8 ratio of the CAR-T cell product between responders and nonresponders, but responders (SD or PR) exhibited higher levels of IL-2 in plasma following IV GD2 CAR-T administration, potentially reflecting increased T cell activation in these patients	Median overall survival for patients treated on arm A was 20.6 months from diagnosis, with 2 patients with DIPG alive and followed subsequent to data cut-off. For patients with DIPG, median overall survival was 17.6 months and for sDMG 31.96 months

Table 1 (continued)

Study	DMG	Study population	Pre-adjuvant therapies	Median time from diagnosis to enrollment	Anti-inflammatory interventions	Adverse effects and toxicities	Clinical results	Biologic results	Survival results
Lin et al., 2023	8	Refractory or recurrent	Radiation therapy, 11 (100%)	NA	Early signs of non-dose-limiting CRS and CAR-T-associated pseudoprogression were managed with anti-cytokine agents (tocilizumab and anakinra) and corticosteroids	No adverse events in GD2 CAR-T patients. 7 (63.6%) developed grade 1 TIAN and 6 (54.5%) CRS (grade 1 $n = 5$, grade 4 $n = 1$)	5 (45.4%) stable disease, 2 (14.2%) PR, and 4 (36.4%) showed PD	Elevated expression of granzyme B as well as interferon (IFN)-g, among other cytokines, in patients treated with C7R-GD2 CAR-Ts compared with those receiving GD2 CAR-Ts	NA
Gu et al., 2025	1	Refractory or recurrent	Radiation and chemotherapy 2 (100%), surgery 1 (50%)	NA	NA	NA	2 (100%) PD	NA	NA
Gust et al., 2025	2	Refractory or recurrent	Surgery and radiation 4 (100%), chemotherapy 3 (75%)	22.5 (8–30)	Max dexamethasone of 10 mg BID	No CRS, 4 (100%) TIAN	3 (75%) PD, 1 (25%) SD	NA	NA

Summary of early phase clinical studies evaluating chimeric antigen receptor (CAR)-T cell therapies in pediatric and young adult patients with primary central nervous system tumors. Data shown include trial identifiers, antigen targets, route of administration, dosing strategies, patient demographics, tumor histology, disease status at enrollment, prior and concurrent therapies, anti-inflammatory interventions, toxicity profiles, clinical and radiographic outcomes, biologic correlates, and survival outcomes. Where applicable, outcomes are reported for treated patients

CAR chimeric antigen receptor, *CAR-T* chimeric antigen receptor T cell, *VSTs* virus-specific T cells, *CNS* central nervous system, *DMG* diffuse midline glioma, *DIPG* diffuse intrinsic pontine glioma, *GBM* glioblastoma, *ATRT* atypical teratoid rhabdoid tumor, *H3K27M* histone H3 lysine 27 to methionine mutation, *ROA* route of administration, *ICV* intraventricular, *IV* intravenous, *DR* dose regimen, *DL* dose level, *CRS* cytokine release syndrome, *ICANS* immune effector cell-associated neurotoxicity syndrome, *TIAN* tumor inflammation-associated neurotoxicity, *ICP* intracranial pressure, *CRP* C-reactive protein, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CSF* cerebrospinal fluid, *IFN-γ* interferon gamma, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *CXCL10* C-X-C motif chemokine ligand 10, *CCL2* C-C motif chemokine ligand 2, *IL-2* interleukin-2, *IL-7* interleukin-7, *QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, *QLQ-BN20* European Organisation for Research and Treatment of Cancer Brain Neoplasm Module, *NA* not available

most recent radiotherapy and CAR-T cell administration was not consistently specified.

3.3 Safety and Toxicity

CAR-T cell therapy has demonstrated feasibility in multiple studies, with no treatment-related mortalities reported. Immune-mediated toxicities were prevalent and exhibited variability depending on the specific antigen target and the route of administration. Cytokine release syndrome (CRS) was observed in 50–100% of patients involved in GD2-directed trials, predominantly manifesting as grade 1–2, with infrequent instances of grade ≥ 3 CRS and lower or variably reported rates in other antigen targets. Neurotoxic effects, including immune effector cell-associated neurotoxicity syndrome (ICANS) and TIAN, were particularly notable following locoregional delivery, often presenting as cerebral edema or increased intracranial pressure. These adverse effects were generally reversible and could be effectively managed with corticosteroids, tocilizumab, anakinra, and supportive care. Importantly, there were no reported cases of on-target, off-tumor toxicity across the reviewed studies. Detailed data regarding the timing of prior radiotherapy relative to CAR-T cell infusion were not consistently reported across studies, and therefore, a meaningful correlation between radiation exposure and neurological toxicities could not be assessed.

3.4 Clinical and Radiographic Outcomes

Radiographic response assessment demonstrated limited objective tumor responses. Partial responses were reported in 6–27% of treated patients across studies. Stable disease was observed in 33–83% of patients across studies, including in GD2-directed CAR-T cell trials. In GD2-directed CAR-T cell trials, individual study cohorts reported disease stabilization or partial response in approximately 65–75% of treated patients [17, 21, 26], whereas outcomes across other antigen targets were more heterogeneous, ranging from approximately 25–80% [22–25, 27]. Progressive disease remained common, reflecting the heavily pretreated nature of the population. Across response-evaluable patients, 65% achieved disease control (stable disease or partial response), whereas 35% demonstrated progressive disease, reflecting the aggressive biology of these tumors despite early biologic activity. Clinical or radiographic improvement, including reductions in tumor volume or T2/fluid-attenuated inversion recovery (FLAIR) signal intensity, was reported in several studies, with improvement observed in a substantial proportion of patients within individual cohorts. Reporting of duration of response was inconsistent across studies, precluding meaningful comparison between trials. Radiographic response assessment criteria varied across studies, with some trials applying modified RANO or iRANO frameworks, while others used study-specific definitions, limiting direct comparability across cohorts.

3.5 Biologic Correlates of Response

All studies reporting correlative analyses demonstrated evidence of immune activation following CAR-T cell infusion. Post-treatment analyses consistently showed elevated inflammatory cytokines, including C-X-C motif chemokine ligand 10 (CXCL10), interferon gamma (IFN-γ), granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and chemokine (C-C motif) ligand 2 (CCL2) in cerebrospinal fluid and/or plasma, supporting on-target CAR-T cell activity and CNS trafficking. In GD2-directed trials, patients with disease stabilization or partial response exhibited higher IL-2 levels post-infusion, suggesting enhanced T cell activation. Studies incorporating cytokine-enhanced CAR constructs demonstrated increased granzyme B and interferon-γ expression, indicative of augmented effector function.

3.6 Survival Outcomes

The median overall survival following CAR-T cell infusion ranged from 3 to 20.6 months. The median overall survival from the point of initial diagnosis ranged from 13 to 31.9 months. Notably, in the B7-H3-directed CAR-T cell trial, three patients remained alive at 44.6, 45.6, and 52.5 months from diagnosis at the time of reporting. Extended survival was most frequently observed in GD2-directed and B7-H3-directed CAR-T cell trials, exceeding historical prognoses for DMG in certain instances.

4 Discussion

In this systematic review, we synthesized early phase clinical experience with CAR-T cell therapy for pediatric and young adult primary CNS tumors. Across eight first-in-human and phase I studies, CAR-T cell therapy targeting antigens such as GD2, B7-H3, HER2, EGFR806, and prostate-specific membrane antigen-GD2 (PSMA-GD2) was feasible, showed consistent activity within the CNS, and had a distinct but largely manageable toxicity profile. Although objective radiographic responses were uncommon, disease stabilization and prolonged survival were observed in a subset of patients, particularly in DMG. Collectively, these findings demonstrate biologic proof of concept for CAR-T cell therapy in CNS malignancies and highlight key lessons for the design and interpretation of future trials.

From a neuro-oncology perspective, these findings must be interpreted within the context of diseases that have

historically exhibited poor outcomes and limited responsiveness to therapy [3, 6, 33]. DMG and pediatric high-grade gliomas have demonstrated little progress in improving survival rates over many decades, despite extensive investigation of systemic agents [5, 6, 8]. In this context, the recurrent observation of disease stabilization and the appearance of long-term survivors exceeding historical benchmarks are clinically notable indicators, even in the absence of high objective response rates [17, 21, 23, 31]. Importantly, conventional radiographic endpoints may inadequately reflect therapeutic benefits in CNS immunotherapy trials, where phenomena such as treatment-related inflammation, edema, and delayed responses complicate response assessment [17, 21, 31, 34]. These challenges emphasize the significance of implementing and, where appropriate, refining existing neuro-oncology immunotherapy response frameworks such as iRANO, particularly within the context of cellular therapies and locoregional delivery [31]. However, it is important to note that these frameworks rely substantially on contrast-enhancing disease, whereas many diffuse midline gliomas are non-enhancing, thereby limiting the applicability of RANO/iRANO criteria and complicating response assessment in this population. While iRANO offers guidance on pseudoprogression and response assessment in immunotherapy, early CAR-T trials reveal additional practical considerations, including catheter-related imaging alterations, compartmental delivery effects, steroid dependence as a confounding factor, and the integration of neurological function and immune-correlative endpoints [31]. These factors may necessitate cell-therapy-specific operationalization either within or alongside established criteria.

From an immunotherapy perspective, a fundamental and consistent observation across various studies was the evidence of on-target immune activation within the CNS [17, 18, 21, 35]. Multiple clinical trials demonstrated the trafficking of CAR-T cells to the cerebrospinal fluid and the induction of inflammatory cytokines such as CXCL10, INF-γ, GM-CSF, and IL-2 following infusion [17, 21–27]. These findings directly contest historical assumptions regarding the immune privilege of the brain and provide compelling evidence that engineered T cells are capable of accessing and engaging the tumor microenvironment within the CNS [17, 21–27]. Notably, elevated cytokine levels post-infusion were observed in patients exhibiting disease stabilization or partial response across several studies, suggesting that immune activation rather than early radiographic changes may serve as a more sensitive indicator of therapeutic engagement in this context [17, 21–27]. Among studies, disease stabilization or partial response was observed in GD2-directed CAR-T cell trials, whereas outcomes across other antigen targets appeared more heterogeneous. However, cross-study comparisons are limited by small sample sizes, differences in tumor type, and variability in trial design, and no definitive conclusions regarding comparative efficacy can be drawn.

A defining feature emerging from this synthesis is the distinct toxicity phenotype of CNS-directed CAR-T cell therapy. While CRS and ICANS were observed, particularly following systemic delivery [28], locoregional approaches revealed a CNS-specific inflammatory syndrome often described as TIAN [21, 29]. This entity, characterized by cerebral edema and increased intracranial pressure, reflects localized immune activation within the confined intracranial compartment rather than systemic toxicity [21, 29]. Importantly, although many of these toxicities were manageable and reversible with corticosteroids, cytokine-directed therapies, and neurocritical care support, they were frequently clinically significant and, in some cases, severe, including high-grade CRS, neurotoxicity, and symptomatic intracranial hypertension, particularly at higher dose levels [17, 21, 29]. Recognition and standardized reporting of CNS-specific immune toxicities will be essential as CAR-T cell therapy advances in neuro-oncology.

Several trial design principles emerge from this early clinical experience. First, locoregional delivery via intraventricular or intratumoral routes has been increasingly adopted in recent trials, with observed differences in toxicity profiles compared with systemic administration, although definitive conclusions regarding CNS exposure or comparative safety cannot be drawn from the current data [17, 18, 21]. The choice of delivery route may also be influenced by disease distribution, as locoregional approaches have primarily been utilized in patients with localized CNS disease, whereas systemic administration may be more appropriate in the setting of disseminated or metastatic disease requiring broader CAR-T cell distribution [17, 21].

Additionally, most studies enrolled patients with advanced, recurrent, or refractory disease, often with substantial tumor burden at the time of CAR-T cell infusion, which may limit therapeutic efficacy and influence observed response rates [17, 21, 26].

Second, advances in CAR engineering, including cytokine-augmented constructs and intra-patient dose escalation, may help overcome immunosuppressive features of the CNS tumor microenvironment [36, 37]. Finally, heterogeneity in dosing strategies, response criteria, and correlative analyses highlights the need for greater harmonization to enable cross-trial comparison and accelerate progress [28, 31, 34].

The geographic distribution of trials also highlights the current concentration and the expanding global momentum of CNS CAR-T cell development. Most published early phase studies to date originate from US centers, reflecting the infrastructure required for Good Manufacturing Practice (GMP) manufacturing, locoregional delivery platforms, and neurocritical care support [17, 21–26]. However,

Table 2 Ongoing clinical trials of CAR-T cell therapy in pediatric and adolescent/young adult CNS tumors

Trial (NCT)	Antigen target(s)	Delivery (ROA)	Country	Population/key CNS diagnoses	Age	Phase	Status[a]
NCT04185038	B7-H3	ICV	USA	DIPG/DMG and recurrent/refractory CNS tumors	Pediatric/AYA (per record) (ClinicalTrials)	Phase 1	Recruiting
NCT04196413	GD2	IV and/or ICV	USA	H3K27M-mutant DMG/DIPG	Pediatric through adult (per record) (ClinicalTrials)	Phase 1	Recruiting
NCT04099797	GD2 (±C7R/IL-7R augmentation)	IV	USA	High-grade pediatric CNS tumors (includes DMG/HGG; also other rare CNS tumors)	Pediatric/AYA (per record) (ClinicalTrials)	Phase 1	Recruiting
NCT05768880	B7-H3, EGFR806, HER2, IL13-zetakine (Quad CAR)	ICV	USA	DIPG/DMG and recurrent/refractory CNS tumors	Pediatric or young adult	Phase 1	Active, not recruiting
NCT05835687	B7-H3 (Loc3CAR)	ICV	USA	Primary CNS tumors and DMG (pediatric-focused)	≤ 21 years	Phase 1	Recruiting
NCT05298995	GD2 (iC9-GD2 CAR-T)	IV	Italy	Pediatric brain tumors	Pediatric or young adult	Phase 1	Recruiting
NCT05544526	GD2 (DMG-focused program)	IV and/or ICV	UK	DMG/DIPG	2–16 years	Phase 1	Recruiting
ACTRN 12622000675729	GD2	IV and/or ICV	Australia	DMG/DIPG	< 21 years	Phase 1	Recruiting

Summary of ongoing or active early phase clinical trials evaluating chimeric antigen receptor (CAR)-T cell therapies in pediatric and adolescent/young adult patients with primary central nervous system (CNS) tumors. Trials are listed by ClinicalTrials.gov identifier and include antigen target(s), route of administration (ROA), country, key CNS diagnoses, age eligibility, trial phase, and recruitment status at the time of manuscript preparation

CAR chimeric antigen receptor, *CNS* central nervous system, *ROA* route of administration, *ICV* intraventricular, *IV* intravenous, *DIPG* diffuse intrinsic pontine glioma, *DMG* diffuse midline glioma, *H3K27M* histone H3 lysine-27-to-methionine mutation, *HGG* high-grade glioma, *AYA* adolescent and young adult, *IL* interleukin, *iC9* inducible caspase-9, *EGFR* epidermal growth factor receptor

[a]Trial status reflects information available on ClinicalTrials.gov, Australia New Zealand Clinical Trials Registry, and Chinese Clinical Trial Register at the time of manuscript preparation and is subject to change

contemporary trial activity increasingly extends beyond North America, with active or emerging clinical programs in Europe (the UK and Italy) and Asia (China). This broadening footprint is significant, as global participation can accelerate enrollment in rare tumor populations such as DMG, promote harmonization of toxicity mitigation and response assessment strategies, and improve generalizability across healthcare systems. Continued multinational collaboration and data-sharing will be essential to refine patient selection, standardize correlative immunology endpoints, and efficiently advance next-generation CAR-T cell approaches for CNS malignancies. Several ongoing clinical trials are currently evaluating next-generation CAR-T cell strategies in pediatric and young adult CNS tumors, reflecting continued evolution in antigen targeting, delivery approaches, and CAR construct design (Table 2). Early phase trials are actively recruiting across North America, Europe, and Australia, targeting antigens such as GD2 and B7-H3 through both systemic and locoregional delivery strategies. Despite remaining largely in phase I, these studies demonstrate increasing international investment in CNS-directed cellular immunotherapy. Broader geographic participation will be essential to accelerate therapeutic development and enhance the generalizability of emerging clinical data.

An important and underexplored opportunity for future CNS CAR-T cell trials is the integration of patient-reported outcomes (PROs) as prognostic and complementary efficacy measures. In neuro-oncology, baseline health-related quality of life and functional PRO domains have been shown to independently predict overall and progression-free survival, even after adjustment for established clinical and molecular prognostic factors [38]. In the immunotherapy setting, radiographic response may be confounded by inflammation-driven pseudoprogression [32]; therefore,

PROs may provide complementary information on neurological function, symptom burden, and patient resilience that is not fully captured by imaging alone [31, 34, 38, 39]. Incorporating validated instruments such as the EORTC QLQ-C30 and brain-tumor-specific modules into CAR-T cell trials could improve risk stratification, contextualize survival outcomes, and capture patient-centered benefit not reflected by imaging alone [31, 34, 38, 39]. Integration of PROs alongside biologic correlates may therefore enhance trial interpretability and inform patient selection in future CNS-directed cellular immunotherapy studies.

4.1 Limitations

This review has limitations. The available evidence is derived exclusively from small, early phase, noncomparative studies with heterogeneous patient populations, CAR constructs, delivery strategies, and outcome reporting. Quantitative synthesis was not feasible, and survival comparisons must be interpreted cautiously given the absence of control arms. Follow-up duration remains limited in several cohorts, and long-term durability of responses and late toxicities remain uncertain. Several key variables, including duration of response, detailed radiographic response criteria, and timing of prior radiotherapy relative to CAR-T cell infusion, were inconsistently reported across studies, limiting the ability to perform detailed comparative analyses and to assess potential associations with clinical outcomes. In addition, most included studies enrolled heavily pretreated patients with advanced or refractory disease, often with substantial tumor burden at the time of CAR-T cell administration, which may further limit observed therapeutic efficacy and restrict the generalizability of outcomes to earlier disease settings. Nevertheless, these limitations are inherent to the early developmental stage of CNS CAR-T cell therapy and highlight the importance of systematic synthesis to contextualize emerging data.

5 Conclusions

Early clinical experience demonstrates that CAR-T cell therapy for pediatric and young adult CNS tumors is biologically active and clinically feasible in a subset of patients. Reported toxicities are distinct from conventional cytotoxic therapies and are frequently reversible with prompt recognition and protocolized management, although severe and potentially life-threatening complications have been described. While durable objective responses remain uncommon, consistent immune activation, frequent disease stabilization, and prolonged survival in select patients support continued investigation. Future trials should prioritize optimized antigen targeting, standardized toxicity management, immunotherapy-appropriate response assessment, and integration of patient-reported outcomes alongside biologic and survival endpoints to fully define the therapeutic potential of CAR-T cell therapy in CNS malignancies.

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Declarations

Conflict of interest Sai Sanikommu, Alejandro N. Santos, Bashar Dawoud, Khushi H. Shah, Sima Vazquez, Ashish H. Shah, and Victor M. Lu declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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