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Next-generation CAR-T therapy for malignant brain tumors: latest updates from the 2026 AACR Annual Meeting

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Abstract

The 2026 AACR Annual Meeting showcased rapid progress in chimeric antigen receptor (CAR) T-cell therapy for malignant brain tumors. This correspondence synthesizes 12 clinical and translational abstracts addressing early efficacy, resistance mechanisms, target discovery, and next-generation engineering. Phase I studies in glioblastoma demonstrated feasibility, manageable toxicity, cellular persistence, and preliminary radiographic activity, while revealing antigen loss and treatment-associated myeloid suppression. Longitudinal and spatial analyses further identified limited CAR T-cell persistence, anti-CAR immune responses, and remodeling of suppressive tumor niches. Preclinical strategies sought to overcome these barriers through programmable antigen recognition, alternative KIR/DAP12 signaling, stress-granule modulation, inducible metabolic support, membrane-tethered cytokine agonists, resistance to transforming growth factor beta, and dual targeting of tumor cells and immunosuppressive macrophages. Surfaceome profiling and affinity-guided receptor optimization also identified promising targets in glioblastoma and medulloblastoma. Collectively, these findings support mechanism-informed CAR T-cell platforms, while emphasizing that durability, neurotoxicity, trafficking, immunogenicity, and patient selection require validation in larger clinical studies.

Keywords CART-cell therapy, Glioblastoma, Malignant brain tumors, Immunotherapy, AACR 2026

To the editor,

AACR 2026 highlighted CAR T-cell advances in malignant brain tumors. Clinical studies demonstrated feasibility along with initial safety and activity. Translational analyses identified barriers to durability, including antigen escape, myeloid immunosuppression, limited persistence, metabolic stress, and anti-CAR immunity. Engineering strategies used programmable recognition, alternative signaling, metabolic enhancement, cytokine

armoring, and targeting of malignant and microenvironmental compartments. These findings support mechanism-informed cellular platforms.

Clinical translation reveals activity and resistance mechanisms

Early studies supported CAR-T feasibility in glioblastoma (GBM) but exposed developmental limitations (Table 1). E-SYNC T cells use an EGFRvIII-responsive synthetic Notch receptor to induce an EphA2/IL13R α 2-directed CAR, combining tumor-specific priming with recognition of heterogeneous GBM cells. Eight patients received treatment without experiencing dose-limiting toxicities. Cells persisted in their blood for at least 40 weeks, and two patients stayed progression-free for 15 and 20

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Table 1 Clinical and translational CAR-T studies in malignant brain tumors

References	Tumor	CAR-T/target	Study type	Main findings	Main limitation
[1]	Glioblastoma	EGFRvIII-synNotch → EphA2/IL13Rα2	Phase I, 8 patients	No DLTs; persistence ≥ 40 weeks; two patients progression-free for 15 and 20 months from initial resection	Loss of EGFRvIII in two early recurrences
[2]	Recurrent GBM	GD2 CAR-T	Phase I, 8 patients	Three partial responses and four stable diseases reported; PFS6 33%; median OS 8.3 months; feasible and safe	Transient stabilization and cytokine-driven myeloid suppressive response
[3]	Recurrent GBM	EGFR/IL13Rα2 CAR-T	Paired clinical samples, 6 patients	At progression, fewer suppressive myeloid/B-cell niches and increased interferon/T-cell programs	Small correlative cohort; analysis conducted at progression
[4]	H3K27M diffuse midline glioma	GD2 CAR-T	Longitudinal single-cell study, 13 patients	Poor CAR-T persistence and coexisting humoral and cellular anti-CAR immunity	Mechanistic correlative study in a limited cohort

months following initial surgical resection. However, tumors from two early recurrences lost EGFRvIII despite E-SYNC infiltration, indicating that programmable circuits remain vulnerable to loss of their priming antigen [1].

In the KARPOS phase I trial, intravenously administered GD2-CAR T cells were feasible and safe in recurrent GD2-positive GBM. Eight patients were enrolled, with three partial responses and four instances of stable disease. Nevertheless, the authors characterized clinical activity as limited and tumor stabilization as transient; six-month progression-free survival was 33%, and median overall survival was 8.3 months. Post-infusion cytokine changes and expansion of myeloid-derived suppressor cells suggested that treatment-induced myeloid responses may restrict efficacy, supporting myeloid-directed combinations and evaluation of intracerebroventricular delivery [2].

Spatial profiling of paired recurrent GBM samples from six patients, collected before treatment and at radiographic progression after intracerebroventricular EGFR/IL13Rα2 CAR-T therapy, showed reduced suppressive myeloid- and B-cell-rich niches, increased interferon-responsive programs, and greater T-cell-associated activation. These findings suggest that CAR-T exposure can leave the primary site more immunologically engaged even at progression, potentially facilitating sequential immunotherapy [3].

In H3K27M-mutant diffuse midline glioma, longitudinal profiling of 13 patients receiving repeated GD2-CAR T infusions revealed poor CAR-T persistence and a suppressive immune environment that limits CAR-T activity. Anti-CAR antibodies accompanied relapse in three initially sustained responders, emphasizing CAR immunogenicity as another determinant of durability [4].

Engineering CAR-T cells to overcome brain tumor barriers

AACR 2026 showcased strategies addressing exhaustion, metabolic restriction, antigen heterogeneity, and suppressive tumor ecosystems (Table 2). Replacing conventional 4-1BB/CD3ζ signaling with multichain KIR/DAP12 signaling produced a more naïve-like T-cell phenotype and improved tumor regression and survival in resistant murine GBM models; the most effective multi-EGFR-targeted construct achieved complete antitumor responses [5]. G3BP1 overexpression improved GD2-CAR T-cell control of subcutaneous GBM without impairing manufacturing expansion or acute cytotoxicity, linking stress-granule regulation to antitumor efficacy [6].

Antigen-inducible GLUT3 expression enhanced metabolic fitness and produced long-lasting control in intracranial GBM xenografts without signs of toxicity. In contrast, constitutive GLUT3 expression caused T-cell apoptosis, exhaustion, terminal differentiation, adverse events, and mouse deaths [7]. Membrane-tethered engineered cytokine agonists improved IL13Rα2 CAR-T proliferation and cytotoxicity after repeated in vitro challenge and increased antitumor activity, with preliminary evidence of no toxicity in an orthotopic glioma model [8]. AZD5851, a GPC3 CAR-T product armored with a dominant-negative TGF-β receptor, was well tolerated and significantly prolonged survival in two of five patient-derived orthotopic models, specifically the medulloblastoma and atypical teratoid/rhabdoid tumor models [9].

Surfaceome profiling and quantitative antigen-density mapping prioritized the oncofetal antigen GPC2 in medulloblastoma. GPC2 CAR-T cells achieved durable control in intermediate-density models. Repeated dosing or cJUN overexpression improved control in an aggressive GPC2-high model, whereas only cJUN-overexpressing CAR-T cells maintained responses in a GPC2-low model [10]. GPNMB-directed CAR-T cells targeted GBM cells and immunosuppressive GPNMB-positive macrophages, producing complete remission in patient-derived

Table 2 Engineering strategies for next-generation CAR-T cells

References	Tumor	Strategy	Barrier addressed	Main finding
[5]	GBM	KIR/DAP12 signaling	CD3-based signaling exhaustion	More naïve-like phenotype and better regression/survival; the most effective multi-EGFR construct achieved complete responses in resistant murine models
[6]	GBM	G3BP1 modulation	Cellular stress	G3BP1 overexpression improved GD2 CAR-T control in a subcutaneous model without impairing expansion or acute cytotoxicity
[7]	GBM	Antigen-inducible GLUT3	Metabolic restriction	Long-lasting intracranial control without toxicity; constitutive GLUT3 caused exhaustion, adverse events, and mouse deaths
[8]	GBM-targeting/orthotopic glioma	Membrane-tethered engineered cytokine agonists	Exhaustion	Improved IL13Ra2 CAR-T proliferation and repeated-challenge cytotoxicity; greater activity with preliminary evidence of no toxicity in vivo
[9]	Medulloblastoma/ATRT/HGG	GPC3 CAR-T + dnTGFβRII	TGF-β-mediated suppression	Well tolerated; significant survival benefit in 2/5 orthotopic models (medulloblastoma and ATRT)
[10]	Medulloblastoma	Surfaceome-guided GPC2 targeting	Lack of suitable antigens	Durable control at intermediate density; repeated dosing or cJUN improved GPC2-high disease, while only cJUN maintained responses in GPC2-low disease
[11]	GBM	GNPMB CAR-T	Tumor cells and suppressive macrophages	Complete remission in PDXs, sustained syngeneic control, regression in most humanized mice, and selective removal of suppressive macrophages
[12]	GBM	Affinity-tuned PTPRZ1 CAR-T	Target heterogeneity and receptor design	Affinity/architecture screening defined functional design features; minimal off-tumor cytotoxicity and preserved neural architecture in human cortical slices

xenografts, sustained control in syngeneic models, and regression in most animals in a humanized recurrent-GBM model [11]. Finally, affinity-tuned PTPRZ1 binders and a combinatorial CAR library were used to determine how binder affinity and architectural domains influenced activation, cytotoxicity, proliferation, exhaustion resistance, and durability. PTPRZ1-targeting CAR T cells showed minimal off-tumor cytotoxicity and preserved neural architecture in human cortical slice cultures [12].

Advanced therapy medicinal products, including CAR-T therapy, for the treatment of malignant brain tumor are moving toward integrated engineering. Translation will likely require preventing antigen escape, sustaining cellular fitness, reducing immunogenicity, overcoming myeloid suppression, and preserving central nervous system safety. Biomarker-guided selection and assessment of trafficking, persistence, and neurotoxicity will be important for converting responses into durable clinical benefit.

Acknowledgements

We acknowledge that the AACR 2026 Annual Meeting featured numerous high-quality studies across diverse areas of CAR T-cell therapy. Given space constraints, we selected 12 abstracts that represent key clinical, translational, and engineering advances in malignant brain tumors. Many other relevant contributions could not be included, and we regret these unavoidable omissions. Furthermore, our analysis is based exclusively on the published abstracts. Although they provide valuable preliminary insights, definitive interpretation of each study will require access to full manuscripts, complete datasets, and additional methodological details.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

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