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Cellular immunotherapies for central nervous system cancers

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Abstract

Cellular Immunotherapies have transformed therapeutic options for individuals with hematologic malignancies over the past 10 years. There are several distinct types of cellular immunotherapies, each with potential applications to CNS cancers. Here, we review cancer cellular therapeutics for cancers of the brain and spinal cord, focusing on the preclinical and clinical studies that have been done in glioblastoma, diffuse intrinsic pontine glioma/diffuse midline glioma, medulloblastoma and lymphoma involving the central nervous system. Numerous potential therapeutic targets have been identified, and several early clinical trials have demonstrated safety and feasibility of administering CAR T and CAR NK cells for intracranial tumors. Addressing mechanisms of treatment failure, while safely and effectively studying the most promising therapies will advance the treatment landscape for these extremely challenging diseases.

Key Points

1. Cellular immunotherapies for CNS cancers are beginning to show promise in clinical trials.
2. Understanding and overcoming the immune-suppressive environment of the CNS will be necessary for cellular immunotherapies to achieve transformative progress for patients.

Background

Types of Cellular Immunotherapies

Cellular immunotherapies encompass a rapidly expanding therapeutic landscape with dramatic benefit in hematologic malignancies, emerging promise in solid tumors, and also across other diseases including autoimmune neurologic conditions such as multiple sclerosis and myasthenia gravis. Chimeric Antigen Receptor T cell (CAR T cell) therapy has become a transformative therapy in relapsed/refractory hematologic malignancies over the past decade, with 6 CAR T cell therapies gaining Food and Drug Administration (FDA) approval, and numerous others under investigation.

CAR T cells are created by harvesting T lymphocytes from an individual patient (autologous), or a donor (allogeneic) via leukapheresis. The native T cells are bioengineered to incorporate a transmembrane protein with an antigen-binding domain that targets an antigen highly expressed on the cell surface of tumor cells and not expressed or expressed at low levels on other host cells. There are a variety of potential CAR T cell antigen-binding domains, with options increasing as new tumor antigens are identified. The CAR also includes an intracellular co-stimulatory domain, which regulates the T cell response and expansion after antigen-binding. The most common co-stimulatory molecule endodomains in clinical applications include a CD3ζ signaling domain combined with a second signaling domain (either 41BB or CD28). Preclinical

and clinical evidence (Table 1) supporting the promise of CAR T cell therapy for cancers of the central nervous system (CNS) are presented below.

Natural Killer (NK) cell-based immunotherapy is distinct from CAR T cell therapy. NK cells are a smaller population that differ from T lymphocytes in that they do not require human lymphocyte antigen (HLA) compatibility. This allows NK cells to be used for allogeneic therapy in which donor cells may be given to an unmatched recipient. To enhance antigen recognition, NK cells may be bioengineered

Table 1. Cellular therapy targets and clinical trials

Single target	Tumor	Antigen Expression	Construct	Mode of delivery	Number of subjects	reference	Notes
IL-13Rα2	Glioblastoma	50%	Auto CART	ICV, IT—RD	3	17, 18	Corticosteroid receptor knockout
			Allo CART	IT	6	19	
EGFR/EGFRviii	Glioblastoma	25%	Auto CART	IV—RD	7	23	Combined with pembrolizumab
B7H3	DMG		Auto CART	ICV—RD	3	47	
HER-2	Glioblastoma	80%	Auto CART	IV—SD	10 adults; 7 children	29	
			Auto CAR NK	IT*—SD	9	30	*Intraoperative administration
	Ependymoma		Auto CART	ICV or IT—RD	2	48	
	Anaplastic astrocytoma		Auto CART	ICV or IT—RD	1	48	
GD2	DMG - H3K27M	>95%	Auto CART	IV, ICV	11	43, 45	
	DMG - H3K27M		Auto CART	IV	2	46	
	ATRT		Auto CART	IV	1	46	
CD-19	CNS Lymphoma		Auto CART	IV	8	57	
Combination therapies							
EGFR epitope 806**/ IL-13Rα2	Glioblastoma	**50%–60%	Auto CART	ICV—SD	6	25	
EGFRviii/EGFR BITE Ab	Glioblastoma		Auto CAR T + BITE	ICV—SD	3	26	
C7R-GD2	DMG		Auto CAR T + C7R	IV	6	46	
	Medulloblastoma		Auto CAR T + C7R	IV	2	46	
Active trials/future directions							
IL-13Rα2	DMG		Auto CART	ICV			
	Medulloblastoma		Auto CART	ICV		52, 53, 54	
EGFR/EGFRviii	Glioblastoma		Auto CAR NK	ICV		2	
EGFRviii/ IL-13Rα2	Glioblastoma					24	
B7H3	Glioblastoma	64%	Auto CART	ICV, IT—RD			
	Medulloblastoma					32	
HER-2	DMG		Auto CART				
GD2	Glioblastoma						
GPC2	Medulloblastoma					55	
	Embryonal Tumors						
EPHA2	Medulloblastoma						

Abbreviations: IL-13Rα2 = interleukin-13 receptor alpha-2; auto = autologous; allo = allogeneic; IVC = intracerebroventricular;. IV = intravenous; IT = intratumoral; RD = repeat dosing; SD = single dose; NK = natural killer; EGFR = epidermal growth factor receptor; HER-2 = human estrogen receptor-2; BITE = bispecific t cell engager; C7R = constitutively active interleukin-7 receptor.

to incorporate a CAR, creating a CAR-NK cell. Tolerability of NK cell therapy has generally been favorable, with a lower incidence of cytokine release syndrome (CRS) or neurotoxicity than that seen with CAR T cell therapy for solid and hematologic malignancies.[1] One early limitation of CAR-NK therapy is that NK cells tend to have less ability to expand, and have shorter persistence compared to CAR T cells, which may necessitate alterations in CAR-NK design or multiple administrations.[1] A preclinical study of CAR-NK therapy for glioblastoma targeting epidermal growth factor receptor (EGFR) and EGFRvIII demonstrated inhibition of tumor growth in culture and in orthoptic xenograft mouse models.[2]

Another distinct cancer cell immunotherapy that has demonstrated effectiveness in the treatment of advanced melanoma and that hold promise for brain tumors is tumor-infiltrating lymphocyte (TIL) therapy. TILs are T lymphocytes harvested from a patient's excised tumor and expanded ex vivo. Unlike other cellular immunotherapies, TILs are not modified or bioengineered to express specific tumor antigens. Following lymphodepleting (LD) chemotherapy, TILs are reintroduced intravenously, and a series of interleukin-2 injections are given to promote cellular expansion and anti-tumor activity.[3]

Cellular Immunotherapies in non-CNS Malignancies

The past decade has been characterized by rapid progress in the development and implementation of cancer cell immunotherapy. The earliest FDA-approved clinical application of cellular immunotherapy was CD-19-directed CAR T cell therapy for pediatric acute lymphoblastic leukemia (ALL), and adults with relapsed aggressive lymphomas.[4,5] Early clinical trials testing Axicabtagene ciloleucel (Axi-cel) in 3rd line or later treatment-refractory large B cell lymphoma demonstrated objective response rates of over 80%, complete responses in 54% (compared to 7% for existing therapies), and an over 18-month median survival (compared to 6.3 months for existing therapies).[2,6] These dramatic results led to the approval of Axi-cel in 2018. Cancer cellular immunotherapies have also demonstrated effectiveness in ALL (tisagenlecleucel/Kymriah, brexucabtagene autoleucel/Tecartus), follicular lymphoma, mantle cell lymphoma and multiple myeloma (ciltacabtagene autoleucel,cilta-cel; Carvykti and idecabtagene vicleucel, ide-cel; Abecma). To date there are 16 FDA approvals for 6 CAR T cell therapies to treat hematologic malignancies. Notably, nearly all CAR T cell clinical trials for the treatment of hematologic malignancies have excluded known or active CNS involvement, which limits insights into the safety or efficacy of CAR T therapies for hematologic malignancies with CNS spread.

In February 2024, the first FDA approval was granted for cellular immunotherapy in non-hematological solid tumors. Lifileucel (Amtagvi), a form of TIL (tumor infiltrating lymphocyte) therapy, was approved to treat unresectable or metastatic melanoma unresponsive to at least 1 line of therapy. Lifileucel demonstrated a 36% overall response rate and disease control in 80% of individuals with a mean of 3.3 prior therapies in a single-arm phase 2 study.[7] This cohort included 11% of individuals with melanoma brain metastasis. In a prospective, randomized trial comparing TIL therapy to the checkpoint inhibitor ipilimumab (monoclonal antibody to inhibit cytotoxic T lymphocyte associated protein-4 (CTLA-4) activity) for the first or second line treatment of advanced melanoma, TIL therapy demonstrated superior median overall (25.8 vs. 18.9 month) and progression-free (7.2 vs. 3.1 month) survival.[3] Side-effects associated with TIL therapy are common, and either related to LD chemotherapy (nausea, vomiting, cytopenia), IL-2 administration (fevers, chills, capillary leak syndrome), or the TIL therapy itself (hypopigmentation, uveitis). Most occur in the immediate post-treatment period and are short-lived.

Cellular Immunotherapies in Primary CNS Tumors

Glioblastoma

The heterogeneity and proliferative potential of glioblastoma have made it especially difficult to target with molecular and immune therapies. The median OS for IDH-wild-type glioblastoma in the United States is 17.1 months for methylguanine methyltransferase (*MGMT*) methylated, and 12.4 months for *MGMT* unmethylated tumors.[8] Reported 5-year survival ranges from 4-17%.[9] Fractionated radiation in combination with temozolomide chemotherapy has been the mainstay of treatment for glioblastoma for the past 20 years. Bevacizumab demonstrated radiographic responses in 38-46% of glioblastomas treated in the recurrent setting, leading to its FDA approval in 2009.[10,11] Tumor-treating fields (TTF) are approved in the recurrent (2011) treatment of GBM, having demonstrated noninferiority to chemotherapy.[12] TTF was also approved for up-front therapy (2015), with benefit for both progression-free and overall survival compared to standard chemoradiation.[13] Immune checkpoint inhibitor therapies alone or in combination are generally well-tolerated, but have not demonstrated survival benefit in glioblastoma.[14,15] An urgent need for effective therapies to treat glioblastoma still exists. Multiple cellular immunotherapies are being actively investigated in the treatment of glioblastoma.[16]Currently available cellular immunotherapies for primary CNS tumors are summarized in Figure 1 .

IL-13Rα2

CAR T cell therapy directed at the interleukin-13 receptor IL-13Rα2 was one of the earliest clinical CAR T-cell strategies for GBM.[17,18] IL-13Rα2 is expressed on ~50% of glioblastomas, and most associated with the mesenchymal GBM subtype. IL-13Rα2-CAR T therapy was shown to be feasible to deliver intracerebroventricularly (ICV) and intratumorally,[17] and resulted in regression of a progressive glioblastoma with leptomeningeal spread when administered multiple times intratumorally and ICV in one patient, sustained for 7.5 months.[17,18] There is also limited experience with an allogeneic IL-13Rα2-CAR T construct, introducing the possibility of using donor T-cells that are not MHC-specific.[19] The IL-13Rα2-CAR T cells are designed

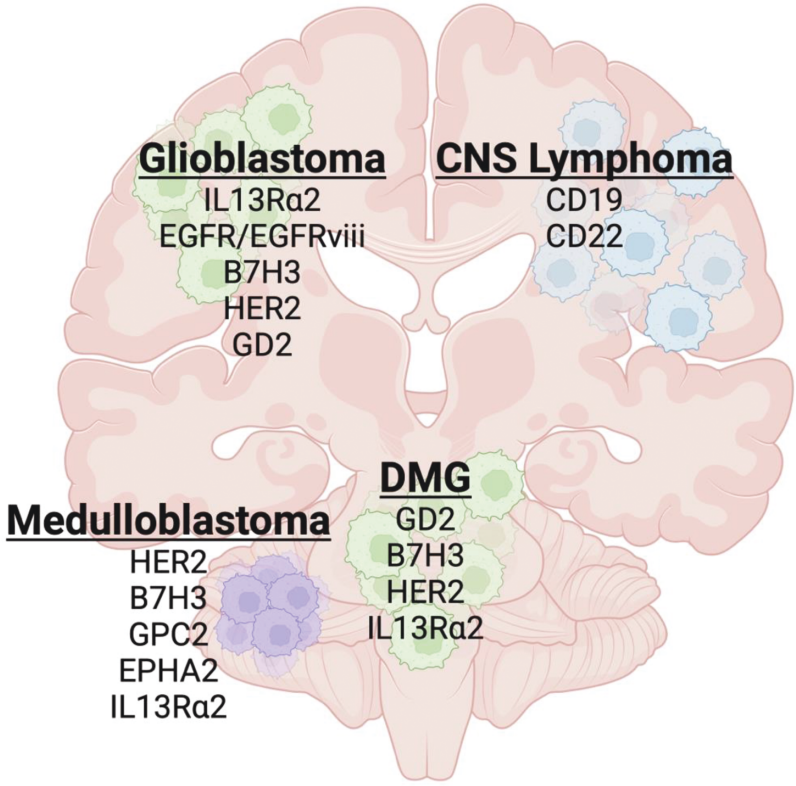

Figure 1. Targets for cellular immunotherapy in CNS cancers. Antigens identified for cancer cellular therapy, illustrated together with common sites for individual cancers of the central nervous system. Figure made with BioRender.

with a corticosteroid receptor knockout, allowing the use of corticosteroids for symptomatic management without impacting CAR T cell viability.[17] While there has been tolerability and some activity demonstrated in phase 1 trials with IL-13Rα2-CAR T cells, the limited expression of IL-13Rα2 in some tumors, and intratumoral heterogeneity may potentially limit the efficacy of this approach.[20]

EGFR and EGFRvIII

Epidermal Growth Factor Receptor variant III (EGFRvIII) mutation has been found in ~25% of glioblastomas, and has been the target of other immunotherapies such as vaccines. In transgenic EGFRvIII GBM mouse models, administration of a murine EGFRvIII-targeting CAR T cell therapy resulted in tumor reduction, prolonged survival and selective antigen loss.[21] The coadministration of interleukin 12 (IL-12) with EGFRvIII-CAR T cells in an orthoptic GBM mouse model increased the potency of CAR T cell activity and prolonged survival without evidence of severe systemic side-effects.[22] A phase I human trial of serial intravenous EGFRvIII-CAR T therapy (up to 3 infusions) in combination with pembrolizumab was feasible with minimal toxicity.[23] There was some evidence of EGFRvIII antigen loss, but CAR T persistence and expansion were minimal, and the progression-free survival (5.2mo) and overall survival (11.8mo) were not suggestive of clinical activity in this small exploratory cohort.

CAR NK cells targeting EGFR receptors may provide an alternate treatment strategy to CAR T cells. Human NK-92 and NKL cell lines engineered to target both wild-type EGFR and EGFRvIII were found to cause tumor cell lysis, reduction in tumor size, and prolonged survival when injected intraventricularly into orthoptic GBM mouse models.[2] Targeting wild-type EGFR raises the potential for on-target off-tumor toxicity in normal EGFR-expressing tissues, though the intracranial administration appeared to result in limited CAR T cell migration outside the CNS, suggesting it may be well-tolerated.[2]

Combination Strategies Targeting EGFR

One potential strategy to augment the activity of CAR T cell constructs with partial efficacy is to engineer multiple targets into the same CAR T cell. In preclinical mouse models, the use of a bivalent CAR T cell targeting EGFRvIII and IL-13Rα2 termed "TanCAR T" resulted in more durable and extensive tumor responses in heterogeneous GBM xenograft mouse models.[24] A different combination using a CAR T cell that targets EGFR epitope 806 and IL-13Rα2 has been investigated in a phase I trial enrolling individuals with recurrent EGFR-amplified isocitrate dehydrogenase 1 (IDH1) wild-type GBM, administered in a single ICV dose.[25] EGFR epitope 806 is present on 50-60% of glioblastomas, and does not bind native EGFR. Brain MRI at 24-48 hours after administration demonstrated reduced contrast

enhancement and enhancing tumor volume, though none met the criteria for an objective response. The CAR T cell expansion peaked at post-treatment day 1-7, with elevations in IFNγ, IL-2, TNFα, and IL-6 that normalized within 14 days post-treatment.[25] A third approach to augment the activity of EGFRvIII CAR T therapy is combination of the EGFRvIII CAR T with EGFR bispecific T cell engager (BITE) antibodies. The phase I results from the first 3 subjects treated with this combination (CARv3-TEAM-E) as a single ICV infusion reported a decrease in gadolinium enhancement on MRI within days of administration, a reduction in EGFR and EGFRvIII DNA in peripheral blood, and in CSF extracellular-vesicle RNA. The tumors grew within 1 month of infusion in 2 of 3 subjects, and for the 3rd subject response was sustained > 5 months.[26,27] Grade 3 encephalopathy in one patient and grade 3 fatigue in another were the only severe toxicities related to the treatment.[26,27] The marked radiographic responses with reduction or normalization of contrast enhancement on brain imaging within days of infusion are striking, and warrant further investigation. Radiographic improvement, especially with the subsequent observation of tumor growth within weeks raises the possibility that either there is rapid, transient but incomplete elimination of the tumor, or that the imaging changes are not be a result of tumor cell death, but instead reflect an effect on blood vessel permeability that reduces contrast enhancement.

HER-2

Human Epidermal Growth Factor Receptor-2 (HER-2) is overexpressed in up to 80% of glioblastomas. Preclinical work targeting HER-2 in GBM cell lines and xenograft mouse models has demonstrated effective tumor reduction when injected locally around the tumor.[28] A phase I clinical trial tested single-dose IV administration of HER-2-CAR T cell therapy in 10 adults and 7 children with glioblastoma.[29] The treatment-related toxicities were: grade 4 cerebral edema, grade 3 lymphopenia, headache, fatigue, weakness and hydrocephalus. Lymphopenia was the most common grade 2 toxicity. Roughly half of the subjects had evidence of CAR T cell persistence at 6 weeks. One subject had a radiographic partial response, 7 had stable disease and 8 had progressive disease as their best response. The median overall survival for the cohort was 11.1 months following infusion and 24.5 months after GBM diagnosis.[29]

Another phase I study investigated the local administration of HER-2-targeting CAR-NK cells into the surgical resection bed for HER-2-expressing GBM at the time of recurrence, following up-front standard-of-care radiation therapy and temozolomide. Of the 9 subjects treated, 5 had stable disease and 4 had progressive disease. Two were determined to have pseudoprogression, and overall, the treatment was tolerated well, with no evidence of CRS or immune effector cell-associated neurotoxicity syndrome (ICANS). Median PFS was 7 weeks and median OS was 31 weeks following surgery.[30]

B7-H3

B7-H3 (CD 276) is expressed in up to 64% of high-grade gliomas[31] including pediatric high-grade glioma tumor types.[32] It is an immune checkpoint molecule belonging to the B7-CD28 pathway, and is found at lower levels on multiple normal tissues as well, including liver, heart, prostate, spleen and thymus.[33] B7-H3 has a suppressive effect on T cell activation, and may also inhibit NK cell activation.[34] B7-H3 expression promotes tumor migration, invasion, angiogenesis, chemoresistance, and is associated with a poorer prognosis.[34]

Clinical experience with B7H3 CAR T cell therapy is emerging, as there are 2 phase I clinical trials of B7H3-CAR T cell therapy currently enrolling for adult GBM in the United States (NCT05474378, NCT05366179), and 3 additional studies in China (NCT04385173, NCT05241392, NCT04077866). A case report describes a 56-year-old woman with recurrent glioblastoma who received B7-H3-CAR T cell therapy on an intratumoral dose-escalation protocol. She experienced radiographic regression of tumor, and received a total of 7 CAR T infusions before coming off study for progressive disease. There were no grade 3 adverse events, and headache was the main treatment-related symptom during the first 5 cycles.[35]

H3K27M-Altered Diffuse Midline Gliomas

H3K27M-altered diffuse midline glioma of the pons, also called diffuse intrinsic pontine glioma (DIPG), and diffuse midline gliomas of the thalamus and spinal cord are the leading cause of brain-tumor-related death in children, associated with a median survival of 11 months (DIPG) and 13 months (non-brainstem DMGs), and a 5-year survival of less than 1%.[8,36,37] Radiation therapy remains the only established treatment option.[38] Clinical trials of numerous chemotherapies have not demonstrated additional benefit in the treatment of DMG/DIPG.[39] Heterogeneity of the tumor, limited penetration of systemic chemotherapy across the blood-brain barrier, the critical location affecting vital brainstem or spinal cord structures, and the immunosuppressive tumor microenvironment are all factors that have contributed to the challenges in finding effective therapies.[40] However, in recent years, CAR T cell strategies for H3K27M-altered DMGs have begun to show promise.

GD2

The disialoganglioside GD2 is a surface glycolipid that is present to varying degrees on several solid tumors including neuroblastoma, melanoma, retinoblastoma, small cell lung cancer, sarcomas and gliomas.[41] Cell surface antigen screening of patient-derived H3K27M-mutant DMG cells revealed GD2 as the most highly expressed cell surface antigen amongst over 200 antigens screened.[42] The H3K27M mutation results in epigenetic dysregulation of GD2 synthesis enzymes, and thus GD2 is highly and uniformly expressed on H3K27M-mutant tumor cells, but is not expressed highly on H3 WT DMG tumors.[42] Preclinical studies demonstrate eradication of H3K27M-mutant tumors in patient-derived orthoptic mouse xenograft models of DIPG, spinal cord DMG and thalamic DMG.[42] Of note, CAR T cell therapy for thalamic DMGs led to obstructive hydrocephalus and consequent herniation that was lethal in mice, underscoring the importance of neurocritical care precautions and the differential risk of inducing therapeutic

inflammation in precarious neuroanatomical locations differentially prone to herniation.[42] Based on this foundational work identifying GD2 as appealing target for CAR T cell therapy in H3K27M-mutant tumors of the brainstem and spinal cord, a phase 1 clinical trial of GD2 CAR T therapy was initiated in 2020 for H3K27M-mutant DIPG and spinal cord DMG (NCT04196413). The initial arm of this study investigated intravenous (IV) administration following LD chemotherapy at two dose levels (1 million CAR T cells/Kg and 3 million CAR T cells/Kg), with subsequent infusions of CAR T cells administered ICV through an Ommaya catheter or similar device.[43] Ommaya catheters were placed in all patients to enable measurement of intracranial pressure, immediate treatment of hydrocephalus, and to administer subsequent CAR T cell infusions ICV should patients experience imaging and/or clinical benefit from the first infusion. IV administration was associated with high rates of CRS, which was severe (grade 4) in some cases treated at the second dose level (3 million CAR T cells/Kg) and proved to be the dose-limiting toxicity for IV administration. The subsequent ICV infusions tended to be more well-tolerated, with minimal to no CRS. All patients experienced tumor inflammation-associated neurotoxicity (TIAN)[44] to varying degrees ranging from low- to high-grade, and that was manageable with close monitoring and interventions such as CSF drainage through a butterfly needle secured in the Ommaya catheter.[43,45] Of the 11 patients treated on the initial arm of the trial, 9 demonstrated neurological benefit, and 4 had major (> 50%) reductions in tumor volume.[45] One patient experienced a complete response and numerous clinical improvements, durable for over 30 months at the time of data cutoff and ongoing.[45] Another patient with spinal cord DMG experienced a > 90% reduction in tumor volume and major improvements in lower extremity strength, bowel and bladder function and neuropathic pain, enabling improvement from profound paraplegia and wheelchair use to walking with a cane, with response durable for more than a year.[45] An additional patient with H3K27M-mutant spinal cord DMG treated off-trial on a single patient compassionate use IND had a greater than 90% reduction in tumor volume, with marked neurological improvements transiently.[43] Ongoing arms of this phase I trial seek to test ICV-only administration and the role of preconditioning chemotherapy. Additional clinical trials of GD2-targeting CAR T cell therapy have now opened internationally, including a second US trial of GD2-CAR T cells modified with a constitutively active interleukin (IL)-7 receptor (NCT04099797) administered IV following standard LD chemotherapy[46] and trials in the UK (NCT05544526) and Australia. In the CR7-GD2-CAR T cell trial, lower doses (10-30 million cells/ m2) were used compared to the trial discussed above. Lower grade CRS and low-grade TIAN were seen in the DMG patients on this trial, with two of seven DMG patients exhibiting transient partial responses by MRI imaging and most experiencing transient clinical improvements.[46] Together, these two GD2-targeting clinical trials highlight the therapeutic potential of this approach for H3K27M-mutant DIPG/DMG and encourage further work to optimize the dose, route, frequency, and preconditioning regimen, and possible combination therapies. Results from the UK and Australian trials have not yet been reported.

B7H3

The immune checkpoint molecule B7-H3 (CD276) is highly expressed in atypical teratoid rhabdoid tumor, DMG, medulloblastoma, and high-grade gliomas.[32] A study investigating an B7-H3 CAR T-cell therapy in children and young adults reported preliminary safety and feasibility in 3 individuals with DIPG, 2 of whom were treated at the time of recurrence. The study involved weekly fixed-dose ICV administration of CAR T-cells cells. Neither biopsy nor confirmation of the H3K27M mutation were required for enrollment. Headache, nausea/vomiting and fever were the most common treatment-related adverse events, occurring within 24 hours of infusion and lasting up to 72 hours. The study also demonstrated persistence of CAR T cells throughout the course of therapy.[47]

HER-2

Human growth factor receptor 2 (HER-2) is highly expressed in DMG, and a HER-2 CAR T cell therapy demonstrated effective anti-tumor effect in cell culture and patient-derived xenograft mouse models of DMG.[11] An early report of a phase I trial (NCT03500991) of HER-2 CAR T cell therapy showed safety and feasibility in the treatment of 3 adolescent/young adults with ependymoma (n = 2) and anaplastic astrocytoma (n = 1).[48] The same trial includes eligibility for DMG, and will investigate clinical administration of HER-2 CAR T cell therapy in this population.

IL-13Rα2

A trial (NCT04510051) is presently ongoing to test IL-12Ra2-targeting CAR T cell therapy delivered intracerebroventricularly following lymphodepleting chemotherapy for children and young adults with recurrent or refractory brain tumors that express IL-12Ra2, including DIPG/DMG. Enrollment requires demonstration of IL-12Ra2 expression on biopsy tissue.

Medulloblastoma

Medulloblastoma is an embryonal tumor of the cerebellum that is the second most common malignant CNS tumor in childhood after pediatric high-grade gliomas. The peak incidence is in children aged 5-9 (0.62 per 100,000).[8] Treatment involves surgical resection, with combination chemotherapy and craniospinal irradiation. Medulloblastoma is characterized from low to very high risk depending on: age, extent of surgical resection, the presence or absence of metastases, and molecular subtyping.[49] There are 4 main medulloblastoma subtypes, with distinct clinical, histopathological, and molecular features. Wingless/INT1 (WNT) activated medulloblastoma occurs most frequently in children age 7-14, and accounts for up to 20% of adult medulloblastoma. WNT-activated medulloblastoma is characterized by a classic histopathology, and favorable outcomes with overall survival close to 100%.[50] The second main medulloblastoma subgroup is characterized by activation of sonic hedgehog (SHH) signaling pathway.

Overall, the prognosis for SHH-activated medulloblastoma is intermediate between WNT-activated medulloblastoma and groups 3&4. The non-WNT, non-SHH-activated medulloblastoma tumors tend to present with widely disseminated disease throughout the leptomeninges and cerebrospinal fluid. Group 3 tumors tend to present in infancy and childhood, while group 4 tumors are present in older children and young adults. MYC overexpression is a poor prognostic factor in these individuals. Five-year overall survival ranges from 45-80%.[50] Recurrent medulloblastoma may have additional genetic alterations compared to the original tumor, and therefore re-biopsy prior to initiating targeted therapy is important.[49] There are limited treatment options for recurrent medulloblastoma, as reflected in the median survival of only 19-27 months.[51]

Preclinical studies have identified multiple potential targets for cellular immunotherapy in medulloblastoma, including EPHA2, HER-2, IL-13Rα2,[52–54] B7-H3.,[32] and GPC2.[55] Some medulloblastomas express GD2.[56] CAR T cell trials for medulloblastoma are now beginning. The CR7-GD2 CAR T cell trial mentioned above included DMG and also other GD2-expressing tumors, and two children with medulloblastoma were treated, both of whom exhibited transient clinical improvements.[46]

CNS Lymphoma

In most of the initial trials evaluating CAR T cell therapy for systemic lymphoma, individuals with active CNS disease were excluded. However, given the tendency for aggressive lymphomas to involve the CNS, there were a small number of individuals who developed CNS involvement during bridging therapy, and were still treated. In this small cohort, tisagenlecleucel was administered IV, and toxicities were mild (grade 0-1 CRS and neurotoxicity). CNS involvement was parenchymal (3), leptomeningeal (3), and both (2). Four of the 8 individuals had CNS complete responses.[57] Pooled analyses of CAR T trials in large B-cell lymphoma and primary CNS lymphoma (PCNSL) similarly indicate that severe ICANS is not very common (~25%), and that complete responses are achievable in about 50% of individuals.[58–60] PCNSL trials have demonstrated mild toxicities, high rates of responses, and encouraging overall survival outcomes.[61–63]

Treatment Considerations

Centers will collectively learn how to most effectively target CNS tumors as we gain more experience with different CAR T constructs and treatment regimens in primary CNS malignancies and other solid tumors. It is extremely important that phase 1 trials are designed in a way that facilitates rigorous assessment of safety, as well as obtaining data regarding CAR T expansion, on-tumor effects, and the comprehensive side-effect profile, including potential long-term sequelae.

Trial design elements such as route of delivery (IV or via intracranial), whether to require molecular analysis for target expression on the tumor for enrollment, and if/how to treat with LD chemotherapy, are key considerations for clinical results interpretation and therapy optimization. Selecting the most appropriate target or targets is also extremely important. Targeting antigens that are only present on tumors is a way to minimize side-effects, since cells will not recognize non-tumor tissue. However, several promising targets are present both on normal and tumor tissue, albeit at different levels of antigen expression. Pursuing these therapeutic targets raises the potential for on-target off-tumor side effects. However, the importance of antigen density to CAR T cell function creates a therapeutic window, consistent with the early experience with HER-2, GD2 and B7H3 for which on-target, off-tumor toxicity has not been seen. While many CAR T-related adverse events are mild, it is important to have specialized education for care teams to identify and preemptively manage acute complications such as CRS, ICANS, TIAN, hyponatremia and hydrocephalus. Immunotherapy-related neurotoxicity requires collaboration between neuro-oncology, inpatient neurologists and neurointensivists, bone marrow transplant/cellular therapy specialists, and neurosurgical teams to be managed safely.

Response and toxicities of cellular therapies are distinct from cytotoxic chemotherapy, as efficacy and toxicity are determined by a complex interplay of tumor biology, the host-immune response, and T cell characteristics.[64] In the solid tumor experience to date, the same principles of dose-finding apply (underdosing negatively impacting efficacy, and excess dosing compromising safety), though there may be more inherent variability based on these and other host-immune system factors which is not possible to determine in small phase I trials. It is still appropriate to determine maximum tolerated dosing in a traditional dose-escalation trial design, as has been done in cellular therapy for systemic hematologic malignancies.

The majority of GBM trials have only investigated cellular therapies in the recurrent setting, so response and safety in the up-front setting is unknown. As host T cell populations are often diminished through administration of systemic chemotherapy, and tumor biology changes, with escalating resistance mechanisms in the setting of recurrent disease, it is possible that up-front treatment would be more effective. There is also an opportunity in the up-front post-surgical setting to confirm tumor antigen expression density, which may be altered at recurrence. In DMG/DIPG, however, individuals have been treated in the immediate post-radiation setting as well as at recurrence with similar safety

Treatment-related adverse events vary depending on the specific CAR T therapy, the dosing, whether or not the individual is immunosuppressed, and the route of delivery. CRS (fever +/- hypotension, +/- respiratory compromise), and ICANS (disorientation, psychomotor slowing, language dysfunction, ataxia) tend to be seen more commonly in IV CAR T infusions. With some CD-19-CAR T therapies, CRS is nearly universally present, and rates of ICANS may vary from 10-50%, with 5-30% graded as severe (grade 3-4).[6] ICANS occurs in the setting of CRS with elevated systemic inflammatory markers such as C-reactive protein, ferritin and cytokine levels. TIAN more commonly occurs with rapid onset with ICV or intratumoral CAR T infusion, and is characterized by headache, fevers, and onset or worsening of neurologic deficits referable to the location of the tumor in the CNS.[44] Obstructive and nonobstructive

Table 2. Mechanisms of cancer cell therapy treatment failure and corresponding mitigation strategies

Mechanism of treatment failure	Potential mitigation strategy
Immunosuppressive tumor microenvironment	LD Chemotherapy, Armored CARs, IL-2
Tumor heterogeneity	Identify a more uniformly expressed target, target multiple antigens (e.g. bispecific CART cell)
Antigen escape	Targeting multiple antigens, (e.g. bispecific CART cell)
CART cell exhaustion	repeat infusions, optimizing cell viability, minimizing factors in the tumor microenvironment that promote T cell exhaustion

hydrocephalus, and hyponatremia have also been observed with TIAN, and require critical care monitoring and interventions such as CSF diversion. The tendency for TIAN to decrease in severity with serial CART infusions has been observed in clinical trials.[45] The exact mechanism for this is unknown. One possibility is that there may be less exposed target due to either cytoreduction or antigen escape. Another possibility is that there may be increased immune-suppressive mechanisms following the first treatment, such as increased regulatory T cells and increased suppressive myeloid cells, both of which have been observed following the first infusion of GD2-CAR T cells for DMG in patient CSF.[32] Another possibility is that the host may develop anti-CAR antibodies, which on repeat administrations could lead to lysis of CART cells.[65]

Given their immunosuppressed status—due to LD chemo and to immune-suppressive effects of the CNS tumors themselves—individuals must also be monitored closely for signs and symptoms of infection, especially those who receive LD chemotherapy and/or are cytopenic.

Mechanisms of Treatment Failure

While there have been some promising responses to CAR T therapy in tumors that have been refractory to numerous other lines of treatment including chemotherapy, radiation and other immunotherapies, these are too often insufficiently complete and insufficiently durable. There are several potential mechanisms for CNS-directed CAR T therapy to be ineffective (Table 2). For example, the immunosuppressive tumor microenvironment that interferes with host immunity and promotes tumor proliferation may also inhibit CAR T cell activity by hindering T cell trafficking into the tumor, inhibiting T cell function, and promoting T cell exhaustion.[66] This is a particularly important consideration for CNS immunotherapy, as the neural microenvironment may be uniquely immune-suppressive through neuronal-immune-cancer cross-talk. Preconditioning regimens are one approach to reduce immune-suppressive effects of endogenous immune cells and create a more favorable environment for CAR T cell function. The ideal preconditioning regimen may be need to be developed for the unique immune system of the CNS and potentially immune-modulatory effects of nervous system signaling molecules such as neurotransmitters and neuropeptides.

There are several other potential mechanisms of treatment failure. Tumor heterogeneity, a known challenge especially in GBM, creates a situation in which many tumor cells may not express the CAR T extracellular antigen. In cases where the target antigen is expressed heterogeneously, it may be necessary to identify an additional target or targets. Antigen escape is a distinct phenomenon, in which tumors exposed to one directed therapy downregulate expression of the target antigen, leading to proliferation of tumor cells that no longer express the cellular target. Bispecific or multi-specific CART cells may be designed to make this less likely to occur. And finally, T cell exhaustion is well-described in high-grade hematologic malignancies, in which T cells become less able to expand and promote the anti-cancer immune response over time. Repeat infusions lessen the impact of CART cell exhaustion.

Future Directions

The clinical and translational science of cancer cell therapies for CNS malignancies is rapidly evolving. More fully understanding interactions between CAR T cells and the tumor as well as the tumor microenvironment will be critical to optimizing these therapies for brain tumors. Combination CAR T therapies, with multiple antigen-binding domains may be helpful to address the resistance to therapy conferred by tumor heterogeneity and antigen loss.[67] Allogeneic cellular therapies hold the potential to streamline the production process and make these therapies less costly and more widely available.[68,69] Finally, effective immunotherapy for cancers in the nervous system is likely to require a deeper understanding of the neuroscience of cancer immunotherapies, given extensive neuron-cancer-immune cell cross-talk (for review, see Mancusi and Monje, 2023 Nature[70]).

Drawing from the experience in hematologic malignancies over the past 10 years, as we gain increased experience with the application of cellular therapies in solid and specifically CNS tumors, there will need to be a concomitant way to equip teams and hospitals to reliably administer and monitor cellular immunotherapies, and consistently identify and treat adverse events. Cancer cell therapy has rapidly expanded the therapeutic landscape in CNS tumors. With a deeper understanding of targets, immune interactions between tumor, host, and treatment, cellular immunotherapy holds the potential to more effectively treat some of the most challenging and historically treatment-refractory central nervous system cancers.

Keywords

cellular immunotherapy | chimeric antigen receptor T cell | chimeric antigen receptor natural killer cell | glioblastoma | diffuse intrinsic pontine glioma/diffuse midline glioma

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References

1. Page A, Chuvin N, Valladeau-Guilemond J, Depil S. Development of NK cell-based cancer immunotherapies through receptor engineering. *Cell Mol Immunol.* 2024;21(4):315–331.
2. Han J, Chu J, Keung Chan W, et al. CAR-engineered NK cells targeting wild-type EGFR and EGFRvIII enhance killing of glioblastoma and patient-derived glioblastoma stem cells. *Sci Rep.* 2015;5(1):11483.
3. Rohaan MW, Borch TH, Van Den Berg JH, et al. Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *N Engl J Med.* 2022;387(23):2113–2125.
4. Braendstrup P, Levine BL, Ruella M. The long road to the first FDA-approved gene therapy: chimeric antigen receptor T cells targeting CD19. *Cytotherapy.* 2020;22(2):57–69.
5. Bouchkouj N, Kasamon YL, De Claro RA, et al. FDA approval summary: axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma. *Clin Cancer Res.* 2019;25(6):1702–1708.
6. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531–2544.
7. Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *J Clin Oncol.* 2021;39(24):2656–2666.
8. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015–2019. *Neuro-Oncology.* 2022;24(Supplement_5):v1–v95.
9. Girardi F, Matz M, Stiller C, et al; CONCORD Working Group. Global survival trends for brain tumors, by histology: analysis of individual records for 556,237 adults diagnosed in 59 countries during 2000–2014 (CONCORD-3). *Neuro-Oncology.* 2023;25(3):580–592.
10. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733–4740.
11. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res.* 2007;13(4):1253–1259.
12. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48(14):2192–2202.
13. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA.* 2017;318(23):2306–2316.
14. Nayak L, Molinaro AM, Peters K, et al. Randomized phase II and biomarker study of pembrolizumab plus bevacizumab versus pembrolizumab alone for patients with recurrent glioblastoma. *Clin Cancer Res.* 2021;27(4):1048–1057.
15. Omuro A, Vlahovic G, Lim M, et al. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. *Neuro-Oncology.* 2018;20(5):674–686.
16. Goutnik M, Iakovidis A, Still MEH, et al. Advancements in chimeric antigen receptor-expressing T-cell therapy for glioblastoma multiforme: literature review and future directions. *Neurooncol. Adv.* 2024;6(1):vdae025.
17. Brown CE, Badie B, Barish ME, et al. Bioactivity and safety of IL13Rα2-redirected chimeric antigen receptor CD8+ T cells in patients with recurrent glioblastoma. *Clin Cancer Res.* 2015;21(18):4062–4072.
18. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N Engl J Med.* 2016;375(26):2561–2569.
19. Brown CE, Rodriguez A, Palmer J, et al. Off-the-shelf, steroid-resistant, IL13Rα2-specific CAR T cells for treatment of glioblastoma. *Neuro-Oncology.* 2022;24(8):1318–1330.
20. Brown CE, Hibbard JC, Alizadeh D, et al. Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial. *Nat Med.* 2024;30(4):1001–1012.
21. Chuntova P, Hou Y, Naka R, et al. Novel EGFRvIII-CAR transgenic mice for rigorous preclinical studies in syngeneic mice. *Neuro-Oncology.* 2022;24(2):259–272.
22. Agliardi G, Liuzzi AR, Hotblack A, et al. Intratumoral IL-12 delivery empowers CAR-T cell immunotherapy in a pre-clinical model of glioblastoma. *Nat Commun.* 2021;12(1):444.
23. Bagley SJ, Binder ZA, Lamrani L, et al. Repeated peripheral infusions of anti-EGFRvIII CAR T cells in combination with pembrolizumab show no efficacy in glioblastoma: a phase 1 trial. *Nat Cancer.* 2024;5(3):517–531.
24. Schmidts A, Srivastava AA, Ramapriyan R, et al. Tandem chimeric antigen receptor (CAR) T cells targeting EGFRvIII and IL-13Rα2 are

effective against heterogeneous glioblastoma. *Neurooncol. Adv.* 2023;5(1):vdac185.

25. Bagley SJ, Logun M, Fraietta JA, et al. Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results. *Nat Med.* 2024;30(5):1320–1329.
26. Choi BD, Gerstner ER, Frigault MJ, et al. Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma. *N Engl J Med.* 2024;390(14):1290–1298.
27. Jenkins MR, Drummond KJ. CAR T-cell therapy for glioblastoma. Phimister EG, ed. *N Engl J Med.* 2024;390(14):1329–1332.
28. Li X, Zhao L, Li W, Gao P, Zhang N. HER2-targeting CAR-T cells show highly efficient anti-tumor activity against glioblastoma both in vitro and in vivo. *Genes Immun.* 2024;25(3):201–208.
29. Ahmed N, Brawley V, Hegde M, et al. HER2-specific chimeric antigen receptor–modified virus-specific T cells for progressive glioblastoma: a phase 1 dose-escalation trial. *JAMA Oncol.* 2017;3(8):1094–1101.
30. Burger MC, Forster MT, Romanski A, et al. Intracranial injection of natural killer cells engineered with a HER2-targeted chimeric antigen receptor in patients with recurrent glioblastoma. *Neuro-Oncology.* 2023;25(11):2058–2071.
31. Tang X, Zhao S, Zhang Y, et al. B7-H3 as a Novel CAR-T therapeutic target for glioblastoma. *Mol Ther Oncolytics.* 2019;14:279–287.
32. Majzner RG, Theruvath JL, Nellan A, et al. CAR T cells targeting B7-H3, a pan-cancer antigen, demonstrate potent preclinical activity against pediatric solid tumors and brain tumors. *Clin Cancer Res.* 2019;25(8):2560–2574.
33. Picarda E, Ohaegbulam KC, Zang X. Molecular pathways: targeting B7-H3 (CD276) for human cancer immunotherapy. *Clin Cancer Res.* 2016;22(14):3425–3431.
34. Kontos F, Michelakos T, Kurokawa T, et al. B7-H3: an attractive target for antibody-based immunotherapy. *Clin Cancer Res.* 2021;27(5):1227–1235.
35. Tang X, Wang Y, Huang J, et al. Administration of B7-H3 targeted chimeric antigen receptor-T cells induce regression of glioblastoma. *Signal Transduct Target Ther.* 2021;6(1):125.
36. Cooney T, Lane A, Bartels U, et al. Contemporary survival endpoints: an international diffuse intrinsic pontine glioma registry study. *Neuro-Oncology.* 2017;19(9):1279–1280.
37. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell.* 2017;32(4):520–537.e5.
38. Gallitto M, Lazarev S, Wasserman I, et al. Role of radiation therapy in the management of diffuse intrinsic pontine glioma: a systematic review. *Adv Radiat Oncol.* 2019;4(3):520–531.
39. Van Den Bent M, Saratsis AM, Geurts M, Franceschi E. H3 K27M-altered glioma and diffuse intrinsic pontine glioma: Semi-systematic review of treatment landscape and future directions. *Neuro-Oncology.* 2024;26(Supplement_2):S110–S124.
40. Persson ML, Douglas AM, Alvaro F, et al. The intrinsic and microenvironmental features of diffuse midline glioma: implications for the development of effective immunotherapeutic treatment strategies. *Neuro-Oncology.* 2022;24(9):1408–1422.
41. Nazha B, Inal C, Owonikoko TK. Disialoganglioside GD2 expression in solid tumors and role as a target for cancer therapy. *Front Oncol.* 2020;10:1000.
42. Mount CW, Majzner RG, Sundaresh S, et al. Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas. *Nat Med.* 2018;24(5):572–579.
43. Majzner RG, Ramakrishna S, Yeom KW, et al. GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. *Nature.* 2022;603(7903):934–941.
44. Mahdi J, Dietrich J, Straathof K, et al. Tumor inflammation-associated neurotoxicity. *Nat Med.* 2023;29(4):803–810.
45. Monje M, Mahdi J, Majzner R, et al. Intravenous and intracranial GD2-CAR T cells for H3K27M+ diffuse midline gliomas. *Nature.* 2025;637(8046):708–715.
46. Lin FY, Stuckert A, Tat C, et al. Phase I Trial of GD2.CART cells augmented with constitutive interleukin-7 receptor for treatment of high-grade pediatric CNS tumors. *J Clin Oncol.* 2024;42(23):2769–2779.
47. Vitanza NA, Wilson AL, Huang W, et al. Intraventricular B7-H3 CAR T cells for diffuse intrinsic pontine glioma: preliminary first-in-human bioactivity and safety. *Cancer Discov.* 2023;13(1):114–131.
48. Vitanza NA, Johnson AJ, Wilson AL, et al. Locoregional infusion of HER2-specific CAR T cells in children and young adults with recurrent or refractory CNS tumors: an interim analysis. *Nat Med.* 2021;27(9):1544–1552.
49. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol (Berl).* 2016;131(6):821–831.
50. WHO Classification of Tumors Editorial Board. *Central nervous system tumors.* Vol 6. 5th ed. International Agency for Research on Cancer; 2021.
51. Cooney T, Lindsay H, Leary S, Wechsler-Reya R. Current studies and future directions for medulloblastoma: a review from the pacific pediatric neuro-oncology consortium (PNOC) disease working group. *Neoplasia.* 2023;35:100861.
52. Donovan LK, Delaidelli A, Joseph SK, et al. Locoregional delivery of CAR T cells to the cerebrospinal fluid for treatment of metastatic medulloblastoma and ependymoma. *Nat Med.* 2020;26(5):720–731.
53. Nellan A, Rota C, Majzner R, et al. Durable regression of Medulloblastoma after regional and intravenous delivery of anti-HER2 chimeric antigen receptor T cells. *J ImmunoTher Cancer.* 2018;6(1):30.
54. Vitanza NA, Johnson AJ, Wilson AL, et al. Locoregional infusion of HER2-specific CAR T cells in children and young adults with recurrent or refractory CNS tumors: an interim analysis. *Nat Med.* 2021;27(9):1544–1552.
55. Heitzeneder S, Bosse KR, Zhu Z, et al. GPC2-CAR T cells tuned for low antigen density mediate potent activity against neuroblastoma without toxicity. *Cancer Cell.* 2022;40(1):53–69.e9.
56. Ciccone R, Quintarelli C, Camera A, et al. GD2-Targeting CAR T-cell therapy for patients with GD2+ medulloblastoma. *Clin Cancer Res.* 2024;30(11):2545–2557.
57. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood.* 2019;134(11):860–866.
58. Asghar N, Masood A, Dhaliwal A, et al. Chimeric antigen receptor T-Cell (CAR T-Cell) therapy for primary and secondary central nervous system lymphoma: a systematic review of literature. *Clin Lymphoma Myeloma Leuk.* 2023;23(1):15–21.
59. Cook MR, Dorris CS, Makambi KH, et al. Toxicity and efficacy of CAR T-cell therapy in primary and secondary CNS lymphoma: a meta-analysis of 128 patients. *Blood Adv.* 2023;7(1):32–39.
60. Elgohary G, Yang Y, Gergis M, Yi D, Gergis U. Chimeric antigen receptor T - cell therapy for large B-cell lymphoma patients with central nervous system involvement, a systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk.* 2024;24(4):e142–e151.
61. Choquet S, Soussain C, Azar N, et al. CAR T-cell therapy induces a high rate of prolonged remission in relapsed primary CNS lymphoma: Real-life results of the LOC network. *Am J Hematol.* 2024;99(7):1240–1249.
62. Frigault MJ, Dietrich J, Gallagher K, et al. Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. *Blood.* 2022;139(15):2306–2315.
63. Karschnia P, Blobner J, Teske N, et al. CAR T-Cells for CNS lymphoma: driving into new terrain? *Cancers.* 2021;13(10):2503.

64. Eckert T, Zobaer MS, Boulos J, et al. Immune resistance in glioblastoma: understanding the barriers to ICI and CAR-T cell therapy. *Cancers*. 2025;17(3):462.
65. Wagner DL, Fritsche E, Pulsipher MA, et al. Immunogenicity of CAR T cells in cancer therapy. *Nat Rev Clin Oncol*. 2021;18(6):379–393.
66. Kankeu Fonkoua LA, Sirpilla O, Sakemura R, Siegler EL, Kenderian SS. CAR T cell therapy and the tumor microenvironment: current challenges and opportunities. *Mol Ther Oncolytics*. 2022;25:69–77.
67. De Billy E, Pellegrino M, Orlando D, et al. Dual IGF1R/IR inhibitors in combination with GD2-CAR T-cells display a potent anti-tumor activity in diffuse midline glioma H3K27M-mutant. *Neuro-Oncology*. 2022;24(7):1150–1163.
68. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. *Nat Rev Drug Discov*. 2020;19(3):185–199.
69. Martínez Bedoya D, Dutoit V, Migliorini D. Allogeneic CAR T Cells: an alternative to overcome challenges of CAR T cell therapy in glioblastoma. *Front Immunol*. 2021;12:640082.
70. Mancusi R, Monje M. The neuroscience of cancer. *Nature*. 2023;618(7965):467–479.