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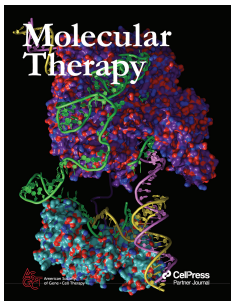

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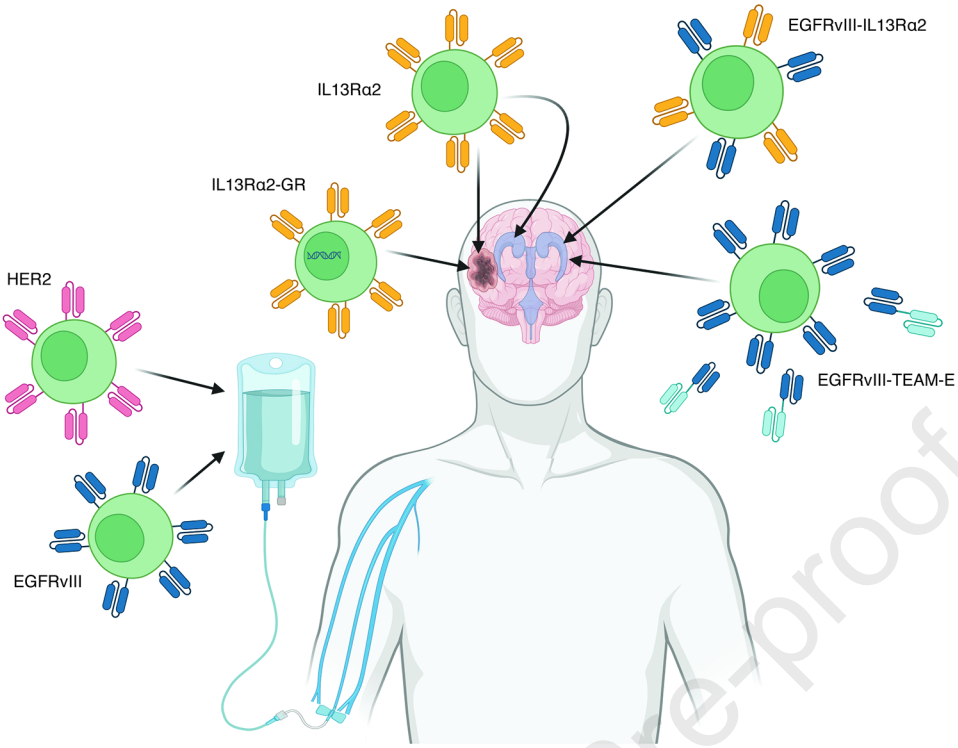

CAR T Cell Therapy for Glioblastoma: A Review of the First Decade of Clinical Trials

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ABSTRACT

Glioblastoma (GBM) is an aggressive primary brain tumor with a poor prognosis and few effective treatment options. Focus has shifted towards using immunotherapies, such as chimeric antigen receptor (CAR) T cells, to selectively target tumor antigens and mediate cytotoxic activity within an otherwise immunosuppressive tumor microenvironment. Between 2015-2024, the results of eight completed and two ongoing phase I clinical trials have been published. The majority of studies have treated recurrent GBM patients, although the inter- and intra-patient tumor heterogeneity has been historically challenging to overcome. Molecular targets have included EGFR, HER2, and IL13Rα2 and there has been continued development in improving receptor constructs, identifying novel targets, and adding adjuvant enhancers to increase efficacy. CAR T cells have been safely administered through both peripheral and locoregional routes but with variable clinical and radiographic efficacy. Most trials utilized autologous T cell products to avoid immune rejection yet were unable to consistently show robust engraftment and persistence within patients. Nonetheless, targeted immunotherapies such as CAR T cell

therapy remain the next frontier for GBM treatment, and the popularity and complexity of this undertaking is evident in the past, present, and future landscape of clinical trials.

INTRODUCTION

Glioblastoma (GBM), the most common primary brain tumor, is aggressive and unfortunately often progressive with a poor prognosis.[1] Despite standard of care treatment with maximal safe resection followed by radiotherapy with adjuvant temozolomide, GBM recurrence is common.[1,2] This persistent behavior is likely multi-factorial, but the tumoral heterogeneity and capability to mutate and escape via anti-tumor pathways make treating both de novo and recurrent GBM difficult. Progressive GBMs can become hypermutated upon recurrence, a phenomenon which is hypothesized to be related to treatment with alkylating chemotherapies.[3] Due to both inter- and intra-tumoral heterogeneity, there are no defining molecular aberrations for straightforward targeted treatment. However, pre-clinical studies have identified several potential targets including interleukin 13Rα2 (IL13Rα2), EphA2, EGFRvIII, and HER2.[4]

Immunotherapies have been established for various solid and liquid tumors.[5] These approaches have now been turned to the brain.[6] Most immunotherapies employ immune checkpoint inhibitors, ideally enabling the host immune system to successfully eliminate cancer cells.[6] However, GBM has numerous immunosuppressive elements, including a formidable immunosuppressive tumor microenvironment (TME), that enable the tumor to ignore these blockades. Chimeric antigen receptor (CAR) T cells are approved for use against hematologic malignancies including leukemias, lymphomas, and myeloma. These engineered T cells are redirected to engage with known tumor targets via the insertion of antigen-specific synthetic T cell receptor complexes.[7] Autologous or allogeneic T cells are modified via a viral vector to express an extracellular antigen-binding region and intracellular activation and costimulatory domains.[8] As these T cells are innately cytotoxic and do not require the host immune system for their anti-malignancy effect, they are a promising route for GBM treatment despite the immunosuppressive TME.[6,8]

Over the past decade, applying CAR T therapy for GBM has become an increasingly popular avenue for research. In the United States alone there have been ten clinical trials that have published results during this period, and they reflect both the successes and challenges of CAR T cells for the treatment of GBM [Table 1].

REVIEW OF TRIALS

The first-in-human study evaluating the safety and feasibility of treating recurrent GBM with CAR T cells was published in 2015. Three patients received an intracavitary delivery of autologous IL13Rα2-targeting CD8+ cytolytic T cells. 12 escalating doses were delivered over four weeks with two patients at the highest dosage experiencing transient adverse effects.[9] On post-treatment MRI, all three patients demonstrated increased contrast enhancement and FLAIR signal at the site of infusion and the degree of inflammation appeared to correlate with IL13Rα2 expression. Two patients showed no recurrence within the treated tumor cavity near the site of T cell infusion. The third patient progressed and underwent repeat resection, with pathology demonstrating significantly decreased IL13Rα2 expression levels compared to pre-T-cell therapy levels.

In 2016, a modified version of the previously prior IL13Rα2 CAR construct was delivered to one patient.[9,10] Despite recurrent multifocal and leptomeningeal disease in both the brain and spinal cord, this patient demonstrated the a transient but robust response. He received six intracavitary infusions into the largest resected tumor and while this lesion remained stable, continued disease progression of several old and new lesions (both in the brain and spine) prompted ten additional treatments via an intraventricular catheter. Brown et al. proposed that intracavitary delivery may have prevented local but not distant recurrence. All intracranial and spinal tumors decreased in size over the treatment period, becoming unmeasurable on both MRI and PET. This clinical response was sustained for 7.5 months after CAR T cell initiation and no initial tumors recurred. Unfortunately, this patient did experience progressive disease and based upon preliminary data, these new lesions likely demonstrate decreased IL13Rα2 antigen expression. Despite detecting increased inflammatory cytokines in the CSF following infusion, no grade 3 toxic effects were seen.

In 2017, a novel CAR construct targeting EGFRvIII was first delivered to glioblastoma patients.[11] Unlike the prior trials, only a single dose was delivered peripherally to ten patients with recurrent, EGFRvIII+ GBM (the majority also with multifocal disease). Despite the physiologic expression of EGFR in the lungs, no patients experienced off-tumor toxicity or cytokine release syndrome (CRS). In the subgroup of patients who underwent surgery at differing time points after CAR T cell treatment there was variable infiltration of T cells into the tumor tissue. Expression seemed to mirror peripheral blood engraftment and patients who underwent surgery less than two weeks after infusion had greater intracranial expression of CAR+ T cells than in the peripheral blood, suggesting effective trafficking and expansion. Consistent with prior trials, tissue from recurrent tumors often demonstrated a decrease in antigen (EGFRvIII) expression post-treatment.

A HER2-targeting virus-specific T cell (VST) that provides both CAR and viral antigen-mediated antitumor effects was developed for patient use in 2017.[4] HER2 is a member of the EGFR family that is involved with myocardial homeostasis and its use as a therapeutic target in other malignancies (such as breast cancer) can be limited by cardiac dysfunction.[12] 17 patients, including ten adult and seven pediatric patients, were treated with escalating doses of this novel CAR, with six patients receiving multiple doses. No dose-limiting toxicities were seen, and ventricular function remained unchanged. Peak expansion occurred from 0-14 days after infusion, but HER2-CAR VST levels steadily declined over a year, indicating that these cells did not expand after infusion, even in patients receiving multiple doses. Radiographically, mixed responses to treatment were seen, and although six patients showed increased peritumoral edema, it was unknown whether this was due to progressive disease or a T cell-mediated anti-tumor effect.

Work on an EGFRvIII-targeting CAR was expanded upon in 2019, using a different CAR construct targeting a fragment of human EGFRvIII monoclonal antibody 139 and including additional intracellular costimulatory domains. 18 recurrent, EGFRvIII+ GBM patients were treated with escalating peripheral doses of EGFRvIII-targeted CAR T cells.[13] Pulmonary effects were seen in a dose-dependent manner at the highest dose level and one patient developed acute dyspnea requiring intubation and eventually expired. No objective

responses were seen on follow-up MRI and 16/17 patients progressed within 3 months of infusion. At one month, presence of CAR+ cells correlated with cell dose, but not with survival.

The previous work with IL13Rα2 CAR T cells was expanded upon in 2022 and was the first study to utilize allogeneic rather than autologous T cells.[14] Previously, CAR T therapy required the manufacturing of individualized therapeutic products prior to infusion. Although allogeneic products may shorten the period between enrollment and treatment, there is a higher risk of both graft vs. host disease (GVHD) and host vs. graft response. To alleviate this risk, these CAR T cells were engineered with resistance to glucocorticoid treatment, allowing steroids to be used to attenuate tumor-related edema and infusion cell rejection. Six patients with nonresectable recurrent GBM underwent biopsy to confirm recurrence and intratumoral catheter placement for administration of IL13Rα2 CAR T cells. All patients received four doses over two weeks, without dose-limiting toxicities or evidence of rejection. However, no objective clinical responses or significant survival benefits were seen. Although tumor necrosis was seen radiographically and pathologically near the site of infusion in four patients, on tissue analysis, few CAR+ cells persisted past 10 weeks. It is unclear if immunosuppression from continued steroid treatment, previous GBM treatment, or the TME prevented engagement of the endogenous immune system against the tumor and therefore a stronger anti-tumor response.

The first study treating de novo, rather than recurrent, GBM with CAR T cell therapy was published in 2023.[15] Although EGFRvIII is found in approximately 30% of recurrent GBM tumors, approximately half of patients lose this mutation at time of recurrence.[11,16] Seven patients with newly diagnosed EGFRvIII+ GBM received 1-4 cycles of EGFRvIII-targeted CAR T-cells and pembrolizumab (an anti-PD1 monoclonal antibody) following a course of hypofractionated radiation. No dose-limiting toxicities, including CRS or neurotoxicity, were seen after CAR T cell treatment. Peak engraftment levels were much lower than those seen in their prior trial despite this cohort of patients receiving three doses instead of one.[11] Of all the patients who underwent recurrence surgery after CAR T cell infusion, CAR+ cells were only detected in tumor from the patient whose operation was a week after treatment. Although there was no change in the immune cell composition of the TME

after treatment, there was an increase in activated and exhausted T cells. There was confirmed reduction in target antigen after CAR-T administration, but no clinical response or efficacy was observed.

The largest cohort to date of recurrent high-grade glioma patients treated with CAR T cell therapy was published in 2024.[17] 65 patients (including 41 with GBM) were treated with IL13Rα2-directed CAR T-cells in five experimental arms based upon the route of locoregional delivery (intracavitary after biopsy or resection, intraventricular, or a combination of both) and manufacturing platforms. While no dose-limiting toxicities were seen with repeated delivery, 35% of patients experienced grade 3 or higher adverse effects. 50% of patients achieved stable disease or better (although all who saw complete or partial regression had IDH mutations) and patients who received combined intracavitary and intraventricular infusions had a significantly longer overall survival. Elevated inflammatory and immune modulatory cytokine levels were seen in the CSF after each infusion and researchers hypothesized that the IFNγ pathway may serve as a potential biomarker of CAR activity in the CNS. Four of the experimental arms utilized central memory T cells while one arm pioneered a platform focused on central and naïve, stem cell memory phenotypes (Tn/mem). Production of Tn/mem cells yielded greater total T cells available for engineering and a more balanced population of CD4+ and CD8+ T cells that, in preclinical studies, demonstrated superior proliferation and anti-tumor activity. Brown et al. intend to pursue this manufacturing platform for further clinical trials.

ONGOING CLINICAL TRIALS

As of 2024, two ongoing clinical trials have published results after interim analysis [Table 2].

The results of treating six patients with bivalent CAR T-cells targeting both EGFR (epitope 806) and IL13Ra2 has been published.[18] All patients have recurrent and multifocal GBM and were treated with intraventricular delivery of CAR T-cells at one of two dose levels. All patients did display early onset neurotoxicity with low grade cytokine release syndromes but only one patient had dose-limiting toxic effects, however all these were transient and manageable. As compared to their prior trial utilizing peripheral delivery, peak engraftment levels were substantially higher with intrathecal delivery.[11] All six patients had reductions in

the size of enhancing tumors on first post-treatment MRI, however none met RANO criteria for an objective response. Rapid increases in CSF cytokine levels after infusion supported CAR T cell activation and cytotoxic activity.

Three recurrent GBM patients have been treated with an intraventricular delivery of CARv3-TEAM-E T cells that target both EGFRvIII, via a CAR, and wild-type EGFR, via a T-cell-engaging antibody molecule (TEAM).[19] No dose-limiting toxicity was seen but some grade 3 adverse effects were observed and all three patients had fevers that peaked two days after infusion. One patient demonstrated rapid radiographic regression one day after infusion, but this effect was transient. They received a subsequent infusion but still progressed. Another patient had a decrease in tumor volume that remained durable for 150 days after a single infusion. The final patient had near-complete tumor regression after five days, but recurrence within a month. On liquid or pathologic biopsy, two patients demonstrated a decrease in both EGFRvIII and EGFR copy numbers while the third patient had a decrease in only EGFRvIII.

DISCUSSION

Here we have reviewed the clinical trials completed in the US that have investigated CAR T cell therapy for GBM patients. Evaluating these eight completed trials and two ongoing trials with published interim analyses have demonstrated trends in the development of CAR T cell therapy for GBM as well as highlighted some future directions for further research.

All trials have been published within the past decade, between 2015 and 2024. This is the same time period during which CAR T therapy has become a pillar of oncologic medicine and focus has shifted from the success with hematologic malignancies to applications for solid tumors.[20] The vast majority of these trials have been conducted by groups from two major institutions: the University of Pennsylvania and the City of Hope Research Institute. Despite one trial focusing on de novo GBM,[15] all other trials have treated recurrent high-grade gliomas or GBMs with CAR T cells. All ten of the referenced trials have been Phase 1 trials focusing on safety and feasibility, with exploratory analyses of clinical and biological efficacy. Early trials utilized either intracranial or

intravenous delivery of CAR T cells, but the most recent trials have exclusively used intracranial delivery with either intracavitary or intraventricular routes of administration. Although trials have utilized different routes of administration, dosing has generally ranged from 10^6 – 10^8 cells. Regarding CAR design, EGFR and IL13Rα2 have been the most widely utilized antigens, with only one trial utilizing a different target (HER2).[4] However, over time, constructs have become more complex, featuring modifications to intracellular costimulatory domains and most recently with bivalent extracellular domains and the secretion of T cell engaging antibodies.[18, 19]

Recruiting and upcoming trials tend to be focused on one of two directions for CAR advancements: switching to novel targets or boosting existing target efficacy by including adjuvant immunotherapy, additional antigen targets, or molecular enhancers [Table 3]. All upcoming trials are phase I trials and focus remains on establishing the safety of these novel therapeutics without comparison to standard or existing therapies. While all but one of the published trials have exclusively focused on recurrent GBM, some upcoming trials plan to treat only de novo patients or allow the enrollment of either primary or recurrent GBM patients. Although more recently published trials have focused on locoregional delivery of CAR T cell products, either intracavitary/tumoral or intraventricular, upcoming trials employ a mix of peripheral and locoregional infusions.

FUTURE DIRECTIONS

In a relatively short period of time, significant advancements have been made in the use of CAR T cells for the treatment of GBM. However, there are still challenges to overcome and areas for improvement (Figure 1).

Thus far, CAR T cells remain a personalized medicine, requiring preparation of cell product on a patient-by-patient basis. The use of autologous cells decreases the risk of GVHD and host versus graft disease that would be possible with allogeneic cells, but it does add another procedure and more time to the manufacturing process. Avoiding this production delay with allogeneic CAR T cells (such as those utilized by Brown et al in 2022) would enable the delivery of cells directly into the surgical cavity immediately post-resection.[14] Use of an "off-the shelf" product then expands the vehicles by which CAR T cells could be delivered, such as via a biomaterial product that does not require additional hardware implantation (such as an Omaya catheter) and can bridge the gap

between surgery and initiation of systemic treatments. Additionally, while further modifications and improvements to the manufacturing process, such as the memory T cell-enriched production published in 2024, may not shorten production time, the improvements in function and efficacy can only improve CAR T cell success for GBM.

There has been a shift away from the peripheral delivery of CAR T cells and towards locoregional delivery, into either the ventricles or tumor cavity. Although intracranial delivery bypasses the blood brain barrier and, in the case of EGFR-targeting cells, decreases the risk of life-threatening pulmonary edema, studies have shown that central infusions can still lead to neurotoxic effects and systemic cytokine release syndromes.[13, 17, 18] While some of these adverse effects have been managed with steroids or lymphodepletion or infusions of cytokines like IL2, all these strategies could impair the recruitment and efficacy of the host immune system. Even without these adjuvants potentially impairing host immune response, patients with GBM are often in a state of immunosuppression, both due to the disease process and, in the case of recurrent GBM, as a side effect of prior chemotherapy and radiation.[21] Studies on CAR T cells for lymphoma and leukemia have reported enhanced persistence and efficacy of T cells after prior conditioning chemotherapy.[22] This may explain why the one trial treating de novo GBM saw a lack of success with notably low engraftment levels.[15] Further research will be necessary to find the balance between recruiting the host immune system to work in parallel with CAR T cells and prevent over activation and self-inflicted damage by those same immune cells.

Even after a safe and effective product travels to the tumor, CAR T cells must overcome the innate heterogeneity that characterizes GBM. Antigen expression varies widely both between patients with GBM and within each tumor itself and there are no defining molecular aberrations that can be widely targeted. Treatment with CARs directed at only one molecular target can lead to antigen escape and loss of target in subsequent recurrence.[10, 11, 19] Both ongoing clinical trials have utilized dual-target T cells that can attack a greater proportion of tumor cells[18, 19]. It is likely that GBM treatment will require a multi-faceted approach, whether within a single product or across multiple sessions, in order to effect the ever-changing molecular landscape of this disease.

As CAR T cell infusions are not given with the same frequency as other anti-neoplastic treatments, there is need for improvement in the persistence and engraftment of CAR T cells in order to generate durable responses. Some trials have shown clinical benefit from CAR T therapy, but often this response is transient and accompanied by a decrease in CAR+ cells in the weeks after treatment. The immunosuppressive TME has been a pervasive barrier to the success of immunotherapies for solid cancers, including GBM, and has likely contributed to the lack of success seen in clinical trials thus far. Pro-tumor elements, such as transforming growth factor-beta (TGF-β), proinflammatory cytokines (IL-18), and tumor-associated macrophages and microglia (TAMs) have been the target of much preclinical work.[23, 24] A bispecific IL13Rα2/TGF-β CAR that converts TGF-β to an immunostimulant has improved T cell infiltration and reduced myeloid cells in tumor-bearing brain in murine GBM models.[23] The addition of a dominant-negative TGF-β receptor II (dnTGF-βRII) to the previously described bicistronic EGFR-IL13Rα2 CAR construct reduces the environmental TGF-β concentration and significantly improve T cell proliferation, fitness, and response in both *in vitro* and *in vivo* studies.[24] Armoring of CAR T cells has been trialed in patients with Hodgkin lymphoma and prostate cancer, with success in the former and only transient antitumor effects and dose-dependent toxicity in the latter.[25] Another published method of improving T cell persistence and function involves CD19 CAR T cells that secrete IL-18, a pro-inflammatory cytokine, in order to recruit more immune cells to the TME.[25] In an *in vivo* melanoma model, these CD19-IL-18 CAR T cells significantly enhanced T cell proliferation and augmented antitumor effects. Macrophages in the TME have a robust immunosuppressive phenotype that can block the antitumor effects of T cells, and no effective approaches are clinically ready. Preclinical work targeting the macrophage activation pathway have exploited macrophage colony-stimulating factor (CSF-1), PI 3-kinase, Toll-like receptor 4, CD40, and CD47, with less than robust responses.[26] Promising research has utilized small molecules and oncolytic adenoviruses to overcome the immunosuppressive TME.[26, 27] There will need to be a multifaceted approach to GBM treatment utilizing both tumor targeting and immune modulation.[28]

Finally, there remains difficulty in differentiating between true disease progression after CAR T cell treatment and pseudo-progression as a consequence of the administration and effect of CAR T cells, especially in

the context of current imaging approaches. While this challenge is not unique to those patients treated with immunotherapies like CAR T cells, it does make it difficult to determine clinical efficacy in ongoing and future trials.

CONCLUSIONS

In summary, CAR T cell therapy for GBM has been a relatively recent advancement in the field of neuro-oncology and its increasing popularity has been driven by several major research groups. Promising targets, such as EGFR and IL13Rα2, have been identified but there is continued development in both the advancing the CAR constructs and identifying novel targets. With all of these studies being phase I trials, there has been evidence that CAR T cells can be delivered through both peripheral and locoregional routes with relatively consistent safety but variable efficacy. Trial results have shown some promising clinical benefit, but further advancements will be necessary to hopefully provide durable effects. With the shift toward utilizing molecular criteria for the diagnosis of central nervous system tumors, the selection of the ideal patient population to receive CAR T therapy is not straightforward. A combination of clinical and molecular criteria are being used for trial enrollment and with the innate heterogeneity found in GBMs, it is likely that an equally heterogenous population could benefit from CAR therapy. Ultimately, it will require trials comparing CAR T cell therapy to standard of care regiments and other established primary or salvage therapies to quantify the meaningful benefits for GBM patients. Nonetheless, targeted immunotherapies such as CAR T cell therapy remain the next frontier for GBM treatment, and the popularity and complexity of this undertaking is evident in the current landscape of clinical trials.

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AUTHOR CONTRIBUTIONS

SLB and ZAB were responsible for the conceptualization. DMO and ZAB supervised the work. SLB did the original draft writing. SLB, DMO, and ZAB reviewed and edited the final submission.

DECLARATIONS OF INTEREST

DMO and ZAB are listed as inventors on patents licensed to Kite for CAR T cell constructs discussed in this review.

KEYWORDS

Chimeric antigen receptor T cells, CAR T cells, clinical trials, EGFR, IL13Rα2, glioblastoma.

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FIGURE LEGENDS

Figure 1. Representative images summarizing challenges facing CAR T cell therapy for GBM and some areas of study that hope to overcome them. From top to bottom, the boxes illustrate (1) limitations in autologous CAR T cell production, (2) difficulty in cell trafficking to tumors within the brain, (3) limitations to persistence and engraftment including the immunosuppressive TME, and (4) tumor/antigen heterogeneity.

Table 1. Completed clinical trials investigating CAR T-cell therapy for GBM.

Study Details								Results			
Study	**Year**	**Trial identifier**	**Antigen target**	**ROA**	**Dosing**	**N**	**Cohort demographics**	**Adverse effects & toxicities**	**Clinical results**	**Biologic results**	**Survival**
Brown et al.[9]	2015	NCT00730613	IL13Rα2	ICT	12 doses; escalating from 10^7 - $5x10^7$ - 10^8	3	rGBM	transient CNS inflammation	transient anti-glioma response in 2 patients	reduced IL13Ra2 within tumor following treatment	n/a
Brown et al.[10]	2016	NCT02208362	IL13Rα2	ICT & ICV	first dose at $2x10^6$ then remaining ICV and ICT doses at $10x10^6$	1	rGBM, multifocal, LMD, IDH1wt, MGMT-	no DLT	regression of all intracranial and spinal tumors	increase in inflammatory cytokines and immune cells in the CSF	response for 7.5 months after initiation
O'Rourke et al.[11]	2017	NCT02209376	EGFRvIII	IV	single dose; 1-$5x10^8$	10	rGBM, 9/10 multifocal, MGMT-	no EGFR toxicity, no CRS	9/10 progressed	transient expansion of CAR+ cells in peripheral blood	mOS 251 days

Ahmed et al.[4]	2017	NCT01109095	HER2	IV	single or multiple doses; $1x10^6/m^2$ to $1x10^8/m^2$	17	10 adult, 7 pediatric; rGBM	no DLT or cardiac toxicities	8/16 stable disease or partial response	peripheral persistence up to 12 months, trafficking of CAR+ cells to tumor, antigen decrease in 5/7 patients	mPFS 3.5 months, mOS 11.1 months
Goff et al.[13]	2019	NCT01454596	EGFRvIII	IV	dose escalation from 10^7 to 10^{10}	18	rGBM	severe hypoxia in 2 patients including 1 treatment-related mortality	no objective responses	persistence of CAR+ cells correlated with dose	mPFS 1.3 months, mOS 6.9 months
Brown et al.[14]	2022	NCT01082926	IL13Rα2	ICT	4 doses 10^8	6	rGBM, nonresectable	no DLT	radiographic evidence of tumor necrosis; no objective clinical response	pathologic evidence of tumor necrosis	no significant survival benefit
Bagley et al.[15]	2023	NCT03726515	EGFRvIII	IV	$2x10^8$	7	de novo GBM, MGMT-,	no DLT	no objective responses	increased exhausted, regulatory, and IFN-stimulated T cells at relapse	mPFS 5.2 months, mOS 11.8 months
Brown et al.[16]	2024	NCT02208362	IL13Rα2	ICT, ICV, or dual	$2\text{-}200x10^6$	65	HGG	no DLT	stable disease or better in 50% patients	increased inflammatory cytokines associated with CAR T-cell activity	mOS 7.7 months

GBM: glioblastoma. CAR: chimeric antigen receptor. CNS: central nervous system. CRS: cytokine release syndrome. CSF: cerebrospinal fluid. DLT: dose-limiting toxicity. HGG: high grade glioma. ICT: intracavitary. ICV: intraventricular. IV: intravenous. LMD: leptomeningeal disease. mOS: median overall survival. mPFS: median progression-free survival. rGBM: recurrent glioblastoma. ROA: route of administration.

Table 2. Ongoing clinical trials investigating CAR T-cell therapy for GBM, including interim results.

Study	Year	Trial identifier	Antigen target	ROA	Dosing	N	Cohort demographics	Results

Choi et al.[17]	2024	NCT05660369	CAR: EGFRvIII TEAM: wildtype EGFR	ICV	$10x10^6$ CAR+	3	rGBM	rapid but transient response in 2/3, durable response in 1/3; no DLT
Bagley et al.[18]	2024	NCT05168423	EGFRvIII-IL13Ra2	ICV	$1x10^7$ & $2.5x10^7$	6	recurrent, multifocal GBM	early-onset neurotoxicity; 1 DLT, reduced tumor size/enhancement but no ORR

GBM: glioblastoma. CAR: chimeric antigen receptor. DLT: dose-limiting toxicity. ICV: intraventricular. ORR: objective response rate. rGBM: recurrent glioblastoma. ROA: route of administration. TEAM: T -cell engaging antibody molecule.

379 Table 3. Upcoming and ongoing clinical trials investigating CAR T-cell therapy for GBM.

Trial identifier	Study range	Antigen target	ROA	Estimated enrollment (#)	Cohort	Study details	Phase
NCT04214392	2020-2025	CLTX	ICT or ICV/ICT	36	MMP2+, recurrent GBM	Dose escalation trial	I
NCT04003649	2019-2025	IL13Ra2 +/- nivolumab +/- ipilimumab	ICT/ICV	60	resectable, recurrent GBM		I
NCT03389230	2018-2024	HER2	ICT or ICV/ICT	29	Recurrent grade III-IV glioma	Memory enriched T cells	I
NCT02664363	2017-2019	EGFRvIII	IV	3	De novo GBM	CAR T-cells prior to SOC; Study terminated due to end of grant funding	I
NCT05353530	2023-2027	IL-8 receptor modified CD70	IV	18	CD70+ de novo GBM	Dose escalation trial	I
NCT05474378	2022-2025	B7-H3	Locoregional	39	Recurrent IDHwt GBM		I
NCT05366179	2022-2030	B7-H3	ICV	36	Recurrent GBM	Dose escalation trial	I
NCT06186401	2024-2026	EphA2/IL13Ra2	IV	20	EGFRvIII+ de novo or recurrent GBM		I
NCT05660369	2023-2026	CARv3-TEAM-E	ICV	21	De novo or recurrent GBM		I

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381 GBM: glioblastoma. CAR: chimeric antigen receptor. CLTX: chlorotoxin. ICT: intracavitary. ICV:

382 intraventricular. IV: intravenous. ROA: route of administration. SOC: standard of care. TEAM: T -

383 cell engaging antibody molecule.

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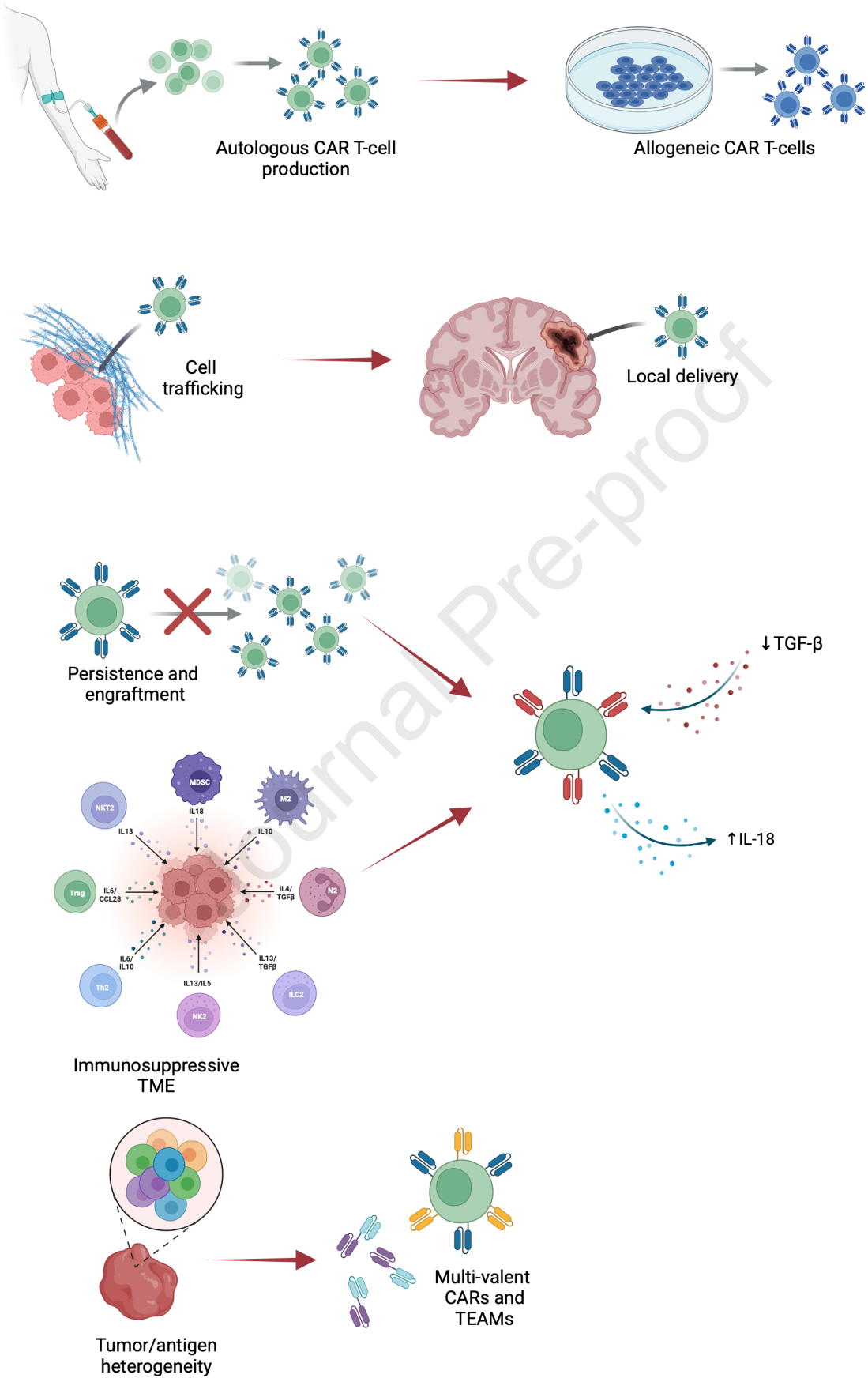

Begley and colleagues review the eight completed and two ongoing clinical trials studying CAR T cell therapy for glioblastoma published between 2015 and 2024. They describe trends in route of administration, antigen targets, and CAR design and identify areas for further study regarding CAR T cell trafficking, persistence, and targeting.