A Phase 1 Study to Evaluate Chimeric Antigen Receptor (CAR) T Cells Incorporating a Chlorotoxin Tumor-Targeting Domain for Patients With MMP2+ Recurrent or Progressive Glioblastoma (NCT04214392)

#340697

Behnam Badie,[1] Michael E Barish,[1] Ammar Chaudhry,[1] Massimo D'Apuzzo,[1] Stephen J Forman,[1] Jana Portnow,[1] Shirong (Sean) Wang,[1] Julie A Ressler,[1] Jennifer Simpson,[1] Julie Kilpatrick,[1] Paige McNamara,[1] Jamie Wagner,[1] Suzette Blanchard,[1] Dongrui Wang,[2] Christine Brown[1]

[1]City of Hope National Medical Center, Duarte, CA; [2]MD Anderson Cancer Center, Houston, TX

Abstract

Background:

Glioblastoma (GBM) is the most common and most aggressive primary brain tumor. Around 294,900 new cases are diagnosed globally with 241,000 deaths each year. The 5-year survival is only 5%. Median overall survival from first recurrence is only 5-8 months. There is no established standard of care for recurrent GBM.

City of Hope (COH) has developed and optimized a CAR T cell therapy utilizing the chlorotoxin peptide (CLTX) as the CAR's tumor recognition domain against GBM. CLTX-CAR T cells specifically and broadly target GBM through recognition of a receptor complex including membrane-bound matrix metalloproteinase 2 (MMP-2). CLTX-CAR T cells do not exhibit off-tumor recognition of normal human or murine cells and tissues in preclinical models.

In in vitro studies, COH evaluated patient-derived brain tumor (PBT) cell lines for CLTX binding and expression of IL13Rα2, HER2 and EGFR, three targets of CAR T cell trials for GBMs. Strong CLTX binding to tumor cells was observed in the majority of primary GBM lines, independent of these other antigens.

In preclinical studies using in vivo mouse models, a single intratumoral (ICT) injection of CLTX-CAR T cells (1×10^6 CAR+ T cells) exhibited robust anti-tumor activity against ffLuc+ PBT106 tumors orthotopically-engrafted in NSG mice. Overall, when compared to mice treated with mock-transduced Tn/mem (no CAR) T cells, the CLTX(EQ)28ζ/CD19t+ T cells reduced tumor burden and significantly increased survival.

Taken together, these preclinical findings support the potential safety and efficacy of CLTX-CAR T cells, and provide the rationale for clinical testing of this therapy. As cellular heterogeneity intrinsic to GBM likely contributes to resistance to therapy and limited response rates, CLTX-CAR T cells may provide greater tumor eradication in a higher proportion of patients with GBM.

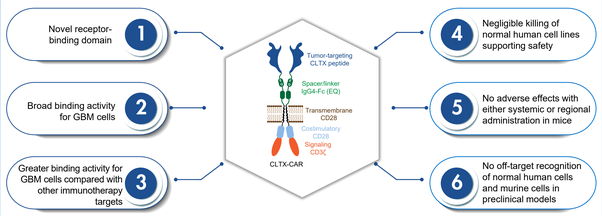
Methods:

This study is a phase 1, single center, safety and maximum tolerated dose (MTD) finding study of CLTX-CAR T cells for patients with MMP2+ recurrent or progressive GBM. A safety lead-in of 3−6 patients receiving CLTX-CAR T cells by ICT delivery will be completed first. Subsequently, subjects would receive cells administered through both ICT and intraventricular (ICV) catheters; i.e. dual delivery) in two dose schedules. Patients will be evaluated for safety and tolerability, and may continue to receive treatment until disease progression. Time to progression, overall survival, and disease response by Response Assessment in Neuro-Oncology (RANO) criteria, will be evaluated and descriptively compared to historical data. The study is actively enrolling patients.

Introduction

- Glioblastoma (GBM) is the most common and aggressive brain and central nervous system malignancy[1] and has substantial heterogeneity[2]
- GBM has a 5-year survival rate of 5.1%[3] and median overall survival (OS) of 5-8 months following recurrence[4,5]
- Furthermore, no standard of care is currently available for recurrent GBM; treatment options include further surgery (if viable), clinical trials, or further chemotherapy[6]
- Antitumor bioactivity of glioma-targeting chimeric antigen receptor (CAR) T cells was suggested in patients with malignant glioma (including GBM) in an ongoing clinical trial (NCT02208362); however, tumor heterogeneity possibly led to an inadequate overall response rate and limited potency of adoptively transferred CAR T cells
- Chlorotoxin (CLTX)-CAR T cells (CLTX-EQ-28ζ/CD19t+ T cells; Figure 1), a novel immunotherapy developed by City of Hope, uses CLTX as the tumor-recognition domain that identifies a multireceptor complex comprising membrane-bound matrix metalloproteinase 2 (MMP2) on GBM cells for binding[2]

Figure 1: CLTX-CAR T Cells

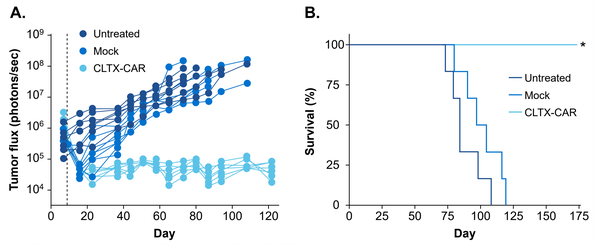


CAR, chimeric antigen receptor; CLTX, chlorotoxin; Fc, fragment crystallizable; GBM, glioblastoma; Ig, immunoglobulin.
Wang D, et al. *Sci Transl Med*. 2020;12(533):eaaw2672.

Preclinical In Vivo Antitumor Activity

- In vitro studies have exhibited strong binding of CLTX to a broad spectrum of GBM cells, including patient tumor cells and patient-derived GBM cell lines[2]
- CLTX binds to a greater number of GBM tumors and a higher proportion of malignant GBM cells compared with other GBM immunotherapy targets,[2] including interleukin (IL)13Rα2,[7] human epidermal growth factor receptor 2 (HER2),[8] and epidermal growth factor receptor (EGFR)[9]
- Furthermore, a single intracranial intratumoral (ICT) administration of CLTX-CAR T cells (1×10^6 CAR T cells) compared with that of mock-transduced (no CAR) T cells demonstrated potent in vivo antitumor activity in orthotopic GBM-xenograft mouse models[2]
  - Quantification of firefly luciferase flux (photons/sec) for each mouse treated with CLTX-CAR T cells showed tumor regression (Figure 2A)
  - Kaplan-Meier survival curve demonstrated significantly improved survival in mice treated with CLTX-CAR T cells (p=0.0004; Figure 2B)

Figure 2: Preclinical In Vivo Antitumor Activity



*p=0.0004 using the log-rank (Mantel-Cox) test; p=0.008 for CLTX-CAR versus mock therapy.
CAR, chimeric antigen receptor; CLTX, chlorotoxin.
Wang D, et al. *Sci Transl Med*. 2020;12(533):eaaw2672.

First-in-Human Phase 1 Study of CLTX-CAR T Cells in GBM

Primary Objectives

- To assess the feasibility and safety of dual delivery of CLTX-CAR T cells in patients with recurrent or progressive GBM after completing a preliminary lead-in of ICT delivery
- To determine the maximum tolerated dose (MTD) and a recommended phase 2 dosing (RP2D) plan for dual delivery of CLTX-CAR T cells in patients with recurrent or progressive GBM

Secondary Objectives

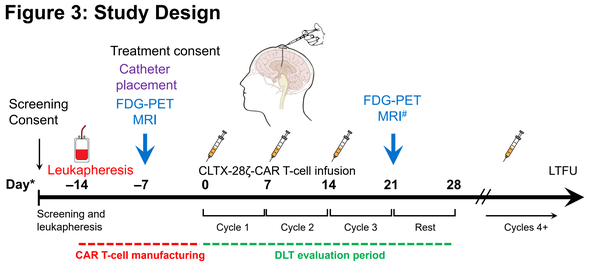
- To describe the persistence, expansion, and phenotype of CLTX-CAR T cells and endogenous cells in peripheral blood (PB), tumor cyst fluid (TCF), and cerebrospinal fluid (CSF)
- To describe cytokine levels in PB, TCF, and CSF
- To assess the 6-month progression-free survival (PFS) rate, 9-month OS rate, disease response rates, and median OS
- To evaluate the persistence and location of CAR T cells and expression levels of the CLTX-targeted antigen on tumor tissue before and after CAR T-cell therapy in relation to the injection site
- To evaluate treatment benefit using biomathematical modeling of tumor growth

Methods

Study Design

- This is a phase 1, single-center, dose-finding, feasibility/safety study for the adoptive transfer of CLTX-CAR T cells for treatment of patients with MMP2+ recurrent or progressive GBM; the study is currently recruiting patients
- The study data will be collected using City of Hope's electronic capture system and entered into protocol-specific electronic case report forms
- Study treatment begins with surgery (~day –7), followed by cycle 1 CAR T-cell infusion on day 0 (Figure 3)
- The dose-limiting toxicity (DLT) period is cycle 1 through cycle 3 plus 1 additional week to assess the potential for late subacute adverse events (~28 days)

Figure 3: Study Design



*Days shown are approximate.
#Imaging can occur any time between day 21 and day 35.
CAR, chimeric antigen receptor; CLTX, chlorotoxin; DLT, dose-limiting toxicity; FDG-PET, fluorodeoxyglucose–positron emission tomography; LTFU, long-term follow up; MRI, magnetic resonance imaging.

Treatment Plan

- Treatment Arm 1 (ICT) will open first. When a dose level is determined to be safe (i.e., 0 DLTs in 3 patients or ≤1 DLT in 6 patients), then Arm 1 will be put on hold; Arm 2 dual delivery (ICT and ICV) will open at the safe dose from Arm 1
- The first 3 patients in each Arm will be treated one at a time and followed up through the DLT period before the next patient may receive the initial infusion
- All subsequent patients will be treated in cohorts of 3
- The dose-escalation plan calls for intrapatient escalation through dose levels labeled with letters (A-D, F, H), as well as intercohort dose escalation through dosing schedules 1 and 2 (Table 1)
- Currently, 4 patients are enrolled and have initiated treatment

Table 1: Treatment Schema for Phase 1

Planned cycle	DS 1 de-escalation	DS 1	DS 2 de-escalation	DS 2
Cycle 1	A: 2×10^6	A: 4×10^6	C: 10×10^6	F: 20×10^6
Cycle 2	B: 10×10^6	C: 20×10^6	D: 50×10^6	H: 100×10^6
Cycle 3	B: 10×10^6	C: 20×10^6	D: 50×10^6	H: 100×10^6
Total dose*	25×10^6	44×10^6	110×10^6	220×10^6
Evaluation/restaging				
Cycles 4+	≤10×10^6	≤20×10^6	≤25×10^6	≤100×10^6
Cycles unrestricted#	<10×10^6	<20×10^6	<25×10^6	<100×10^6

*The dose listed for each cycle is the CAR T-cell dose intended for each delivery route. For dual delivery, 2 infusion doses will be prepared per infusion cycle, 1 each for the ICT and ICV delivery routes. To qualify for the dose-escalation portion of the study, the patient product must be able to deliver at least 80% of the total required cell dose for 3 cycles.
#Unrestricted cycles are available after disease progression or if a patient has required a contraindicated drug.
CAR, chimeric antigen receptor; DS, dosing schedule; ICT, intracranial intratumoral; ICV, intraventricular.

Key Eligibility Criteria

Inclusion Criteria

- Age ≥18 years, Karnofsky performance status (PS) ≥60%, and Eastern Cooperative Oncology Group PS ≤2
- Histopathological verification of World Health Organization (WHO) grade IV GBM or prior histologically confirmed diagnosis of a grade II or III glioma and now with radiographic progression consistent with a grade IV GBM
- Relapsed disease: radiographic evidence of recurrence/progression of measurable disease after standard therapy and ≥12 weeks from completion of front-line radiation therapy
- Documented expression (≥20%) of CLTX-targeted antigen MMP2 (moderate and/or high expression [2+/3+]) by immunohistochemistry (IHC) at the initial tumor presentation or recurrent disease

Exclusion Criteria

- Previous bevacizumab therapy
- Inadequate organ function
- Concurrent illness, malignancy, or comorbid conditions

Endpoints and Assessments

- Primary endpoints: DLTs, cytokine release syndrome, and all other toxicities (assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5.0)
- Secondary endpoints: (i) CAR T-cell and endogenous T-cell levels (absolute number per μL by flow), phenotype, and cytokine levels in PB, TCF, and CSF; (ii) PFS, disease response by Response Assessment in Neuro-Oncology criteria with the need for bevacizumab as an additional indicator of progression, and survival time; (iii) detection of CAR T cells by IHC and CLTX antigen expression levels by pathology H-score in tumor tissue; and (iv) biomathematical modeling of tumor growth using perfusion and growth parameters based on serial brain magnetic resonance imaging

Statistical Analysis

- The expected sample size is 18, with 3 (max=6) patients in Arm 1 and 15 (max=24) patients in Arm 2, and approximately 6 for replacement of unevaluable patients.
- A sample size of 12 at the MTD is expected to achieve (i) a maximum margin of error of 0.25 for a 90% confidence interval (CI) for the DLT rate and (ii) the ability to detect a toxicity with a true rate of 0.20 in 93% of trials
- The RP2D will be determined based on the MTD, toxicities in later cycles, and the activity data. The toxicity equivalence range design of Blanchard and Longmate (2011)[10] will be used to determine the MTD
- Rate and associated Clopper-Pearson binomial 90% CI will be estimated for patients experiencing DLTs at the RP2D schedule
- Statistical and graphical methods will be used to describe the persistence and expansion of CAR T cells and cytokine levels in TCF, PB, and CSF
- Rates (90% CIs) of PFS at 6 months, OS at 9 months, and disease response will be evaluated in study patients who receive the full schedule of 3 doses of CLTX-CAR T cells
- CAR T-cell persistence and location and CLTX-targeted antigen levels in tumor tissue will be analyzed in patients who undergo an additional biopsy/resection or autopsy

Conclusions and Future Directions

- CLTX-CAR T-cell therapy is a novel immunotherapy that may extend the range of solid tumors targetable by CAR T cells and has the scope to deliver a broad immuno-oncology platform
- Results from this first-in-human phase 1 study are expected to demonstrate the safety and feasibility of dual delivery of CLTX-CAR T cells in patients with recurrent or progressive GBM
- This phase 1 study will also determine the MTD and an RP2D plan
- The study is actively enrolling; 4 patients have been dosed as of mid-April 2021

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Author contact: Christine Brown: cbrown@coh.org

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