Background Chimeric antigen receptor (CAR) T cell therapy is being explored in early-stage clinical trials as a strategy to improve treatment outcomes for high-grade gliomas (HGGs). We report here, a completed phase I trial (NCT02208362) evaluating locoregionally delivered IL13Rα2-targeted CAR T cells in 65 patients with recurrent HGG (rHGG), the majority being recurrent glioblastoma (rGBM).

Methods This five-arm trial evolved to evaluate three routes of locoregional CAR T cell administration: (i) intratumoral (ICT) following tumor biopsy (Arm 1) or resection (Arm 2); (ii) intraventricular (ICV; Arm 3); and (iii) dual ICT/ICV (Arm 4). The final treatment arm (Arm 5) evaluated dual ICT/ICV delivery with a modified manufacturing process. Primary objectives were feasibility and safety. Secondary objectives evaluated therapy-related cytokine dynamics by cytometric bead array, CAR T cell persistence by flow cytometry and PCR, and clinical outcomes by radiographic imaging and survival. The pretreatment tumor immune landscape was evaluated by immunohistochemistry.

Results Feasibility and safety were established for all three routes of locoregional CAR T cell delivery (ICT, ICV and dual ICT/ICV). IL13Rα2-CAR T cells were well-tolerated with clinically manageable adverse events at all dose levels, and no dose limiting toxicities observed. Stable disease or better was achieved in 50% of patients, with two partial responses, one complete response (CR), and a second CR after additional CAR T cycles off protocol therapy. Median overall survival (OS) for rGBM patients (68% treated at 2nd recurrence or later) was 7.7 mo. Post-hoc analysis revealed that Arm 5 rGBM patients exhibited the best median OS of 10.2 months, compared to 6.1 months for other treatment arms (Arms 1–4). Increase in inflammatory cytokines, including IFNγ, CXCL9, and CXCL10, was observed in the cerebrospinal (CSF) and tumor fluid after each infusion. Further, pretreatment intratumoral CD3 T cell levels were positively associated with survival.

Conclusions We report the largest CAR T cell clinical trial in brain tumors to date, assessing the feasibility, safety, and bioactivity of IL13Rα2-CAR T cells in rHGG. Key findings include: (1) repetitive locoregional administration of IL13Rα2-CAR T cells is feasible and safe, with clinical benefit observed in a subset of patients; (2) elevations in IFNγ-related chemokines in the CSF was associated with CAR T cell administration and bioactivity; and (3) tumor immune contexture was identified as a determinant of patient outcome to CAR T cell therapy. These findings advance our understanding of CAR T cell immunotherapy for malignant brain tumors.

Ethics Approval This study was conducted in accordance with the Institutional Review Board and Independent Ethics Committee at The City of Hope National Medical Center as well as the U.S. Food and Drug Administration (FDA). All subjects provided written informed consent.