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Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results

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Abstract

Recurrent glioblastoma (rGBM) remains a major unmet medical need, with a median overall survival of less than 1 year. Here we report the first six patients with rGBM treated in a phase 1 trial of intrathecally delivered bivalent chimeric antigen receptor (CAR) T cells targeting epidermal growth factor receptor (EGFR) and interleukin-13 receptor alpha 2 (IL13Rα2). The study's primary endpoints were safety and determination of the maximum tolerated dose. Secondary endpoints reported in this interim analysis include the frequency of manufacturing failures and objective radiographic response (ORR) according to modified Response Assessment in Neuro-Oncology criteria. All six patients had progressive, multifocal disease at the time of treatment. In both dose level 1 (1×10^7 cells; n = 3) and dose level 2 (2.5×10^7 cells; n = 3), administration of CART-EGFR-IL13Rα2 cells was associated with early-onset neurotoxicity, most consistent with immune effector cell-associated neurotoxicity syndrome (ICANS), and managed with high-dose dexamethasone and anakinra (anti-IL1R). One patient in dose level 2 experienced a dose-limiting toxicity (grade 3 anorexia, generalized muscle weakness and fatigue). Reductions in enhancement and tumor size at early magnetic resonance imaging timepoints were observed in all six patients; however, none met criteria for ORR. In exploratory endpoint analyses, substantial CAR T cell abundance and cytokine release in the cerebrospinal fluid were detected in all six patients. Taken together, these first-in-human data demonstrate the preliminary safety and bioactivity of CART-EGFR-IL13Rα2 cells in rGBM. An encouraging early efficacy signal was also detected and requires confirmation with additional patients and longer follow-up time. ClinicalTrials.gov identifier: NCT05168423 .