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Intracranial delivery of B7-H3-targeting CAR-T cells for recurrent glioblastoma: a phase 1 trial

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Abstract

Recurrent glioblastoma (rGBM) is a leading brain malignancy with few therapeutic options. Here we present the complete results of a phase 1 trial investigating the safety and efficacy of autologous B7-H3-targeting chimeric antigen receptor T (CAR-T) cell (TX103) therapy for the treatment of rGBM. In this open-label, 3 + 3 dose-escalation trial, patients aged 18-75 years with B7-H3-positive (≥30%) rGBM received intracranial infusion of TX103 at three dose levels (DLs-2 × 10^7, 6 × 10^7 and 1.5 × 10^8 cells per infusion). Primary endpoints were safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D). Secondary endpoints included survival, pharmacokinetics and immunological response. Fifteen patients received a total of 72 intracranial infusions and 13 underwent repeated infusions. TX103 therapy was well tolerated, with no dose-limiting toxicities or MTD identified. Treatment-related adverse events (TRAEs) included low-grade cytokine release syndrome (86.7%), sinus tachycardia (53.3%), vomiting (53.3%), hypertension (53.3%) and elevated intracranial pressure (46.7%). Three grade 3 TRAEs considered serious adverse events occurred (elevated intracranial pressure, epilepsy and depressed consciousness), two at DL3. The 12-month overall survival (OS) rate was 66.7% and median OS was 19.1 months (95% confidence interval = 8.93, not reached) from first infusion. Disease control (stable disease or better) was achieved in 8 of 14 patients with measurable disease, including one complete response sustained through the latest follow-up. Cerebrospinal fluid showed a marked increase in CAR gene copy numbers and cytokine release, with minimal peripheral activity and no cumulative toxicity after repeated infusions. In conclusion, intracranial TX103 infusion demonstrated acceptable safety and encouraging efficacy in rGBM, supporting a future phase 2 evaluation at the RP2D (DL2, 6 × 10^7 cells per infusion). ClinicalTrials.gov registration: NCT05241392 .