Clinical Trial in Progress

1525 INITIAL CLINICAL EXPERIENCE WITH CHLOROTOXIN-REDIRECTED CAR T CELLS FOR PATIENTS WITH RECURRENT GliOBlastoma

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Background A major barrier to achieving effective therapies for patients with glioblastoma multiforme (GBM) is the phenotypic heterogeneity seen both between patients and within individual tumors, the later creating multiple subpopulations contributing to disease recurrence. One strategy for creating more efficacious therapies is to design novel immunotherapies targeting higher proportions of tumors and tumor cells than current options. Chlorotoxin (CLTX) is a 36-amino acid peptide component of scorpion venom that selectively binds to glioma cells of all malignancy grades while sparing normal brain cells and non-malignant tissues. With this understanding, we developed chimeric antigen receptor (CAR) T cells incorporating the CLTX peptide as a tumor-recognition ligand, thereby redirecting T cells to target GBM cells and tumors. Preclinical studies suggested broad yet specific CLTX binding to patient-derived GBM cells. Preclinical data also suggested a role for cell surface matrix metalloproteinase-2 (MMP-2) in CLTX-CAR T cell activation.

Methods We designed a non-randomized and dose escalating phase 1 trial evaluating intracavitary/intratumoral (ICT) delivery of CLTX-CAR T cells to patients with recurrent/progressing GBM (NCT04214392; approved by the City of Hope National Medical Center protocol review committee, written consent obtained for leukapheresis and treatment), with the primary objectives of feasibility and safety.

Results Here we report clinical outcomes and correlative observations for four lead-in research participants, all of whom had a histopathological diagnosis of glioblastoma, idh wild type, grade 4, and who had received prior temozolomide as well as radiation and other treatments. The key enrollment criterion was MMP-2 expression in tissue biopsies at levels greater than 20% (moderate and/or high expression) as assessed by immunohistochemistry. Participants received three infusions of 4, 20, and 20 x 10^6 CLTX-CAR T cells at weekly intervals. There were no CRS events or DLTs observed. Three of the four participants (75%) achieved stable disease. Participants survived a median of 5.75 months (min = 2.4, max = 20.5) after CAR T cell infusion. The presence of CLTX-CAR T cells in tumor fluid collected before and one day after each infusion indicated persistence of CLTX-CAR T cells. IgG1 was absent in these samples, suggesting non-immunogenicity of the exogenous CLTX peptide.

Conclusions Phase 1 clinical observations to date confirm the feasibility and safety of CLTX-CAR T cell immunotherapy for patients with GBM. These studies will lead to determination of a maximum tolerated dose/maximum feasible dose.

REFERENCES