CHARACTERIZATION OF CT-0508, AN ANTI-HER2 CHIMERIC ANTIGEN RECEPTOR MACROPHAGE (CAR-M), MANUFACTURED FROM PATIENTS ENROLLED IN THE PHASE 1, FIRST IN HUMAN, CLINICAL TRIAL OF CT-0508

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Background

Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies but have had less success in those with solid tumors. Macrophages are actively recruited and abundantly present in the solid tumor microenvironment (sTME). Tumor associated macrophages are predominantly immunosuppressive and support tumor growth (M2), while a subset of proinflammatory macrophages enhance anti-tumor immunogenicity (M1). M1 macrophage function can be augmented by CAR expression to selectively recognize and phagocytose antigen overexpressing cancer cells. Moreover, CAR macrophages can reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immune memory. Human Epidermal Growth Factor Receptor 2 (HER2) overexpression promotes tumorigenesis in many solid tumors. CT-0508 is a cell product comprised of autologous monocyte-derived proinflammatory macrophages expressing an anti-HER2 CAR and is being investigated in a currently ongoing first in human clinical trial (NCT04660929).

Methods

Using the chimeric adenoviral vector Ad5f35, we manufactured CT-0508 product from apheresis material collected from patients enrolled in group 1 of the CT-0508 phase 1 clinical trial. To assess the activity of pre-infusion CT-0508 products, in vitro cell based assays were utilized including killing, phagocytosis, cytokine secretion, and transcriptomics analysis. Donor-matched untransduced (UTD) macrophages served as controls. Additionally, healthy donor derived products were used in some experiments.

Results

CT-0508 was successfully manufactured with high viability, purity and CAR expression for patients enrolled in group 1. CT-0508 products demonstrated enhanced killing and phagocytosis of HER2-expressing tumor cells over autologous UTD macrophages. CITE-Seq analysis of CT-0508 confirmed an M1 macrophage transcriptional signature compared with pre-manufacturing monocyte and apheresis populations. Using healthy donor derived CT-0508 products, cell product activation was demonstrated by ex vivo CAR engagement and led to an increase in secreted immunostimulatory cytokines and chemokines, consistent with pro-inflammatory macrophage activation including TNF, IL-6, MIP-1α, and MIP-1β. Secreted factor analysis also showed HER2 responsive changes in extracellular matrix remodeling factors and growth factors. Additionally, transcriptomic and proteomic analysis revealed that CAR engagement further enhanced CAR-M M1 polarization. CAR engagement mediated effects are also being investigated in patient derived products.

Conclusions

Together, these results demonstrate that functional CT-0508 CAR-M were successfully manufactured with an M1 phenotype and that CAR-antigen interaction drives cell product activation and amplifies the M1 polarization status of CT-0508 CAR-M.