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A PHASE 1, FIRST IN HUMAN (FIH) STUDY OF AUTOLOGOUS MACROPHAGES CONTAINING AN ANTI-HER2 CHIMERIC ANTIGEN RECEPTOR (CAR) IN PARTICIPANTS WITH HER2 OVEREXPRESSING SOLID TUMORS

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Background Macrophages are phenotypically plastic cells that are abundant in the solid tumor microenvironment (sTME) and can promote tumor growth (M2) or enhance anti-tumor immunity (M1). Macrophage function can be redirected by CAR expression to selectively target and phagocytose antigen overexpressing cancer cells. CAR macrophages can reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immune memory.¹ HER2 overexpression promotes tumorigenesis in many solid tumors (table 1). CT-0508 is comprised of autologous monocyte-derived proinflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies showed that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden, prolonged survival, and was safe and effective in humanized xenograft mouse models of human HER2 overexpressing ovarian cancer. In immunocompetent mouse models of HER2 overexpressing solid tumors, syngeneic anti-HER2 CAR-M mediated tumor control and improved overall survival as compared to untreated or control untransduced macrophage (UTD) treated mice. Notably, anti-HER2 CAR-M treatment led to significant activation of the sTME, with notable infiltration of CD8+ and CD4+ T cells, NK cells, dendritic cells, and an increase in activated CD8+ tumor infiltrating lymphocytes. Anti-HER2 CAR-M were evaluated in a PD1 blockade resistant syngeneic model – mice that received both therapies had improved tumor control, overall survival, and TME activation as compared to either treatment alone, indicating synergy and the capacity for CAR-M to sensitive solid tumors to checkpoint blockade.

Methods This Phase 1, FIH study is evaluating safety, tolerability, cell manufacturing feasibility, trafficking, TME activation, and preliminary evidence of efficacy of investigational product CT-0508 in 18 participants with locally advanced (unresectable)/metastatic solid tumors overexpressing HER2. Pts previously treated with anti-HER2 therapies are eligible. Filgrastim mobilizes autologous hematopoietic progenitor cells for monocyte collection by apheresis. CT-0508 is manufactured, prepared, and cryopreserved from mobilized peripheral blood monocytes. Group 1 participants (n = 9; enrollment complete) received CT-0508 infusion split over Days 1, 3, and 5. Group 2 participants (n = 9) will receive CT-0508 single infusion on D1. Additional study cohorts include: CT-0508 co-administered with pembrolizumab and CT-0508 monotherapy administered intraperitoneally in participants with peritoneal predominant disease. Correlative assessments include pre- and post-treatment biopsies and blood samples for safety (immunogenicity), trafficking (PCR, RNA scope), CT-0508 persistence in blood and tumor, target antigen engagement, TME modulation (single cell RNA sequencing), immune response (TCR sequencing) and others.

Trial Registration NCT04660929

REFERENCE

1. Klichinsky M, Ruella M, Shestova O. *et al.* Human chimeric antigen receptor macrophages for cancer immunotherapy. *Nat Biotechnol.* 2020;**38**:947–953.

Ethics Approval This study has been approved by each participating site: University of Pennsylvania Abramson Cancer Center IRB approval #844106, University of North Carolina Lineberger Cancer Center IRB approval #20201732, City of Hope Cancer Center IRB approval #20201732, The University of Texas MD Anderson Cancer Center IRB approval #2021-0327, Sarah Cannon Research Institute IRB #20201732. All participants gave their informed consent before taking part in the study.

Abstract 633 Table 1: HER2 Overexpression Across Tumor Types

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Tumor	HER2 Overexpression (%)
Bladder	8 - 70
Salivary duct / mucoepidermoid	30 – 40 / 17.6
Gastric	7 - 34
Ovarian / Cervical / Uterine	26 / 2.8 – 3.9 / 3
Breast	11 - 25
Esophageal	12 - 14
Gallbladder / Cholangiocarcinoma	9.8 – 12.8 / 6.3 - 9
Colorectal	1.6 - 5
Testicular	2.4

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