A Phase 1, First-in-Human (FIH) study of autologous macrophages engineered to express an anti-HER2 chimeric antigen receptor (CAR) in participants (pts) with HER2 overexpressing solid tumors.

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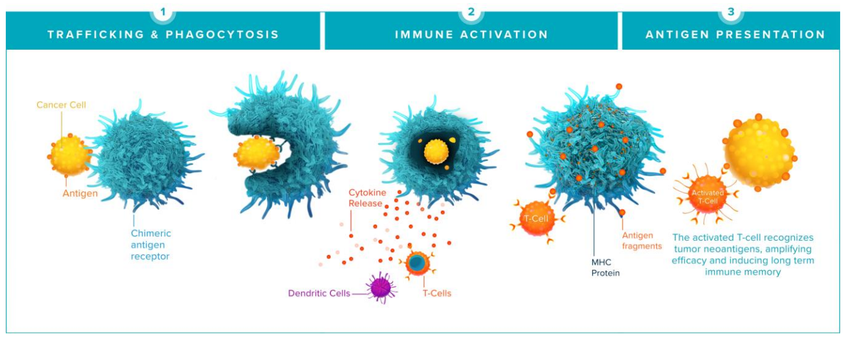
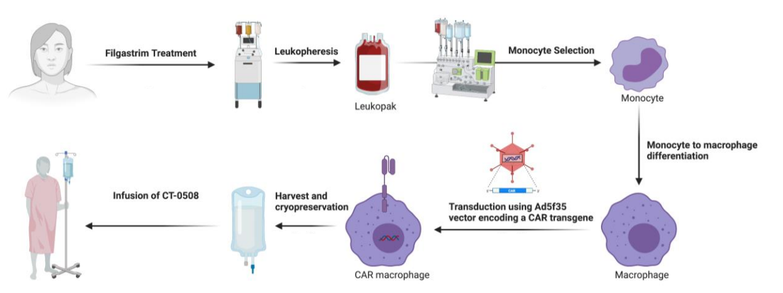
Introduction

- Macrophages 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 using CAR technology to selectively target and phagocytose antigen overexpressing cancer cells.
- 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.
- Notably, anti-HER2 CAR-M treatment led to activation of the sTME, with infiltration of CD8+ and CD4+ T cells, NK cells, dendritic cells, and increased activated CD8+ tumor infiltrating lymphocytes. This demonstrates the potential to lead to epitope spreading and anti-tumor immunity.
- In a pre-clinical model of anti-PD1 resistant solid tumors, mice that received anti-HER2 CAR-M and anti-PD1 mAb demonstrated improved tumor control, overall survival, and TME activation when compared to either treatment alone, indicating synergy and capacity for CAR-M to sensitize solid tumors to checkpoint blockade.
- This Phase 1, FIH study is evaluating safety, tolerability, cell manufacturing feasibility, trafficking, TME activation, and preliminary evidence of efficacy of CT-0508 in patients with locally advanced (unresectable) / metastatic solid tumors overexpressing HER2. Additionally, based on the encouraging pre-clinical data, a Phase 1b sub-study examining co-administration of CT-0508 with pembrolizumab is ongoing.

CT-0508 Mechanism of Action

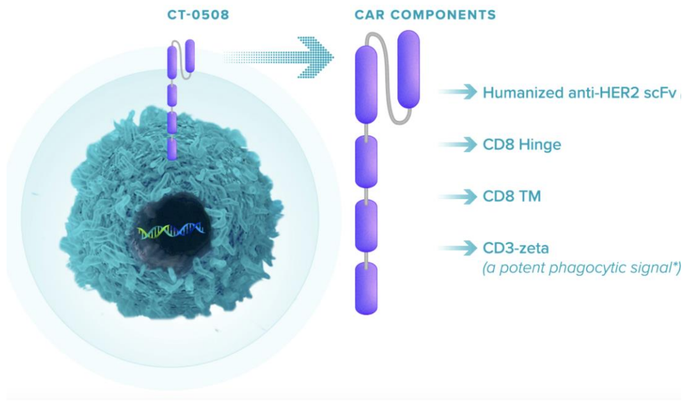


CT-0508 Manufacturing Process



CT-0508 HER2 targeted CAR-M

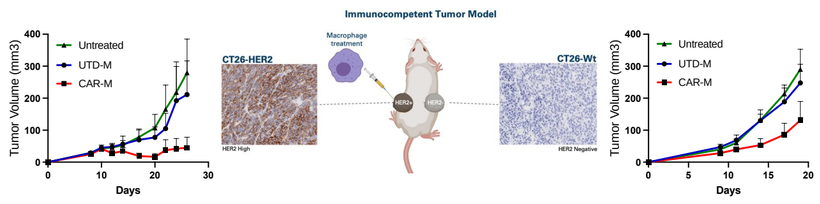
CT-0508 is comprised of autologous monocyte-derived proinflammatory macrophages engineered using a chimeric adenoviral vector Ad5f35 that delivers a first generation anti-HER2 CAR and simultaneously induces an M1 phenotype.



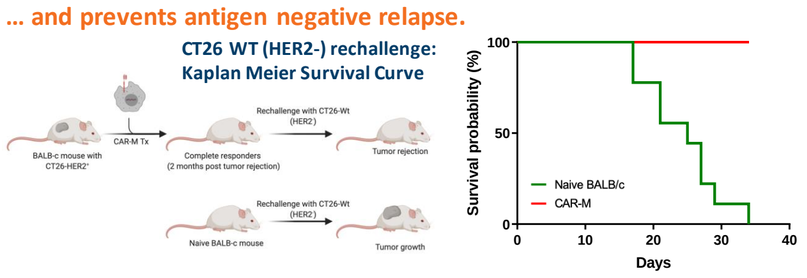
www.HER2MacrophageTrial.com

CT-0508 Demonstrates Anti-Tumor Activity in Preclinical Model as Monotherapy and Synergizes With Checkpoint Blockade Inhibitors

CT-0508 leads to epitope spreading *in vivo*…

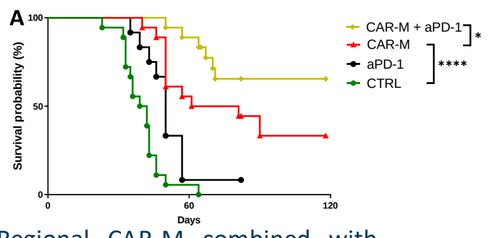


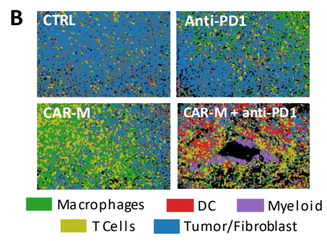
… and prevents antigen negative relapse.



CT-0508 sensitizes anti-PD1 resistant tumors to checkpoint blockade.

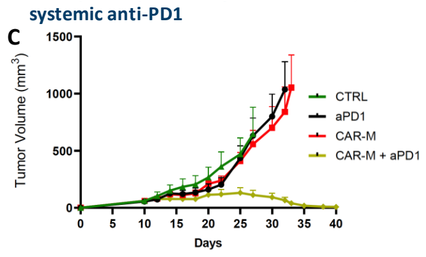
CT26 (HER2+) model: Intratumoral CAR-M / systemic anti-PD1





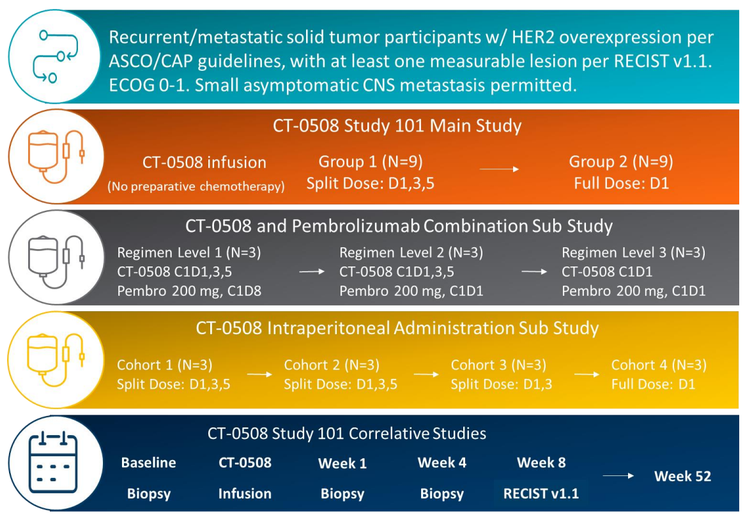
Regional CAR-M combined with an anti-PD1 inhibitor leads to improved tumor growth control (A) and enhanced TME modulation (B). In addition, systemic CAR-M / anti-PD1 mAb combination leads to significant tumor control (C).

CT26 (HER2+) model: systemic CAR-M / systemic anti-PD1



CT-0508 Clinical Trial Design (NCT04660929)

This is an ongoing open label, first-in-human Phase 1 study to evaluate the safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of the investigational cell product CT-0508 in participants with advanced solid tumors overexpressing HER2.



Filgrastim (G-CSF), is being used to mobilize autologous monocytes into the peripheral blood for collection by apheresis. There is no preparative chemotherapy prior to the cell product infusion. The CT-0508 cell product is then prepared, cryopreserved and released. Approximately 9 participants in Group 2 will receive up to 5×10^9 of total manufactured CT-0508 cells on Day 1. Please see the treatment schedules for CT-0508 given in combination with pembrolizumab, and CT-0508 administered via intraperitoneal administration. AE reporting begins at the start of mobilization and continues until any toxicities resolve or are deemed irreversible. Participants are continually reassessed for evidence of acute and/or cumulative toxicity.

Study Objectives

Primary

- Assess the safety and tolerability of CT-0508 in participants with HER2 overexpressing solid tumors.
- Assess the feasibility of manufacturing CT-0508.

Secondary

- Characterize the in vivo cellular kinetics profile (levels, persistence, trafficking) of CT-0508 transgene into peripheral blood and target tissues.
- Estimate the objective response rate (ORR), according to RECIST v1.1, of at least 1 dose of CT-0508 among participants with HER2 overexpressing solid tumors.
- Estimate overall survival (OS).
- Estimate progression-free survival (PFS).
- Estimate duration of response (DOR).
- Estimate rates of 6-month and 12-month survival.

Tertiary/Exploratory

- Estimate iORR, iPFS, and iDOR.

Main Inclusion Criteria

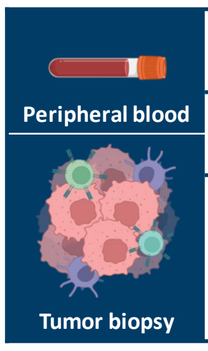
- Participants with HER2-positive tumors after most recent therapy, by immunohistochemistry (IHC) using standard local assay resulting 3+, or 2+ with confirmation by in Situ Hybridization (ISH).
  - IHC, ISH assays and interpretation must follow the most recent ASCO/CAP guidelines and performed in an accredited laboratory. Other tumor types (non-breast, non-gastroesophageal) will be tested according to the breast cancer ASCO/CAP guidelines
- Female or male, at least 18 years of age
- Recurrent or metastatic solid tumor for which there are no available curative treatment options, AND after failure of, or ineligibility to receive the approved HER2 targeted agents, when available
- Willingness to undergo serial biopsies
- At least one measurable lesion per RECIST v1.1 criteria
- ECOG 0-1
- No concurrent infections or use of chronic steroids
- Good organ function

Safety Observations and Assessments

- Adverse events of special interest have been selected according to experience from other cell therapies and HER2 targeted agents and will be closely monitored. They include fever, cytokine release syndrome, hypersensitivity reactions, cardiovascular toxicity, ICANS and others. Cytokine release syndrome will be graded and treated following ASTCT Guidelines.
- Dose limiting toxicities will be observed for a period of 4 weeks and reviewed by an independent Safety Review Committee.

Correlative Studies

- Peripheral blood: Samples are collected over a period of 52 weeks for biomarker evaluation.
- Tumor Biopsy: Participants enrolled in Study 101 undergo one pre-treatment and 2 on-treatment biopsies (7 days and 4 weeks post infusion).



Safety Correlates	• Serum cytokines • Immunogenicity
Cellular Kinetics	• Blood persistence • Trafficking
Mechanism of action	• Target engagement • TME activation • Immune cell recruitment • Adaptive immune response

Current Status

7 clinical sites are currently enrolling participants in the USA:

- University of Pennsylvania, Philadelphia, PA
- University of North Carolina, Chapel Hill, NC
- City of Hope, Duarte, CA
- MD Anderson Cancer Center, Houston, TX
- Sarah Cannon Research Institute, Nashville, TN
- Fred Hutchinson Cancer Center
- OHSU Knight Cancer Center

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