A Phase 1, First in Human Study of Adenovirally Transduced Autologous Macrophages Engineered to Contain an Anti-HER2 Chimeric Antigen Receptor (CAR) in Subjects with HER2 Overexpressing Solid Tumors

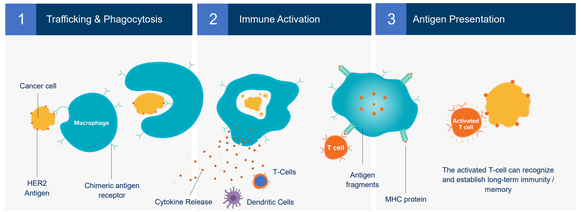
Kim A. Reiss[1], Debora Barton[2], Amy Ronczka[2], Daniel Cushing[2], Michael Klichinsky[2], Elizabeth Claire Dees[3]

[1]University of Pennsylvania, Philadelphia, PA, [2]Carisma Therapeutics, Philadelphia, PA, [3]University of North Carolina, Chapel Hill, NC.

INTRODUCTION

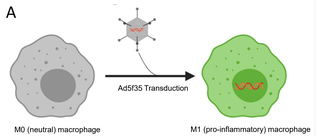
- CAR-T cell therapies have shown success in numerous hematologic malignancies, solid tumors remain a major challenge in the field.
- Macrophages are actively recruited into solid tumors and are abundant in the solid tumor microenvironment (sTME), and typically evince immunosuppressive behavior. Macrophages are capable of direct anti-tumor activity and antigen presentation to T cells.
- Autologous, nonengineered macrophages, as well as monocyte-derived autologous cells have been adoptively transferred into cancer patients in the last few decades. Up to 16.9 × 10^9 cells (cumulative dose) were injected by a variety of routes including intravenous, were well tolerated, and trafficked to tumors. Non-engineered macrophages did not achieve meaningful efficacy, as these cells did not have the ability to recognize and attack tumor cells and were not phenotypically locked into the pro-inflammatory M1 phenotype.
- To address these shortcomings, we have developed CAR macrophages (CAR-M) and demonstrated that these engineered myeloid cells traffic to tumors, reduce tumor burden, reprogram the TME, and induce a broad anti-tumor adaptive immune response in pre-clinical models of HER2 overexpressing solid tumors.
- CT-0508 is a cell product comprised of autologous peripheral blood monocyte-derived macrophages, which are transduced with an adenoviral vector containing an anti-HER2 chimeric antigen receptor (CAR) and locked into an M1 phenotype.

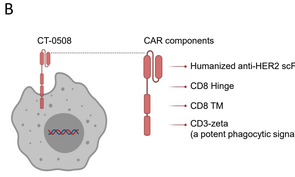
CT-0508 Mechanism of Action:

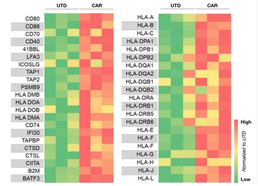


CT-0508 is an M1-polarized anti-HER2 CAR-M

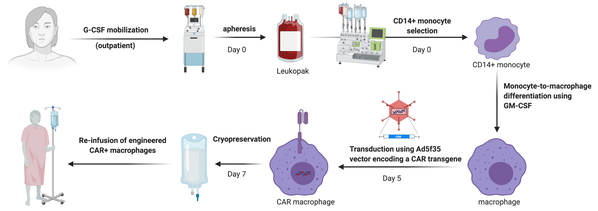
The chimeric adenoviral vector Ad5f35 is a pro-inflammatory, high-efficiency vector (A), that delivers the CAR (B) and simultaneously induces an M1 phenotype (C).







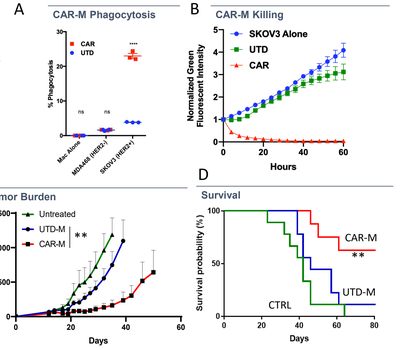
Manufacturing Process



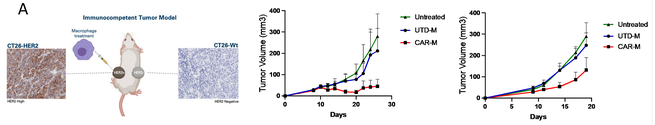
CT-0508 is effective in pre-clinical models

Insertion of a CAR confers on the macrophages the ability to selectively recognize, phagocytose (A) and kill HER2 overexpressing SKOV3 cancer cells, leading to targeted tumor cell eradication (B) and cytokine production (not shown).

In a CT26-HER2 immunocompetent mouse model, CAR-M control tumor growth (C) and improve overall survival (D).

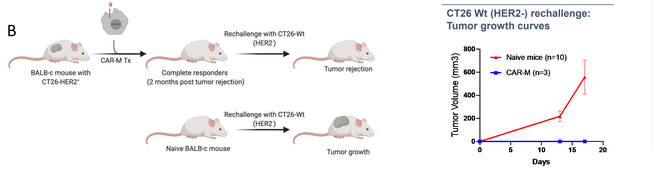


CT-0508 lead to epitope spreading in vivo and prevents antigen negative relapse



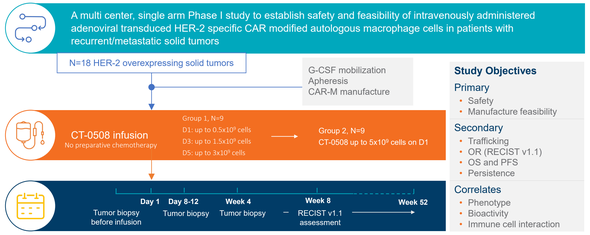
Abscopal effect is observed on HER2 negative tumor after intratumoral injection on HER2 positive tumor (A).

CAR-M epitope spread led to rejection of antigen negative tumor rechallenge (B).



CT-0508 Clinical Trial Design

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 18 subjects with advanced solid tumors overexpressing HER2.



- Filgrastim (G-CSF), is being used to mobilize autologous monocytes into the peripheral blood for collection by apheresis.
- The CT-0508 cell product is then prepared, cryopreserved and released.
- The first 3 subjects in the study will be hospitalized for 8 days after the first infusion of CT-0508 (Day 1 to Day 8). There is no preparative chemotherapy prior to the cell product infusion.
- The first 9 subjects (Group 1) will be treated at least two weeks apart, with an intra subject dose escalation:
  - up to 0.5×10^9 cells on Day 1,
  - up to 1.5 × 10^9 cells on Day 3, and
  - up to 3.0 × 10^9 cells on Day 5.
- AE reporting begins at the start of mobilization and continues until any toxicities resolve or are deemed irreversible. Subjects are continually reassessed for evidence of acute and/or cumulative toxicity.
- Approximately 9 subjects in Group 2 will receive:
  - up to 5 × 10^9 of total manufactured CT-0508 cells on Day 1.

Objectives

Primary

- Assess the safety and tolerability of CT-0508 in subjects 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 subjects 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

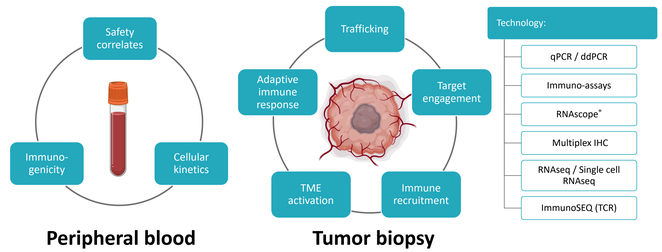
- Subjects with HER2-positive tumors after most recent therapy, by immunohistochemistry (IHC) using standard local assay resulting 3+, or 2+ with confirmation by in Situ Hybridization (ISH).
  - IHC and ISH assays and interpretation must follow the most recent ASCO/CAP guidelines and performed in an 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 criteria
- ECOG 0-1
- No concurrent infections or use of chronic steroids
- Good organ function

Safety Observations and Assessments

- As this is the first in human clinical trial of CT-0508, there are currently no identified risks related to the product.
- Adverse events of special interest have been selected according to other cell therapies and HER2 targeted agent experience 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 addressed by an independent Safety Review Committee.

Correlative Plan

- Tumor tissue samples: subjects enrolled in Study 101 undergo one pre-treatment and 2 on-treatment biopsies to assess trafficking, target antigen engagement, TME reprogramming, epitope spreading, and other PK/PD assessments.
- Blood samples: collected over a period of 52 weeks for biomarker evaluation.



Current Status

- 3 clinical sites are currently enrolling patients in the United States of America:
  - University of Pennsylvania, Philadelphia
  - University of North Carolina at Chapel Hill
  - City of Hope, California

1. *Klichinsky M, Ruella M, Shestova O, et al. Human chimeric antigen receptor macrophages for cancer immunotherapy. Nat Biotechnol. 2020;38(8):947-953.*

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