A Phase 1, First-in-Human (FIH) Study of Autologous Anti-HER2 Containing an Anti-HER2 Chimeric Antigen Receptor Macrophage (CAR-M) in Participants (pt) with HER2 Overexpressing Solid Tumors

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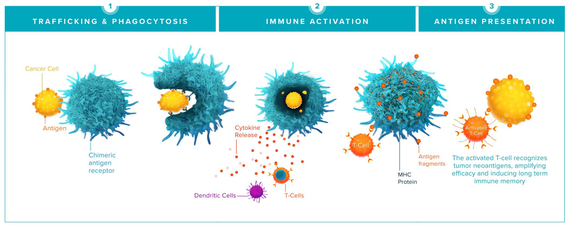
Introduction

Macrophages are abundant in the solid tumor microenvironment (sTME) and can exhibit both pro- and anti-tumor functions. Macrophages can be redirected by CAR expression to phagocytose cancer cells in an antigen-specific manner. CAR-M can reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immune immunity.

CT-0508 is comprised of autologous monocyte-derived pro-inflammatory 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. Notably, anti-HER2 CAR-M treatment led to activation of the sTME with infiltration of CD8+ and CD4+ T cells, and increased activation of CD8+ tumor infiltrating lymphocytes. In a pre-clinical model of an advanced solid tumor resistant to PD1 blockade, mice treated with anti-HER2 CAR-M combined with a PD1 blocking antibody demonstrated improved tumor control, overall survival, and TME activation compared to either treatment alone, indicating CT-0508 may be synergistic with PD1 blocking immune checkpoint inhibition.

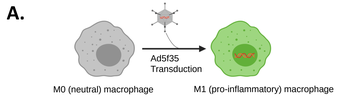
The FIH Phase 1 study is evaluating safety, tolerability, cell manufacturing feasibility, trafficking and preliminary evidence of efficacy of investigational product CT-0508 in 18 pts with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2 with progression on available therapies, including anti-HER2 therapies when indicated. Based on the encouraging pre-clinical data, additional sub-studies including a Phase 1b cohort investing the co-administration of CT-0508 with pembrolizumab are being investigated.

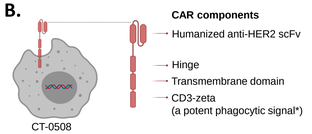
CT-0508 Mechanism of Action

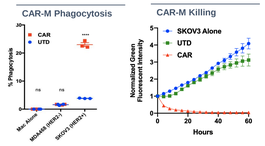


CT-0508 is an M1-Polarized Anti-HER2 CAR-M

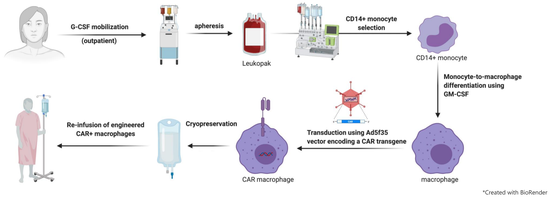
The chimeric adenoviral vector Ad5f35 is a pro-inflammatory, high-efficiency vector (A), that delivers the CAR (B) and enables targeted phagocytosis and killing (C).



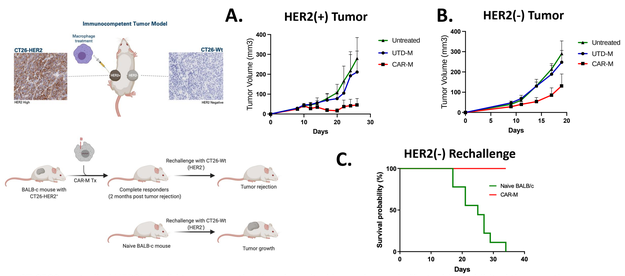




Manufacturing Process

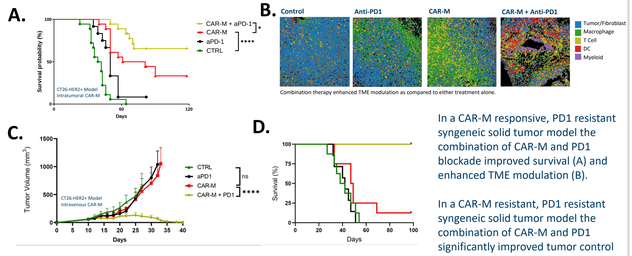


Epitope Spreading Prevents Antigen Negative Relapse



CT-0508 controlled HER2(+) solid tumor growth (A) and resulted in an abscopal effect which inhibited the growth of a HER2(-) tumor on the contralateral flank (B). Mice the achieved a complete response to CT-0508 rejected antigen negative recurrence in an immunocompetent HER2(-) tumor rechallenge model (C).

CT-0508 Enhances Response to Anti-PD1 Therapy



In a CAR-M responsive, PD1 resistant syngeneic solid tumor model the combination of CAR-M and PD1 blockade improved survival (A) and enhanced TME modulation (B).

In a CAR-M resistant, PD1 resistant syngeneic solid tumor model the combination of CAR-M and PD1 significantly improved tumor control (C) and overall survival (D).

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 18 participants with advanced solid tumors overexpressing HER2.

N=18 Recurrent/metastatic solid tumor participants w/ HER2 overexpression per ASCO/CAP guidelines, with at least one measurable lesion per RECIST v1.1. ECOG 0-1. Small asymptomatic CNS metastasis permitted.

CT-0508 infusion (No preparative chemotherapy) — Group 1 (N=9) Split Dose: D1,3,5 → Group 2 (N=9) Full Dose: D1

CT-0508 Sub Study: CT-0508 and Pembrolizumab Combination
Regimen Level 1 (N=3): CT-0508 C1D1,3,5 Pembro 200 mg, C1D8 → Regimen Level 2 (N=3): CT-0508 C1D1,3,5 Pembro 200 mg, C1D1 → Regimen Level 1 (N=3): CT-0508 C1D1 Pembro 200 mg, C1D1

CT-0508 Sub Study: CT-0508 Intraperitoneal Administration
Cohort 1 (N=3) Split Dose: D1,3,5 | Cohort 2 (N=3) Split Dose: D1,3,5 | Cohort 3 (N=3) Split Dose: D1,3 | Cohort 4 (N=3) Full Dose: D1

BASELINE BIOPSY | CT-0508 INFUSION | Week 1 BIOPSY | Week 4 BIOPSY | Week 8 RECIST v1.1 → Week 52

G-CSF mobilization and apheresis; CT-0508 manufacture, bridging therapy; Baseline staging

Primary Objectives
- Safety
- Manufacture feasibility

Secondary
- Cell kinetics
- OR (RECIST 1.1)
- OS and PFS

Mechanism of Action
- CT-0508 Phenotype
- TME Remodeling
- Epitope Spreading

- 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.

Objectives

Primary

- Assess the safety and tolerability of CT-0508 in participants with HER2 overexpressing solid tumors.
- Assess the safety and tolerability of CT-0508 in combination with pembrolizumab 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 (and pembrolizumab as appropriate) 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.
- In participants who undergo IP administration, estimate the Clinical Benefit Rate at week 13.

Main Eligibility Criteria

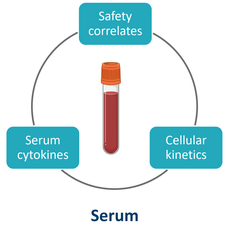
- Participants with HER2-positive tumors after most recent therapy, by immunohistochemistry (IHC) using standard local assay resulting 3+, or 2+ with confirmation by In Situ Hybridization (ISH)
  - IHC and ISH assays and interpretation must follow the most recent ASCO/CAP guidelines and performed in 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
- Satisfactory organ function

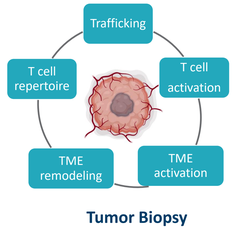
Safety Observations and Assessments

- 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 reviewed by an independent Safety Review Committee.

Correlative Plan

- Tumor tissue samples: participants 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.





Acknowledgements

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

www.HER2MacrophageTrial.com