A Phase 1, First-In-Human (FIH) Study of the Anti-HER2 CAR Macrophage CT-0508 in Participants with HER2 Overexpressing Solid Tumors

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Introduction

- Myeloid cells are abundant in the solid tumor microenvironment (TME), and macrophage-based cancer immunotherapy represents a promising therapeutic approach.
- Pre-clinical studies have shown that chimeric antigen receptor macrophages (CAR-M) infiltrate tumors, phagocytose tumor cells, activate the tumor microenvironment (TME), recruit T cells, and present tumor antigens to T cells leading to epitope spreading and robust anti-tumor immunity.[1,2]
- CT-0508 is a first in class CAR-M, comprised of autologous monocyte derived macrophages expressing an anti-HER2 CAR.
- Here we present preliminary clinical results from the CT-0508 Phase 1 FIH study in participants (pts) with HER2 overexpressing solid tumors.

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

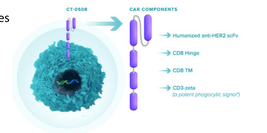
Cells: Autologous monocyte derived macrophages

Vector: Ad5f35

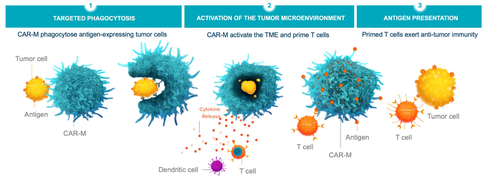
Phenotype: M1-polarized

Target: HER2

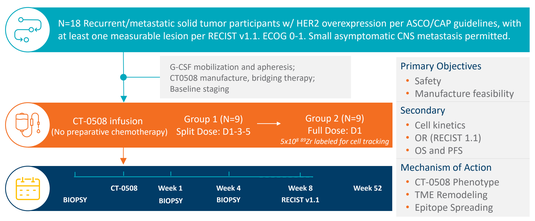
FDA Fast Track Designation Granted Sept 2021



CT-0508 Mechanism of Action



Phase 1 Clinical Trial Design



CT-0508 Manufacturing Process Overview

Source: Autologous mobilized peripheral blood

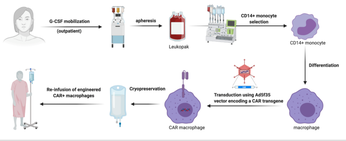
Manufacturing time: 1 week

Vein to vein: ~3 weeks

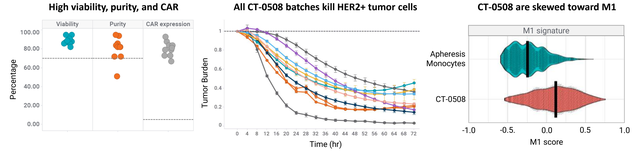
Vector: Ad5f35

Process: Automated

Fill format: Cryopreserved



CT-0508 Product Characterization and Function



CT-0508 was successfully manufactured from participant material with high viability, purity and CAR expression (left panel). Functionality was assessed as the ability to kill HER2 expressing tumor cell lines in vitro (middle panel – each line represents a manufactured product) and M1 polarization was demonstrated based on single cell RNAseq analysis (n=5).

Summary of Treated Participants

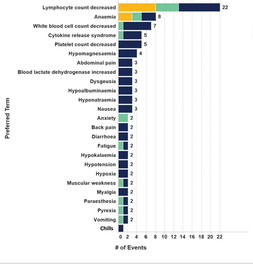
Summary of Participant and Tumor Characteristics			
Characteristic	**N = 7**	**Characteristic**	**N = 7**
Median age (range), years	64 (49, 73)	Tumor Type, n (%) Breast Cancer Esophageal Cancer Cholangiocarcinoma Ovarian Cancer Salivary Carcinoma	 2 (28.6) 2 (28.6) 1 (14.3) 1 (14.3) 1 (14.3)
Gender, n (%) Male	 3 (42.9)		
Race, n (%) White	 7 (100)	Median Number of Prior Cancer Therapies, n (range)	3 (2, 11)
ECOG PS, n (%) 0 1	 4 (57.1) 3 (42.9)	Median Number of Prior Anti-HER2 Therapies, n (range)	2 (0, 9)
HER2 Overexpression, n (%) IHC 3+ IHC2+/FISH+	 5 (71.4) 2 (28.6)	Prior Radiotherapy, n (%) Yes	 3 (42.9)

CT-0508 Is Well Tolerated With No Dose Limiting Toxicities

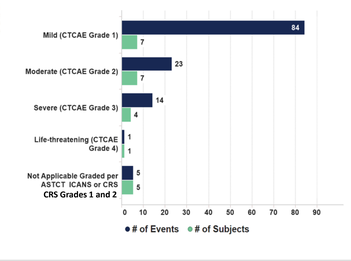
- 1 CRS Grade 2 on D3, characterized by fever and hypotension, resolved on D4 with acetaminophen, cefepime and fluids. All other CRS were Grade 1.
- No ICANS reported.
- 1 related SAE of CRS & Infusion Reaction; 2 SAEs not related: 1 upper GI hemorrhage related to PD, 1 worsening dyspnea related to PD.
- No AEs leading to CT-0508 dose modification or discontinuation.
- No major organ toxicity observed.
- Majority of AEs are Grades 1 and 2.

Overview of Treatment-Emergent Adverse Events (Safety Population)	
Category	**N = 7 (%)**
Treatment-emergent Adverse Event (TEAE)	7 (100.0)
TEAE, Related to CT-0508	6 (85.7)
TEAE, Serious AE	3 (42.9)
TEAE, Serious AE Related to CT-0508	1 (14.3)
TEAE, AEs of Special Interest CRS (cytokine release syndrome) - Pyrexia Infusion related reaction	5 (71.4) 1 (14.3) 1 (14.3)
Discontinued CT-0508 due to TEAE	0 (0.0)

Summary of AEs by Preferred Term



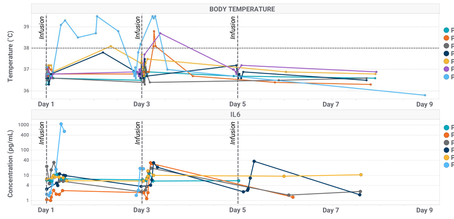
Summary of AEs by Severity



Preliminary Response:

Evaluated Participants	**N = 7**
Best Overall Response (RECIST 1.1)	Stable Disease: 4 (57.1%)

CT-0508 Leads to Transient Low-Grade Fever, Elevations of Pro-Inflammatory Cytokines in Peripheral Blood



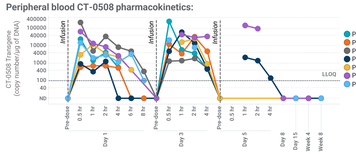
Transient and low-grade fever observed in 5 out of 7 patients post CT-0508 infusion. All fevers resolve within 48 hours.

In concordance with clinical observations, minor and transient increase in serum IL-6 observed.

Other pro-inflammatory serum cytokines (IL-8, IL1β, TNFα, IFNγ) present a similar profile (data not shown).

CT-0508 Rapidly Migrates Out of the Blood and is Detected Within the TME of All Participants Evaluated

Peripheral blood CT-0508 pharmacokinetics:



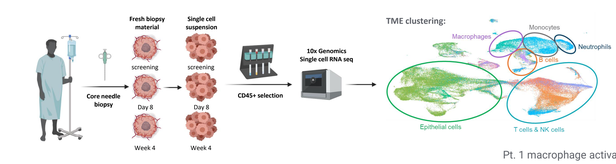
CT-0508 infiltration of the TME:

Pt	Screening	Day 8	Week 4
1	Not Detected	Detected	Detected
2	Not Detected	Detected	Detected
3	Not Detected	Detected	Not Detected
4	Not Detected	Not Detected	Detected
5	Not Detected	Detected	N/A
6	Not Detected	Detected	Not Detected

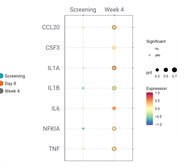
Similar kinetic profile is observed for all 7 participants with CT-0508 detectable only on infusion days for 4-8 hours post-infusion, consistent with rapid migration of CAR-M from the blood to tissues following infusion.

CT-0508 is detected within the TME of all 6 participants evaluated to date using RNAscope™ technology.

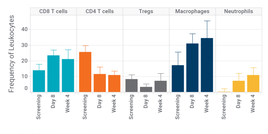
Single Cell RNAseq Analysis Demonstrates Remodeling of the Tumor Immune Landscape Following CT-0508 Infusion



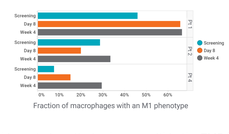
Pt. 1 macrophage activation:



Immune landscape:



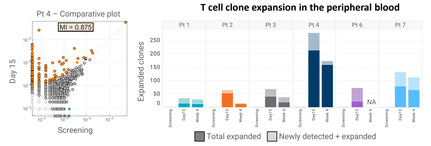
Increased fraction of M1 macrophages:



ScRNAseq analysis was performed on fresh tumor biopsy to investigate changes within the TME following CT-0508 infusion. Analysis of screening (n=5), Day 8 post-infusion (n=5) and week 4 post-infusion (n=3) biopsies reveals increases in CD8 T cells, macrophages and neutrophils on treatment consistent with inflammation and activation of an immune response.

These increases are also associated with reprogramming of the infiltrating macrophages toward an M1 phenotype by week 4.

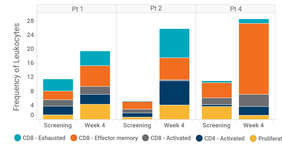
Early Expansion of T Cells in the Periphery Following CT-0508 Infusion



TCR repertoire analysis reveals an expansion of T cell clones in the blood of participants post CT-0508 infusion. These changes are indicative of initiation of an adaptive immune response. These expanded clones are significantly enriched for clones found in the TME (data not shown).

MI = Morisita Index.

CT-0508 Leads to Expansion and Activation of Effector T Cells Within the TME

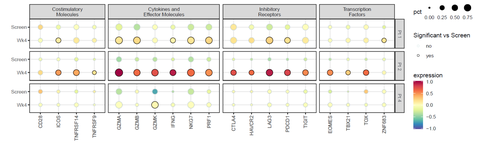


Frequency of effector T cells in TME:

Frequency of effector T cells increases in all 3 participants with available screening and week 4 biopsies (scRNAseq). Participant 1 demonstrates increase in proliferating and effector memory CD8 T cells. Participant 2 has increase of all subsets except activated CD8 T cells, and Participant 4 has increase in activated CD4, activated CD8 and effector memory CD8 T cells.

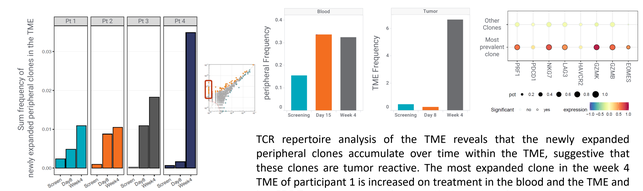
Selected gene expression in CD8 T cells:

Differential gene expression demonstrates increased expression of genes associated with T cell activation in the CD8 TILs for all 3 participants.



Peripherally Expanded T Cell Clones Accumulate in the TME and Adopt a Cytotoxic Phenotype

Most prevalent T cell clone in the week 4 TME of participant 1:



TCR repertoire analysis of the TME reveals that the newly expanded peripheral clones accumulate over time within the TME, suggestive that these clones are tumor reactive. The most expanded clone in the week 4 TME of participant 1 is increased on treatment in the blood and the TME and is a CD8 T cell clone presenting an activated cytotoxic phenotype.

Conclusions

Successful Manufacturing

CT-0508 was successfully manufactured from autologous mobilized monocytes

Participant product demonstrated high CAR expression, purity, viability, M1 polarization and confirmed functionality

Preliminary Clinical Profile

No dose limiting toxicities observed

No AEs leading to dose modification or discontinuation

No severe CRS, no ICANS, and no major organ system toxicity observed

Serum cytokine elevation was transient and self-limiting

Best Overall Response of Stable Disease (RECIST 1.1) achieved in 4 of 7 participants

Mechanism of Action

CT-0508 tumor infiltration detected in 6 of 7 evaluated participants (1 unevaluated)

Increased infiltration of CD8 T cells and M1 macrophages in TME post CT-0508

Significant expansion of novel T cell clones in the TME with concomitant CD8 T cell activation, suggesting induction of anti-tumor immunity

1. Klichinsky M, et al. Human chimeric antigen receptor macrophages for cancer immunotherapy. Nat Biotechnol. 2020;38(8):947-953.
2. Pierini S, et al. Chimeric Antigen Receptor Macrophages (CAR-M) Induce Anti-Tumor Immunity and Synergize With T Cell Checkpoint Inhibitors in Pre-Clinical Solid Tumor Models. AACR (2021) #63.

Acknowledgements

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