LBA (951): A Phase 1 first in human study of adenovirally transduced anti-HER2 CAR Macrophages in subjects with HER2 overexpressing solid tumors: preliminary safety, pharmacokinetics, and TME reprogramming data

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Introduction

- CAR-T cell therapies have shown success in numerous hematologic malignancies, but 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, and were well tolerated. 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 kill tumor cells through phagocytosis, 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 is an M1-Polarized Anti-HER2 CAR-M

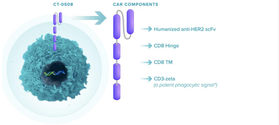
Cells: Autologous monocyte derived macrophages

Vector: Ad5f35

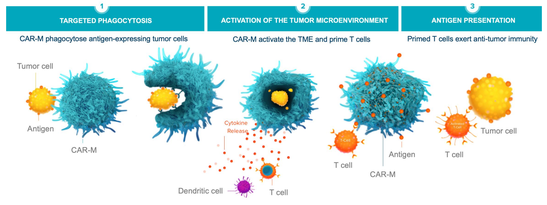
Phenotype: M1-polarized

Target: HER2

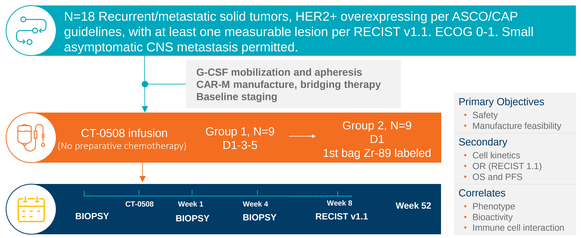
FDA Fast Track Designation Granted Sept 2021



CT-0508 Mechanism of Action



Phase 1 Clinical Trial Design



Primary Objectives
- Safety
- Manufacture feasibility

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

Correlates
- Phenotype
- Bioactivity
- Immune cell interaction

Manufacturing Process

Source: Autologous mobilized peripheral blood

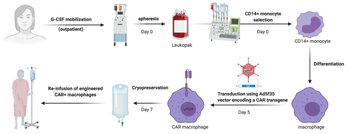
Manufacturing time: 1 week

Vein to vein: 3 weeks

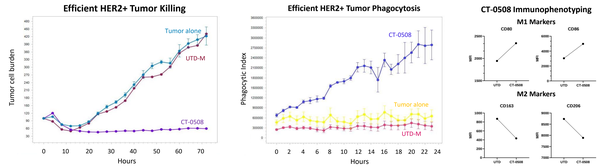
Vector: Ad5f35

Process: Automated

Fill format: Cryopreserved



CT-0508 demonstrates functionality and M1 polarization



CT-0508 was successfully manufactured from patient material with transduction efficiency of 86%. Viability and purity were both >90%. Patient matched untransduced macrophages (UTD-M) are used as controls.

Summary of Treated Subjects

Subject number	Subject 1	Subject 2
Demographics	Male, 72yo	Female, 68yo
Histology	Esophageal adenocarcinoma, poorly differentiated	Cholangiocarcinoma
Tumor status	Metastatic: lymph nodes, bone	Metastatic: lung and lymph nodes
Prior therapies	• FOLFOX + trastuzumab → trastuzumab maintenance • Palliative Radiation therapy • Pembrolizumab	• Surgery: partial Whipple • FOLFOX • FOLFIRI + trastuzumab
HER2	IHC 2+, ISH positive	IHC 3+
Dose Limiting Toxicities	None	None
Relevant AEs/SAEs	Tumor bleeding Grade 4*	Grade 2 CRS on D3 (resolved on D4)
Best Overall Response	Disease Progression	Stable Disease

* Not related to study drug, 88 days after last CT-0508 infusion

CT-0508 is well tolerated With No Dose Limiting Toxicities

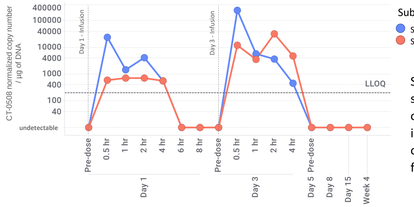
Table of all AEs with start date on or after the first dose of CT-0508:

AE Term	Grade*	DLT	SAE
Abdominal pain	1	No	No
Back pain	1	No	No
Concentration impairment	1	No	No
Cytokine release syndrome	2	No	No
Diarrhea	1	No	No
Dysgeusia	1	No	No
Hoarseness	1	No	No
Hypertension	1	No	No
Hypotension	1	No	No
Lymphocyte count decreased	3	No	No
Paresthesia	2	No	No
Platelet count decreased	1	No	No
Pruritis	1	No	No
Upper GI hemorrhage	4	No	Yes
Urinary retention	2	No	No
White blood cell count decreased	2	No	No
Worsening anemia	3	No	No
Worsening lymphocyte count decrease	3	No	No

* Worst Grade reported

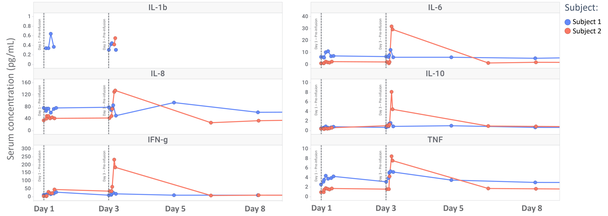
- Majority of AEs were Grade 1
- No AEs leading to CT-0508 dose modification or discontinuation
- 1 CRS Grade 2 on D3, characterized by fever and hypotension, resolved on D4 with acetaminophen, cefepime and fluids
- 1 SAE of Upper GI Hemorrhage 88 days after last CT-0508 infusion, deemed unrelated to therapy

CT-0508 Rapidly Migrates Out of the Blood



Similar profile is observed for both subjects with CAR-M detectable only on infusion days for 4 hours post-infusion consistent with rapid migration of CAR-M from the blood to tissues following infusion.

CT-0508 Leads to Transient and Self-Resolving Elevations of Pro-Inflammatory Cytokines in Peripheral Blood

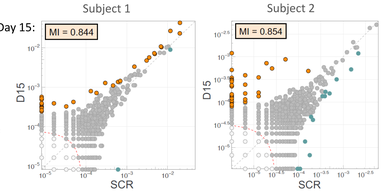


Transient and minor increase in cytokines levels are observed in both patients peaking 2 hours post-infusion and self-resolving within 48 hours.

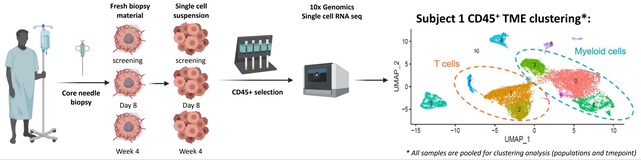
Early Expansion of T Cells in the Periphery Following CT-0508 Infusion

Repertoire comparison between Screening and Day 15:

TCR repertoire analysis reveals an expansion of T cell clones in the blood of both subjects, post CT-0508 infusion. These changes are indicative of an adaptive immune response similar to the one observed in case of viral infection (MI of 0.818 reported in case of acute infection[2]).
MI: Morisita Index (1: No disparity; 0: complete disparity)

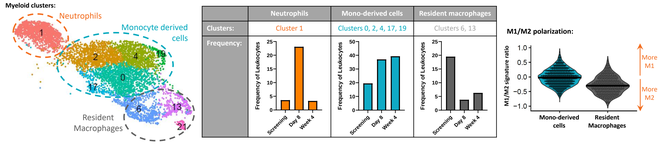


Tumor Microenvironment Analysis Using Single Cell RNAseq



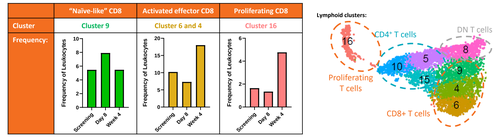
** All samples are pooled for clustering analysis (populations and timepoint)*

Subject 1 - CT-0508 Reprogrammed the Tumor Infiltrating Myeloid Cell Compartment



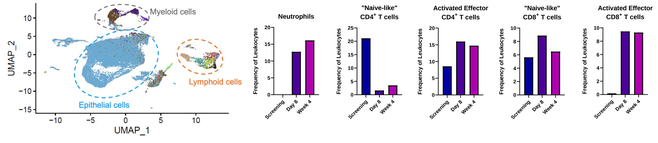
● Early recruitment of neutrophils is observed consistent with inflammation. ● Monocyte derived cells, which trended toward an M1 phenotype, are expanded on treatment while ● resident macrophages, which trended toward an M2 phenotype, are contracted on treatment.

Subject 1 - CT-0508 Induces Intra-Tumoral CD8 T Cell Expansion and Activation



Transient increased in ● naïve CD8⁺ T cells is observed early on treatment. Expansion of total CD8⁺ T cell, ● activated CD8⁺ T cells and ● proliferating T cells is observed at week 4.

Subject 2 - Preliminary Analysis of TME Demonstrates T Cell Expansion and Activation



Similar to the observation made for subject 1, an early recruitment of neutrophils is observed consistent with inflammation. The frequency of naïve CD4⁺ T cells is decreased on treatment while an increase in activated CD4⁺ T cells is observed. Naïve CD8⁺ T cells are transiently increased early on treatment and finally a significant increase in activated effector CD8⁺ T cells is observed (0.2% to 9%) at both on treatment time point.

Conclusions

Successful manufacturing	Preliminary safety profile	PK & TME Reprogramming
CT-0508 was successfully manufactured from autologous mobilized monocytes	No dose limiting toxicities observed	Rapid egress from peripheral blood
Patient product demonstrated high CAR expression, purity, viability, M1 polarization and confirmed functionality	No AEs leading to dose modification or discontinuation	Transient serum cytokine elevation
	No major organ system abnormality observed	Broad reprogramming of the TME
		Intratumoral T cell expansion and activation, with altered peripheral T cell repertoire

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.*
2. *DeWitt WS, et al. Dynamics of the cytotoxic T cell response in a model of acute viral infection. J Virol. 2015*