# Case Report: Metastatic Gastrointestinal Cancer Patient Responded to Repeated Administration of Anti-Claudin 18.2 CAR-T cells

Dan Zhao MD, PhD[1]*, Amanda Olson MD[2], Mariela Blum Murphy, MD[1], So Jung Hong[1], Hong Ma MD[3], Raffaele Baffa, MD, PhD[3]; Zonghai Li, MD, PhD[3]
[1]Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
[2]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[3]CARsgen Therapeutics, Inc, Houston, TX
*Correspondence: Dan Zhao, MD, PhD, email: dzhao3@mdanderson.org

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## Background

Cellular therapy for the treatment of solid tumors is challenging due to various factors including an immune-suppressing and hostile tumor microenvironment[1]. Claudin 18.2 (CLDN18.2) is a tight junction protein overexpressed in gastric and other cancers[2]. Anti-claudin 18.2 CAR-T cells (CT041) are currently under development and being tested in US and China clinical trials[3]. Here we present preliminary results of a gastric cancer patient who received repeated infusions of anti-Claudin 18.2 CAR-T cells (NCT04404595) in order to overcome the resistance encountered in solid tumors and improve the overall response.

## Methods

CLDN18.2 positive patients were selected and underwent apheresis for CAR-T manufacturing. Patients received a pre-conditioning regimen of fludarabine, cyclophosphamide, and 100mg/m$^2$ nab-paclitaxel before CT041 CAR-T infusion. Safety, efficacy, and cellular kinetic profile of CT041 were evaluated. Adverse Events (AEs) were graded per CTCAE 5.0. Cytokine release syndrome (CRS) and Immune Effector Cell Associated Neurotoxicity (ICANS) were scored and managed per American Society for Transplantation and Cellular Therapy (ASTCT) and Immune Effector Cell Therapy Toxicity Assessment and Management (CARTOX). Tumor response was assessed by the investigator per RECIST 1.1.

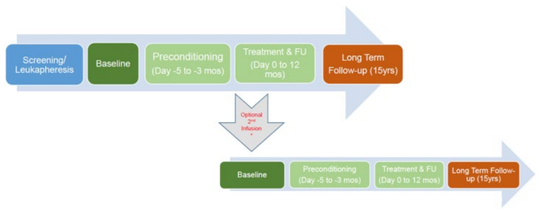


**Fig 1. Treatment pathway for patients.** A patient is eligible for an optional repeated infusion at approximately 3 months after the first infusion if there is no progression of disease (stable disease, partial response, or complete response).

## Results

A 57-year-old male patient with metastatic gastric cancer to the liver (HER2 negative, PD-L1 CPS 10%) progressed after 5 cycles of FOLFOX+Nivolumab and 4 cycles of FOLFIRI/Ramucirumab. After the patient resulted to be CLDN18.2 positive via IHC (2+, 5%, and 3+94%), the patient was treated with 600 × 10$^6$ CT041 cells after preconditioning chemotherapy. During monthly CT scans, images revealed a decrease in tumor size by -19.2%, -24.4%, and -26.9% (Fig 2). The patient experienced G1 CRS with fever during days 2-5 after infusion (Tab 1), which was resolved after one dose of tocilizumab. Three months after the first infusion, the patient received a second dose of 600 × 10$^6$ CT041 cells. The patient experienced G1 CRS with fever on days 1-2 after the second infusion, which resolved without tocilizumab. Monthly CT scan after the second infusion reported a continued decrease of tumor size from the baseline by -34.6%, and -41.0% (4 and 5 months after the 1st infusion, respectively). There have been no serious adverse event reported for the patient to date and there have been no GI bleeding related AE either. Only transient Grade 3 or 4 hematological toxicity events were reported, all other AEs were Grade 1 or Grade 2.

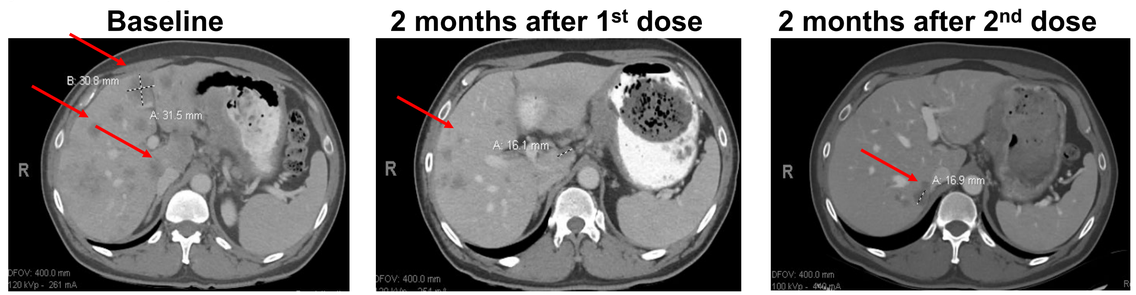


**Fig 2. Representative CT scan images for the patient receiving repeated infusions of anti-claudin 18.2 CAR-T cells (CT041). Red arrows: multiple liver lesions.**

Analysis of the cellular kinetics of CT041 reveals rapid expansion of cells in peripheral blood, with a peak at days 1 and 3 after the first and second infusion, respectively (Fig 3A). This peak in CT041 expansion correlated with an evident decrease in tumor size (Fig 3A). Although CRP and ferritin levels noticeably increased after each infusion (Fig 3B), CRP levels remained less than 10mg/dL, and Ferritin levels did not surpass 200ug/dL, neither reaching marked elevation. Similarly, serum cytokine levels spiked and peaked one day after infusion, which coincided with the reported CRS but quickly returned to undetectable levels (Fig 3C).

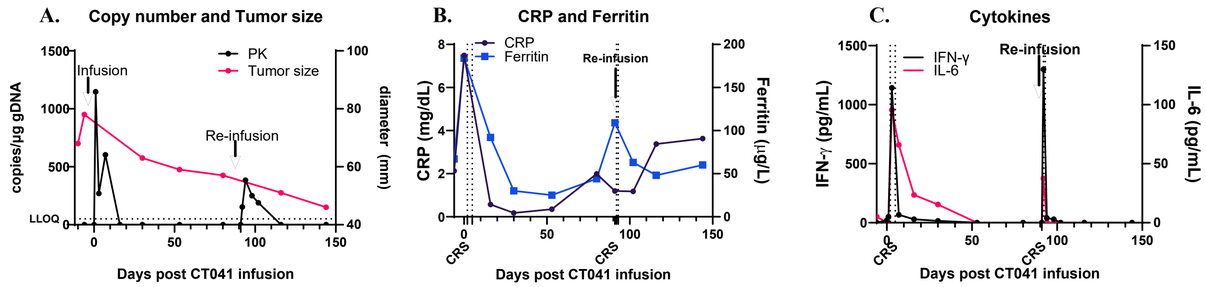


**Fig 3. PK/PD data of patient after the first and second infusion of CT041.** A. CT041 copy numbers were analyzed in patient blood at several time points after CT041 infusion, and plotted in relation to the sum of tumor diameter of the patient; B. CRP and Ferritin levels were analyzed in the patient over time after infusion; C. Cytokine levels including IFN-γ and IL-6 levels were measured in the serum at several time points after each CT041 infusion.

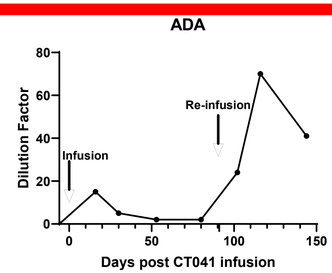


**Fig 4. Anti-drug antibody (ADA) titers of patient after CT041 infusion.** Serum was collected at various time points post-CT041 infusion and analyzed for ADA.

Anti-drug antibodies were detected in the serum of the subject at 2 weeks post-infusion, steadily declined, and rebounded after the second infusion (Fig 4). Analysis for the presence of neutralizing drug antibodies is still ongoing. No correlation of appearance of ADA with reduced tumor response was observed.

**Tab 1. CRS after the first and second infusion.**

| G1 CRS/fever | 1st Infusion | 2nd infusion |
|---|---|---|
| Start date | Day 2 | Day 1 |
| End date | Day 5 | Day 2 |

## Conclusions

Repeated dosing of anti-claudin 18.2 CAR-T cells (CT041) deepened the overall anti-tumor response in this gastric cancer patient. The safety profile did not reveal any unexpected events. Further data analysis is pending from additional patients treated with CT041 in the US.

## References

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