Multicenter Phase 1b Trial of Salvage CT041 CLDN18.2-specific Chimeric Antigen Receptor T Cell Therapy for Patients with Advanced Gastric and Pancreatic Adenocarcinoma

Gregory P. Botta, MD, PhD[1*]; Carlos Becerra, MD[2]; Zhaohui Jin, MD[3]; Dae Won Kim, MD[4]; Dan Zhan, MD, PhD[5]; Heinz-Josef Lenz, MD[6]; Hong Ma, MD[7]; Audrey Ween[1], BS; Petra Acha, BS[7]; Zonghai Li, MD, PhD[7]; Harry H. Yoon, MD[3]. [1]University of California San Diego, San Diego, CA; [2]Baylor Scott & White Charles A. Sammons Cancer Center, Dallas, TX; [3]Mayo Clinic, Rochester, MN; [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]University of Southern California, Los Angeles, CA; [7]CARsgen Therapeutics, Inc, Houston, TX; ***Corresponding author: gbotta@health.UCSD.edu**

Background

- Claudin 18.2 (CLDN18.2) is a highly selective and expressed cell surface marker in advanced gastric cancer (GC) and pancreatic cancer (PC).[1]
- Results from an ongoing trial in an Asian population using CLDN18.2 CAR T cells (CT041) showed an objective response rate (ORR) of ~60% in subjects with GC.[2]

Methods

- Single-arm, open-label, phase 1b trial in 6 centers in the U.S (NCT04404595).
- CLDN18.2 positive patients who had GC with ≥ 2 prior lines of systemic therapy or PC with ≥ 1 prior line were enrolled.
- CT041 were manufactured per **Figure 1**.
- Fludarabine, cyclophosphamide, and nab-paclitaxel (100 mg or 100 mg/m^2; FNC) preconditioning prior to CT041 infusion
- Tumor response was assessed per RECIST 1.1; CRS and ICANS by ASTCT criteria; AEs per CTCAE v5.0

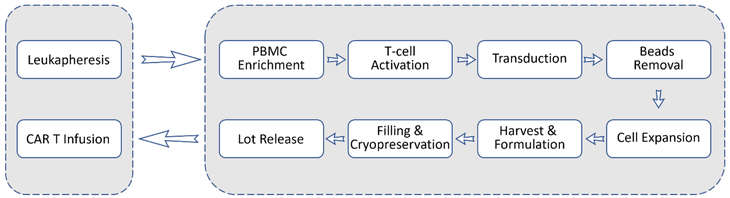

Figure 1. Manufacturing process flow of CT041 cell product

Results

- As of 06-May-2022, 14 patients have enrolled (5 GC, 9 PC) with a median of 3 prior lines of therapy (range 1-5) and having received 18 total cycles of CT041
- Dose levels (DL): DL1: 2.5-3.0x10^8 cells (n=6), DL2: 3.75-4.0x10^8 cells (n=6), and DL3: 6.0x10^8 cells (n=2)

Key Findings

(1) Safety

- No dose-limiting toxicities or treatment-related deaths
- No ≥ Grade 3 CRS (**Table 1**), ICANS, GI bleed or acute gastric mucosal injury
- Preconditioning did not increase hematologic toxicities
- Tocilizumab given for Grade 2 CRS in two patients

(2) Efficacy

- Dose-dependent responses:
  - DL1: 16.7% ORR, 50% DCR
  - DL2: 33.3% ORR, 83.3% DCR
- ORR = 60% in GC (**Table 2**)
- Tumor shrinkage in 80% (4 of 5) of patients with SD (4 PCs)
- CAR T expansion correlated with ctDNA reduction
- Median duration of response and progression-free survival have not been reached
- Two patients in DL3 did not have tumor response assessments by the data cut-off date

Table 1. CRS Details

Patients with CRS, n (%)	13 (93)
Onset post, days (range)	2 (1-3)
Duration, days (range)	2 (1-8)
CRS Grade 1, n (%)	11 (79)
CRS Grade 2, n (%)	2 (14)

Table 2. Tumor Response

	GC (n=5), n (%)	PC (n=7), n (%)
CR	1 (20)	0 (0)
PR	2 (40)	0 (0)
SD	1 (20)	4 (57.1)
PD	1 (20)	3 (42.9)

Abbreviations: AE=adverse event; ASTCT= American Society for Transplantation and Cellular Therapy; AUC=area under the curve; CAR=Chimeric Antigen Receptor; CLDN18.2=claudin18.2; CR=Complete response, CRS=Cytokine release syndrome; ctDNA=circulating tumor DNA; CTCAE= Common Terminology Criteria for Adverse Events; DCR=disease control rate; DL=dose level; FNC=Fludarabine, cyclophosphamide, and nab-paclitaxel; GC=gastric cancer; GEJ=gastroesophageal junction cancer; GI=gastrointestinal; ICANS=Immune effector cell-associated neurotoxicity syndrome; IHC= Immunohistochemistry; ORR=objective response rate; PC=pancreatic cancer; PD=progressive disease; PK=pharmacokinetics; PR=partial response; SD=stable disease

Imaging of Two Confirmed PR Patients at Dose Level 2

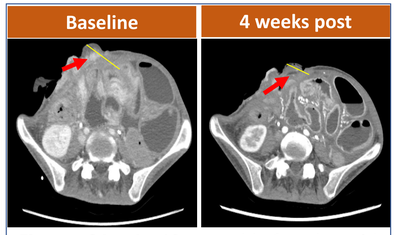

Figure 2A. A 48-year-old female with diffuse metastatic GC was previously treated with FOLFOX, FOLFIRI, capecitabine, zolbetuximab (CLDN18.2 antibody), pembrolizumab + cabozantinib, and nab-paclitaxel. CLDN18.2 IHC showed 2+ 5% and 3+ 95%. CT showed a 7.6 cm mass extended through stoma to the exterior abdominal surface. CT 4 weeks post CT041 showed significant tumor reduction in exterior stoma lesions.

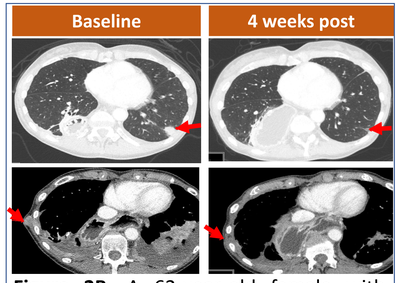

Figure 2B. A 62-year-old female with invasive, moderately differentiated, metastatic GEJ cancer after 2 prior lines of therapy. CLDN18.2 IHC showed 2+ 20% and 3+ 80%. CT scans confirmed the disappearance of one target lesion and a significant reduction in the other two target lesions in the chest (one shown) 4 weeks post CT041.

PK, Cytokines & ctDNA

- No significant difference in copy number (**Figure 3**) or cytokine AUCs between DLs. Copy number peaked day 3–7
- Rapid ctDNA reduction post CT041 (DL2) in one PC patient with SD up to Week 8 (**Figure 4**)

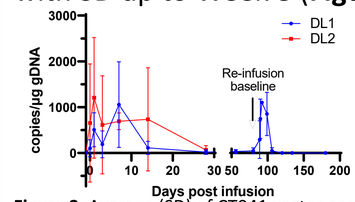

Figure 3. Average (SD) of CT041 vector copy number over time by dose level.

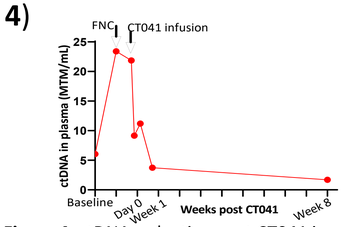

Figure 4. ctDNA reduction post CT041 in patient with SD and tumor shrinkage.

Conclusion

In heavily pre-treated gastric cancer, CT041 CLDN18.2 CAR T cells may have significantly improved anti-tumor activity compared to historical treatment regimens.

Acknowledgement: Thank you to the participating centers, volunteers, sponsor.

References
(1) Jiang H et al. *JNCI* (2019). https://doi.org/10.1093/jnci/djy134;
(2) Qi C et al. *Nat Med* (2022). https://doi.org/10.1038/s41591-022-01800-8.

CARSGEN THERAPEUTICS