CARSGEN
THERAPEUTICS

CLDN 18.2-targeted CAR-T cell therapy (CT041) in patients with cancers of the digestive system

September 2021

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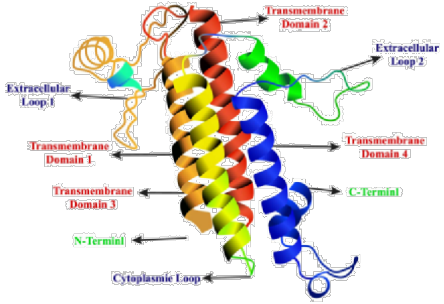
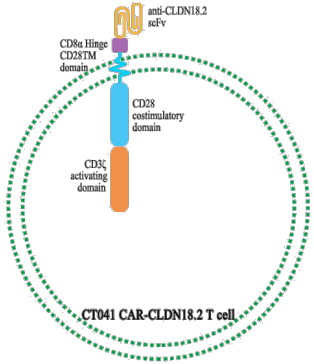
CT041 : A Humanized Claudin18.2-redirected CAR-T

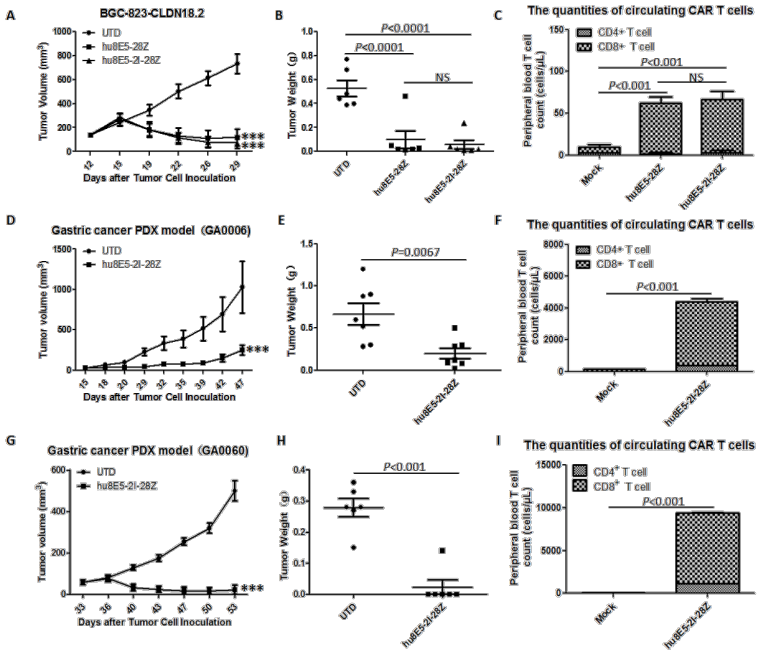
- Claudin18.2 (CLDN18.2) a pan-cancer target
- Expressed in a diverse variety of epithelial tumor types[1]
- Medium to high expression in ~60% GC/GEJ patients[2,3]





- Patient–derived (autologous) CAR T cell product
- Chimeric antigen receptor design:
  - Humanized CLDN18.2 scFV
  - CD8α hinge region, CD28 transmembrane region
  - CD28 intracellular signal domain
  - CD3ζ intracellular signal region
- IND clearance by China NMPA and US FDA
- Received orphan drug designation from FDA, EMA

Potent antitumor activities of CT041 in NOD/SCID mouse models bearing gastric cancer xenografts[3]



1. Singh et al. JHO, 2017; 10:105.
2. Sahin U, et al. CCR 2008;14:7624-34.
3. Jiang H, et al. JNCI, 2019;111(4): DJY134.

Study Design

- 18-75 years of age
- Previously treated advanced digestive system cancers confirmed by pathology
- CLDN18.2 expression: ≥+, ≥10%
- ECOG: 0 or 1

Apheresis

Manufacturing CT041 (2w-3w)

Bridging chemotherapy

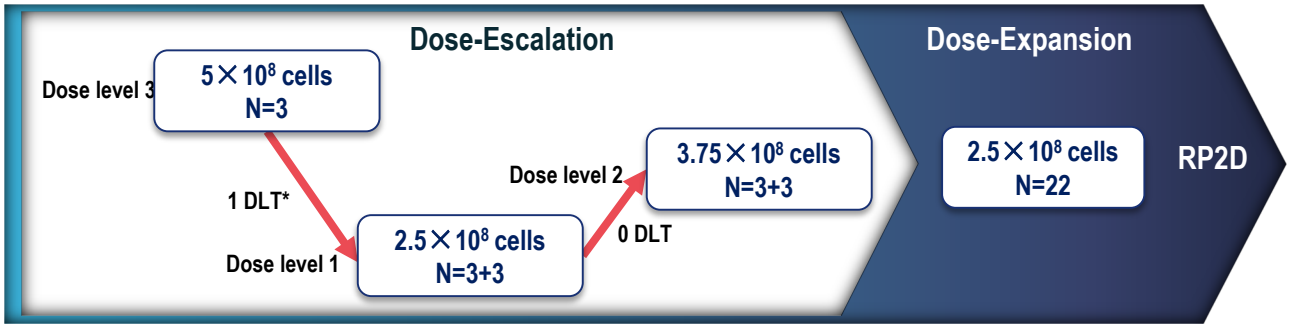
Preconditioning therapy #

CT041 infusion

Progressive disease or Intolerable toxicity

Survival follow up

Reinfusion (Depend on Subject's condition)



Primary Objectives: Safety and tolerability

Secondary Objectives : Efficacy, Pharmacokinetics

Explorative Objectives : Covariate analysis for efficacy, biodistribution of CT041

#Fludarabine 25 mg/m²/day(D–4~D–3)+Cyclophosphamide 250 mg/m²/day (D–4~D–2)+Nab-paclitaxel 100mg or gemcitabine 1000mg (D–3)

*One patient suffered gastrointestinal hemorrhage in D51 after reinfusion, which was considered to be caused by obvious tumor regression. After discussion among the investigators, DMC and partners, it was decided to lower the dose to 2.5×10^8 cells.

Patient Demographics and Baseline Characteristics

Characteristics of all patients	Total (N = 37)
Median age (range), year	53.0 (25–74)
Disease Type, n(%)	
GC/GEJ	28 (75.7)
PC	5 (13.5)
Other	4 (10.8)
ECOG, n (%)	
0	2 (5.4)
1	35 (94.6)
Bridging therapy, n (%)	28(75.7)
Expression intensity and rate of CLDN 18.2 in tumor tissue, n (%)	
Low expression	5 (13.5)
Medium expression	13 (35.1)
High expression	19 (51.4)
Numbers of metastatic organs	
Median	3.0
Min, Max	1.0, 7.0
Median no. of previous lines, n (%)	
1	6 (16.2)
2	19 (51.4)
≥ 3	12 (32.4)

GC/GEJ: gastric carcinoma / gastroesophageal junction
PC: pancreatic adenocarcinoma

Characteristics of GC	Total (N = 28)
Histological classification(WHO classification), n (%)	
Mucinous adenocarcinoma	1 (3.6)
Signet ring cell carcinoma	12 (42.9)
Other	14 (50.0)
Expression intensity and rate of CLDN 18.2 in tumor tissue, n (%)	
Low expression	2 (7.1)
Medium expression	7 (25.0)
High expression	19 (67.9)
Numbers of metastatic organs	
Median	2.5
Min, Max	1.0, 7.0
Peritoneal metastases, n (%)	19 (67.9)
Liver metastases, n (%)	10 (35.7)
Lauren classification, n (%)	
Intestinal type	10 (35.7)
Diffuse type	9 (32.1)
Mixed type	7 (25.0)
Previous systemic therapies, n (%)	
Fluorouracil	28 (100)
Platinum	27 (96.4)
Taxanes	21 (75.0)
Paclitaxel	18 (64.3)
Albumin paclitaxel	7 (25.0)
Anti-PD-(L)1 antibody	12 (42.9)
Polykinase inhibitor	10 (35.7)

Adverse Event Summary

Overall well tolerated

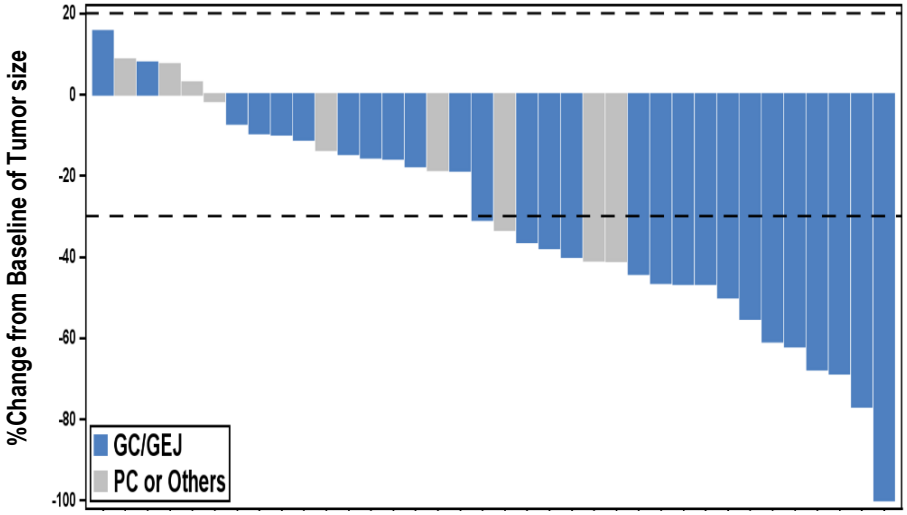
- Most common AEs ≥ Grade 3 were hematologic toxicities and recovered within 2 weeks.
- 35 patients (94.5%) experienced Grade 1/2 CRS, No ≥ Grade 3 CRS occurred.
- No CRES / ICANS.
- 1 DLT of gastrointestinal hemorrhage post 2nd infusion at D51 resulted in dose reduction for further enrollment.
- 6 subjects reported mucosal injury with 1 at Grade 3.
- No obvious difference in safety profile among 3 dose levels.
- No treatment related death.

	Dose Escalation			Dose Expansion	Total
	$2.5x10^8$ (N=6)	$3.75x10^8$ (N=6)	$5x10^8$ (N=3)	$2.5x10^8$ (N=22)	(N=37)
ALL AEs	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
DLT	0	0	1 (33.3)	0	1 (2.7)
AE leading to study withdrawal	0	0	0	0	0
AE leading to drug withdrawal	0	0	1 (33.3)	0	1 (2.7)
AE leading to death	0	0	0	0	0
Treatment related SAE	0	0	1 (33.3)	2 (9.1)	3 (8.1)
Treatment related AEs	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
≥Grade 3 fever	1 (16.7)	0	1 (33.3)	1 (4.5)	3 (8.1)
Grade 3	1 (16.7)	0	1 (33.3)	1 (4.5)	3 (8.1)
Grade 4	0	0	0	0	0
≥Grade 3 hematological toxicity	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
Grade 3	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
Grade 4	5 (83.3)	6 (100)	3 (100)	21 (95.5)	35 (94.6)
CRS	5 (83.3)	6 (100)	3 (100)	21 (95.5)	35 (94.6)
Grade 1	2 (33.3)	4 (66.7)	0	11 (50.0)	17 (45.9)
Grade 2	3 (50.0)	2 (33.3)	3 (100)	10 (45.5)	18 (48.6)
≥Grade 3 neurotoxicity	0	0	0	0	0
≥Grade 3 infections	0	0	0	0	0
Gastric mucosal injury	0	0	0	6 (27.3)	6 (16.2)
≥Grade 3	0	0	0	1 (4.5)	1 (2.7)

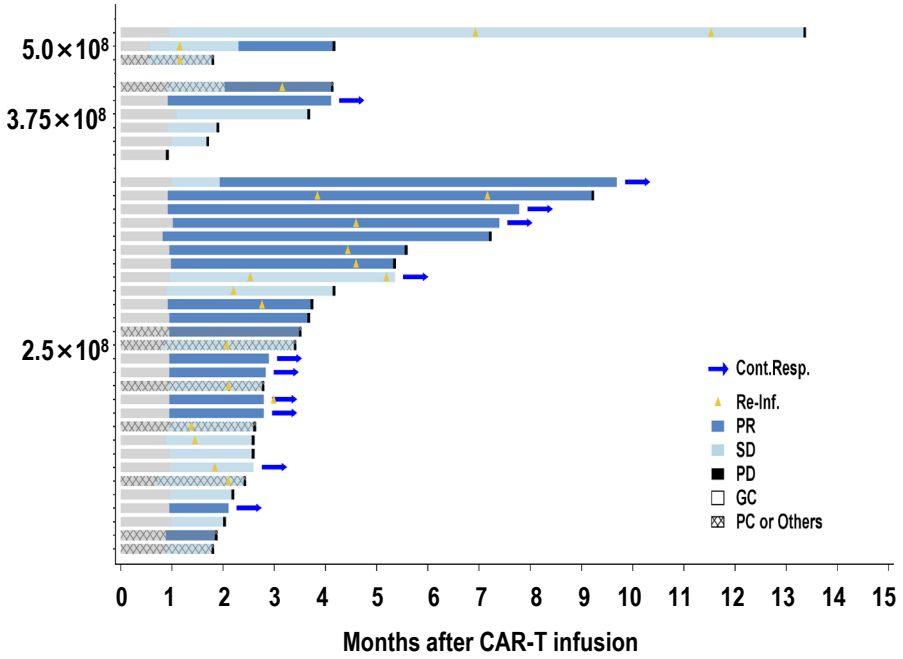
Efficacy : All patients

Thirty-six of the 37 subjects had target lesions. 31 subjects had different degrees of shrinkage of target lesions.

According to RECIST 1.1, ORR and DCR reached **48.6%** (18/37) and **73.0%** (27/37) respectively.



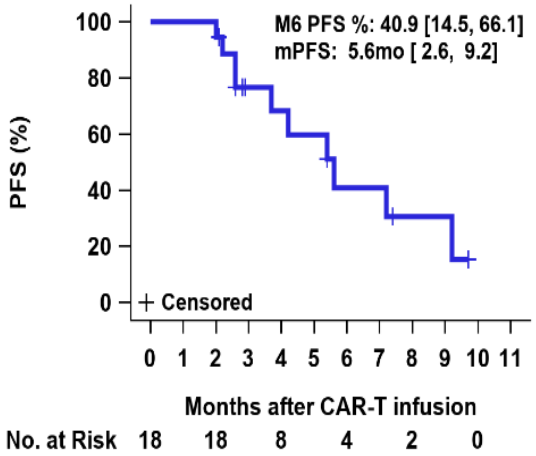
GC/GEJ: gastric carcinoma / gastroesophageal junction
PC: pancreatic adenocarcinoma

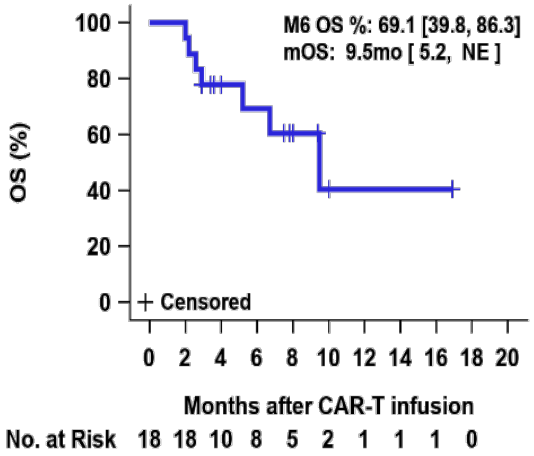


Efficacy : ≥2 prior lines GC/GEJ treated at RP2D

GC/GEJ patients who failed at least 2 prior lines of therapy (especially more than 40% patients ever exposed to an anti-PD-(L)1 antibody) at the dose of 2.5×10^8 CAR T cells achieved an ORR of **61.1%**, DCR of **83.3%**, mPFS* of **5.6m**, mDOR of **6.4m**, mOS* of **9.5m** with a median follow up duration* of 7.6m (95%CI 5.6, 8.6) .

≥2 lines GC patients at 2.5×10^8 cells (N=18)	
Best Overall Response	
CR	0
PR	11 (61.1%)
SD	4 (22.2%)
PD	3 (16.7%)
ORR [95% CI]	**11 (61.1%)** [35.75, 82.70]
DCR [95% CI]	**15 (83.3%)** [58.58, 96.42]
mPFS*	**5.6m** [2.6, 9.2]
mOS*	**9.5m** [5.2, NE]
mDOR	**6.4m** [2.7, NE]





*PFS, OS and follow up duration were calculated from CAR-T infusion date.

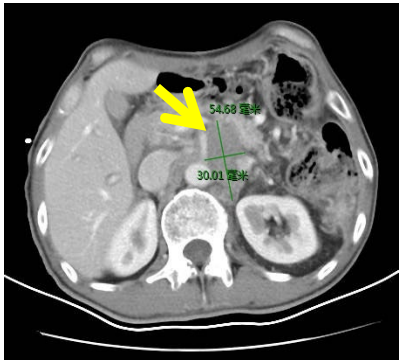
Subgroup Analysis of ORR in GC/GEJ Patients

	Number of subjects	ORR
CLDN18.2 expression		
High expression (≥2+ , ≥ 70%)	19	57% (37.2, 75.5)
Medium expression (≥2+, ≥40% and < 70%)	7	58% (33.5, 79.7)
Low expression (+ or < 40%)	2	50% (1.3, 98.7)
Anti-PD-(L)1 Antibody		
Not used	16	63% (35.4, 84.8)
Used	12	50% (21.1, 78.9)
Peritoneal Metastasis		
Yes	19	58% (33.5 , 79.7)
No	9	56% (21.2, 86.3)
WHO Classification		
Signet ring cell carcinoma	12	58% (27.7, 84.8)
Others	15	60% (32.3, 83.7)
Lauren Classification		
Intestinal	10	70% (34.8, 93.3)
Diffused / Mixed	16	50% (24.7, 75.3)

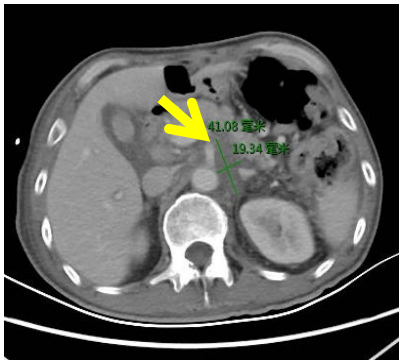
Case Sharing : Rapid and sustained tumor lesion remission

Pt04, 53/M, GC with liver, lung, bone metastasis and multiple lymph node and peritoneum metastasis, had received 2 prior lines of therapy including PD-1 antibody, achieved PR till 32 weeks, CLDN18.2 3+ 60%.

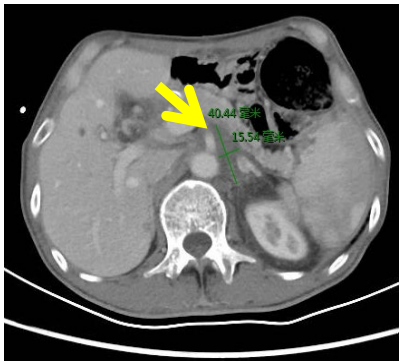
Retroperitoneal Lymph Node



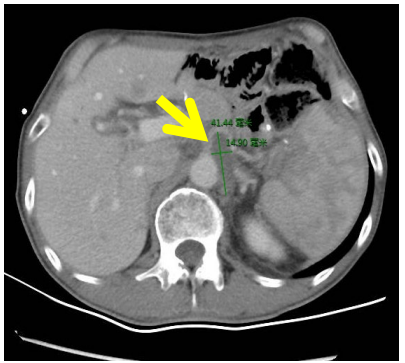
Pre-infusion



Post-infusion W4



W8

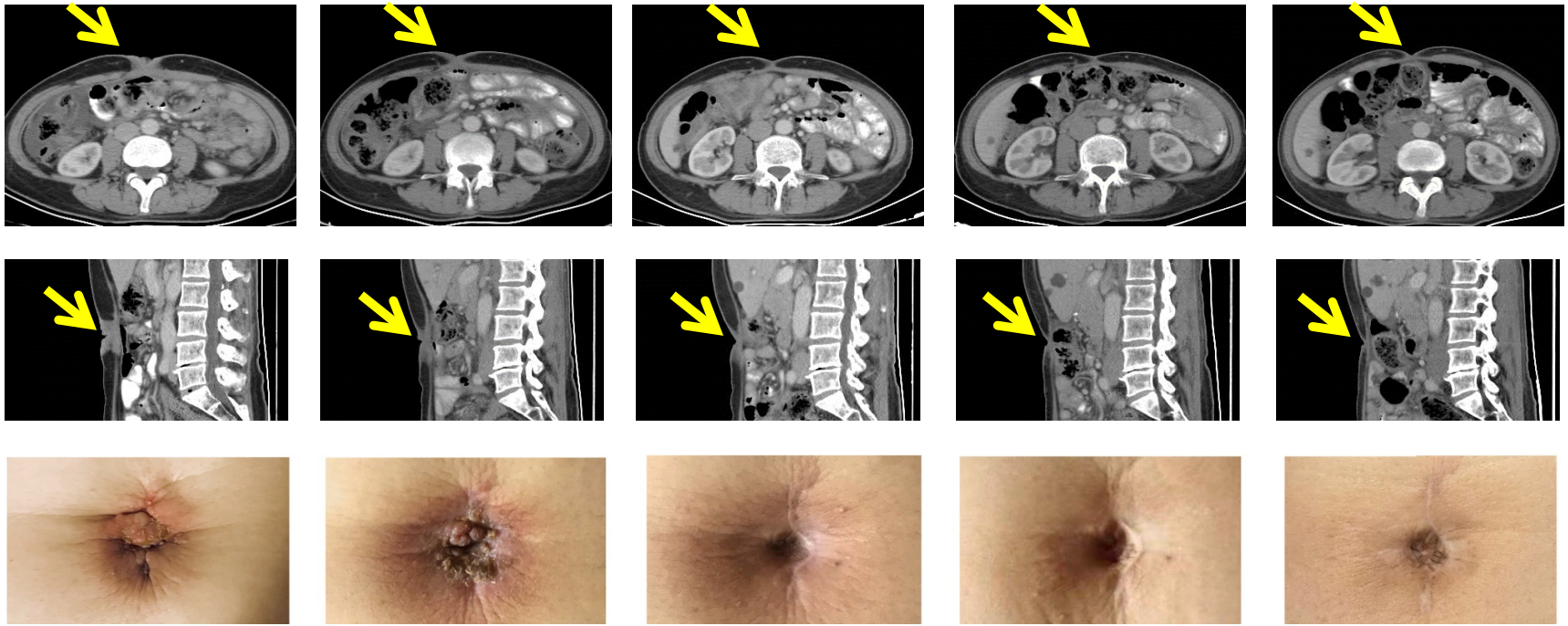


W32

Short Axis	30mm	19mm	16mm	15mm

Case Sharing : Long-term tumor response

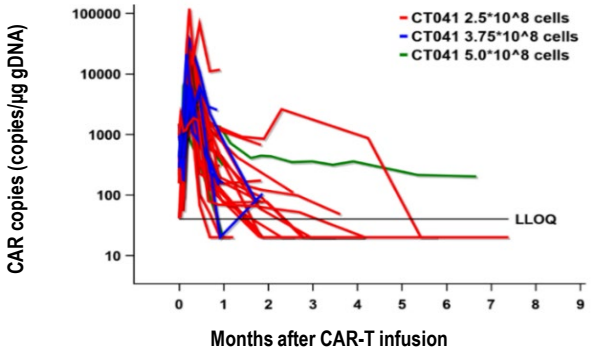
Pt08, 57/F, GC with peritoneal metastasis and Sister Mary Joseph nodule, had received 3 prior lines of therapy including PD-1 antibody, achieved PR and ongoing response more than 56 weeks, CLDN18.2 2+ 80%.

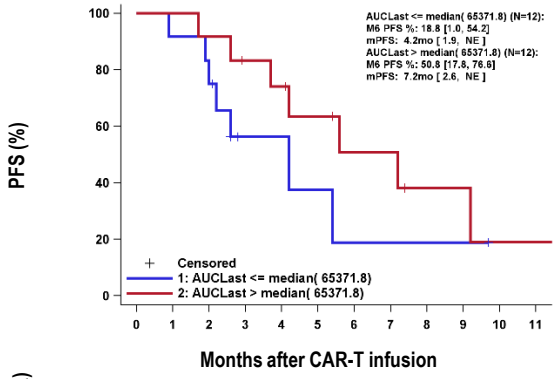


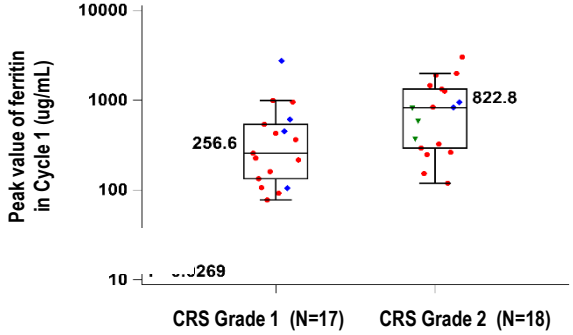
Pre-infusion | Post-infusion W4 | W12 | W24 | W40

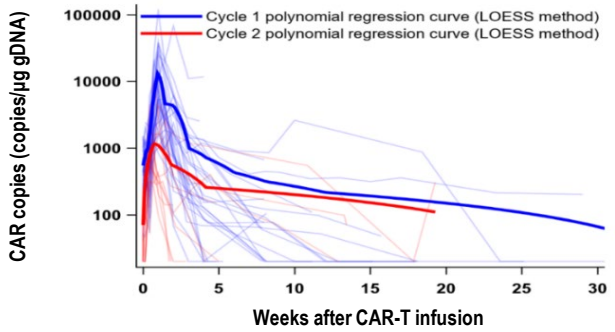
CT041 CAR T-cell Expansion and Serum Biomarkers

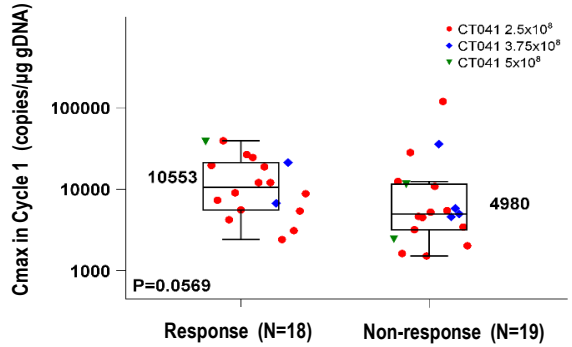
- In average, the CAR copies peaked around Day 7and persisted still Week 4, and CAR copies peak decreased post 2nd - 3rd dose ;
- Responders had relative higher CAR copies peak;
- The prolonged PFS positively correlated with increased AUC_{last} ;
- Patients with Grade 2 CRS had higher IL-6 and ferritin peak value than those with Grade 1.

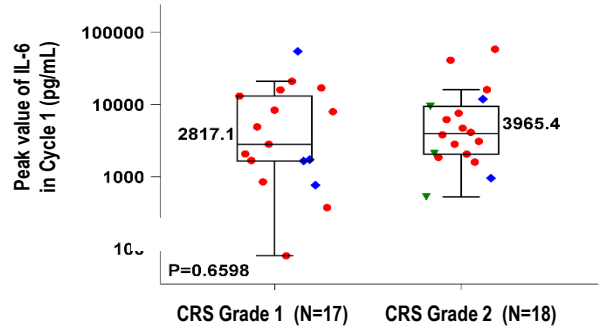












Conclusions

Safety Summary

- No treatment-related death, DLT occured in 28 days, and immune effector cell-associated neurotoxicity syndrome (ICANS) were reported;
- Grade 1 or Grade 2 CRS occurred in 94.6% subjects, no ≥ Grade 3 CRS reported.

Efficacy Summary

- The ORR for all patients was 48.6%, and DCR reached 73%. The mOS and mDOR have not reached;
- GC/GEJ patients who failed at least 2 prior lines of therapy (especially more than 40% patients ever exposed to anti-PD-(L)1 antibody) at a dose of 2.5×10^8 CAR T cells achieved ORR of **61.1%**, DCR of **83.3%**, mPFS of **5.6** months (95%CI, 2.6 9.2), mOS of **9.5** months (95%CI, 5.2, NE);

Pharmacokinetics characteristics

- The CAR copies peaked around 7 days, median persistent duration of one month
- The CAR copies peak was significantly higher in the responders than in the nonresponders. The prolonged PFS positively correlated with increased AUC_{last} .

CT041 at dose levels of 2.5-5.0×10^8 CAR-T cells was well tolerated in patients with CLDN18.2 positive digestive system cancers and delivers high response rate and sustained remission in the previously treated GC/GEJ patients.

Thanks

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