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Claudin18.2-specific CAR T Cells in gastrointestinal cancers: phase 1 trial final results

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Key Takeaways

- Satricabtagene autoleucel (satri-cel)/CT041 demonstrated its highly promising efficacy and manageable safety profile in patients with CLDN18.2-positive advanced gastrointestinal (GI) cancers.
- The trial explored various cohorts, including combination therapy with anti-PD1, frontline therapy, and early apheresis.
- Additionally, an exploratory analysis of potential factors was performed on the efficacy and safety of satri-cel.

Background

- Claudin 18.2 (CLDN18.2) is highly expressed in GI tumors, rendering it one of the most popular targets for anti-tumor interventions[1,2].
- Satricabtagene autoleucel (satri-cel)/CT041, a CLDN18.2-specific CAR T cell therapy, has shown promising responses and a manageable safety profile in previous results[3].
- Herein, we present the final results of this single-arm, open-label, phase 1 trial, which evaluated the safety and efficacy of satri-cel in patients with CLDN18.2-positive advanced GI cancers.

1. Qi, C. et al. Chin. J. Cancer Res. 36, 78–89 (2024).
2. Kubota, Y. et al. ESMO Open 8, 100762 (2023).
3. Qi, C. et al. Nat. Med. 28, 1189–1198 (2022).

Trial Design and Procedure schema

A multicenter, open-label, phase I trial.

Dose Escalation/ Dose de-Escalation

Modified '3+3' design
- DL# 1: 2.5×10^8
- DL 2: 3.75×10^8
- DL 3: 5.0×10^8
- DL 4: 10.0×10^8

N=15

→ RD*

Dose Expansion

- Cohort 1 - Satri-cel monotherapy in patients with standard chemotherapy-refractory GI cancers (N=53-70)
- Cohort 2 - Satri-cel plus anti-PD-1 therapy in patients with standard chemotherapy-refractory GI cancers (N=12-16)
- Cohort 3 - Satri-cel as sequential treatment after first-line therapy in patients with GI cancers (N=9-12)
- Cohort 4 - Satri-cel monotherapy in patients with anti-CLDN18.2 monoclonal antibody-refractory gastric cancer (N=3-6)

Endpoints

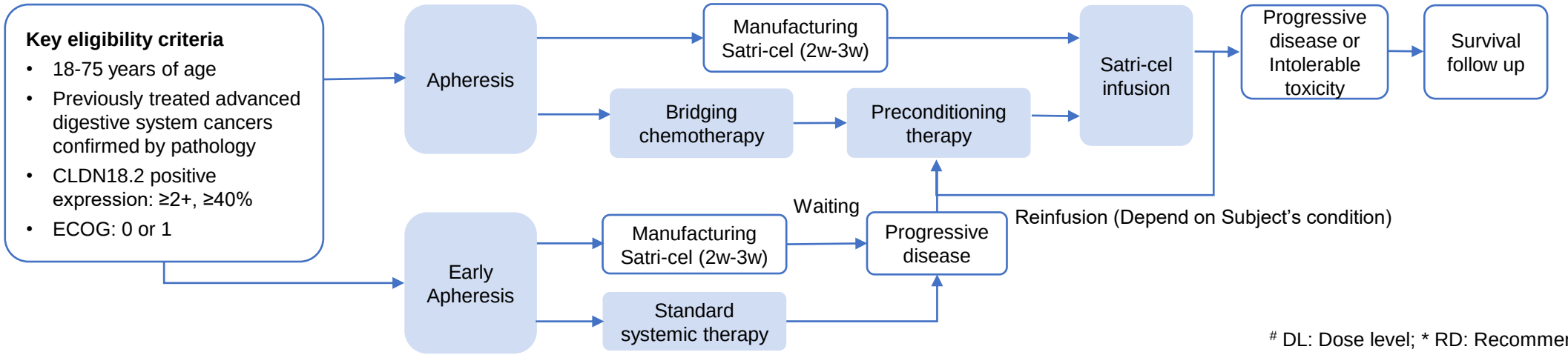
Primary Endpoint:
- Safety and tolerability

Secondary Endpoints:
- Efficacy, Pharmacokinetics

Exploratory Endpoints：
- Influencing factors of Efficacy, Distribution of Satri-cel

Data cutoff：January 26, 2024

Key eligibility criteria
- 18-75 years of age
- Previously treated advanced digestive system cancers confirmed by pathology
- CLDN18.2 positive expression: ≥2+, ≥40%
- ECOG: 0 or 1



DL: Dose level; * RD: Recommended dose

Baseline Characteristics

Characteristics	Total N = 98	Characteristics	Total N = 98
Median age (range), year	50.0 (25–74)	**Previous systemic therapies, n (%)**	
Male, n (%)	54 (55.1)	Fluorouracil/analogs & derivatives	96 (98.0)
Disease type, n (%)		Taxanes	67 (68.4)
Gastric/ gastroesophageal junction (GC/GEJ)	73 (74.5)	Platinum	83 (84.7)
Pancreatic cancer (PC)	10 (10.2)	Anti-PD-1/PD-L1 antibody	30 (30.6)
Intestinal cancer	8 (8.2)	Polykinase inhibitor [b]	22 (22.4)
Biliary Tract Cancer (BTC)	4 (4.1)	**No. of metastatic organs, n (%)**	
Other	3 (3.1)	≤2	54 (55.1)
ECOG, n (%)		≥3	44 (44.9)
0	6 (6.1)	**Metastatic organs, n (%)**	
1	92 (93.9)	Liver	25 (25.5)
CLDN18.2 expression, n (%) [a]		Lung	18 (18.4)
Low expression	5 (5.1)	Peritoneal	70 (71.4)
Medium/high expression	93 (94.9)	Bone	14 (14.3)
No. of previous lines, n (%)		Distant lymph node	47 (48.0)
1	28 (28.6)		
2	44 (44.9)		
≥3	26 (26.5)		

a CLDN18.2 expression level by immunohistochemical staining intensity was graded as either 1+, 2+, or 3+ and multiplied by the percentage of tumor cells that were positive. Low expression was defined as any intensity with a percentage of <40% or intensity 1+ with any percentage, medium expression was defined as intensity 2+ or 3+ with a percentage of 40% (inclusive) to 69%, and high expression was defined as intensity 2+ or 3+ with a percentage of ≥70%.
b Polykinase inhibitor: multi-target tyrosine kinase inhibitor including apatinib, anlotinib, etc.

Safety

- No predefined dose-limiting toxicities (DLTs) within 28 days after the first infusion were observed, and no long-term complications were observed.
- The primary AEs of grade 3 or higher were mostly ***preconditioning-related hematologic toxicities***, which occurred within 28 days after the first infusion and generally recovered within a median of 6–14 days.
- Ninety-five (96.9%) patients experienced grade 1/2 CRS. ***No ≥ grade 3 CRS occurred***.
- No immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis (HLH), or treatment-related death were observed.
- Gastric mucosal injuries were identified in 8 (8.2%) patients, incl. grade 1/2 in 7 patients and grade 3 in 1 patient.

TEAE in ≥25% of patients, n (%)	≥Grade 3	Total
Hematology		
Lymphopenia	**97 (99.0)**	97 (99.0)
Leukopenia	**83 (84.7)**	97 (99.0)
Neutropenia	**71 (72.4)**	93 (94.9)
Anemia	**43 (43.9)**	91 (92.9)
Thrombocytopenia	**13 (13.3)**	47 (48.0)
GI disorders		
Nausea	1 (1.0)	66 (67.3)
Vomiting	3 (3.1)	52 (53.1)
Abdominal pain	1 (1.0)	39 (39.8)
Diarrhea	2 (2.0)	38 (38.8)
Abdominal distension	0	30 (30.6)
Immune system disorders		
Cytokine release syndrome	0	**95 (96.9)**
Other		
Pyrexia	5 (5.1)	95 (96.9)
Hypoproteinemia	2 (2.0)	81 (82.7)
Occult blood positive	0	75 (76.5)
Hypoalbuminemia	0	73 (74.5)
Alanine aminotransferase increased	9 (9.2)	67 (68.4)
Activated partial thromboplastin time prolonged	0	64 (65.3)
Bilirubin conjugated increased	22 (22.4)	62 (63.3)
Aspartate aminotransferase increased	8 (8.2)	61 (62.2)
Hyponatremia	5 (5.1)	61 (62.2)
Sinus tachycardia	2 (2.0)	54 (55.1)
Hypokalemia	12 (12.2)	52 (53.1)
Hypotension	1 (1.0)	49 (50.0)
Prothrombin time prolonged	0	48(49.0)
Blood bilirubin increased	14 (14.3)	47 (48.0)
Blood glucose increased	0	45 (45.9)
Proteinuria	0	44 (44.9)
Weight decreased	4 (4.1)	43 (43.9)
Lipase increased	5 (5.1)	33 (33.7)
Temperature intolerance	0	32 (32.7)
Hypophagia	0	31 (31.6)
Rash	3 (3.1)	29 (29.6)
Edema peripheral	0	25 (25.5)
Blood fibrinogen decreased	4 (4.1)	25 (25.5)

Efficacy

	Dose Escalation n = 15	Cohort 1 n = 61	Cohort 2 n = 15	Cohort 3 n = 5	Cohort 4 n = 2	All N = 98
Best overall response						
CR, n (%)	0	1 (1.6)	0	0	0	1 (1.0)
PR, n (%)	7 (46.7)	21 (34.4)	4 (26.7)	4 (80.0)	1 (50.0)	37 (37.8)
SD, n (%)	7 (46.7)	36 (59.0)	7 (46.7)	1 (20.0)	1 (50.0)	52 (53.1)
PD, n (%)	1 (6.7)	3 (4.9)	4 (26.7)	0	0	8 (8.2)
ORR, n (%) [95% CI]	7 (46.7) [21.3, 73.4]	22 (36.1) [24.2, 49.4]	4 (26.7) [7.8, 55.1]	4 (80.0) [28.4, 99.5]	1 (50.0) [1.3, 98.7]	**38 (38.8)** [29.1, 49.2]
DCR, n (%) [95% CI]	14 (93.3) [68.1, 99.8]	58 (95.1) [86.3, 99.0]	11 (73.3) [44.9, 92.2]	5 (100) [47.8, 100.0]	2 (100) [15.8, 100.0]	**90 (91.8)** [84.5, 96.4]
mPFS (months) [95% CI]	4.2 [1.8, 9.2]	4.2 [3.4, 6.6]	4.4 [0.9, 9.4]	15.2 [6.8, NR]	4.7 [4.1, NR]	**4.4** [3.7, 6.6]
mOS (months) [95% CI]	9.0 [3.70, 9.8]	9.3 [7.1, 12.5]	6.7 [3.0, 9.8]	16.4 [7.0, NR]	7.2 [5.8, NR]	**8.8** [7.1, 10.2]
mDOR (months) [95% CI]	6.4 [1.9, NR]	5.5 [2.9, 8.3]	18.8 [8.4, NR]	NR [5.8, NR)	4.4 [NR, NR]	**6.4** [4.6, 8.4]

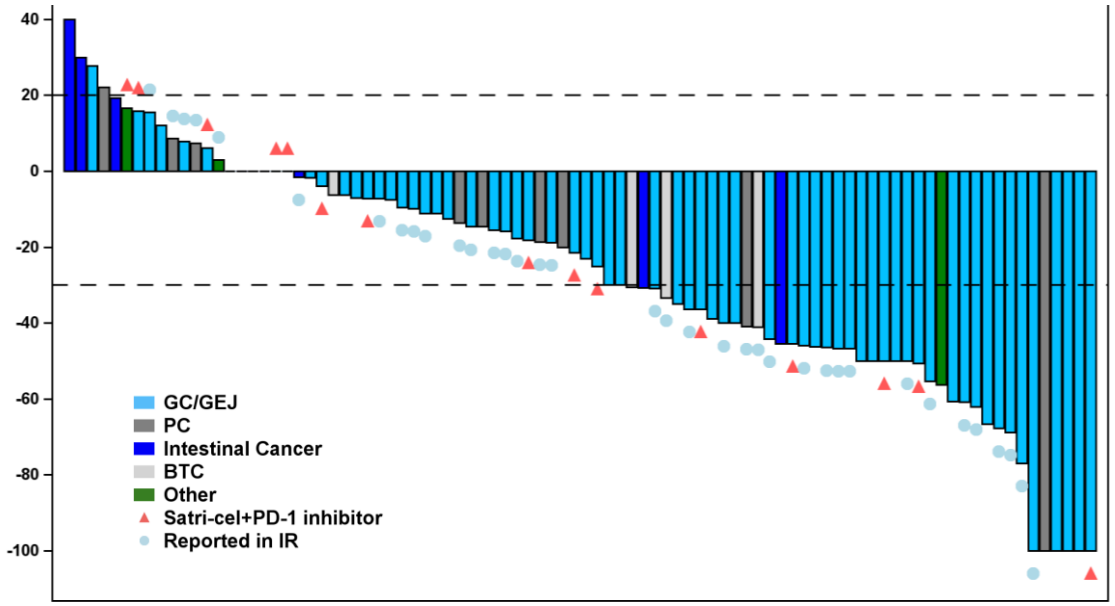
Efficacy

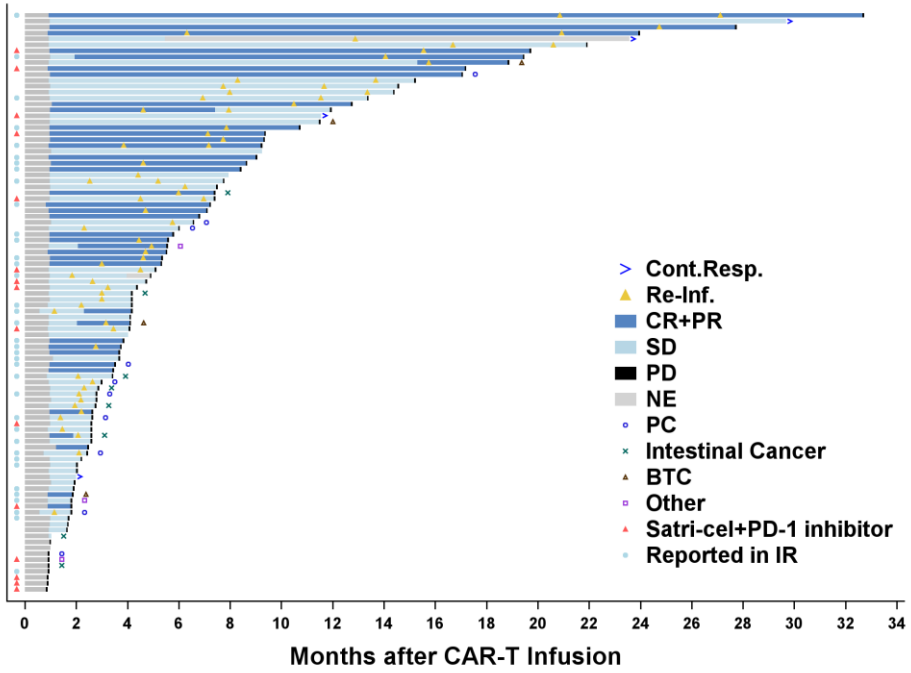
Efficacy in patients with target lesions received satri-cel monotherapy

Variable	GC/GEJ n = 51	PC n = 10	Intestinal cancer n = 8	BTC n = 4	Other n = 2	All N = 75
Best overall response*						
CR, n (%)	1 (2.0)	0	0	0	0	1 (1.3)
PR, n (%)	27 (52.9)	2 (20.0)	1 (12.5)	2 (50.0)	1 (50.0)	33 (44.0)
SD, n (%)	21 (41.2)	7 (70.0)	6 (75.0)	2 (50.0)	1 (50.0)	37 (49.3)
PD, n (%)	2 (3.9)	1 (10.0)	1 (12.5)	0	0	4 (5.3)
ORR, n (%) [95% CI]	**28 (54.9) [40.3, 68.9]**	2 (20.0) [2.5, 55.6]	1 (12.5) [0.3, 52.7]	2 (50.0) [6.8, 93.2]	1 (50.0) [1.3, 98.7]	**34 (45.3) [33.8, 57.3]**
DCR, n (%) [95% CI]	49 (**96.1**) [86.5, 99.5]	9 (90.0) [55.5, 99.7]	7 (87.5) [47.3, 99.7]	4 (100.0) [39.8, 100.0]	2 (100.0) [15.8, 100.0]	71 (94.7) [86.9, 98.5]
mDOR (months) [95% CI]	**6.4 [4.6, 8.3]**	9.4 [2.6, NR]	6.4 [NR, NR]	2.8 [2.1, NR]	3.5 [NR, NR]	**6.2 [4.4, 8.3]**

ORR objective responses rate; CR complete response; PR partial response; SD stable disease; PD progression disease; DCR disease control rate; DOR duration of response.
* Tumor response was confirmed based on investigator assessment according to RECIST version 1.1.
Two-sided 95% CI for ORR and DCR was calculated using by Clopper-Pearson exact method. DOR was estimated by Kaplan-Meier method, and the corresponding two-sided 95% confidence interval was calculated using Brookmeyer-Crowley method.

Tumor Response

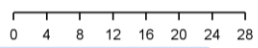




- Among 90 patients with target lesions at baseline, 70 patients showed various degrees of tumor shrinkage.
- GC/GEJ cancer patients with monotherapy (n=59)
  - 51 patients had target lesions: ORR 54.9% (28/51), DCR 96.1% (49/51), mDOR 6.4 months (95% CI, 4.6, 8.3).
  - mPFS 5.8 months (95% CI, 4.1, 8.0), mOS 9.0 months (95% CI, 7.0, 11.9).

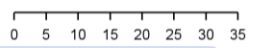
Efficacy - Subgroup Analysis in GC/GEJ

Subgroup	No.of Patients Who Could Be Evaluated	No.of Patients With Event	PFS Estimate [95% CI]
Age			
<=60	49	40	5.6 [3.8, 8.0]
>60	10	9	5.8 [1.9, 14.4]
Sex			
F	29	21	8.0 [5.3, 12.7]
M	30	28	4.2 [3.4, 7.5]
Line of Therapy			
1	22	16	9.3 [3.7, 14.6]
2	26	23	7.1 [3.8, 8.4]
>=3	11	10	4.1 [2.2, 5.3]
Number of Types of Chemotherapy Drugs			
<=2	22	16	6.8 [2.8, 14.6]
>=3	37	33	5.6 [4.0, 8.0]
Lauren Classification			
Diffuse type	26	20	8.0 [4.0, 14.6]
Intestinal type	13	12	5.3 [2.6, 7.5]
Mixed type	12	10	4.2 [2.0, 13.4]
Unknown	8	7	7.2 [1.9, NR]
WHO Classification			
Mucinous adenocarcinoma	1	1	8.6 [NR, NR]
Other	22	19	5.4 [2.6, 7.5]
Signet ring cell carcinoma	33	26	6.8 [3.7, 9.3]
Unknown	3	3	4.2 [3.4, NR]
Claudin18.2 Expression intensity & Rate			
High Expression	46	36	7.1 [4.2, 9.3]
Low/Medium Expression	13	13	4.2 [2.2, 7.2]
Tocilizumab			
N	18	13	4.2 [1.9, 9.3]
Y	41	36	5.8 [3.8, 8.6]
Glucocorticoid			
N	49	41	7.1 [4.2, 8.6]
Y	10	8	3.7 [2.6, 13.4]
Bridging therapy			
N	18	13	6.8 [3.7, 15.2]
Y	41	36	5.6 [4.0, 8.6]
GCSF within 7 days post infusion			
N	52	42	5.8 [3.7, 8.4]
Y	7	7	5.6 [4.2, 13.4]
LD dose adjustment			
N	25	20	4.2 [2.0, 8.6]
Y	34	29	7.1 [4.1, 9.2]
Have Used PD-1/PD-L1			
N	39	31	7.1 [4.1, 9.3]
Y	20	18	5.4 [2.5, 7.8]
Used taxanes			
N	16	11	7.8 [2.0, 27.7]
Y	43	38	5.5 [4.0, 8.0]
Bone Metastatic			
N	51	41	7.5 [5.3, 9.2]
Y	8	8	3.1 [1.7, 3.8]
Liver Metastatic			
N	47	38	7.1 [4.2, 9.2]
Y	12	11	3.9 [1.9, 7.2]
Peritoneum Metastatic			
N	12	11	6.3 [2.6, 13.4]
Y	47	38	5.8 [3.8, 7.8]



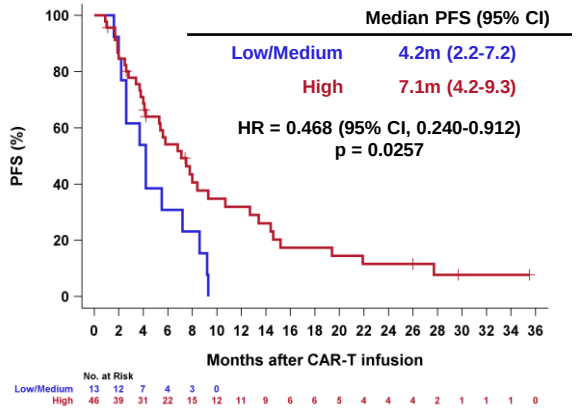
Subgroup Analysis of PFS

Subgroup	No.of Patients Who Could Be Evaluated	No.of Patients With Event	OS Estimate [95% CI]
Age			
<=60	49	41	9.3 [5.8, 11.9]
>60	10	10	8.8 [3.3, 14.6]
Sex			
F	29	23	10.5 [5.8, 21.7]
M	30	28	8.1 [5.7, 11.5]
Line of Therapy			
1	22	18	11.1 [6.9, 17.8]
2	26	22	10.1 [6.7, 20.4]
>=3	11	11	5.7 [2.6, 8.0]
Number of Types of Chemotherapy Drugs			
<=2	22	16	13.9 [5.8, 32.7]
>=3	37	35	8.1 [5.7, 10.5]
Lauren Classification			
Diffuse type	26	21	10.1 [7.0, 17.8]
Intestinal type	13	11	7.4 [5.8, 14.4]
Mixed type	12	12	8.0 [2.0, 29.5]
Unknown	8	7	7.6 [2.6, 18.0]
WHO Classification			
Mucinous adenocarcinoma	1	1	14.4 [NR, NR]
Other	22	17	8.8 [5.8, 20.4]
Signet ring cell carcinoma	33	30	8.1 [4.0, 13.1]
Unknown	3	3	11.5 [7.1, NR]
Claudin18.2 Expression intensity & Rate			
High Expression	46	38	9.2 [6.9, 16.4]
Low/Medium Expression	13	13	8.1 [2.2, 11.5]
Tocilizumab			
N	18	13	14.0 [5.7, 21.7]
Y	41	38	8.1 [5.8, 10.5]
Glucocorticoid			
N	49	41	9.7 [7.1, 14.4]
Y	10	10	6.1 [2.6, 8.1]
Bridging therapy			
N	18	14	9.2 [6.7, 21.7]
Y	41	37	9.0 [5.7, 13.1]
GCSF within 7 days post infusion			
N	52	44	8.3 [6.7, 11.9]
Y	7	7	11.5 [5.8, 29.5]
LD dose adjustment			
N	25	20	9.3 [6.7, 21.7]
Y	34	31	8.3 [5.7, 13.1]
Have Used PD-1/PD-L1			
N	39	31	11.5 [7.1, 17.8]
Y	20	20	6.9 [2.8, 9.0]
Used taxanes			
N	16	11	15.8 [7.0, NR]
Y	43	40	8.0 [5.7, 10.5]
Bone Metastatic			
N	51	43	9.7 [7.1, 14.6]
Y	8	8	4.0 [2.1, 8.1]
Liver Metastatic			
N	47	40	9.5 [7.0, 13.1]
Y	12	11	8.3 [2.6, 18.0]
Peritoneum Metastatic			
N	12	12	14.0 [5.2, 30.3]
Y	47	39	8.1 [6.7, 10.5]

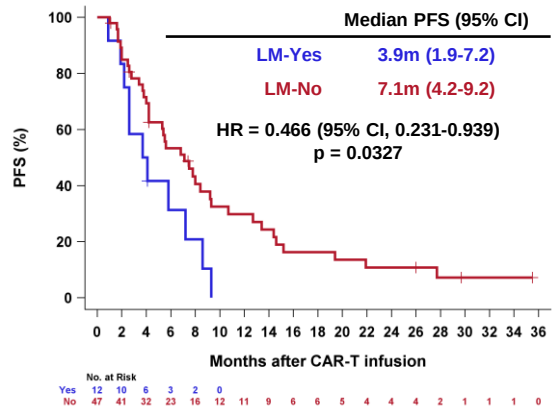


Subgroup Analysis of OS

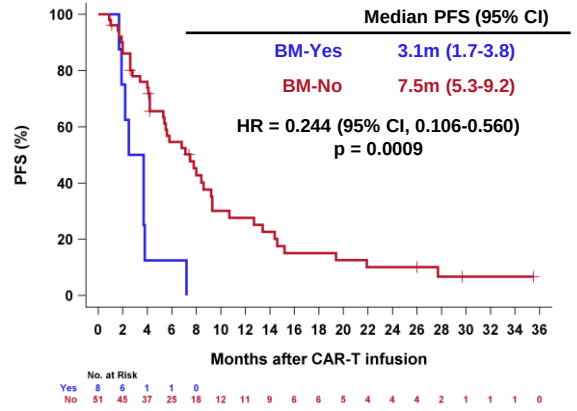
Efficacy - Subgroup Analysis in GC/GEJ



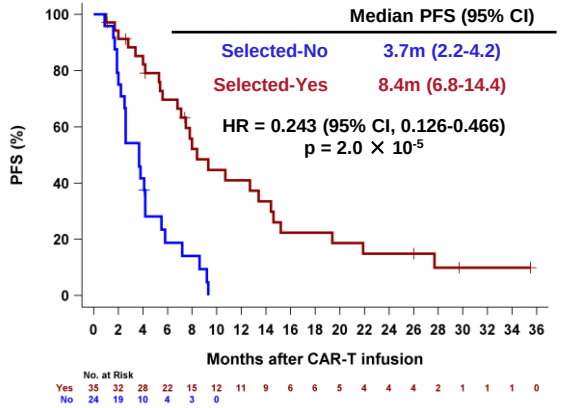
CLDN18.2 expression High vs. Low/Medium

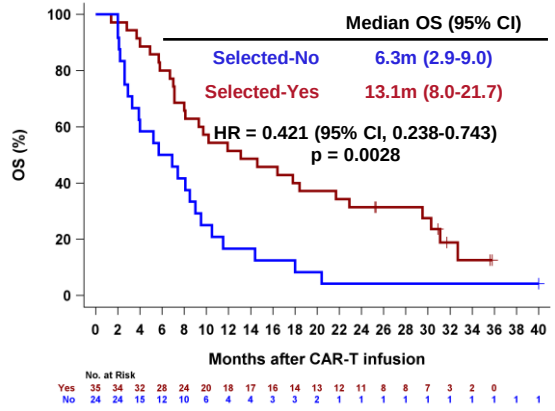


With liver metastasis vs. without liver metastasis



With bone metastasis vs. without bone metastasis

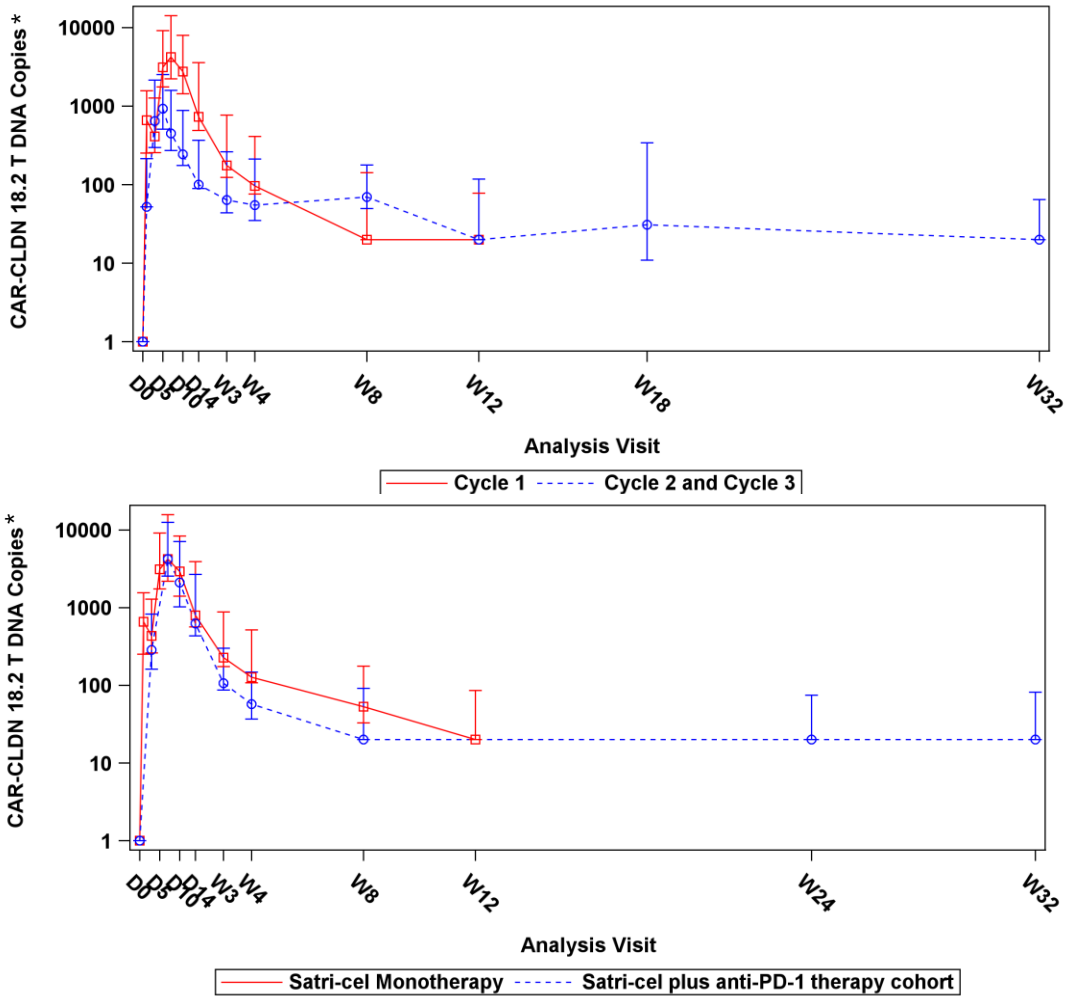




Selected group (CLDN18.2 high expression without liver or bone metastasis) vs. the others

More favorable efficacy signals were identified in those GC/GEJ patients with CLDN18.2 high expression who didn't have liver or bone metastases

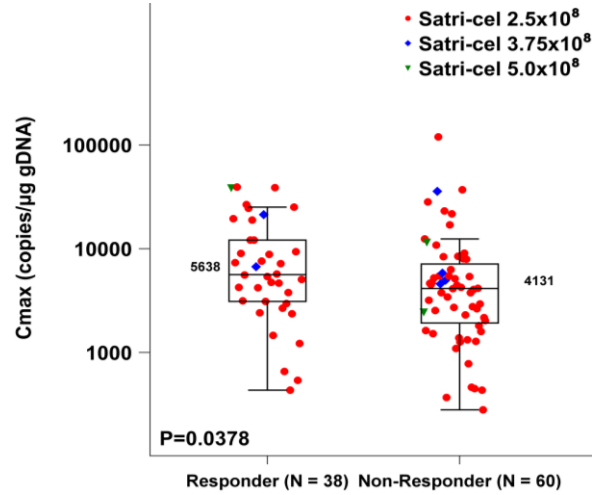
CAR expansion and persistence



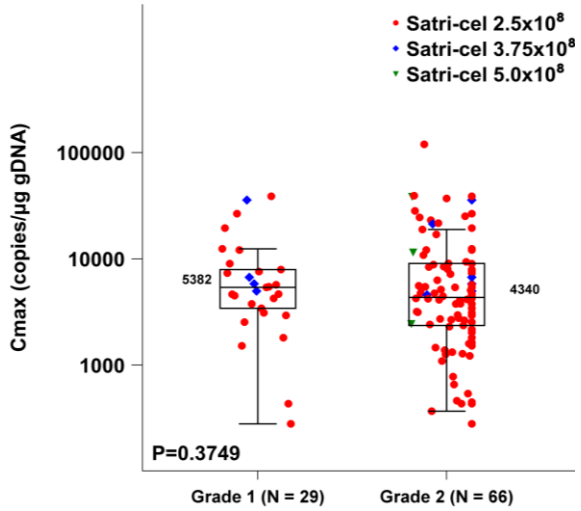
- CAR copies were detected in the peripheral blood of all 98 patients following satri-cel infusion. Generally, the CAR copies can be detected within several hours post infusion.
- After the first infusion, the median time to maximum effect ($\mathbf{T_{max}}$) was **7 d (1–28);** median maximum concentration ($\mathbf{C_{max}}$) was **4,613 copies per µg genomic DNA (gDNA) (280–119,581)**; median persistence ($\mathbf{T_{last}}$) in peripheral blood was 28 d (6–615).
- For the second infusion, the median T_{max} was 3 d (0–10), and the median C_{max} decreased to 1,128 copies per µg gDNA (20–9,877).
- No significant difference was observed in the median C_{max} and persistence of CAR copies after the first infusion between satri-cel monotherapy (n=83) and satri-cel plus Toripalimab (n=15).

*Unit: copies per µg genomic DNA (gDNA)

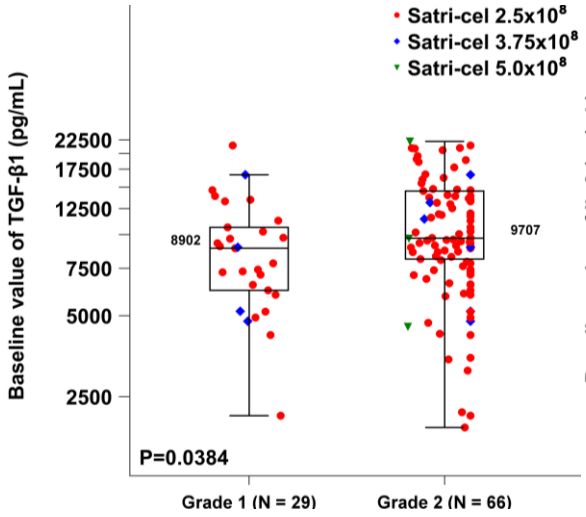
Exploratory Outcomes

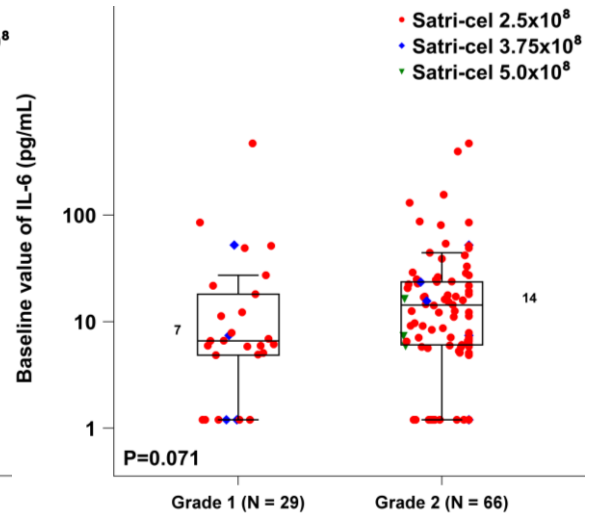


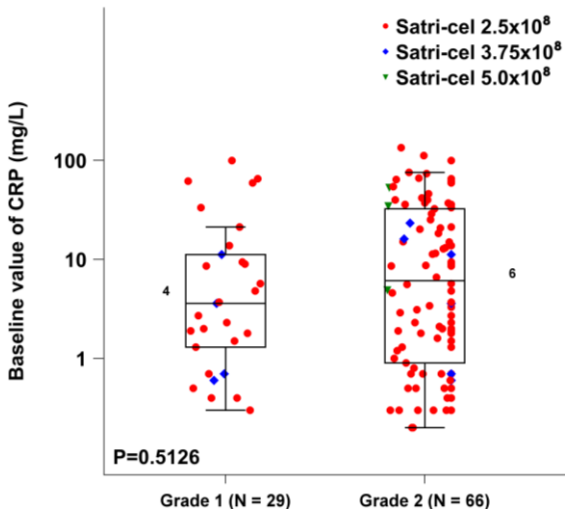
Association between C_{max} and efficacy

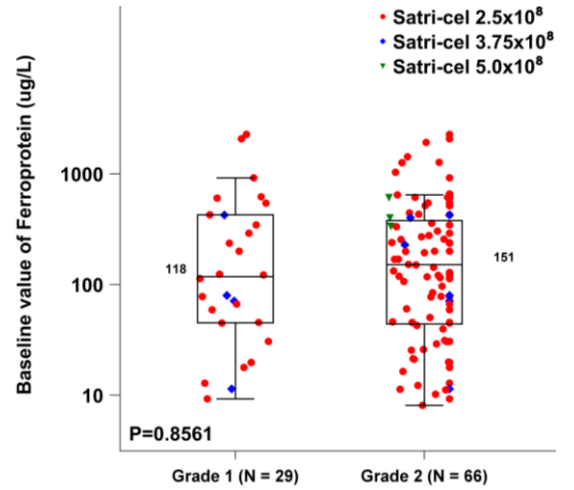


Association between C_{max} and CRS grade









Association between inflammatory markers at baseline and CRS grade

Limitations

- As the majority of GC/GEJ patients at the trial site opted to participate in first-line phase 3 clinical trials including double-blinded ones, there were major challenges in enrolling in Cohort 3 and 4, resulting in a small sample size that affects data interpretability.
- Aside from GC/GEJ cancer, only 14 patients with pancreatic cancer or BTC were enrolled. These cohorts of different treatment modes or tumor types warrant further exploration with larger sample sizes to guide future CAR T treatment strategies and clinical trial designs.
- Regarding the dynamic monitoring of various T cell subsets after CAR T infusion, including the circulation of CAR positive T cells in peripheral blood and CAR T cells infiltration in the lesion sites, warrants further investigation from more prospects.
- This trial was an open-label, single-arm trial design, and did not investigate the effect of satri-cel on quality of life (QoL).

Conclusions/Key takeaways

- Long-term follow-up of satricabtagene autoleucel/CT041 trial demonstrated its highly promising efficacy and manageable safety profile in pretreated patients with CLDN18.2-positive advanced GI cancers, especially GC/GEJ cancer.
- In comparison with traditional anti-tumor approaches, it may greatly impact the existing treatment landscape and propel broader innovative investigations.
- Different combination strategies, frontline and perioperative applications, and molecular biomarkers of efficacy are worthy of exploration in the future.

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