2024 ASCO® ANNUAL MEETING

Phase I study of C-CAR031, a GPC3-specific TGFβRIIDN armored autologous CAR-T, in patients with advanced hepatocellular carcinoma (HCC)

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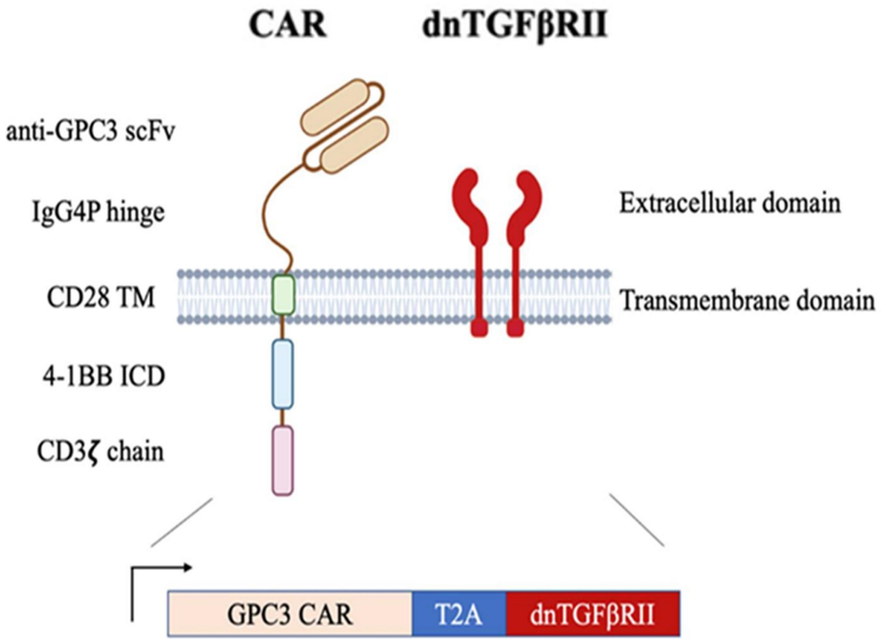
C-CAR031: a dnTGFβRII armored GPC3 CAR-T

GPC3 is an ideal HCC target

- Glypican 3 (GPC3) is highly expressed in the majority of HCC[1] patients and virtually absent in normal adult tissues[2]
- C-CAR031 employs an affinity-tuned anti-GPC3 scFv, further enhancing safety[3]



dnTGFβRII armoring enhances efficacy

- Transforming growth factor (TGF)-β is a potent immunosuppressive cytokine, abundant in the HCC microenvironment[4]
- Co-expression of a dominant negative (dn) receptor protects C-CAR031 from TGF-β-driven immunosuppression, enhancing efficacy[5]

[1]. Moek KL et al, Am J Pathol. 2018 Sep;188(9):1973-1981; [2]. Batra et al, Cancer Immunol Res. 2020 Mar;8(3):309-320; [3]. Giardino Torchia MI et al, Cytotherapy. 2022 Jul;24(7):720-732; [4]. Dahmani and Delisle Implications for Cancer Immunotherapy. Cancers (Basel). 2018 Jun 11;10(6):194; [5]. Wieser et al, Mol Cell Biol. 1993 Dec;13(12):7239-47.

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C-CAR031 Study Design

A phase I, open-label, dose escalation and expansion study conducted in China

Primary Objectives:

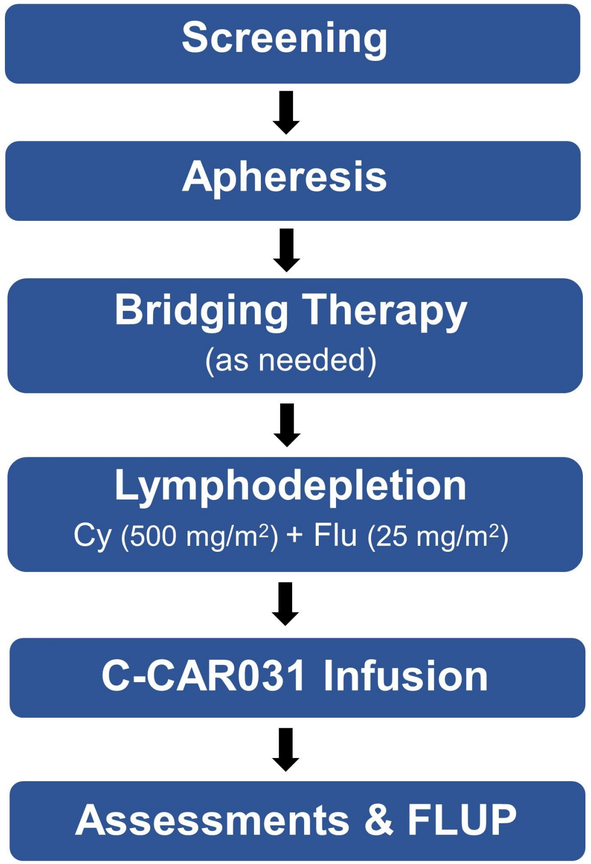
- Safety and Tolerability (incidence and severity of TEAEs including DLTs)

Secondary Objectives:

- Investigator-assessed ORR, DCR, DoR, PFS per RECIST v1.1, and OS

Key Eligibility Criteria:

- 18-75 years of age
- Histologically confirmed GPC3+ HCC
- BCLC B/C, Child-Pugh A
- Relapsed/progressed/intolerant to HCC systemic therapies (≥1 line)
- No active CNS involvement



Screened
(N=87)

Infused
(N=24)

Safety Analysis Set
(N=24)

Efficacy Analysis Set*
(N=23)

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*. One patient (at DL3) who had major protocol deviation was not included for PK/PD and efficacy analysis.

TEAE, Treatment Emergent Adverse Event; DLT, Dose Limiting Toxicitiy; ORR, Objective Response Rate; DCR, Disease Control Rate; DoR, Duration of Response; PFS, Progression Free Survival; OS, Overall Survival; CNS, Central Nervous System; Cy, Cyclophosphamide; Flu, Fludarabine; FLUP, follow-up

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Demographic and Baseline Characteristics

Characteristics	DL 1 N=1	DL 2 N=6	DL 3 N=9	DL 4 N=8	Overall N=24
Male, n (%)	1 (100)	6 (100)	9 (100)	6 (75.0)	22 (91.7)
Median Age, years (range)	50	48 (27, 62)	51 (35, 57)	49 (25, 59)	50 (25, 62)
ECOG PS, n (%)					
• 0	0	0	2 (22.2)	0	2 (8.3)
• 1	1 (100)	6 (100)	7 (77.8)	8 (100)	22 (91.7)
BCLC Stage C, n (%)	1 (100)	6 (100)	9 (100)	8 (100)	24 (100)
Child-Pugh Score, n (%)					
• 5-6	0	6 (100)	9 (100)	7 (87.5)	22 (91.7)
• ≥7[1]	1 (100)	0	0	1 (12.5)	2 (8.3)
Cirrhosis, n (%)	1 (100)	5 (83.3)	7 (77.8)	5 (62.5)	**18 (75.0)**
HBV Infection, n (%)	1 (100)	6 (100)	9 (100)	8 (100)	**24 (100)**
Baseline Target Lesions					
• Intrahepatic Lesions, n (%)	1 (100)	3 (50.0)	4 (44.4)	6 (75.0)	14 (58.3)
• Extrahepatic Metastasis, n (%)	**1 (100)**	**6 (100)**	**7 (77.8)**	**6 (75.0)**	**20 (83.3)**
• Lung[2]	0	5 (83.3)	6 (66.7)	6 (75.0)	**17 (70.8)**
• Lymph node[2]	1 (100)	2 (33.3)	2 (22.2)	0	5 (20.8)
Median SLD (mm)[3], (range)	**77.9**	**87.6 (13.3, 121.7)**	**52.3 (12.9, 125.3)**	**84.4 (33.6, 179.4)**	**73.8 (12.9, 179.4)**
Median Number of Prior Lines of Therapies, (range)	**4**	**2.5 (1, 6)**	**3 (1, 4)**	**5 (3, 6)**	**3.5 (1,6)**
• ≥3, n (%)	**1 (100)**	**3 (50.0)**	**6 (66.7)**	**8 (100)**	**18 (75.0)**
Received Both IO and VEGF(R) inhibitors[4]	**1 (100)**	**6 (100)**	**8 (88.9)**	**8 (100)**	**23 (95.8)**

[1]. Data collected at baseline. All enrolled patients had Child-Pugh score of 5-6 at screening; [2]. listed selected extrahepatic metastasis only, not all; [3]. Per RECIST1.1; [4]. IO defined as immune checkpoint inhibitors, and VEGF(R) inhibitors defined as anti-angiogenesis agents such as Bevacizumab (or its biosimilars), Tyrosine kinase inhibitors such as Sorafenib, Lenvatinib, Apatinib and etc.

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C-CAR031 Showed Favorable Safety Profile

Most patients experienced Grade 1/2 CRS

Adverse Events	N=24 n (%)
TRAEs[1]	24 (100)
• Grade 3/4	9 (37.5)
• Grade 5	0
SAE[2]	5 (20.8)
AESI	22 (91.7)
• CRS*	22 (91.7)
• Grade 3	**1 (4.2)**
• ICANS*	0

CRS	DL 1 N=1	DL 2 N=6	DL 3 N=9	DL 4 N=8	Overall N=24
***CRS, n (%)**	1 (100)	5 (83.3)	8 (88.9)	8 (100)	22 (91.7)
• Grade 1/2	1 (100)	5 (83.3)	8 (88.9)	7 (87.5)	21 (87.5)
• Grade 3	0	0	0	**1 (12.5)**	**1 (4.2)**
Median Days to Onset, d (range)	7 (7, 7)	3 (2, 3)	3 (2, 4)	2 (1, 3)	**3 (1, 7)**
Median Days to Resolution, d (range)	4 (4, 4)	6 (4, 8)	3 (2, 6)	5 (3, 8)	**4 (2, 8)**
Treated with					
• Tocilizumab, n (%)	0	4 (66.7)	6 (66.7)	7 (87.5)	17 (70.8)
• Corticosteroids, n (%)	0	2 (33.3)	1 (11.1)	1 (12.5)	4 (16.7)

TRAE, treatment-related adverse event; SAE, serious adverse event; AESI, adverse event of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

[1]. Defined as C-CAR031 related; [2]. Only 2 cases were C-CAR031 related; *, CRS/ICANS were graded per ASTCT Consensus (2019)

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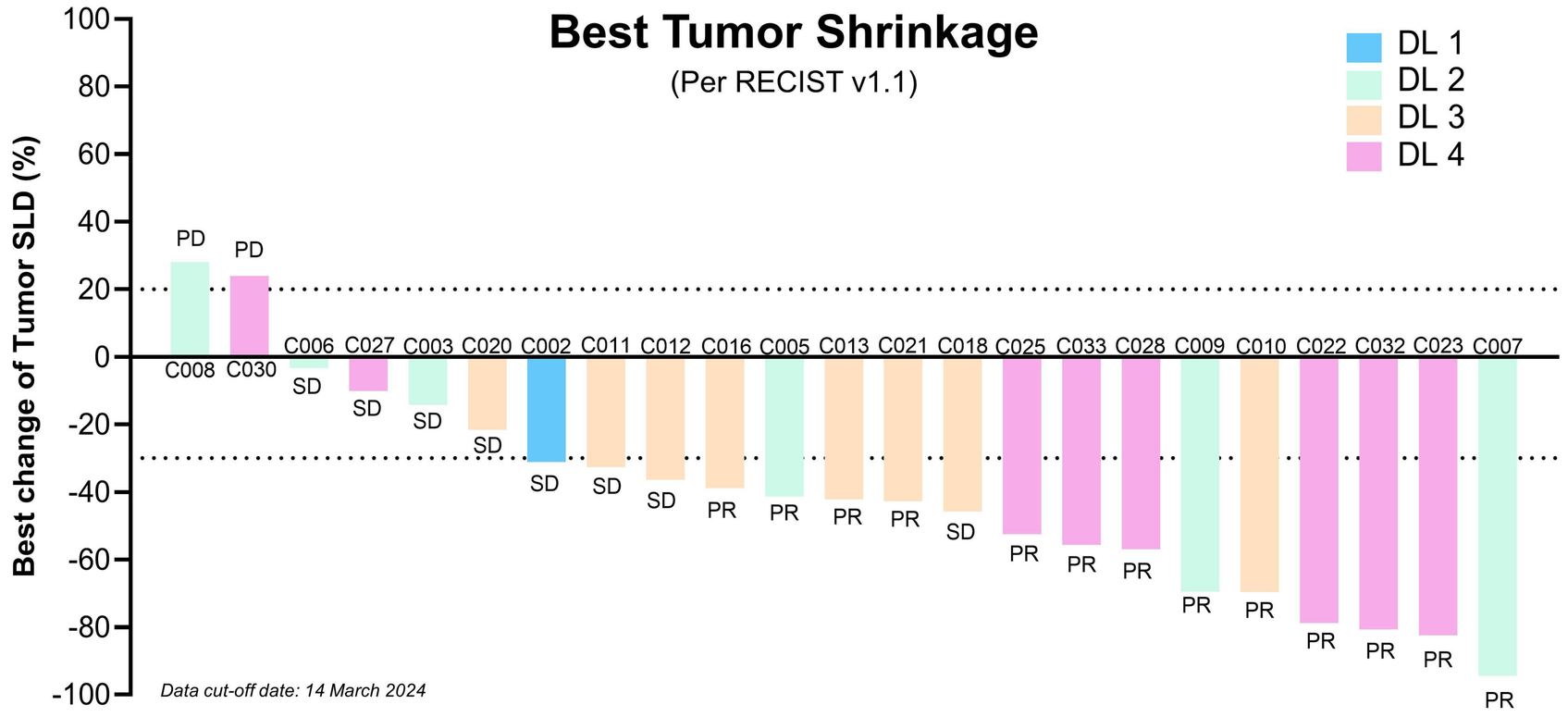
C-CAR031 Showed Encouraging Tumor Responses in Late Line HCC



ORR (all confirmed PR)

- **56.5%** overall
- **75.0%** at DL 4

DCR

- **91.3%** overall

Tumor Size Reductions

- **42.2%** median target lesion reductions (range: -28.1% to 94.4%)

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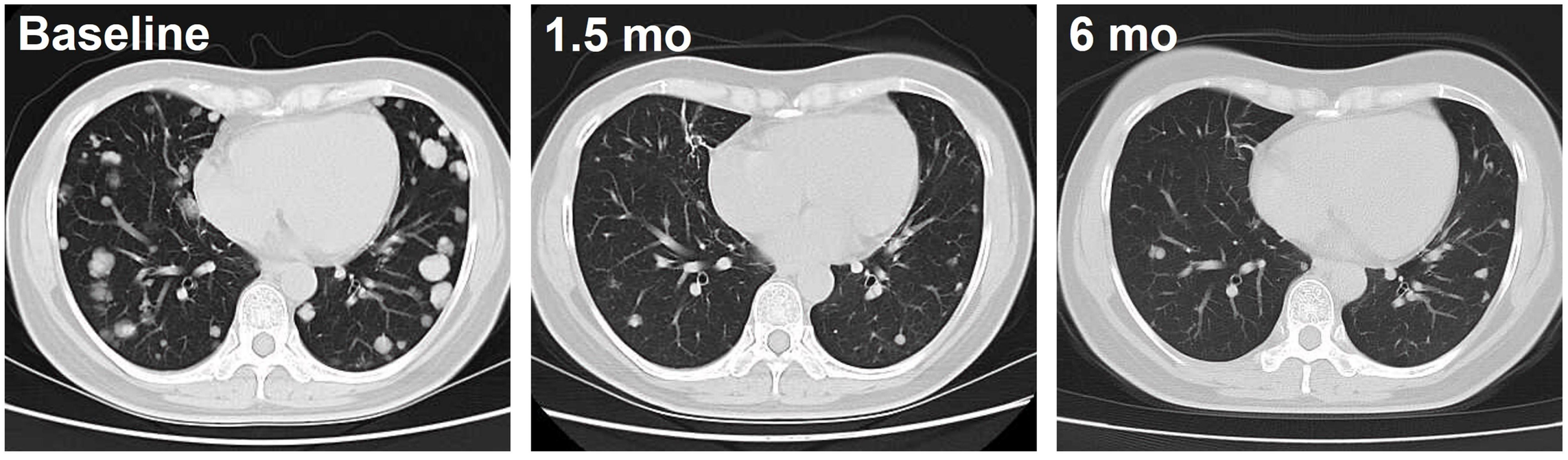
C-CAR031 Showed Encouraging Tumor Responses in Late Line HCC

C023 (at DL 4) showed deep response in lung metastases starting from 1.5 mo



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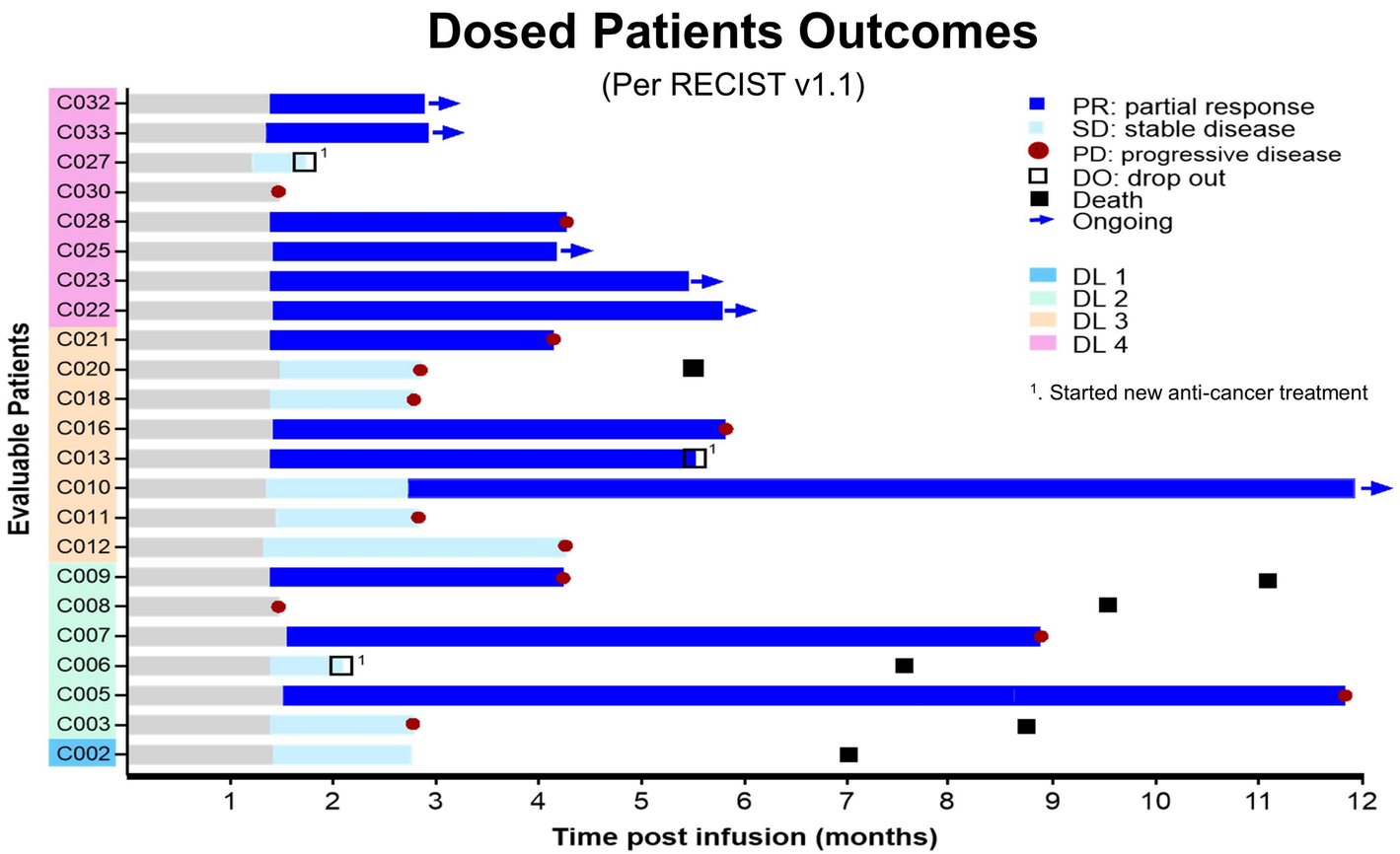
C-CAR031 Showed Early Signs of Durability



- **mFLUP: 9.03 Mo**
- FLUP continuing
- **mDoR: 7.36 Mo (2.9-NE）**
- **5/10** evaluated pts had durable response at 6 Mo
- **mOS: not reached**
- KM estimated mOS: 11.14 Mo (7.4-NE)

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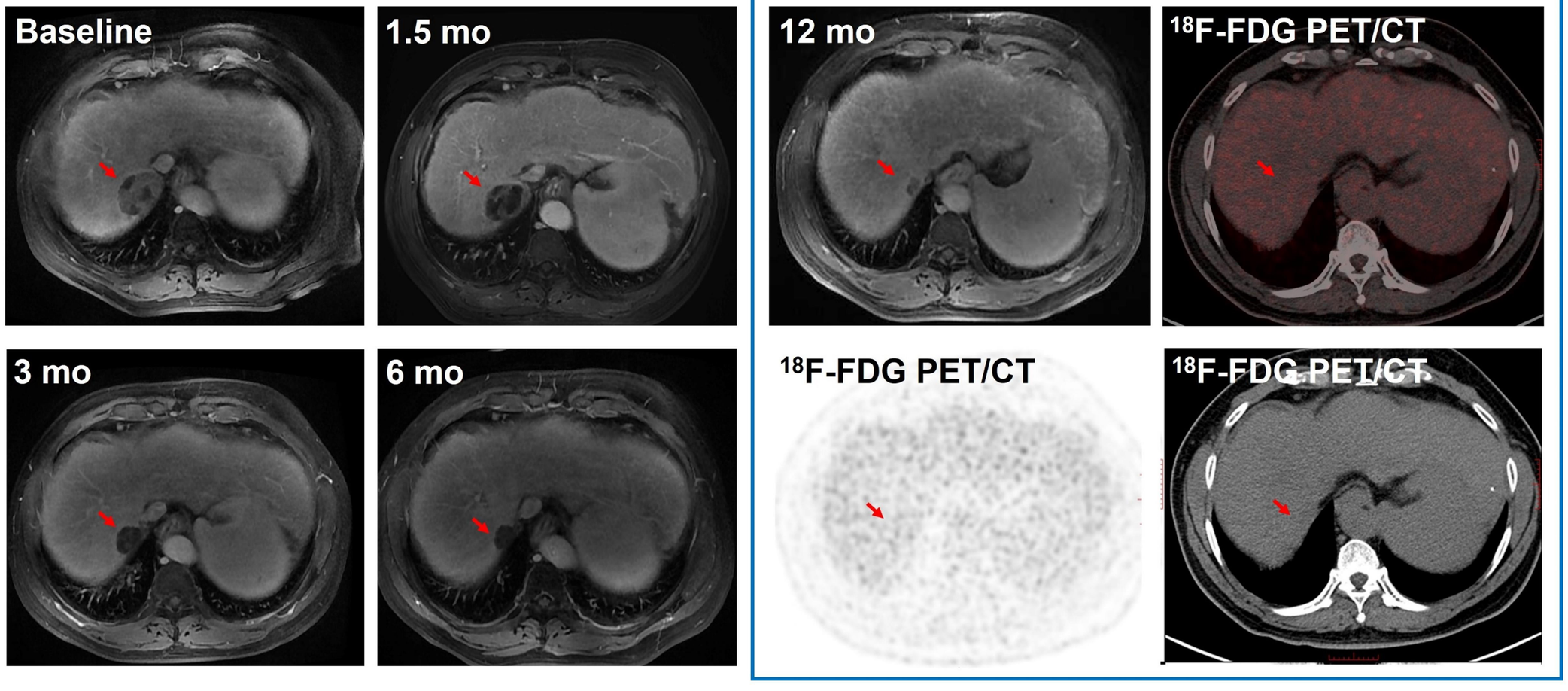
C-CAR031 Showed Early Signs of Durability

C010 (at DL 3) showed durable response up to 12 mo and potentially beyond



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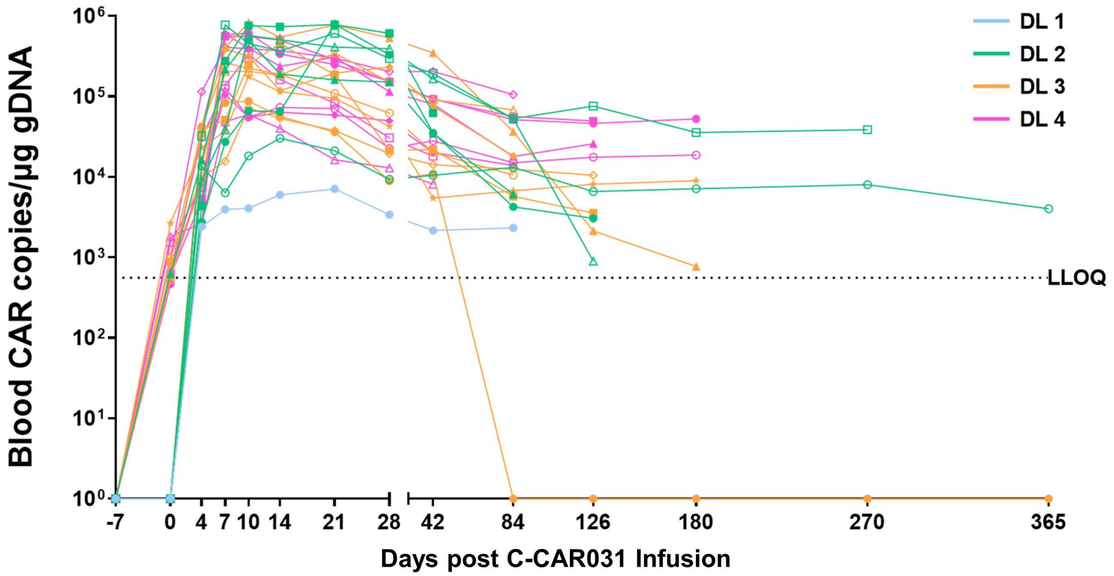
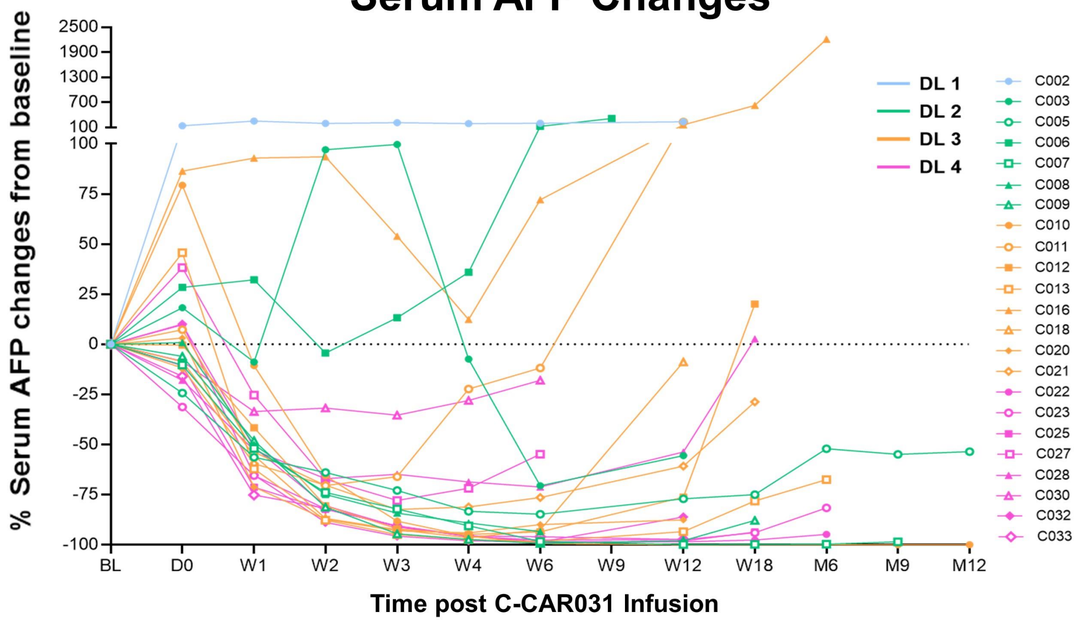
C-CAR031 Demonstrated Rapid, Robust Cellular Expansion and Persistency with Significant AFP Reduction in Patients

CAR-T Cellular Kinetics



Serum AFP Changes



Cellular Kinetics Parameters	$AUC_{0\sim28day}$ (CAR copies/μg gDNA*day)	C_{max} (CAR copies/μg gDNA)	T_{max} (days)	T_{last} (days)
Median (range)	4.5×10^6 (1.3×10^6, 14.3×10^6)	3.9×10^5 (7.1×10^3, 8.3×10^5)	10 (7, 21)	125+ (43, 271+)

Best Change of AFP from Baseline	DL 1 N=1	DL 2 N=6	DL 3 N=8	DL 4 N=8	Overall N=23
Median% (range)	193 (193, 193)	-89 (-4, -100)	-94 (12, -99)	-97 (-35, -100)	-94 (193, -100)

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C-CAR031: Conclusions

- In this FIH study, C-CAR031 was **well tolerated**
- C-CAR031 showed **rapid, robust expansion and persistency**
- C-CAR031 showed **encouraging early efficacy** in heavily treated HCC patients:
  - **56.5% ORR** overall, **75.0% ORR** at DL4
  - Tumor reductions in both **intra- and extra-hepatic lesions**
- With a median FLUP time of 9.03 months, C-CAR031 showed **promising durability**

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Acknowledgments

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- This study was funded by AbelZeta and AstraZeneca

- The study can be found at *ClinicalTrials.gov* with identifier of NCT05155189
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