First report of preliminary safety, efficacy, and pharmacokinetics of C-CAR031 (GPC3-specific TGFβRIIDN CAR-T) in patients with advanced HCC

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ABSTRACT

Introduction: Chimeric antigen receptor (CAR) T cells can mediate deep and durable responses in hematologic malignancies, however, achieving success in solid tumors has been so far limited largely by the lack of suitable solid tumor-associated antigens and the immunosuppressive tumor microenvironment (TME). GPC3 is a surface antigen overexpressed in hepatocellular cancer (HCC) and virtually absent on healthy tissues. In this first-in-human (FIH) study, we investigated the feasibility, safety and initial anti- HCC efficacy of C-CAR031. C-CAR031 is an autologous, GPC3-directed armored CAR-T with affinity-tuned scFv to enhance its safety profile, and a 4-1BB and CD3z signaling domain. The C-CAR031 transgene includes a T2A viral self-cleaving peptide and a dominant negative TGF-β receptor II (TGFβRIIDN). The expression of TGFβRIIDN protects the cells against the immunosuppressive HCC TME and the T2A peptide allows for equimolar expression of the two transgene products. **Methods:** This FIH, open-label dose escalation trial employs an accelerated titration plus i3+3 design. Histologically confirmed GPC3+ advanced HCC patients (pts) who failed systemic treatments received a single-dose i.v. infusion of C-CAR031 following standard lymphodepletion. The primary objective was to assess the safety and tolerability. Adverse events (AEs) were graded using CTCAE 5.0, and cytokine release syndrome (CRS) / immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT 2019 criteria. **Results:** As of Dec. 31st 2022, 7 pts received two dose levels (DL1, n=1; DL2, n=6) of C-CAR031. The median number of prior lines of therapies was 4 (range 1-6). The median follow-up was 77 (40-213) days. Six pts with ≥28 days' follow-up were eligible for safety evaluation. The only ≥Gr3 non-hematologic product-related AE observed was transient Gr3 AST elevation in two pts. Five of 6 pts experienced Gr1/2 CRS, with median time to onset of 3 (range 2-7) and duration of 4 (4-6) days. No DLT or ICANS was observed. Of the 5 pts evaluable for preliminary efficacy, 4 pts had unconfirmed PR, which are currently pending confirmation. AFP was also stabilized or reduced in all 4 patients with uPR. All 5 pts had reduction in tumor burden, with a median change of -31.2% (range -3.4- -60.6%) / -41.4% (-3.4- -56.6%) per RECIST v1.1 / modified RECIST (2010). C-CAR031 showed a robust cellular kinetic profile. In DL2, the median T_{max}, C_{max} and $AUC_{0\text{-}28Day}$ were 15 days, 772,014 copies/μg gDNA and 7,747,054 days*copies/μg gDNA, respectively. CAR-T cells were detectable in blood of all pts in the last follow-up.

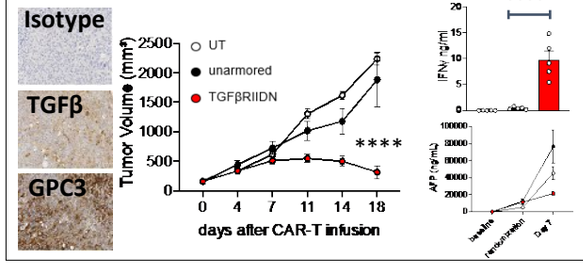
------ The poster has been updated with a later cut-off of Mar. 2nd, 2023. ------

PRECLINICAL STUDIES

Figure 1. Schematic of CAR construct

- GPC3 CAR contains a 4-1BB+CD3ζ cytoplasmic domain.
- TGFβRIIDN is expressed following a T2A peptide.

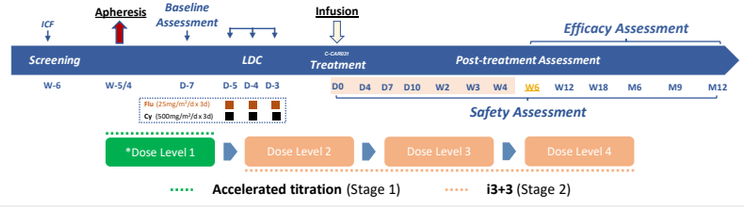
Figure 2. TGFβRIIDN armored CAR-T achieves enhanced anti-tumor efficacy in TGFβ^{hi} HCC PDX models



5 x 10^6 CAR-T cells were injected into NSG mice bearing GPC3$^+$ TGFβ$^+$ HCC PDX tumors. Serum levels of IFNγ were quantified 7 days post-CAR-T infusion. AFP was quantified in serum of mice before tumor implantation (baseline) , at randomization and at day 7 post T cell-infusion.

STUDY DESIGN

Figure 3. C-CAR031 Study Design (Phase 1 Trial)



Endpoints:

- Primary: Safety and Tolerability defined as incidence and severity of AEs including DLTs per CTCAE v5.0, ICANS and CRS per ASTCT Consensus Grading (2019)
- Secondary: Efficacy defined as investigator assessed Objective Response Rate (ORR), Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
- Exploratory: CAR-T expansion and persistence; ORR, DOR, PFS and OS per modified RECIST (2010) (mRECIST)

Key Eligibility Criteria:

- 18-75 years of age
- Histologically confirmed GPC3+ HCC
- Failure or intolerant of ≥ 1 prior line(s) of systemic therapy, or refused prior systemic therapy
- BCLC B/C, Child-Pugh ≤ 6
- ≥ 1 measurable target lesion(s) per RECIST 1.1
- ECOG 0/1, life expectancy ≥ 3 months
- No active CNS involvement or extensive bone metastasis

RESULTS

Table 1. Patient Characteristics

Baseline Characteristics	Total (N=7)
Age, Median (range), year	48 (27–62)
Sex [n (%)]	
Male	7 (100)
Female	0
ECOG PS=1 [n (%)]	7 (100)
BCLC Stage [n (%)]	
B	0
C	7 (100)
Extrahepatic metastasis [n (%)]	6 (85.7)
Child-Pugh [n (%)]	
5	5 (71.4)
6	1 (14.3)
8	1 (14.3)
Number of prior lines of therapy [n (%)]	
1	1 (14.3)
2	2 (28.6)
4	3 (42.9)
6	1 (14.3)
Prior Therapies [n (%)]	
TKI	4 (57.1)
ICI	2 (28.6)
TKI+ICI	5 (71.4)
ICI+VEGF mAb	2 (28.6)
Others	1 (14.3)
Received Bridging Therapy [n (%)]	3 (42.9)

Table 2. Treatment Emergent Adverse Events (TEAEs) (>20%)

Preferred Term	Total (N=7) Any grade n (%)	Total (N=7) Grade ≥3 n (%)
Hematological toxicity		
Lymphocyte count decreased	7 (100)	7 (100)
White blood cell count decreased	7 (100)	6 (85.7)
Neutrophil count decreased	7 (100)	5 (71.4)
Anemia	5 (71.4)	0
Platelet count decreased	3 (42.9)	2 (28.6)
Non-hematological toxicity		
Cytokine release syndrome	6 (85.7)	0
Cough	5 (71.4)	0
Aspartate aminotransferase increased	3 (42.9)	2 (28.6)
Hypokalaemia	3 (42.9)	1 (14.3)
Abdominal distension	3 (42.9)	0
Pyrexia	3 (42.9)	0
Myalgia	3 (42.9)	0
Productive cough	3 (42.9)	0
COVID-19	2 (28.6)	
Abdominal pain	2 (28.6)	1 (20.0)
Proteinuria	2 (28.6)	0
Hypoalbuminemia	2 (28.6)	0

Table 3. Cytokine Release Syndrome (CRS)

CRS, n (%)	Any grade (N=6)	Grade ≥3 (N=0)
Median days to onset, days (range)	3 (2–7)	NA
Median days to resolution, days (range)	5 (4–6)	NA
Treated with tocilizumab, n (%)	4 (66.7%)	NA
Treated with steroids, n (%)	3 (50.0%)	NA

Good safety profile at explored dose levels

- **DLT**: not observed
- **ICANS**: not observed
- **Mild CRS only:** Gr2, 2/7; Gr1, 4/7

Figure 4. Early Efficacy Readout

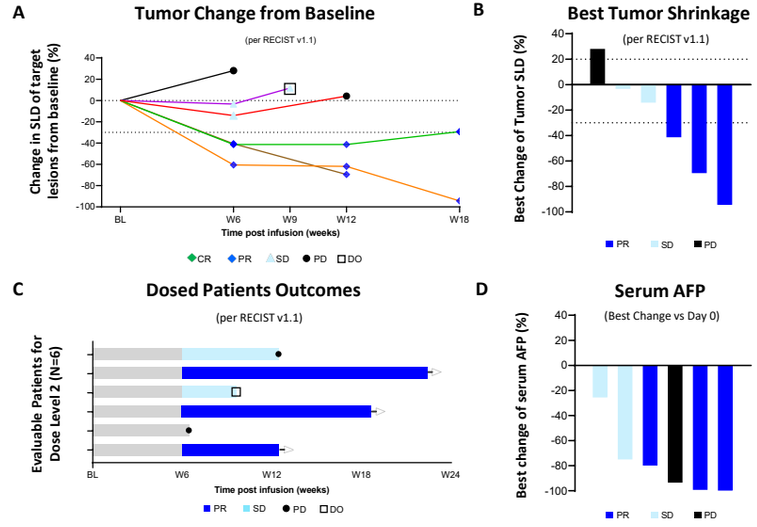


Table 4. Preliminary Pharmacokinetic Summary

Patient ID	$AUC_{0\text{-}28d}$ (days*copies/μg gDNA)	C_{max} (copies/μg gDNA)	T_{max} (days)	T_{last} (days)	FLUP Last (days)
1	7,747,054	789,517	21	149+	149
2	368,852	30,132	15	130+	130
3	9,887,115	781,716	21	67+	67
4	9,058,864	772,014	8	131+	131
5	4,907,518	500,277	10	80+	80
6	7,290,957	572,924	10	88+	88

Results: As of Mar 2nd, 2023, all 6 patients at dose level 2 (DL2) are evaluable for efficacy. Per RECIST v1.1, 5 patients showed tumor shrinkage post C-CAR031 treatment, 3 patients had confirmed PR and the other 2 patients had stable disease (SD). One of the SD patients was PR per mRECIST at W6. (Fig. 4A-4C). The first and only patient in DL1 had stable disease (SD) with tumor shrinkage at W6, unconfirmed PR at W12 and dropped out thereafter (data not shown). AFP was stabilized or reduced in all of the 6 pts in DL2 (Fig. 4D). C-CAR031 showed a robust cellular kinetic profile including strong expansion in peripheral blood. Presented are the summarized PK data for the 6 patients in DL2, and the CAR-T cells were detectable in blood of all pts in the last follow up (67-149 days) (Table 4).

CONCLUSIONS

In this FIH study, C-CAR031 is well tolerated and shows promising anti-tumor activity. Enrollment is ongoing to confirm initial results.

REFERENCE/ACKNOWLEDGEMENT

Abstract 2837, AACR Annual Meeting 2022.
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