C-CAR039, a Novel Anti-CD20/CD19 Bi-Specific CAR T-Cell Therapy Shows Deep and Durable Clinical Benefits in Patients with Relapsed or Refractory (r/r) B-Cell Non-Hodgkin Lymphoma (B-NHL) in Long Term Follow up

Ping Li[1], Wenjuan Yu[2], Lili Zhou[1], Min Yang[2], Shiguang Ye[1], Judy Zhu[3], Jiaqi Huang[3], Yan Zhang[4], Lanfang Li[5], Jing Zhao[5], Kevin Zhu[6], Jing Li[3], Chengxiao Zheng[3], Liping Lan[3], Hui Wan[3], Yihong Yao[3], Huilai Zhang[5], Daobin Zhou[4], Jie Jin[2], Aibin Liang[1]

[1] School of Medicine, Tongji Hospital of Tongji University, Shanghai, China; [2] The First Affiliated Hospital, Zhejiang University School of Medicine; [3] Shanghai AbelZeta Ltd., Shanghai, China; [4] Peking Union Medical College Hospital; [5] Tianjin Medical University Cancer Institute & Hospital; [6] University of Maryland School of Medicine

Background

- Anti-CD19 CAR T-cell therapies have proven to be efficacious in r/r B-NHL patients. However, ~20% of LBCL patients and ~10% of indolent patients are non-responders[1-5], and responders may relapse due to the emergence of CD19-negative tumor clones[6]
- Targeting two different antigens may reduce the risk of relapse by preventing antigen escape
- C-CAR039, an autologous anti-CD20/CD19 bispecific CAR-T, previously demonstrated a favorable safety profile and promising efficacy among 28 patients with r/r B-NHL[7]
  - **ORR was 92.6%, with 85.2% CR**
  - **At a median follow-up of 7 months, 6-month PFS rate was 83.2%**
- Here, we present updated results to include additional patients and a longer follow-up of 30.0 months

r/r, Relapsed or Refractory; B-NHL, B-Cell Non-Hodgkin Lymphoma; ORR, Overall Response Rate; CR, Complete Response; PFS, Progression-Free Survival.

1. N Engl J Med. 2017 Dec 28;377(26):2531-2544. 2. N Engl J Med. 2019 Jan 3;380(1):45-56. 3. Lancet. 2020 Sep 19;396(10254):839-852. 4. Lancet Oncol. 2022 Jan;23(1):91-103. 5. Nat Med. 2022 Feb;28(2):325-332. 6. Blood. 2021 Sep 23;138(12):1081-1085. 7. Liang et al. ASCO 2021. #2507

Study Design

- A phase 1, open-label, dose escalation and expansion study conducted at four sites in China

Primary Objective:
- Incidence and severity of treatment-emergent adverse events

Secondary Objectives:
- ORR, DOR, PFS, OS by investigator (Lugano 2014)

Key Eligibility Criteria
- 18-75 years
- r/r B-NHL including DLBCL, FL, MCL
- Either CD19 or CD20 positive
- No active CNS involvement
- Prior regimens including anti-CD20 monoclonal antibodies

Screening
↓
Apheresis
↓
Bridging Therapy
(if needed)
↓
Lymphodepletion
Cy (300 mg/m^2) + Flu (30 mg/m^2)
↓
C-CAR039 infusion
1.0-5.0×10^6/Kg
↓
Assessments & Follow-Up

Apheresed
(N=53)
↓
Infused
(N=48)
↓
Safety analysis Set
(N=48)
↓
Efficacy analysis Set*
(N=47)

Cutoff date: Sep 25, 2023

*1 patient who had no measurable disease at baseline was not included.

ORR, Overall Response Rate; DOR, Duration of Response; PFS, Progression-Free Survival; OS, Overall Survival; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular Lymphoma; MCL, Mantle Cell Lymphoma; CNS, Central Nervous System.

Demographic and Baseline Characteristics

Characteristics	N=48
Median Age, years (range)	55 (25-71)
• Age ≥ 65, n (%)	11 (22.9)
Male, n (%)	30 (62.5)
NHL Subtype, n (%)	
• DLBCL,NOS	37 (77.1)
• tFL	4 (8.3)
• PMBCL	3 (6.3)
• FL	3 (6.3)
• MCL	1 (2.1)
Dose Level, n (%)	
• 1.0×10^6/kg	4 (8.3)
• $2.0/2.5 \times 10^6$/kg	31 (64.6)
• $4.0/5.0 \times 10^6$/kg	13 (27.1)

Characteristics	N=48
ECOG PS, n (%)	
• 0	31 (64.6)
• 1	17 (35.4)
IPI Score 3/4, n (%)	15 (31.3)
Ann Arbor Stage III / IV, n (%)	36 (75.0)
Double-expressor Lymphoma, n (%)	15 (31.3)
Median Number of Prior Lines of Therapy, (range)	3 (1-7)
• ≥4, n (%)	16 (33.3)
Never Achieved CR of Prior Therapies, n (%)	22 (45.8)
Prior Therapy, n (%)	
• CD20	48 (100)
• ASCT	8 (16.7)
Received Bridging Therapy, n (%)	12 (25.0)

- **Of 48 patients, 44 (91.7%) were large B-cell lymphoma (LBCL), which includes DLBCL, NOS, tFL, and PMBCL**

NHL, Non-Hodgkin Lymphom; DLBCL,NOS, Diffuse large B-cell lymphoma, Not Otherwise Specified; PMBCL, Primary Mediastinal Large B-cell lymphoma; tFL, Transformed Follicular Lymphoma; FL, Follicular Lymphoma; MCL, Mantle Cell Lymphoma; IPI, International Prognostic Index; CR, Complete Response; ASCT, Autologous Stem Cell Transplant.

C-CAR039 Demonstrates A Favorable Safety Profile with No New Safety Signals Observed after More Than 2 Years

AESI, n (%)	N=48
CRS	45 (93.8)
• Grade≥3	1 (2.1)
• Median days to onset, d (range)	3 (1-12)
• Median days to resolution, d (range)	5 (2-78)
ICANS	3 (6.3)
• Grade≥3	0
• Median days to onset, d (range)	6 (5-29)
• Median days to resolution, d (range)	12 (3-53)
Prolonged Cytopenia*	
• Neutropenia	26 (54.2)
• Thrombocytopenia	10 (20.8)
• Anemia	10 (20.8)
Infections	32 (66.7)
• Grade ≥3	12 (25.0)
Secondary Primary Malignancy	3 (6.3)
• Acute myeloid leukemia	2 (4.2)
• EBV+ cytotoxic T-cell lymphoma §	1 (2.1)

- **No new safety signals observed** with longer follow-up
- **Most patients experienced Grade 1/2 CRS**
  - Only 1 patient experienced grade 3 CRS, and recovered after tocilizumab and corticosteroids treatment
- **No patients experienced ICANS at the RP2D**
  - 3 patients who experienced ICANS all received C-CAR039 at the 5.0×10^6/kg dose
- 66.7% experienced infection, most were grade 1/2
- SPM occurred in 3 patients, none of them were related to C-CAR039

*Defined as grade 3 or higher cytopenias not resolved by Day 30 following C-CAR039 infusion
§ One EBV+ DLBCL patient diagnosed EBV+ T-cell lymphoma at 8 months after infusion. The tumor biopsy was negative for CAR transgene. Treatment-free remission for T cell lymphoma was 26 months by cutoff date
AESI: Adverse Events of Special Interest; CRS: Cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome; EBV+: Epstein-Barr virus-positive; SPM: Secondary primary malignancy; RP2D, Recommended phase 2 dose

Serious Adverse Events and Death

SAE, n (%)	N=48
SAE	19 (39.6)
• Related to C-CAR039	11 (22.9)
SAE Starting Time	
• ≤ 90 days after infusion	10 (20.8)
• >90 days of infusion	14 (29.2)
Most Common SAE (≥5%)	
• Febrile neutropenia	4 (8.3)
• Pneumonia	4 (8.3)
• Pneumonitis	3 (6.3)

- 19 patients had SAEs (11 were C-CAR039 related)
- Most common (≥5%) C-CAR039-related SAE was febrile neutropenia (8.3%)

Death, n	N=48	Median days of death post infusion, (range)
Total death to cutoff date, n	15	336 (94-948)
• **Due to disease progression**	11*	218 (94-948)
• **AE unrelated to C-CAR039**	4	583 (336-801)
Acute myeloid leukemia	2	565 (336-794)
Unknown cause	1	371
Pulmonary fibrosis §	1	801
• **AE related to C-CAR039**	1*	157
Pneumonia	1*	157

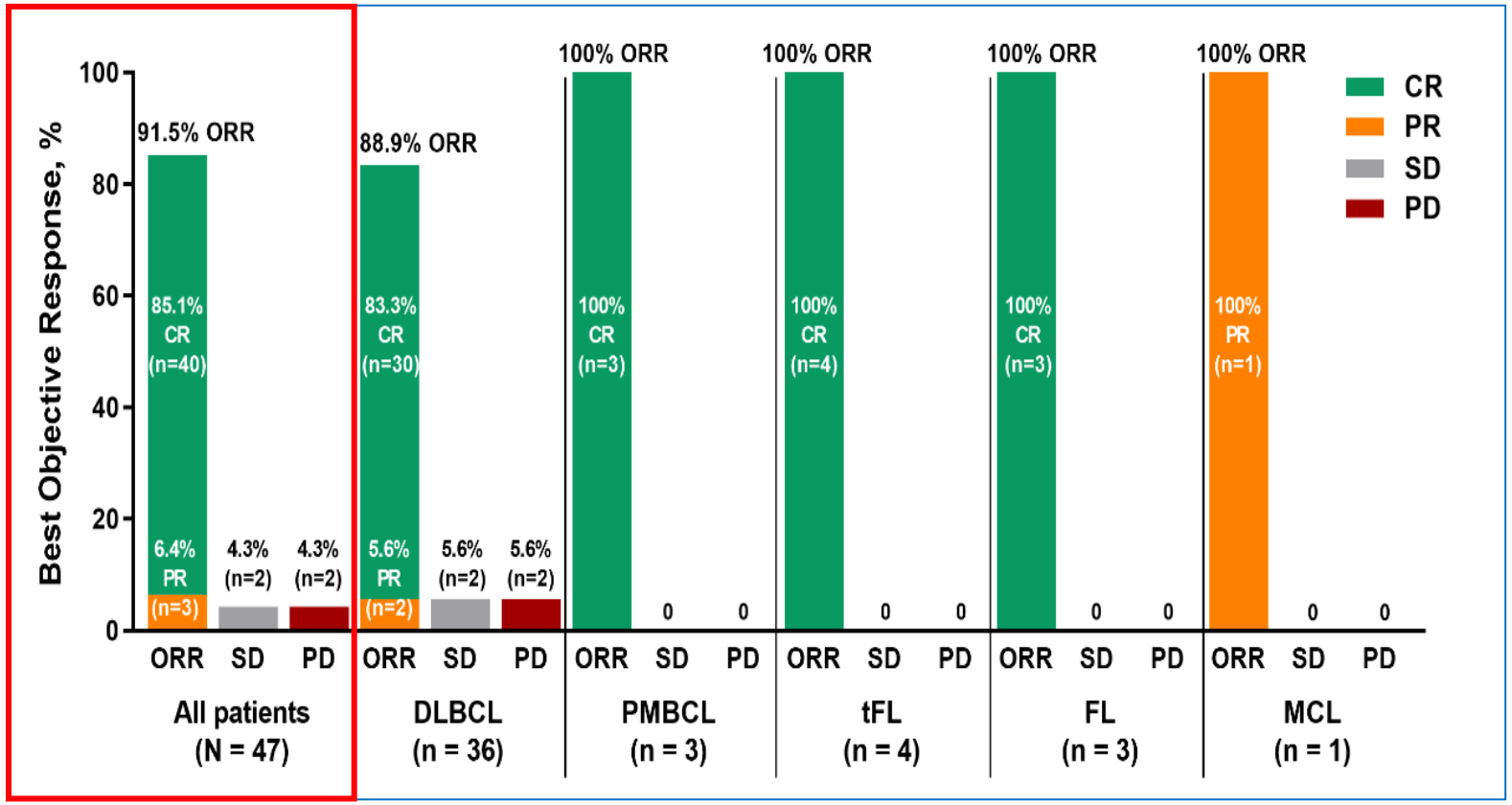
- At data cutoff, 15 deaths occurred; most due to disease progression.

*1 MCL patient experienced disease progression during pneumonia, and died 2 weeks after withdrawal. It was believed that the infection and disease progression together caused patient death

§ Caused by COVID-19 pneumonia

SAE, Serious Adverse Event

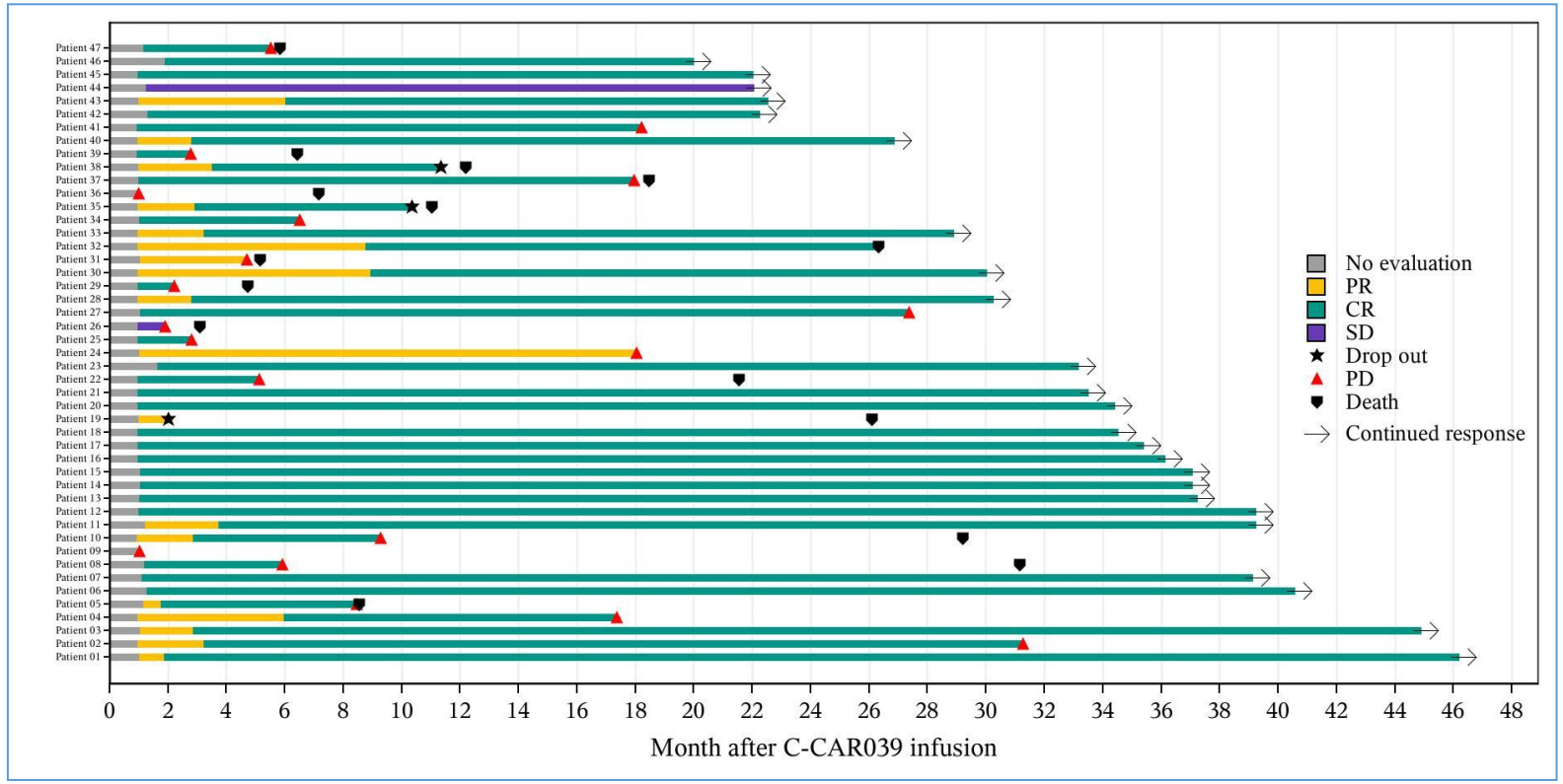
High Response Rates Observed, Even in Patients with Aggressive Lymphoma



- **91.5% ORR** across all patients
- **85.1% and 86.0% CR rates** for all patients and LBCL patients, respectively
- The median time to first response for all patients was 1.0 month (range, 0.9-1.9)
- The median time to CR for all patients was 1.2 month (range, 0.9, 8.9)

LBCL includes DLBCL, NOS, tFL, and PMBCL.
LBCL, Large B-cell Lymphoma; ORR, Overall Response Rate; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, progressive disease.

Responses with C-CAR039 are Deep and Durable

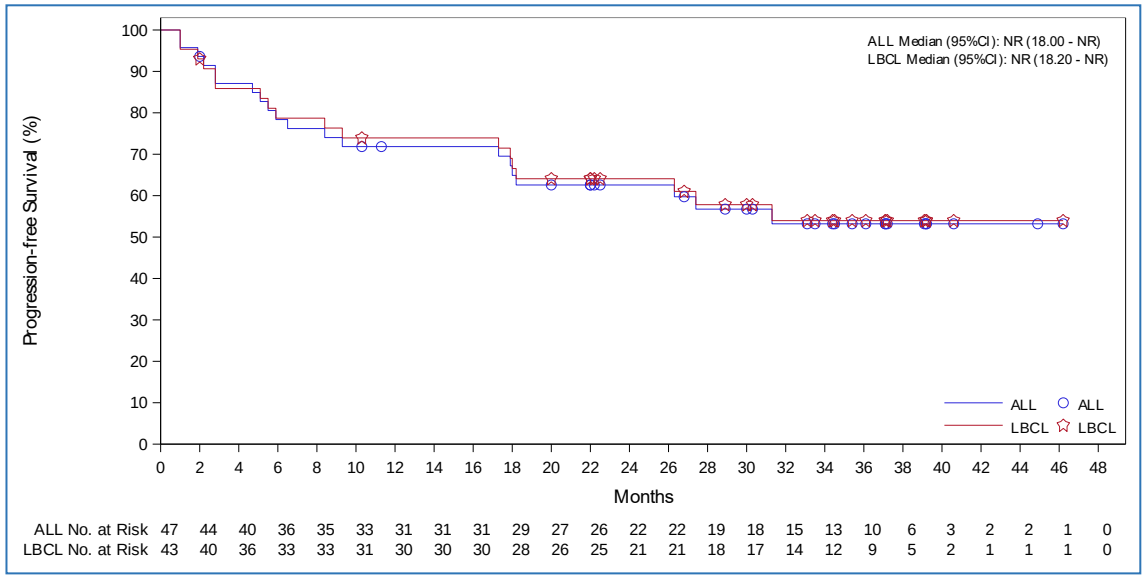


- With a median follow-up of 30.0 months (range, 3.1-46.2), **median duration of response was not reached**
- As of Sep 25, 2023, 23/47 (48.9%) patients remain in CR, 10 of them for more than 36 months

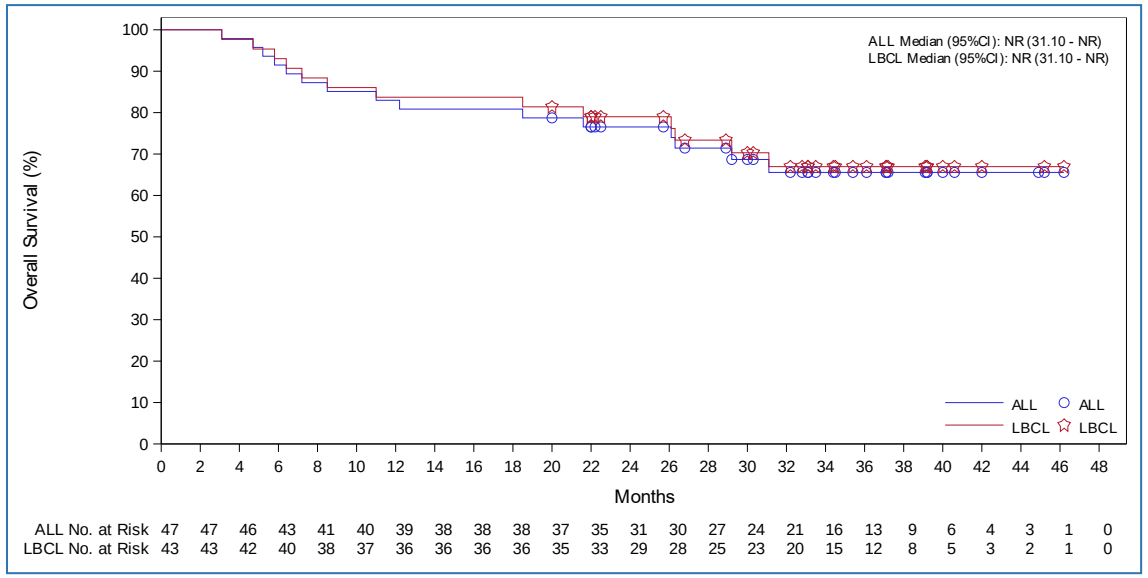
CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, progressive disease.

With a Median Follow-up of 30.0 Months, Median PFS and OS were Not Reached

Progression Free Survival



Overall Survival

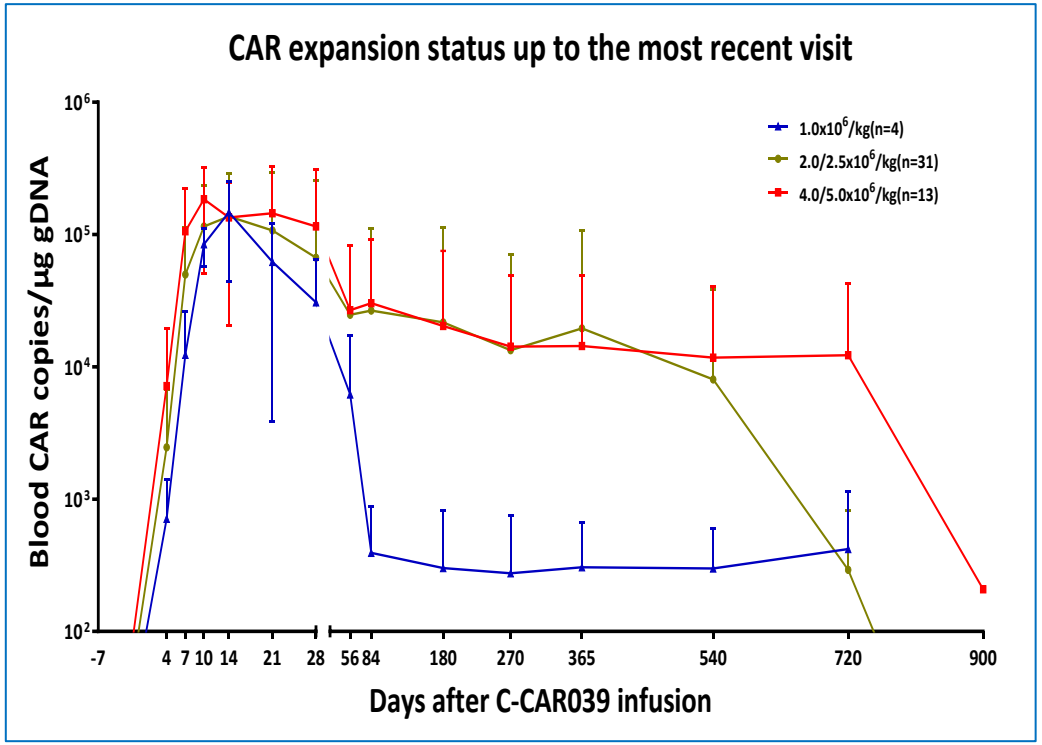


- **Median PFS and was not reached** (Median follow-up of 30.0 months (range, 3.1-46.2))
- KM estimates of 24-m PFS rate are 62.6% (all patients) and 64.1% (LBCL patients)

- **Median OS was not reached** (Median follow-up of 30.0 months (range, 3.1-46.2))
- KM estimates of 24-m OS rate are76.5% (all patients) and 79.0% (LBCL patients)

KM: Kaplan-Meier; PFS: Progression-Free Survival; OS: Overall Survival

The Pharmacokinetic Profile Shows C-CAR039 has Robust Expansion and Long-Term Persistence

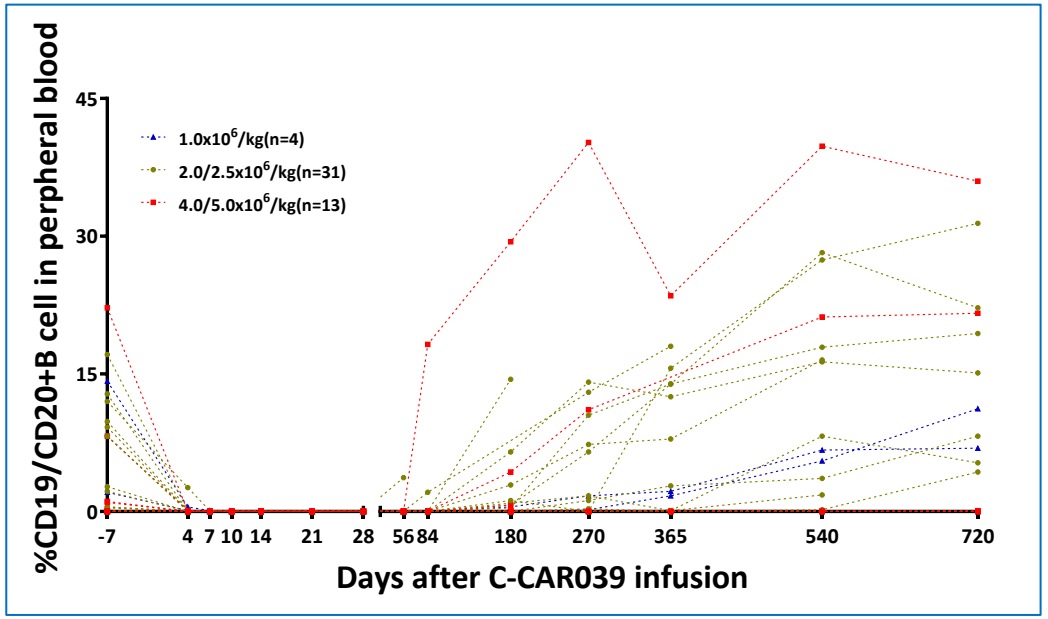


Parameter, Median (range)	1.0×10^6/kg (N=4)	$2.0/2.5\times10^6$/kg (N=31)	$4.0/5.0\times10^6$/kg (N=13)	Total (N=48)
$AUC_{0\text{-}28d}$, copies/μg gDNA*day	1,670,432 (286,426-2,580,272)	1,067,201 (3,818-11,594,913)	3,158,722 (223,150-8,117,064)	1,513,442 (3,818-11,594,913)
C_{max}, copies/μg gDNA	158,324 (46,198-259,462)	114,041 (708-962,445)	302,300 (54,447-715,187)	139,416 (708-962,445)
T_{max}, days	13.5 (10-14)	12 (7-28)	10 (7-31)	11.5 (7-31)
T_{last}, days	316 (56-727+)	269 (10-729+)	180 (27-947+)	216 (10-947+)

- **Robust C-CAR039 expansion in patients**
  - The median Tmax of 11.5 days

- **Long-term persistence of C-CAR039 In Patients**
  - The median T_{last} was 216 days
  - 35% of patients at 500 days had CAR-T in blood

C-CAR039 Effectively Depletes Peripheral B-Cells



B Cell Status	1.0×10^6/kg (N=4)	$2.0/2.5\times10^6$/kg (N=31)	$4.0/5.0\times10^6$/kg (N=13)	Total (N=48)
Median days (range) to B cell depletion	8.0 (7-9)	4.0 (4-10)	4.5 (4-8)	5.0 (4-10)
Patient with B cell recovery, n (%)	2 (50)	13 (41.9)	4 (30.8)	19 (39.6)
Median days (range) to B cell recovery	230.5 (182-279)	185.0 (60-545)	180.0 (84-747)	185.0 (60-747)

- **C-CAR039 could effectively deplete B cells in peripheral blood**
  - The median time to B cell depletion was 5.0 days

- **Only 39.6% patients showed B cell recovery during 2-year follow-up**
  - The median time to B cell recovery was 185.0 days.

Conclusions

- **C-CAR039 is a novel bispecific CAR-T targeting CD19 and CD20 B-Cell antigens**
- **C-CAR039 demonstrates a manageable safety profile with no new safety signals observed with more than 2 years of follow up**
  - The majority of CRS cases were Grade 1-2 and no ICANS was observed at the RP2D of 2.0-2.5x10^6/kg
- **With median follow-up of 30.0 months, C-CAR039 shows deep and durable responses in r/r B-NHL patients, especially those with LBCL**
  - ORR was 90.7% with 86.0% CR in LBCL patient
  - Median PFS has not been reached; KM estimates of 24-m PFS rate were 62.6% (all patients) and 64.1% (LBCL)
  - Median OS has not been reached; KM estimates of 24-m OS rate were 76.5% (all patients) and 79.0% (LBCL)
- **These encouraging data suggest C-CAR039 is a promising next generation CAR-T therapy for patients with B-NHL, including patients with LBCL**
- **A registration study is ongoing at R2PD in Chinese patients with r/r LBCL (NCT05800977)**

Investigation of C-CAR039 Globally

- Further investigation of C-CAR039, in a global patient population (excluding Greater China), will be led by J&J
- A phase Ib, multicenter, open-label study of JNJ-90014496 (Formally C-CAR039) for the treatment of adult participants with relapsed or refractory B-cell Non-Hodgkin lymphoma (R/R B-NHL) is currently open and enrolling (NCT05421663)

Scan for more details about the clinical trial

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Contact: Dr Aibin Liang lab7182@tongji.edu.cn