Phase 1 study of C-CAR088, a novel humanized anti-BCMA CAR T-cell therapy in relapsed/refractory multiple myeloma

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ABSTRACT

Background Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CAR T) therapy showed remarkable efficacy in patients with relapsed or refractory multiple myeloma (RRMM). This phase 1 dose-escalation and expansion study developed C-CAR088, a novel second-generation humanized anti-BCMA CAR T-cell therapy, and assessed the safety and efficacy of three dosages of C-CAR088 in patients with RRMM.

Methods Patients received lymphodepletion with three doses of cyclophosphamide (300 mg/m^2) and three doses of fludarabine (30 mg/m^2) on days −5, −4, and −3, followed by an infusion of C-CAR088 on day 0. Doses of 1.0×10^6, 3.0×10^6, and 6.0×10^6 CAR T cells/kg (±20%) were tested in the dose-escalation cohorts and expansion cohorts. The primary endpoint was treatment safety, including the rate of treatment-emergent adverse events after cell infusion. Secondary endpoints were the overall response rate and progression-free survival. The exploratory endpoints were the quantification of C-CAR088 CAR T cells, selection of cytokines and chemokines in blood, and measurement of tumor BCMA expression.

Results As of July 2, 2021, 31 patients had been infused with C-CAR088. Any grade cytokine release syndrome (CRS) occurred in 29 patients (93.5%), and grade 3 CRS occurred in 3 patients (9.7%). One patient from the high-dose group ($4.5–6.0\times10^6$ CAR T cells/kg) developed grade 1 neurotoxicity. No dose-limiting toxicities were observed in any dose group, and all adverse events were reversible after proper management. The overall response, stringent complete response, complete response (CR), and very good partial response rates were 96.4%, 46.4%, 10.7%, and 32.1%, respectively. The CR rate in the medium-dose (3.0×10^6 CAR T cells/kg) and high-dose ($4.5–6.0\times10^6$ CAR T cells/kg) groups was 54.5% and 71.4%, respectively. In the CR group, 15 (93.7%) patients achieved minimal residual disease (MRD) negativity (test sensitivity >$1/10^{−5}$). All seven patients with double-hit or triple-hit multiple myeloma achieved MRD-negative CR.

Conclusions The present study demonstrated that C-CAR088 had a good safety profile and high antitumor activity in patients with RRMM, constituting a promising treatment option for RRMM.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T cell (CAR T)-cell therapy has excellent results in clinical trials. Nevertheless, the overall response rate (range, 73.0–100%), complete response rate (range, 33.0–76.5%), and treatment-associated complications vary widely across trials, and a subset of patients experience relapse a short time after treatment, which may be due to clonal evolution, loss of subclones, immunosuppression in the tumor microenvironment, and CAR T-cell exhaustion. C-CAR088 cells are genetically-modified anti-BCMA autologous CAR T cells. This study assessed the safety and efficacy of C-CAR088 T cell therapy in patients with relapsed or refractory multiple myeloma (RRMM).

WHAT THIS STUDY ADDS

⇒ This study provided evidence for the safety profile and high antitumor activity of C-CAR088 in patients with RRMM. No dose-limiting toxicities were observed in patients treated with different doses of C-CAR088, and this novel therapy had a manageable safety profile. The overall response rate in RRMM was 96.4%. Deep and durable responses were observed in the medium-dose and high-dose groups, and progression-free survival at 12 months in these two groups was 69.5% (95% CI: 51.6% to 93.6%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The present study demonstrated that C-CAR088 had a good safety profile and high antitumor activity in patients with RRMM, constituting a promising treatment option for RRMM.

BACKGROUND

Multiple myeloma (MM) is a common hematologic malignancy characterized by

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the clonal proliferation of abnormal plasma cells in the bone marrow (BM).[1] MM accounts for approximately 15% of hematopoietic neoplasms, and its aberrantly expanded immunoglobulins can damage relevant tissues and organs as a result of hypercalcemia, renal failure, anemia, or lytic bone lesions.[2 3] With the recent development of therapeutic agents, including proteasome inhibitors, immunomodulators, monoclonal antibodies, and epigenetic drugs, the survival of patients with MM has improved significantly. However, MM remains incurable because most patients ultimately relapse or become refractory to treatment; thus, treatment focuses on controlling disease progression, improving quality of life, and prolonging survival.[4–6] Chimeric antigen receptor-modified T (CAR T) cell immunotherapy acts through mechanisms distinct from those of MM therapies because of its ability to target specific cell-surface antigens by modifying patient or donor T cells. B-cell maturation antigen (BCMA), a transmembrane glycoprotein from the tumor necrosis factor (TNF) receptor superfamily, is preferentially expressed in plasmacytes, and its overexpression and activation in malignant plasma cells make it a potential therapeutic target.[7 8] Anti-BCMA CAR T-cell therapy has shown excellent results in clinical trials.[9–14] A meta-analysis showed that the overall response rate (ORR) of this therapy in patients with relapsed or refractory MM (RRMM) was 85.2% (95% CI: 0.797 to 0.910), and the complete response (CR) rate was 47.0% (95% CI: 0.378 to 0.583).[15]

C-CAR088 cells were genetically-modified anti-BCMA autologous CAR T cells. This study assessed the safety and efficacy of C-CAR088 T-cell therapy in patients with RRMM following lymphodepletion with fludarabine and cyclophosphamide.

METHODS

C-CAR088

The structure of the second-generation CAR targeting the BCMA was shown in figure 1A. The single-chain variable fragment (scFv) of C-CAR088 was derived from a human IgG1 antibody and had a high binding affinity (KD=0.08 nM) for epitome cluster E3 in the BCMA extracellular domain using a surface plasmon resonance sensor (online supplemental table 1 and figure 1; Biacore, Uppsala, Sweden). The specificity of scFv to human BCMA was validated by protein microarrays and tissue cross-reactivity assays under good laboratory practice conditions (online supplemental table 2, figures 2 and 3) and was further confirmed by C-CAR088 preclinical study (online supplemental figures 4–6). In a preclinical study, human T cells transduced with the lentiviral vector encoding C-CAR088 exhibited unique functions in vitro, including CAR T-cell proliferation, cytokine production, and toxicity to BCMA-positive tumor cells (online supplemental figures 7–9). C-CAR088 cells were not activated by soluble BCMA (online supplemental figure 10) and patient with MM's sera. In addition, C-CAR088 showed a strong dose-dependent tumor inhibition effect and survival benefit in animal studies (online supplemental figures 11–13).

C-CAR088 design

C-CAR088 was designed by Shanghai Cellular Biomedical Group using autologous CAR T cells in a serum-free, automated, and closed system according to good manufacturing practices.

Ethics approval

The study protocols conformed to the ethical guidelines of the Declaration of Helsinki and the International
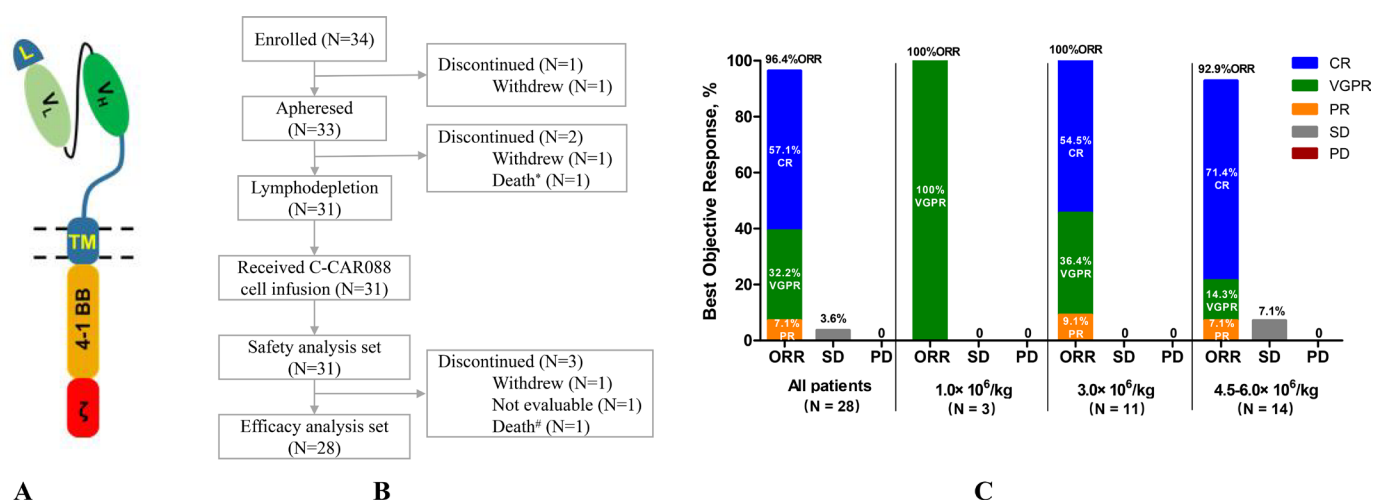
Figure 1 Trial contents and curative effect. (A) Schematic diagram of C-CAR088 CAR, a second-generation anti-BCMA CAR. The scFv of C-CAR088 is derived from a human IgG1 antibody targeting the BCMA extracellular domain. (B) Flowchart of this trial. *Died of progressive disease before C-CAR088. #Died of septic shock on day 3 after C-CAR088. (C) Best overall response at each dose level. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; ORR, overall response rate; PD, disease progression; PR, partial response; scFv, single-chain variable fragment; SD, stable disease; VGPR, very good partial response.

Conference on Harmonization Guidelines for Good Clinical Practice (ICH E6).

Study design

This first-in-human, single-arm, open-label, phase 1, dose-escalation and expansion study evaluated the safety and efficacy of C-CAR088 in patients with RRMM admitted to four clinical centers in China. Eligible patients were aged 18–75 years and were diagnosed with MM according to International Myeloma Working Group (IMWG) diagnostic criteria for MM and an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1. The positivity of BM malignant plasma cells to BCMA was confirmed by flow cytometry (FC) or immunohistochemistry. Patients received at least two lines of treatment for MM, including immunomodulatory agents and proteasome inhibitors, and disease progression during or after the last treatment cycle was assessed according to IMWG criteria. Patients with one or more measurable MM lesions and one of the following conditions were included in the study: (1) serum M-protein ≥1 g/dL (10 g/L), (2) urine M-protein ≥200 mg/24 hours, (3) serum-free light chain (sFLC) ≥10 mg/dL, and abnormal κ/λ ratio. Patients received lymphodepletion with three doses of cyclophosphamide ($300 \, mg/m^2$) and three doses of fludarabine ($30 \, mg/m^2$) on days −5,−4, and −3, followed by an infusion of C-CAR088 on day 0. Doses of 1.0×10^6, 3.0×10^6, and 6.0×10^6 CAR T cells/kg (±20%) were tested in the dose-escalation cohorts and expansion cohorts.

Treatment safety

The primary endpoint was treatment safety, including the rate of treatment-emergent adverse events (TEAEs) after cell infusion. The rate of TEAEs was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events V.5.0. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy consensus grading system. Dose-limiting toxicities (DLTs) were defined according to pre-established criteria.[16]

Clinical response

Secondary endpoints were the ORR and progression-free survival (PFS). Clinical response and disease progression were assessed according to IMWG Uniform Response Criteria for MM. The ORR was defined as the percentage of patients who achieved partial response (PR) or better. PFS was defined as the time from C-CAR088 infusion to first disease progression or death from any cause. Patients were closely followed by serum and urine protein electrophoresis, serum and urine immunofixation electrophoresis, sFLC assay, bone radiography, MRI, or positron emission tomography/CT. Minimal residual disease (MRD) in BM followed EuroFlow Consortium criteria using two eight-color FC panels. The first panel included antibodies against CD81, CD27, CD138, CD56, CD19, CD20, CD38, and CD45, and the second panel included antibodies against CD138, CD56, CD19, CD20, CD38, and CD45. B-cell clonality was assessed by the FC analysis of cytoplasmic kappa and lambda antibodies. Samples were analyzed on a Canto II flow cytometer (Becton Dickinson). The sensitivity of MRD assessment was up to 1×10^{-5}. Plasma cell myeloma BCMA expression was assessed by FC as described previously.[17] All antibodies were recommended by EuroFlow.

The explore study

The endpoints were the quantification of C-CAR088 CAR T cells, selection of cytokines and chemokines in blood, and measurement of tumor BCMA expression. The expansion and persistence of C-CAR088 were monitored in peripheral blood at baseline and follow-up. C-CAR088 transgene copies were measured by quantitative PCR. The area under the receiver operating characteristic curve ($AUC_{0-28 \, days}$) was calculated using non-compartmental analysis.[18] Maximum transgene level (C_{max}), time to reach Cmax (T_{max}), and time of last measurable transgene level (T_{last}) were also measured.

Cytokines interleukin (IL)-2, IL-4, IL-6, IL-10, TNF-α, and interferon (IFN)-γ were monitored in peripheral blood at baseline and follow-up (within 28 days after C-CAR088 infusion) by FC using a BD Cytometric Bead Array kit.

Statistical analysis

Continuous variables were expressed as means and SD or medians with minimum and maximum. Categorical variables were expressed as numbers and percentages, and 95% CIs were calculated using the Clopper-Pearson exact method. Duration of response (DOR), overall survival (OS), PFS, and associated 95% CIs were estimated using the Kaplan-Meier method. Censoring of data for PFS and DOR was based on Food and Drug Administration (FDA) rules. DOR was defined as the time from the first evaluation of stringent CR (sCR), CR, very good partial response (VGPR), or PR to the first evaluation of relapse or death from any cause.

RESULTS

Efficacy of C-CAR088 in vitro and in vivo

Human T cells transduced with the lentiviral vector encoding C-CAR088 exhibited unique functions in vitro, including 4-1BB expression, cytokine production, and toxicity to BCMA-positive tumor cells (online supplemental figures 7–9). C-CAR088 cells were not activated by soluble BCMA (online supplemental figure 10) and patients with MM's sera. However, these cells killed BCMA-positive tumor cells in vivo, including RPMI-8226 MM cells. In addition, C-CAR088 showed a high dose-dependent tumor inhibition effect and survival benefit in animal studies (online supplemental figures 11–13).

Patient enrollment and disease characteristics

Between January 11, 2019, and July 2, 2021, 34 subjects were enrolled, and 33 underwent apheresis. One patient

withdrew from the study because of fast disease progression, and one patient died of MM before lymphodepletion. Thirty-one patients were treated with C-CAR088 (figure 1B). Baseline patient and disease characteristics are shown in table 1.

The median age of the cohort was 61 (range, 45–74) years. Seventeen (54.8%) patients were men, and 14 (45.2%) were women. Nineteen (61.3%) and 12 (38.7%) patients had ECOG-PS score of 0 and 1, respectively. Four (12.9%), 21 (67.7%), and 5 (16.2%) patients were classified as revised International Staging System stages I, II, and III, respectively. The most common types of MM were IgG (15, 48.4%), light chain (9, 29.0%), IgA (5, 16.1%), IgD (1, 3.2%), and non-secretory (1, 3.2%). Three (9%) patients had extramedullary disease, and 15 (48.4%) had double-hit or triple-hit MM, defined by the presence of two or three high-risk genetic abnormalities, including t(4;14), t(14;16), t(14;20), del(17p), and p53 mutation or 1q gain.

The median number of prior lines of therapy was four (range, 2–13). All 31 (100%) patients were previously treated with immunomodulatory agents and protease inhibitors, 7 (22.6%) had undergone autologous stem cell transplantation (ASCT), and 7 (22.6%) had received anti-CD38 monoclonal antibodies (mAbs). Seven patients received bridge therapy before C-CAR088 infusion. BM aspirates were analyzed in 30 (96.8%) patients at baseline. Aspiration failed (dry tap) in one case. Twenty-eight patients had abnormal plasma cells in the BM at baseline, and one patient had extramedullary disease. The median proportion of BCMA-positive abnormal plasma cells was 49.12% (range, 0.44–99.13%). The median BCMA density in BCMA-positive malignant plasma cells in the BM was 836 (range, 61–8003) molecules/cell.

Treatment safety

As of July 2, 2021, 31 patients were treated with C-CAR088. The median follow-up was 9.4 (range, 1.9–24.2) months. No DLT was observed. Common adverse events (rate ≥20%) are shown in online supplemental table 3, and common grade 3 or higher adverse events are shown in table 2.

The most common event was hematologic toxicity, including neutropenia (100% of cases), leukopenia (100%), thrombocytopenia (90.3%), and anemia (83.9%). These toxic effects of lymphodepleting chemotherapy were expected. The common grade ≥3 events were mostly hematologic toxicity. Sixteen (51.6%) patients had prolonged cytopenia, defined as grade ≥3 neutropenia or thrombocytopenia within 28 days after C-CAR088 therapy. CRS occurred in 29 (93.5%) patients with a median time to onset of 6 days (range, 1–11) and a median duration of 5 days (range, 2–14). Most cases of CRS (26/31, 83.9%) were grade 1 or 2, three cases (9.7%) were grade 3, and no cases were grade 4. The most frequent (≥20%) symptoms of CRS were fever (29/29, 100%), hypoxemia (8/29, 27.6%), increased D-dimer (7/29, 24.1%), tachycardia (7/29, 24.1%),

hypotension (6/29, 20.7%), and increased transaminase (6/29, 20.7%). One patient in the high-dose group had grade 1 ICANS for 24 hours on day 8 of treatment and recovered after treatment with glucocorticoids. Three (9.7%) patients used tocilizumab alone, and six (19.4%) patients used tocilizumab and corticosteroids. Twenty-one patients (67.7%) had infections after infusion. Safety data are shown in table 3.

Clinical efficacy

Response to treatment was assessed on day 28 with ≥1 month of follow-up. One patient discontinued treatment on week 2, one patient died of septic shock caused by *Vibrio cholerae* infection on day 3 after C-CAR088 infusion, and one patient was not evaluable. Among 28 evaluable patients, the ORR was 96.4% (13 sCR, 3 CR, 9 VGPR). The CR rate increased to 71.4% as the dose increased (figure 1C, table 4). In the low-dose group, the best response in three (100%) patients was VGPR. The rate of CR/sCR in the medium-dose group (N=11) and high-dose group (N=14) was 54.5% and 71.4%, respectively, and the ORR in these groups was 100% and 92.9%, respectively. The median time to CR was 2.0 (0.5–9.5) months. In the intent-to-treat population (n=31), the ORR was 87.1% (13 sCR, 3 CR, 9 VGPR) (table 5).

Among 15 evaluable patients with at least two high-risk genetic abnormalities, the ORR was 93.3% (sCR, CR, and VGPR of 33.3%, 13.3%, and 46.7%, respectively). Of these, 13 patients received a medium-dose or a high dose, and the ORR was 92.3% (sCR, CR, and VGPR of 38.5%, 15.4%, and 38.5%, respectively). The two patients with triple-hit MM achieved CR.

Seven (22.6%) patients from dose 3.0–6.0×10⁶/kg cohort received anti-CD38 mAb prior to C-CAR088 therapy, all of them were responsive to C-CAR088, and four (57.1%) achieved sCR. PFS (HR: 1.39 (0.26, 7.38), p=0.7) and DOR (HR: 1.56 (0.28, 8.67), p=0.6) did not have significant differences between patients with or without prior anti-CD38 mAb treatment in these dose cohorts. Only one death was reported as of the cut-off date so it did not have enough data points to run the Cox proportional hazards regression model for OS. However, the trends of the curve in all three graphs indicated that C-CAR088 demonstrated similar efficacy in both patient groups (online supplemental figure 14).

In cohorts receiving a medium or a high dose, the median follow-up was 9.5 months (range, 1.9–24.2). In these groups, PFS and OS at 12 months was 69.5% (95% CI: 51.6% to 93.6%) and 94.4% (95% CI: 84.4% to 100%), respectively, and the median PFS, OS, and DOR were not reached (figure 2A–C).

Subgroup analysis was performed to assess the effect of several factors, including baseline clinical and therapeutic characteristics, on CR and sCR (figure 2D). Patients in the medium-dose and high-dose groups were more likely to achieve CR/sCR.

Table 1 Baseline patient characteristics

Characteristics	Low-dose group (n=4)	Medium-dose group (n=13)	High-dose group (n=14)	Total (n=31)
Median age, years (range)	60.5 (54–72)	64.0 (52–74)	59.5 (45–71)	61.0 (45–74)
≥65, n (%)	2 (50.0)	6 (46.2)	4 (28.6)	12 (38.7)
Male sex, n (%)	2 (50.0)	7 (53.8)	8 (57.1)	17 (54.8)
ECOG-PS, n (%)				
0	3 (75.0)	5 (38.5)	11 (78.6)	19 (61.3)
1	1 (25.0)	8 (61.5)	3 (21.4)	12 (38.7)
Staging based on the R-ISS, n (%)				
I	0 (0.0)	2 (15.4)	2 (14.3)	4 (12.9)
II	4 (100.0)	9 (69.2)	8 (57.1)	21 (67.7)
III	0 (0.0)	2 (15.4)	3 (21.4)	5 (16.2)
UK	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.2)
Double-hit or triple-hit MM, n (%)				
Double-hit	2 (50.0)	5 (38.5)	6 (42.9)	13 (41.9)
Triple-hit	0 (0.0)	1 (7.7)	1 (7.1)	2 (6.5)
High lactate dehydrogenase	0 (0.0)	2 (15.4)	1 (7.1)	3 (9.7)
MM type, n (%)				
IgA-κ	0 (0.0)	1 (7.7)	0 (0.0)	1 (3.2)
IgA-λ	0 (0.0)	2 (15.4)	2 (14.3)	4 (12.9)
IgD-λ	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.2)
IgG-κ	2 (50.0)	2 (15.4)	4 (28.6)	8 (25.8)
IgG-λ	0 (0.0)	5 (38.5)	2 (14.3)	7 (22.6)
Light chain	2 (50.0)	3 (23.1)	4 (28.6)	9 (29.0)
κ	1 (25.0)	2 (15.4)	2 (14.3)	5 (16.1)
λ	1 (25.0)	1 (7.7)	2 (14.3)	4 (12.9)
Non-secretory	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.2)
Extramedullary MM, n (%)	0 (0.0)	1 (7.7)	2 (14.3)	3 (9.7)
% bone marrow BCMA+plasma cells, median (range)	0.4912 (0.026–0.4092)	0.44 (0.0044–0.916)	0.6921 (0.0587–0.9913)	0.4912 (0.0044–0.9913)
BCMA density, median (range)	7637 (136–8003)	1023 (61–2756)	572.5 (203–4422)	806 (61–8003)
Previous therapeutic regimens, median (range)	7.0 (5–7)	4.0 (2–13)*	4.0 (3–12)	4.0 (2–13)
Immunomodulatory agents and proteasome inhibitors	4 (100.0)	13 (100.0)	14 (100.0)	31 (100.0)

Continued

Table 1 Continued

Characteristics	Low-dose group (n=4)	Medium-dose group (n=13)	High-dose group (n=14)	Total (n=31)
ASCT	2 (50.0)	1 (7.7)	4 (28.6)	7 (22.6)
Anti-CD38 mAb	0 (0.0)	3 (23.1)	4 (28.6)	7 (22.6)
Received bridging therapy, n (%)	0 (0.0)	3 (23.1)	4 (28.6)	7 (22.6)

*Two patients received two lines of anti-MM therapy.
ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; double-hit MM, two high-risk genetic abnormalities; ECOG-PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; MM, multiple myeloma; R-ISS, Revised International Staging System; triple-hit MM, three or more high-risk genetic abnormalities; UK, unknown.

MRD

MRD was determined in CR patients. None of the patients in the low-dose group achieved CR or better. In the medium-dose and high-dose groups, 15 (93.7%) patients achieved MRD negativity among 13 patients with sCR and 3 patients with CR. The seven patients with at least two high-risk genetic abnormalities achieved MRD-negative CR. Nonetheless, after a median follow-up of 9.4 months, two patients relapsed at 200 and 255 days after CR, respectively.

Pharmacokinetic and pharmacodynamic profile of C-CAR088

The pharmacokinetic profile of C-CAR088 was assessed by measuring the number of C-CAR088 transgene copies in the peripheral blood. Thirty patients had evaluable data. C-CAR088 pharmacokinetic parameters, including C_{max}, T_{max}, $AUC_{0-28\,days}$, and T_{last}, were shown in figure 3A.

The median T_{max} was 14 (range: 9–23) days. The median C_{max} was 750,061 (range: 21,860–1,772,476) copies/µg genomic DNA (gDNA). The median $AUC_{0-28days}$ was 7,558,634 (range: 286,934–21,326,789) copies/µg gDNA/day. T_{last} varied from 14+ to 566+ days. There were significant differences in these parameters between the groups. The pharmacokinetics of C-CAR088 between the groups was analyzed using Tukey's honestly significant difference test. T_{max} was significantly shorter in the medium-dose and high-dose groups (p<0.05). There were no significant intergroup differences in the other kinetic parameters (figure 3B–E).

Changes in blood/urine M-protein and sFLC levels were used as a pharmacodynamic biomarker of CAR088. Blood/urine M-protein and sFLC levels after C-CAR088 infusion were compared with baseline. In the low-dose group, the average blood/urine M-protein or sFLC levels decreased to 68±39%, 41±44%, 30±54%, 13±15%, and 5±7% of baseline at 2, 4, 8, 12, and 16 weeks after infusion, respectively. Blood/urine M-protein or sFLC levels were 12±16% and 55±12% of baseline at 20 weeks and 6 months after infusion. These results suggested that the lowest dose did not completely inhibit tumor cells.

In 12 patients from the medium-dose group, the average blood/urine M-protein or sFLC level decreased to 43±35%, 18±17%, 3±7%, 7±12%, 7±14%, 9±20%, 6±16%, and 3±8% of baseline at 2, 4, 8, 12, 16, and 20 weeks, 6 months, and 9 months, respectively. At 12 and 18 months, blood/urine M-protein or sFLC levels were undetectable.

In 14 patients from the high-dose group, the average blood/urine M-protein or sFLC levels decreased to 27%±29%, 19%±33%, 16%±43%, 4%±5%, 3%±4%, 2%±3%, 0%±0%, 1%±3% at 2, 4, 8, 12, 16, 20 weeks, 6 months and 9 months, respectively. At 12 months after infusion, blood/urine M-protein or sFLC levels were undetectable. The decrease in M-protein or sFLC levels in blood/urine was inversely correlated with C-CAR088 expansion (figure 3F).

Table 2 Common grade 3 or higher adverse events (≥20%)

	Low-dose group	Medium-dose group	High-dose group	Total
	N=4	N=13	N=14	(n=31)
Hematologic				
Leukopenia	4 (100)	11 (84.6)	14 (100)	29 (93.5)
Lymphopenia	4 (100)	12 (92.3)	14 (100)	30 (96.8)
Neutropenia	4 (100)	11 (84.6)	13 (92.9)	28 (90.3)
Thrombocytopenia	4 (100)	4 (30.8)	4 (28.6)	12 (38.7)
Anemia	3 (75.0)	6 (46.2)	6 (42.9)	15 (48.4)
Others				
Pneumonia	0 (0.0)	3 (23.1)	4 (28.6)	7 (22.6)

The serum levels of IL-6 and IFN-γ increased transiently within 30 days after infusion. The peak levels of IL-6 and IFN-γ tended to correlate with CRS severity (figure 3G).

DISCUSSION

Anti-BCMA CAR T-cell therapy is considered one of the most promising therapeutic strategies for RRMM. In the past 5 years, many clinical trials of anti-BCMA CAR T cells have been registered at https://clinicaltrials.gov.

Nevertheless, the ORR (range, 73.0–100%), CR rate (range, 33.0–76.5%), and treatment-associated complications vary widely across trials, and a subset of patients experience relapse a short time after treatment,[12 19–23] which may be due to clonal evolution, loss of subclones, immunosuppression in the tumor microenvironment, and CAR T-cell exhaustion.[24 25] Increasing the efficacy of anti-BCMA CAR T-cell therapy depends largely on improving the structure and function of these cells.[26]

Table 3 Adverse events of special interest after C-CAR088 T cell infusion (N=31)

Variable, n (%)	Low-dose group (n=4)	Medium-dose group (n=13)	High-dose group (n=14)	Total (n=31)
CRS grade	3 (75.0)	13 (100)	13 (92.9)	29 (93.5)
1	3 (75.0)	7 (53.8)	8 (57.1)	18 (58.1)
2	0 (0.0)	4 (30.8)	4 (28.6)	8 (25.8)
3	0 (0.0)	2 (15.4)	1 (7.1)	3 (9.7)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Common CRS symptoms (>20%)				
Fever	3 (100)	13 (100)	13 (100)	29 (100)
Hypoxia	0 (0.0)	5 (38.5)	3 (23.1)	8 (27.6)
Fibrin D dimer Increased	1 (33.3)	4 (30.8)	2 (15.4)	7 (24.1)
tachycardia	2 (66.7)	1 (7.7)	4 (30.8)	7 (24.1)
Hypotension	0 (0.0)	3 (23.1)	3 (23.1)	6 (20.7)
Increased transaminase	1 (33.3)	2 (15.4)	3 (23.1)	6 (20.7)
CRS onset, days (range)	9 (4–10)	8 (2–12)	4 (2–10)	7 (2–12)
CRS duration, days (range)	6 (4–17)	4 (2–9)	5 (3–14)	5 (2–17)
Tocilizumab alone	0 (0.0)	2 (15.4)	1 (7.1)	3 (9.7)
Corticosteroids alone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tocilizumab and corticosteroids	0 (0.0)	3 (23.1)	3 (21.4)	6 (19.4)
ICANS	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.2)
Infection	2 (50.0)	10 (76.9)	9 (64.3)	21 (67.7)
≥Grade 3 cytopenia not improved within 28 days	3 (75.0)	4 (30.8)	9 (64.3)	16 (51.6)

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Table 4 Response to C-CAR088 T cell therapy in response-evaluable population

Best overall response, n (%)	Low-dose group	Medium-dose group	High-dose group	Total
Response-evaluable population	**n=3**	**n=11**	**n=14**	**n=28**
ORR	3 (100.0)	11 (100)	13 (92.9)	27 (96.4)
sCR	0 (0.0)	5 (45.5)	8 (57.1)	13 (46.4)
CR	0 (0.0)	1 (9.1)	2 (14.3)	3 (10.7)
VGPR	3 (100.0)	4 (36.4)	2 (14.3)	9 (32.1)
PR	0 (0.0)	1 (9.1)	1 (7.1)	2 (7.1)
SD	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.6)

CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

In this study, we used an scFv from a humanized BCMA antibody, maintaining the high affinity of the antibody and potentially reducing immunogenicity. This scFv also recognized macaque and mouse BCMA, suggesting that C-CAR088 might be effective to patients with RRMM with mutations in the BCMA gene. In this respect, one patient with MM treated with anti-BCMA CAR T cells developed biallelic loss of the BCMA gene due to the deletion of one allele and a point mutation that created an early stop codon on the other allele, resulting in relapse.[27] In addition, C-CAR088 showed no cross-reactivity to other tissue parenchymal cells, despite its degeneracy for the BCMA epitope. It has been reported that most of the amino acid residues in the extracellular domain involved in ligand binding are located in the E2 domain of BCMA.[28] The E2 domain could be blocked by natural ligands of BCMA. The epitope of scFv of C-CAR088 is located in the E3 domain, which is different from the E2 domain, increasing the binding affinity of C-CAR088 to BCMA, providing clinical benefit to patients.

In the present trial, the overall median manufacturing time of C-CAR088 was 7 days (range, 5–11 days), with a median time of 7, 6, and 7.5 days in the low-dose, medium-dose, and high-dose groups, respectively. The median vein-to-vein time was 18 days (range, 14–84 days),

obviating the need for bridging therapy for some of our patients. The median turnaround time (time from receipt to release of product) for ciltacabtagene auto-leucel (Cilta-cel) was 29 days,[23] and the median time from leukapheresis to Abecma availability was 33 days (range: 26–49 days).[29] This characteristic of our product partially contributes to its uniqueness and superiority over other BCMA-directed CAR T products in the market or under investigation.

In this phase 1 study, C-CAR088 was infused as a single dose of 1.0–6.0×10^6 cells/kg. Among 28 evaluable patients, the ORR was 96.4% (sCR, 46.4% and CR, 10.7%). Of these, three patients belonged to the low-dose group. The lower dose was ineffective given the lack of CR, inevitable disease progression (3/3), and significant prolongation of time when the number of C-CAR088 transgene copies peaked. In patients treated with 3.0–6.0×10^6 cells/kg, the ORR was 96.0% (sCR, 52.0% and VGPR, 12.0%) and 1-year PFS was 69.5%. sCR was 71.4% using $\geq 4.5 \times 10^6$ cells/kg. There was no clinical evidence of DLT; thus, the maximum tolerated dose has not been determined.

Idecabtagene vicleucel (Idel-cel; bb2121) has recently received FDA approval for RRMM based on a phase 2 study involving 128 patients with RRMM; of these, 73% responded to therapy, and 33% had CR or better.[12]

Table 5 Response to C-CAR088 T cell therapy in ITT population

Best overall response, n (%)	Low-dose group	Medium-dose group	High-dose group	Total
ITT population	**n=4**	**n=13**	**n=14**	**n=31**
ORR	3 (75.0)	11 (84.6)	13 (92.9)	27 (87.1)
sCR	0 (0.0)	5 (38.5)	8 (57.1)	13 (41.9)
CR	0 (0.0)	1 (7.7)	2 (14.3)	3 (9.7)
VGPR	3 (75.0)	4 (30.8)	2 (14.3)	9 (29.0)
PR	0 (0.0)	1 (7.7)	1 (7.1)	2 (6.5)
SD	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.2)
Not evaluable	1 (25.0)	2* (15.4)	0 (0.0)	3 (9.7)

*One patient withdrew on week 2 and the other one died on day 3.
CR, complete response; ITT, intention-to-treat; ORR, overall response rate; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response.
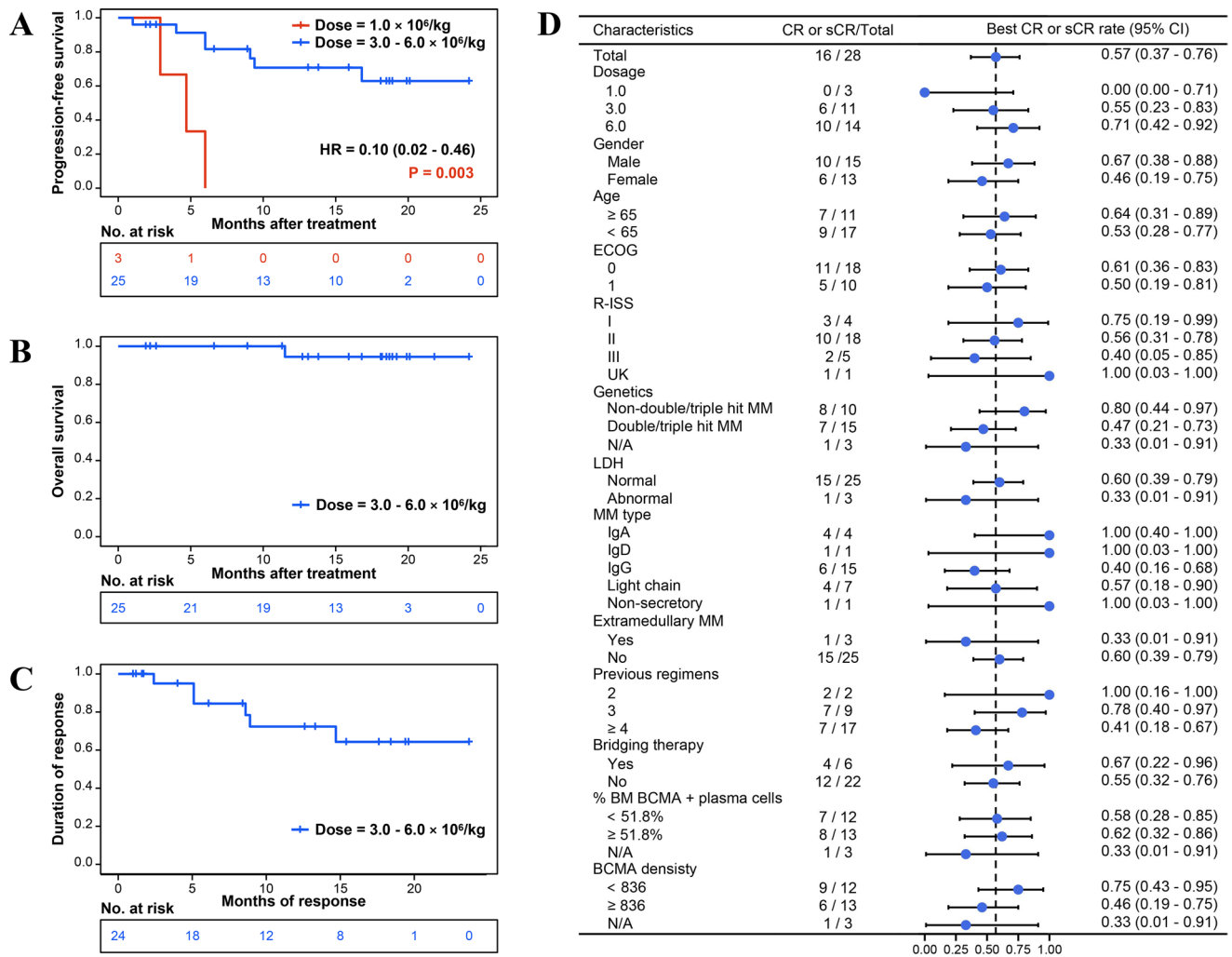
Figure 2 Evaluation index. (A) Progression-free survival in the treatment groups. (B) Overall survival in the medium-dose and high-dose groups. (C) Duration of response in the medium-dose and high-dose groups. (D) Effect of baseline characteristics on CR and sCR to C-CAR088 T-cell therapy. BM, bone marrow; BCMA, B-cell maturation antigen; CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, Revised International Staging System; sCR, stringent CR; UK, unknown.

Nonetheless, a phase 1 trial showed that 6 of 15 patients treated with Idel-cel who achieved CR experienced a relapse at 6 months of follow-up.[30] Cilta-cel has FDA approval, with an ORR of 94.8%, sCR of 55.7%, VGPR of 32.0%, 1-year PFS of 77%, and 1-year OS of 89%.[23] LCAR-B38M, a non-humanized CAR T-cell therapy targeting two BCMA epitopes, had an ORR of 88.2% (sCR, 76.5% and VGPR, 11.8%) in 17 patients with RRMM, and 1-year PFS and OS were 52.9% and 82.3%, respectively.[31] The humanized anti-BCMA CT103A achieved an ORR of 100% and a CR rate of 72% in a phase 1 trial involving 18 patients with RRMM, and PFS and OS at 12 months were 58.3% and 75%, respectively.[22] However, the utility of CT103A in patients with genetic mutations was not assessed. Several clinical trials on anti-BCMA CAR T-cell therapy for RRMM are underway; however, patient populations cannot be compared across studies. Our results showed that the short-term and long-term efficacy of C-CAR088 for patients with RRMM was similar to that of other anti-BCMA CAR T-cell therapies.

The rate of CR was high in our cohort. In addition, MRD negativity increased to 60% (15/25) as the C-CAR088 dosage increased. Although MRD negativity did not translate into continuous remission for all patients, and two patients relapsed at 6–8 months after treatment, the rate of MRD-negative CR was lower than that of bb2121 (13.3% vs 37.5%),[12] which might be attributed to the refractory nature of this patient population.

Disease burden was high in our cohort. Based on the Mayo Stratification of Myeloma and Risk-Adapted Therapy (www.msmart.org), 25 (89.3%) patients presented at least one high-risk genetic abnormality, of which 13 and 2 patients were classified into the double-hit and triple-hit group, respectively. Nonetheless, response rates were high (ORR, 93.3% and sCR/CR rate, 46.7%) in this high-risk cohort, suggesting the wide applicability of C-CAR088 in patients with RRMM.

In addition to high-risk cytogenetics, prior treatment with more than three therapeutic lines, extramedullary disease, and light-chain MM are associated with poor
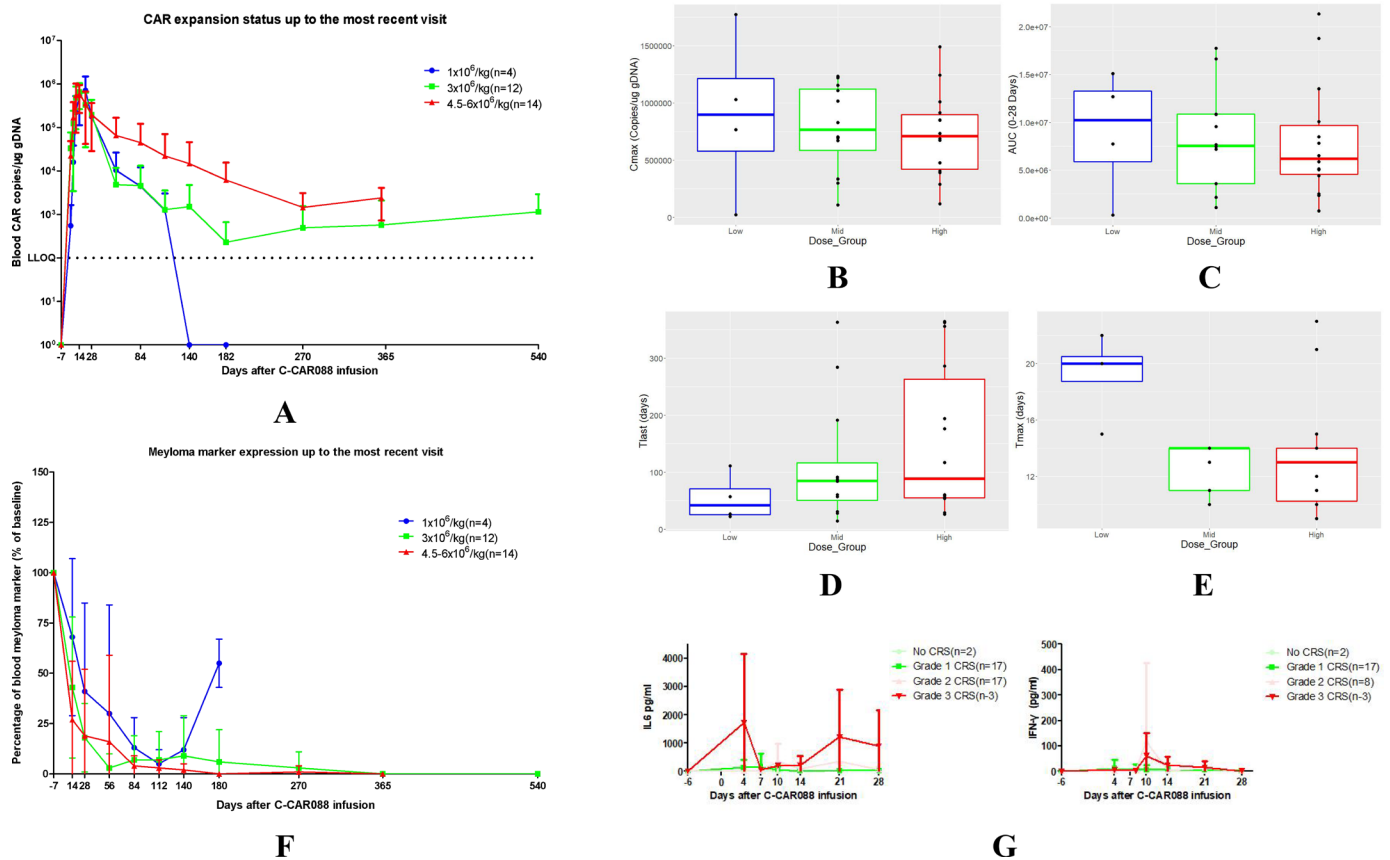
Figure 3 Pharmacokinetics of CAR T cells and changes after C-CAR088 infusion. (A) Number of CAR copies at serial time points up to the most recent visit at the cut-off date; (B) C_{max} of CAR T-cell levels; (C) Area under the curve of CAR T-cell levels; (D) T_{last} of CAR T-cell levels; (E) T_{max} of CAR T-cell levels. (F) Changes in the levels of M-protein or serum-free light chain in the blood/urine of patients; (G) Changes in the serum levels of IL-6 and IFN-γ in the first month after C-CAR088 CAR T-cell infusion. The horizontal line within each box is the median. The lower and upper limits of each box represent the 25th and the 75th percentiles, respectively, and the error bars are 95% CIs. AUC0-28 days, area under the receiver operating characteristic curve; CAR, chimeric antigen receptor; Cmax, maximum transgene level; CRS, cytokine release syndrome; gDNA, genomic DNA; IFN, interferon; IL, interleukin; Tlast, time of last measurable transgene level; Tmax, time to reach Cmax.

PFS.[32 33] The median number of prior lines of therapy in our cohort was 4 (range, 2–13), consistent with previous trials.[22 31] Given the limited supply of some pharmaceutical drugs in China, the median number of previous antimyeloma regimens was less than that in the Idel-cel trial (median, 6; range, 3–16).[12] Moreover, patients with less than four therapeutic lines were more likely to achieve sCR or CR than those receiving four or more lines (81.8% vs 41.2%, p=0.054). Thus, a more frontline C-CAR088 should be used in patients with RRMM. The three (9.7%) patients with extramedullary lesions achieved CR, PR, or PD (one patient each); median PFS was 4.8 months, and 1-year PFS was 50.0%, similar to previous studies. The proportion of patients with light-chain MM (n=9, 29.0%) was slightly higher than that reported in a previous study (15–20%). The group with light-chain MM achieved sCR (four patients), PR (one patient), or PD (one patient). There were no significant differences in treatment efficacy between patients with extramedullary disease and patients with light-chain MM; however, these results should be interpreted with caution because of the small sample size.

The proportion of patients treated with anti-CD38 mAb and ASCT was relatively low in our cohort, which could be explained by treatment landscape differences between China and western countries. Daratumumab was first approved in China in July 2019 for RRMM monotherapy, followed by the combination with lenalidomide and dexamethasone (Rd) / bortezomib and dexamethasone (Vd) for RRMM (≥1 lines of therapies), the combination with Rd or bortezomib, melphalan and predisone (VMP) for transplant-ineligible newly diagnosed MM, which were approved in 2021. The availability and higher cost of daratumumab relative to other classic antimyeloma drugs might explain the limited data on treatment with this drug. Other anti-CD38 antibodies have not been approved in China to date. In addition, the overall ASCT rate in Chinese patients with MM is much lower than in the USA and Europe. The limited access to melphalan (withdrawal from China in 2012 and re-launch in 2018), physicians' concerns about patients' age (usually restricted to patients younger than 65 years), and patients' low willingness for transplantation contributes to the situation. The transplantation rate in China

is increasing with the development of therapeutic drugs but is lower than that in other countries. The percentage of patients treated with daratumumab and ASCT in our cohort is similar to that of other CAR-T trials in China.[22 34 35]

The expansion and persistence of C-CAR088 were notable. Expansion peaked within 9 days at doses of at least 3.0×10^6 cells/kg, which was earlier than that in previous trials, indicating that the onset of action of C-CAR088 might be faster.[12 22] As of July 2021, CAR T cells persisted for more than 566 days. Durability will be assessed at follow-up.

Whether there is a threshold or a range of BCMA expression on MM cells for optimal recognition and killing is unknown.[9 36] Patients with any level of BCMA expression at baseline were enrolled. In line with a previous study, there was no significant association between baseline BCMA density on tumor plasma cells and response to C-CAR088 therapy.[36]

CRS is one of the most common TEAEs, with a reported incidence of 76–100% (grade 3–4 AEs, 5–41%).[12 19 20 30 31 36] Most CRS cases in our trial were mild (grade 1 or 2, 83.9%; grade 3, 9.7%) and easily managed or reversible. The rate of use of tocilizumab+corticosteroids in our cohort was 29%, slightly higher than that reported in a trial with Idel-cel (21%) but much lower than that of other treatments (LCAR-B38M, 52.9%; CT103A, 61.1%; Cilta-cel, 69%).[12 22 23 31] CRS occurred at a median of 6 days post-infusion, which was later than that for Idel-cel (median, 1 day), CART-BCMA (median, 4 days), and CT103A (median, 2 days).[12 22 36] The median duration of CRS was 5 days, slightly longer than that for Cilta-cel (4 days).[23] Neurotoxicity (n=1, grade 1) and ICANS (n=1, grade 1) were mild. High-grade hematologic toxicity was notable and somewhat persistent, which might be due to lympho-depleting chemotherapy and the potential effect of C-CAR088 on hematopoietic progenitor cells. In addition, the need for lymphodepletion remains controversial.[36]

The incidence of infectious events was consistent with that in an Idel-cel trial (67.7% vs 69%).[12] The rate of grade ≥3 infections was lower than that of CT103A (38.7% vs 44.4%).[22] One patient died of *V. cholerae* infection on day 3 after infusion. Deaths due to infection are common in patients undergoing anti-BCMA CAR T-cell therapy.[12 20 22 23 31 36] BCMA is essential for maintaining humoral immunity.[37] The 'on-target, off-tumor' activity of anti-BCMA CAR T-cell therapy eliminates normal plasma cells and causes immunosuppression, increasing the risk of infection.[38] Additionally, CAR T-cell toxicity may be due to tumor-induced immune dysfunction, the effects of previous therapies, lymphodepletion, use of corticosteroids and tocilizumab for treating CRS, and prolonged cytopenia and hypogammaglobulinemia.[39–41] One study showed that anti-BCMA CAR T cells caused a 7-month aplasia of normal BM plasma cells and a longer period of hypogammaglobulinemia.[42] Thus, protecting this patient population from infections is essential.

CONCLUSIONS

The present study demonstrates that C-CAR088 has a good safety profile and high antitumor activity in patients with RRMM, constituting a promising treatment option for RRMM. Nonetheless, large multicenter clinical trials are necessary to confirm our results.

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