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B-cell maturation antigen-targeted CAR T cell as a salvage therapy for progressive multiple myeloma after anti-G protein-coupled receptor, class C group 5 member D CAR T-cell therapy

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Running heads

BCMA CAR T-cells for RRMM after GPRC5D CAR T-cells

Data availability

Original data are available with panbinsam@163.com upon request.

Competing interests

AHC is a founding member of Shanghai YaKe Biotechnology, a biotechnology company focusing on research and development of tumour cellular immunotherapy. All other authors declare no competing interests.

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Authors' contributions

BP, ZY, JC, and AHC designed the study. XZ, KQ, JX, DZ, QS, HZ, and XW collected research data. XZ and FX did the statistical analysis. XZ drafted the manuscript. BP, ZY, JC, and AHC performed critical revision of the manuscript for important content. All authors contributed to the manuscript and interpretation of the data and approved the final version of the manuscript.

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Clinical trial registration information

Clinical trials were registered at www.chictr.org.cn as # ChiCTR1900026219, # ChiCTR2000033567 and www.clinicaltrials.gov as # NCT05509530.

Abstract

Repeat infusion of chimeric antigen receptor (CAR) T-cell is effective for patients with refractory or relapsed multiple myeloma (RRMM) after failing a prior CAR T-cell therapy. It is unknown whether B-cell maturation antigen (BCMA) CAR T-cell is effective for patients with RRMM after anti-G protein-coupled receptor, class C group 5 member D (GPRC5D) CAR-T cell therapy. In this study, 20 subjects with RRMM after a prior anti-GPRC5D CAR T-cell therapy received BCMA-targeted CAR T-cell therapy as a salvage treatment. During a median follow-up of 13.4 months (IQR 3.6 - 21.2), 13 subjects showed responses including 9 with stringent complete response (sCR) and 4 with partial response. The median duration of response was 10.2 months (95% CI, 2.6 - not reached). The median progression-free survival (PFS) were 9.2 months (95% CI, 3.0 - 13.6) in all subjects and 20.8 months (95% CI, 5.3 - not reached) in subjects with sCR. There is no statistic difference in overall response rate (ORR) and median PFS between this study and our previous study, which enrolled 37 subjects with RRMM receiving anti-GPRC5D CAR T-cells after failing anti-BCMA CAR T-cell therapies (ORR: 65% *vs* 84%, $P = 0.18$; PFS: 9.2 *vs* 4.5 months, $P = 0.93$). The most common adverse events were grade ≥3 haematological toxicities (n=18). Fourteen subjects (78%) had cytokine release syndrome (grade ≥3, n=1). In conclusion, anti-BCMA CAR T-cell therapy was effective for RRMM after failing an anti-GPRC5D CAR T-cell therapy, and the safety profile was acceptable.

Introduction

B-cell maturation antigen (BCMA) is the most widely explored and used target for immunotherapies in multiple myeloma (MM), while G protein-coupled receptor, class C group 5 member D (GPRC5D) is emerging as another potential target. We and others previously reported that both anti-BCMA chimeric antigen receptor (CAR) T-cell and anti-GPRC5D CAR T-cell therapies showed high response rates in relapsed or refractory MM (RRMM) including overall response rates (ORR) of 70%-100% and complete response rates (CRR) of 30%-80%.[1-6] However, a considerable part of patients experienced disease progression, including refractory and relapse after response.[4,5,7,8] There is no standard-of-care therapy for these patients after failing CAR T-cell therapies. Repeat infusion of CAR T-cell might be an option.

Different therapies were used to treat patients with RRMM after BCMA-targeted CAR T-cell therapy,[9] and immunotherapies induced responses in these patients. Repeat infusion of CAR T-cells showed efficacy in patients with RRMM who had failed a prior CAR T-cell therapy. In KarMMa trial 28 subjects with RRMM received a second infusion of idecabtagene vicleucel. Six responded to the second infusion of CAR T-cell including 1 with very good partial response and 5 with partial response (PR).[10] In a multicenter study 7 subjects with RRMM failing anti-BCMA CAR T-cell therapies received anti-GPRC5D CAR T-cell, 6 responded to anti-GPRC5D CAR T-cell and the median progression-free survival (PFS) was 18.2 months (95% confidence interval [CI], 14.4 - not estimatable).[11] These findings suggested that a second infusion of CAR T-cells was feasible and changing the target of CAR T-cell

seemed to be more effective.

It is important to evaluate whether anti-BCMA T-cell and anti-GPRC5D CAR T-cell could be salvage therapies for each other, and which treatment sequence would be better. In our previous study, 37 subjects with RRMM who failed a prior anti-BCMA CAR T-cell therapy received anti-GPRC5D CAR T-cell. Thirty-one subjects responded to anti-GPRC5D CAR T-cell, including 13 with complete response (CR).[12] The number of patients treated by anti-GPRC5D CAR-T cell was limited, and those who received a second infusion of CAR T-cell were even fewer. Thus, few studies have systematically evaluated the efficacy of repeat infusion of CAR T-cell in patients who had failed a prior anti-GPRC5D CAR-T cell therapy. In this study, we retrospectively investigated the efficacy and safety of anti-BCMA CAR T-cell therapy for 20 subjects with RRMM after anti-GPRC5D CAR-T cell therapy, and compared the efficacy with that in the cohort of receiving anti-GPRC5D CAR T-cell after failing anti-BCMA CAR T-cell therapies.

Methods

Study design and subjects

From March 2022 to October 2025, 24 subjects with RRMM involved in 3 clinical trials (ChiCTR1900026219, ChiCTR2000033567, and NCT05509530) conducted in our institution were screened for this study. All the subjects had RRMM after a prior anti-GPRC5D CAR T-cell therapy and underwent apheresis for the productions of BCMA-targeted CAR T-cells. Inclusion and exclusion criteria was described

previously.[13-15] Four subjects did not receive BCMA-targeted CAR T-cells due to CAR T-cell production failure, withdrawal of consent, and death. Twenty subjects who received BCMA-targeted CAR T-cells were included in the analysis (**Figure 1**). This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY-2018-KL003-01, XYFY2020-KL062-01, XYFY2022-KL118-01), and informed consent was obtained from each participant, in compliance with the Declaration of Helsinki.

CAR-T cell manufacturing

The productions of anti-BCMA CAR T-cells, anti-BCMA/CD19 CAR T-cells, and anti-BCMA/GPRC5D CAR T-cells were performed as previously described.[13-15] Briefly, peripheral blood mononuclear cells were obtained by a blood cell separator, and T lymphocytes were sorted using anti-CD3 magnetic beads. T lymphocytes were transduced with lentiviruses encoding the second-generation CAR structural fragments (scFv/4-1BB/CD3ζ) and amplified *in vitro* for 5-10 days prior to examination and infusion.[13-15] The bispecific BCMA/CD19-CAR scFv and the bispecific BCMA/GPRC5D scFv constructs were described previously.[14,15]

Clinical procedures

Subjects could receive bridging antimyeloma therapies, which should be ended at least 14 days before lymphodepletion. Expressions of BCMA on myeloma cells were confirmed by flow cytometry for all subjects before lymphodepletion (Table S1, Figure S1), which comprised of fludarabine (30 mg/m^2/day) for 3 days and cyclophosphamide (750 mg/m^2/day) for 1 day followed by 2 days of interval before

CAR T-cell infusion. Subjects received a median dose of intravenous CAR T-cell at 1.6×10^6 cells per kg (IQR 1.3-2.0).

Response and toxicity assessment

After CAR T-cell infusion, responses were assessed since day 14 according to the International Myeloma Working Group criteria.[16] The assessment indicators included measurable residual disease (MRD) in the bone marrow, serum paraprotein, immunoglobulin concentration, immunofixation electrophoresis, free immunoglobulin light chains, and quantitation of 24-hour urine protein. MRD negativity was defined as the absence of phenotypically aberrant clonal plasma cells, which was assessed by multi-colour flow cytometry according to the EuroFlow protocol (minimum sensitivity, 1 in 10^5).[17] The assessment of extramedullary disease included imaging techniques and physical examination. Cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome were graded according to the American Society for Transplantation and Cellular Therapy criteria.[18] Haematological toxicities, other neurologic toxicities and adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Outcomes

The primary end point was ORR referring to best overall response which included stringent complete response (sCR), CR, very good partial response and PR as assessed according to the International Myeloma Working Group criteria.[16] Secondary end points were PFS, duration of response (DOR) and safety (including CRS, neurologic

toxicities and other AEs).

Statistical analysis

Descriptive statistics include medians with inter-quartile range (IQR) for continuous variables and counts and percentages for categorical variables. Clopper-Pearson 95% CIs and Fisher's exact test were used for categorical variables. Continuous variables were tested by Mann-Whitney *U* test for two groups. DOR and PFS of subjects were determined using Kaplan-Meier and compared using the log-rank test. All analyses were performed with Statistical Package for the Social Sciences 26 or GraphPad Prism 10. *P* values < 0.05 (two-tailed) were considered significant.

Results

Baseline characteristics

A total of 20 subjects with RRMM receiving a second CAR T-cell infusion were included in the study. Clinical characteristics of subjects are presented in **Table 1** and **Table S1**. Median age was 61 years (IQR 58 - 64) and 12 of 20 (60%) subjects were male. The median time at the second CAR T-cell infusion since diagnosis was 69.3 months (IQR 31.7 - 85.2). Fourteen subjects (70%) had Second Revision of the International Staging System III/IV disease,[19] 5 subjects (25%) had extramedullary disease, and 16 subjects (80%) had high-risk cytogenetic abnormalities. The 20 subjects had received a median of 6 lines of previous therapy (IQR 4 - 8), 17 (85%) were refractory to at least one proteasome inhibitor and 18 (90%) were refractory to at least one immunomodulatory drug. Six subjects (30%) had received auto-transplants

and 10 (50%) had triple-class refractory diseases. The median DOR was 10.3 months (95% CI, 4.7 - 18.2) in 12 evaluable subjects who achieved PR or better in the prior anti-GPRC5D CAR T-cell therapies. The median time from anti-GPRC5D CAR T-cell infusion to anti-BCMA CAR T-cell infusion was 14.4 months (IQR 4.8 - 22.3).

Efficiency

During a median follow-up of 13.4 months (IQR 3.6 - 21.2), 13 of 20 subjects (65%) achieved responses, including 9 (45%) with sCR and 4 with (20%) PR (**Figure 2A, B**). The median time to initial response was 26 days (IQR 14 - 57), and the median time to best response was 31 days (IQR 18 - 57). Bone marrow MRD was evaluated in 17 subjects. In the 4 subjects who were bone marrow MRD-negative before anti-BCMA CAR T-cell infusion, 2 achieved sCR and 1 achieved PR after CAR T-cell infusion. In the 13 subjects who were bone marrow MRD-positive before anti-BCMA CAR T-cell infusion, bone marrow MRD turned negative after CAR T-cell infusion in 11 subjects including 7 with sCR and 2 with PR (Figure 2C).

In the 13 subjects with responses, the median DOR was 10.2 months (95% CI, 2.6 - not reached) (**Figure 3A**), and 7 subjects experienced disease progression during the follow-up (**Figure 2A**). The median PFSs were 9.2 months (95% CI, 3.0 - 13.6) in all subjects with responses and 20.8 months (95% CI, 5.3 - not reached) in the 9 subjects with sCR (**Figure 3B**). Although there was no statistically significant difference in ORR and CRR between this study and our recent study (ORR: P = 0.18, CRR: P = 0.57),[12] the ORR in this study seems lower than that in the cohort of our recent study, which reported the ORR was 84% (n=31) in 37 subjects with RRMM receiving anti-

GPRC5D CAR T-cells after failing a prior anti-BCMA CAR T-cell therapy.[12] We also compared the PFS with that in our recent study, which showed the median PFS was 4.5 months (95% CI, 2.9 - 6.2) in all subjects and was not reached in subjects with CR or better during a median follow-up of 12.6 months,[12] and no statistical difference was observed (all subjects: 9.2 *vs.* 4.5 months, $P = 0.93$; CR or better: 20.8 *vs.* not reached, $P = 0.20$).[12]

Following disease progression after anti-GPRC5D CAR T-cell therapy, 11 subjects received anti-myeloma therapies before anti-BCMA CAR T-cell treatment, with 5 subjects receiving 2 lines of treatment. Eight subjects received anti-CD38 antibody-based therapies, and 1 of 3 responders achieved CR. One of 3 subjects receiving aponermin-based therapies achieved an objective response. None responded to triplet or quadruplet combination of approved agents (**Table S2**). Among the 9 subjects who achieved sCR in the salvage anti-BCMA CAR-T cell therapy, 8 had responses in the prior anti-GPRC5D CAR-T cell therapy including 6 with sCR and 2 with PR. Among the 7 subjects refractory to the prior anti-GPRC5D CAR-T cell therapy, 4 responded (sCR, n=1; PR, n=2; minimal response, n=1) to the salvage anti-BCMA CAR-T cell therapy (**Table S2**).

Safety

The AEs within the first 30 days are evaluated in 18 subjects (**Table 2)**. Before lymphodepletion, 13 (72%) subjects had cytopenia to different extent, including 11 (61%) with neutropenia, 8 (44%) with lymphopenia, 9 (50%) with anaemia, and 9 (50%) with thrombocytopenia. After infusion of anti-BCMA CAR-T cells, all the 18

subjects had grade ≥3 haematological AEs, including lymphopenia (18 [100%]), leukopenia (n=15 [83%]), and neutropenia (n=15 [83%]). The median duration of grade ≥3 lymphopenia was 11 days (IQR 5 - 15), leukopenia 10 days (IQR 3 - 12), and neutropenia 9 days (IQR 3 - 19). Eight subjects (44%) had grade ≥3 thrombocytopenia and 5 (28%) were with grade ≥3 anaemia.

Within the first 30 days after anti-BCMA CAR T-cell infusion, 14 (78%) subjects had CRS including 1 with grade 3 CRS. The median time to onset of CRS was 7 days (IQR 5 - 9), and the median duration was 4 days (IQR 3 - 7). Nine subjects (64%) received glucocorticoids, and 1 received tocilizumab. Levels of IL-6, ferritin, and C-reactive protein were measured twice weekly after infusion of anti-BCMA CAR T-cells. The median time of reaching peak levels of IL-6, ferritin, and C-reactive protein were 9 days (IQR 8 - 11), 11 days (IQR 9 - 15), and 10 days (IQR 7 - 11) after anti-BCMA CAR T-cell infusion, respectively. In the subjects with CRS, the peak levels of IL-6, ferritin, and C-reactive protein were significantly higher than baselines (IL-6: $P < 0.05$, ferritin: $P = 0.05$, C-reactive protein: $P < 0.0001$) (**Figure S2**). Neurotoxic event was observed in 1 subject (5%) who showed brief self-limited headache but without disturbance of consciousness, paraphasia or dysgraphia. Immune effector cell associated neurotoxicity syndrome was not observed in all the 18 subjects.

All non-hematologic toxicity effects resolved quickly with supportive care without severe organ damage. Grade ≥3 non-hematological toxic events occurred in 4 subjects including 1 with grade 3 increase of alanine aminotransferase level, 1 with grade 3 increase of aspartate aminotransferase level, 1 with decrease of fibrinogen level, and 1

with infection. The other non-hematological toxic events included grade 1 or 2 malignant nausea (n=8 [44%]), hypophosphataemia (n=12 [67%]), hypocalcaemia (n=7 [39%]), hypoalbuminemia (n=7 [39%]), and prolonged activated partial thromboplastin time (n = 10 [56%]).

Lymphocyte subset data were available in 13 subjects. B-cell percentage in peripheral blood lymphocytes decreased during the first 30 days after CAR T-cell infusion (**Figure S3**). In 17 evaluable subjects, 15 showed decreased levels of two or three uninvolved immunoglobulins, and 1 showed decreased level of one uninvolved immunoglobulin (IgA) within 60 days after CAR T-cell infusion (**Figure S4**).

Discussion

There is no standard-of-care therapy for patients with RRMM after failing CAR T-cell therapies. In this study, 20 subjects with RRMM received salvage anti-BCMA CAR T-cell therapies after failing a prior anti-GPRC5D CAR T-cell therapy. Thirteen (65%) subjects showed responses to anti-BCMA CAR T-cell therapies, and the median PFS was 20.8 months in the 9 (45%) subjects who achieved sCR. The efficacy in this study is comparable to that in the cohort of our recent study, in which 37 subjects with RRMM received anti-GPRC5D CAR T-cells after failing a prior anti-BCMA CAR T-cell therapy.[12] Our studies systematically documented that the two targets (BCMA and GPRC5D) could be used alternatively when repeat infusion of CAR T-cell is considered for treating RRMM. The same is true for other BCMA or GPRC5D-directed therapies. Joiner and colleagues reported BCMA-directed therapies,

including bi-specific antibodies and CAR T-cell, were effective in subjects with RRMM after failing GPRC5D-directed therapies.[20] In subjects with RRMM receiving GPRC5D bi-specific antibodies as a salvage treatment after anti-BCMA CAR T-cell therapies, the ORR and CRR were 70%-80% and 40%, and the 12-month DOR was 50%-60%.[21,22] Repeat infusion of CAR T-cell also showed effectiveness in other hematological malignancies. In a phase-1/-2 trial 44 subjects with refractory B-cell malignancies (acute lymphoblastic leukemia, n=14; chronic lymphocytic leukemia, n=9; non-Hodgkin lymphoma, n=21) failing a first infusion of anti-CD19 CAR T-cells received a second infusion of anti-CD19 CAR T-cells. 39% responded to the second infusion, and 2-year PFS and OS were 23% (95% CI, 9-59) and 36% (95% CI, 19-71) in subjects who achieved PR or better at day 28 after the second infusion.[23] In a phase-1 trial anti-CD22 CAR T-cell therapy was used to treat 37 subjects with advanced LBCL who relapsed after anti-CD19 CAR T-cell therapies. The ORR and CRR were 68% and 53%, and the median DOR was 27.8 months (95% CI, 5.1-not evaluable).[24]

Although statistical significance was not reached (P = 0.18), the ORR in the anti-BCMA after anti-GPRC5D cohort of this study seems lower than that in the anti-GPRC5D after anti-BCMA cohort of our previous report.[12] We deduce the lower response rate might result from the disease *per se*, because the percent of subjects with high-risk cytogenetic profile in this study was higher than that in the previous study (80% *vs.* 43%).[12] BCMA is more extensively expressed on myeloma cells as compared with GPRC5D.[2,12,25] Anti-BCMA CAR T-cells used in front might eliminate

myeloma sub-clones more extensively, comparing with anti-GPRC5D CAR T-cells used in front. Others reported that anti-GPRC5D CAR T-cells potentially limited the expansion of anti-BCMA CAR-T cells when they were used concurrently.[26] There was a 14.4-month interval between infusion of the two types of CAR T-cells in this study, and both CAR T-cells could expand well *in vivo* when used as salvage therapies in our studies (data not shown).[12] Thus, the two types of CAR T-cells might not have a direct impact on each other herein. These findings suggested the treatment sequence of anti-GPRC5D CAR T-cells after anti-BCMA CAR T-cells might be a better choice for RRMM. Nonetheless, the PFS in this study was comparable to that in our previous report,[12] which indicated the anti-BCMA CAR T-cells were effective even been used as a salvage therapy. At the cutoff date of follow-up, 8 of 9 subjects with sCR in this study are alive.

The efficacy of repeat infusion of CAR T-cell could be affected by factors such as antigen escape and T-cell fitness. Loss of BCMA or GPRC5D antigen was observed among patients with MM who relapsed after anti-BCMA CAR T-cell or anti-GPRC5D CAR T-cell therapies.[27-30] We found one patient with deletion mutations of both TNFRSF17 (encoding BCMA) and GPRC5D genes after sequential anti-BCMA CAR T-cell and anti-GPRC5D CAR T-cell therapies.[30] These findings suggest that myeloma cells heterogeneity and genomic instability can facilitate clonal outgrowth of antigen-negative myeloma cells under selective pressure of CAR T-cells. In addition, modification of proteins also causes antigen-loss such as gamma-secretase mediated shedding of BCMA from membrane of myeloma cells.[31,32] We recently

reported that plasma cell tumors were GPRC5D-negative in 8 of 10 subjects with MM relapsing after anti-GPRC5D CAR T-cell therapies,[30] and it is reasonable to change the target when repeat infusion of CAR T-cell is considered for these patients. Tumor cells were BCMA-positive in all subjects before receiving anti-BCMA CAR T-cells in this study. These results could interpret why anti-BCMA CAR T-cells remain effective after failing anti-GPRC5D CAR T-cell therapies. Both the anti-GPRC5D after anti-BCMA sequence and anti-BCMA after anti-GPRC5D sequence showed effectiveness in our studies, which indicated that neither anti-GPRC5D CAR-T cells nor anti-BCMA CAR T-cells significantly decreased the expression of the other target antigen. However, the underlying mechanism is unknown.

T-cell function and persistence are crucial factors associated with CAR T-cell efficacy.[33] Our previous studies showed both anti-GPRC5D CAR-T cells and anti-BCMA CAR T-cells expanded well *in vivo* in most patients who had not been treated by CAR T-cells, and the CAR T-cells persisted as long as 1 year in a small part of patients.[2,13-15] When be used after a prior CAR T-cell therapy, the expansion and persistence of anti-GPRC5D CAR-T cells and anti-BCMA CAR T-cells might be affected by more complex factors such as a higher tumor burden and a more immunosuppressive tumor microenvironment which mediated resistance to CAR T-cells.[34-36]

CAR T-cells often lead to significant toxic reactions because of activation of immune system. It is important to re-evaluate the safety when repeat of CAR T-cell therapy is conducted. In this study and our previous study,[12] the grade ≥3 CRS was

comparable (6% *vs.* 5%) and most of AEs were manageable, and none died from CAR T-cell infusion. The most common grade ≥3 AEs were early haematotoxicities, which was potentially resulted from chemotherapy drugs and inflammation induced by CAR T-cells. Other studies also showed the most common grade ≥3 AEs were haematotoxicities in RRMM subjects receiving anti-BCMA CAR T-cell therapy, with incidences of more than 85%.[4,13,14,37] The incidences of CRS were 75% to 95%, and the majority were grade 1 or 2.[4,13,14,37] The incidences of AEs were not increased in subjects with B-cell malignancies or plasma cell tumors after the second infusion of CAR T-cells.[12,24,38] These studies, together with ours, indicated that a second use of CAR T-cell therapy might not increase AEs.

Our study has limitations. The findings from this retrospective study with limited sample size need to be confirmed in a larger clinical trial. The long-term efficacy and safety of repeat infusion of CAR T-cell reported in this study is unknown and needs to be validated in a prolonged follow-up duration. Nevertheless, this study has implications for the options after failing a CAR T-cell therapy in patients with RRMM.

In conclusion, anti-BCMA CAR T-cell as a salvage therapy was effective for patients with RRMM who had been treated by anti-GPRC5D CAR T-cells, and the safety was acceptable.

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Table 1: Baseline characteristics

Characteristic	Value
Age	
Median age, years	61 (58-64)
Gender	
Female	8 (40%)
Male	12 (60%)
ECOG performance status score	
0	7 (35%)
1	7 (35%)
2	6 (30%)
Median time since diagnosis, months	69.3 (31.7-85.2)
Median time of interval between two infusions of CAR T-cells, months	14.4 (4.8-22.3)
Monoclonal globulin	
IgA	1 (5%)
IgD	2 (10%)
IgG	14 (70%)
K light chain	1(5%)
λ light chain	2 (10%)
R2-ISS	
I	2 (10%)
II	4 (20%)
III	9 (45%)
IV	5 (25%)
Extramedullary disease*	5 (25%)
High-risk cytogenetic profile†	16 (80%)
Previous therapy lines	6 (4-8)
Previous autotransplant	6 (30%)
Triple-class refractory disease‡	10 (50%)
Infused cells	
Isolated BCMA	11 (55%)
Bispecific BCMA and CD19	7 (35%)
Bispecific BCMA and GPRC5D	2(10%)
Median dose ($\times 10^6$/kg)	1.6(1.3-2.0)

Data are median (IQR) or n (%). Percentages might be not total 100 because of rounding.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; GPRC5D, G protein-coupled receptor, class C group 5 member D; R2-ISS, Second Revision of the International Staging System.

*Extramedullary diseases included tissue masses in extraosseous locations and bone-related plasmacytomas. †High-risk cytogenetic profile was defined as the presence of del(17p), t(4;14), t(14;16), and amp(1q). ‡Triple-class refractory disease was defined as disease refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Table 2: Adverse events within the first 30 days after anti-BCMA CAR T-cell infusion

	All grades	Grade 3-4
Haematological disorders		
Leukopenia	18(100%)	15(83%)
Neutropenia	18(100%)	15(83%)
Lymphopenia	18(100%)	18(100%)
Anaemia	15(83%)	5(28%)
Thrombocytopenia	15(83%)	8(44%)
Gastrointestinal disorders		
Nausea	8(44%)	0
Diarrhoea	3(17%)	0
Abdominal discomfort	1(6%)	0
Metabolism and nutrition disorders		
Hypophosphataemia	12(67%)	0
Hypocalcaemia	7(39%)	0
Hyponatraemia	5(28%)	0
Hypokalaemia	5(28%)	0
Hypoalbuminemia	7(39%)	0
Hypoglycemia	1(6%)	0
Respiratory and cardiac disorders		
Cough	3(17%)	0
Productive cough	2(11%)	0
Nasal discharge	3(17%)	0
Others		
Prolonged activated partial thromboplastin time	10(56%)	0
Decreased fibrinogen	5(28%)	1(6%)
Elevated alanine aminotransferase level	3(17%)	1(6%)
Elevated aspartate aminotransferase level	3(17%)	1(6%)
Elevated cardiac troponin T level	4(22%)	0
Increased lactate dehydrogenase	4(22%)	0
Heart failure	2(11%)	0
Headache	1(6%)	0
Muscular soreness	1(6%)	0
Facial edema	1(6%)	0
Fatigue	2(11%)	0
Infection	5(28%)	1(6%)
Cytokine release syndrome	14(78%)	1(6%)
Immune effector cell–associated neurotoxicity syndrome	0	0

Data are n (%).

Figure Legends

Figure 1. Trial profile.

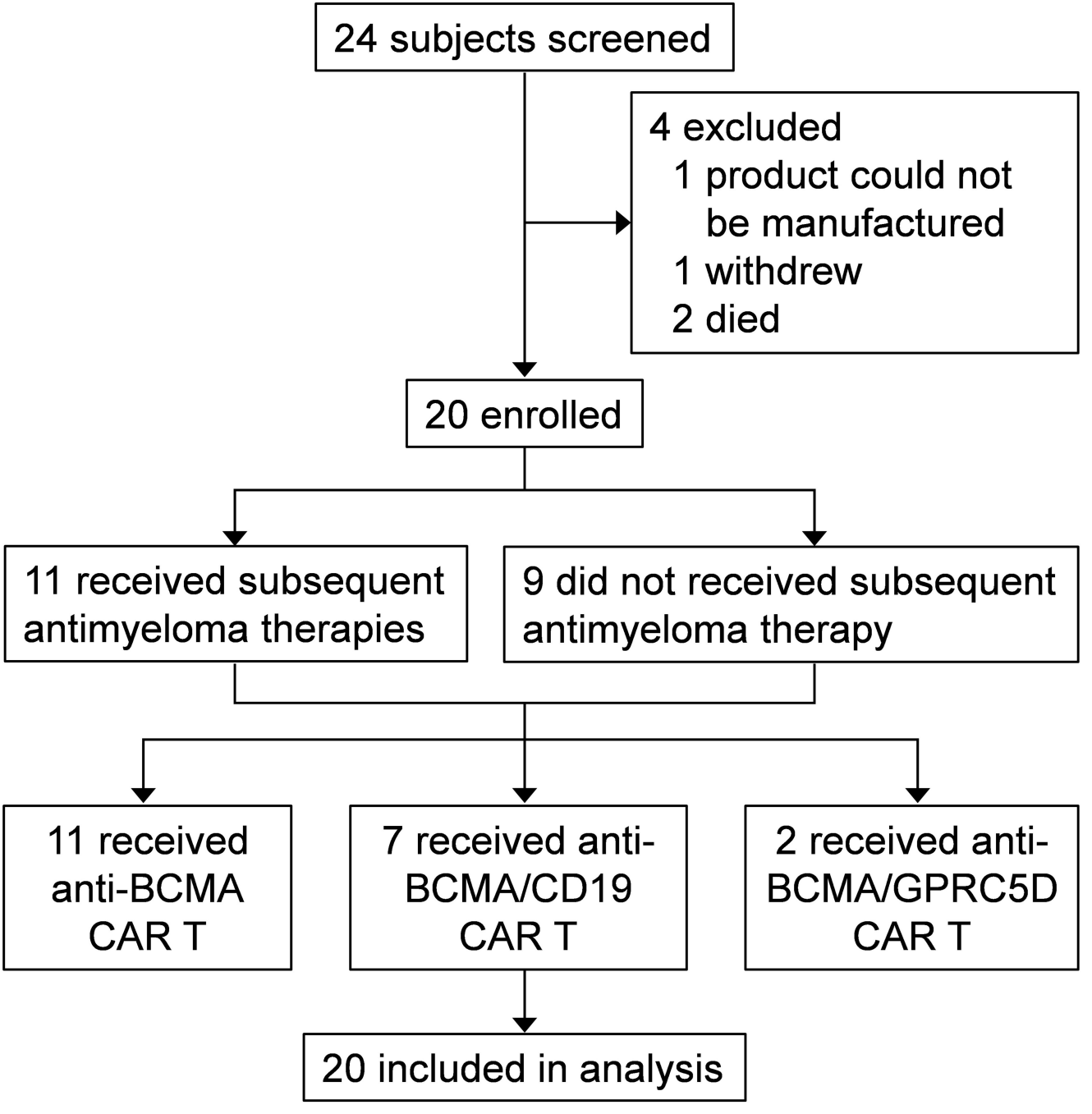
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

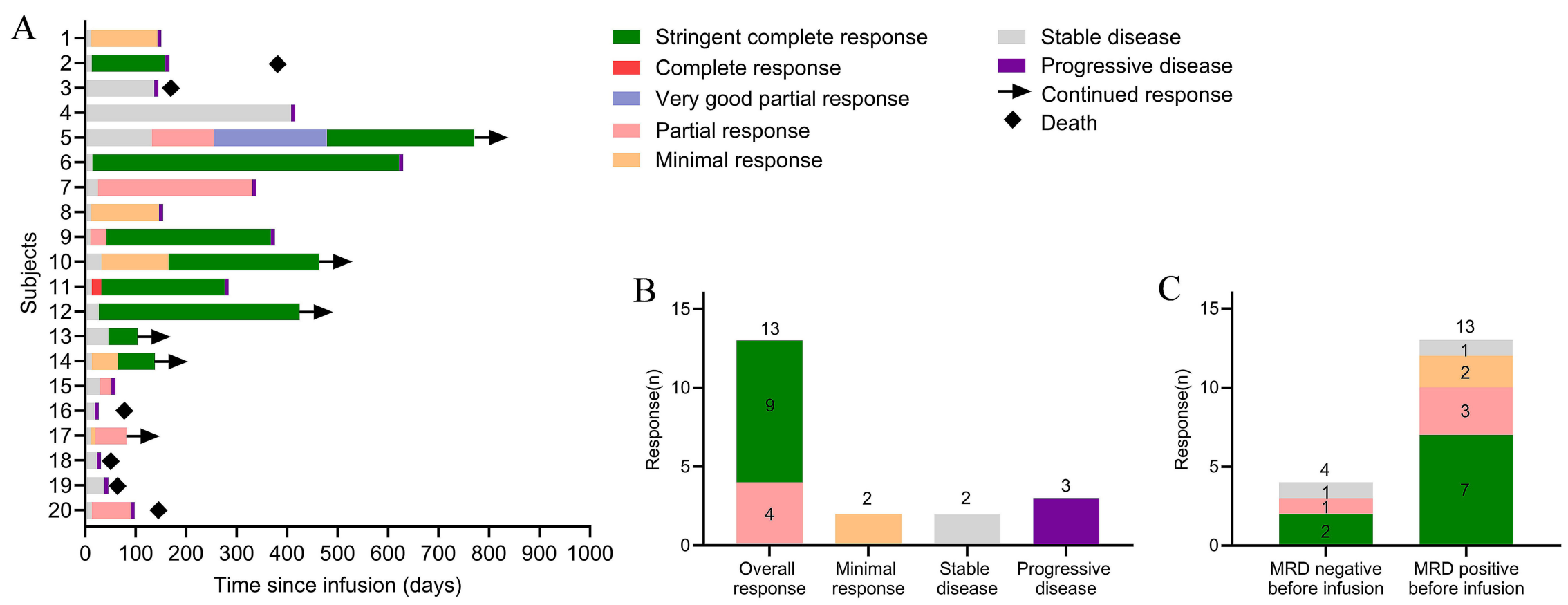
Figure 2. Overall responses.

(A) Swimmer plot of clinical responses to anti-BCMA CAR T-cells. (B) The number of overall response, minimal response, stable disease, and progressive disease in all 20 enrolled subjects. (C) The number of overall response, minimal response, and stable disease in all 17 subjects receiving evaluation of MRD after infusion. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MRD, minimal residual disease.

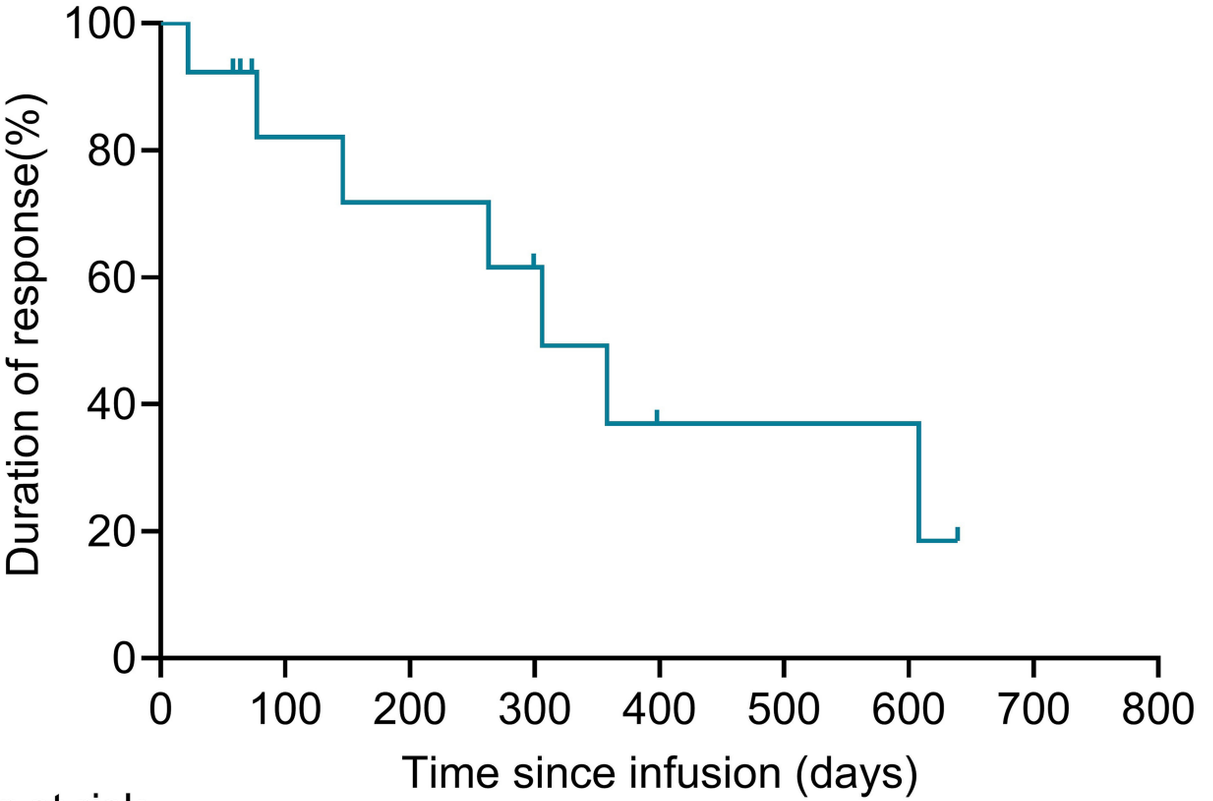
Figure 3. Kaplan-Meier analysis of the DOR and PFS.

(A) Kaplan-Meier curve of DOR in subjects with partial response or better. (B) Kaplan-Meier curve of PFS in patients treated with anti-BCMA CAR T-cells. DOR, defined as the time from the date of first ≥ PR evidence to disease progression or death from any cause. PFS, defined as the time from CAR T-cell infusion to disease progression or death from any cause. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; DOR, duration of response; GPRC5D, G protein-coupled receptor, class C group 5 member D; PFS, progression-free survival.


24 subjects screened
4 excluded
1 product could not be manufactured
1 withdrew
2 died
20 enrolled
11 received subsequent antimyeloma therapies
9 did not received subsequent antimyeloma therapy
11 received anti-BCMA CAR T
7 received anti-BCMA/CD19 CAR T
2 received anti-BCMA/GPRC5D CAR T
20 included in analysis

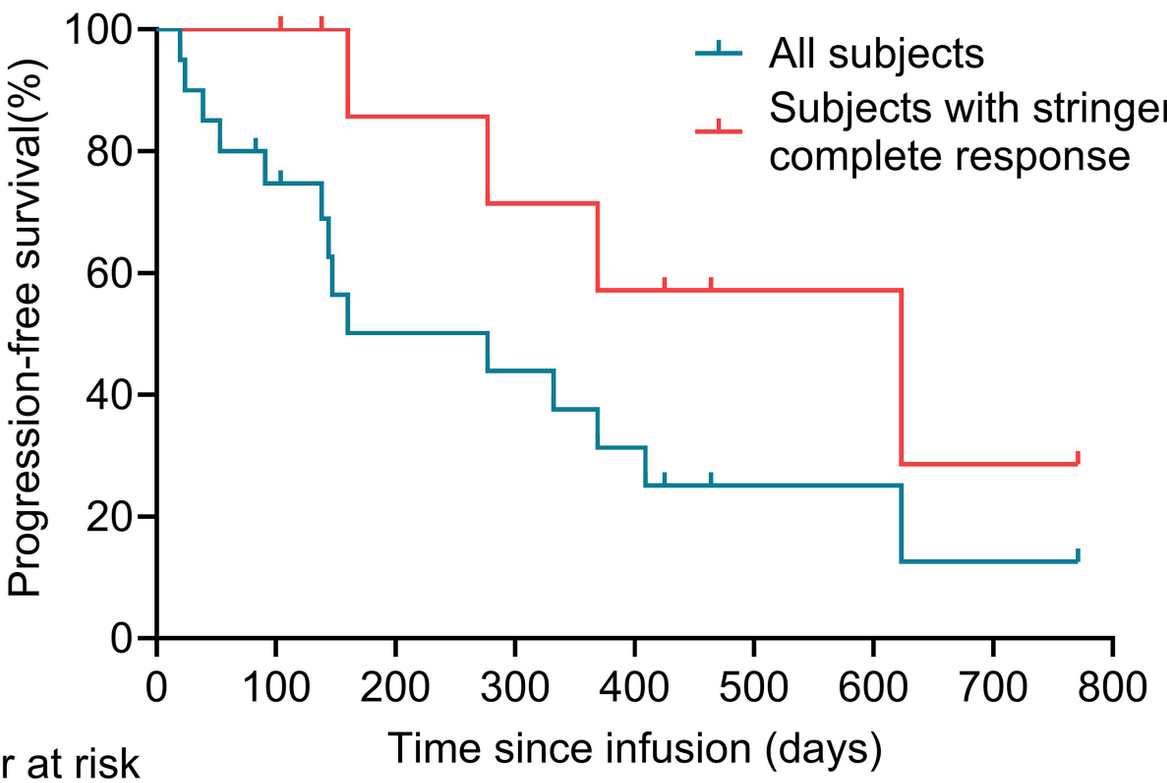

A
Subjects
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
0
100
200
300
400
500
600
700
800
900
1000
Time since infusion (days)
Stringent complete response
Complete response
Very good partial response
Partial response
Minimal response
Stable disease
Progressive disease
Continued response
Death
B
Response(n)
15
10
5
0
13
9
4
2
2
3
Overall response
Minimal response
Stable disease
Progressive disease
C
Response(n)
15
10
5
0
4
1
1
2
13
1
2
3
7
MRD negative before infusion
MRD positive before infusion

A



Number at risk (number censored)									
Subjects with partial response or better	13(0)	8(3)	7(3)	5(4)	2(5)	2(5)	2(5)	0(6)	0(6)

B



Number at risk (number censored)									
All subjects	20(0)	14(1)	8(3)	7(3)	5(3)	2(5)	2(5)	1(5)	0(6)
Subjects with stringent complete response	9(0)	9(0)	6(2)	5(2)	4(2)	2(4)	2(4)	1(4)	0(5)

Supplementary Data

Table S1. Baseline characteristics

Characteristic		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age, years		64	58	63	46	58	68	60	59	62	60
Gender		Male	Male	Female	Male	Female	Male	Female	Female	Male	Male
ECOG performance status		1	0	2	0	0	1	2	1	2	0
Time since diagnosis, months		8·9	9·5	42·1	86·3	45·1	80·2	71·1	29·5	75·0	100·9
Time of interval between two infusions of CAR T-cells, months		3.4	2.7	5.0	6.6	19.5	16.9	4.8	22.8	10.3	27.5
Monoclonal globulin		IgG	IgG	IgG	IgG	IgG	λ light chain	IgG	IgG	IgD	IgG
R2-ISS disease stage		II	II	III	I	IV	III	III	III	IV	I
Extramedullary disease*		None	None	Liver, uterus	None	None	None	soft tissue	None	None	None
High-risk cytogenetic profile†		None	None	amp(1q)	amp(1q)	amp(1q), del(17p)	amp(1q)	NE	amp(1q)	amp(1q)	amp(1q)
BCMA antigen expression		BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+
Previous therapy lines		3	3	5	4	4	8	9	3	8	6
Previous autotransplant		None	None	None	None	None	Yes	None	None	Yes	None
Previous proteasome inhibitors											
Bortezomib	Exposed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Refractory‡	Yes	Yes	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes
Ixazomib	Exposed	None	None	None	None	None	Yes	Yes	Yes	Yes	Yes
	Refractory	None	None	None	None	None	NE	Yes	NE	Yes	None
Carfilzomib	Exposed	None	None	None	None	None	None	None	None	Yes	None
	Refractory	None	None	None	None	None	None	None	None	Yes	None
Previous immunomodulatory drugs											
Thalidomide	Exposed	None	None	None	Yes	Yes	Yes	Yes	None	None	Yes
	Refractory	None	None	None	None	None	None	Yes	None	None	Yes
Lenalidomide	Exposed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	None
	Refractory	Yes	Yes	Yes	None	Yes	Yes	Yes	None	Yes	None
Pomalidomide	Exposed	None	None	None	None	None	None	Yes	None	Yes	None
	Refractory	None	None	None	None	None	None	Yes	None	Yes	None
Previous selinexor											
Exposed		None	None	None	None	None	None	Yes	None	Yes	None
Refractory		None	None	None	None	None	None	Yes	None	Yes	None
Previous anti-CD38 monoclonal antibodies											
Exposed		Yes	None	None	Yes	None	Yes	Yes	None	Yes	None
Refractory		None	None	None	None	None	None	Yes	None	Yes	None
Triple-class refractory disease§		None	None	None	None	None	None	Yes	None	Yes	None
Infused CAR T-cells		anti-BCMA/ CD19	anti-BCMA/ CD19	anti-BCMA/ CD19	anti-BCMA/ CD19	anti-BCMA	anti-BCMA	anti-BCMA/ CD19	anti-BCMA/ CD19	anti-BCMA	anti-BCMA
Average dose ($\times 10^6$/kg)		1.3	1.7	1.5	0.9	1.5	1.5	1.6	1.7	1.1	0.9

(continued in next column)

Table S1. Baseline characteristics (continued)

Characteristic		Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16	Patient 17	Patient 18	Patient 19	Patient 20
Age, years		64	62	60	68	60	57	63	62	49	67
Gender		Male	Female	Male	Male	Male	Male	Female	Female	Male	Female
ECOG performance status		2	2	0	0	1	1	0	2	1	1
Time since diagnosis, months		31·4	18·0	86·4	74·3	81·9	32·6	124·7	88·5	48·4	67·5
Time of interval between two infusions of CAR T-cells, months		18.0	3.2	9.6	12.6	16.1	3.9	30.0	20.8	32.8	27.5
Monoclonal globulin		IgA	IgD	λ light chain	IgG	K light chain	IgG	IgG	IgG	IgG	IgG
R2-ISS disease stage		III	III	IV	III	II	IV	II	IV	III	III
Extramedullary disease		None	None	None	None	Pleura/thoracic cavity	soft tissue	None	Thoracic cavity	None	None
High-risk cytogenetic profile		amp(1q)	amp(1q)	amp(1q), del(17p)	NE	del(17p)	amp(1q), del(17p)	amp(1q)	amp(1q), del(17p)	amp(1q)	t(4:14)
BCMA antigen expression		BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA+	BCMA
Previous therapy lines		7	4	7	5	11	9	6	12	6	8
Previous autotransplant		Yes	None	None	None	None	Yes	None	Yes	None	Yes
Previous proteasome inhibitors											
Bortezomib	Exposed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Refractory	Yes	None	None	None	Yes	Yes	Yes	Yes	Yes	Yes
Ixazomib	Exposed	None	None	Yes	None	Yes	None	None	Yes	None	None
	Refractory	None	None	Yes	None	Yes	None	None	Yes	None	None
Carfilzomib	Exposed	Yes	None	None	None	Yes	Yes	Yes	Yes	Yes	Yes
	Refractory	Yes	None	None	None	Yes	Yes	None	Yes	Yes	Yes
Previous immunomodulatory drugs											
Thalidomide	Exposed	None	None	None	None	None	None	None	Yes	None	Yes
	Refractory	None	None	None	None	None	None	None	Yes	None	None
Lenalidomide	Exposed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	None	Yes
	Refractory	Yes	Yes	Yes	Yes	Yes	Yes	None	Yes	None	Yes
Pomalidomide	Exposed	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Refractory	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Previous selinexor											
Exposed		None	None	None	None	None	Yes	None	Yes	Yes	Yes
Refractory		None	None	None	None	None	Yes	None	Yes	Yes	None
Previous anti-CD38 monoclonal antibodies											
Exposed		Yes	None	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes
Refractory		Yes	None	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes
Triple-class refractory disease		Yes	None	Yes	None	Yes	Yes	Yes	Yes	Yes	Yes
Infused CAR T-cells		anti-BCMA	anti-BCMA	anti-BCMA	anti-BCMA	anti-BCMA/ CD19	anti-BCMA	anti-BCMA	anti-BCMA/ GPRC5D	anti-BCMA/ GPRC5D	anti-BCMA
Average dose ($\times 10^6$/kg)		2.6	1.9	1.3	1.6	2	1.4	1.4	2	2	2

BCMA, B-cell maturation antigen; CAR, Chimeric Antigen Receptor; ECOG, Eastern Cooperative Oncology Group; GPRC5D, G protein-coupled receptor class C group 5 member D; NE, not estimable; R2-ISS, Second Revision of the International Staging System.

*Extramedullary disease was defined as tissue masses in extraosseous locations. †High-risk cytogenetic profile was defined as the presence of del(17p), t(4;14), t(14;16), and amp(1q). ‡Refractory was defined as disease progression on or within 60 days after the last dose of the most recent drug given in each drug class. §Triple-class refractory disease was defined as disease refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Table S2. Efficacy of anti-GPRC5D T-cells, antimyeloma therapies and anti-BCMA CAR T-cells

Patients	Best response to anti-GPRC5D CAR T-cells	Antimyeloma therapies/best response before anti-BCMA CAR T-cells	Best response to anti-BCMA CAR T-cells
patient 1	PD	Dd/PR	MR
patient 2	PR	None/None	sCR
patient 3	PD	None/None	SD
patient 4	PD	D-Vd/PR	SD
patient 5	sCR	None/None	sCR
patient 6	sCR	Dd/PD	sCR
patient 7	SD	D-MRd combined with radiotherapy/SD	PR
patient 8	sCR	None/None	MR
patient 9	sCR	SKCd/PD	sCR
patient 10	PR	None/None	sCR
patient 11	sCR	D-Kd/PD	sCR
patient 12	PD	None/None	sCR
patient 13	sCR	None/None	sCR
patient 14	sCR	None/None	sCR
patient 15	PD	D-Kd/PD, Apo-Vd/PR	PR
patient 16	SD	SKCd/PD, Apo-Kd/PD	PD
patient 17	sCR	None/None	PR
patient 18	VGPR	MPT/PD, Apo-Vd/PD	PD
patient 19	PR	D-KPd/CR, D-SKd/PD	PD
patient 20	CR	KPd/SD, D-Kd/PD	PR

Apo-Kd, Aponermin-carfilzomib-dexamethasone; Apo-Vd, Aponermin-bortezomib-dexamethasone; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Dd, daratumumab-dexamethasone; D-Kd, daratumumab-carfilzomib-dexamethasone; D-KPd, daratumumab-carfilzomib-pomalidomide-dexamethasone; D-MRd, daratumumab-melphalan-lenalidomide-dexamethasone; D-SKd, daratumumab-selinexor-carfilzomib-dexamethasone; D-Vd, daratumumab-bortezomib-dexamethasone; GPRC5D, G protein-coupled receptor class C group 5 member D; KPd, carfilzomib-pomalidomide-dexamethasone; MPT, melphalan-prednisone-thalidomide; MR, Minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; SKCd, selinexor-carfilzomib-cyclophosphamide-dexamethasone.

Supplementary Figure Legends

Figure S1. BCMA expression on bone marrow plasma cells by flow cytometry.

Bone marrow was collected before lymphodepletion. The expression of BCMA on myeloma cells was detected according to EuroFlow antibody panels for plasma cell disorders. These are the representative detection results of BCMA expression on bone marrow plasma cells from three patients. BCMA, B-cell maturation antigen.

Multiple myeloma Flow-MRD: antibody panel.

PacO	APC-CY7	APC	PerCP-CY5.5	PE-CY7	FITC	PE
CD45	CD38	CD138	CD19	BCMA	CyIgκ	CyIgλ

Procedure

Flow cytometric analysis was performed on fresh specimens and isotype control antibody was used in each sample for normalization. Plasma cells were gated according to the expression of CD45 and CD38. Phenotype of plasma cells was defined as low level of CD45 and intermediate-to-high level of CD38, which was abbreviated as CD45low $CD38^{int/hi}$ thereafter. Plasma cells were further analyzed for the expression BCMA. No less than 1.0×10^5 cells were acquired in analysis for each sample.

Figure S2. Comparison between baseline and peak levels of IL-6, ferritin, and CRP after CAR T-cell infusion. Median ± interquartile range values are shown. (Peak value of serum (A) IL-6, (B) Ferritin and (C) CRP in patients with CRS. * $p<0.05$, *** $p<0.001$, **** $p<0.0001$. CAR, chimeric antigen receptor; CRP, C-reactive protein; CRS, cytokine release syndrome; IL, interleukin.

Figure S3 Percent of peripheral blood B lymphocytes after CAR T-cell infusion. Each line represents a single patient. CAR, chimeric antigen receptor.

Figure S4 Uninvolved immunoglobulin concentration change after CAR T-cell infusion. Changes in immunoglobulin (A) IgA, (B) IgM, (C) IgG concentration from baseline. Each line represents a single patient. CAR, chimeric antigen receptor.

Figure S1

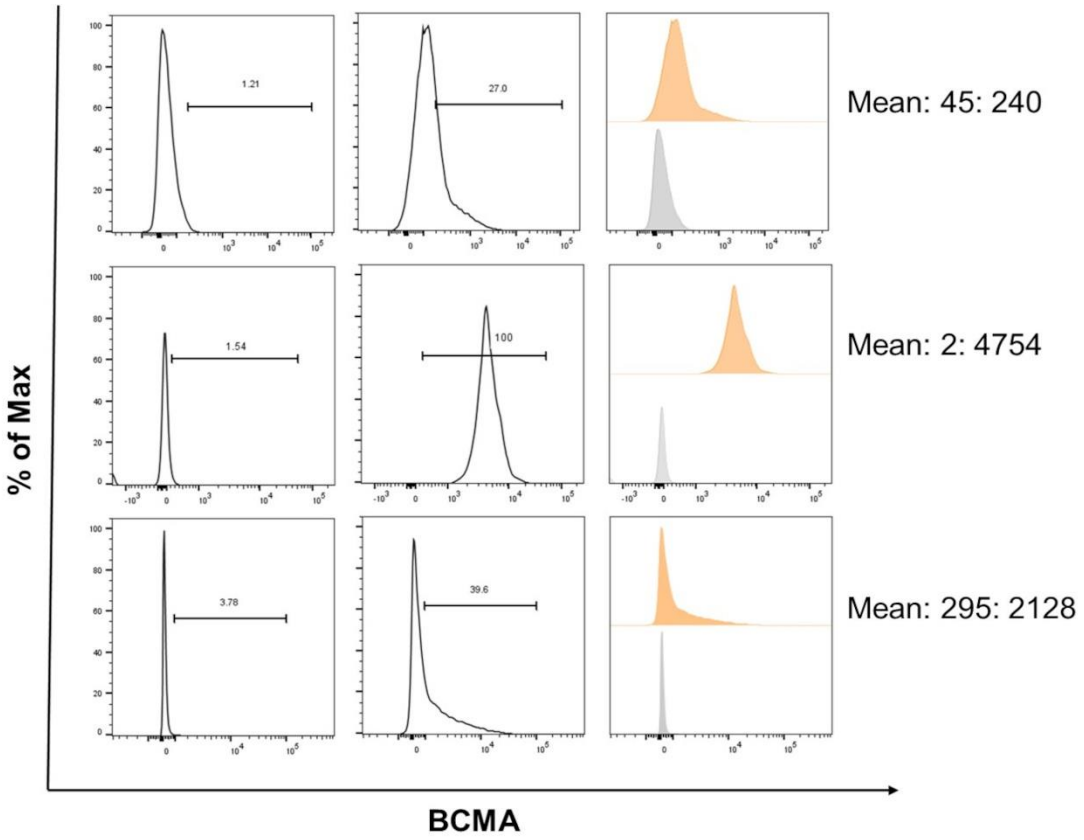
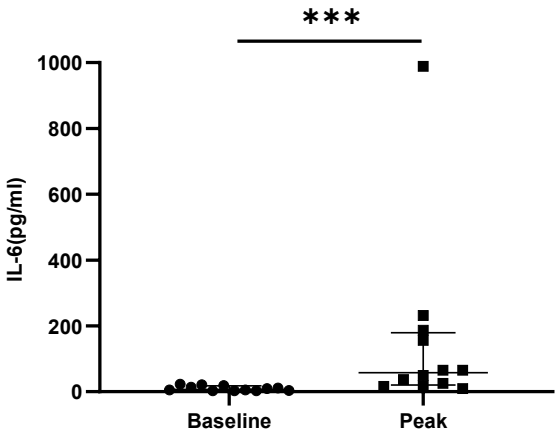

1.21
27.0
Mean: 45: 240
1.54
100
Mean: 2: 4754
3.78
39.6
Mean: 295: 2128
% of Max
BCMA

Figure S2

A



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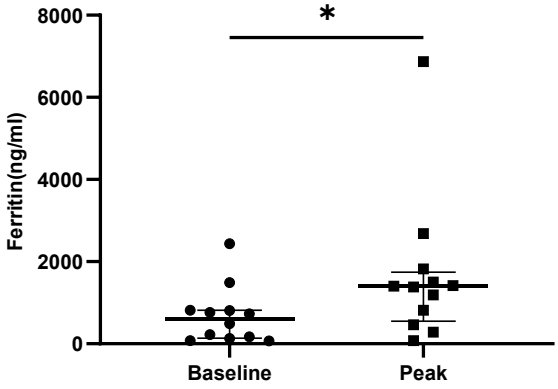

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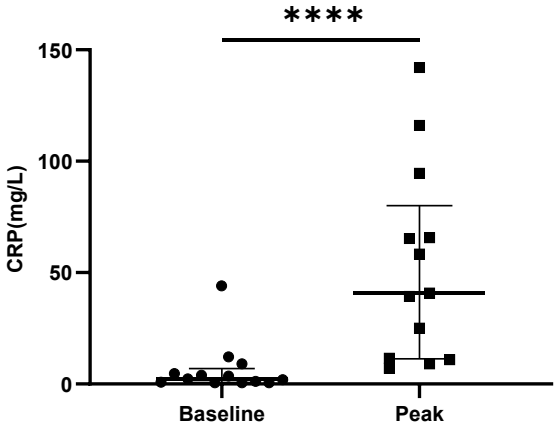


Figure S3

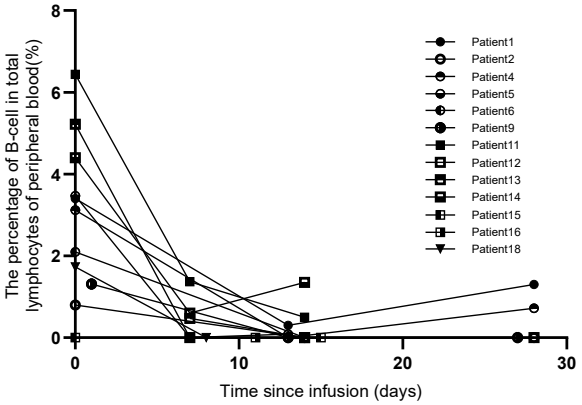
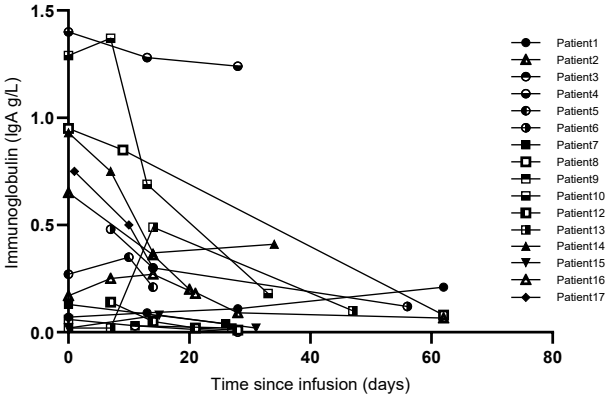
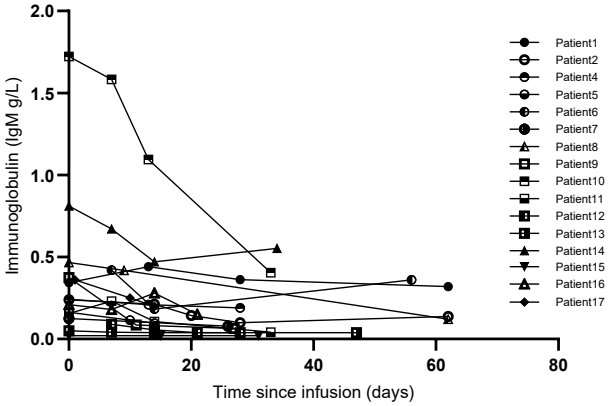

The percentage of B-cell in total lymphocytes of peripheral blood(%)
Time since infusion (days)
0
2
4
6
8
0
10
20
30
Patient1
Patient2
Patient4
Patient5
Patient6
Patient9
Patient11
Patient12
Patient13
Patient14
Patient15
Patient16
Patient18

Figure S4

A



B



C