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Key predictors of long-term outcomes in BCMA-targeted CAR-T therapy for relapsed/refractory multiple myeloma

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Abstract

Background B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy exhibits high response rates in patients with relapsed/refractory multiple myeloma (r/r MM). However, the specific factors that influence the response duration remain poorly understood.

Methods This single-centre, retrospective observational study included 56 patients with r/r MM who received BCMA CAR-T therapy (equecabtagene autoleucel) at Tongji Hospital, China. We analysed response rates and long-term clinical outcomes and identified key factors contributing to the long-term efficacy of BCMA CAR-T therapy.

Results At a median follow-up of 39.6 months, the overall response rate (ORR) was 96.4%. Among the patients, 96.4% (54 of 56) achieved minimal residual disease (MRD) negativity, whereas 80.4% (45 of 56) achieved complete response (CR) or stringent complete response (sCR). Poorer outcomes were observed in patients with triple exposure, high cytogenetic risk, or failure to achieve CR. Better outcomes were associated with a CAR-T cell persistence of at least six months and sustained MRD negativity. Prolonged MRD negativity was strongly correlated with longer progression-free survival (PFS), with median PFS durations of 58 months, 64 months, and not reached (NR) for patients who maintained MRD negativity for 12, 24, and 36 months, respectively. Patients who remained MRD-negative and progression-free exhibited higher CAR-T cell expansion peaks. Additionally, CAR-T cell persistence was positively correlated with the duration of MRD negativity duration, PFS, and overall survival (OS).

Conclusions BCMA CAR-T therapy provides durable responses in a subset of patients with r/r MM. Early intervention may improve patient prognosis by promoting sustained MRD negativity, thus improving overall treatment outcomes.

Trial registration Trial registration Chinese Clinical Trial Registry, ChiCTR2000033946 (https://www.chictr.org.cn/showproj.html?proj=53503), Registered June 18, 2020. Trial registration Chinese Clinical Trial Registry, ChiCTR1800018137 (https://www.chictr.org.cn/showproj.html?proj=30653), Registered August 31, 2018.

Keywords R/R multiple myeloma, BCMA CAR-T, MRD, CAR-T cell

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Background

B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell (CAR-T) therapy represents a major breakthrough in the treatment of relapsed/refractory multiple myeloma (r/r MM), achieving high overall response rates (ORRs) and durable remission. This advancement has provided critical treatment options for patients with previously limited alternatives. Engineered CAR-T cells recognize BCMA-expressing tumor cells in an MHC-independent manner, triggering cytotoxic activity through immune synapse formation and cytokine release. This targeted approach enables the selective elimination of malignant plasma cells [1]. Over the past decade, four BCMA-directed CAR-T therapies have been approved globally for multiple myeloma: idecabtagene vicleucel (Ide-cel) and ciltacabtagene autoleucel (Ciltacel) by the U.S. Food and Drug Administration (FDA), and equecabtagene autoleucel (Eque-cel) and zevorcabtagene autoleucel (Zevo-cel) by China's National Medical Products Administration (NMPA) [2–5]. These findings highlight the significant clinical impact of BCMA-targeted therapies.

Despite targeting the same antigen, the clinical efficacy of these therapies varies considerably, with significant differences in response rates and remission durations observed across clinical trials and real-world applications. For instance, the reported ORRs for Ide-cel and Cilta-cel are 72% and 97.9%, with CR of 39.0% and 82.5%, respectively, while more recent trials of Eque-cel and Zevo-cel show ORRs of 98.9% and 92.2%, with CR of 82.4% and 71.6%, respectively [5–8]. Therefore, achieving and maintaining durable responses, as well as extending overall survival (OS), remain substantial challenges. A considerable proportion of patients who initially respond eventually experience disease progression, underscoring the need for further investigation into the factors influencing long-term outcomes. Previous studies have identified high-risk disease characteristics, such as adverse cytogenetic abnormalities and the presence of extramedullary disease (EMD), as predictors of poorer prognosis. Additionally, early achievement of minimal residual disease (MRD) negativity has been associated with improved outcomes in BCMA CAR-T therapy [9–11].

While these studies have contributed valuable insights, most focus on short-term outcomes, particularly early progression [12, 13] Variability in patient demographics, CAR-T cell constructs, and treatment protocols complicates the generalization of these findings. Moreover, MRD negativity–which reflects deep remission and tumour clearance–and the persistence of CAR-T cells, indicating ongoing immune surveillance, are dynamic factors that significantly affect long-term outcomes [14, 15]. However, the interactions between MRD dynamics and CAR-T cell persistence in BCMA CAR-T therapy have not been sufficiently explored.

To address these gaps, the present study focused on a cohort of 56 patients with r/r MM treated with equecabtagene autoleucel. We conducted a comprehensive analysis of multiple risk factors influencing long-term outcomes, with a particular focus on the dynamics of MRD and CAR-T cell persistence. Our findings aim to provide novel insights that could enhance clinical management strategies for r/r MM patients receiving CAR-T therapy, potentially leading to more durable and sustained treatment responses.

Methods

Study population

A total of 65 patients with multiple myeloma (MM) who received anti-BCMA CAR-T-cell therapy at our clinical center between March 2017 and December 2023 were evaluated. All patients were registered in the Chinese Clinical Trial Registry (ChiCTR2000033946 and ChiCTR1800018137). Of these, 58 patients successfully received BCMA-targeted CAR-T cell infusion and underwent follow-up assessment. Two patients were excluded due to early mortality, defined as death occurring within one month post-infusion. Consequently, a total of 56 patients met the inclusion criteria and were incorporated into the final analysis (Fig. 1).

Outcome assessments

Efficacy, including ORR, OS, and progression-free survival (PFS), was evaluated on the basis of the International Myasthenia Working Group (IMWG) consensus criteria [16]. The ORR was defined as the percentage of patients who achieved a PR or better. OS was measured from the date of CAR-T cell infusion to the date of death or the study cut-off, while PFS was defined as the time from equecabtagene autoleucel infusion to either disease progression or death from any cause. For patients with EMD, complete response (CR) was assessed through bone marrow aspirate, biopsy, serum and urine M protein analysis, and imaging [17]. MRD was evaluated during bone marrow aspiration, using standardized Euroflow cytometry with a sensitivity threshold of 10^-5 nucleated cells. Sustained MRD negativity was defined as the maintenance time of MRD negativity in bone marrow. Disease stage was determined using the revised Revised International Staging System (R-ISS), incorporating baseline ISS stage, presence of cytogenetic abnormalities, and serum lactate dehydrogenase levels. Due to an insufficient bone marrow sample from one patient, fluorescence in situ hybridization (FISH) analysis could not be conducted. High-risk cytogenetic features were defined by the presence of at least one of the following: del(17), t(4;14), or t(14;16), detected via FISH. Triple-exposure disease was

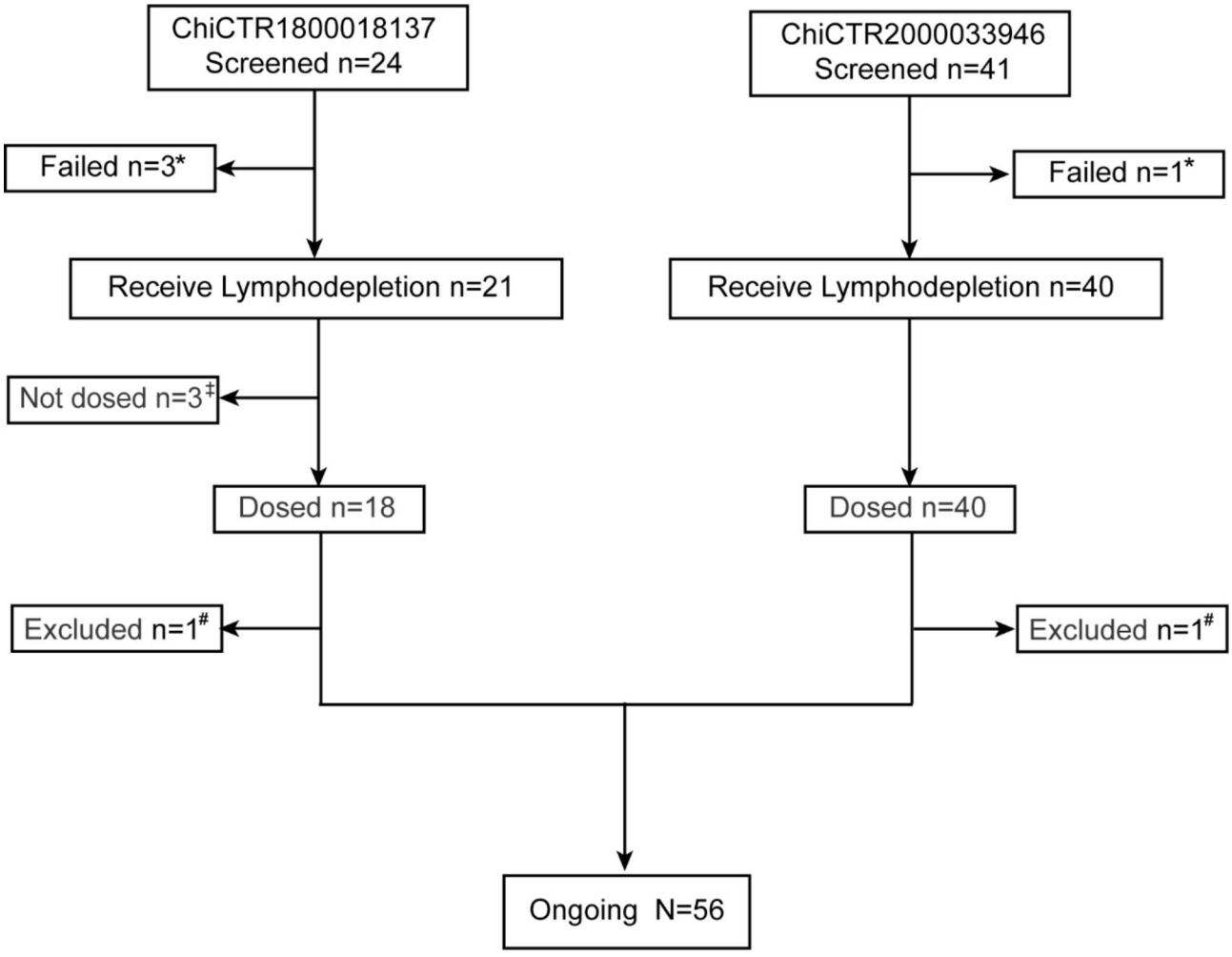

Fig. 1 Study Flowchart. *One patient was excluded from the ChiCTR2000033946 trial because he did not meet the inclusion criteria, and three patients were excluded from the ChiCTR1800018137 trial because they did not meet the inclusion criteria or experienced rapid disease progression. ‡Three additional patients who received lymphodepletion were not dosed because of heart failure, severe liver function impairment, or severe infection. #One patient from both the ChiCTR1800018137 and ChiCTR2000033946 trials was excluded because of severe CRS and brain death

characterized by refractoriness to an immunomodulatory drug, a proteasome inhibitor, and a monoclonal antibody, while penta-exposure disease was refractory to two immunomodulatory agents, two proteasome inhibitors, and a monoclonal antibody. The presence of ADA against equecabtagene autoleucel was assessed using an electrochemiluminescence bridging assay on the MSD-ECL platform (Meso Scale Discovery, Gaithersburg, MD) [18, 19], and CAR transgene copies were quantified using digital droplet polymerase chain reaction (ddPCR) [20]. Not reached (NR) defined that the median survival time could not be estimated because the survival curve did not decline below 50%.

Study approval

The study protocols were reviewed and approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All trials were conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Statistical analyses

Categorical variables were analyzed using the χ^2 test or Fisher's exact test, while continuous variables were compared using Student's t-test. PFS and OS, along with their 95% confidence intervals (CIs), were estimated using the Kaplan–Meier method. All statistical analyses were performed using SPSS version 22 (SPSS, RRID: SCR_002865), and GraphPad Prism 9 (GraphPad Prism, RRID: SCR_002798). A two-tailed *P*-value of ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

Between September 7, 2018, and May 29, 2023, 65 patients were enrolled in the clinical trial, of which 56 patients with r/r MM were included in this analysis (Fig. 1). The median age was 56 years (interquartile range [IQR], 51–61), and 50.0% of the cohort was male. All patients had previously been treated with proteasome inhibitors (PIs) and/or immunomodulatory drugs (IMiDs), and 17.8% had also received monoclonal antibody therapy. Additionally, 28.5% of patients had undergone autologous haematopoietic stem cell transplantation (ASCT). 94.6% of patients had an ECOG performance status score of 1 at enrollment. The median number of prior therapy lines was five (IQR, 4–6). The most prevalent immunoglobulin subtype was IgG (50%), followed by IgA (14.3%) and light chain (30.3%). Regarding disease stage, 7.4% of patients were classified as International Staging System (ISS) Stage III, and 82.1% were classified as Durie-Salmon System Stage III. At baseline, 17.9% of patients presented with EMD and/or plasma cell leukaemia. The median bone marrow plasma cell percentage at enrolment was 60% (IQR, 16.3–80). Cytogenetic abnormalities (CAs) were assessed in 55 patients, with 38.2% exhibiting high-risk CAs, including del(17p), t(4;14), and t(14;16). 32.1% patients received bridging therapy. All patients received lymphodepletion with fludarabine (25 mg/m^2/day) and cyclophosphamide (20 mg/kg/day) for three days prior to infusion. 85.7% patients received a dose of 1×10^6 CAR-T cells/kg, 10.7% patients received a dose of 3×10^6 CAR-T cells/kg, and 3.6% patients received a dose of 6×10^6 CAR-T cells/kg. Additional details are provided in Table S1.

Treatment outcomes

As of June 1, 2024, the median follow-up after CAR-T cell infusion was 39.6 months (range, 1.0–69.3 months). Of the 56 patients, 23 remained on therapy. The primary reason for treatment discontinuation was disease progression, which was noted in 29 patients (51.8%). The median duration of response (DOR) was 30.8 months, PFS was 30.1 months, and overall survival (OS) was NR (Fig. 2A-C). Multivariate Cox regression analysis identified achieving CR as an independent and statistically significant predictor of all major survival outcomes, including DOR, PFS, and OS (Table S2-S4). The 2-year

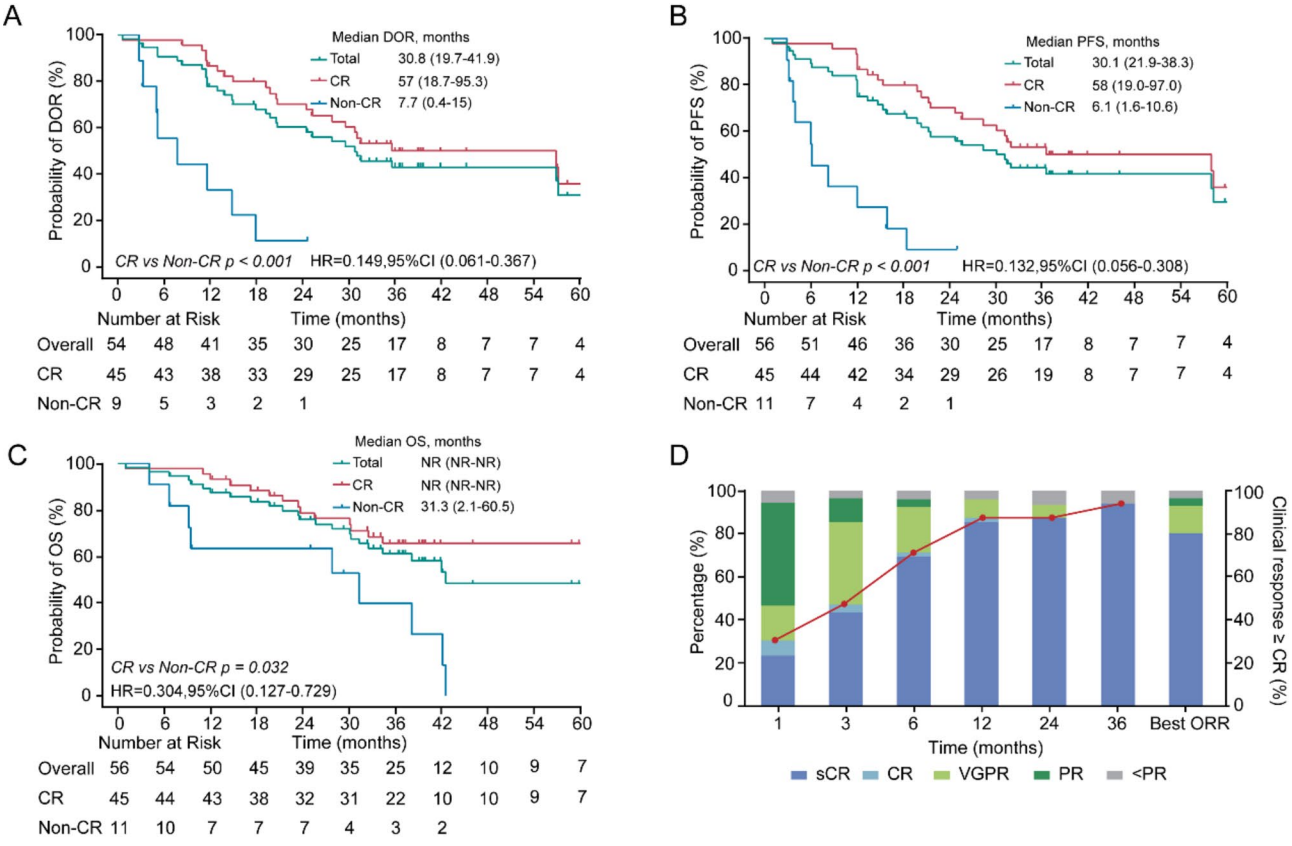

Fig. 2 Survival Outcomes in RRMM Patients Treated with BCMA CAR-T Therapy. (**A**, **B**, **C**) Kaplan–Meier survival curves illustrating the DOR, PFS, and OS for all 56 patients. (**D**) Accumulated best response rates after CAR-T-cell therapy. The red line indicates the progressive increase in the rates of CR or sCR over time. CR, complete response; DOR, duration of response; PFS, progression-free survival; PR, partial response; OS, overall survival; sCR, stringent complete response; VGPR, very good partial response

DOR, PFS, and OS rates for the 45 patients who achieved a CR or stringent complete response (sCR) were significantly higher at 70.0%, 70.0%, and 78.9%, respectively, than those of patients who did not achieve CR ($p < 0.05$, Fig. 2A-C). Among the patients assessed for efficacy, 96.4% (54 of 56) achieved a partial response (PR) or better. Ultimately, 80.4% (45 of 56) of the patients achieved CR or sCR, with the response rate increasing over time (Fig. 2D). In addition, potential contributing factors in patients who failed to achieve CR were analyzed, as summarized in Table S5. To further assess the impact of early response on long-term outcomes, we evaluated the relationship between the time to response and remission persistence. Patients who achieved CR or better by the third month had longer PFS than those who did not achieve CR ($p = 0.017$). However, no significant difference was observed between patients who achieved CR or better and those who did not at the first month (Figure S1).

Predictors of PFS and OS

Univariate Cox regression analysis identified several key prognostic factors for PFS and OS in patients receiving BCMA CAR-T therapy. Significant predictors included triple exposure, high-risk cytogenetic abnormalities, MRD negativity, and CAR-T cell persistence (Fig. 3A-B). Patients with triple exposure demonstrated significantly poorer outcomes, with a hazard ratios (HRs) of 2.752 (95% CI: 1.145–6.487, $p = 0.023$) for PFS and 4.345 (95% CI: 1.636–11.543, $p = 0.003$) for OS. Similarly, the presence of high-risk cytogenetic features was associated with inferior PFS (HR = 2.063, 95% CI: 1.027–4.415, $p = 0.042$) and OS (HR = 2.687, 95% CI: 1.130–6.388, $p = 0.025$). Conversely, patients with CAR-T cell persistence for at least six months had significantly improved PFS (HR = 0.247, 95% CI: 0.113–0.540, $p < 0.001$) and OS (HR = 0.295, 95% CI: 0.121–0.718, $p = 0.007$). Sustained MRD negativity was also strongly correlated with prolonged PFS (HR = 0.910, 95% CI: 0.875–0.947, $p < 0.001$) and OS (HR = 0.914, 95% CI: 0.878–0.952, $p < 0.001$).

Patients with triple exposure had a median PFS of 12.0 months, compared with 32.0 months for those without, whereas the median OS for these groups was 12.0 months versus NR (Figure S2 A–B). Similarly, patients with high-risk cytogenetic features had a median PFS of 12.0 months, compared with 32.0 months for those without, and a median OS of 19.7 months versus 36.5 months (Figure S2 C–D). Patients with CAR-T cell persistence less than six months had a median PFS of 11.9 months, whereas those with persistence for six months or more had a median PFS of 36.5 months, with corresponding OS values of 30.1 months versus NR (Figure S3 E–F).

Other factors, such as age, the presence of EMD, prior BCMA CAR-T therapy, high tumour burden at enrolment (> = 50%), soluble BCMA (sBCMA) levels, and the

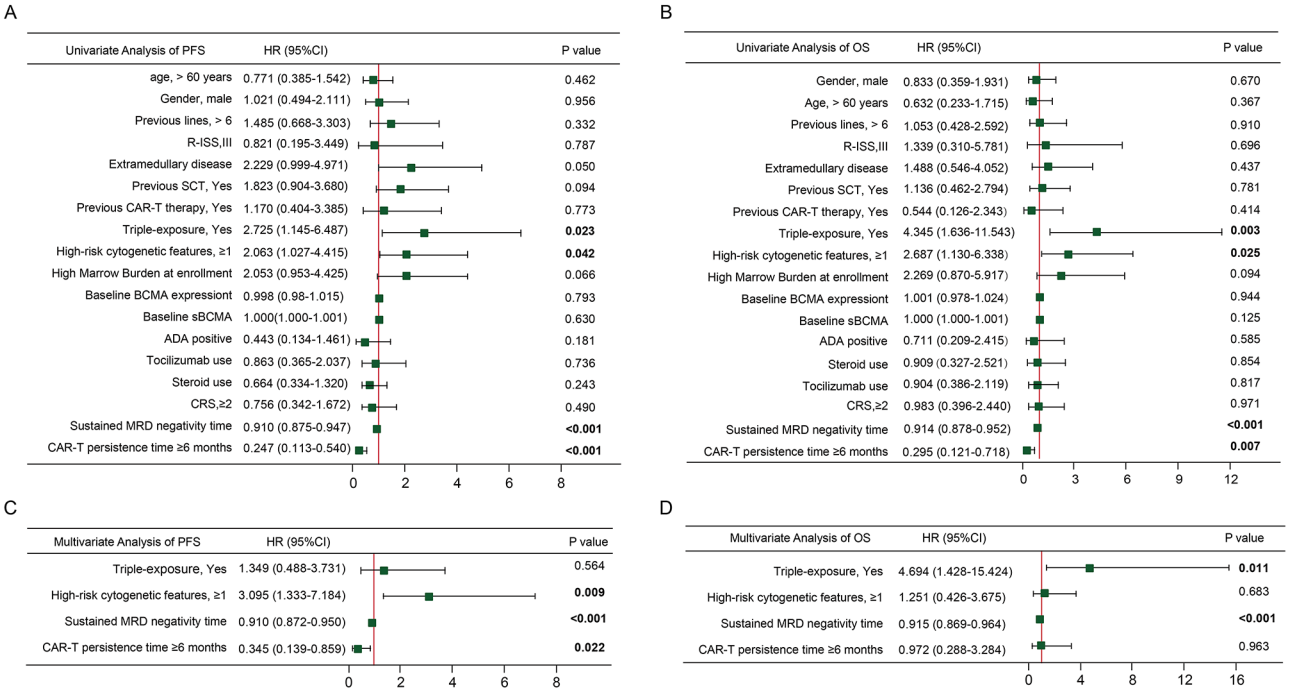

Fig. 3 Univariate and multivariate survival analysis of PFS and OS. (**A**-**D**) Forest plots showing hazard ratios for PFS and OS estimated by univariate and multivariate Cox proportional hazards regression outcome analyses. Forest plots showing the association between risk factors and survival in our center. ADA, Anti-drug antibodies; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; EMMR-ISS, Revised International Staging System; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; sBCMA, Plasma levels of soluble BCMA

use of tocilizumab or steroids during CAR-T therapy, did not significantly impact PFS or OS (Fig. 3). Multivariate Cox regression confirmed that high-risk cytogenetic features, sustained MRD negativity, and CAR-T cell persistence of at least six months were independent predictors of PFS. For OS, sustained MRD negativity and triple exposure remained significant predictors (Fig. 3C-D).

In addition, a systematic analysis of absolute lymphocyte count (ALC) at baseline (ALC baseline) and the peak value within 15 days post-infusion (ALC max) was conducted across different clinical response subgroups. As shown in Figure S3 A-B, no statistically significant differences were observed in either baseline ALC ($p = 0.160$) or ALC max ($p = 0.422$) between the CR and non-CR groups. Furthermore, we evaluated the association between ALC baseline and ALC max with OS and PFS. The analysis demonstrated no statistically significant differences in these parameters across OS and PFS subgroups (Figure S3C-F).

Besides, the ORR and CR rate were compared between patients with and without triple- or penta-exposure disease. The results showed no statistically significant differences in either ORR or CR rate between these subgroups (Figure S4).

Dynamics of MRD

Among the 56 patients included in the study, 96.4% (54 patients) achieved MRD negativity. The median time to the first MRD-negative status was 0.5 months. Following a median follow-up of 30.1 months from the time of MRD negativity, 21 patients (37.5%) remained MRD-negative and alive, 4 patients (7.2%) died with MRD negativity, 29 patients (51.7%) experienced a loss of MRD negativity, and 2 patients (3.6%) maintained persistent MRD-positive status, and Fig. 4 provides an overview of treatment duration and MRD dynamics among the patient cohort.

Further analysis of the relationship between the duration of MRD negativity and remission persistence indicated that patients who remained MRD-positive post-CAR-T infusion were more likely to experience disease progression than those who either sustained or lost MRD negativity ($p < 0.001$, Fig. 5A). Patients with MRD negativity lasting ≥ 12 months exhibited significantly longer PFS than those whose MRD negativity lasted < 12 months (median PFS: 58 months vs. 8.2 months, $p < 0.001$, Fig. 5B). The PFS curves decreased with increasing MRD negativity duration ($p < 0.001$, Fig. 5C-D), with the median PFS reaching 64 months for patients who maintained MRD negativity for ≥ 24 months and NR for those with ≥ 36 months. Among the 11 patients who maintained MRD negativity for three or more years, all had achieved sCR, although three eventually lost their MRD-negative status.

Predictors of MRD

Our analysis revealed that a greater bone marrow burden at enrolment (> = 50%) was significantly associated with shorter MRD negativity duration compared to those with a lower bone marrow burden (2-year cumulative incidence [CI]: 48.6% vs. 72.2%; $p = 0.032$, Fig. 5E). Additionally, patients with triple-exposure disease exhibited shorter MRD negativity duration than did those without triple exposure (2-year CI: 24% vs. 65.5%; $p = 0.041$, Fig. 5F).

Furthermore, patients who achieved CR by the third month had significantly longer durations of MRD negativity than did non-CR patients (2-year CI: 46% vs. 76.2%; $p = 0.035$, Fig. 5G). The persistence of CAR-T cells for more than six months was also a significant predictor of a longer duration of MRD negativity duration (2-year CI: 25.6% vs. 66.9%; $p < 0.001$, Fig. 5H). According to Cox regression analysis, factors such as sex, age, R-ISS stage, high-risk cytogenetic abnormalities, prior CAR-T cell therapy, and the presence of EMD did not significantly affect the duration of MRD negativity (Table S6). Multivariate Cox regression further confirmed that triple exposure and CAR-T cell persistence for more than six months were independent predictors of MRD negativity duration.

CAR-T cell pharmacokinetics and pharmacodynamics

The median time to peak CAR-T cell concentration (Tmax) was 12 days (range: 7–22 days), followed by a significant decline in CAR-T cell proliferation after day 28. The duration of CAR transgene persistence varied among patients, with a median of 9.0 months (range: 0–66.0 months). A strong association was observed between CAR-T cell expansion and MRD status. Patients with sustained MRD negativity exhibited greater peak CAR-T cell expansion (Cmax) than did those who remained MRD-positive ($p = 0.009$, Fig. 6A). Additionally, MRD-positive patients presented lower area under the curve (AUC) values for CAR-T cell proliferation both at 28 days (AUC0–28d) and at the last measured day (AUC0–last) in comparison to MRD-negative patients ($p < 0.001$, Fig. 6B-C).

CAR-T cell persistence was detected at ≥ 6 months in 43 patients, ≥ 12 months in 22 patients, ≥ 24 months in 14 patients, and ≥ 36 months in 4 patients. Correlations between CAR-T cell persistence and clinical outcomes, such as MRD negativity duration ($p < 0.001$, $r = 0.708$; Fig. 6D), PFS ($p < 0.001$, $r = 0.625$; Fig. 6E), and OS ($p < 0.001$, $r = 0.580$; Fig. 6F), were observed.

Besides, factors influencing the peak CAR-T cell copy number expansion were analyzed. patients achieving CR/sCR had significantly higher Cmax compared to those with PR or less ($p = 0.036$), though no significant difference was seen between CR/sCR and very good partial

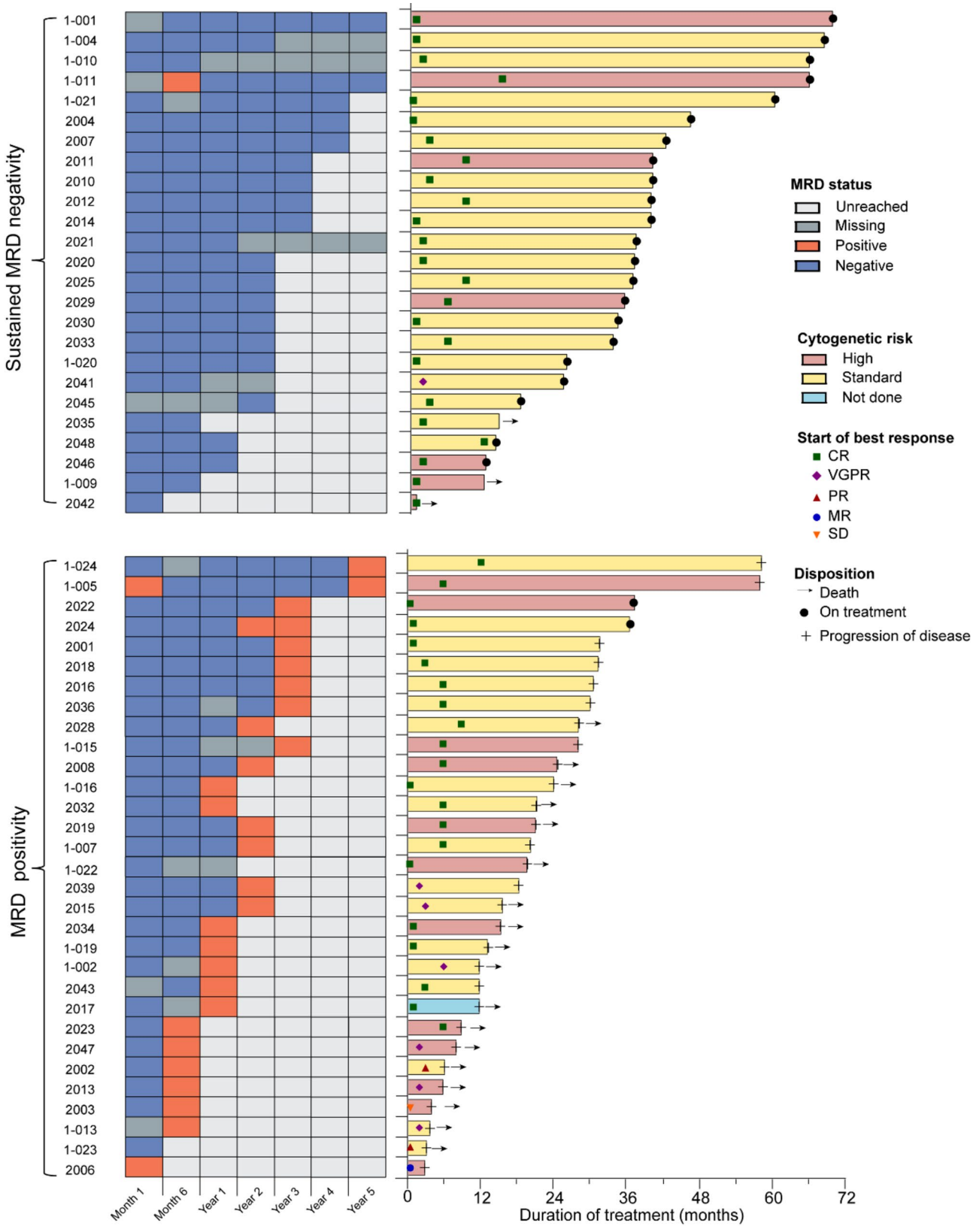

Fig. 4 Treatment Duration Relative to MRD Dynamics. Each row represents an individual patient categorized by the durability of MRD status. Annotations include cytogenetic data, patient disposition, and best response achieved. In the MRD-positive group, patients with progressive disease did not undergo MRD testing. CR, complete response; MR, minimal response; MRD, minimal residual disease; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response

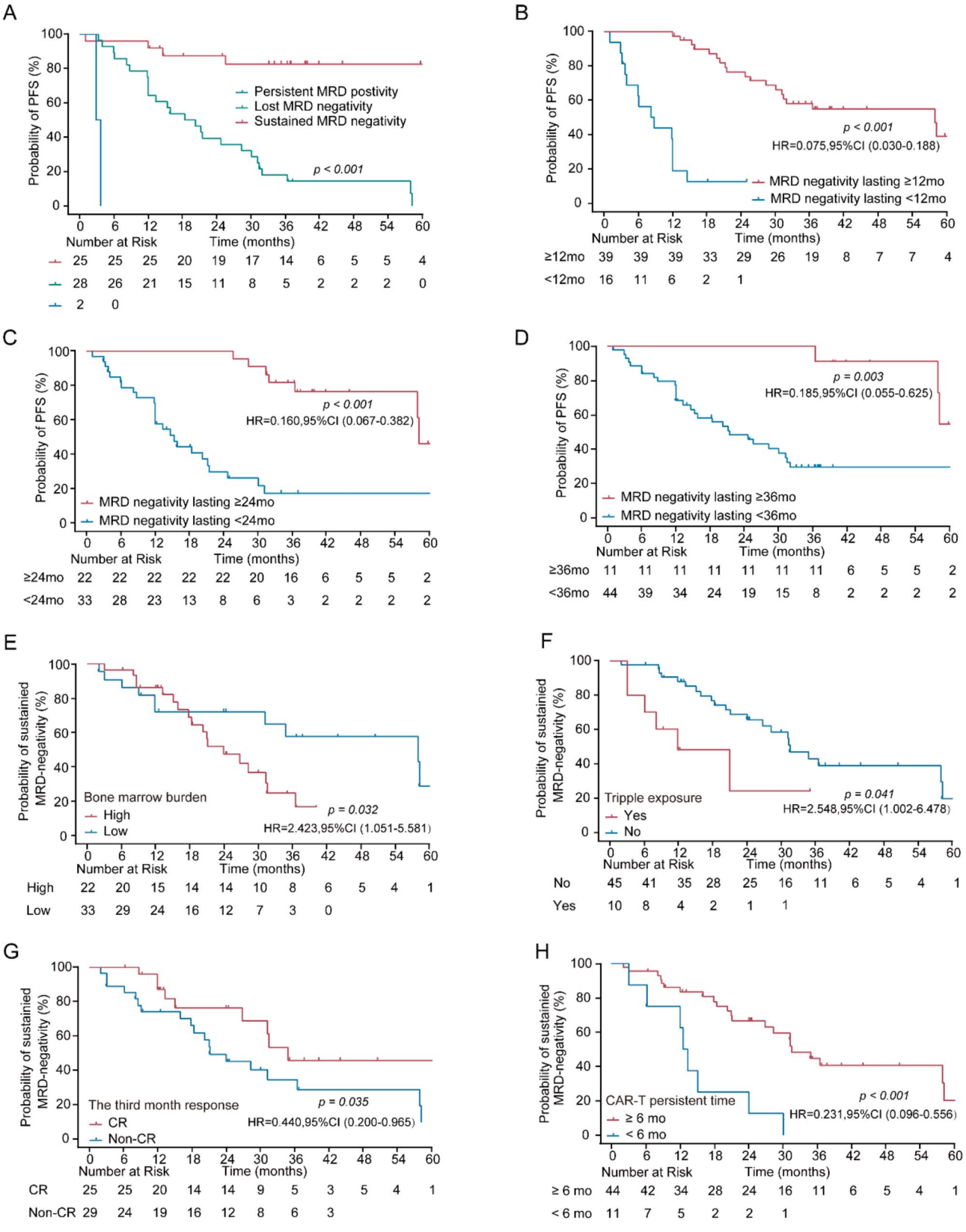

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Fig. 5 Correlations between MRD negativity duration, PFS, and MRD dynamics, and identification of predictors associated with sustained MRD negativity. (**A**) PFS comparison among patients with sustained MRD negativity, persistent MRD positivity, and those who lost MRD-negative status post-BCMA CAR-T therapy. (**B**, **C**, **D**) PFS among MRD-negative patients sustained at 12, 24, and 36 months. (**E**) Probability of sustained MRD negativity stratified by bone marrow burden. (**F**) Probability of sustained MRD negativity stratified by triple exposure. (**G**) Probability of sustained MRD negativity stratified by achieving CR at the third month. (**H**) Probability of sustained MRD negativity stratified by CAR-T persistence time. CAR, chimeric antigen receptor; CR, complete response; Mo, month; MRD, minimal residual disease; PFS, progression-free survival

response (VGPR) ($p = 0.958$) (Fig. 6G-H). No significant differences were observed with respect to extramedullary disease, tumour burden, high-risk cytogenetics, or prior CAR-T therapy (Figure S5).

Safety

A total of 92.9% of patients (52/56) experienced cytokine release syndrome (CRS), with 85.7% presenting with grade 1–2 CRS and 7.1% with grade 3 CRS. Patients were stratified into low-grade (grades 0–1) and high-grade (grades 2–3) CRS groups. We compared Cmax, AUC0-28d, and CAR-T long-term persistence between these groups (Figure S6A-C). No statistically significant differences were identified. However, the AUC0-last day was significantly higher in the high-grade CRS group (Figure S6D). Importantly, there were no differences in response rates (first-month CR or best CR) between the CRS severity groups (Figures S6E-F).

Humoral immunogenicity

Anti-drug antibodies (ADAs) were assessed in all patients prior to infusion and during follow-up visits post-infusion. Nine patients tested positive for ADAs, whereas the remaining patients were negative. No significant differences in the Cmax, AUC0–28d, and AUC0–last were observed between ADA-positive and ADA-negative patients ($p > 0.05$, Figure S7A-C). However, ADA-positive patients exhibited significantly shorter CAR-T cell persistence compared to ADA-negative patients ($p = 0.010$, Figure S7D).

Discussion

BCMA-targeted CAR-T therapy has significantly transformed the treatment landscape for r/r MM, achieving unprecedented remission rates and extending survival for patients who previously had limited therapeutic options [2–5]. Although the efficacy of this novel therapy is well documented, interest in understanding the long-term factors that influence patient outcomes, particularly the duration of MRD negativity and CAR-T cell persistence, is growing. Sustained MRD negativity has long been recognized as a predictor of prolonged PFS in conventional multiple myeloma therapies [21, 22]. Similarly, CAR-T cell persistence has emerged as a critical prognostic factor in CD19-targeted CAR-T therapies [23]. However, its importance in BCMA-targeted CAR-T therapy remains less clear. A comprehensive understanding of these factors is essential for optimizing treatment strategies and improving clinical outcomes. This study examined response rates and long-term clinical outcomes in relation to various disease characteristics and treatment variables, with a focus on the interaction between sustained MRD negativity, CAR-T cell persistence, and patient prognosis.

Our findings reaffirm that depth of response is a crucial determinant of durable remission in multiple myeloma patients. Patients who achieved CR showed a longer median PFS of 58 months, with a median follow-up of 39.6 months, though the median OS had not yet been reached. Achieving a deep response correlated strongly with favorable long-term outcomes. However, early CR within the first month of CAR-T therapy did not predict long-term benefits. In contrast, patients who achieved CR or sCR at three months showed significantly improved PFS compared to those who did not achieve CR. This observation aligns with data from Cilta-cel studies, where early CR was not always indicative of long-term success [24].

While achieving CR is important, MRD negativity provides a deeper measure of remission and is increasingly regarded as a more reliable prognostic indicator [25, 26]. The IMWG recommends sustained MRD negativity for at least one year as the optimal outcome for multiple myeloma patients [16]. Early MRD negativity has been linked to peak CAR-T cell expansion and enhanced tumour clearance [27]. Furthermore, studies indicate that MRD-negative status at six months is strongly associated with superior survival outcomes, reinforcing the role of MRD-negative status as a key predictor of disease progression and overall survival following CAR-T therapy [28].

Our study builds on these findings by demonstrating the critical role of MRD negativity in patients with r/r MM treated with BCMA CAR-T therapy. Among the 56 patients, 54 (96.4%) achieved MRD negativity post-infusion, with 43 (73.2%) maintaining this status for more than 12 months. Patients with residual disease or shorter MRD negativity durations had poorer outcomes compared to those with sustained MRD negativity. Most patients who remained MRD-positive or lost MRD negativity experienced disease progression, underscoring the importance of maintaining MRD negativity in multiple myeloma treatment, particularly in the context of BCMA CAR-T therapy. Factors such as high bone marrow

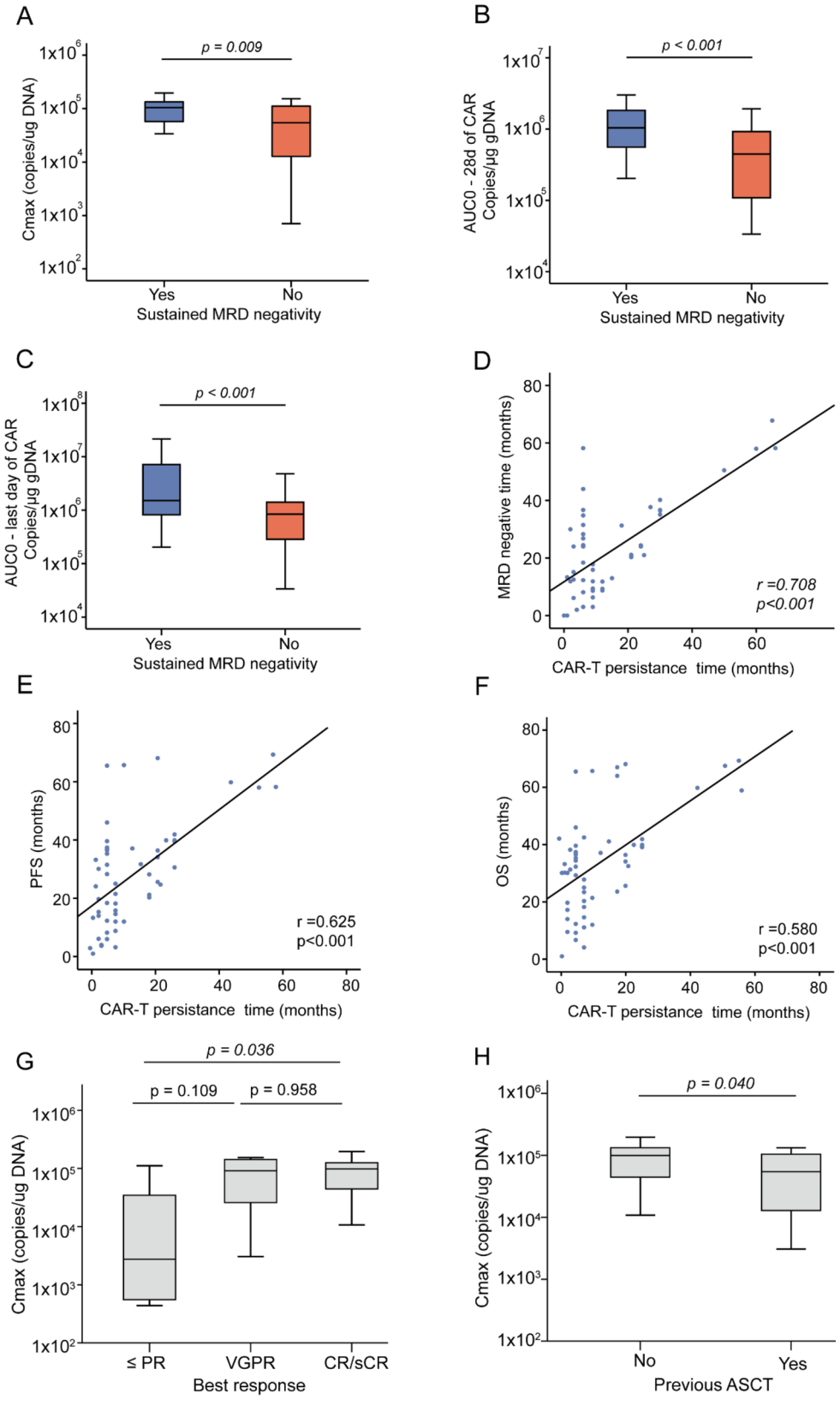

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Fig. 6 Associations between CAR-T cell expansion, sustained MRD negativity, survival outcomes, and influencing clinical factors. (**A**) Peak CAR-T-cell expansion in patients with sustained MRD negativity versus those with MRD positivity. (**B**, **C**) Area under the curve (AUC) for transgene levels from infusion to 28 days (AUC0–28d) and to the last recorded day (AUC 0–last day) in patients with sustained MRD negativity versus MRD positivity. (**D**) Univariate analysis of MRD negativity and CAR-T-cell persistence. (**E**) Univariate analysis of PFS and CAR-T-cell persistence. (**F**) Univariate analysis of OS and CAR-T-cell persistence. (**G**) Peak CAR-T cell expansion across different best response. (**H**) Peak CAR-T cell expansion in patients with or without previous ASCT. Spearman correlation coefficients (r) and corresponding *p* values are provided. ASCT, autologous haematopoietic stem cell transplantation; CAR, chimeric antigen receptor; CR, complete response; Mo, month; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response

burden, triple-exposure disease, CAR-T cell persistence of less than six months, and failure to achieve CR at three months were associated with shorter MRD negativity durations and poorer outcomes. These results emphasize the necessity of dynamic monitoring and maintaining MRD negativity to prolong PFS.

In addition to MRD status, CAR-T cell expansion and persistence are critical determinants of long-term prognosis in patients receiving CAR-T therapy [29]. Our study confirms this finding by showing that equecabtagene autoleucel provides superior CAR-T cell persistence. Among the patients studied, 76.7% maintained CAR-T cell persistence for over six months, and 40% maintained it for more than twelve months. Patients with MRD positivity showed reduced CAR-T cell persistence and expansion compared to those with sustained MRD negativity. Additionally, sustained CAR-T cell persistence was strongly correlated with MRD negativity, PFS, and OS, highlighting its significance in determining long-term therapeutic success. Similar results were observed with Cilta-cel, where CAR-T cell persistence beyond 280 days was associated with better prognosis [30]. These findings are consistent with previous research conducted in B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL) [31, 32].

One factor that may influence CAR-T cell persistence is the presence of ADAs, which can reduce CAR-T cell longevity. In our study, the incidence of ADA was lower than that reported in previous studies, suggesting that fully human CAR-T constructs may have lower immunogenicity [30, 33]. Although it remains unclear whether ADA significantly affects CAR-T cell expansion, the ADA-positive patients in our cohort experienced shorter CAR-T cell persistence.

Studies have explored post-infusion maintenance using lenalidomide or pomalidomide, which have shown promise in enhancing CAR-T expansion and anti-myeloma activity. Additionally, the use of selinexor and bispecific antibodies—particularly as bridging therapy—may synergize with CAR-T efficacy by modulating immune dynamics [34–38]. However, Larger-scale clinical studies are required to validate these findings and establish their clinical applicability.

Recent clinical trials (KarMMa-3, CARTITUDE-4, CARTITUDE-2) have demonstrated favorable efficacy of BCMA CAR-T therapy in patients with early relapse or lenalidomide-refractory disease [6, 39, 40]. Notably, dual-targeting CAR-T therapy has shown excellent outcomes in newly diagnosed high-risk MM patients [41]. These findings suggest that early application may improve T-cell fitness, reduce tumor burden, and improve safety and efficacy profiles. Further studies are warranted to confirm long-term benefits and optimize treatment sequencing.

This study is a single-center retrospective analysis, which may be susceptible to selection bias. To address this limitation and improve the external validity of the findings, it is recommended that future research incorporate multi-center data. Larger, multi-center clinical trials are essential to identify patient subgroups that are most likely to benefit from combination therapies, particularly those at high risk for MRD conversion. Furthermore, optimizing the timing and selection of therapeutic agents to extend the duration of MRD negativity following BCMA CAR-T therapy should be a primary focus of future investigations.

Abbreviations

ADAs	Anti drug antibodies
ALC	Absolute lymphocyte count
ASCT	Autologous haematopoietic stem cell transplantation
B-ALL	B-cell acute lymphoblastic leukemia
BCMA	B-cell maturation antigen
CAR-T	Chimeric antigen receptor T-cell
CAs	Cytogenetic abnormalities
CI	Confidence interval
CR	Complete response
CRS	Cytokine release syndrome
ddPCR	Digital droplet polymerase chain reaction
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
EMD	Extramedullary disease
FDA	Food and drug administration
HRs	Hazard ratios
IMiDs	Immunomodulatory drugs
IMWG	International myasthenia working group
ISS	International staging system
IQR	Interquartile range
MM	Multiple myeloma
MRD	Minimal residual disease
NMPA	National medical products administration
NR	Not reached
ORRs	Overall response rates
OS	Overall survival
PFS	Progression-free survival
PIs	Proteasome inhibitors
PR	Partial response
r/r	MM Relapsed/refractory multiple myeloma
sBCMA	Soluble BCMA
sCR	Stringent complete response
SCT	Stem cell transplantation
VGPR	Very good partial response

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Chunrui Li conceptualized and supervised the clinical study. Ning An and Juan Li conducted data analysis and contributed to the writing and revision of the manuscript. Ning An, Pan Luo, Di Wang, Peiling Zhang, Chang Shu, Qiuxia Yu, Xinyu Wen, were responsible for clinical data collection. Ning An, Songbai Cai, Xinran Wang, Wei Mu and Jianlin Hu performed the statistical analyses. Di Wang, Peiling Zhang, and Chunrui Li were involved in patient enrollment and care. All authors read and approved the manuscript in its final form, agreed with its submission, and take full responsibility for its content, including the accuracy of the data.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Informed consent were signed by all study participants.

Consent for publication

Not applicable.

Competing interests

Songbai Cai is employee of Nanjing IASO Medical Technology Co., Ltd. and holds interests in the company. All other authors declared no competing interests.

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