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SHORT REPORT OPEN ACCESS

Early Free Light-Chain Suppression as a Prognostic Marker in Relapsed and Refractory Myeloma Patients Treated With BCMA-Directed CAR-T Cells

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ABSTRACT

Background: Relapsed/refractory multiple myeloma (RRMM) remains difficult to treat despite advances in therapy. B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapies, such as idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have improved outcomes, yet many patients relapse within a year. Current International Myeloma Working Group (IMWG) criteria for deep response require prolonged observation. Early, practical biomarkers could enable timelier risk stratification and intervention.

Objective: To evaluate whether serum free light-chain (FLC) suppression at Day +28 after BCMA-directed CAR-T infusion predicts progression-free survival (PFS) and overall survival (OS) in RRMM.

Methods: We conducted a retrospective multicenter analysis of 80 consecutive RRMM patients treated with in-label ide-cel or cilta-cel between January 2022 and July 2024 at four tertiary centers. Patients with oligo-/non-secretory myeloma were excluded. FLC suppression—defined as undetectable κ or λ light chains using the Freelite assay—was assessed at Day +28 (window: Days 27–31) and at 3 months post-infusion. Survival analyses used a landmark approach from Day +28. Multivariate Cox regression adjusted for prior BCMA/T-cell-directed therapy, high-risk cytogenetics (HRC), extramedullary disease (EMD), and pre-CAR-T response status.

Results: At Day +28, 51 patients (63.8%) achieved FLC suppression. Median follow-up was 11.8 months. FLC suppression correlated with markedly longer median PFS (23.4 vs. 4.1 months, $p < 0.001$) and improved OS (12-month OS: 88.0% vs. 18.1%, $p = 0.013$). Benefits were observed across CAR-T products, but suppression rates were higher with cilta-cel (81.6%) than ide-cel (45.2%). HRC remained an adverse factor even in suppressed patients, while EMD showed a less consistent effect. In multivariate analysis, absence of FLC suppression independently predicted inferior PFS.

Conclusions: FLC suppression at Day +28 post-CAR-T is an early, inexpensive biomarker associated with superior PFS and OS in RRMM. It often precedes IMWG-defined complete response and could support risk-adapted post-CAR-T management. Prospective validation is warranted to integrate FLC suppression into early response assessment strategies.
Trial Registration: The authors have confirmed clinical trial registration is not needed for this submission

Multiple myeloma (MM) involves clonal plasma cell proliferation, causing significant morbidity and mortality. Despite current advances relapsed/refractory myeloma (RRMM) remains challenging to treat. The introduction of chimeric antigen receptor T-cell (CAR-T) therapy targeting the B-cell maturation antigen (BCMA) has opened new possibilities for patients with RRMM. Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) are currently approved options with others in development [1, 2]. However, a substantial subset of patients relapses within a year of treatment [3]. While established response criteria, such as those from the International Myeloma Working Group (IMWG), provide comprehensive assessments, they often require prolonged observation periods. The need for early, practical biomarkers to guide real-time clinical decisions in the rapidly evolving landscape of CAR-T therapy is paramount, particularly given the potential for delayed traditional response assessments.

Our study examines whether free light-chain (FLC) response at Day +28 post-CAR-T associates with progression-free (PFS) and overall survival (OS) in RRMM. We assessed FLC suppression, defined as undetectable serum light chains (either κ or λ), using The Binding Site Freelite assay across all participating centers. Suppression status and IMWG response criteria were determined based on a measurement at Day +28 post-CAR-T infusion (window: Days 27–31) and repeated at 3 months after infusion. This may serve as a cost-effective biomarker for identifying high-risk patients needing closer monitoring or additional interventions. We retrospectively analyzed 80 consecutive RRMM patients receiving in-label CAR-T (ide-cel or cilta-cel) at four tertiary centers between January 1, 2022 and July 1, 2024. Data lock was October 1, 2024. Patients had at least 3 months of follow-up, excluding those with oligo- or non-secretory myeloma. Extramedullary disease (EMD) included extraosseous soft-tissue involvement only. Baseline demographics, disease characteristics, and side effects are in Table 1.

With a median follow-up of 11.8 months (range: 5–34), patients had a median of 6.5 prior treatments before CAR-T. Six patients received talquetamab, one teclistamab, and eight belantamab-mafodotin pre-CAR-T. Bridging therapies are listed in the Table S1. The overall response rate (ORR) was 88.8%. At Day +28 after CAR-T administration, 51 patients (63.8%) demonstrated FLC suppression, while 29 (36.3%) did not. At Day +28, among patients achieving a CR, only one did so without prior FLC suppression. Conversely, four patients showed FLC suppression without having yet reached a CR (see Figure S2). Two of these patients went on to attain a CR by 3 months (bringing the total to 65%) while one patient had died. Notably, only one patient achieved both FLC suppression and CR after Day +28, specifically on Day +43.

The cohort's median PFS was 11.5 months. Patients with a Day +28 FLC suppression had a median PFS of 23.4 months and a 12-month OS rate of 88.0%, while those without Day +28 FLC suppression had a median PFS of 4.1 months and OS of 18.1 months. Landmark Kaplan–Meier curves (Figure 1) show significantly worse outcomes for patients without FLC suppression (log-rank $p < 0.001$ for PFS, $p = 0.013$ for OS; the 3-month analysis is shown in Figure S3), regardless of the CAR-T product used. FLC suppression was observed in 45.2% of ide-cel and 81.6% of cilta-cel patients.

Patients with HRC had significantly reduced PFS ($p < 0.0001$, Figure 1C) and OS ($p = 0.025$). When stratified by FLC suppression at Day +28 (Figure 1F), the worst outcomes were observed in patients with HRC and no FLC suppression. Notably, even among patients who achieved FLC suppression, those with HRC had inferior outcomes compared to standard-risk patients. This suggests that FLC suppression improves prognosis across risk groups but does not fully overcome the negative impact of high-risk cytogenetics when measured after 1 month. Presence of EMD showed a nonsignificant reduced PFS and OS for the entire cohort but also demonstrated the same significant effect of negative FLC compared to positive FLC (Figure 1E) ($p = < 0.0001$). Increased CRP levels at Infusion of lymphodepleting chemotherapy was not associated with inferior PFS ($p = 0.45$). Our findings were confirmed in a multivariate Cox regression model adjusting for key clinical confounders. The corresponding forest plot is provided in Figure S1.

Our findings indicate that FLC suppression at Day +28 post-CAR-T may serve as a potential early indicator of outcomes in RRMM. This accessible biomarker supports risk-adapted management and personalized treatment strategies. A significant advantage of FLC suppression is its rapidity compared to the comprehensive, but often slower, IMWG response criteria, which define CR based on negative serum and urine immunofixation, resolution of soft-tissue plasmacytomas, and < 5% plasma cells in bone marrow aspirates [4]. In contrast to these more complex and often invasive evaluations, FLC measurement is simple, minimally burdensome, and feasible in routine clinical practice. Crucially, we observed that FLC suppression at Day +28 often preceded the attainment of an IMWG-defined CR. Despite this initial lag, the overall IMWG-CR rates reported in the KarMMA-3 and CARTITUDE-4 studies are strikingly similar to the FLC negativity rates observed in our cohort by 3 months [2, 4]. This suggests that while FLC suppression offers a faster, more immediate signal of deep response, it ultimately aligns closely with the comprehensive IMWG assessment over a slightly longer timeframe. This makes FLC a valuable early surrogate marker, providing actionable information sooner than a full IMWG evaluation. While MRD-negativity is also achieved quicker than

TABLE 1 | Description of baseline characteristics and outcomes of treated patients stratified by free light-chain suppression at +28 days after CAR-T cells.

Category	FLC not suppressed ($N = 29$)	FLC suppressed ($N = 51$)	Total ($N = 80$)
Age, median (SD)	65.2 (7.99)	65.3 (7.94)	65.3 (7.90)
Ide-cel	22 (75.9%)	20 (37.3%)	42 (52.5%)
Cilta-cel	7 (24.1%)	31 (60.8%)	38 (47.5%)
ISS stage at diagnosis			
Stage I/II	12 (41.4%)	39 (76.5%)	51 (63.8%)
Stage III	17 (58.6%)	12 (23.5%)	29 (36.3%)
High-risk cytogenetics	21 (72.4%)	13 (25.5%)	34 (42.5%)
Extramedullary disease	10 (34.5%)	16 (31.4%)	26 (32.5%)
Previous BCMA/T-cell-directed Therapy	10 (34.5%)	4 (7.8%)	14 (17.5%)
Prior therapies, median	7.00 [2.00, 14.0]	6.00 [2.00, 14.0]	6.50 [2.00, 14.0]
Disease status before CAR-T			
PD	19 (65.5%)	27 (52.9%)	46 (57.5%)
PR	4 (13.8%)	3 (5.9%)	7 (8.8%)
SD	5 (17.2%)	9 (17.6%)	14 (17.5%)
VGPR	1 (3.4%)	11 (21.6%)	12 (15.0%)
CR	0 (0%)	1 (2.0%)	1 (1.3%)
Vein-to-vein time, median	64.0 [36.0, 141]	63.0 [52.0, 151]	63.0 [36.0, 151]
CRS I	15 (51.7%)	27 (52.9%)	42 (52.5%)
CRS II	6 (20.7%)	19 (37.3%)	25 (31.3%)
CRS III	4 (13.8%)	1 (2.0%)	5 (6.3%)
ICANS I	5 (17.2%)	5 (9.8%)	10 (12.5%)
ICANS II	0 (0%)	1 (2.0%)	1 (1.3%)
Tocilizumab use	23 (79.3%)	46 (90.2%)	69 (86.3%)

Abbreviations: CR = complete remission, CRS = cytokine-release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome, PD = progressive disease, PR = partial remission, SD = stable disease, VGPR = very good partial remission.

IMWG-defined CR in peripheral blood and often precedes it [5]. MRD negativity rate surpassed initial CR rate in both trials.

Despite strong responses, most CAR-T patients eventually relapse due to BCMA loss, high-soluble BCMA, an immunosuppressive microenvironment, treatment timing, suboptimal CAR-T function, and manufacturing challenges [6]. Identifying patients at risk for early relapse is challenging and requires close monitoring, while factors driving long-term responses remain unclear. Fischer et al. found CAR-T cell expansion correlates with better outcomes, with responders and nonresponders showing distinct CAR and non-CAR T cell compositions, detectable even at leukapheresis [7].

Recently Freeman et al. showed that high levels of soluble (sBMCA) and high metabolic tumor volume measured by PET-CT were associated with increased relapse rates [8]. Moreover, a longer time to sBCMA recurrence correlated with longer duration of response in the KarMMA-1 trial [9]. But PET-CT remains limited by availability and reimbursement issues in myeloma, while soluble BCMA is a practical tumor burden marker but not yet widely used clinically.

Lack of FLC suppression signals significantly shorter PFS and OS, highlighting the need for early interventions post-CAR-T. Strategies may include bispecific antibodies or cereblon E3 ligase modulators. Approaches to enhance CAR-T efficacy, addressing BCMA loss, T-cell dysfunction, or anti-CAR-T antibodies, have been summarized by Swan et al. [10].

Our real-world cohort included only patients with lenalidomide-refractory disease, of whom 42.5% had HRC and 32.5% had EMD, defined strictly as extraosseous soft-tissue involvement. As expected, patients with HRC had significantly reduced PFS, and this adverse impact persisted even among those who achieved FLC suppression at Day +28. While FLC suppression was associated with improved outcomes across subgroups, it did not fully offset the negative prognostic impact of HRC. In contrast, the prognostic value of EMD appeared less consistent, potentially due to our narrower definition and limited sample size [11]. These findings emphasize that cytogenetic risk remains a dominant

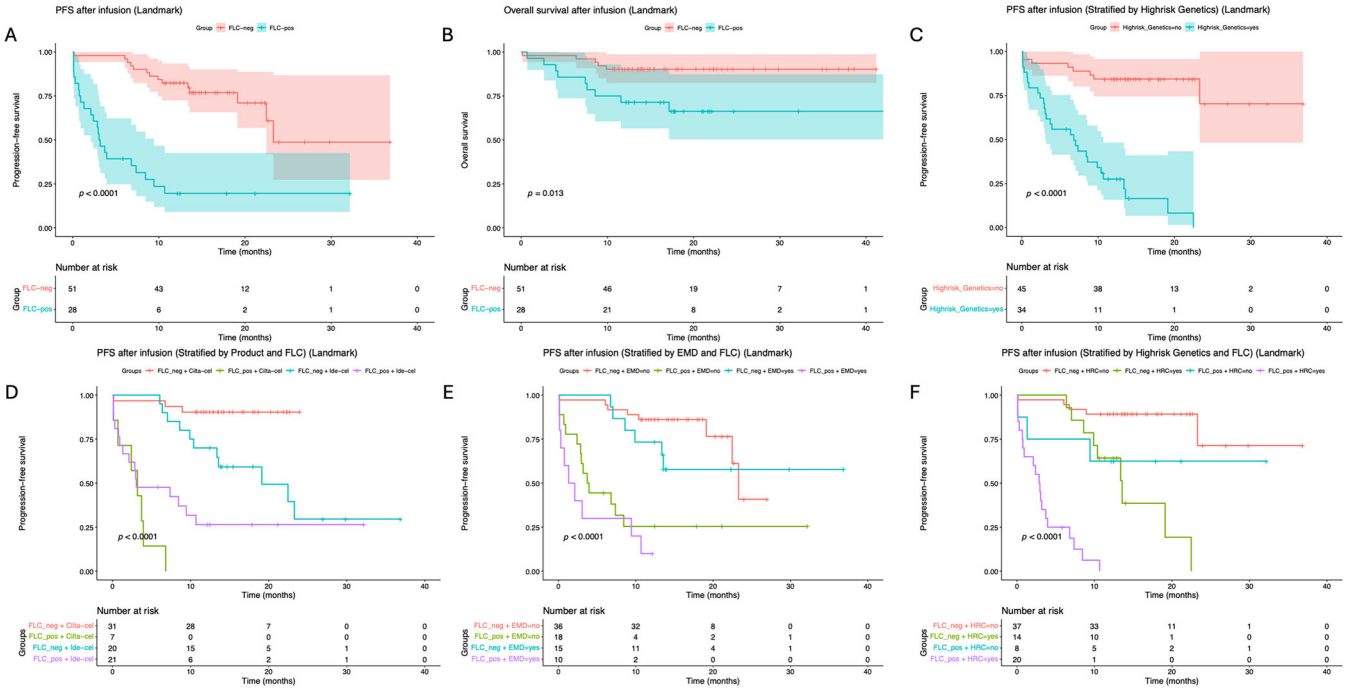

FIGURE 1 | Landmark analysis of early free light-chain (FLC) suppression and other prognostic markers on survival outcomes following BCMA-directed CAR-T cell therapy. (A) Progression-free survival (PFS) and (B) overall survival (OS) stratified by FLC suppression at Day +28. (C) PFS stratified by high-risk cytogenetics (HRC). (D–F) PFS stratified by FLC suppression at Day +28 in combination with CAR-T product used (D), presence of extramedullary disease (E), and HRC (F).

driver of early relapse after BCMA-directed CAR-T therapy, in line with prior observations by Gagelmann et al. [12]. Overall, the PFS and OS results of our cohort are comparable to the data just published by Merz et al. comparing real-life ide-cel with cilta-cel [13]. Future validation in such an independent cohort will be necessary to confirm our results.

Integrating FLC suppression as an early CAR-T response marker could improve patient management, with nonresponders needing further bone marrow evaluation and closer monitoring. This retrospective analysis has limitations, including potential selection bias, treatment variability across centers, missing MRD assessment, and a small sample size that limits generalizability. Moreover, only ide-cel and cilta-cel were studied, and key data on CAR-T persistence, MRD, and soluble BCMA levels were not collected.

In summary, not suppressed FLC at Day +28 post-CAR-T appears to be associated with inferior PFS and OS in patients with RRMM. FLC suppression may represent a simple and cost-effective tool for identifying high-risk individuals who could benefit from tailored interventions. However, given the exploratory nature of this study, these findings should be considered hypothesis-generating. Future research should aim to validate these observations and explore the integration of FLC for tailored interventions with other biomarkers to refine risk-adapted strategies and enhance outcomes of CAR-T therapy in myeloma.

1 | Statistics

Data analysis was performed using R (version 4.4.1). Differences in categorical variables were assessed using Fisher's exact test or Pearson's Chi-squared test, as appropriate. Clinical characteristics were summarized using the R package tableone (version 0.13.2). Kaplan–Meier survival curves were generated, and log-rank tests were performed using the survival (version 3.6.4) and survminer (version 0.4.9) packages. For all survival analyses involving post-baseline variables (e.g., FLC suppression at Day +28 and at 3 month), we performed landmark analyses with time zero defined as Day +28 and 3 month. Only patients alive and evaluable at that time point were included. This approach was used to avoid immortal time bias. To address potential confounding factors, a multivariable Cox proportional hazards model for PFS was fitted, adjusting for relevant clinical variables: Prior BCMA- or T-cell–directed therapy, high-risk cytogenetics, EMD and prior response to CAR-T therapy. To ensure model parsimony and avoid overfitting, we limited the number of covariates according to the number of events following the commonly accepted rule of including no more than one covariate per 10–15 observed PFS events. While extended models were explored, they produced unstable or inconsistent results, likely due to collinearity and event sparsity. Therefore, the final model includes only the most clinically relevant variables selected a priori. High-risk cytogenetics were defined according to IMWG criteria and included del(17p), t(4;14), t(14;16), t(14;20), and gain(1q).

Author Contributions

Tim Richardson and Udo Holtick designed the research and wrote the paper. Hishan Tharmaseelan and Daniel Schütte performed the statistical analysis and created the graphs. Guido Kobbe, Ben-Niklas Baermann, Tobias A. W. Holderried, Friederike Schmitz, and Martina Crysandt provided patient material and clinical data. Philipp Gödel and Nathan

Wolfensberger fact checked and analyzed the data. Michael Hallek and Christof Scheid discussed the results and mentored the overall process.

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Ethics Statement

This study was approved by the institutional review and ethics board of the University of Cologne (reference number 24-1201-retro), with the approval also covering data collection at all participating centers through formal cooperation agreements. All methods were carried out in accordance with the relevant guidelines and regulations and conducted according to the declaration of Helsinki. All patients approved an informed consent to the use of their anonymous data.

Conflicts of Interest

Tim Richardson gave advisory boards for Janssen and Sanofi. Udo Holtick received consultant and/or speaker fees from Bristol-Myers Squibb, Gilead, Janssen, Miltenyi Biotec, and Novartis. Christof Scheid gave advisory boards and received honoraria from Amgen, Abbvie, Bristol-Myers Squibb, Janssen, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, Stemline Menarini, and Takeda, and received research support from Janssen and Takeda. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Figure S2 Supplementary Figure S3 Supplementary Table S1