Extramedullary disease is associated with severe toxicities following B-cell maturation antigen CAR T-cell therapy in multiple myeloma

Andrew J. Portuguese,[1,2] Emily C. Liang,[1,2] Jennifer J. Huang,[1,2] Yein Jeon,[2] Danai Dima,[1,2] Rahul Banerjee,[1,2] Mary Kwok,[1,2] Kara I. Cicero,[1,2] Alexandre V. Hirayama,[1,2] Ryan Basom,[1] Christy Khouderchah,[1,2] Mazyar Shadman,[1,2] Lawrence Fong,[1,2] Andrew J. Cowan[1,2] and Jordan Gauthier[1,2]

[1]Fred Hutchinson Cancer Center and [2]University of Washington, Seattle, WA, USA

Correspondence: A.J. Portuguese
aportugu@fredhutch.org

Received: April 7, 2025.
Accepted: June 10, 2025.
Early view: June 19, 2025.

https://doi.org/10.3324/haematol.2025.287985

Abstract

Extramedullary disease (EMD) in multiple myeloma (MM) is associated with poor outcomes following B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T therapy, yet its impact on treatment-related toxicity remains unclear. This study evaluates the impact of active EMD on toxicity, efficacy, and survival in patients with MM treated with idecabtagene vicleucel (ide-cel) or ciltacabtagene autoleucel (cilta-cel). We conducted a retrospective cohort study of all patients with MM who received ide-cel (N=32) or cilta-cel (N=76) as standard-of-care therapy at our institution from August 2021 to October 2024. EMD was defined as the presence of soft tissue masses in extraosseous locations, and outcomes were compared based on EMD status. Among 108 patients, 26 (24%) had EMD. Patients with EMD experienced higher rates of grade (G)1+ (38% *vs*. 17%; *P*=0.022) and G3+ immune effector cell-associated neurotoxicity syndrome (19% *vs*. 1.2%; *P*=0.003), as well as G1+ (96% *vs*. 78%; *P*=0.041) and G3+ early immune effector cell-associated hematoxicity (31% *vs*. 0; *P*<0.001). Patients with EMD had more prolonged severe neutropenia (median: 7 *vs*. 2 days; *P*<0.001), greater cefepime use (median 10 *vs*. 6 doses; *P*=0.039), and higher rates of bacteremia (15% *vs*. 2.4%; *P*=0.029). In terms of efficacy, patients with EMD had lower complete response rates (20% *vs*. 59%; *P*<0.001), shorter median progression-free survival (7.6 *vs*. 24.6 months; *P*<0.001), and shorter median overall survival (20 months *vs*. not reached; *P*<0.001; 1-year estimates, 53% *vs*. 96%) and higher 1-year non-relapse mortality (21% *vs*. 2.5%; *P*=0.003). EMD is associated with increased toxicity, delayed hematologic recovery, more infectious complications, and reduced survival in patients with MM receiving CAR T therapy.

Introduction

Multiple myeloma (MM) remains a virtually incurable malignancy despite significant therapeutic advances. Patients with extramedullary disease (EMD), defined by the presence of plasmacytomas outside the bone marrow, face poor outcomes, including lower response rates and shorter survival compared to those with bone marrow-confined disease.[1,2] The advent of B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell (CAR T) therapy has transformed the treatment landscape of relapsed or refractory MM, achieving high response rates and durable remissions.[3-7] These successes have led to regulatory approvals and widespread adoption of CAR T therapy into clinical practice. However, emerging data from both clinical trials and real-world studies indicate that EMD negatively impacts CAR T efficacy, resulting in lower response rates and shorter durations of response compared to patients without EMD.[8-14]

While the impaired anti-tumor efficacy of CAR T therapy in EMD is increasingly recognized, its safety profile in this high-risk population remains poorly characterized. Characterizing the impact of EMD on toxicities is relevant given the significant and potentially life-threatening toxicities associated with CAR T therapy, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and early immune effector cell-associated hematotoxicity (eICAHT), all of which often require intensive supportive care.[15,16] Emerging real-world data further suggest that patients with EMD may be at increased risk for hematologic toxicity. In one study, patients with EMD had lower hemoglobin levels at both day 30 and day 90 post-infusion, along with a trend toward

higher rates of grade ≥3 thrombocytopenia compared to patients without EMD.[14] Clarifying the relationship between EMD and treatment-related toxicities is critical, as these complications affect not only patient outcomes but also access to CAR T therapy and healthcare resource utilization. To address this knowledge gap, we conducted a comprehensive analysis of safety and efficacy outcomes in MM patients with EMD treated with Food and Drug Adminstration and European Medicines Agency-approved BCMA-targeted CAR T therapies, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel). By systematically evaluating treatment-related toxicities and their implications in this high-risk population, this study aims to provide crucial insights that will inform clinical decision-making and optimize patient care.

Methods

Patients

The study was approved by the Fred Hutchinson Cancer Center (FHCC) Institutional Review Board, deemed to involve minimal risk, and conducted under a waiver of informed consent. Adult patients (age ≥18 years) with a diagnosis of MM who received cilta-cel or ide-cel at FHCC through October 28, 2024 were included for analysis. Clinical data were collected through April 6, 2025.

Definitions

Treatment response was assessed using the International Myeloma Group uniform response criteria.[17] The following cytogenetic aberrations were classified as high-risk cytogenetic abnormalities (HRCA): del(17p), t(14;16), t(4;14), t(14;20), and gain/amp(1q21).

Active EMD was defined as (i) extramedullary-extraosseous soft tissue plasmacytomas detected on positron emission tomography-computed tomography (PET-CT) or PET-magnetic resonance imaging (PET-MR), with non-physiologic areas of increased ^{18}F-fluorodeoxy glucose (FDG) uptake (standard uptake volume [SUV] max >2.5, based on body weight) and a corresponding extramedullary lesion on structural imaging; and/or (ii) central nervous system (CNS) involvement, identified by MR evidence of epidural or leptomeningeal disease. Paraskeletal disease - defined as osseous tumor extension into adjacent soft tissues due to cortical bone disruption - was not considered EMD. Bridging therapy was defined as myeloma-directed therapy administered between leukapheresis and infusion, excluding corticosteroids and radiation, and was not counted as a line of therapy. Prior lines of therapy were determined per published guidelines.[18]

CRS and ICANS were graded per American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[19] Early ICAHT (day 0-30) was graded according to the European Hematology Association and European Society for Blood and Marrow Transplantation criteria as previously described.[20] CAR-HEMATOTOX scores were calculated as previously described, with scores ≥2 considered high risk (HT^{high}).[21] Fever and severe neutropenia were defined as a body temperature ≥38.0°C and an absolute neutrophil count (ANC) <0.5×10^9/L, respectively. Neutropenia duration was calculated through day +30. Inpatient duration was defined from CAR T infusion through day +60.

Lymphodepletion and supportive care

Lymphodepletion chemotherapy was administered per product-specific guidelines, with most patients receiving fludarabine and cyclophosphamide. Management of CRS and ICANS followed institutional risk evaluation and mitigation strategy protocols. Patients received transfusions and antibiotics as per institutional standards.

Statistical analysis

Analyses were conducted using R Statistical Software (Version 4.4.3; R Core Team 2024).[22] Continuous variables were analyzed using the Wilcoxon rank-sum test, while proportions were compared using Pearson's χ^2 test or Fisher's exact test. Progression-free survival (PFS) events were defined as death, relapse, or progressive disease (PD). Duration of response (DOR) was calculated as the time to relapse, progression, or death for patients who had at least a partial response (PR) after CAR T therapy. Kaplan-Meier (KM) estimates were employed to assess overall survival (OS), PFS, and DOR. The cumulative incidence of relapse or progression was calculated using the tidycmprsk::cuminc() function (Version 1.0.0), treating non-relapse mortality (NRM) as a competing event. Median follow-up time was estimated with the reverse KM method.

Univariate and multivariable associations between variables and binary outcomes were analyzed using logistic regression. For logistic regression models assessing response, only response-evaluable patients were included. Cox regression was employed for univariate and multivariable analyses of associations between variables and time-to-event outcomes.

Multivariable regression models were adjusted for bone marrow plasma cell percentage (BMPC) measured by morphologic assessment, EMD, HRCA status, product type, and age.

Results

Patient characteristics

Between August 2021 and October 2024, 108 patients with MM were treated with ide-cel (N=32) or cilta-cel (N=76) at our center per standard-of-care. EMD was identified in 26 (24%) patients, including 23 with non-bone-adjacent FDG-avid plasmacytomas, six with epidural involvement, and one with leptomeningeal disease. EMD was biopsy-confirmed in eight patients, including seven pre-CAR T

and one obtained on day +23 in a patient with refractory disease. Among these, three cases demonstrated high proliferative indices by Ki-67 (>80%, 90%, and 99%), and a fourth was described as having marked proliferative activity.

Patient and disease characteristics were largely comparable between those with and without active EMD. However, several notable differences emerged. Patients with EMD had significantly higher pre-lymphodepletion LDH levels (179 *vs*. 144 U/L; *P*=0.001; Table 1). Cytogenetic profiles also differed. Although the overall proportion of patients with ≥1 HRCA was similar between EMD and non-EMD groups (73% *vs*. 61%; *P*=0.3), a significantly higher proportion of patients with EMD had a single HRCA (62% *vs*. 33%; *P*=0.009) whereas a numerically lower proportion had ≥2 HRCA (12% *vs*. 28%; *P*=0.086). As shown in *Online Supplementary Figure S1*, the distribution and co-occurrence patterns of HRCA differed between groups.

Bridging therapy following leukapheresis also varied by EMD status, as detailed in *Online Supplementary Table S1*. Patients with EMD were more likely to receive cisplatin-containing regimens (23% *vs*. 6.1%; *P*=0.022) and less likely to receive carfilzomib-based therapy (19% *vs*. 43%; *P*=0.031).

Among patients with EMD, those with epidural or leptomeningeal involvement had received significantly more prior lines of therapy (median 6 *vs*. 5; *P*=0.014) and were numerically more likely to have received autologous stem cell transplantation (100% *vs*. 53%; *P*=0.058). Most were triple refractory (6 of 7) and penta-drug exposed (6 of 7). However, none met criteria for full penta-refractoriness.

Toxicity

Increased incidence, severity, and duration of immune effector cell-associated neurotoxicity syndrome in patients with extramedullary disease post-CAR T therapy

All patients were evaluable for CRS and ICANS assess-

Table 1. Baseline characteristics by extramedullary disease status.

Characteristic	Overall[1]	EMD N=26[1]	No EMD N=82[1]	*P*[2]
Age, years, median (range)	65 (38-80)	64 (42-75)	65 (38-80)	0.8
Female sex, N (%)	49 (45)	12 (46)	37 (45)	>0.9
ECOG 0-1, N (%)	105 (97)	25 (96)	80 (98)	0.6
IgG heavy chain, N (%)	62 (57)	18 (69)	44 (54)	0.2
κ light chain, N (%)	64 (59)	14 (54)	50 (61)	0.5
Light chain disease, N (%)	20 (19)	2 (7.7)	18 (22)	0.15
Number of HRCA, N (%) 0 1 2+	 39 (36) 43 (40) 26 (24)	 7 (27) 16 (62) 3 (12)	 32 (39) 27 (33) 23 (28)	0.029
Paraskeletal disease, N (%)	17 (16)	11 (42)	6 (7.3)	<0.001
Prior LOT, N (%)	5 (4, 6)	5 (4, 7)	5 (4, 6)	0.7
M-spike, g/dL	0.20 (0.00, 1.00)	0.40 (0.10, 1.30)	0.10 (0.00, 0.85)	0.074
Involved FLC, mg/dL	12 (2, 32)	17 (3, 85)	9 (2, 27)	0.13
BMPC, %	5 (0, 30)	1 (0, 60)	6 (0, 25)	0.8
Pre-LD ANC, x10^9/L	2.68 (1.76, 3.70)	2.58 (1.69, 3.98)	2.73 (1.80, 3.68)	0.9
Pre-LD ALC, x10^9/L	0.65 (0.37, 0.96)	0.44 (0.31, 0.81)	0.69 (0.43, 0.98)	0.10
Pre-LD LDH, U/L	146 (124, 179)	179 (142, 330)	144 (123, 166)	0.001
Bridging therapy, N (%)	105 (97)	24 (92)	81 (99)	0.14
Product received, N (%) Cilta-cel Ide-cel	 76 (70) 32 (30)	 17 (65) 9 (35)	 59 (72) 23 (28)	0.5
Out-of-specification, N (%)	15 (14)	5 (19)	10 (12)	0.3

[1]Median (Min-Max); median (Q1, Q3). [2]Wilcoxon rank sum test; Pearson's χ^2 test; Fisher's exact test. EMD: extramedullary disease; ECOG: Eastern Cooperative Oncology Group performance status; LOT: lines of therapy; HRCA: high-risk cytogenetic abnormality; FLC: free light chain; BMPC: bone marrow plasma cell percentage by morphologic assessment; D0: day 0; Pre-LD: pre-lymphodepletion; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; LDH: lactate dehydrogenase; cilta-cel: ciltacabtagene autoleucel; ide-cel: idecabtagene vicleucel.

ment, while 107 patients were evaluable for eICAHT assessment. As illustrated in Figure 1, patients with EMD experienced significantly higher rates of G1+ ICANS (38% *vs*. 17%; *P*=0.022), G2+ ICANS (31% *vs*. 4.9%; *P*=0.001), and G3+ ICANS (19% *vs*. 1.2%; *P*=0.003). Additionally, ICANS duration was significantly longer in patients with EMD (8.0 *vs*. 2.0 days; *P*=0.010). Although the incidence and severity of CRS did not differ significantly between EMD and non-EMD patients, the duration of CRS was prolonged in those with EMD (4 *vs*. 3 days; *P*=0.003).

Given the known differences in CRS and ICANS onset between cilta-cel and ide-cel, we further analyzed onset times by product type. Among cilta-cel-treated patients, those with EMD had a median CRS onset of 5 days (interquartile range [IQR], 1-5) compared to 6 days (IQR, 5-8) in non-EMD patients (*P*=0.003), and a median ICANS onset of 5 days (IQR, 3-6.5) compared to 8.5 days (IQR 6-11; *P*=0.060). In ide-cel-treated patients, CRS onset occurred at a median of 1 day for both groups (IQR, 0-1 for both; P=0.7), while ICANS onset occurred at a median of 2.5 days (IQR, 1-5) in patients with EMD *versus* 1 day (IQR, 1-1) in non-EMD patients (*P*=0.060).

Because the association between EMD and ICANS severity could be influenced by other factors such as disease burden and baseline inflammation, we performed a multivariable analysis adjusting for BMPC percentage, HRCA status, product type, and age (Table 2). EMD remained independently associated with significantly higher odds of developing G2+ ICANS (adjusted odds ratio [aOR] =5.22; 95% confidence interval [CI]: 1.15-25.4; *P*=0.032).

More severe hematologic toxicity in patients with extramedullary disease

Patients with EMD experienced significantly higher rates of severe neutropenia compared to those without EMD. Nearly all patients with EMD developed severe neutropenia (96% vs. 78%; *P*=0.039), and its median duration was more prolonged (7 *vs*. 2 days; *P*<0.001). Additionally, patients with EMD had a significantly lower nadir absolute neutrophil count (ANC; 0.14 *vs*. 0.33x10^9/L; *P*<0.001).

The eICAHT grading system further highlighted the severity of hematologic toxicity in patients with EMD, who had sig-

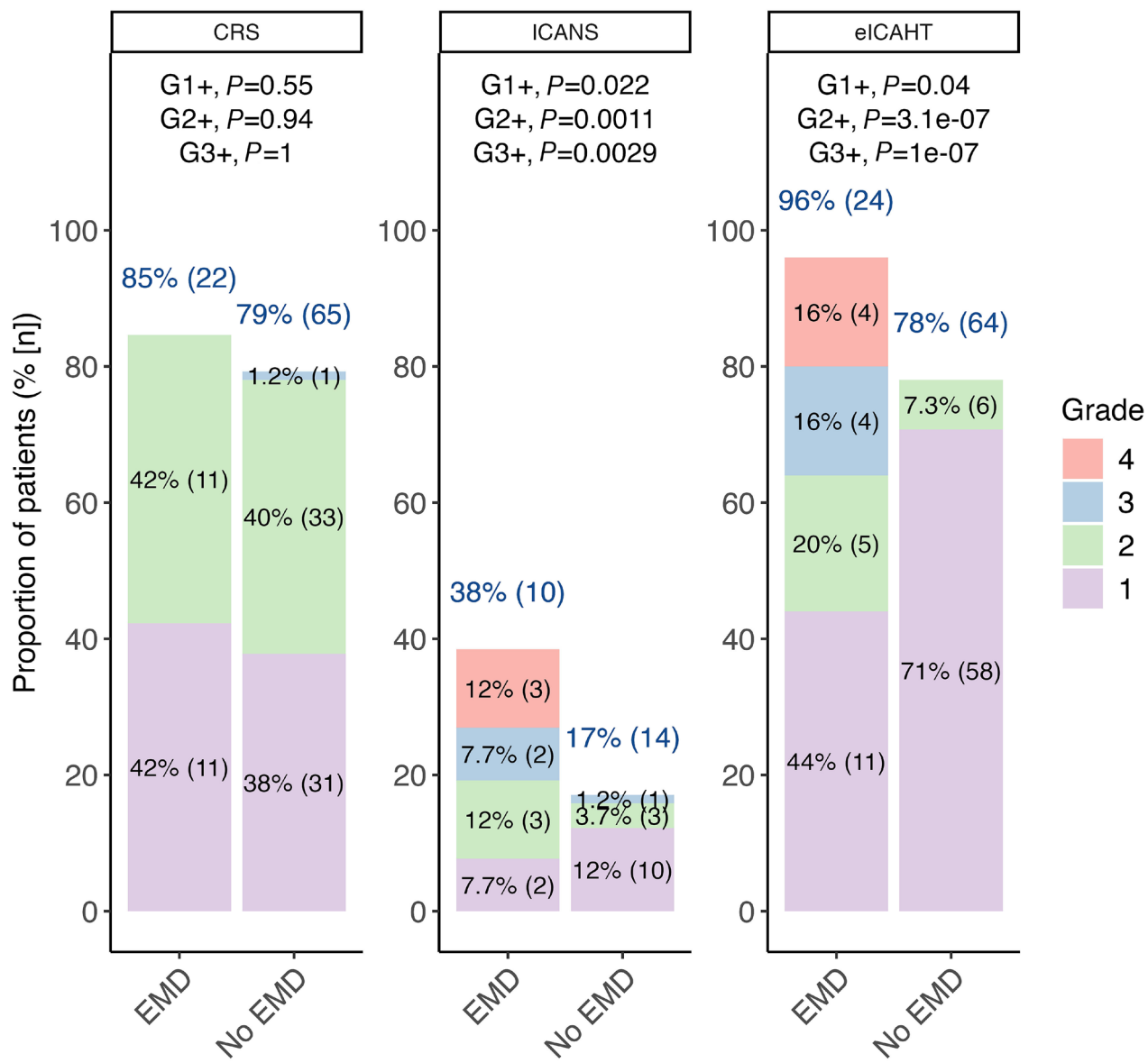

Figure 1. Comparisons of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and early immune effector cell-associated hematotoxicity. *P* values for comparisons of toxicities were derived from the χ^2 test, except when the expected cell count was less than 5, in which case Fisher's exact test was used. EMD: extramedullary disease; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; eICATH: early immune effector cell-associated hematotoxicity; G: grade.

nificantly higher rates of G1+ eICAHT (96% *vs*. 78%; *P*=0.041), G2+ eICAHT (50% *vs*. 7.3%; *P*<0.001) and G3+ eICAHT (31% *vs*. 0%; *P*<0.001). Notably, cases of G3+ eICAHT occurred exclusively in patients with EMD.

Table 2. Summary of univariate and multivariable regression analyses for grade 2 or higher toxicity and efficacy outcomes.

		Univariate			Multivariable		
	N	**Estimate[1]**	**95% CI**	***P***	**Estimate[1]**	**95% CI**	***P***
CRS grade 2+							
EMD	108	1.04	0.42-2.52	>0.9	0.80	0.28-2.17	0.7
BMPC	105	1.11	0.96-1.29	0.2	1.08	0.92-1.28	0.4
Age	108	0.97	0.93-1.01	0.11	0.96	0.92-1.01	0.12
HRCA	108	1.73	0.77-3.99	0.2	1.63	0.66-4.18	0.3
Cilta-cel	108	0.36	0.15-0.82	0.017	0.39	0.16-0.96	0.043
ICANS grade 2+							
EMD	108	8.67	2.46-35.5	0.001	5.22	1.15-25.4	0.032
BMPC	105	1.45	1.18-1.81	<0.001	1.29	1.04-1.65	0.028
Age	108	1.02	0.95-1.09	0.6	1.01	0.93-1.10	0.8
HRCA	108	3.14	0.77, 21.1	0.2	1.63	0.26-14.1	0.6
Cilta-cel	108	0.25	0.07-0.86	0.028	0.34	0.07-1.51	0.2
eICAHT grade 2+							
EMD	108	12.7	4.25-42.0	<0.001	9.70	2.77-37.7	<0.001
BMPC	105	1.43	1.20-1.75	<0.001	1.30	1.06-1.65	0.017
Age	108	1.00	0.95-1.06	>0.9	1.00	0.93-1.08	>0.9
HRCA	108	6.05	1.60-39.6	0.021	3.94	0.79-31.2	0.13
Cilta-cel	108	0.51	0.18-1.45	0.2	0.77	0.20-3.13	0.7
≥Complete response							
EMD	99	0.17	0.05-0.47	0.001	0.19	0.05-0.55	0.004
BMPC	96	0.90	0.77-1.05	0.2	0.93	0.76-1.12	0.5
Age	99	1.04	1.00-1.09	0.066	1.05	1.00-1.11	0.050
HRCA	99	0.89	0.39-2.01	0.8	1.64	0.63-4.39	0.3
Cilta-cel	99	1.89	0.80-4.58	0.15	1.63	0.61-4.43	0.3
Overall survival							
EMD	108	7.31	2.86-18.7	<0.001	11.5	4.09-32.2	<0.001
BMPC	105	1.02	0.86-1.19	0.8	0.86	0.73-1.01	0.061
Age	108	0.99	0.95-1.04	0.8	1.03	0.98-1.08	0.2
HRCA	108	2.35	0.78-7.10	0.13	4.11	1.20-14.1	0.025
Cilta-cel	108	0.39	0.16-0.99	0.048	0.27	0.10-0.76	0.013
Progression-free survival							
EMD	108	2.72	1.49-4.97	0.001	2.86	1.51-5.42	0.001
BMPC	105	1.00	0.90-1.12	>0.9	0.93	0.83-1.04	0.2
Age	108	0.96	0.93-0.99	0.004	0.97	0.94-1.00	0.025
HRCA	108	2.22	1.13-4.39	0.021	2.05	1.00-4.21	0.052
Cilta-cel	108	0.47	0.26-0.83	0.010	0.54	0.29-0.99	0.047
Duration of response							
EMD	90	2.10	1.07-4.13	0.032	2.02	0.99-4.11	0.053
BMPC	87	0.93	0.82-1.06	0.3	0.91	0.80-1.03	0.15
Age	90	0.97	0.94-1.00	0.040	0.98	0.95-1.01	0.3
HRCA	90	2.26	1.07-4.78	0.033	2.14	0.94-4.86	0.069
Cilta-cel	90	0.81	0.43-1.51	0.5	1.02	0.52-2.00	>0.9
Non-relapse mortality							
EMD	108	10.5	2.04-54.5	0.005	16.5	2.96-91.5	0.001
BMPC	105	0.81	0.52-1.27	0.4	0.72	0.50-1.03	0.073
Age	108	1.00	0.92-1.08	>0.9	1.05	0.96-1.14	0.3
HRCA	108	4.03	0.48-33.5	0.2	7.81	0.86-70.9	0.068
Cilta-cel	108	0.53	0.12-2.36	0.4	0.33	0.05-2.03	0.2

[1]Estimate: β, odds ratio, or hazard ratio. CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; eICAHT: early immune effector cell-associated hematotoxicity; EMD: extramedullary disease; BMPC: bone marrow plasma cell percentage; HRCA: high-risk cytogenetic abnormality; CI: confidence interval; cilta-cel: ciltacabtagene autocel. The predictors were scaled as follows: BMPC was scaled to 10% and age was scaled to 1 year.

Beyond neutropenia, EMD was also associated with broader hematologic suppression. Median nadir hemoglobin levels (7.8 *vs*. 8.3 g/dL; *P*<0.001) and platelet counts (30 *vs*. 58x10³/μL; *P*=0.005) were significantly lower in patients with EMD, suggesting more profound myelosuppression. LOESS-smoothed curves illustrating ANC, hemoglobin level, and platelet count trends over time are shown in Figure 2.

Multivariable regression analysis, adjusted for BMPC percentage, HRCA status, product type, and age, confirmed that EMD was an independent predictor of G2+ eICAHT (aOR=9.70, 95% CI: 2.77-37.7; *P*<0.001) and prolonged duration of severe neutropenia (adjusted β +5.5 days, 95% CI: 3.4-7.6; *P*<0.001; *Online Supplementary Table S2*). To further assess the impact of EMD on the duration of severe neutropenia while accounting for predictors used in the CAR-HEMATOTOX model, an additional regression analysis was conducted incorporating pre-lymphodepletion laboratory values (hemoglobin, platelets, ANC, ferritin, and C-reactive protein [CRP]) along with BMPC percentage. EMD remained the strongest independent predictor of prolonged severe neutropenia, with an adjusted β of +4.4 days (95% CI: 2.3-6.5; *P*<0.001). A visual comparison of the two multivariable models is presented in Figure 3.

Increased systemic inflammation and more severe coagulopathy following CAR T infusion in patients with extramedullary disease

Before CAR T infusion (day 0), patients with EMD exhibited significantly higher median baseline levels of inflammatory markers compared to non-EMD patients (Figure 4), including CRP (15 *vs*. 4 mg/dL; *P*<0.001), ferritin (698 *vs*. 197 ng/mL; *P*<0.001), IL-6 (21 *vs*. 5 pg/mL; *P*<0.001), D-dimer (1.22 *vs*. 0.57 mg/L; *P*=0.002), and LDH (183 *vs*. 150 U/L; *P*=0.017). These findings suggest that patients with EMD enter CAR T therapy with a heightened inflammatory state, which may contribute to subsequent toxicity.

Although the overall incidence and severity of CRS were not significantly different between EMD and non-EMD patients, peak inflammatory marker levels were significantly higher in patients with EMD, including CRP (101 *vs*. 67 mg/dL; *P*=0.030), ferritin (2,923 vs. 589 ng/mL; *P*<0.001), and IL-6 (2,622 *vs*. 142 pg/mL; *P*=0.005). The absolute increase from baseline to peak was also significantly greater in patients with EMD for ferritin (2,138 *vs*. 331 ng/mL; *P*<0.001), suggesting a more pronounced inflammatory response following CAR T infusion.

In addition to heightened systemic inflammation, patients with EMD were more likely to develop a consumptive coagulopathy. Median D-dimer peak levels were significantly

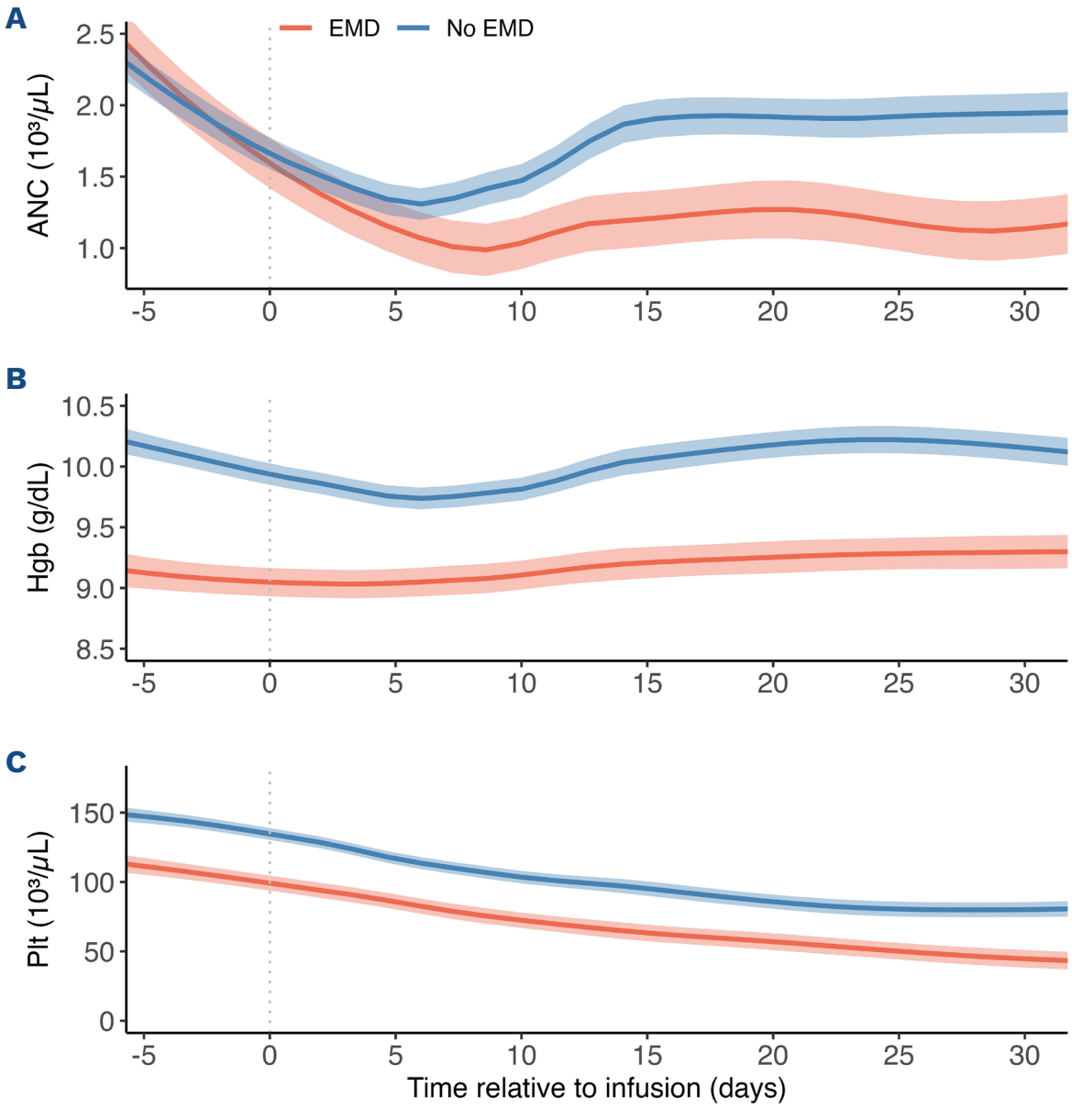

Figure 2. Hematologic recovery following CAR T infusion differs by extramedullary disease status. LOESS-smoothed curves depicting trends in (A) absolute neutrophil count (ANC), (B) hemoglobin (Hgb), and (C) platelet count (Plt) following chimeric antigen receptor (CAR) T infusion, stratified by the presence of extramedullary disease (EMD). Shaded regions represent 95% confidence intervals.

higher (5.1 *vs*. 2.4 mg/L; *P*=0.003), and patients with EMD had more pronounced hypofibrinogenemia (164 *vs*. 250 mg/dL; *P*=0.045) and thrombocytopenia (30 *vs*. 58x10³/μL; *P*=0.005). There was also a trend toward more prolonged peak International Normalized Ratio (INR) values (1.30 *vs*. 1.20; *P*=0.067). The decline in fibrinogen from baseline to nadir was higher in patients with EMD (299 *vs*. 202 ng/mL; *P*=0.027), and the log10-transformed day 0-to-nadir fibrinogen ratio was significantly higher (0.40 *vs*. 0.23; *P*=0.019), indicating a greater degree of CAR T-induced coagulopathy in this group.

Increased rate of infectious complications in patients with extramedullary disease

Patients with EMD experienced a higher incidence of infectious complications. Bacteremia occurred more frequently in patients with EMD compared to non-EMD patients (15% *vs*. 2.4%; *P*=0.029). The incidence of CMV viremia was similar between groups (15% *vs*. 8.5%; *P*=0.5).

Increased healthcare utilization and medication administration in patients with extramedullary disease

Patients with EMD had a longer median inpatient stay compared to those without EMD (16 *vs*. 12 days; *P*<0.001) and were more likely to require multiple hospital admissions (≥2 admissions: 42% *vs*. 20%; *P*=0.019). Patients with EMD received more antimicrobial therapy, with higher doses of cefepime (median 10 *vs*. 6, mean 9 *vs*. 7; *P*=0.039) and vancomycin (median 0 doses for both, mean 6 *vs*. 1; *P*=0.042). They also required greater immunosuppressive therapy for CRS/ICANS, with increased dexamethasone (median 3 *vs*. 0, mean 11 *vs*. 2; *P*=0.002) and anakinra (median 0 doses for both, mean 10 *vs*. 1; *P*<0.001). More patients with EMD received dexamethasone (69% *vs*. 45%; *P*=0.032) and anakinra (31% *vs*. 6.1%; *P*=0.002). Tocilizumab use was comparable between groups, with no significant difference in doses (median 1.0 *vs*. 0.5, mean 1.15 *vs*. 0.76; *P*=0.11) or overall receipt (62% *vs*. 50%; *P*=0.3), consistent with similar CRS severity. Patients with EMD received more G-CSF doses (median 11 *vs*. 3, mean 13 *vs*. 5; *P*<0.001). Additionally, patients with EMD required more platelet (median 3 *vs*. 0, mean 12 *vs*. 2; *P*=0.006) and red blood cell transfusions (median 4 *vs*. 1.5, mean 6.5 *vs*. 2.7; *P*=0.004).

Atypical neurologic toxicities and secondary malignancies in patients with and without extramedullary disease

Five patients experienced peripheral nervous system complications following cilta-cel infusion. Approximately 1 month post-infusion, four non-EMD patients developed Bell's palsy, while one EMD patient was diagnosed with Guillain-Barré syndrome.

Additionally, a CNS complication was observed in a non-EMD patient, who developed treatment-associated Parkinsonism approximately 3 months after cilta-cel infusion.

Four patients were diagnosed with myeloid neoplasms. Two non-EMD patients developed AML about 1 year after CAR T infusion - one following cilta-cel and the other after ide-cel. Two non-EMD patients were diagnosed with MDS 2 years after ide-cel infusion. One non-EMD patient was diagnosed with a stage I colon adenocarcinoma 3 months after cilta-cel infusion, treated with hemicolectomy.

Two patients developed immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) approximately 1 week after cilta-cel infusion - one non-EMD patient and another EMD patient with epidural involvement.

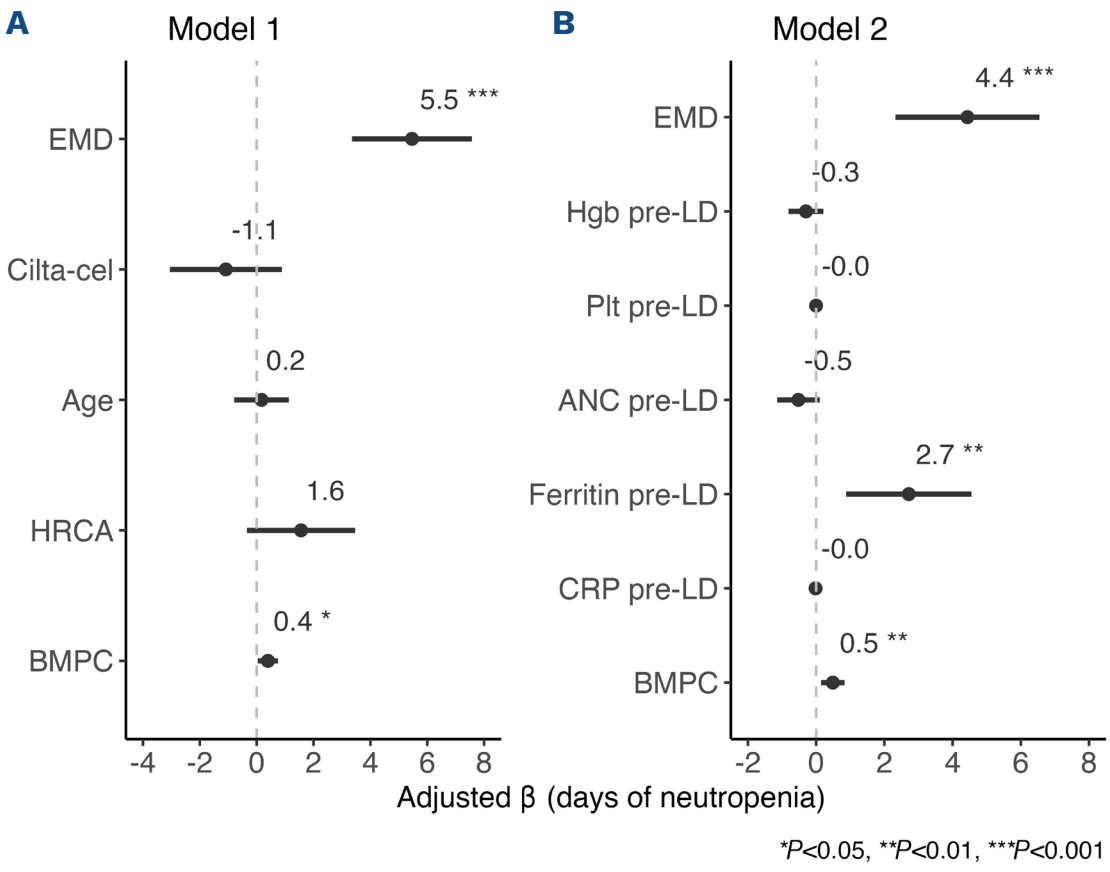

Figure 3. Comparison of two multivariable linear regression models for duration of neutropenia. (A) Model 1 adjusts for product type (reference: ide-cel), age (per 10 years), the presence of a high-risk cytogenetic abnormality (HRCA), extramedullary disease (EMD), and bone marrow plasma cell burden (BMPC, per 10% increase). (B) Model 2 adjusts for EMD, BMPC (per 10% increase), and pre-lymphodepletion (LD) hemoglobin (Hgb, per g/dL), platelet count (Plt, x10⁹/L), absolute neutrophil count (ANC, x10⁹/L), ferritin (per 1,000xng/mL), and C-reactive protein (CRP, per 10xmg/dL). Note: day 0 laboratory values were used when pre-LD laboratory data were unavailable. Cilta-cel: cilta-cabtagene autocel; CRP: C-reactive protein.

Response rates

Among response-evaluable patients (N=99), overall response rates were comparable between those with and without EMD (88% *vs*. 92%; *P*=0.7). However, significantly fewer patients with EMD achieved a sCR/CR compared to non-EMD patients (20% *vs*. 59%; *P*<0.001). Among patients with both pre- and post-treatment marrow evaluations (N=95), the proportion achieving bone marrow flow cytometry negativity was similar between EMD and non-EMD groups (74% *vs*. 88%; *P*=0.3). Detailed response rates are shown in Figure 5.

Multivariable analysis further highlighted the independent impact of active EMD on clinical outcomes (Table 2). In a model including BMPC percentage, HRCA status, product type, and age, patients with EMD had significantly lower odds of achieving a sCR/CR (aOR=0.19, 95% CI: 0.05-0.55; *P*=0.004).

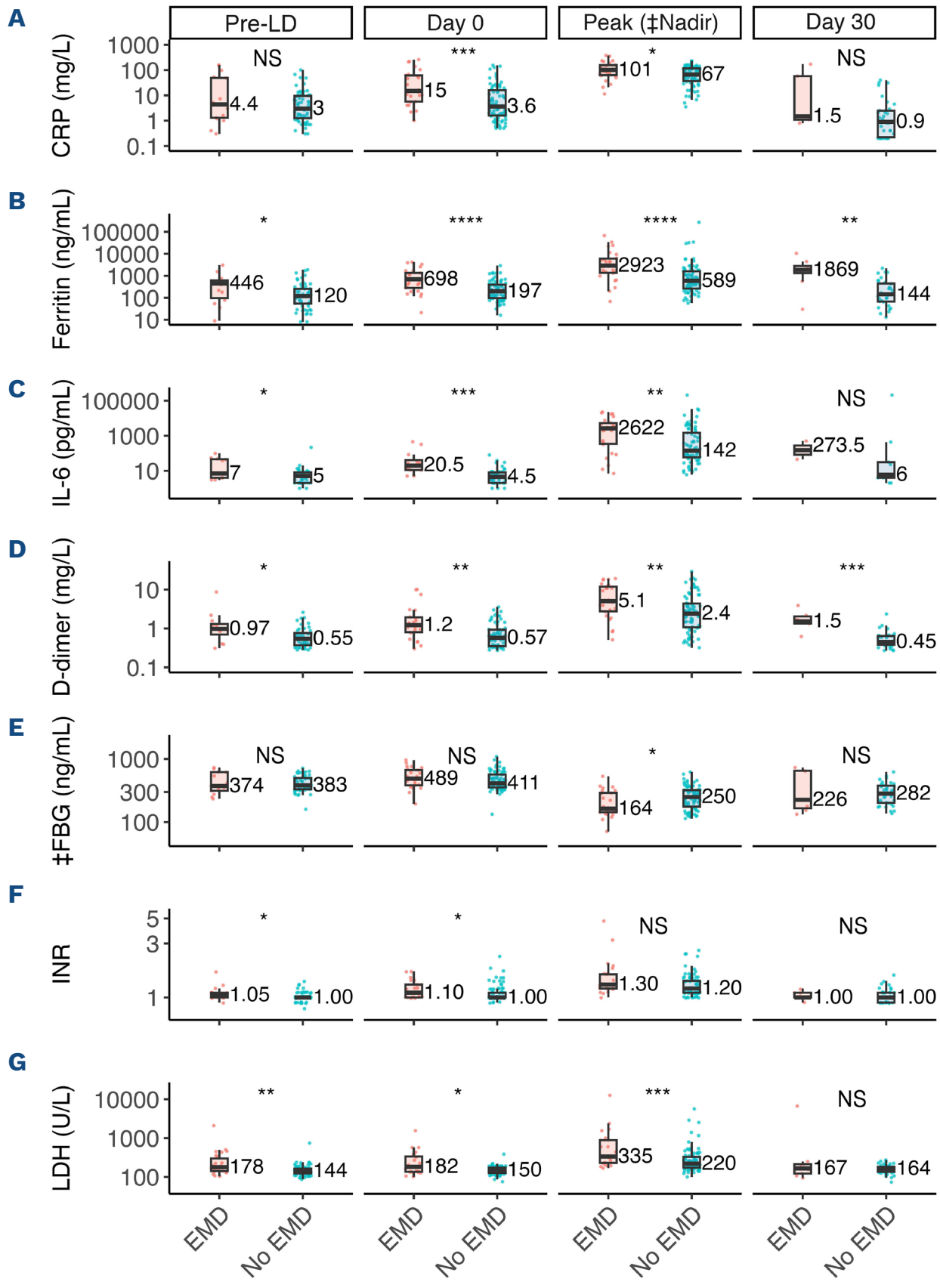

Figure 4. Inflammatory and coagulation biomarkers differ by extramedullary disease status in CAR T recipients. Box plots depicting levels of (A) C-reactive protein (CRP), (B) D-dimer, (C) ferritin, (D) interleukin (IL)-6, (E) lactate dehydrogenase (LDH), (F) International Normalized Ratio (INR), and (G) fibrinogen (FBG) at various time points relative to chimeric antigen receptor (CAR) T infusion, stratified by extramedullary disease (EMD) status. For all biomarkers except fibrinogen, extreme values represent peak levels; for fibrinogen, extreme values correspond to nadir levels. Median values are indicated. Statistical significance was determined using the Wilcoxon rank-sum test *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; NS: not significant.

Long-term outcomes

With a median follow-up of 25.8 months, patients with EMD had significantly worse outcomes compared to those without EMD, as illustrated in *Online Supplementary Figure S2*. Patients with EMD demonstrated significantly shorter median OS (20 months *vs*. not reached; *P*<0.001), PFS (7.6 *vs*. 24.6 months; *P*<0.001), and DOR (10.7 *vs*. 23.4 months; *P*=0.025). Additionally, the 12-month cumulative incidence of NRM was significantly higher in the EMD group (21% *vs*. 2.5%; *P*=0.003).

The primary causes of NRM were infections (N=6) and hemorrhagic stroke (N=2). Among non-EMD patients, two deaths were attributed to infections. In the EMD group, NRM occurred exclusively in patients with epidural or leptomeningeal involvement, with five of seven patients exhibiting these features experiencing NRM. Within 2 months of CAR T infusion, three patients with EMD with epidural involvement succumbed to infections, including two cases of bacteremia and one case of invasive fungal infection. Additionally, two patients with EMD - one with epidural involvement and one with leptomeningeal involvement - died of hemorrhagic stroke within 1 year. *Online Supplementary Figure S3* illustrates that patients with EMD involving epidural, or leptomeningeal sites had a significantly shorter median OS of 8.6 months compared to those without such involvement, whose median OS was not reached (*P*=0.002). Furthermore, the 1-year cumulative incidence of NRM was strikingly higher in this group (100% *vs*. 0%; *P*<0.001; Figure 6).

In multivariable models adjusting for BMPC percentage, HRCA status, product type, and age, EMD was consistently identified as an independent predictor of worse long-term outcomes, as detailed in Table 2. Patients with EMD demonstrated significantly higher hazards for OS (aHR=11.5; 95% CI: 4.09-32.2; *P*<0.001), PFS (aHR=2.86; 95% CI: 1.51-5.42; *P*=0.001), and DOR (aHR=2.23; 95% CI: 1.08-4.58; *P*=0.029). Furthermore, the cause-specific hazard for NRM was substantially elevated (aHR=16.5; 95% CI: 2.96-91.5; *P*=0.001). When applying Firth penalization to address separation, the association with NRM remained significant (aHR=14.5; 95% CI: 2.68-79.0; *P*<0.001).

Inclusion of extramedullary disease adds prognostic information to the CAR-HEMATOTOX scoring system for clinical outcomes

Regression analysis (*Online Supplementary Table S3*), adjusted for EMD and HT^{high} CAR-HEMATOTOX scores, confirmed that EMD was independently associated with duration of neutropenia (adjusted β =+7.0; 95% CI: 4.5-9.5; *P*<0.001), G2+ eICAHT (aOR=12.0, 95% CI: 3.17-52.8; *P*<0.001), G2+ ICANS (aOR=9.37, 95% CI: 2.26-45.2; *P*=0.003), sCR/CR (aOR=0.29, 95% CI: 0.08-0.91; *P*=0.046, OS (aHR=7.34, 95% CI: 2.37-22.7; *P*<0.001), PFS, (aHR=2.29, 95% CI: 1.14-4.60; *P*=0.020), and NRM (aHR=8.08, 95% CI: 1.47-44.6; *P*=0.016).

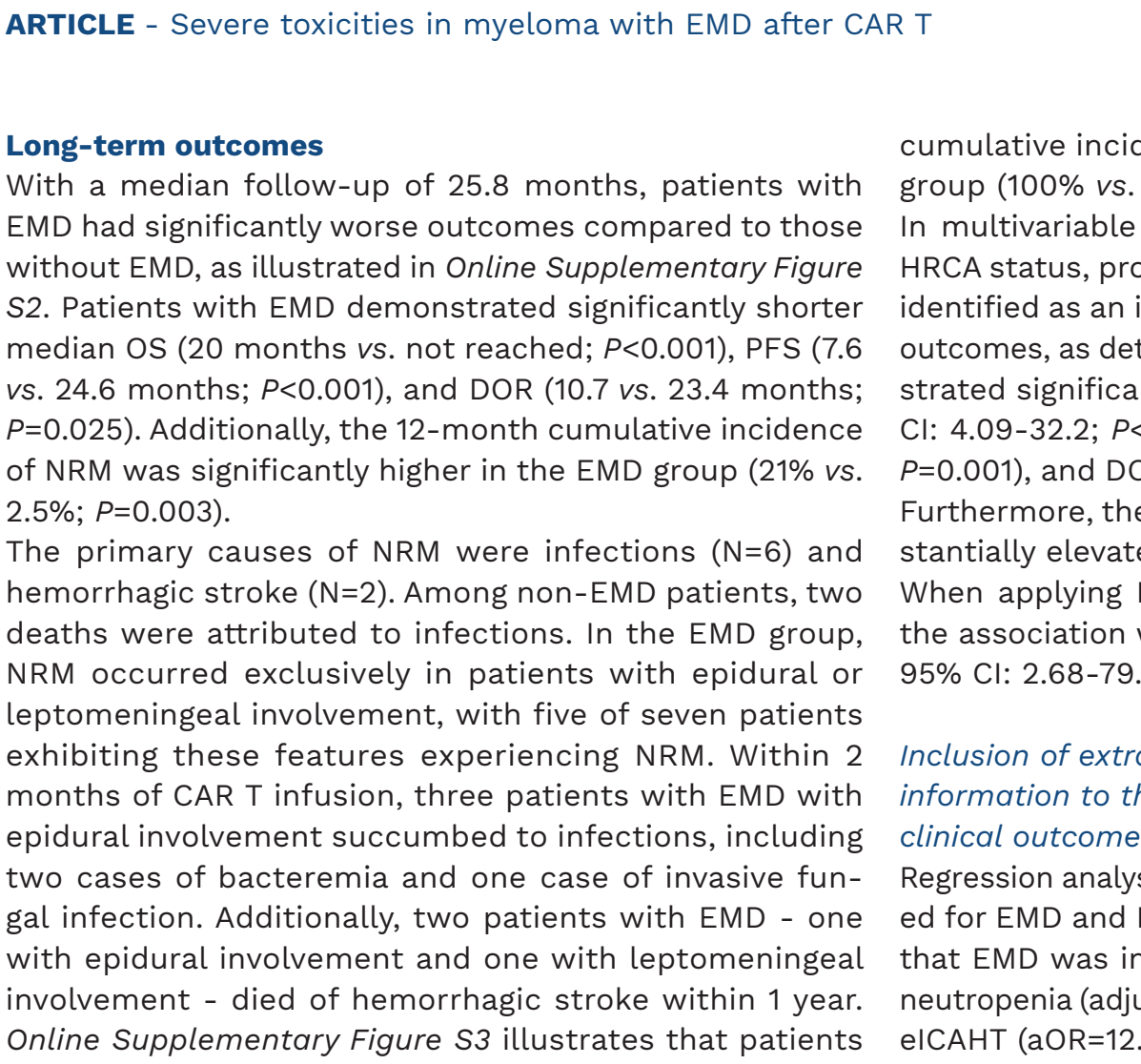

Figure 5. Comparisons of best response to CAR T therapy stratified by extramedullary disease status. *P* values for comparisons of response were derived from the χ^2 test, except when the expected cell count was less than 5, in which case Fisher's exact test was used. ORR: overall response rate; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; EMD: extramedullary disease.

Discussion

Our study demonstrates that patients with MM who have EMD experience significantly higher rates of severe toxicity following BCMA-targeted CAR T therapy. While prior research has established the negative impact of EMD on treatment efficacy and survival,[8-12] our findings reveal a substantial increase in early post-infusion complications. Compared to non-EMD patients, those with EMD had higher rates and greater severity of ICANS and eICAHT, prolonged CRS and ICANS resolution, extended severe neutropenia, and increased rates of NRM. Notably, all cases of grade ≥3 eICAHT occurred exclusively in the EMD cohort, highlighting the disproportionate hematologic toxicity burden in this population.

Although a recent multicenter analysis reported similar rates of ICANS in patients with and without EMD,[14] several methodological differences may account for the discrepancy with our findings. In that study, EMD classification was based on imaging performed at participating institutions, and it is unclear whether all cases reflected active disease at the time of CAR T infusion. In contrast, all patients treated at our center undergo standardized cross-sectional imaging as part of their pre-CAR T workup, enabling consistent identification of active EMD. Additionally, the use of uniform CAR T administration, toxicity grading, and supportive care protocols improves the reliability of toxicity attribution. These differences may explain the higher ICANS rates observed in our EMD cohort.

Furthermore, EMD was the strongest independent predictor of prolonged severe neutropenia, even after adjusting for baseline hematologic parameters, suggesting that EMD-associated inflammation may impair bone marrow function and contribute to persistent cytopenias. Additionally, EMD status independently predicted both severe toxicity and NRM, even after adjusting for CAR-HEMATOTOX HT^{high} status. These findings support the inclusion of EMD as a key variable in future predictive models to enhance risk stratification and inform early intervention strategies.

The clinical consequences of this heightened toxicity burden are significant. Prolonged neutropenia in patients with EMD led to an increased infection risk, with higher rates of bacteremia and greater use of broad-spectrum antibiotics. The severity of cytopenias further compounded these challenges, increasing the need for red blood cell and platelet transfusions to support hematologic recovery. Managing these complications required intensive supportive care, including greater use of antibiotics, steroids, and anakinra. Despite these interventions, the persistence of toxicities resulted in extended inpatient stays and higher re-admission rates, reflecting the substantial healthcare burden associated with EMD.

Patients with EMD with epidural or leptomeningeal involvement faced the highest risk of complications, with an exceptionally high NRM (1-year cumulative incidence: 100%). Careful patient selection is essential when considering CAR T therapy in this high-risk subgroup, and risk-adapted strategies may offer additional benefit. Since infections were the leading cause of death, implementing preemptive measures - such as prophylactic antibiotics, antifungals, and early consideration of granulocyte colony-stimulating factor (G-CSF) administration - may help reduce morbidity and mortality.

The increased duration and severity of toxicities in patients

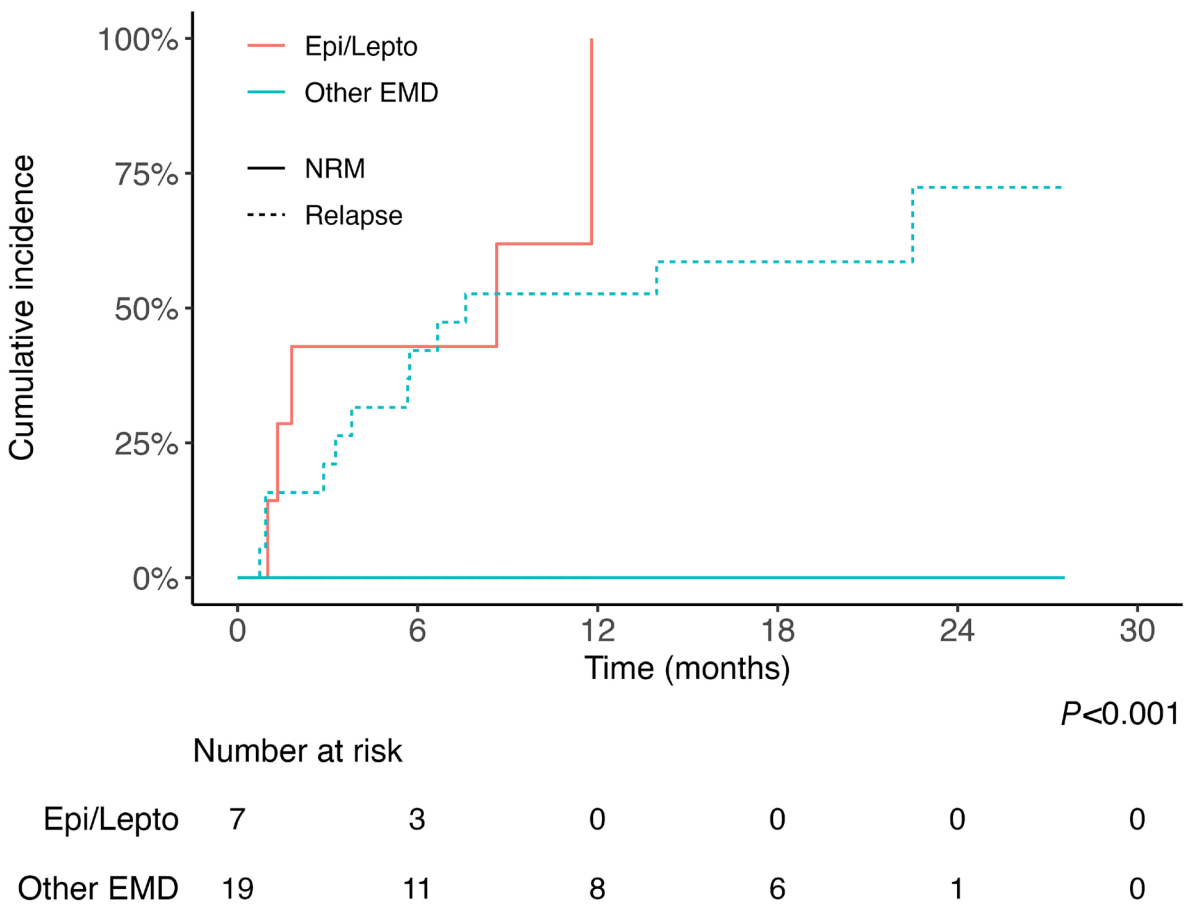

Figure 6. Patients with epidural or leptomeningeal involvement show significantly higher non-relapse mortality compared to other patients with extramedullary disease. The *P* value was derived from Gray's test. The number at risk represents patients who remain free of any competing event (i.e., neither relapse nor non-relapse mortality [NRM]), in accordance with standard cumulative incidence methodology. Epi/Lepto: epidural or leptomeningeal.

with EMD may be driven by a combination of an underlying proinflammatory state and dysregulated coagulation pathways.[23] Compared to non-EMD patients, those with EMD exhibited higher levels of systemic inflammation at baseline and post-infusion, reflected by higher peak serum CRP, ferritin, and IL-6. In addition to increased systemic inflammation, EMD was associated with severe coagulopathy, characterized by thrombocytopenia, elevated D-dimer and INR, and hypofibrinogenemia. These abnormalities are consistent with the increased severity of ICANS in patients with EMD, which is driven by endothelial activation and blood-brain barrier dysfunction.[24-28]

Given the high toxicity burden observed in patients with EMD, future studies should focus on tailored mitigation strategies. Pre-infusion radiation may serve as both a cytoreductive tool and a modulator of inflammatory cytokines that drive toxicity, potentially lowering tumor burden and reducing severe immune effector cell-associated toxicities.[29] Additional approaches might include interventions that dampen cytokine-driven inflammation or stabilize endothelial function, as both systemic inflammation and coagulopathy appear to play central roles in the pathogenesis of immune effector cell-associated toxicities.

While toxicity reduction is essential, optimizing CAR T design could further improve outcomes. Dual-antigen targeting CAR T therapies (BCMA/CD38, BCMA/GPRC5D, BCMA/CD19) may improve response rates and prevent antigen escape,[30-32] addressing the clonal heterogeneity observed in spatial transcriptomics of EMD biopsies.[33] Furthermore, armored CAR T cells engineered to express cytokines such as IL-15 or IL-18, or those incorporating switch receptors, may reprogram the immunosuppressive tumor microenvironment, augment endogenous immune responses, and enhance anti-tumor efficacy while maintaining safety.[34-37]

Despite the strengths of our analysis, several limitations should be acknowledged. As a single-center retrospective study, our findings require validation in larger, multi-institutional cohorts. Additionally, the low incidence of high-grade and atypical immune effector cell-associated toxicities limited our ability to construct detailed regression models, restricting comparisons between risk groups. Given the retrospective nature of our analysis, we did not have access to CAR T pharmacokinetic data, such as quantitative polymerase chain reaction or flow cytometry for CAR detection, which could provide further mechanistic insights into toxicity risk. Furthermore, observational studies are inherently subject to potential confounding, and unmeasured variables may have influenced the associations observed. Differences in bridging regimens between EMD and non-EMD patients may have contributed to post-infusion cytopenias or toxicity, but the heterogeneity and small numbers within individual treatment subgroups limited our ability to assess their independent impact. We may also have been underpowered to detect subtle differences in CRS rates; while not statistically significant, a slightly higher incidence was observed in the EMD group. Lastly, due to the low number of patients receiving targeted EMD treatments, such as radiation, we were unable to assess their impact on toxicity outcomes.

While our analysis focuses on toxicity, the poor outcomes observed in patients with EMD likely also reflect the aggressive disease biology characteristic of this subgroup. EMD is associated with high-risk features such as adverse cytogenetics, clonal heterogeneity, elevated LDH, cytopenias, and high-risk gene expression profiles.[2,33,38,39] These factors may contribute to increased treatment vulnerability alongside CAR T-related complications.

In conclusion, EMD is associated with a substantial toxicity burden in patients with MM undergoing CAR T therapy, particularly severe ICANS and hematologic toxicity, prolonged neutropenia, and increased non-relapse mortality. These findings emphasize the need for enhanced supportive care, risk-adapted patient selection, and further investigation into the inflammatory and coagulopathic pathways driving toxicity in EMD. Given the high risk of complications in this population, future research should focus on integrating targeted interventions to optimize both safety and efficacy in CAR T-treated patients with EMD.

Disclosures

AJP reports receiving consultancy fees or honoraria from Capvision and Karyopharm Therapeutics. AVH has received research funding from Juno Therapeutics and Nektar Therapeutics, and honoraria from Bristol Myers Squibb. MS has served as a consultant for AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeiGene, Bristol Myers Squibb, MorphoSys/Incyte, Kite Pharma, Eli Lilly, Fate Therapeutics, Nurix, and Merck; holds stock options in Koi Biotherapeutics. MS has received research funding from Mustang Bio, Genentech, AbbVie, BeiGene, AstraZeneca, Genmab, MorphoSys/Incyte, and Vincerx. LF reports receiving research funding from Abbvie, Bristol Myers Squibb, Merck, and Roche/Genentech; has served on scientific advisory boards for Abbvie, Actym, AstraZeneca, BioAtla, Bristol Myers Squibb, Daiichi Sankyo, Dendreon, ImmunoGenesis, Innovent, Merck, Nutcracker, RAPT, Senti, Sutro, and Roche/Genentech; and holds ownership interests in Actym, BioAtla, ImmunoGenesis, Nutcracker, RAPT, Senti, and Therapaint. JG reports receiving honoraria as an ad hoc consultant for Bristol Myers Squibb, Sobi, Legend Biotech, Janssen, Kite Pharma, and MorphoSys; has received research funding from Sobi, Juno Therapeutics (a BMS company), Celgene (a BMS company), Angiocrine Bioscience, Faron Pharmaceuticals, CARGO Therapeutics, and CytoAgents; and has served on an independent data review committee for Century Therapeutics. All other authors have no conflicts of interest to disclose.

Contributions

AJP interpreted data and drafted the manuscript. JG conceived of the study and provided critical oversight. ECL com-

puted early ICAHT scores and interpreted data. All authors reviewed and edited the manuscript.

Funding

AJP received support from the Kuni Foundation (Imagination Grant). JJH received support from the National Cancer Institute (5T32CA009515-39). ECL received support from the National Heart, Lung, and Blood Institute (T32 HL007093). JG received support from Swim Across America and the National Cancer Institute (P30 CA015704-45).

Data-sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Bladé J, Beksac M, Caers J, et al. Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer J. 2022;12(3):45.
2. Weinstock M, Ghobrial IM. Extramedullary multiple myeloma. Leuk Lymphoma. 2013;54(6):1135-1141.
3. Munshi N, Martin T, Usmani SZ, et al. S202: cartitude-1 final results: phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma. Hemasphere. 2023;7(Suppl):e612468.
4. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med. 2023;389(4):335-347.
5. Munshi NC, Anderson Jr LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.
6. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med. 2023;388(11):1002-1014.
7. Hansen DK, Sidana S, Peres LC, et al. Idecabtagene vicleucel for relapsed/refractory multiple myeloma: real-world experience from the myeloma CAR T consortium. J Clin Oncol. 2023;41(11):2087-2097.
8. Dima D, Abdallah A-O, Davis JA, et al. Impact of extraosseous extramedullary disease on outcomes of patients with relapsed-refractory multiple myeloma receiving standard-of-care chimeric antigen receptor T-cell therapy. Blood Cancer J. 2024;14(1):90.
9. Qi Y, Qiao J, Li Z, Xu K. Efficacy and safety of BCMA-specific CAR T cell-based therapy in relapsed/refractory multiple myeloma patients with extramedullary disease. Blood. 2023;142(Supplement 1):4844.
10. Li W, Liu M, Yuan T, Yan L, Cui R, Deng Q. Efficacy and follow‐up of humanized anti‐BCMA CAR‐T cell therapy in relapsed/refractory multiple myeloma patients with extramedullary‐extraosseous, extramedullary‐bone related, and without extramedullary disease. Hematol Oncol. 2022;40(2):223-232.
11. Que Y, Xu M, Xu Y, et al. Anti-BCMA CAR-T cell therapy in relapsed/refractory multiple myeloma patients with extramedullary disease: a single center analysis of two clinical trials. Front Immunol. 2021;12:755866.
12. Pan D, Mouhieddine TH, Fu W, et al. Outcomes after CAR T cells in multiple myeloma patients with extramedullary and paramedullary disease. Blood. 2023;142(Suppl 1):1006.
13. Hansen DK, Peres LC, Dima D, et al. Comparison of standard-of-care idecabtagene vicleucel and ciltacabtagene autoleucel in relapsed/refractory multiple myeloma. J Clin Oncol. 2025;43(13):1597-1609.
14. Zanwar S, Sidana S, Shune L, et al. Impact of extramedullary multiple myeloma on outcomes with idecabtagene vicleucel. J Hematol Oncol. 2024;17(1):42.
15. Chohan KL, Siegler EL, Kenderian SS. CAR-T cell therapy: the efficacy and toxicity balance. Curr Hematol Malig Rep. 2023;18(2):9-18.
16. Davis JA, McGann M, Marini J, Hashmi H. How to manage prolonged immune effector cell-associated hematotoxicity (ICAHT) related to BCMA-directed myeloma therapy. Expert Rev Anticancer Ther. 2024;24(6):335-338.
17. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
18. Rajkumar SV, Richardson P, San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood. 2015;126(7):921-922.
19. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
20. Liang EC, Rejeski K, Fei T, et al. Development and validation of an automated computational approach to grade immune effector cell-associated hematotoxicity. Bone Marrow Transplant. 2024;59(7):910-917.
21. Rejeski K, Hansen DK, Bansal R, et al. The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma. J Hematol Oncol. 2023;16(1):88.
22. R Core Team. R: a language and environment for statistical computing. Version 4.4.3 (2025-02-28). Vienna, Austria: R Foundation for Statistical Computing; 2025. https://www.R-project.org/
23. Juluri KR, Wu QV, Voutsinas J, et al. Severe cytokine release syndrome is associated with hematologic toxicity following CD19 CAR T-cell therapy. Blood Adv. 2022;6(7):2055-2068.
24. Sterner RC, Sterner RM. Immune effector cell associated neurotoxicity syndrome in chimeric antigen receptor-T cell therapy. Front Immunol. 2022;13:879608.
25. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2022;22(2):85-96.
26. Khatib H, Parizat A, Halloun J, et al. Reduction in platelet counts may predict the development of immune effector cell associated neurotoxicity syndrome in patients receiving CD19 CAR-T cell therapy for relapsed/refractory large B cell lymphoma. Blood. 2024;144(Suppl 1):1748.
27. Belbachir S, Tudesq JJ, Lamure S, et al. Coagulopathy following chimeric antigen receptor T cell therapy in R/R adult B cell malignancies: a single center experience. Blood. 2021;138(Suppl 1):4839.

28. Johnsrud A, Craig J, Baird J, et al. Incidence and risk factors associated with bleeding and thrombosis following chimeric antigen receptor T-cell therapy. Blood Adv. 2021;5(21):4465-4475.
29. Manjunath SH, Cohen AD, Lacey SF, et al. The safety of bridging radiation with anti-BCMA CAR T-cell therapy for multiple myeloma. Clin Cancer Res. 2021;27(23):6580-6590.
30. Mei H, Li C, Jiang H, et al. A bispecific CAR-T cell therapy targeting BCMA and CD38 in relapsed or refractory multiple myeloma. J Hematol Oncol. 2021;14(1):161.
31. Zhou D, Sun Q, Xia J, et al. Anti-BCMA/GPRC5D bispecific CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, single-centre, phase 1 trial. Lancet Haematol. 2024;11(10):e751-e760.
32. Shi M, Wang J, Huang H, et al. Bispecific CAR T cell therapy targeting BCMA and CD19 in relapsed/refractory multiple myeloma: a phase I/II trial. Nat Commun. 2024;15(1):3371.
33. John M, Helal M, Duell J, et al. Spatial transcriptomics reveals profound subclonal heterogeneity and T-cell dysfunction in extramedullary myeloma. Blood. 2024;144(20):2121-2135.
34. Hawkins ER, D'Souza RR, Klampasta A. Armored CAR T-cells: the next chapter in T-cell cancer Immunotherapy. Biologics. 2021;15:95-105.
35. Shi H, Li A, Dai Z, et al. IL-15 armoring enhances the antitumor efficacy of claudin 18.2-targeting CAR-T cells in syngeneic mouse tumor models. Front Immunol. 2023;14:1165404.
36. Svoboda J, Landsburg DJ, Gerson J, et al. Enhanced CAR T-cell therapy for lymphoma after previous failure. N Engl J Med. 2025;392(18):1824-1835.
37. Ma Q, He X, Zhang B, et al. A PD-L1-targeting chimeric switch receptor enhances efficacy of CAR-T cell for pleural and peritoneal metastasis. Signal Transduct Target Ther. 2022;7(1):380.
38. Touzeau C, Moreau P. How I treat extramedullary myeloma. Blood. 2016;127(8):971-976.
39. Usmani SZ, Heuck C, Mitchell A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica. 2012;97(11):1761.