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

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Supplemental Materials

TABLES

Supplemental Table 1. Post-leukapheresis bridging regimens for patients with and without extramedullary disease (EMD).

Characteristic	Overall[1]	EMD N = 26[1]	No EMD N = 82[1]	p-value[2]
Bridging				
Carfilzomib	40 (37%)	5 (19%)	35 (43%)	0.031
Cyclophosphamide	33 (31%)	9 (35%)	24 (29%)	0.6
Anti-CD38	18 (17%)	2 (7.7%)	16 (20%)	0.2
Pomalidomide	18 (17%)	3 (12%)	15 (18%)	0.6
Doxorubicin	16 (15%)	7 (27%)	9 (11%)	0.060
Cisplatin	11 (10%)	6 (23%)	5 (6.1%)	0.022
Talquetamab	10 (9.3%)	2 (7.7%)	8 (9.8%)	>0.9
Elotuzumab	9 (8.3%)	2 (7.7%)	7 (8.5%)	>0.9
Lenalidomide	9 (8.3%)	4 (15%)	5 (6.1%)	0.2
Selinexor	9 (8.3%)	1 (3.8%)	8 (9.8%)	0.7
Venetoclax	8 (7.4%)	2 (7.7%)	6 (7.3%)	>0.9
Hyperfractionated cyclophosphamide	5 (4.6%)	3 (12%)	2 (2.4%)	0.089
Bendamustine	2 (1.9%)	1 (3.8%)	1 (1.2%)	0.4
Ixazomib	2 (1.9%)	0 (0%)	2 (2.4%)	>0.9

[1] n (%)

[2] Pearson's Chi-squared test; Fisher's exact test

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Supplemental Table 2. Univariate and multivariable models for the duration of severe neutropenia.

		Univariate			Multivariable		
Neutropenia	**N**	**Beta**	**95% CI[1]**	**p-value**	**Beta**	**95% CI[1]**	**p-value**
Model 1							
EMD	108	6.8	4.6, 9.0	<0.001	5.5	3.4, 7.6	<0.001
Age	108	0.24	-0.92, 1.4	0.7	0.17	-0.79, 1.1	0.7
Cilta-cel	108	-2.4	-4.7, -0.07	0.044	-1.1	-3.1, 0.89	0.3
HRCA	108	2.6	0.38, 4.8	0.022	1.6	-0.34, 3.5	0.11
BMPC	105	0.70	0.33, 1.1	<0.001	0.40	0.04, 0.75	0.031
Model 2							
EMD	108	6.8	4.6, 9.0	<0.001	4.4	2.3, 6.5	<0.001
Hgb pre-LD	108	-1.1	-1.7, -0.55	<0.001	-0.30	-0.81, 0.21	0.2
Plt pre-LD	108	-0.02	-0.03, -0.01	0.003	0.00	-0.01, 0.01	0.7
ANC pre-LD	108	-0.11	-0.78, 0.56	0.7	-0.52	-1.1, 0.10	0.10
Ferritin pre-LD	107	4.5	3.1, 5.9	<0.001	2.7	0.88, 4.6	0.004
CRP pre-LD	107	0.04	0.02, 0.07	<0.001	-0.02	-0.04, 0.01	0.2
BMPC	105	0.70	0.33, 1.1	<0.001	0.49	0.14, 0.83	0.006

[1] CI = Confidence Interval

Abbreviations: EMD = extramedullary disease; HRCA = high risk cytogenetic abnormality; BMPC = bone marrow plasma cell; pre-LD = pre-lymphodepletion; Hgb = hemoglobin; Plt = platelet; ANC = absolute neutrophil count; CRP = C-reactive protein; CI = confidence interval. The predictors were scaled as follows: age to 10 years, BMPC to 10%, Hgb to g/dL, Plt to 10 × K/uL, ANC to 10 × K/μL, ferritin to 1000 × ng/mL, and CRP to 10 × mg/L. Note: Day 0 laboratory values were used when pre-LD labs were unavailable.

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Supplemental Table 3. Univariate and multivariable regression models assessing the impact of extramedullary disease and high risk (HT^{high}) CAR-HEMATOTOX scores on clinical outcomes.

		Univariate			Multivariable		
	N	Estimate[1]	95% CI	p-value	Estimate[1]	95% CI	p-value
Duration of Neutropenia							
EMD	108	6.8	4.6, 9.0	<0.001	7.0	4.5, 9.5	<0.001
HT high	86	4.7	2.3, 7.1	<0.001	4.1	2.0, 6.1	<0.001
eICAHT Grade 2+							
EMD	108	12.7	4.25, 42.0	<0.001	12.0	3.17, 52.8	<0.001
HT high	86	6.71	1.67, 45.1	0.017	7.34	1.59, 55.1	0.022
ICANS Grade 2+							
EMD	108	8.67	2.46, 35.5	0.001	9.37	2.26, 45.2	0.003
HT high	86	10.8	1.93, 204	0.027	11.1	1.79, 218	0.031
≥Complete Response							
EMD	108	0.21	0.06, 0.56	0.004	0.29	0.08, 0.91	0.046
HT high	86	0.48	0.20, 1.14	0.10	0.51	0.21, 1.24	0.14
Overall Survival							
EMD	108	7.31	2.86, 18.7	<0.001	7.34	2.37, 22.7	<0.001
HT high	86	1.88	0.58, 6.12	0.3	1.91	0.58, 6.29	0.3
Progression-Free Survival							
EMD	108	2.72	1.49, 4.97	0.001	2.29	1.14, 4.60	0.020
HT high	86	2.39	1.15, 4.97	0.019	2.30	1.11, 4.79	0.026
Duration of Response							
EMD	90	2.10	1.07, 4.13	0.032	1.90	0.91, 3.96	0.087
HT high	72	1.92	0.89, 4.15	0.10	1.98	0.91, 4.29	0.083
Non-Relapse Mortality							
EMD	108	10.5	2.04, 54.5	0.005	8.08	1.47, 44.6	0.016
HT high	86	1.88	0.34, 10.3	0.5	1.59	0.29, 8.72	0.6

[1] Estimate = Beta, odds ratio, or hazard ratio

Abbreviations: EMD = extramedullary disease; HT high = CAR-HEMATOTOX high risk; ICANS = immune effector cell-associated neurotoxicity syndrome; eICAHT = early immune effector cell-associated hematotoxicity; CI = confidence interval.

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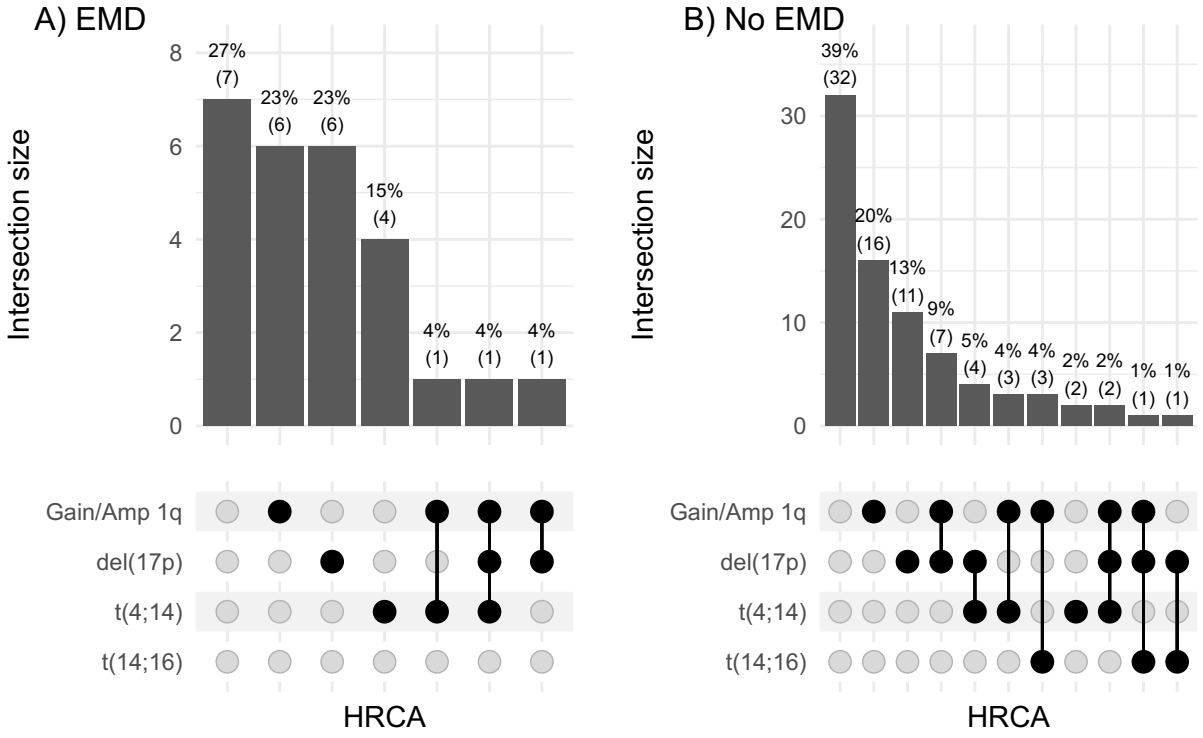
FIGURES



Supplemental Figure 1. UpSet plots illustrating the frequency and overlap of high-risk cytogenetic abnormalities (HRCAs) among patients A) with extramedullary disease (EMD) and B) without EMD. Each vertical bar represents the number of patients with the indicated combination of HRCAs; filled circles in the matrix below indicate the specific abnormalities present in each combination. Numerical annotations above each bar indicate the percentage of patients within the respective group, followed by the absolute count in parentheses.

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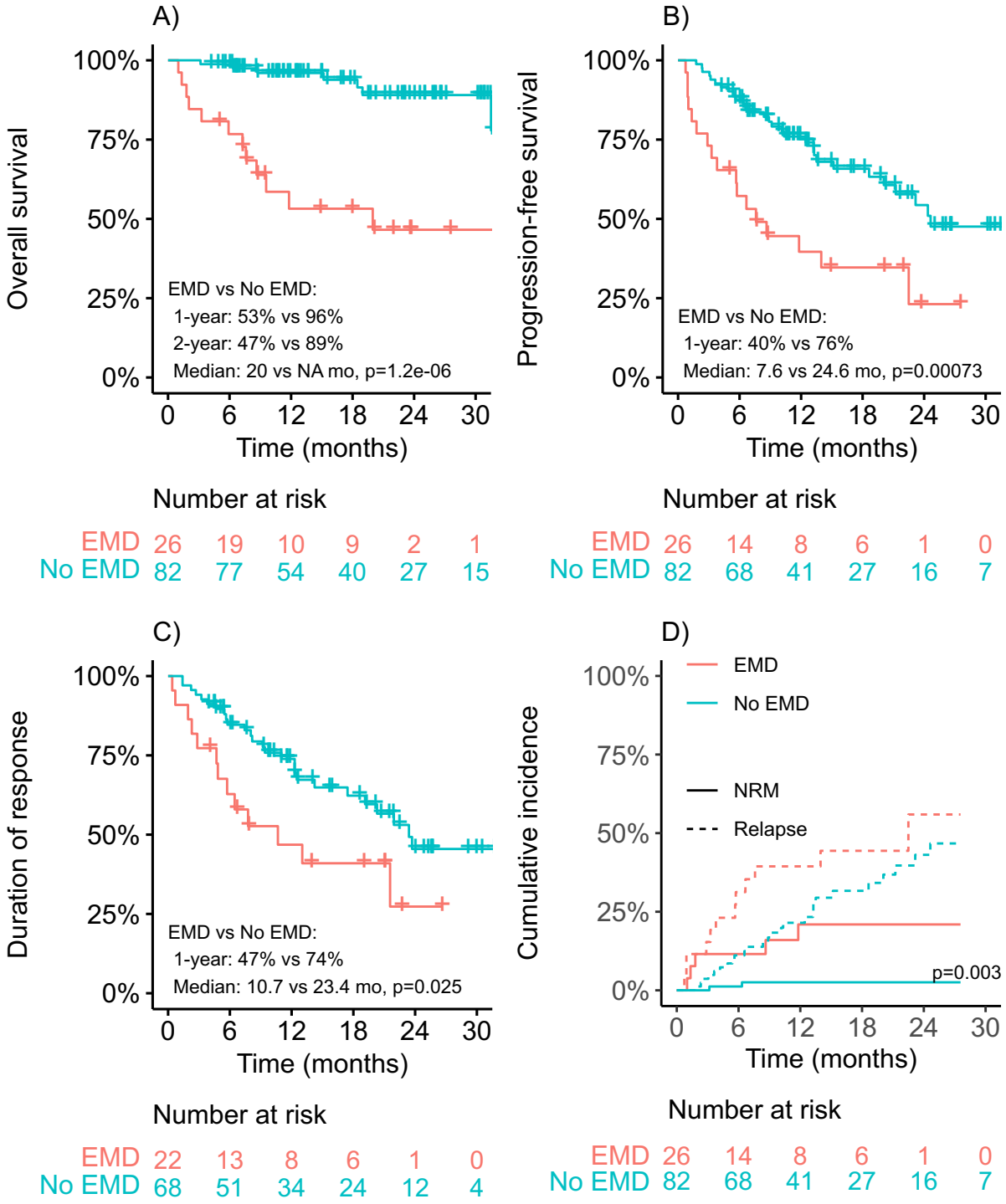

Supplemental Figure 2. Kaplan-Meier (KM) plots illustrating A) overall survival, B) progression-free survival, and C) duration of response, along with D) cumulative incidence (CI) plots for relapse and non-relapse mortality (NRM), stratified by EMD status. P-values for the KM plots were calculated using the log-rank test, while the p-value for NRM in the CI plot was derived from Gray's test.

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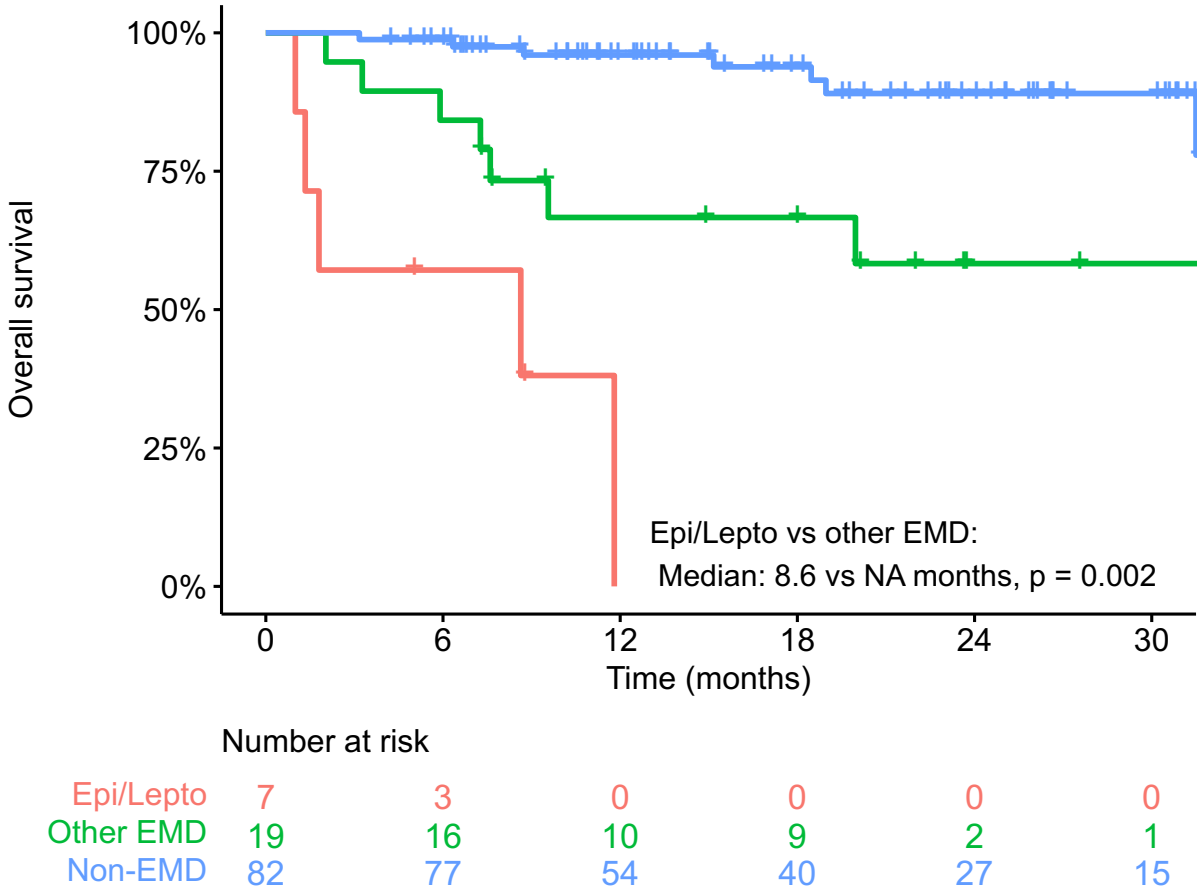

Supplemental Figure 3. Patients with epidural or leptomeningeal (Epi/Lepto) involvement demonstrate significantly worse overall survival compared to other patients with extramedullary disease (EMD). Patients without EMD are included as a reference group. P values were derived from the log-rank test.

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METHODS

Definitions

As part of their pre-CAR-T evaluation, all patients underwent positron emission tomography-computed tomography (PET-CT) or PET-magnetic resonance imaging (PET-MR) prior to lymphodepletion chemotherapy. Additionally, select patients underwent magnetic resonance imaging (MRI) of the brain and/or spine to assess for central nervous system involvement.

PET-CT and PET-MR studies were performed at a median of 13 days (range, 7 to 64) prior to CAR-T infusion, while brain and spine MRIs were conducted at a median of 45 days (range, 2 to 86) prior to infusion.

Time to cytokine release syndrome (CRS)/immune effector cell-associated neurotoxicity syndrome (ICANS) resolution was defined as the interval from CAR-T infusion to the resolution of CRS/ICANS symptoms (first day achieving grade 0 and stable for at least three consecutive days) as previously described.(1)

CAR-HEMATOTOX scores were calculated using pre-lymphodepletion lab values.(2) One point was assigned for ANC ≤ 1.2 x 10^3/μL, hemoglobin ≤ 9.0 g/dl, platelet count 76-175 × 10^3/μL, CRP ≥ 3.0 mg/dL, and ferritin 650-2,000 ng/mL. Two points were assigned for a platelet count ≤ 75 × 10^3/μL and ferritin ≥ 2,000 ng/mL. A total score of 2 or more was classified as high risk (HT^{high}), while a score of 0-1 was considered low risk (HT^{low}).

Lymphodepletion

Most patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide in accordance with the product-specific U.S. Food and Drug Administration package inserts.(3, 4) Three patients without extramedullary disease received lymphodepletion with bendamustine due to renal insufficiency.

Supportive care

Packed red blood cells and platelets were transfused for hematocrit <26% and platelet count <11 × 10^3/μL, respectively, or when clinically indicated. Broad-spectrum intravenous antibiotics were initiated for neutropenic fever per institutional guidelines. In the absence of an allergy or intolerance, empiric treatment with cefepime was provided for NF. Vancomycin was added in the event of skin and soft tissue infection, clinically apparent catheter-related infection, positive blood culture with gram-positive bacteria before susceptibility results or a history of methicillin-resistant *Staphylococcus aureus*.

SUPPLEMENTAL REFERENCES

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