ARTICLE - Plasma Cell Disorders

Comprehensive evaluation of disease characteristics and outcomes of patients with extramedullary multiple myeloma in the modern era

Megan Broughton,[1] Subodh Bhatta,[1] Doshi Sonali,[2] Naresh Bumma,[1] Abdullah M. Khan,[1] Srinivas Devarakonda,[1] Elvira Umyarova,[1] Don Benson,[1] Ashley Rosko[1] and Francesca Cottini[1]

[1]Department of Internal Medicine, Division of Hematology, College of Medicine, The Ohio State University Wexner Medical Center, Columbus and [2]University of Toledo, College of Medicine, Toledo, OH, USA

Correspondence: F. Cottini
Francesca.cottini@osumc.edu

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Title: Comprehensive evaluation of disease characteristics and outcomes of patients with extramedullary multiple myeloma in the modern era

Running title: Extramedullary myeloma remains a clinical challenge.

Authors:

Megan Broughton[1], Subodh Bhatta[1], Doshi Sonali[2], Naresh Bumma[1], Abdullah M. Khan[1], Srinivas Devarakonda[1], Elvira Umyarova[1], Don Benson[1], Ashley Rosko[1], and Francesca Cottini[1].

[1] Department of Internal Medicine, Division of Hematology, The Ohio State University, Columbus, OH, USA.

[2] University of Toledo, College of Medicine, Toledo, OH, USA.

Correspondence:
Francesca Cottini, MD (lead contact)
Assistant Professor of Medicine
Division of Hematology
The Ohio State University, College of Medicine
385G Wiseman Hall | 400 W 12th Ave |
Columbus OH 43210-1240 USA
Email: Francesca.cottini@osumc.edu
ORCID ID: 0000-0001-8481-2281

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Supplementary Methods:

Definitions of plasma cell leukemia, extramedullary multiple myeloma, and solitary plasmacytoma.

Plasma cell leukemia (PCL) was characterized by the presence of more than 5% of plasma cells (PCs) in the peripheral total white blood cell count or an absolute PC count of ≥2 × 10^9/L, following the new consensus definition by the International Myeloma Working Group. Primary PCL (pPCL) was defined when the leukemic phase presented at diagnosis, while secondary PCL (sPCL) occurred when leukemic progression was identified in the context of preexisting MM. Extramedullary multiple myeloma (EMM) was defined as the growth of MM cells outside the bone marrow (BM), either in adjacent bones (osseous EMM) or in other anatomical sites (soft tissue EMM). Solitary plasmacytoma (SP) was defined as the presence of a homogenous infiltrate of monoclonal CD138 positive PCs, with <10% of PCs in the BM and no MM-defining events.

Immunophenotype by flow cytometry.

The assessment of clone size percentages of different markers is routinely performed for clinical purposes on each BM aspirate from MM patients in the Flow Cytometry Laboratory at The Ohio State University Wexner Medical Center, which is regulated under Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity testing. Specifically, flow cytometric analysis was performed using a ten-color technique with a gating strategy based on CD45 staining and light-side scatter characteristics. PCs were positive for CD138 expression, and their clonality was assessed using cytoplasmic kappa and lambda light chain staining. To define the immunophenotype of MM cells, the following markers were evaluated: CD38, CD56, CD117, CD28, CD19, and CD20.

Statistical analysis.

We performed three separate analyses to compare disease characteristics associated with outcomes in: **a)** patients with pPCL or sPCL; **b)** patients with osseous EMM or soft tissue EMM (excluding PCL) at diagnosis (*de novo*), at first relapse, or after at least (≥) 2 lines of therapy (secondary EMM); **c)** patients with SP who did or did not progress to overt MM (**Figure 1**).

a) Time to transformation was from the day of MM diagnosis to the day of development of sPCL. Survival time was calculated from the date of diagnosis (pPCL or MM) or transformation (MM to sPCL) to the last follow-up or death. Cox regression model was used to identify prognostic factors for OS.

b) Survival time was calculated from the date of MM diagnosis and/or EMM diagnosis to the last follow-up or death.

c) Time to progression was calculated from the date of the initial diagnosis of SP to the date of progression to MM. Survival time was calculated from the date of diagnosis or progression to MM to last follow-up, or death. Competing risk analysis was performed to identify factors associated with risk of progression, treating death as a competing event, and the groups were compared using the Gray K-sample test. The following variables were included: age, gender, race, site of SP, presence of a detectable serum monoclonal protein, abnormal FLC ratio, clonality and percentage of BM PCs, hemoglobin, creatinine, calcium, albumin, LDH, and B2M levels at SP diagnosis, type of treatment, and dose of radiation.

Supplementary Table S1. Immunophenotype of primary PCL (pPCL) or secondary PCL (sPCL) cells in the peripheral blood.

	All	pPCL	sPCL	p-value
circulating PCs, %; median (range)				
	31 (10–87)	26.4 (10–81)	38 (11–87)	1.00
CD38 clone size, %; median (range)		n = 16	n = 13	
	98 (0–100)	98.0 (56–100)	74.0 (0–100)	0.20
CD56 clone size, %; median (range)				
	29 (0–99.4)	24.7 (0–93.2)	46.3 (0–99.4)	0.25
CD117 clone size, %; median (range)		n = 14	n = 12	
	0 (0–92.6)	0 (0–16)	0 (0–92.6)	0.86
CD28 clone size, %; median (range)				
	8 (0–99.6)	27.0 (0–95)	9.3 (0.2–99.6)	0.25
CD19 clone size, %; median (range)				
	0.6 (0.1–11.3)	0.6 (0.2–1.6)	0.7 (0.1–11.3)	0.66
CD20 clone size, %; median (range)				
	0.4 (0–98.2)	0.5 (0–98.2)	0.3 (0–42)	0.15

***Abbreviations*:** PCL, plasma cell leukemia; PC, plasma cells.

Supplementary Table S2. Univariable (UVA) and multivariable (MVA) models for overall survival in patients with primary PCL.

Variable	UVA		MVA	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (0.99–1.07)	0.19		
Sex				
Male	1			
Female	0.82 (0.31–2.17)	0.69		
Race				
Non-Hispanic White	1			
Non-Hispanic Black	1.12 (0.39–3.19)	0.84		
Cytogenetic risk group				
Standard	1			
High	1.22 (0.46–3.27)	0.69		
1q+				
No	1			
Yes	1.79 (0.66–4.88)	0.26		
13q deletion				
No	1			
Yes	1.60 (0.58–4.43)	0.36		
17p deletion				
No	1		1	
Yes	4.06 (1.26–13.1)	**0.02**	3.82 (1.22–11.98)	**0.022**
Translocation (11;14)				
No	1			
Yes	1.13 (0.36–3.54)	0.83		
Translocation (4;14)				
No	1			
Yes	0.55 (0.12–2.45)	0.44		
LDH range	1.05 (0.98–1.13)	0.16		
B2M; median, range	1.1 (0.97–1.24)	0.14		
ISS stage at diagnosis				
1–2	1			
3	2.45 (0.81–7.47)	0.12		
% of circulating PCs	1.02 (0.99–1.04)	0.09	1.02 (0.99–1.05)	**0.087**

Abbreviations: HR, hazard ratio; CI, confidence interval; pPCL, primary plasma cell leukemia; LDH, lactate dehydrogenase; B2M, beta-2 microglobulin; ISS, international staging system; PC, plasma cells.

Supplementary Table S3. Univariable (UVA) and multivariable (MVA) models for overall survival in patients with secondary PCL.

Variable	UVA		MVA	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (0.98–1.05)	0.51		
Gender				
Male	1			
Female	1.58 (0.61–4.14)	0.35		
Race				
Non-Hispanic White	1			
Non-Hispanic Black	1.23 (0.16–9.64)	0.85		
LDH range	1.11 (1.02–1.21)	**0.01**	1.17 (0.99–1.38)	**0.059**
B2M; median, range	1.05 (0.96–1.17)	0.29		
ISS stage at diagnosis or transformation				
1–2	1			
3	0.95 (0.30–3.06)	0.94		
% of circulating PCs	0.99 (0.97–1.01)	0.26		
% of CD38-positive PCs	1 (0.99–1.02)	0.61		
% of CD56-positive PCs	0.98 (0.97–1)	**0.07**	0.98 (0.99–1.002)	**0.079**

Abbreviations: HR, hazard ratio; CI, confidence interval; pPCL, secondary plasma cell leukemia; LDH, lactate dehydrogenase; B2M, beta-2 microglobulin; ISS, international staging system; PC, plasma cells.

Supplementary Table S4. Estimate of progression-free survival based on the site of extramedullary multiple myeloma (EMM).

		Site of EMM		
	Total	**Osseous**	**Soft tissue**	
	n = 118	n = 84	n = 34	**p-value**
Number of events	96	63	33	
Median PFS (95% CI) in years	2.49 (2.15–3.46)	2.47 (2.15–4.07)	2.89 (1.76–4.37)	**0.052**
1-year estimate, % (95% CI)	86 (80–93)	87 (80–94)	85 (74–98)	
3-year estimate, % (95% CI)	48 (40–58)	47 (37–59)	50 (36–70)	
5-year estimate, % (95% CI)	28 (21–38)	30 (22–42)	23 (12–43)	
10-year estimate, % (95% CI)	15 (10–24)	22 (14–34)		

Abbreviations: EMM, extramedullary multiple myeloma; PFS, progression free survival; CI, Confidence interval.

Supplementary Table S5. Univariable (UVA) and multivariable models (MVA) for overall survival in patients with EMM.

Variable	UVA		MVA	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.04 (1.01–1.08)	**0.004**	1.06 (1.02–1.09)	**0.002**
Sex				
Male	1			
Female	1.27 (0.78–2.08)	0.335		
Race				
Non-Hispanic White	1			
Non-Hispanic Black	0.56 (0.28–1.1)	**0.091**		
Cytogenetic risk group				
Standard	1			
High	1.82 (1.02–3.23)	**0.042**		
1q+				
No	1			
Yes	1.6 (0.98–2.62)	**0.058**		
13q deletion				
No	1			
Yes	1.66 (1.03–2.69)	**0.039**		
17p deletion				
No	1			
Yes	1.53 (0.70–3.36)	0.286	0.65 (0.26–1.63)	0.360
Translocation (11;14)				
No	1			
Yes	1.54 (0.78–3.01)	0.212		
Translocation (4;14)				
No	1			
Yes	1.72 (0.74–4)	0.207		
R-ISS stage at diagnosis				
1	1			
2	2.51 (1.37–4.59)	**0.0029**	2.59 (1.37–4.89)	**0.003**
3	8.87 (3.56–22.1)	**<0.0001**	12.17 (4.33–34.17)	**<0.0001**
Timing of EMM				
De novo	1			
At first relapse	2.37 (1.25–4.49)	**0.009**	2.55 (1.22–5.30)	**0.013**
After ≥ 2 lines of therapy	1.69 (0.91–3.13)	**0.096**	1.29 (0.65–2.59)	0.470
Site of EMM				
Osseous	1			
Soft tissue	1.36 (0.84–2.22)	0.212		

Abbreviations: EMM, extramedullary multiple myeloma; R-ISS, revised international staging system.

Supplementary Table S6. Estimate of progression-free survival (PFS) from first line of therapy based on the timing of EMM.

		Timing of EMM Timing			
	Total	***De novo***	**At first relapse**	**≥ 2 lines of therapies**	
	n = 118	n = 89	n = 14	n = 15	**p-value**
Number of events	96	67	14	15	
Median PFS (95% CI) in years	2.49 (2.15–3.46)	3.36 (2.34–4.31)	1.98 (1.22–4.62)	1.71 (1.61–4.37)	**0.0025**
1-year estimate, % (95% CI)	86 (80–93)	85 (78–93)	86 (69–100)	93 (82–100)	
3-year estimate, % (95% CI)	48 (40–58)	53 (44, 65)	29 (12–65)	33 (16–68)	
5-year estimate, % (95% CI)	28 (21–38)	34 (25–46)	7 (1–47)	13 (4–48)	
10-year estimate, % (95% CI)	15 (10–24)	21 (12–32)			

Abbreviations*:* EMM, extramedullary multiple myeloma; R-ISS, revised international staging system.

Supplementary Table S7. Estimates of overall survival (OS) from MM diagnosis based on the timing of EMM.

		Timing of EMM from MM diagnosis			
	Total	***De novo***	**At first relapse**	**≥ 2 lines of therapies**	
	n = 118	n = 89	n = 14	n = 15	**p-value**
Number of events	72	47	12	13	
Median OS (95% CI) in years	6.39 (5.58–8.77)	7.52 (6.26–12.8)	4.62 (2.95–NR)	5.82 (3.66–NR)	**0.014**
1-year estimate, % (95% CI)	96 (92–99.5)	94 (90–99)	100	100	
3-year estimate, % (95% CI)	83 (76–90)	83 (75–91)	64 (44–95)	100	
5-year estimate, % (95% CI)	63 (55–73)	70 (60–80)	29 (12–65)	60 (40–91)	
10-year estimate, % (95% CI)	36 (28–48)	41 (30–54)	21 (8–58)	25 (10–62)	

Abbreviations*:* EMM, extramedullary multiple myeloma; OS, overall survival; NR, not reached; CI, Confidence interval.

Supplementary Table S8. Univariable (UVA) and multivariable (MVA) models for competing risk analysis in patients with solitary plasmacytomas (SP).

Variable	UVA		MVA	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (0.96–1.06)	0.82		
Sex				
Male	1			
Female	0.59 (0.22–1.59)	0.29		
Race				
Non-Hispanic White	1			
Non-Hispanic Black	1.63 (0.32–8.33)	0.56		
Site of SP				
Osseous	1			
Soft tissue	0.27 (0.06–1.11)	0.069	0.05 (0.01–0.22)	**< 0.001**
Serum monoclonal protein				
No	1			
Yes	2.44 (0.77–7.75)	0. 13		
Abnormal KLC ratio				
No	1			
Yes	0.68 (0.26–1.77)	0.43		
Monoclonal protein and/or abnormal KLC ratio				
No	1			
Either one	2.26 (0.72–7.05)	0.16		
Both	1.91 (0.44–8.23)	0.39		
BM PCs clonality				
No	1			
Yes	1.07 (0.46–2.48)	0.88		
Hemoglobin	0.89 (0.74–1.07)	0.22		
Creatinine	8.99 (1.24–65.1)	0.03		
Calcium	0.76 (0.38–1.53)	0.45		
Albumin	1.33 (0.57–3.14)	0.51		
LDH	1.57 (1.17–2.10)	**0.003**	2.81 (1.65–4.78)	**< 0.001**
B2M	1.13 (0.43–2.97)	0.81		
% of BM PCs at diagnosis	1.06 (0.82–1.37)	0.67		
Treatment (number, %)				
Local radiation only	1			
Others (radiation + resection or resection only)	0.80 (0.24–2.64)	0.72		
Radiation dose (Gy)	0.97 (0.91–1.03)	0.32		

***Abbreviations**:* KLC, kappa light chain; BM, bone marrow; PCs, plasma cells; LDH, lactate dehydrogenase; B2M, beta-2 microglobulin; Gy, Gray.

Supplementary Figure S1. Immunophenotype of plasma cells from patients with primary or secondary plasma cell leukemia (PCL).

A. CD38, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasma cells in the peripheral blood of patients with primary PCL (n = 16 for CD38 and n = 14 for the other markers) or secondary PCL (n = 13 for CD38 and n = 12 for the other markers).

B. CD38, CD56, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasma cells in the bone marrow of patients with primary PCL (n = 15) or secondary PCL (sPCL, n = 9).

C. CD38, CD56, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasma cells in the peripheral blood (n = 14) or bone marrow (n = 15) of patients with primary PCL.

D. CD38, CD56, and CD28 clone size of CD138-light-chain-restricted plasma cells in the peripheral blood (PB) or bone marrow (BM) of each individual patient with pPCL.

E. CD38, CD56, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasma cells in the peripheral blood (n = 12) or bone marrow (n = 9) of patients with secondary PCL.

Supplementary Figure S2. Outcomes of patients with plasma cell leukemia (PCL).

A. Percentage of responders (CR+VGPR+PR) and non-responders (MR+SD+PD) in patients with pPCL treated with VD-PACE or CyBorD and patients treated with VRD or KRD. CR stays for complete responses, VGPR for very good partial responses, PR for partial responses, MR for minimal responses, SD for stable disease, and PD for progressive disease. VD-PACE is a regimen based on bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide; CyBorD is based on cyclophosphamide, bortezomib, and dexamethasone; VRD includes bortezomib, lenalidomide, and dexamethasone; and KRD consists of carfilzomib, lenalidomide, and dexamethasone.

B. Percentage of responders (CR+VGPR+PR) and non-responders (MR+SD+PD) in patients with pPCL treated with VD-PACE or any other regimen. The abbreviations are the same as those of A.

C. Kaplan-Meier estimates of duration of response to first line of therapy in patients with sPCL from first day of therapy to relapse.

D. Kaplan-Meier estimates of overall survival (OS) among patients with primary PCL based on the presence or absence of 17p deletion (absent, n = 16; present, n = 7) from date of diagnosis to death or last follow-up. $p = 0.014$.

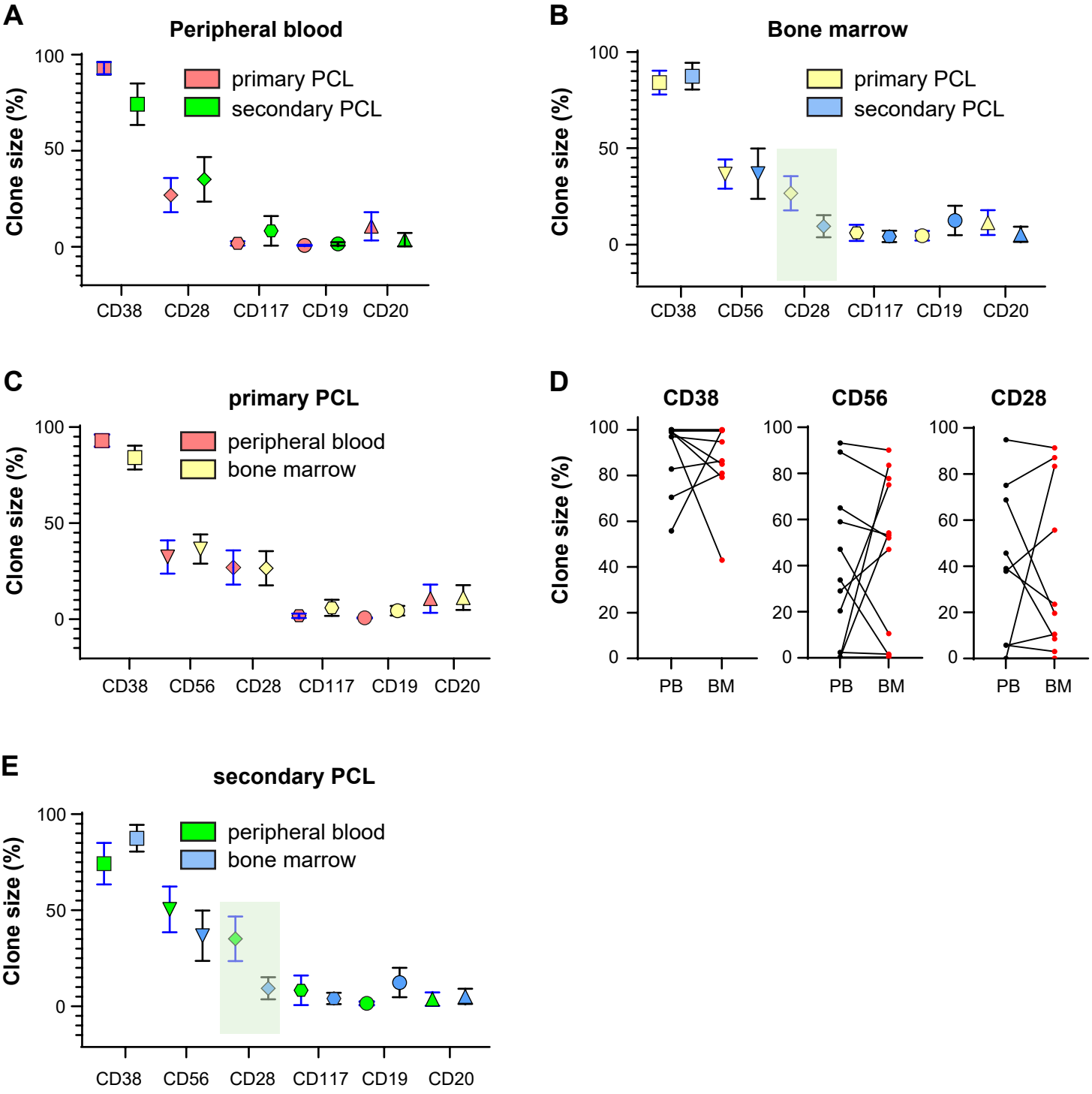
Supplementary Figure S3. Characteristics and outcomes of patients with extramedullary myeloma (EMM).

A. Sites of EMM disease in patients with osseous or soft tissue plasmacytomas. On the *x* axis, the number of patients is reported.

B. Kaplan-Meier estimates of overall survival (OS) among patients with osseous EMM (n = 84) or soft tissue EMM (n = 34) from date of MM diagnosis to death or last follow-up. $p = 0.21$.

C. Kaplan-Meier estimates of OS among patients with *de novo* EMM (n = 89), EMM at first relapse (n = 14), or EMM after ≥ 2 lines of therapy (n = 13) from date of MM diagnosis to death or last follow-up. $p = 0.014$.

Supplementary Figure S1



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B. CD38, CD56, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasma cells in the bone marrow of patients with primary PCL (n = 15) or secondary PCL (sPCL, n = 9).
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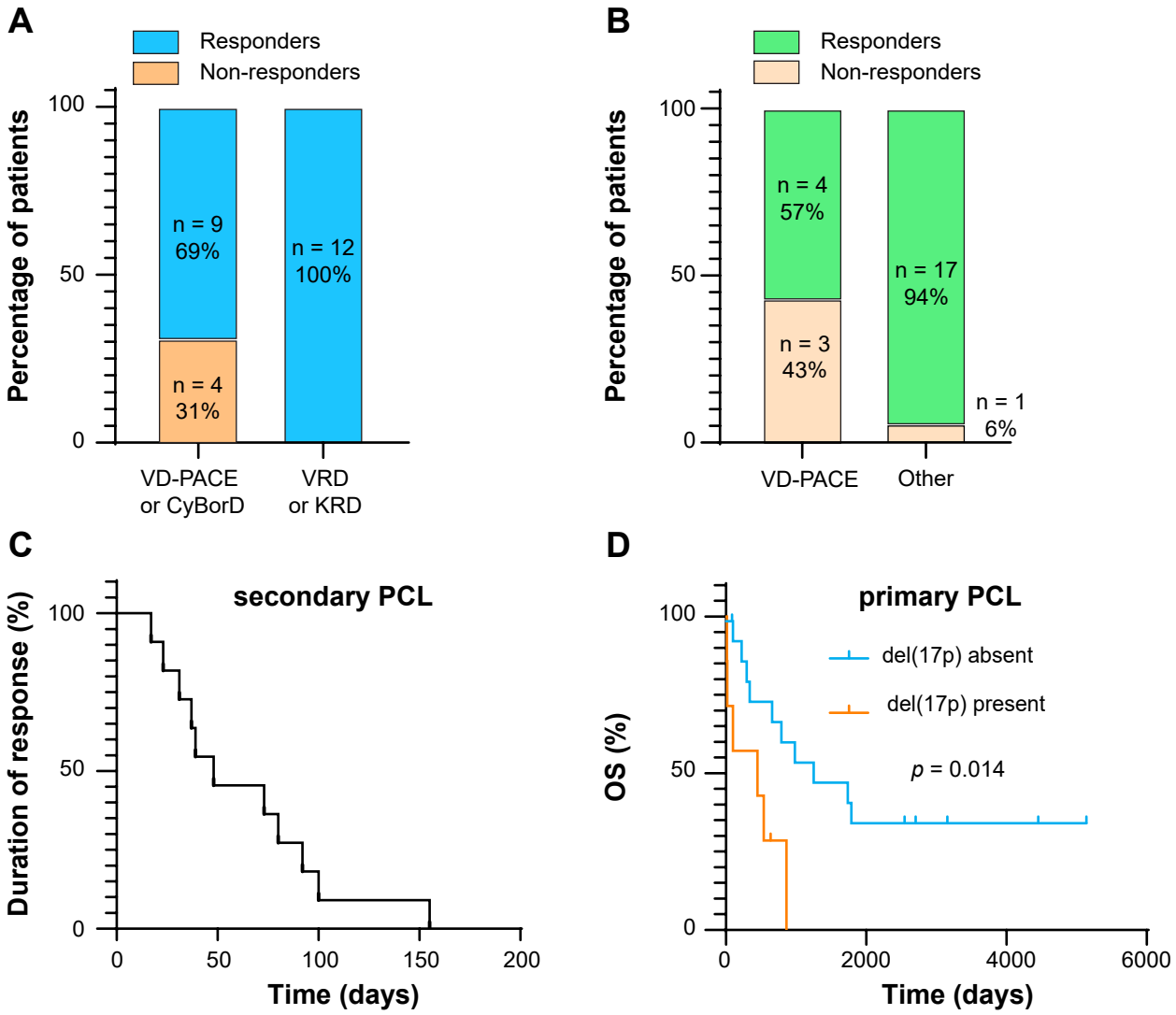
E. CD38, CD56, CD28, CD117, CD19, and CD20 clone size (percentage, %) of CD138-light-chain-restricted plasmacells in the peripheral blood (n = 12) or bone marrow (n = 9) of patients with secondary PCL.

Supplementary Figure S2



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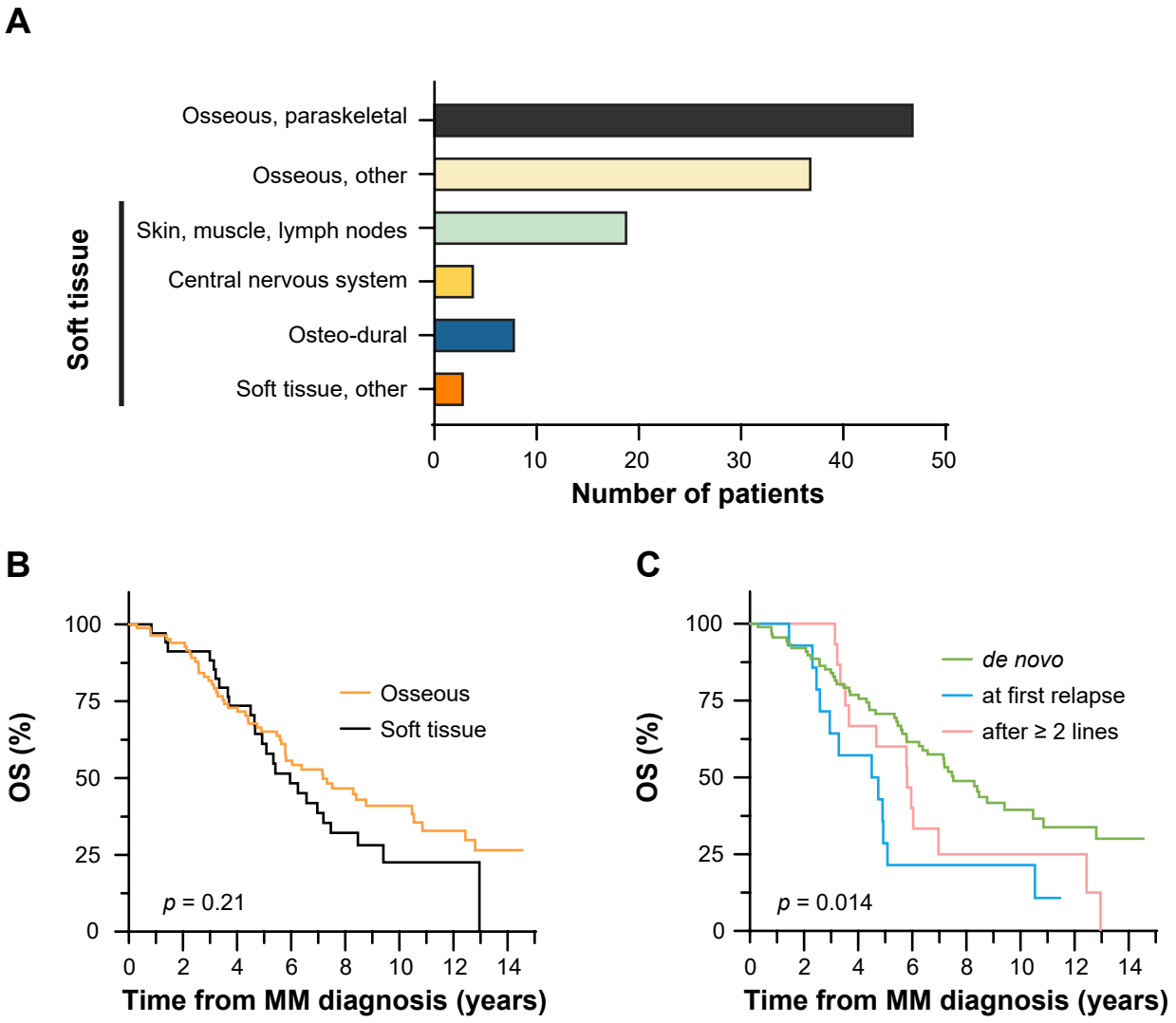
Supplementary Figure S3



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B. Kaplan-Meier estimates of overall survival (OS) among patients with osseous EMM (n = 84) or soft tissue EMM (n = 34) from date of MM diagnosis to death or last follow-up. $p = 0.21$.
C. Kaplan-Meier estimates of OS among patients with *de novo* EMM (n = 89), EMM at first relapse (n = 14), or after ≥ 2 lines of therapy (n = 13) from date of MM diagnosis to death or last follow-up. $p = 0.014$.