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Clinical and genomic features of macrofocal multiple myeloma: a distinct profile

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Running title: Macrofocal multiple myeloma

Key words: Macrofocal multiple myeloma; Clinical characteristics; Genomic profile

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Conflict of interest statement

All authors declare that they have no competing interests.

Data-sharing statement

Any relevant and original data are available from the corresponding authors upon request.

Author contributions

Jin Liu, Jianling Fan, Xinyi Zhou contributed to the study conduct, data analysis, and data interpretation. Xi Chen and Xiaoli Hu contributed to the data acquisition and WES data analysis. Haiyan He and Lina Jin contributed to the data analysis and data interpretation. Weijun Fu contributed to study design. Jian Hou and Juan Du contributed to study design and write the manuscript. Jin Liu and Xinyi Zhou contributed to the statistical analyses. All authors have approved the final version to be published and agree to be accountable for all aspects of the work.

To the editor,

Macrofocal multiple myeloma (MFMM) is a rare subtype of multiple myeloma (MM). Limited data are available in rare series to describe MFMM characterized by young age, low tumor burden and improved survival. [1-6] Owing to the scarcity of patients, the definition of MFMM has not been standardized internationally, and there is a gap in the molecular level of MFMM.

Two definitions are currently used: Definition 1 from the International Myeloma Working Group (IMWG): bone marrow plasma cells (BMPCs) <10%, with multiple lytic lesions/plasmacytomas; [7] Definition 2 from Greco-Israeli Cooperative Myeloma Working Group (CMWG): BMPC <20%, with multiple lytic lesions/plasmacytomas and absence of anemia, renal insufficiency, or hypercalcemia (CRA). [3] However, it is unclear which is more representative. Therefore, we screened 1,640 MM patients from Shanghai Changzheng Hospital (Jan. 2013-Sep. 2023), identifying 95 cases meeting Definition 1 and 130 satisfying Definition 2. Following approval by the Ethical Committee of Shanghai Changzheng Hospital, all subjects provided written informed consent consistent with the Helsinki Declaration. All patients received novel agents. Based on first-line induction regimens, patients were categorized into four groups: the immunomodulatory drug (IMiD)-based group, the proteasome inhibitor (PI)-based group, the combination of IMiD and PI-based group, and the daratumumab-based group. Patients receiving peripheral blood stem cell transplantation (PBSCT) was applied after 4-6 cycles of induction therapy. Those with standard-risk cytogenetics received IMiD-based maintenance therapy, while high-risk patients [defined by del(17p), t(4;14), or t(14;16)] received both a PI and an IMiD. Daratumumab was continued as maintenance therapy if used during induction.

Progression-free survival (PFS) and overall survival (OS) were comparable between the Definition 1 and Definition 2 cohorts (Figure S1A, B), although Definition 1 showed a trend toward better PFS (Definition 1 vs. Definition 2: 78.6 (95%

confidence interval [CI]: 50.5-106.6) months vs. 64.6 (95% CI: 49.9-79.3) months, *P* =0.239). No statistically significant differences were observed between the Definition 1 and Definition 2 cohorts regarding induction treatment regimens (*P* =0.95) and PBSCT rates (33.7%% vs 32.3%, *P* =0.828). Noteworthy in Definition 2, those with BMPCs <10% (N=83) demonstrated a longer PFS than those with BMPCs ≥10% but <20% (N=47) (78.6 [95% CI: 54.5-102.7] months vs 45.8 [95% CI: 21.7-69.9] months; *P* =0.001; Figure S1C), whereas OS remained similar (Figure S1D). No statistically significant differences were noted in induction treatment regimens (*P* =0.611) and PBSCT rates (33.7%% vs 29.8%, *P* =0.644) between the two groups. These results support Definition 1 as more prognostically distinct and clinically representative.

To assess the clinical and laboratory features and survival outcomes in MFMM, we next compared 95 MFMM (Definition 1) to 190 MM controls (1:2 ratio) during the same period. The baseline characteristics of MFMM were shown in Table 1. MFMM patients were younger (median: 58 years [range: 35-77] vs 63 years [range: 28-85]; *P* =0.009), with elevated platelet counts (median: 197 vs 171.5×10^9/L, *P* <0.001) and albumin levels (median: 37.9 vs 35 g/L, *P* <0.001), but lower monoclonal protein (M-protein) levels (median: 2.47 vs 19.2 g/L, *P* <0.001), involved serum free light chain (median: 94.84 vs 856.34 mg/L, *P* <0.001), urine light chain (median: 18.71 vs 326 mg/L, *P* <0.001), and β2-microglobulin levels (median: 2.17 vs 4.31 mg/L, *P* <0.001). Abnormal lactate dehydrogenase (13.7% vs 27.9%, *P* =0.006), the frequency of serum creatinine ≥177umol/L (1.1% vs 17.4%, *P* <0.001), hemoglobin ≤100g/L (11.6% vs 64.7%, *P* <0.001) and serum calcium >2.65mmol/L (1.1% vs 16.8%, *P* <0.001) was less prevalent in MFMM. Cytogenetically, information by Fluorescence in situ hybridization was available for 80/95 (84.2%) MFMM patients and 184/190 (96.8%) typical MM patients. Notably, frequency of 1q21 gains (37.9% vs 61.1%, *P* =0.006), t (11;14) (3.2% vs 14.2%, *P* =0.01), the high-risk cytogenetic abnormalities (44.2% vs 68.4%, *P* =0.004) and 'double hit' (3.2% vs 11.6%, *P* =0.033) was less common in MFMM patients.

Notably, 82.1% MFMM patients exhibited extramedullary multiple myeloma (EMD), far exceeding typical MM (37.4%, P <0.001). Additionally, more MFMM patients harbored multiple lytic lesion (≥5 sites) (83.2% vs 60%, *P* <0.001). MFMM patients also had fewer advanced-stage cases, which was evident in international staging system (ISS) III (2.1% vs 36.3%, *P* <0.001), revised ISS (R-ISS) III (2.1% vs 20.0%, *P* <0.001) and revision 2 of the ISS (R2-ISS) III/IV (21.1% vs 68.4%, *P* <0.001).

As presented in Table 1, no statistically significant difference was found in induction treatment regimens between the MFMM and control cohort. The median follow-up time of the cohort was 59.6 (95% CI: 50-69.1) months, and MFMM cohort demonstrated significantly superior outcomes compared to typical MM: median PFS of 78.6 (95% CI: 50.5-106.6) months vs 28.6 (22.1-35) months *(P* <0.001), and OS not reached (NR) (95% CI: NR-NR) vs 69.9 (45-94.8) months *(P* <0.001) (Figure S2I, J). Simultaneously, PBSCT was more common in MFMM (33.7% vs 22.1%, *P* =0.036) and a younger age at onset (Table 1). Despite this, subgroup analysis confirmed survival advantage in MFMM was independent of age and transplant status (Figure S2A-H).

Univariate Cox regression was performed to identify prognostic factors in MFMM patients. After adjusting for R-ISS stage, MFMM was identified as a significant predictor of both inferior PFS (HR: 2.03; 95% CI: 1-4.14; P=0.0479) (Figure 1A) and OS (HR: 3.57; 95% CI: 1.44-8.83; P=0.0088) (Figure 1B). Interestingly, MFMM patients with and without bone-independent EMD showed comparable PFS and OS (Figure 1A, B). Notably, those with bone-independent EMD had longer PFS (61.1 [95% CI: 0-129.7] months vs 6.7 [95% CI: 2.3-11.1] months; P =0.008) and OS (NR [95% CI: NR-NR] vs 27.2 [95% CI: 0-57.1] months; P =0.011) than patients with typical MM (Figure S2K, L), suggesting a distinct biological mechanism deserving further study. Although no significant differences were observed in induction treatment regimens (P =1) and PBSCT rates (27%% vs 20%, P =1) between the two

groups, MFMM patients still demonstrated superior survival outcomes, indicating treatment-independent survival advantages.

MFMM's hallmark—BMPCs <10%—raises the question: does this persist upon progression? In this study, 12.6% patients had a prior diagnosis of solitary bone plasmacytoma (SBP) before developing MFMM, and 36 out of 95 (37.9%) MFMM patients experienced disease progression. Specifically, 11 (30.6%) patients developed new lytic lesions, 23 (63.9%) exhibited an increased tumor burden (including elevated sFLC or M-protein levels), and 13 (36.1%) presented with new plasmacytomas. However, only 8 out of 36 progressed patients (22.2%) advanced to typical MM, which is defined by having BMPCs greater than 10%. This suggests that MFMM follows a 'relatively indolent' growth pattern and may evolve via a metastatic pattern rather than intramedullary expansion. [8]

To investigate molecular underpinnings, WES was perfomed on 9 BM samples from 9 MFMM patient (baseline characteristics in Table S1) meeting Definition 1 and 4 matched normal peripheral blood samples (Figure 2A). For comparison, 50 typical MM samples with corresponding peripheral blood samples were included. CD138 magnetic beads were used for BM MM cell sorting, and all normal peripheral blood samples was performed on cellular DNA. We identified three mutational signatures in nine patients with MFMM (Figure 2B), including SBSA and SBSB, which closely resembled COSMIC v2 Signature 1 (cosine similarities: 0.74 and 0.79). This signature is an age-related mutational signature, primarily caused by spontaneous deamination of 5-methylcytosine. [9] Additionally, we identified a novel signature, Signature 6-like, which strongly matched COSMIC v2 Signature 6 (cosine similarity: 0.82). This mutational signature is caused by defective DNA mismatch repair. Initially, we examined the distribution of the 67 previously reported MM driver genes [10-12] in MFMM (n =9) and found that the vast majority of these genes (62/67) were absent in MFMM, suggesting that this group may have a unique mutational gene profile (Figure S3A). And then, we proceeded to identify highly mutated genes in MFMM and

identified 8 gene mutations occurred at a frequency of 10% or greater (Figure 2C). To pinpoint the specific mutated genes within this group, we further investigated the mutation frequency of the aforementioned 8 genes in typical MM patients (n =50) and found that 3 genes were also present in this cohort. The other five genes—ANKRD26, CDHR1, PNMA3, CENPO, and UBR5—were exclusive to MFMM (Figure 2C, S3B), with specific mutations detailed in Table S1. ANKRD26 mutation has been linked to hematological malignancies, including MM. [13] CENPO is abnormally overexpressed in a variety of malignancies. [14] UBR5 mutations are associated with mantle cell lymphoma.[15]

The limitations of this study include its single-center, retrospective design, which may result in potential selection bias and incomplete data. In addition, the modest sample size may impact the generalizability of our findings.

In conclusion, our 12-year retrospective analysis not only corroborates the existing research but also deepens our understanding of MFMM as a distinct entity within MM, with clear diagnostic criteria, indolent clonal behavior (evidenced by post-relapse diagnostic persistence), and unique metastatic progression patterns. These findings support developing MFMM-specific management strategies and warrant further molecular investigation.

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Table 1 Baseline patient characteristics: MFMM vs Typical MM

Variable	MFMM (N=95)	Typical MM (N=190)	*P*-value
Age — median (range), y	58 (35-77)	63 (28-85)	**0.009**
Sex — no. (%)			
Male	64 (67.4)	108 (56.8)	0.087
Female	31 (32.6)	82 (43.2)	
M-protein type— no. (%)			
IgG	45 (47.4)	92 (48.4)	
IgA	16 (16.8)	40 (21.1)	
LC	20 (21.1)	34 (17.9)	0.138
NS	9 (9.5)	6 (3.2)	
Other	5 (5.3)	18 (9.5)	
M-protein (range), g/L	2.47 (0-46.67)	19.2 (0-74.6)	**<0.001**
Involved sFLC (range), mg/L	94.84 (8.79-2940)	856.34 (3.86-59490)	**<0.001**
ULC (range), mg/L	18.71 (2-3366)	326 (1.82-30200)	**<0.001**
WBC (range), $\times 10^9$/L	5.7 (1.8-12.9)	5.2 (1-20.2)	0.086
Platelet (range), $\times 10^9$/L	197 (111-485)	171.5 (23-568)	**<0.001**
Albumin (range), g/L	37.9 (21.4-54)	35 (17-52)	**<0.001**
β2-M (range), mg/L	2.17 (0.63-11.46)	4.31 (0.63-56.14)	**<0.001**
LDH >upper normal limit — no. (%)	13 (13.7)	53 (27.9)	**0.006**
Serum creatinine ≥177umol/L— no. (%)	1 (1.1)	33 (17.4)	**<0.001**
Hemoglobin ≤100g/L— no. (%)	11 (11.6)	123 (64.7)	**<0.001**
Serum calcium >2.65mmol/L— no. (%)	1 (1.1)	32 (16.8)	**<0.001**
Del (17p) in FISH— no. (%)			
Yes	2 (2.1)	11 (5.8)	
No	78 (82.1)	173 (91.1)	0.373
NA	15 (15.8)	6 (3.2)	
Del (13q) in FISH— no. (%)			
Yes	17 (17.9)	54 (28.4)	
No	63 (66.3)	130 (68.4)	0.173
NA	15 (15.8)	6 (3.2)	
1q21 gains in FISH— no. (%)			
Yes	36 (37.9)	116 (61.1)	
No	44 (46.3)	68 (35.8)	**0.006**
NA	15 (15.8)	6 (3.2)	
t (11;14) in FISH— no. (%)			
Yes	3 (3.2)	27 (14.2)	**0.01**
No	77 (81.1)	156 (82.1)	

NA	15 (15.8)	7 (3.7)	
t (4;14) in FISH— no. (%)			
Yes	8 (8.4)	25 (13.2)	
No	72 (75.8)	158 (83.2)	0.41
NA	15 (15.8)	7 (3.7)	
t (14;16) in FISH— no. (%)			
Yes	0 (0)	1 (0.5)	
No	80 (84.2)	182(95.8)	1
NA	15 (15.8)	7 (3.7)	
High-risk cytogenetic profile— no. (%)[a]			
Yes	42 (44.2)	130 (68.4)	
No	38 (40)	53 (27.9)	**0.004**
NA	15 (15.8)	7 (3.7)	
Double hit— no. (%)[b]			
Yes	3 (3.2)	22 (11.6)	
No	78 (82.1)	161 (84.7)	**0.033**
NA	14 (14.7)	7 (3.7)	
Triple hit— no. (%)[c]			
Yes	0 (0)	2 (1.1)	
No	81 (85.3)	181 (95.3)	1
NA	14 (14.7)	7 (3.7)	
≥5 lytic lesions — no. (%)			
Yes	79 (83.2)	114 (60)	**<0.001**
No	16 (16.8)	76 (40)	
EMD at diagnosis— no. (%)			
bone-associated EMD	67 (70.5)	66 (34.7)	**<0.001**
bone-independent EMD	11 (11.6)	5 (2.6)	**0.002**
DS stage— no. (%)			
I	2 (2.1)	5 (2.6)	
II	3 (3.2)	14 (7.4)	0.182
III	90 (94.7)	171 (90.0)	
ISS stage— no. (%)			
I	68 (71.6)	38 (20.0)	
II	25 (26.3)	79 (41.6)	**<0.001**
III	2 (2.1)	69 (36.3)	
NA	0 (0)	4 (2.1)	
R-ISS stage— no. (%)			
I	43 (45.3)	27 (14.2)	
II	41 (43.2)	119 (62.6)	**<0.001**
III	2 (2.1)	38 (20.0)	
NA	9 (9.5)	6 (3.2)	

R2-ISS stage— no. (%)			
I	27 (28.4)	10 (5.3)	
II	35 (36.8)	41 (21.6)	
III	19 (20.0)	99 (52.1)	**<0.001**
IV	1 (1.1)	31 (16.3)	
NA	13 (13.7)	9 (4.7)	
First line therapy			
IMiD based therapies	8 (8.4)	12 (6.3)	
PI based therapies	42 (44.2)	90 (47.4)	0.837
IMiD+PI based therapies	43 (45.3)	82 (43.2)	
Daratumumab based therapies	2 (2.1)	6 (3.2)	
PBSCT	32 (33.7)	42 (22.1)	**0.036**

Abbreviations: β2-M: β2-Microglobulin; DS: Durie-Salmon; EMD: extramedullary multiple myeloma; sFLC: serum free light chain; FISH: fluorescence in situ hybridization; Ig: immunoglobulin; ISS: international Staging System; IMiD: immunomodulatory drug; LDH: lactate dehydrogenase; M-protein: monoclonal protein; NS: non-secretory; PI: proteasome inhibitor; PBSCT: peripheral blood stem cell transplantation; R-ISS: revised international staging system; R2-ISS: revision 2 of the international staging system; ULC: urine free light chain; WBC: peripheral white blood cell.

[a]The cooccurrence of any of the following: t (4;14), t (14;16), 1q21 gains and del (17p).

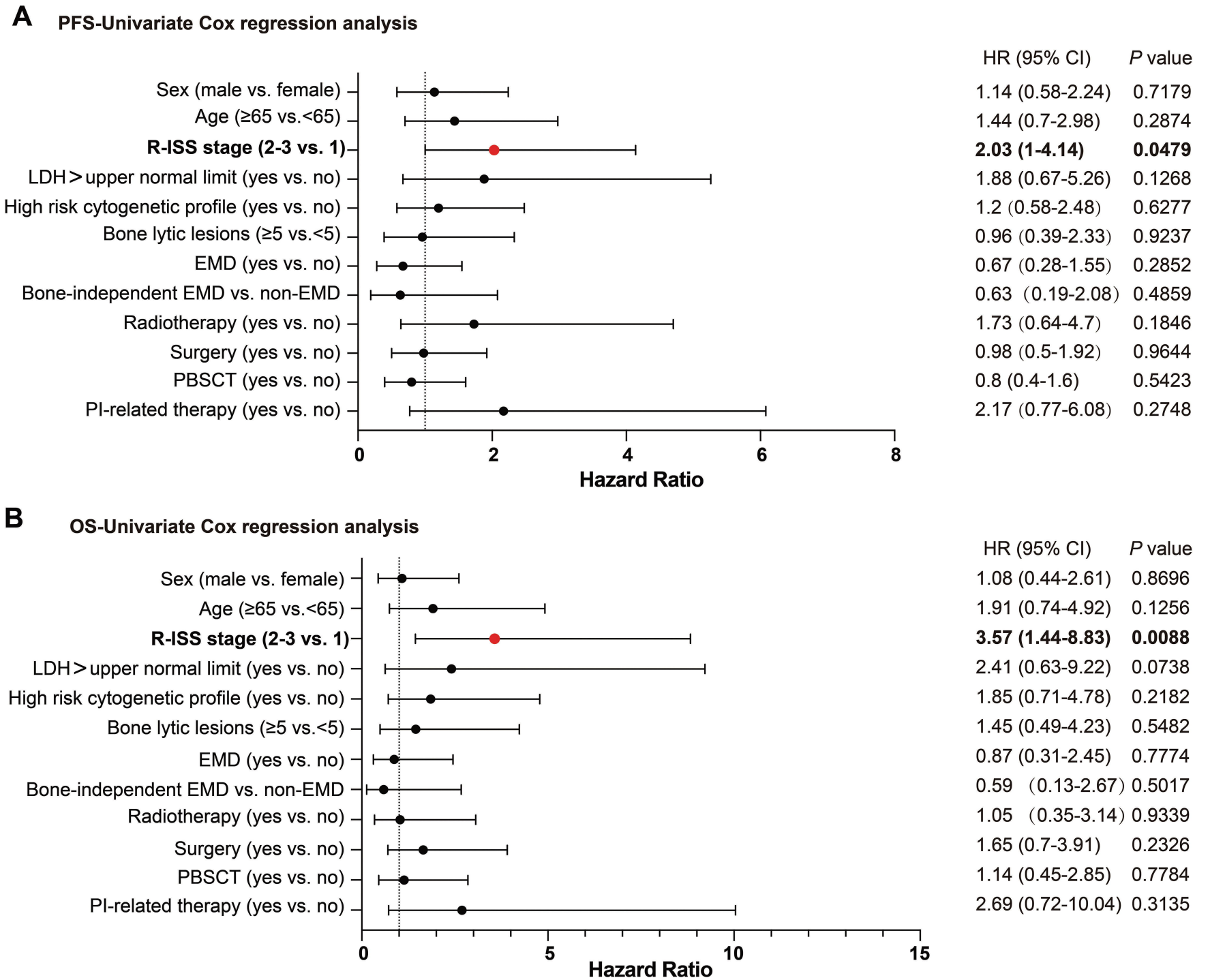
[b]The cooccurrence of any 2 of the following: t (4;14), t (14;16), 1q21 gains and del (17p).

[c]The cooccurrence of any 3 of the following: t (4;14), t (14;16), 1q21 gains and del (17p).

Figure 1. **Factors impacting PFS or OS in MFMM. A,** Forest plots shows the factors impacting PFS from univariate Cox regression analysis. **B,** Forest plots shows the factors impacting OS from univariate Cox regression analysis.

Abbreviations: MFMM: macrofocal multiple myeloma; MM: multiple myeloma; PFS: progression-free survival; CI: confidence interval; EMD: extramedullary multiple myeloma; HR: hazard ratios; LDH: lactate dehydrogenase; OS: overall survival; PBSCT: peripheral blood stem cell transplantation; R-ISS: revised international staging system.

Figure 2. Genomic characteristics of MFMM. A, Schematic workflow of the WES strategy for the 9 bone marrow samples, including the 4 matched peripheral blood. **B,** Mutational signature identified in MFMM patients (n =9). A novel signature termed 'Signature 6-like' was identified. **C,** Waterfall of MFMM patients' gene mutations. All genes are mutated at a high frequency (>10%). Bolded 5 genes are unique to MFMM, absent in typical MM. Figure 5A was created with BioRender.com, with permission. Abbreviations: BM: bone marrow; MFMM, macrofocal multiple myeloma; MM: multiple myeloma; WES: whole exome sequencing.


A
PFS-Univariate Cox regression analysis
HR (95% CI)
P value
Sex (male vs. female)
1.14 (0.58-2.24)
0.7179
Age (≥65 vs.<65)
1.44 (0.7-2.98)
0.2874
R-ISS stage (2-3 vs. 1)
2.03 (1-4.14)
0.0479
LDH > upper normal limit (yes vs. no)
1.88 (0.67-5.26)
0.1268
High risk cytogenetic profile (yes vs. no)
1.2 (0.58-2.48)
0.6277
Bone lytic lesions (≥5 vs.<5)
0.96 (0.39-2.33)
0.9237
EMD (yes vs. no)
0.67 (0.28-1.55)
0.2852
Bone-independent EMD vs. non-EMD
0.63 (0.19-2.08)
0.4859
Radiotherapy (yes vs. no)
1.73 (0.64-4.7)
0.1846
Surgery (yes vs. no)
0.98 (0.5-1.92)
0.9644
PBSCT (yes vs. no)
0.8 (0.4-1.6)
0.5423
PI-related therapy (yes vs. no)
2.17 (0.77-6.08)
0.2748
0
2
4
6
8
Hazard Ratio
B
OS-Univariate Cox regression analysis
HR (95% CI)
P value
Sex (male vs. female)
1.08 (0.44-2.61)
0.8696
Age (≥65 vs.<65)
1.91 (0.74-4.92)
0.1256
R-ISS stage (2-3 vs. 1)
3.57 (1.44-8.83)
0.0088
LDH > upper normal limit (yes vs. no)
2.41 (0.63-9.22)
0.0738
High risk cytogenetic profile (yes vs. no)
1.85 (0.71-4.78)
0.2182
Bone lytic lesions (≥5 vs.<5)
1.45 (0.49-4.23)
0.5482
EMD (yes vs. no)
0.87 (0.31-2.45)
0.7774
Bone-independent EMD vs. non-EMD
0.59 (0.13-2.67)
0.5017
Radiotherapy (yes vs. no)
1.05 (0.35-3.14)
0.9339
Surgery (yes vs. no)
1.65 (0.7-3.91)
0.2326
PBSCT (yes vs. no)
1.14 (0.45-2.85)
0.7784
PI-related therapy (yes vs. no)
2.69 (0.72-10.04)
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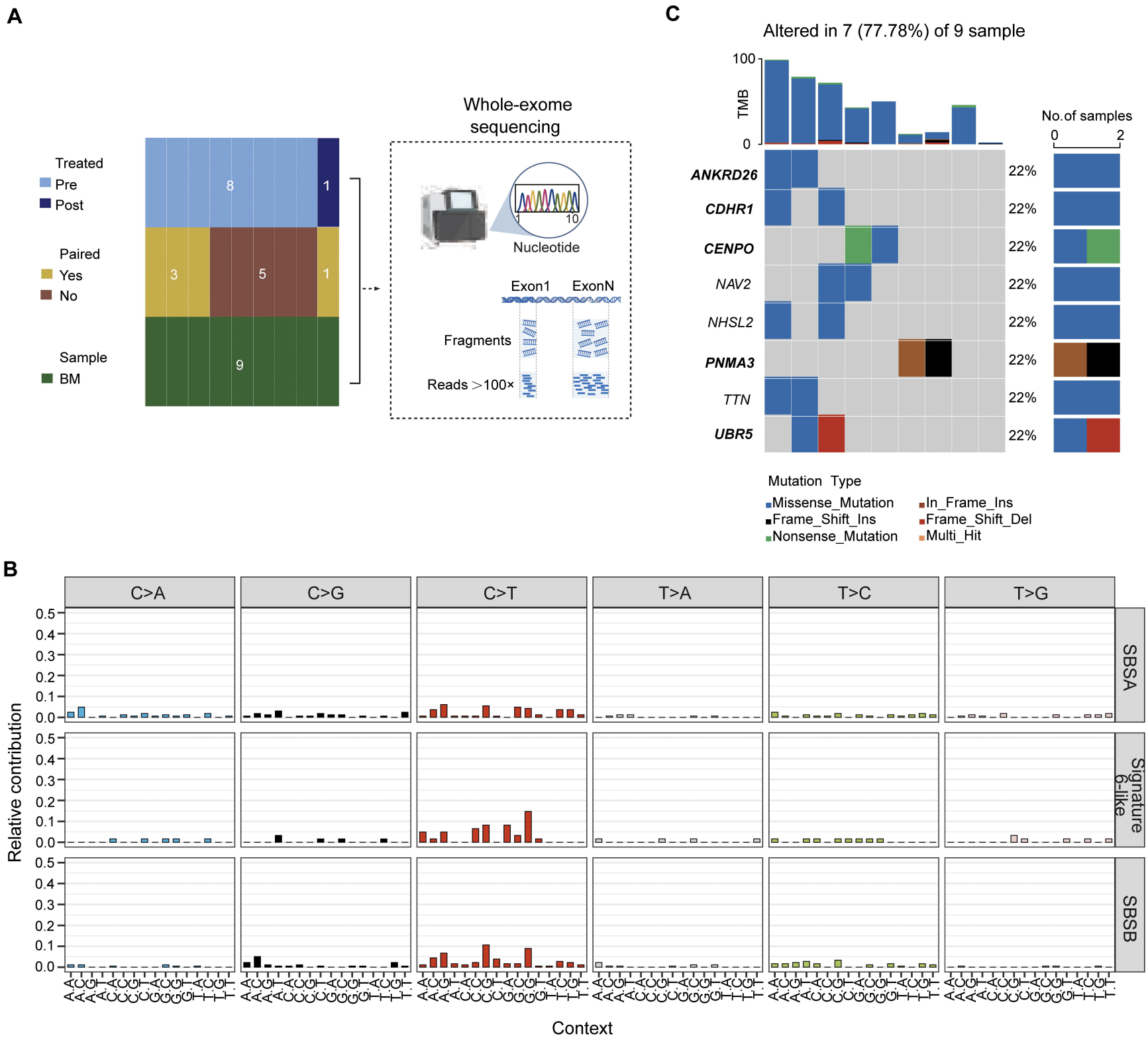
0
5
10
15
Hazard Ratio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Post
Paired
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9
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Exon1
ExonN
Fragments
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Altered in 7 (77.78%) of 9 sample
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TMB
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No.of samples
0
2
ANKRD26
CDHR1
CENPO
NAV2
NHSL2
PNMA3
TTN
UBR5
22%
Mutation Type
Missense_Mutation
In_Frame_Ins
Frame_Shift_Ins
Frame_Shift_Del
Nonsense_Mutation
Multi_Hit
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C>A
C>G
C>T
T>A
T>C
T>G
SBSA
Signature 6-like
SBSB
Relative contribution
0.5
0.4
0.3
0.2
0.1
0.0
Context

Supplemental Materials

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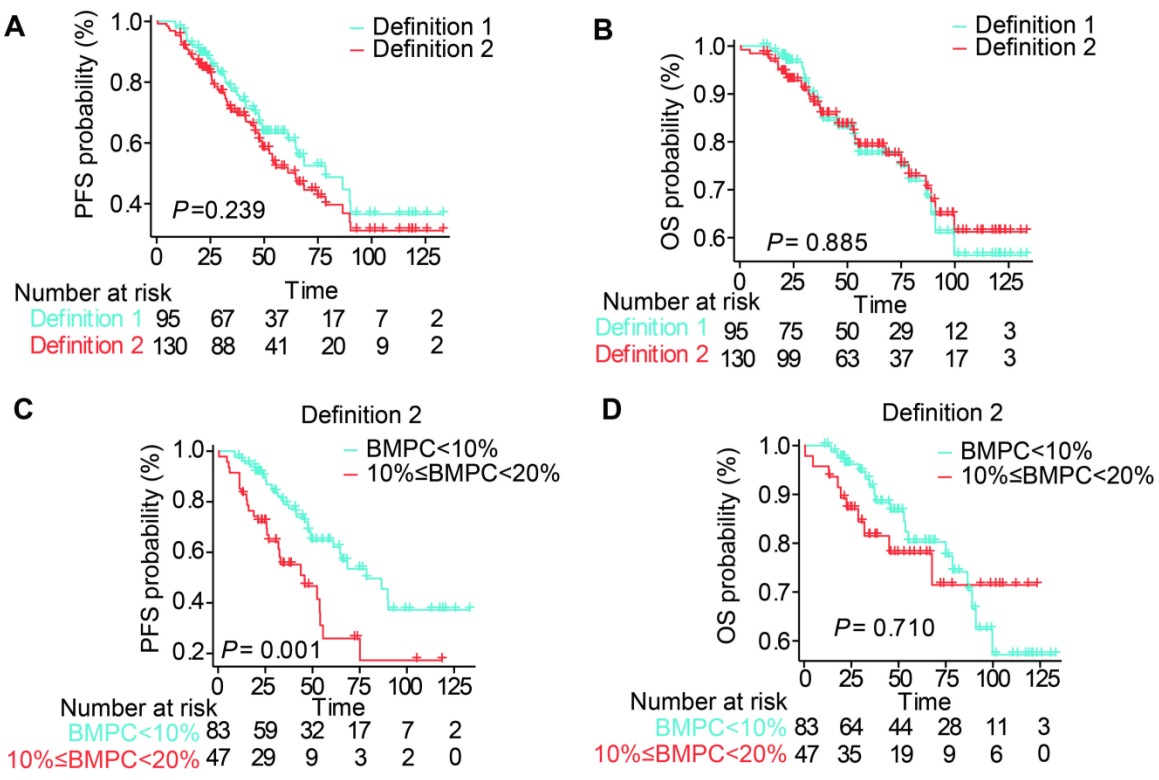
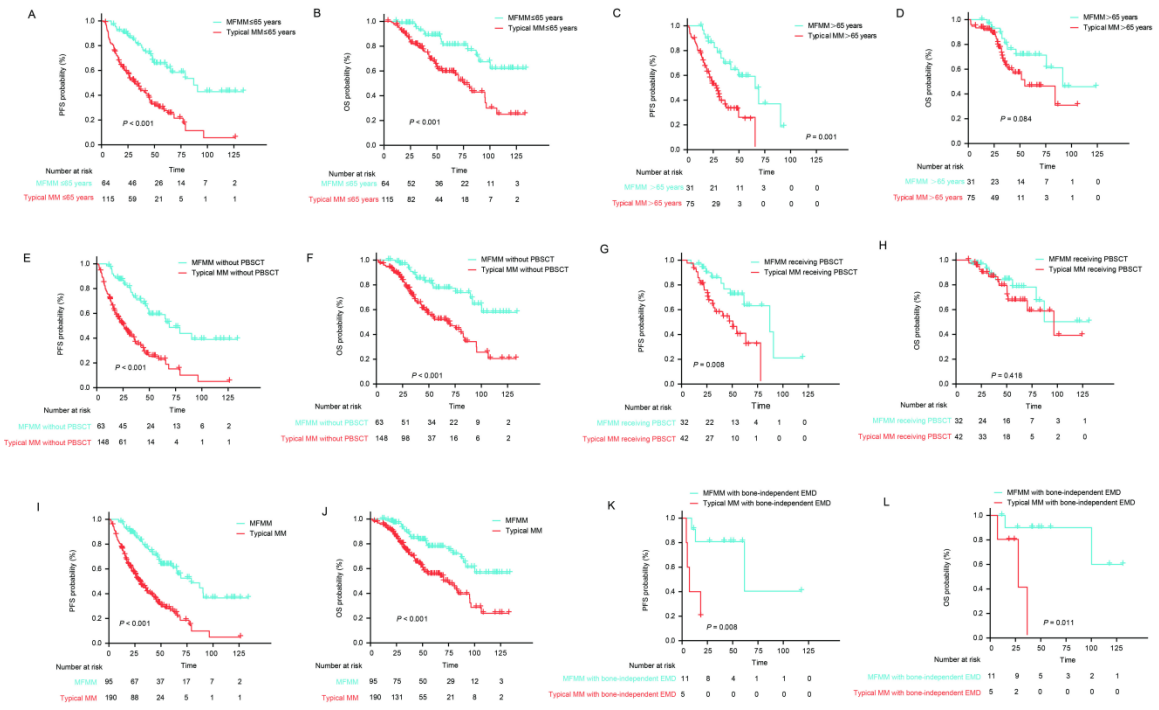


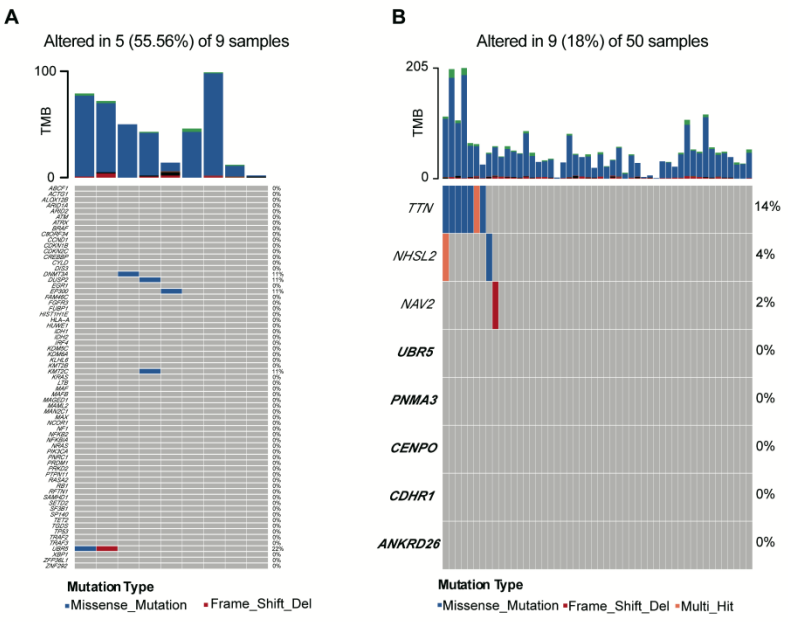
Supplemental figure 1. Survival outcomes in atypical MM. **A,** PFS in atypical MM meeting Definition 1 vs 2. **B,** OS in atypical MM meeting Definition 1 vs 2. **C,** PFS in atypical MM meeting Definition 2 with BMPCs <10% vs BMPCs ⩾10% but <20%. **D,** OS in atypical MM meeting Definition 2 with BMPCs <10% vs BMPCs ⩾10% but <20%.

Abbreviations: BMPCs: Bone marrow plasma cells; OS: Overall survival; PFS: Progression-free survival.



Supplemental figure 2. Survival outcomes in patients with MFMM or typical MM in different groups. A, PFS in MFMM vs typical MM with aged ≤65 years. **B,** OS in MFMM vs typical MM with aged ≤65 years. **C,** PFS in MFMM vs typical MM with aged >65 years. **D,** OS in MFMM vs typical MM with aged >65 years. **E,** PFS in MFMM vs typical MM without PBSCT. **F,** OS in MFMM vs typical MM without PBSCT. **G,** PFS in MFMM vs typical MM receiving PBSCT. **H,** OS in MFMM vs typical MM receiving PBSCT. **I,** PFS in MFMM vs typical MM. **J,** OS in MFMM vs typical MM. **K,** PFS in typical MM vs MFMM with bone-independent EMD. **L,** OS in typical MM vs MFMM with bone-independent EMD.

Abbreviations: EMD: extramedullary multiple myeloma; MFMM: macrofocal multiple myeloma; MM: multiple myeloma; OS: overall survival; PFS: progression-free survival; PBSCT: Peripheral blood stem cell transplantation.



Supplemental figure 3. Waterfall of 67 MM driver genes in MFMM and 8 highly mutational genes in typical MM. A, Waterfall of 67 MM driver genes in MFMM (n =9). **B,** Waterfall of 8 highly mutated genes in typical MM (n =50). Among the 8 high-frequency genes in MFMM, 3 genes are also observed in typical MM, and he remaining 5 genes, including ANKRD26, CDHR1, PNMA3, CENPO and UBR5 are uniquely present in MFMM.

Abbreviations: MFMM, macrofocal multiple myeloma; MM, multiple myeloma.

Supplemental table 1. Baseline information and 5 exclusive genes of MFMM patients in WES cohort

Clinical information									FISH						
Patient ID	M-protein type	Heavy chain	Light chain	Gender	Age at diagnosis	DS stage	ISS stage	R-ISS stage	IGH translocation	t(4;14)	t(11;14)	t(14;16)	17p-	13q-	1q21+
NDMM 01	κ	ND	κ	Male	45	ⅢA	Ⅰ	Ⅰ	14	0	0	0	6	11	16
NDMM 02	IgG-κ	IgG	κ	Male	62	ⅢA	Ⅰ	Ⅰ	0	0	0	0	0	0	0
NDMM 03	IgG-κ	IgG	κ	Male	52	ⅢA	Ⅰ	Ⅰ	34	0	0	0	12	6	80
NDMM 04	IgG-λ	IgG	λ	Male	70	ⅢA	Ⅰ	Ⅱ	62	60	0	0	9	10	86
NDMM 05	IgG-κ	IgG	κ	Male	64	ⅢA	Ⅰ	Ⅰ	26	0	0	0	3	2	40
NDMM 06	κ	ND	κ	Male	58	ⅠA	Ⅰ	Ⅰ	32	0	0	0	12	3	29
NDMM 07	IgG-κ	IgG	κ	Female	55	ⅢA	Ⅰ	Ⅱ	50	46	0	0	22	6	17
NDMM 08	IgG-λ	IgG	λ	Male	74	ⅢA	Ⅰ	Ⅰ	90	0	94	0	2	1	10
RRMM 01	IgD-λ	IgD	λ	Male	64	ⅢA	Ⅱ	Ⅱ	15	0	0	0	10	3	60

5 genes specific in MFMM																
Chromosome	Start _Position	End _Position	Reference _Allele	Tumor _Seq	Tumor _Sample	Hugo _Symbol	Variant _Classification	tx	exon	txChange	aaChange	Variant _Type	sample _id	Func .refGene	Gene .refGene	GeneDetail .refGene	ExonicFunc .refGene	AAChange .refGene

				_Allele2	_Barcode												
chr10	27035701	27035701	A	T	RA201908290198	ANKRD26	Missense_Mutation	NM_001256053	exon24	c.T2746A	p.L916M	SNP	15_sample	exonic	ANKRD26	.	nonsynonymous SNV	ANKRD26:NM_001256053:exon24:c.T2746A:p.L916M,ANKRD26:NM_014915:exon24:c.T2749A:p.L917M
chr10	27035187	27035187	C	T	RA201910120076	ANKRD26	Missense_Mutation	NM_001256053	exon24	c.G3260A	p.R1087K	SNP	15_sample	exonic	ANKRD26	.	nonsynonymous SNV	ANKRD26:NM_001256053:exon24:c.G3260A:p.R1087K,ANKRD26:NM_014915:exon24:c.G3263A:p.R1088K
chr10	84219208	84219208	G	A	RA201910120076	CDHR1	Missense_Mutation	NM_001171971	exon17	c.G2170A	p.A724T	SNP	15_sample	exonic	CDHR1	.	nonsynonymous SNV	CDHR1:NM_001171971:exon17:c.G2170A:p.A724T
chr10	84211081	84211081	C	A	RA202007130147	CDHR1	Missense_Mutation	NM_001171971	exon13	c.C1401A	p.D467E	SNP	15_sample	exonic	CDHR1	.	nonsynonymous SNV	CDHR1:NM_001171971:exon13:c.C1401A:p.D467E,CDHR1:NM_033100:exon13:c.C1401A:p.D467E
chrX	153057493	153057493	-	GTCCAGAACTCT	RA202009110167	PNMA3	In_Frame_Ins	NM_001282535	exon2	c.438_439insGTCCAGAACTCT	p.Q146_T147insVQNSGDIV	INS	15_sample	exonic	PNMA3	.	nonframeshift insertion	PNMA3:NM_001282535:exon2:c.438_439insGTCCA

				GGTGATATAGTC						GGTGATATAGTC							GAACTCTGGTGATATAGTC:p.Q146_T147insVQNSGDIV,PNMA3:NM_013364:exon2:c.438_439insGTCCAGAACTCTGGTGATATAGTC:p.Q146_T147insVQNSGDIV
chrX	153057493	153057493	-	GTCCAGA	RA202108030178	PNMA3	Frame_Shift_Ins	NM_001282535	exon2	c.438_439insGTCCAGA	p.T147Vfs*37	INS	15_sample	exonic	PNMA3	.	frameshift insertion	PNMA3:NM_001282535:exon2:c.438_439insGTCCAGA:p.T147Vfs*37,PNMA3:NM_013364:exon2:c.438_439insGTCCAGA:p.T147Vfs*37
chr8	102361199	102361199	G	C	RA201908290198	UBR5	Missense_Mutation	NM_001282873	exon3	c.C115G	p.P39A	SNP	15_sample	exonic	UBR5	.	nonsynonymous SNV	UBR5:NM_001282873:exon3:c.C115G:p.P39A,UBR5:NM_015902:exon3:c.C115G:p.P39A
chr8	102305098	102305098	A	-	RA202007130147	UBR5	Frame_Shift_Del	NM_001282873	exon21	c.2814delT	p.E940Kfs*47	SNP	15_sample	exonic	UBR5	.	frameshift deletion	UBR5:NM_001282873:exon21:c.28

chr2	24815499	24815499	C	A	RA202004140134	CENPO	Missense_Mutation	NM_001199803	exon4	c.C319A	p.L107I	SNP	15_sample	exonic	CENPO	.	nonsynonymous SNV	14delT:p.E940Kfs*47,UBR5:NM_015902:exon21:c.2814delT:p.E940Kfs*47 CENPO:NM_001199803:exon4:c.C319A:p.L107I,CENPO:NM_001322101:exon5:c.C337A:p.L113I,CENPO:NM_024322:exon5:c.C337A:p.L113I
chr2	24799803	24799803	C	T	RA202010120124	CENPO	Nonsense_Mutation	NM_001199803	exon2	c.C157T	p.R53X	SNP	15_sample	exonic	CENPO	.	stopgain	CENPO:NM_001199803:exon2:c.C157T:p.R53X,CENPO:NM_001322101:exon3:c.C175T:p.R59X,CENPO:NM_024322:exon3:c.C175T:p.R59X

Abbreviations: NDMM: new diagnosed multiple myeloma; RRMM: relapsed/refractory multiple myeloma; M-protein: monoclonal protein; IgG: immunoglobulin G; IgD: immunoglobulin D; ND: not detected; DS: Durie-Salmon; ISS: international Staging System; R-ISS: revised international staging system; FISH: fluorescence in situ hybridization; IGH: immunoglobulin heavy chain gene locus.