

SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of the 3 largest lesions in the FL-HiR patients

ID	Lesion 1	PPD ¹	Map ²	PET ³	Lytic	Lesion 2	PPD ¹	Map ²	PET ³	Lytic	Lesion 3	PPD ¹	Map ²	PET ³	Lytic
1	Rib cage	31.7	2	+	yes	Sacrum	20.1	1	+	yes	Scapula	13.5	0	+	no
2	Sacrum	14.9	0	+	yes	L5	14.7	1	+	yes	Ilium	12.0	1	+	yes
3	Lt ilium	14.8	1	-	yes	Rib cage	6.6	2	+	yes	Clavicle	6.0	3	-	yes
4	Rib cage	7.1	2	+	yes	Ilium	6.8	2	+	yes	Iliac crest	6.5	2	+	yes
5	Humerus	13.7	3	+	yes	Rib cage	6.8	1	+	yes	L3	5.8	2	+	yes
6	Rib cage	19.1	0	ST	yes	L5	7.2	0	+	yes	Rib cage	6.5	0	ST	yes
7	Ilium	34.8	2	+	yes	Rib cage	21.6	1	ST	yes	Clavicle	8.1	2	+	yes
8	Rt pelvis	21.0	3	+	yes	Femur	16.6	3	+	no	Rib cage	8.0	3	+	yes
9	Manubrium	12.2	3	-	yes	Scapula	11.5	0	+	yes	Scapula	6.7	0	-	no
10	Lt pelvis	57.0	3	+	yes	Femur	16.2	3	+	yes	Femur	10.8	3	+	yes
11	Rib cage	11.7	2	+	yes	Rib cage	9.8	3	+	yes	Rt pelvis	6.1	3	+	yes
12	Sacrum	23.4	1	+	yes	T12	6.2	1	+	yes	Ilium	5.4	3	+	yes
13	Rib cage	49.7	3	+	yes	Ilium	29.1	3	+	yes	Rib cage	14.0	3	+	yes
14	Clavicle	21.4	3	ST	yes	Clavicle	15.3	3	+	yes	Sacrum	10.5	3	ST	yes
15	Manubrium	16.0	2	ST	yes	Clavicle	10.7	0	+	yes	Rib cage	8.2	2	ST	yes
16	Sacrum	27.8	3	+	yes	Iliac crest	8.7	3	+	yes	Manubrium	5.6	3	+	yes
17	Humerus	16.7	2	+	yes	Sacrum	7.8	2	+	yes	Sacrum	7.4	2	+	yes
18	Ilium	19.9	1	+	yes	Sacrum	19.6	2	+	yes	Ilium	9.0	2	+	no
19	Ilium	14.0	2	+	yes	Sacrum	11.2	2	+	yes	Rib cage	5.3	2	+	no
20	Sacrum	27.3	3	+	yes	Acetabulum	13.0	3	+	yes	Ischium	11.7	3	+	yes
21	Rt pelvis	94.3	1	+	yes	Iliac crest	16.8	2	+	yes	Femur	9.9	3	+	no
22	Rib cage	40.7	3	+	yes	Sacrum	20.2	2	+	yes	Manubrium	7.9	3	ST	yes
23	Tibia	10.3	3	ST	no	Femur	9.0	3	ST	no	Ilium	6.0	2	-	no

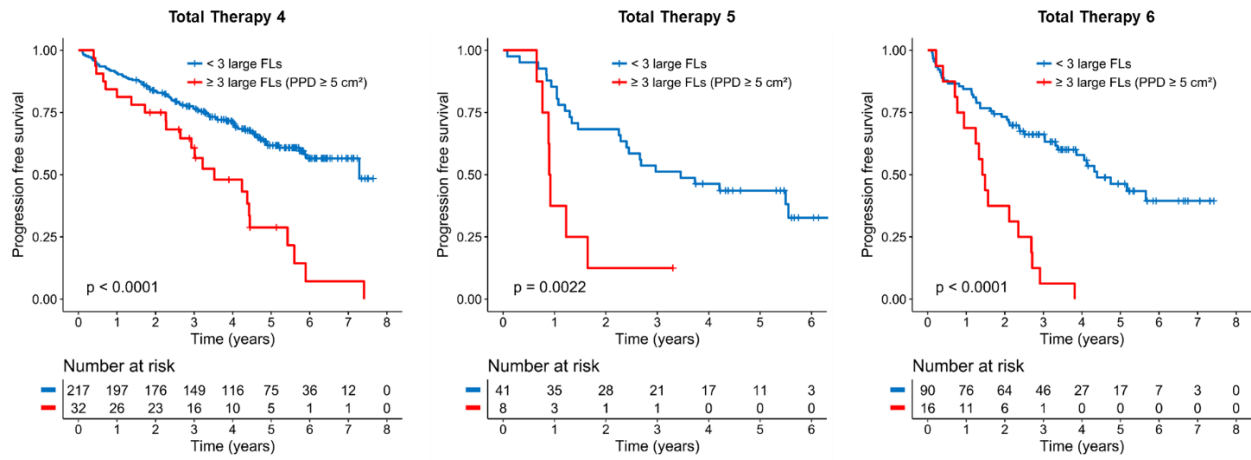
ID	Lesion 1	PPD ¹	Map ²	PET ³	Lytic	Lesion 2	PPD ¹	Map ²	PET ³	Lytic	Lesion 3	PPD ¹	Map ²	PET ³	Lytic
24	Ilium	39.3	1	+	yes	Rib cage	20.4	1	+	yes	Ilium	9.3	1	ST	yes
25	Humerus	16.4	3	+	yes	Scapula	14.7	3	+	yes	Sternum	8.6	3	+	yes
26	Sacrum	47.4	2	ST	yes	Ilium	18.0	2	ST	yes	Ilium	13.9	2	ST	yes
27	Ischium	9.1	2	ST	yes	Manubrium	7.8	2	-	yes	Rib cage	5.0	1	ST	yes
28	Ilium	17.8	0	+	yes	Humerus	11.9	3	+	yes	Acetabulum	6.8	2	+	yes
29	Scapula	22.1	0	+	yes	Humerus	18.6	1	+	yes	L1	11.5	2	+	yes
30	Ilium	20.4	0	+	yes	Ilium	16.7	0	+	yes	Clavicle	7.8	0	+	yes
31	Ilium	20.2	1	+	yes	T6	19.8	0	+	yes	L2	5.4	0	+	yes
32	Ischium	14.2	0	+	yes	Iliac crest	14.0	1	+	yes	Ilium	9.4	0	ST	yes
33	Ilium	11.2	3	-	yes	L2	5.4	2	-	yes	T11	5.3	2	-	yes
34	T8	21.1	3	+	yes	Iliac crest	10.6	3	+	yes	Femur	6.1	3	+	no
35	Humerus	7.8	3	+	no	Rib cage	6.1	2	+	yes	Sacrum	5.1	2	ST	yes
36	Acetabulum	14.0	1	+	no	Sacrum	10.2	0	+	no	Manubrium	9.5	3	+	yes
37	Sacrum	17.0	DWI	+	yes	Humerus	9.0	DWI	+	yes	Femur	7.6	DWI	+	yes
38	Humerus	21.8	DWI	+	yes	Ilium	16.0	DWI	+	yes	Scapula	7.4	DWI	+	yes
39	Femur	8.0	DWI	+	no	Sacrum	7.5	DWI	+	no	Humerus	7.4	DWI	+	no
40	L3	22.6	DWI	+	yes	T9	8.4	DWI	ST	yes	Manubrium	6.2	DWI	+	yes
41	Ilium	31.3	DWI	+	yes	Rt Sacrum	9.5	DWI	+	yes	Ilium	6.8	DWI	+	yes
42	C2-C4	18.4	DWI	+	yes	Rib cage	10.9	DWI	+	yes	Rib cage	7.8	DWI	+	yes
43	Sacrum	24.7	DWI	+	yes	Iliac crest	15.0	DWI	+	yes	Femur	11.6	DWI	+	yes
44	Rib cage	29.0	DWI	+	yes	Iliac crest	13.8	DWI	+	yes	Acetabulum	13.8	DWI	+	yes
45	Sacrum	65.0	DWI	ST	yes	Ischium	13.3	DWI	ST	yes	Humerus	9.9	DWI	ST	yes
46	Ilium	12.9	DWI	+	yes	L1	5.5	DWI	+	yes	Humerus	5.0	DWI	+	yes
47	Scapula	13.9	DWI	+	yes	Scapula	9.0	DWI	+	yes	T7	8.3	DWI	+	yes
48	Sacrum	27.6	DWI	+	yes	Rib cage	11.8	DWI	+	yes	Scapula	6.6	DWI	+	yes
49	Ilium	27.6	DWI	+	yes	T5	15.5	DWI	-	no	Ilium	5.4	DWI	+	yes
50	Rib cage	44.8	DWI	+	yes	Ilium	32.4	DWI	+	yes	Humerus	15.3	DWI	+	no
51	Sacrum	26.5	DWI	+	yes	Sternum	16.3	DWI	+	yes	Humerus	13.4	DWI	+	no
52	Ilium	17.3	DWI	+	yes	T4	11.7	DWI	+	yes	Rib cage	7.2	DWI	+	yes

ID	Lesion 1	PPD ¹	Map ²	PET ³	Lytic	Lesion 2	PPD ¹	Map ²	PET ³	Lytic	Lesion 3	PPD ¹	Map ²	PET ³	Lytic
53	Sacrum	14.4	DWI	+	no	Rib cage	13.5	DWI	+	yes	Scapula	7.8	DWI	+	yes
54	Clavicle	49.9	DWI	+	yes	Manubrium	20.5	DWI	+	yes	Iliac crest	9.8	DWI	+	yes
55	Ilium	19.6	DWI	+	yes	Sacrum	10.4	DWI	+	yes	Ischium	9.3	DWI	+	yes
56	Rib cage	17.2	DWI	+	yes	L3	5.9	DWI	+	yes	Ilium	5.8	DWI	+	yes

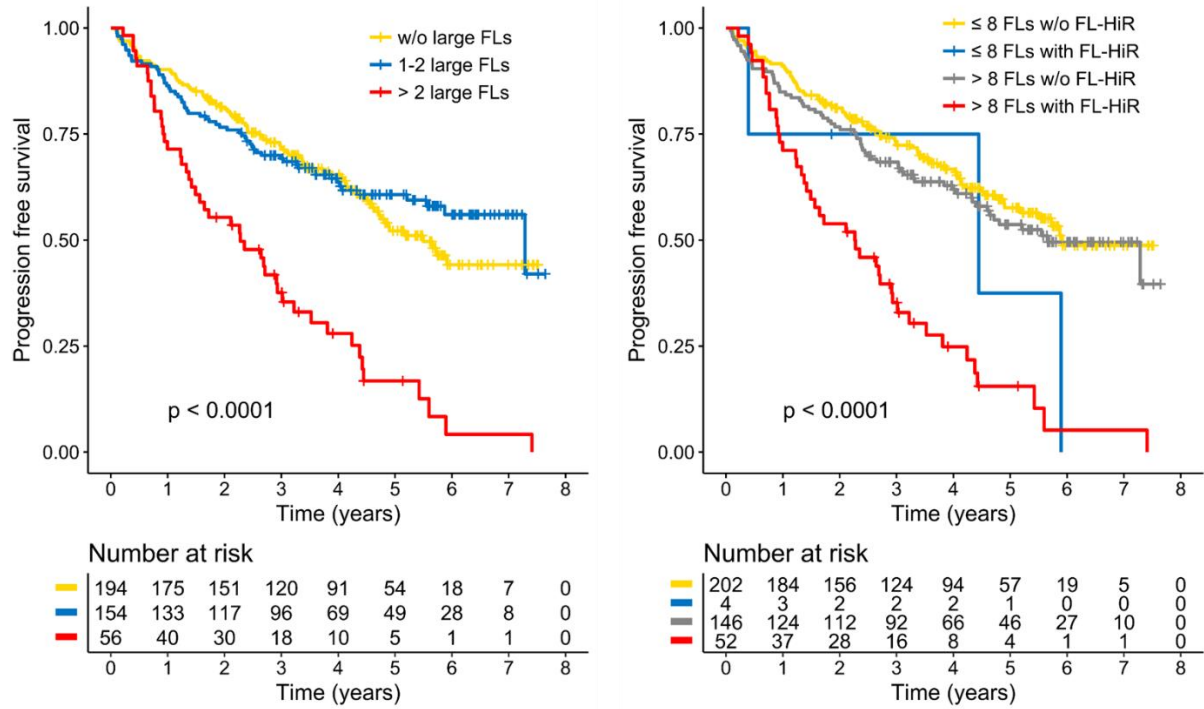
¹PPD: product of the perpendicular diameters in cm²; ² Classification for the level of restriction of lesions seen on EADC maps: 0 = no increased restriction (~signal from muscle tissue adjacent to the pelvis), 1 = increased restriction, but less than signal for diffuse infiltration at lumbar spine, 2 = equal to signal at lumbar spine, 3 = above signal at lumbar spine; ³ Presentation of lesions on PET-CT: + = FDG avid lesion; ST = no focal hypermetabolism but soft tissue tumor in the CT portion of the PET-CT; - = PET-CT negative

Supplementary Table 2. Univariate analysis of risk factors for outcome in newly diagnosed patients.

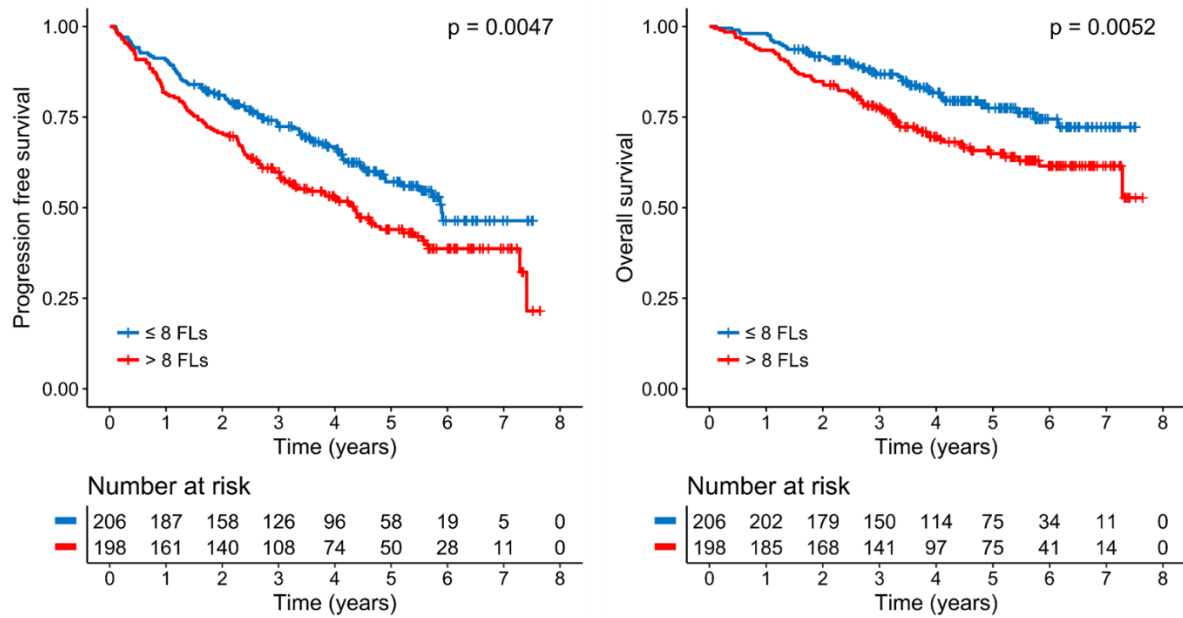
Variable		No.	PFS			OS		
			HR	95% CI	p	HR	95% CI	p
FL-HiR	no	348						
	yes	56	3.00	2.14 to 4.19	<0.001	3.02	1.97 to 4.62	<0.001
FL Number	≤8	206						
	>8	198	1.51	1.13 to 2.1	0.005	1.72	1.17 to 2.54	0.006
GEP70	low	349						
	high	55	2.84	2.01 to 4.01	<0.001	4.48	3.00 to 6.69	<0.001
R-ISS	I	76						
	II	277	2.53	1.55 to 4.14	<0.001	3.24	1.49 to 7.02	0.003
	III	46	4.13	2.30 to 7.41	<0.001	8.45	3.66 to 19.49	<0.001
EMD	no	381						
	yes	23	2.29	1.39 to 3.78	0.001	3.78	2.19 to 6.53	<0.001
gain(1q)	no	236						
	yes	136	1.96	1.46 to 2.64	<0.001	2.74	1.84 to 4.08	<0.001



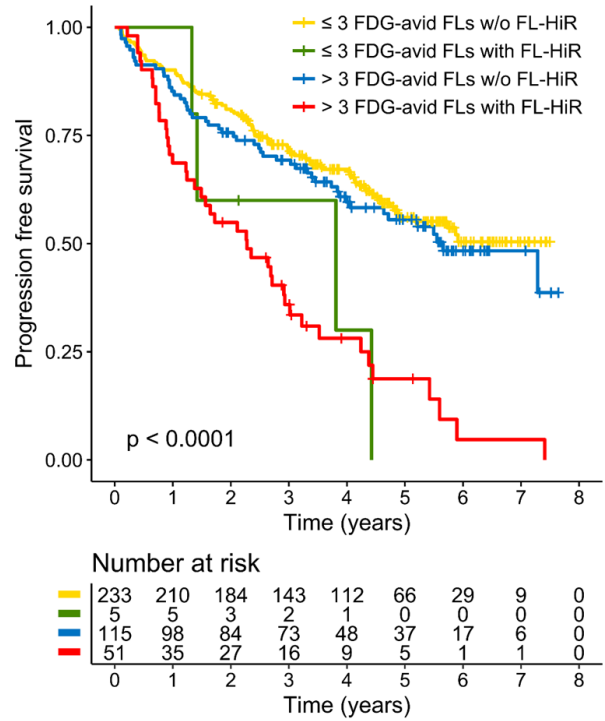
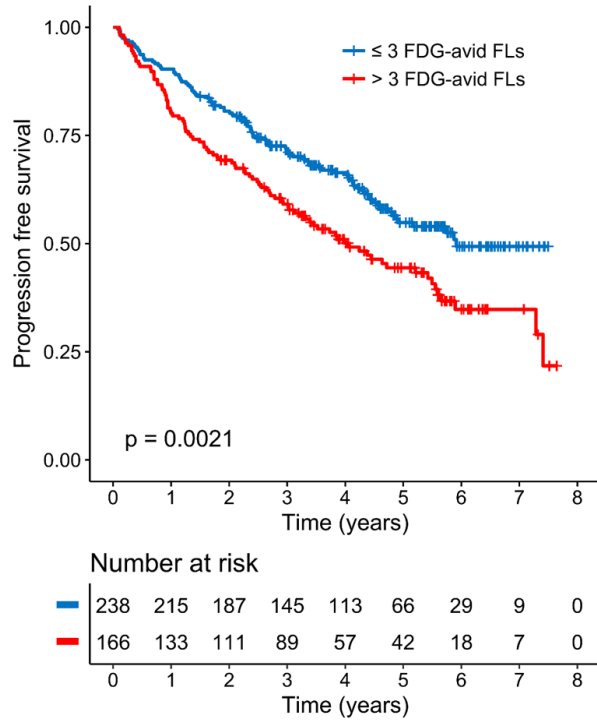
Supplementary Figure 1: Impact of the FL-HiR pattern on outcome for Total Therapy 4 - 6. Progression free survival for newly diagnosed MM patients enrolled into Total Therapies stratified by the presence of ≥ 3 large FLs. Statistical significance was determined using the log-rank test.



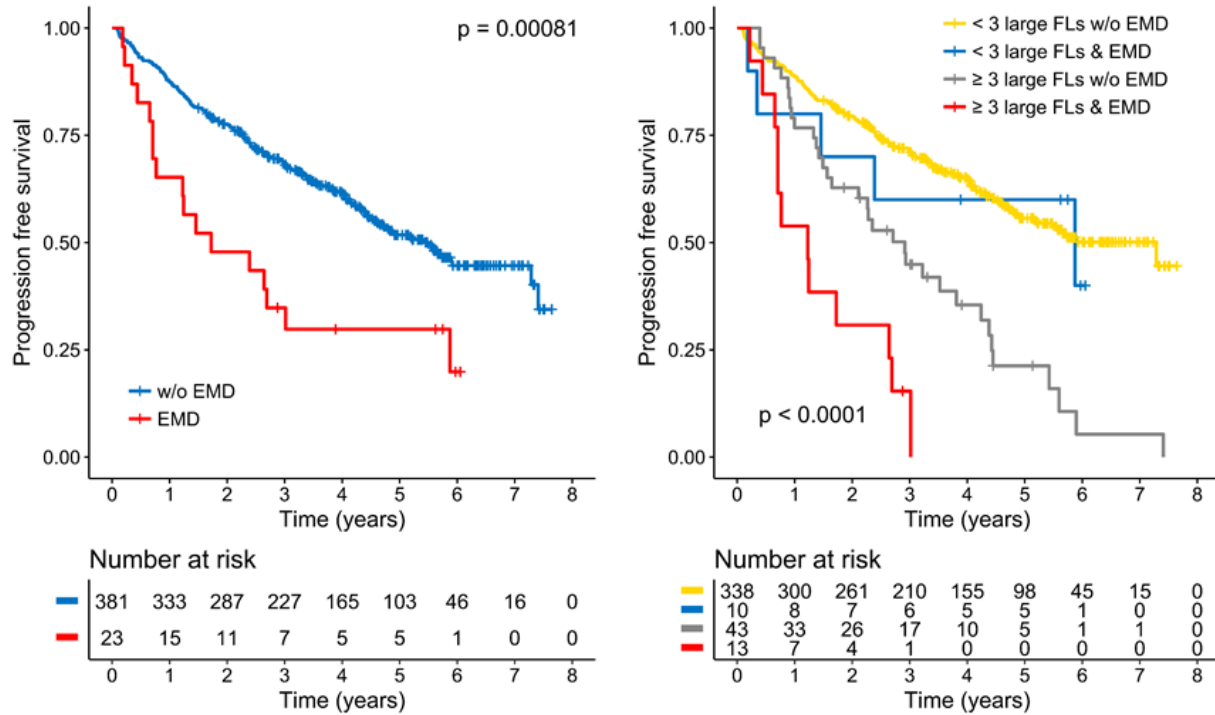
Supplementary Figure 2: Impact of focal lesion number stratified by the FL-HiR pattern. (Left panel) Progression free survival for patients with 1-2 large focal lesions vs. ≥ 3 large focal lesions. (Right panel) Progression free survival for patients with > 8 focal lesions stratified by the FL-HiR pattern. Statistical significance was determined using the log-rank test.



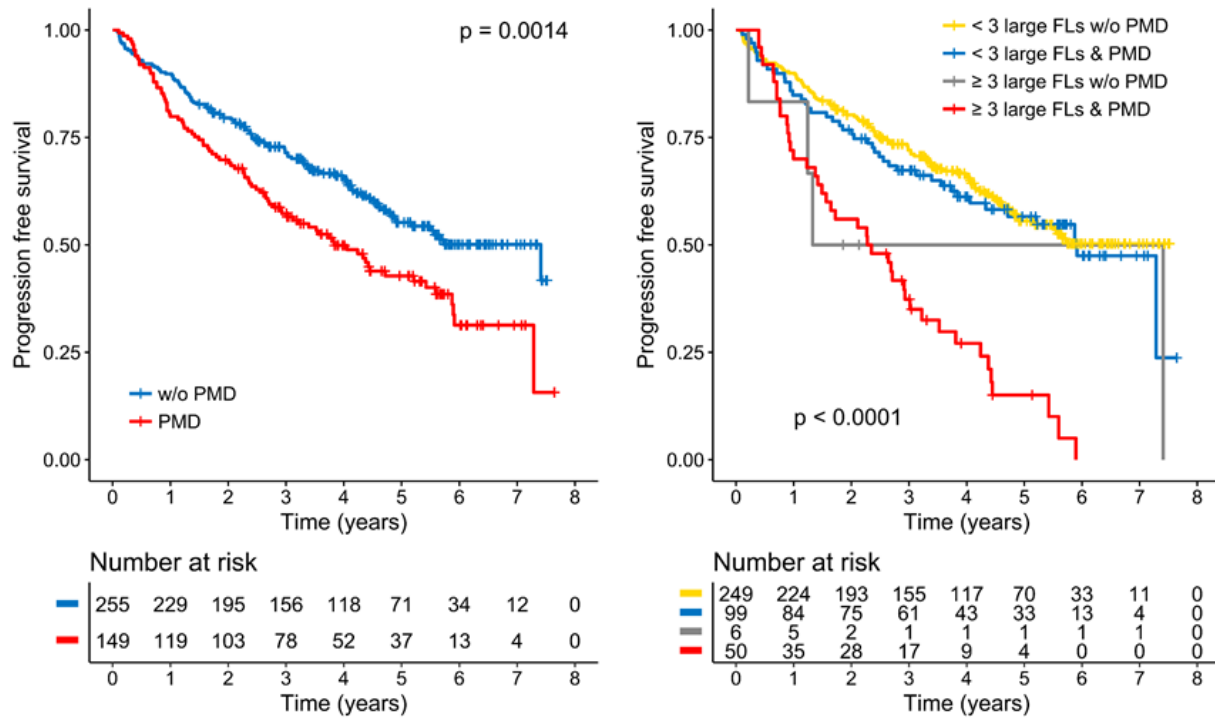
Supplementary Figure 3: Impact of focal lesion number on DWIBS on outcome. Progression free and overall survival for newly diagnosed MM patients enrolled into Total Therapies stratified by the number of focal lesions. Statistical significance was determined using the log-rank test.



Supplementary Figure 4: Impact of focal lesion number on PET-CT stratified by the FL-HiR pattern. (Left panel) Progression free survival for patients stratified by the number of FDG-avid focal lesions. (Right panel) Progression free survival for patients with > 3 focal lesions on PET-CT stratified by the FL-HiR pattern on DWIBS. Statistical significance was determined using the log-rank test.



Supplementary Figure 5: The impact of extramedullary disease on outcome. Progression free survival for patients presenting with extramedullary disease (EMD) in PET-CT at baseline (left panel). Progression free survival for patients with EMD in PET-CT stratified by the presence of ≥ 3 large FLs (*FL-HiR* pattern). The log-rank test was used to calculate p values.



Supplementary Figure 6: The impact of paramedullary disease on outcome. Progression free survival for patients presenting with paramedullary (PMD) components in PET-CT (left panel). Progression free survival for patients with PMD in PET-CT stratified by the presence of ≥ 3 large FLs. The log-rank test was used to calculate p values.