Supplemental Table 1

Comparison of patients characteristics in this study (imaging and biomarkers) and in the CASSIOPET trial.

	This study n=139	CASSIOPET trial n=268
Age *Median (range), years*	60 (26-65)	58 (26-65)
Sex *Male (%)*	74 (53)	152 (57)
ISS grade *I (%)* *II (%)* *III (%)*	57 (41) 63 (45) 19 (14)	118 (44) 111 (41) 39 (15)
High risk cytogenetics *n (%)*	30 (22)	49 (18)
Arm *D-VTd (%)*	73 (53)	137 (51)

Supplemental Table 2

Gene set enrichment analysis performed with MSigDB 7.0 on genes upregulated in samples paired with abnormal/positive PET scans (top rows), or with normal/negative PET scans (bottom rows).

	Gene Set Name	# Genes in Gene Set (K)	# Genes in Overlap (k)	k/K	p-value	FDR q-value
Enriched in Abnormal PET profiles	GO_MITOTIC_CELL_CYCLE	1053	12	0.0114	2.41E-14	2.48E-10
	GO_CELL_CYCLE_PROCESS	1422	12	0.0084	8.33E-13	4.28E-9
	GO_CELL_CYCLE	1881	12	0.0064	2.19E-11	7.5E-8
	GO_CELL_CYCLE_PHASE_TRANSITION	647	8	0.0124	7.48E-10	1.92E-6
	GO_REGULATION_OF_CHROMOSOME_ORGANIZATION	356	6	0.0169	2.29E-8	4.7E-5
	GO_REGULATION_OF_CELL_CYCLE_PROCESS	791	7	0.0088	1.04E-7	1.57E-4
	GO_REGULATION_OF_CELL_CYCLE	1226	8	0.0065	1.07E-7	1.57E-4
	GO_CHROMOSOME_SEPARATION	94	4	0.0426	1.65E-7	2.03E-4
	GO_REGULATION_OF_ORGANELLE_ORGANIZATION	1310	8	0.0061	1.78E-7	2.03E-4
	GO_REGULATION_OF_CHROMOSOME_SEGREGATION	107	4	0.0374	2.78E-7	2.85E-4
Enriched in Normal PET profiles	GO_SECRETION	1618	8	0.0049	1.98E-6	1.26E-2
	GO_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND	1714	8	0.0047	3.04E-6	1.26E-2
	GO_CELLULAR_RESPONSE_TO_OXYGEN_CONTAINING_COMPOUND	1220	7	0.0057	3.81E-6	1.26E-2
	GO_VESICLE_MEMBRANE	806	6	0.0074	4.9E-6	1.26E-2
	GO_EXOCYTOSIS	914	6	0.0066	1,00E-05	1.92E-2
	GO_CARBOHYDRATE_HOMEOSTASIS	246	4	0.0163	1.12E-5	1.92E-2
	GO_MYELOID_LEUKOCYTE_MEDIATED_IMMUNITY	555	5	0.0090	1.37E-5	2.01E-2
	GO_SECRETORY_GRANULE_MEMBRANE	306	4	0.0131	2.63E-5	3.38E-2
	GO_MYELOID_LEUKOCYTE_ACTIVATION	662	5	0.0076	3.19E-5	3.64E-2
	GO_WHOLE_MEMBRANE	1721	7	0.0041	3.56E-5	3.65E-2

Supplemental Table 3

Comparison of high risk gene expression signatures to predict progression-free survival (PFS) with a univariate cox analysis. GEP70/UAMS70: 70-gene high risk signature (1), IFM15: 15-gene high risk signature from the intergroupe francophone du myélome (2), EMC-92: 92-gene high risk signature from the HOVON center (3). HR: Hazard ratio. CI: Confidence interval. LRT: Likelihood ratio test. FDR: False discovery rate.

	HR	HR: 95% CI	LRT	p value	FDR	
GEP70/UAMS70	3.5	(1.5-8.2)	7.2	0.0073	0.01095	*
IFM15	4.3	(1.9-9.4)	12	0.00045	0.00135	**
EMC92	2.8	(1.2-6.8)	4.6	0.032	0.032	*

Supplemental Table 4

Comparison of prognostic significance of FDG-PET biomarkers to predict progression-free survival (PFS) with a univariate cox analysis. HR: Hazard ratio. CI: Confidence interval. LRT: Likelihood ratio test. FDR: False discovery rate.

|	HR	HR: 95% CI	LRT	p value	FDR	
PET *Normal FDG-PET scan*	0.13	(0.018-0.99)	7.5	0.0063	0.018	*
EMD *Presence of extramedullary disease*	3.1	(1.3-7.3)	5.3	0.022	0.026	*
PMD *Presence of paramedullary disease*	5.2	(2.3-11)	13	0.00025	0.0015	**
SUVmaxBM *SUVmax in bone marrow*	1.3	(1.1-1.6)	6.1	0.013	0.02	*
SUVmaxFL *SUVmax in focal lesions*	1.1	(0.99-1.1)	2.8	0.095	0.095	.
FL>3 *Number of focal lesions strictly greater than three*	2.8	(1.3-6.2)	6.8	0.0092	0.018	*

Supplemental Table 5

Multivariate cox modeling of PMD (paramedullary disease), IFM15 (high risk gene expression signature), and R-ISS staging. Likelihood ratio test p value of the model: 2E-6. HR: Hazard ratio. ***R-ISS** Evaluated in 136/139 patients.

|	HR	lower .95	upper .95	p value	
IFM15 *High risk gene expression signature*	2.9	1.3	6.6	0.010	*
PMD *Presence of paramedullary disease*	4.7	2.1	11	0.00020	***
R-ISS (II)* *Revised International Staging System II (ref. level: I)*	2.2	0.50	9.7	0.30	
R-ISS (III)* *Revised International Staging System III (ref. level: I)*	8.9	1.7	47	0.010	*

Supplemental Figure 1

Overview of variables inspected for 139 patients of the CASSIOPET cohort with both RNA-seq and PET scan analysed. **a**. Sample classification into 7 groups of the University of Arkansas for Medical Sciences (UAMS). **b**. High risk classification with the IFM15 gene expression signature. **c**. Distribution of SUVmax in the bone marrow (SUVMaxBM) at baseline. **d**. Distribution of SUVmax in the focal lesions (SUVMaxFL) at baseline for the subset of patients with focal lesions. **e-h**. Baseline annotation of PET scans. Annotation is provided for N=139 patients, except the SUVmaxFL (N=92).
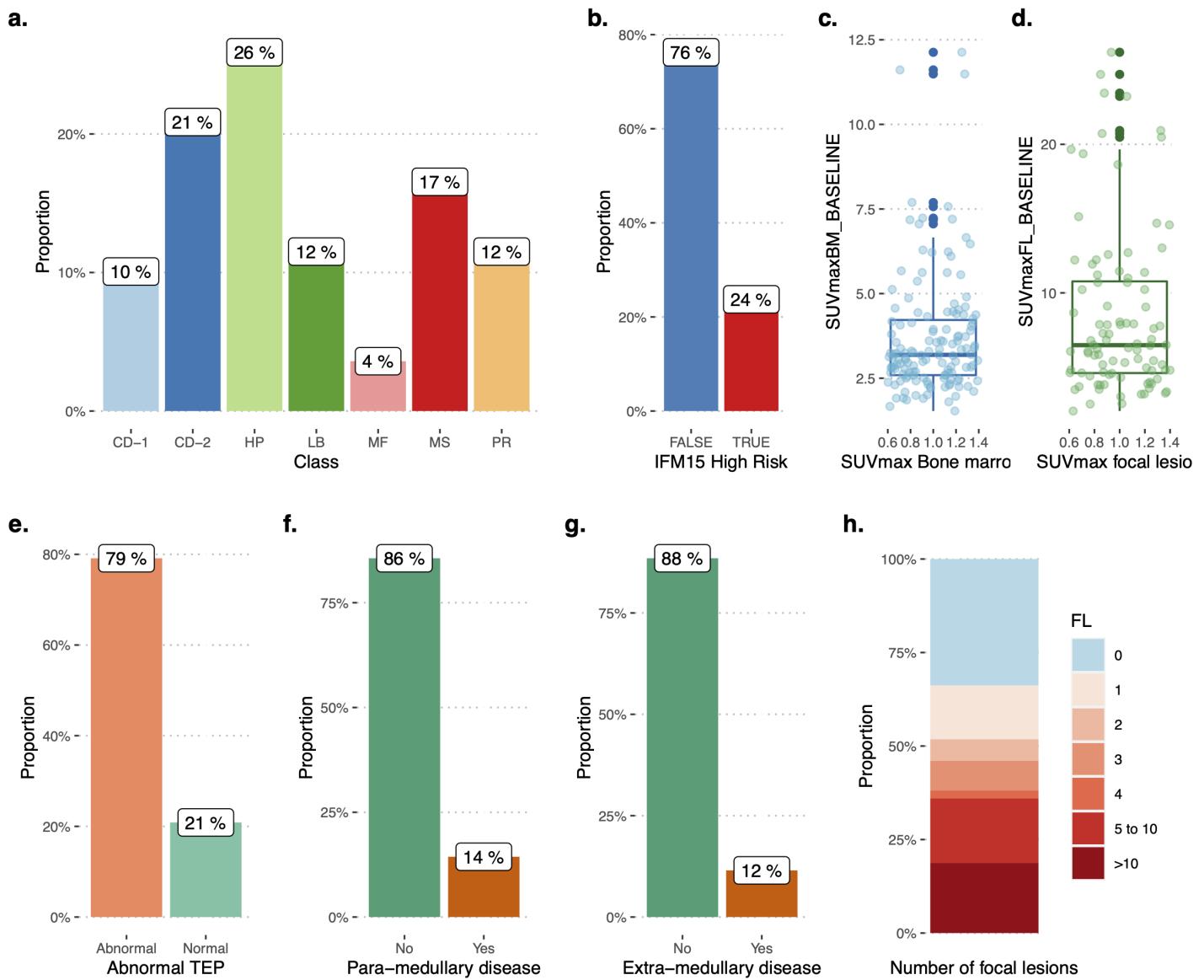
Supplemental Figure 2

Distribution of patients presenting para-medullary disease (A) or extra-medullary disease (B) at baseline according to their GEP70/UAMS70 high risk classification. n.s.: not significant (p>0.05).
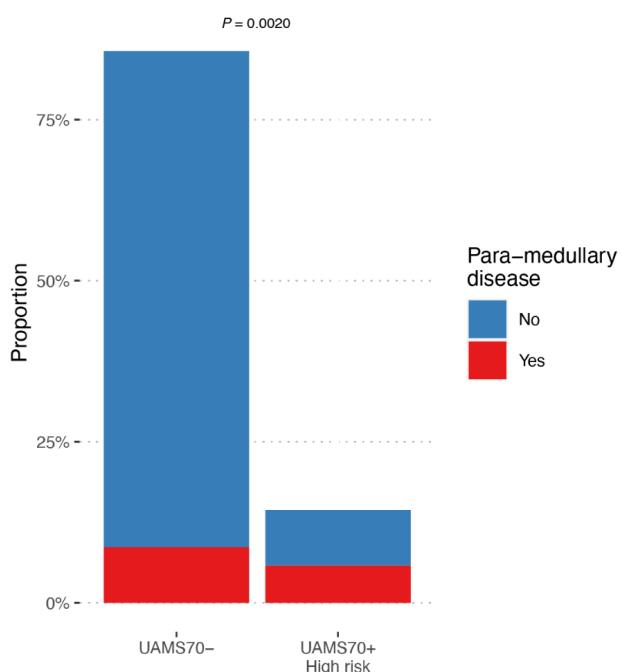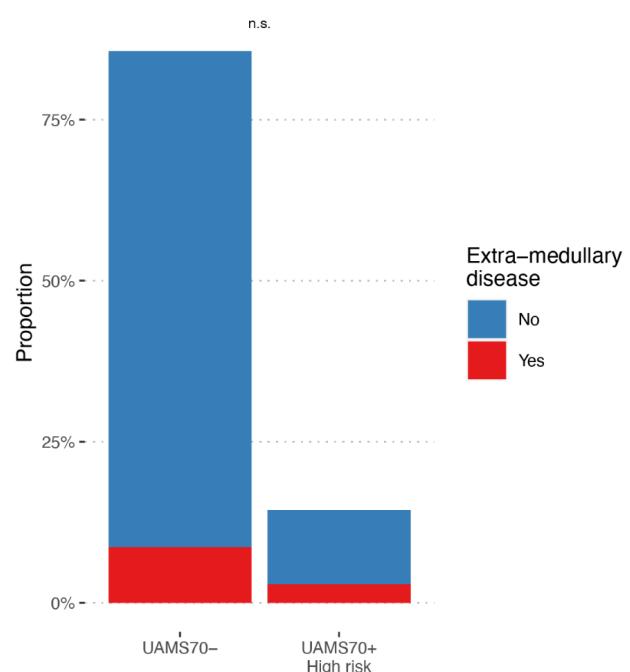
Supplemental Figure 3

Prognostic value of imaging and gene expression profiles in the CASSIOPET cohort. A-B. Distribution of MRD status at day 100 post-ASCT by baseline IFM15 status (A) and baseline PMD status (B). For MRD only, data is available for N=120 patients. C-D. Distribution of stringent complete response (sCR) at day 100 post-ASCT by baseline IFM15 status (C) and presence of PMD at baseline (D). n.s.: not significant (p>0.05).