

**Supplementary Table 1.**

Summary of proteins and antibodies used in the study.

Target					Antibody					
	Protein	Protein intracellular localization	Gene symbol	Gene location	Company	Cat number	Species	Clonality	Dilution Ab	MW peak
<b>1</b>	Aiolos	N, PM, C	<i>IKZF_3</i>	17q12-21	Cell Signaling	12720	rabbit	Polyclonal	1:100	85
<b>2</b>	Cereblon	C, N	<i>CRBN</i>	3p26.2	NovusBio	NBP1-91810	rabbit	Polyclonal	1:80	59
<b>3</b>	Ikaros	N	<i>IKZF_1</i>	7p12.2	Santa Cruz	sc-13039	rabbit	Polyclonal	1:50	70
<b>4</b>	IRF4	N	<i>IRF4</i>	6p25.3	Santa Cruz	sc-6059	goat	Polyclonal	1:100	56
<b>5</b>	gankyrin	N, C	<i>PSMD10</i>	X22.3	Abcam	ab182576	rabbit	Monoclonal	1:50	29
<b>6</b>	PSME1	C, NB	<i>PSME1</i>	14q12	NovusBio	NBP1-83121	rabbit	Polyclonal	1:50	37
<b>7</b>	GCR	N, C, M	<i>NR3C1</i>	5q31.3	Cell Signaling	12041	rabbit	Monoclonal	1:100	100
<b>8</b>	XPO1	N, NM, V, C	<i>CRM1</i>	2p15	Santa Cruz	sc-74454	mouse	Monoclonal	1:50	108
<b>9</b>	PSMA3	C	<i>PSMA3</i>	14q23.1	Santa Cruz	sc-166205	mouse	Monoclonal	1:100	33
<b>10</b>	PSMD1	N,, AF	<i>PSMD1</i>	2q37.1	Santa Cruz	sc-514809	mouse	Monoclonal	1:50	107
<b>11</b>	PSMD4	N, C	<i>PSMD4</i>	1q21.3	Santa Cruz	sc-398033	mouse	Monoclonal	1:100	53
<b>12</b>	AGO2	N, CJ	<i>EIF2C2</i>	8q24.3	Santa Cruz	sc-376696	mouse	Monoclonal	1:50	106
<b>13</b>	GAPDH	PM, C, NM, V	<i>GAPDH</i>	12p13.31	Cell Signaling	2118	rabbit	Monoclonal	1:50	42
<b>14</b>	goat				Santa Cruz	sc-2020	donkey	Polyclonal	1:100	secondary Ab

Protein localization according Human Protein Atlas available from <http://www.proteinatlas.org>

abbreviations: AF- actin filaments; C- cytoplasm; CJ- cell junctions; M- mitochondria; N- nucleoplasm; NB- nuclear bodies; NM- nuclear membrane; PM- plasma membrane; V- vesicles

**Supplementary Table 2.** Univariate cause-specific hazard (CSH) analysis of time to progression and progression-free survival for the competing event (death due other causes)

Protein	cutoff	Group	n	TTP			PFS		
				HR (CI)	Median TTP (months)	p-value	HR (CI)	Median PFS (months)	p-value
<b>Cereblon</b>	0.045	H	139	0.1285 (0.01376-1.2)	NR	<i>0.0719</i>	9.190e+06 (0-Inf)	NR	<b>0.999</b>
		L	10		NR			NR	
<b>Ikars</b>	4.647	H	24	1.231e-08 (0-Inf)	NR	<i>0.999</i>	1.252e-08 (0-Inf)	NR	<b>0.999</b>
		L	125		NR			NR	
<b>Aiolos</b>	0.351	H	41	3.634e-09 (0-Inf)	NR	<i>0.999</i>	3.697e-09 (0-Inf)	NR	<b>0.999</b>
		L	108		NR			NR	
<b>IRF4</b>	0.539	H	111	1.2404 (0.1386-11.1)	NR	<i>0.847</i>	0.5957 (0.05402-6.57)	NR	<b>0.67</b>
		L	40		NR			NR	
<b>PSMD10</b>	0.548	H	112	1.6634 (0.1858-14.89)	NR	<i>0.649</i>	0.8595 (0.07792-9.479)	NR	<b>0.902</b>
		L	37		NR			NR	
<b>PSME1</b>	0.973	H	105	0.6519 (0.1088-3.905)	NR	<i>0.639</i>	3.189e+08 (0-Inf)	NR	<b>0.999</b>
		L	44		NR			NR	
<b>GCR</b>	0.655	H	136	0.4292 (0.04794-3.843)	NR	<i>0.449</i>	7.711e+07 (0-Inf)	NR	<b>0.999</b>
		L	13		NR			NR	
<b>XPO1</b>	2.453	H	89	0.1856 (0.02075-1.661)	NR	<i>0.132</i>	0.3642 (0.03302-4.017)	NR	<b>0.41</b>
		L	62		NR			NR	
<b>PSMA3</b>	4.012	H	15	1.304e-08 (0-Inf)	NR	<i>0.999</i>	1.320e-08 (0-Inf)	NR	<b>0.999</b>
		L	140		NR			NR	
<b>PSMD1</b>	3.458	H	10	3.821e-08 (0-Inf)	NR	<i>0.999</i>	3.839e-08 (0-Inf)	NR	<b>0.999</b>
		L	145		NR			NR	
<b>PSMD4</b>	0.507	H	34	0.94569 (0.1057-8.462)	NR	<i>0.96</i>	1.8993 (0.1722-20.95)	NR	<b>0.6</b>
		L	121		NR			NR	
<b>AGO2</b>	3.510	H	12	3.715e-08 (0-Inf)	NR	<i>0.998</i>	3.753e-08 (0-Inf)	NR	<b>0.999</b>
		L	143		NR			NR	

**Supplementary Table 3.**

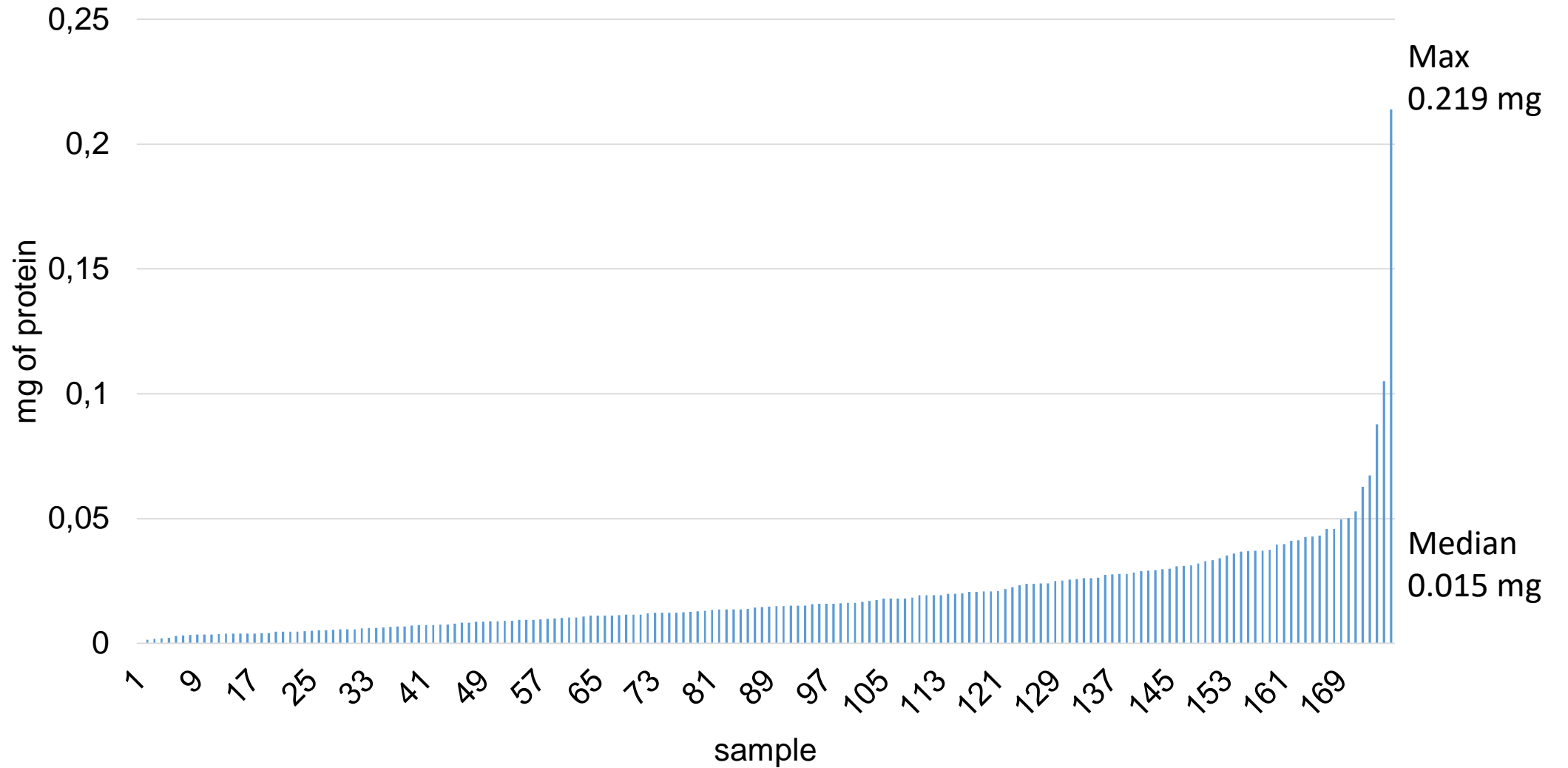
**Patients' characteristics.**

The statistical analysis results using Chi Square or Fisher's exact tests, as appropriate, for categorical variables and the Mann-Whitney U test for continuous variables confirm that the cohort where the expression of the protein was analyzed is a representative for the full cohort analyzed in a GEM2012 and GEM2014MAN trials.

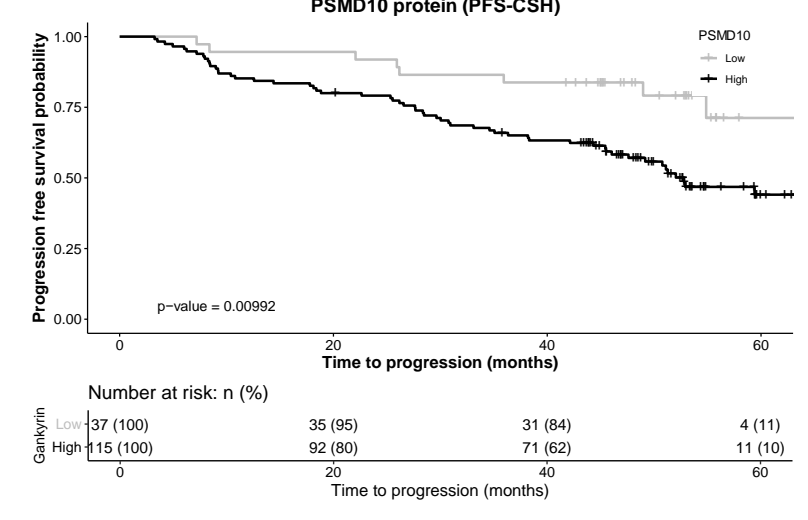
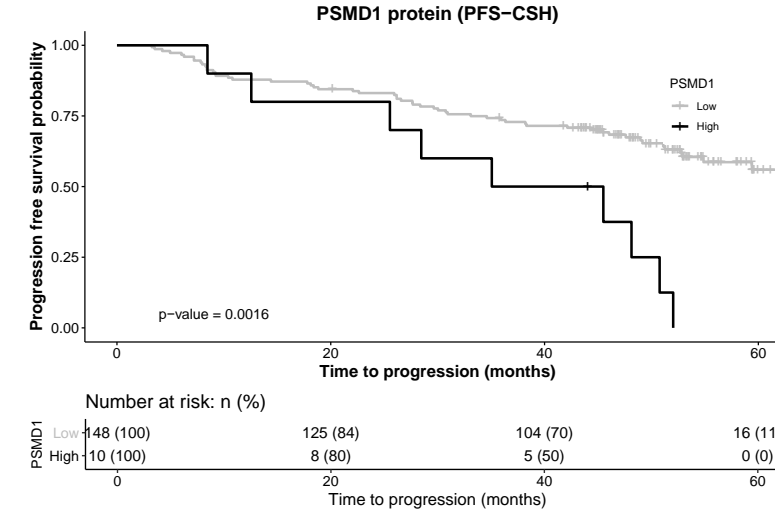
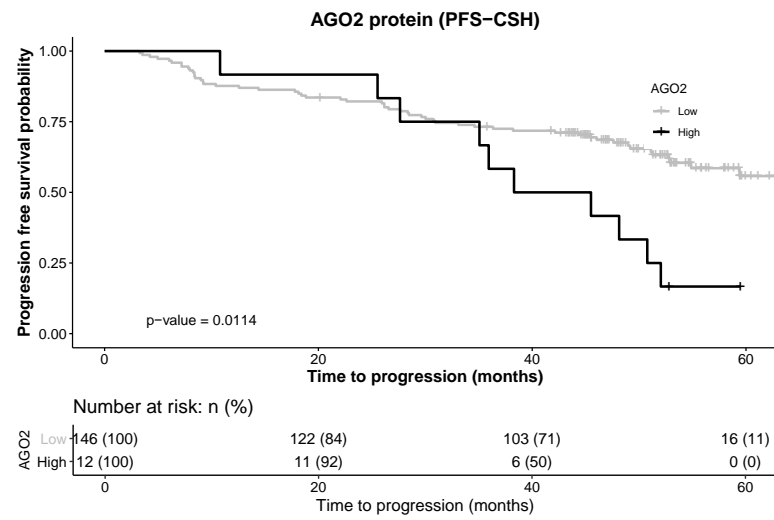
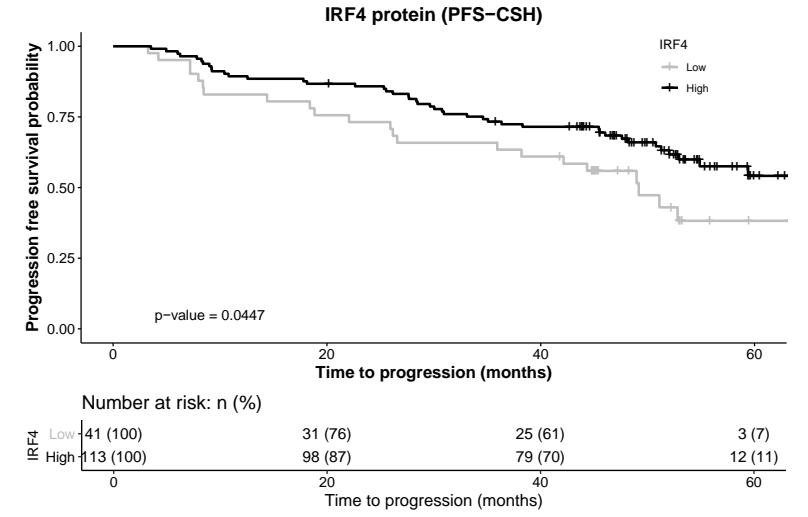
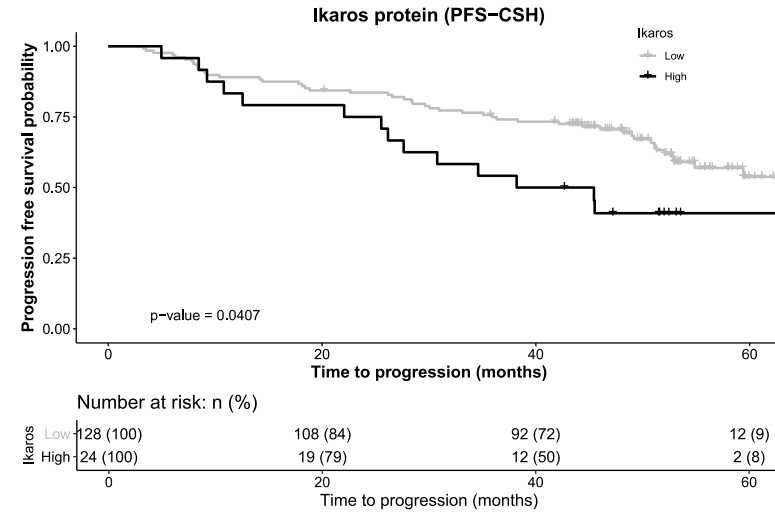
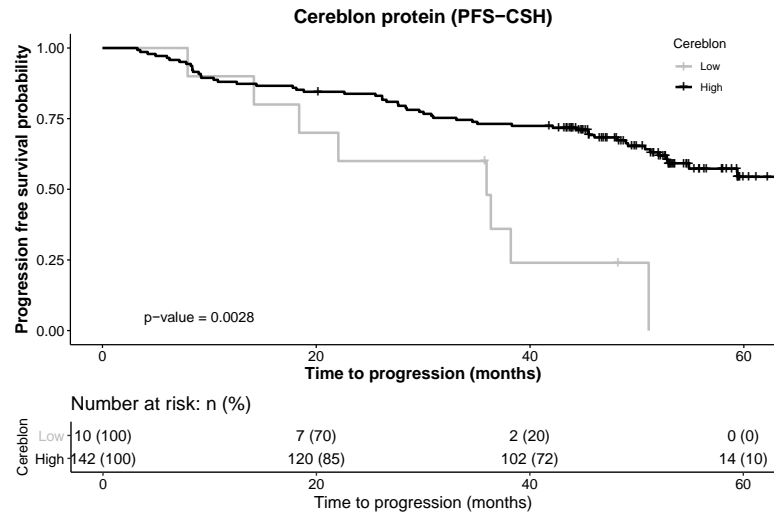
PATIENT CHARACTERISTICS	ALL PATIENTS (n=458)	PROTEIN COHORT (n=174)	p value
Age years	58 (31- 65)	59 (31- 65)	0.744
Gender			0.747
Male	240 (52 %)	88 (50.5 %)	
Female	218 (48 %)	76(49.5 %)	
Myeloma subtype			0.776
IgG	273 (60 %)	110 (63 %)	
IgA	107 (23 %)	39 (23 %)	
Light chain	69 (15 %)	23 (13 %)	
IgD	3 (1 %)	0 %	
Non secretor	6 (1 %)	2 (1 %)	
Durie Stage			0.249
I	54 (12 %)	15 (9 %)	
II	178 (39 %)	79 (45 %)	
III	226 (49 %)	80 (46 %)	
Salmon Stage			0.900
A	449 (98 %)	170 (98 %)	
B	8 (2 %)	4 (2 %)	
ISS Stage			0.275
I	179 (39 %)	56 (33 %)	
II	166 (37 %)	68 (40 %)	
III	107 (24 %)	47 (27 %)	
ISS-R Stage			0.696
I	182 (49 %)	77 (48 %)	
II	151 (40 %)	70 (43 %)	
III	40 (11 %)	14 (9 %)	
ECOG			0.795
0	195 (43 %)	73 (43 %)	
1	182 (40 %)	67 (39 %)	
2	62 (14 %)	22 (13 %)	
3	16 (3 %)	9 (5 %)	
Hemoglobin (g/dl)	10.9 (4.8-16.8)	10.6 (6.7-15.5)	0.099
Creatinine (mg/dl)	0.9 (0.3-2)	0.9 (0.4-2)	0.407
B2-microglobuline (mg/L)	3.6 (0-62)	3.9 (1.6-17.4)	0.056
LDH			0.545
High	65 (15 %)	21 (12 %)	
Normal	376 (85 %)	148 (88 %)	
Plasmacytoma			0.562
Yes	101 (22 %)	34 (20 %)	
No	357 (78 %)	140 (80 %)	
Cytogenetics			
t(4;14)	58/402 (14 %)	24/170 (14 %)	1
t(14;16)	17/394 (4 %)	5/169 (3 %)	0.600
del(17p)	35/388 (9 %)	16/164 (10 %)	0.910
gain(1q)	168/385 (44 %)	82/170 (48 %)	0.362
del(1p)	27/382 (7 %)	16/170 (9 %)	0.437
Cytogenetic risk			0.776
High	92/379 (24 %)	37/163 (23 %)	
Standard	287/379 (76 %)	126/163 (77 %)	
Median follow-up. months	53 (14.7-82.3)	52.2 (24.5-68.4)	0.126

Supplementary table 4. Univariate cause-specific hazard (CSH) analysis of Progression free survival

Protein	cutoff	Group	n	PFS		p-value
				HR (CI)	Median PFS (months)	
Cereblon	0.045	H	142	0.316	NR (52.90-NR)	0.003
		L	10	(0.148-0.673)	35.93 (7.97-NR)	
Aiolos	0.351	H	43	1.68	51.27 (30.77-NR)	0.052
		L	109	(0.996-2.833)	NR (54.87-NR)	
Ikaros	4.647	H	24	1.866	41.82 (25.53-NR)	0.041
		L	128	(1.027-3.39)	NR (52.90-NR)	
AGO2	3.510	H	12	2.396	41.9 (25.53-52.03)	0.011
		L	156	(1.218-4.714)	NR (54.78-NR)	
IRF4	0.539	H	113	0.59	NR (52.90-NR)	0.045
		L	41	(0.352-0.987)	49.17 (26.57-NR)	
PSMA3	3.985	H	17	1.636	48.13 (28.47-NR)	0.155
		L	141	(0.830-3.221)	NR (52.90-NR)	
PSME1	0.981	H	107	1.246	54.87 (50.77-NR)	0.437
		L	45	(0.715-2.171)	NR (48.97-NR)	
PSMD1	3.458	H	10	3.146	40.28 (8.47-50.77)	0.002
		L	148	(1.544-6.41)	NR (54.87-NR)	
PSMD4	0.507	H	34	1.681	48.13 (35.07-NR)	0.059
		L	124	(0.981-2.881)	NR (54.87-NR)	
PSMD10	0.548	H	115	2.652	52.80 (45.50-NR)	0.010
		L	37	(1.264-5.566)	NR (54.87-NR)	
GCR	0.655	H	139	2.077	59.40 (50.77-NR)	0.216
		L	13	(0.651-6.621)	NR (36.33-NR)	
XPO1	2.453	H	91	1.314	52.9 (48.13-NR)	0.292
		L	63	(0.790-2.185)	NR (51.10-NR)	



**Supplementary figure 1.** Amount of protein obtained for each sample. The proteins were extracted from RLT+, as previously described and quantified by Total Protein Assay (ProteinSimple) using WEST™ system (ProteinSimple).



**Supplementary Figure 2. Progression free survival according to levels of protein expression in patients with low and high levels of proteins: cereblon, ikaros, IRF4, Ago2, PSMD1 and PSMD10- gankyrin.**