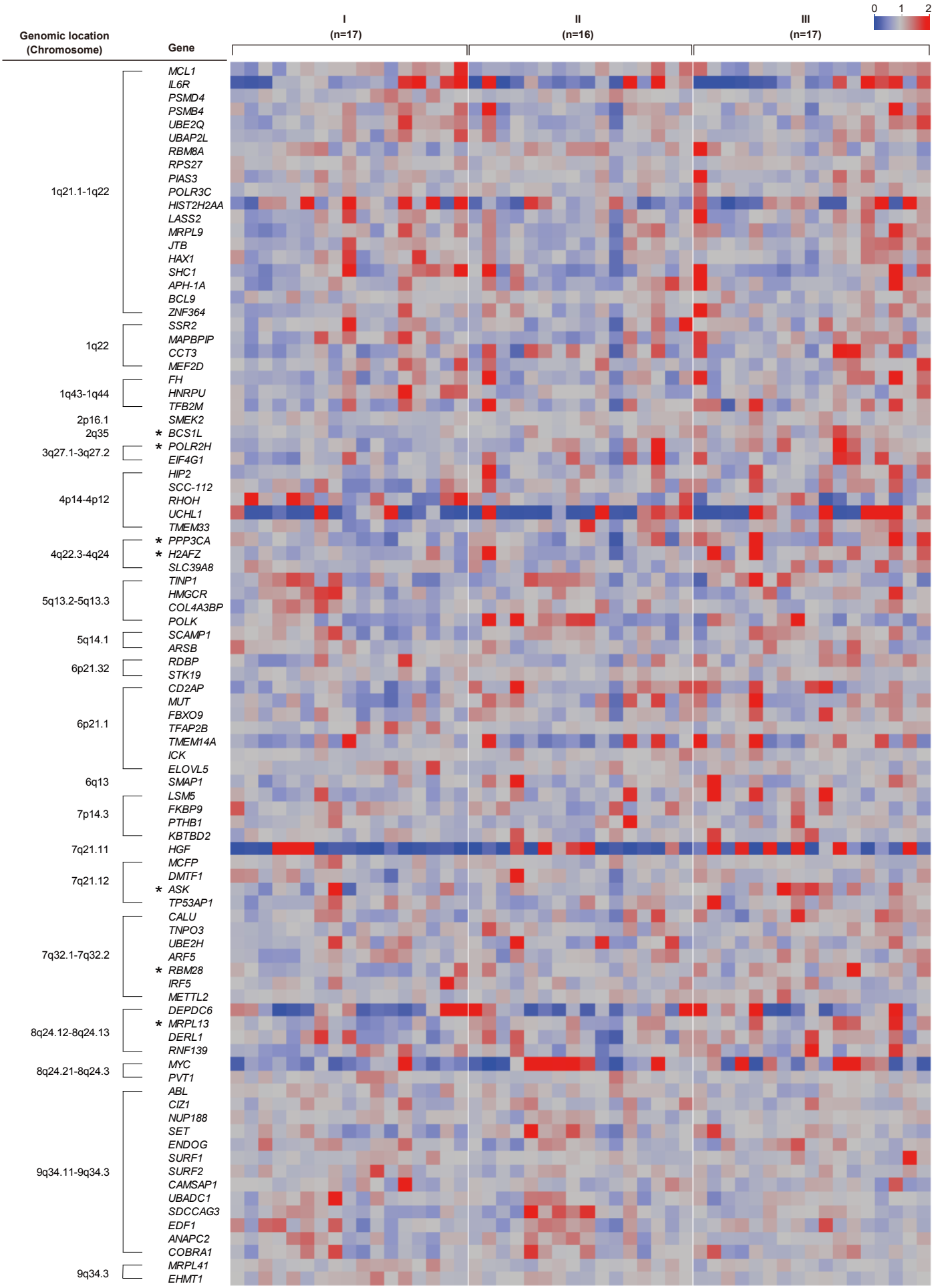
Supplementary Table 1. Characteristics of patients whose *PPP3CA* mRNA expression levels were analyzed.

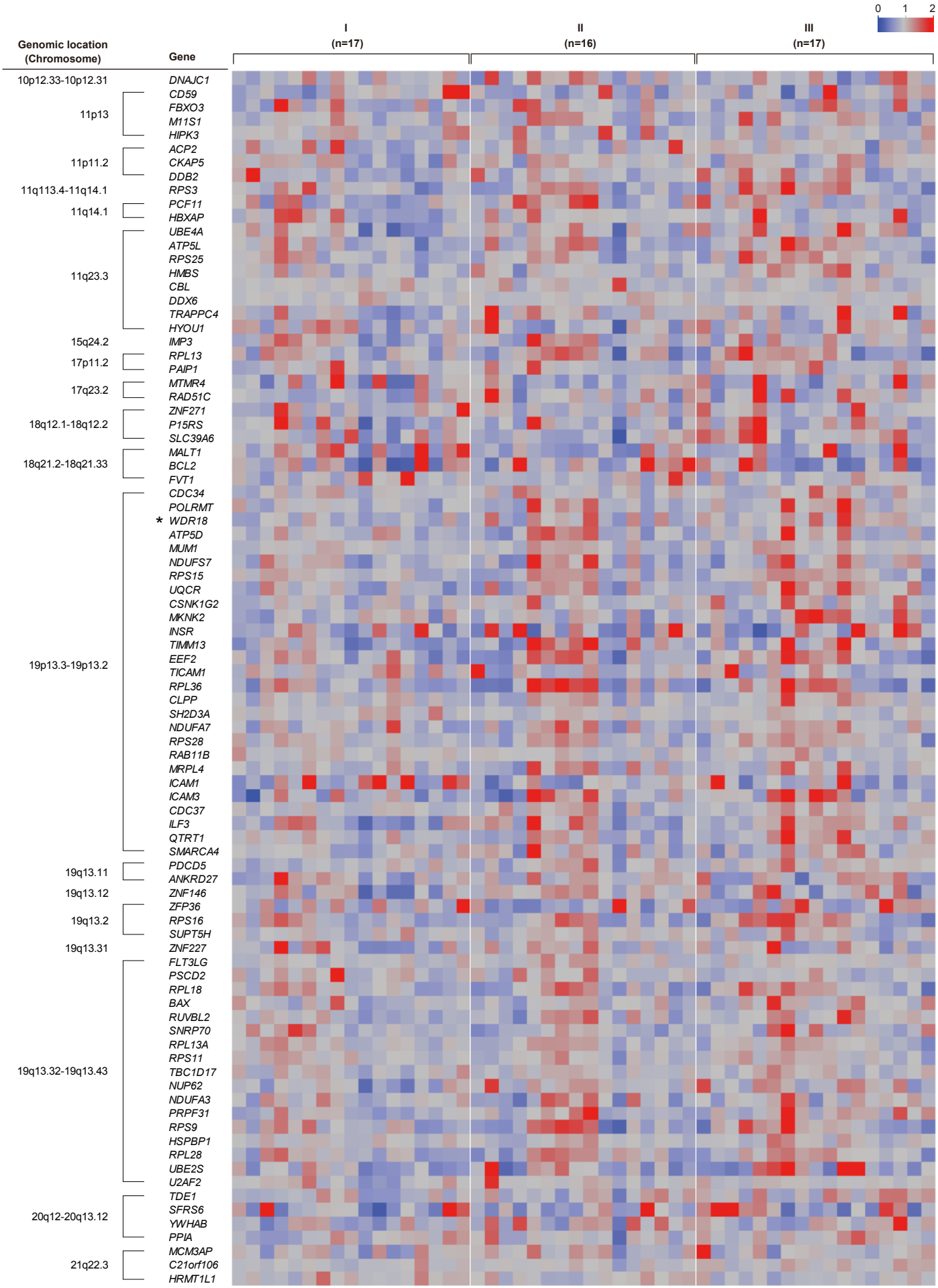
No	*PPP3CA* mRNA	D-S staging	Hb (g/dL)	LDH	therapy, response	response to bortezomib	PFS (days)	censored case
1	1.060	II	10.4	normal	VMP, PR	+	399	–
2	2.174	II	ND	abnormal	VMP, SD	–	172	–
3	1.540	III	10.4	abnormal	VMP, CR	+	899	+
4	0.095	I	13.3	normal	VMP, PR	+	388	–
5	1.367	III	13.9	normal	VMP, CR	+	381	+
6	1.795	III	8.6	NA	VMP, SD	–	92	–
7	1.083	II	11.6	NA	NA	NA	NA	NA
8	0.854	III	11.2	normal	VMP, SD	–	88	–
9	0.565	I	11.5	normal	VMP, PR	+	444	–
10	0.336	III	7.3	abnormal	NA	NA	NA	NA
11	0.608	I	11.7	abnormal	VMP, VGPR	+	548	–
12	0.533	I	11.1	normal	VMP, PR	+	174	–
13	0.457	I	12.3	normal	VMP, PR	+	444	–
14	1.286	II	13.2	normal	BD, sCR	+	295	+
15	1.454	ND	ND	normal	BD, PR	+	264	–
16	0.857	ND	ND	normal	BD, VGPR	+	487	+
17	1.360	ND	ND	normal	VCD, CR	NA	NA	NA
18	4.628	ND	ND	normal	BD, ND	NA	48	–
19	0.954	II	12.6	normal	BD, SD	–	511	+
20	0.508	III	9.8	abnormal	BD, PR	+	487	+
21	0.875	II	11.7	normal	NA	NA	NA	NA
22	0.464	II	10.2	normal	VRD, PR	NA	NA	NA
23	0.442	ND	ND	normal	BD, PR	+	NA	NA
24	1.138	ND	ND	normal	BD, VGPR	+	227	+
25	0.319	II	10.8	normal	NA	NA	NA	NA
26	1.542	III	7.9	normal	VCD, VGPR	NA	NA	NA
27	1.951	III	8.7	abnormal	BD, death	–	60	–
28	1.036	III	9.7	abnormal	BD, CR	+	827	–
29	0.714	III	8.7	abnormal	BD, VGPR	+	825	+
30	1.276	I	8.7	normal	NA	NA	NA	NA
31	0.592	II	11.3	normal	BD, VGPR	+	332	–
32	0.996	ND	ND	normal	BD, VGPR	+	757	–
33	0.603	ND	ND	normal	BD, VGPR	+	294	+
34	0.502	I	9.4	normal	BD, CR	+	924	+
35	0.367	II	10.8	normal	BD, CR	+	885	+
36	0.979	II	9.5	abnormal	NA	NA	NA	NA
37	0.772	I	12.8	NA	VMP, PR	+	516	–
38	0.554	I	11.5	NA	NA	NA	NA	NA
39	0.572	III	11.5	normal	NA	NA	NA	NA
40	1.454	III	13.0	NA	VMP, CR	+	899	+
41	1.115	III	8.9	abnormal	VMP, PR	+	255	+
42	1.663	III	8.4	abnormal	BD, ND	NA	12	–
43	1.271	III	8.2	abnormal	NA	NA	NA	NA
44	0.943	II	9.5	normal	VMP, PR	+	NA	NA
45	0.945	III	12.4	normal	VMP, SD	–	366	–
46	2.658	III	7.3	abnormal	MP, PD	NA	NA	NA
47	1.643	III	9.6	abnormal	VRD, PR	NA	NA	NA
48	1.219	III	7.5	normal	VMP, SD	–	60	+
49	1.777	II	10.9	abnormal	NA	NA	NA	NA
50	1.021	II	9.9	abnormal	VCD, PR	NA	NA	NA

Response to therapy: SD (stable disease), PR (partial response), VGPR (very good partial response), CR (complete response), sCR (stringent CR), death (death during therapy). Bortezomib sensitivity: - (stable disease to VMP or BD, death during BD), + (partial response to VMP or BD or better). PFS: progression-free survival. ND: not determined. NA: not applicable. Censored case corresponds to the dead or missing patient during the observation.

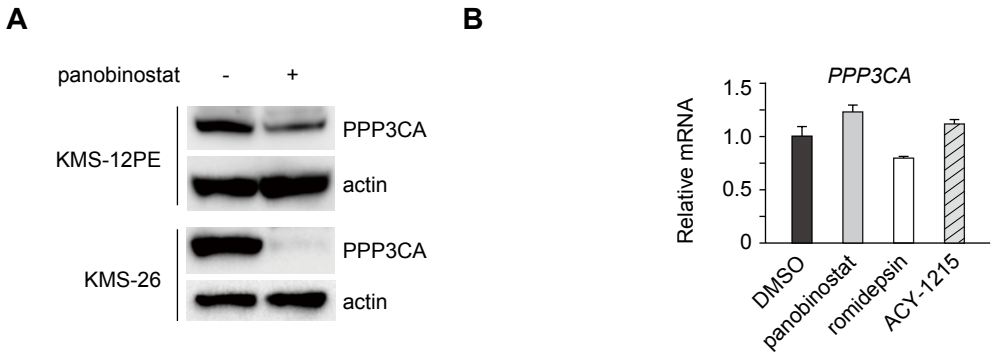
Gene	p. Value
PSMB5: proteasome subunit, β type, 5	2.91E-02
PPP3CA: protein phosphatase 3, catalytic subunit, α isozyme	6.50E-02
CDK5: cyclin-dependent kinase 5	1.34E-01
CYP1A1: cytochrome P450, family 1, subfamily A, polypeptide 1	8.45E-01

Supplementary Table 2. Statistical analyses of *PPP3CA* and several genes associated with bortezomoib resistance in the data set from the millennium trial. Whether expression of each gene in the data set from the millennium trial (58) was higher in non-responsive (no change and progressive disease) than in responsive (minor response and better) patients was analyzed using GEO2R.

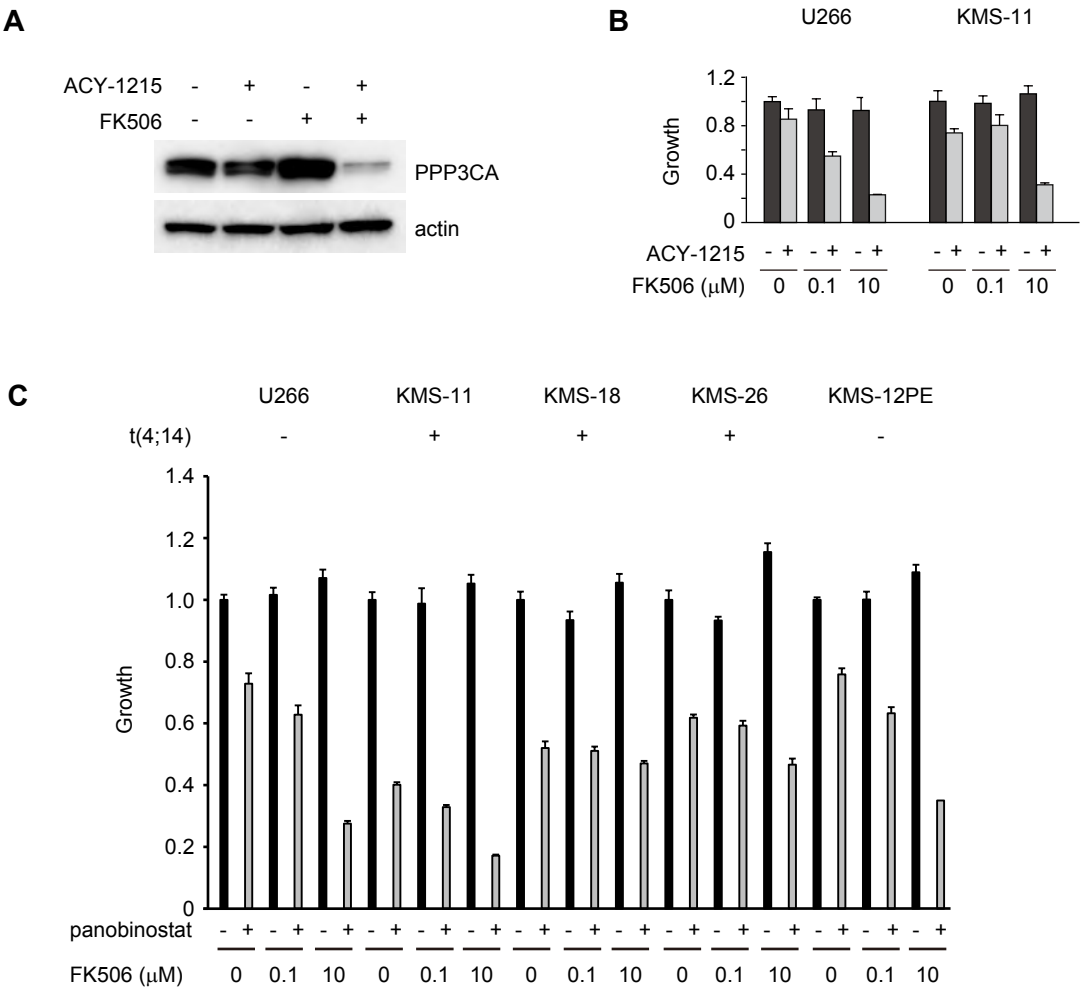

Genomic location (Chromosome)
Gene
I (n=17)
II (n=16)
III (n=17)
0 1 2
1q21.1-1q22
MCL1
IL6R
PSMD4
PSMB4
UBE2Q
UBAP2L
RBM8A
RPS27
PIAS3
POLR3C
HIST2H2AA
LASS2
MRPL9
JTB
HAX1
SHC1
APH-1A
BCL9
ZNF364
1q22
SSR2
MAPBPIP
CCT3
MEF2D
1q43-1q44
FH
HNRPU
TFB2M
2p16.1
SMEK2
2q35
* BCS1L
3q27.1-3q27.2
* POLR2H
EIF4G1
4p14-4p12
HIP2
SCC-112
RHOH
UCHL1
TMEM33
4q22.3-4q24
* PPP3CA
* H2AFZ
SLC39A8
5q13.2-5q13.3
TINP1
HMGCR
COL4A3BP
POLK
5q14.1
SCAMP1
ARSB
6p21.32
RDBP
STK19
6p21.1
CD2AP
MUT
FBXO9
TFAP2B
TMEM14A
ICK
ELOVL5
6q13
SMAP1
7p14.3
LSM5
FKBP9
PTHB1
KBTBD2
7q21.11
HGF
7q21.12
MCFP
DMTF1
* ASK
TP53AP1
7q32.1-7q32.2
CALU
TNPO3
UBE2H
ARF5
* RBM28
IRF5
METTL2
8q24.12-8q24.13
DEPDC6
* MRPL13
DERL1
RNF139
8q24.21-8q24.3
MYC
PVT1
9q34.11-9q34.3
ABL
CIZ1
NUP188
SET
ENDOG
SURF1
SURF2
CAMSAP1
UBADC1
SDCCAG3
EDF1
ANAPC2
COBRA1
9q34.3
MRPL41
EHMT1



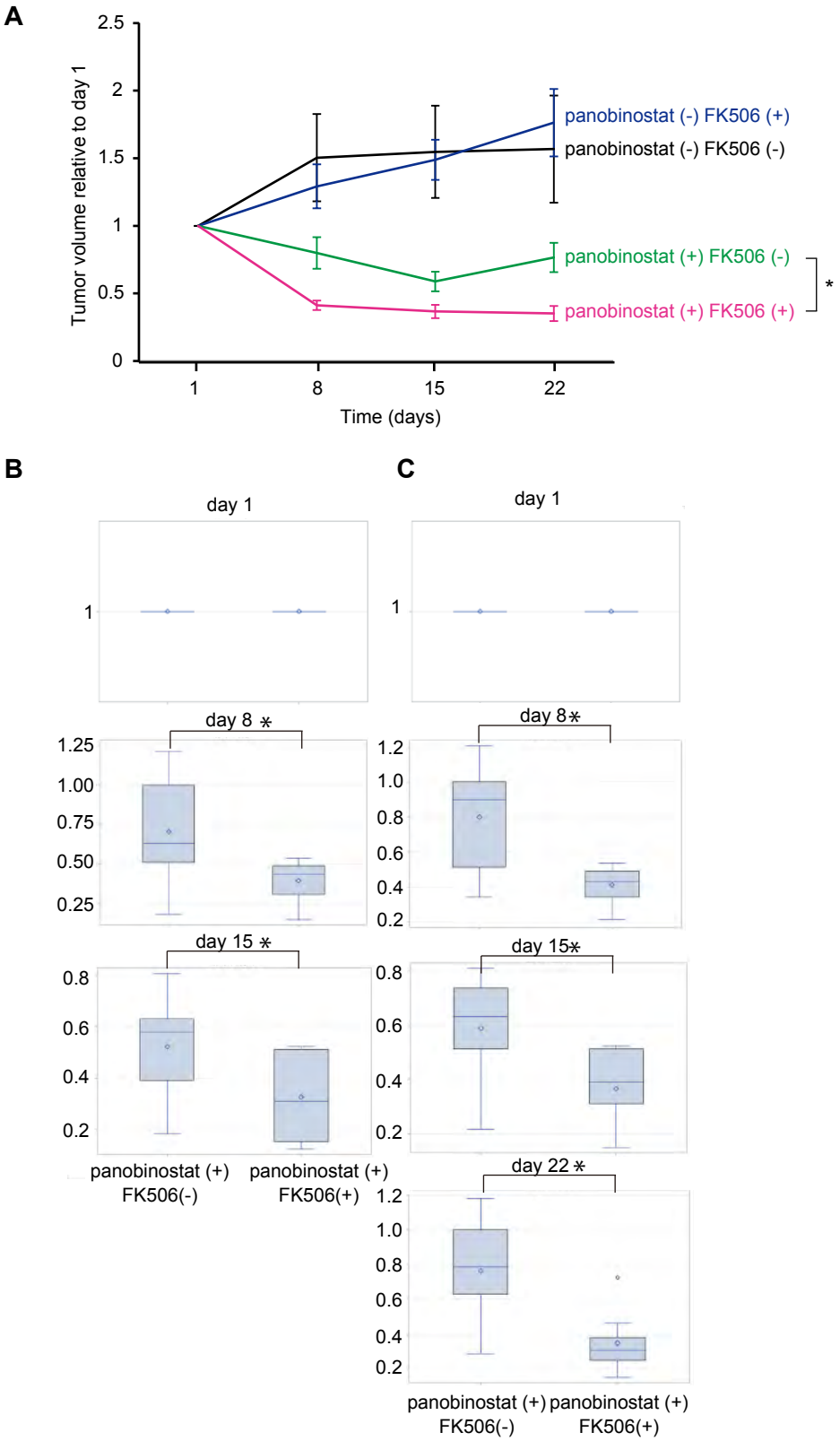
Supplementary Figure 1. Expression analyses of the mRNA of candidate oncogenes in MM patients. mRNA expression data on 179 candidate oncogenes in MM patient samples obtained were analyzed using GEO (20). Each patient' s mRNA amount normalized was displayed by heat maps. Differences between stage I and III patients were analyzed using Tukey-Kramer HSD (honestly significant difference) test. *, significant.



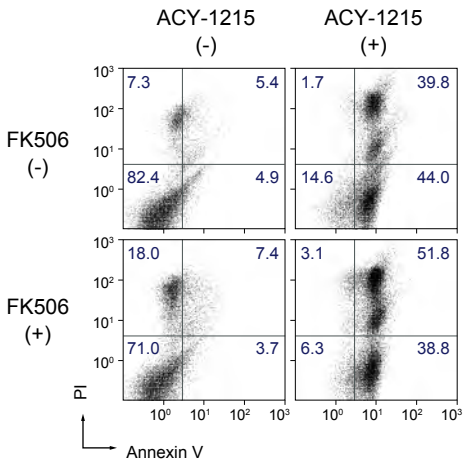
Supplementary Figure 2. PPP3CA is suppressed by HDAC inhibitors in MM cells. (A) Protein expression of PPP3CA in KMS-12PE and KMS-26 treated with 20 nM panobinostat for 48 h. Two biologically independent experiments were performed. (B) Relative mRNA expression of *PPP3CA* in U266 treated with 20 nM panobinostat, 2 nM romidepsin, or 10 mM ACY-1215 for 24 h (n=3). Two biologically independent experiments were performed.



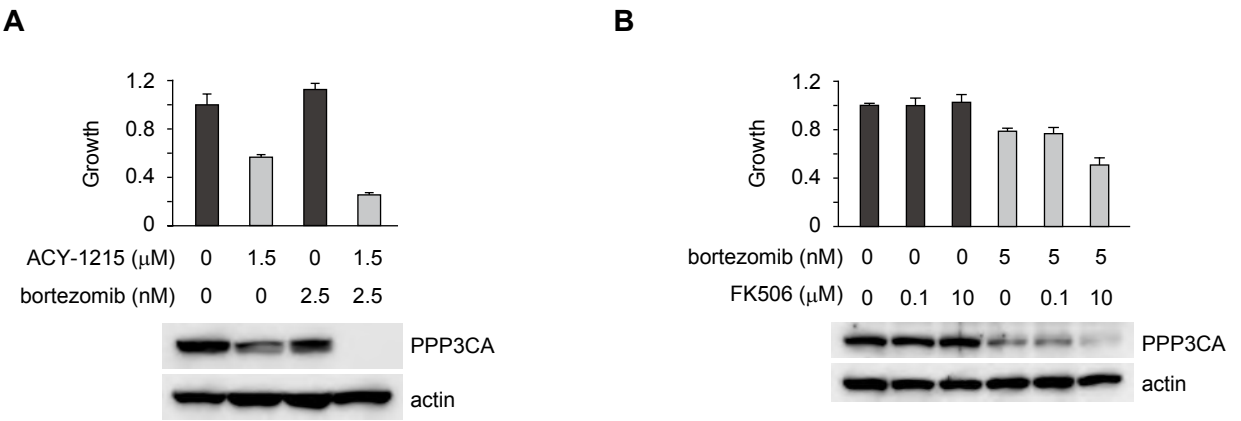
Supplementary Figure 3. Analyses of MM cells treated with HDAC inhibitors and FK506. (A) PPP3CA protein expression in U266 treated with 0.75 μM ACY-1215, 10 μM FK506, or both panobinostat and FK506 as indicated for 48 h. Two biologically independent experiments were performed. (B) MTT assays in U266 treated with 0.75 μM ACY-1215, FK506 or both ACY-1215 and FK506 as indicated for 48 h (n=5). Two biologically independent experiments were performed. (C) MTT assays in U266, KMS-11, KMS-18, KMS-26 and KMS-12PE treated with 15 nM panobinostat, FK506, or both panobinostat and FK506 as indicated for 48 h (n=5). Two biologically independent experiments were performed. The presence or absence of t(4;14) in each cell lines is described.



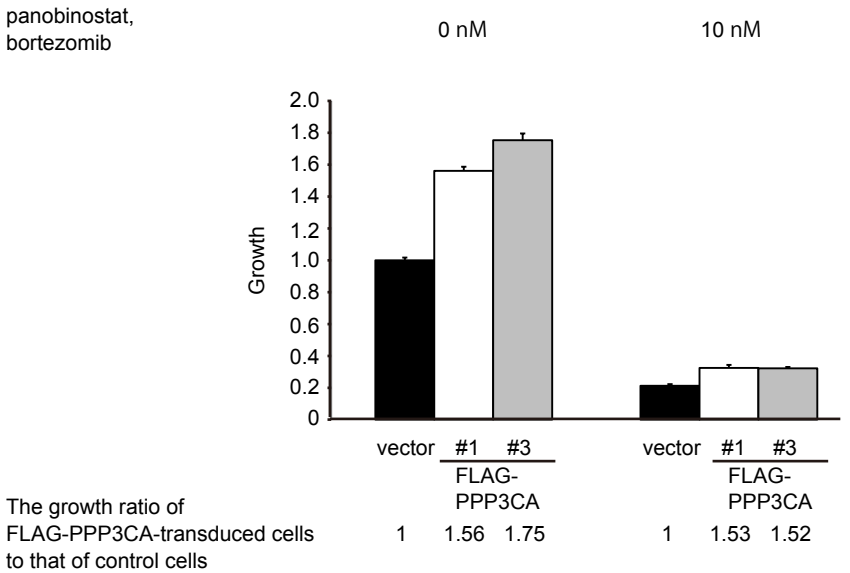
Supplementary Figure 4. Time-dependent variation of tumor volume in xenograft mouse model treated for 22 days and statistical analyses of time-dependent variation of tumor volume in vivo study. (A) NOD/SCID mice bearing U266 cells were treated with vehicle (n=4), panobinostat (n=5), FK506 (n=7), or both panobinostat and FK506 (n=9). Treatment was continued for 22 days. Average of the ratio of the tumor volume on days 8, 15, and 22 to that on day 1 is displayed for each condition. Error bars represent the standard errors. Difference between panobinostat (+) FK506 (-) and panobinostat (+) FK506 (+) on day 22 was analyzed using Scheffe test. *, significant. (B, C) Time-dependent variation of tumor volume in xenograft mouse model was analyzed by SAS ver. 9.4 using GLM procedure. The distribution of tumor volume on designated days is dyplayed by box plot. Diamonds correspond to mean. The difference between two groups on designated days were estimated by Scheffe test analyses. *, siginificant. (B) Panobinostat (+) FK506(-) and panobinostat (+) FK506(+), treatment for 15 days. (C) Panobinostat (+) FK506(-) and panobinostat (+) FK506(+), treatment for 22 days. The ratio of mean volume of panobinostat (+) FK506 (+)-treated mice to that of panobinostat (+) FK506 (-)-treated mice on day 22 (0.459) was less than that on day 15 (0.623).



Supplementary Figure 5. Analyses of MM cells treated with ACY-1215 and FK506. (A) KMS-11 was treated with 0.5 μM ACY-1215, 10 μM FK506, or both ACY-1215 and FK506 as indicated for 36 h. Induced apoptosis was evaluated by flow cytometry. Four biologically independent experiments were performed.



Supplementary Figure 6. Synergistic inhibition of MM cell growth and PPP3CA expression by ACY-1215 and bortezomib or bortezomib and FK506. (A) Cell growth (n=5) and protein expression in U266 treated with ACY-1215, bortezomib, or both ACY-1215 and bortezomib for 48 h. Two biologically independent experiments were performed. (B) Cell growth (n=5) and PPP3CA expression in U266 treated with bortezomib, FK506, or both bortezomib and FK506 as indicated for 72 h. Two biologically independent experiments were performed.



Supplementary Figure 7. Ectopic overexpression of PPP3CA blocks the combination strategy with panobinostat and borterzomib. Cell growth of KMS-11 lentivirally transduced with control vector or FLAG-PPP3CA (clone #1, #3) treated with vehicle or 10 nM of panobinostat and bortezomib for 72 h is displayed (n=5). The growth ratio of FLAG-PPP3CA-transduced cells to that of control cells is displayed. Two biologically independent experiments were performed.