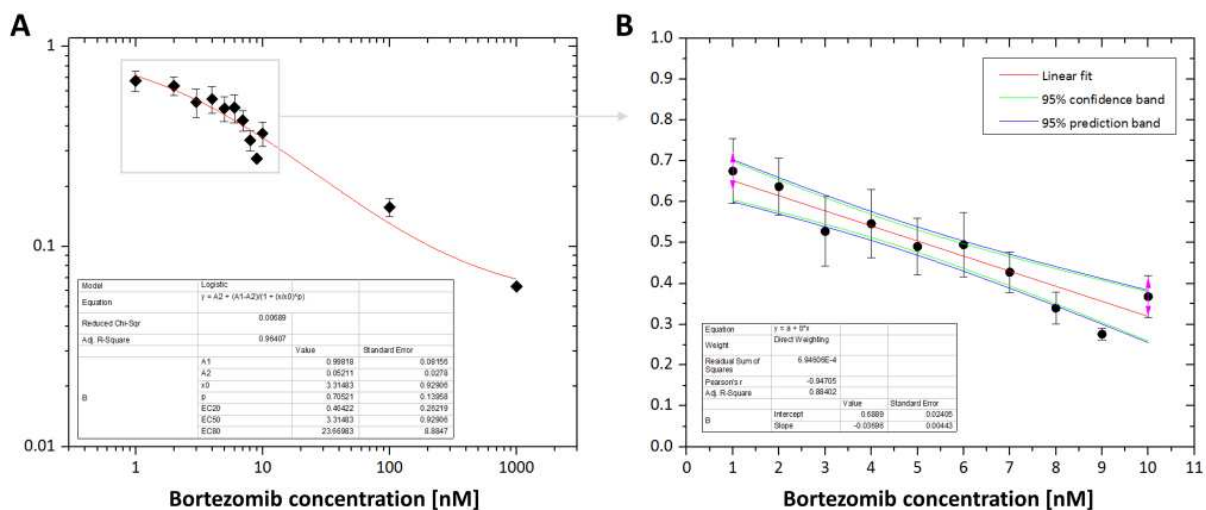**Supplementary Materials**

Figure S1. Inhibition of the proteasome activity in RPMI8226 cells by varying concentrations of bortezomib. The graph on the left shows the decrease in the fraction of proteasome activity in RPMI8226 cells in response to increasing concentrations of bortezomib treated for 105 minutes. The red curve denotes a fitted curve with an R^2 value of 0.964. A different, linear curve was fitted to the 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 nM concentrations of bortezomib, shown on the graph on the right. Error bars are SEM with n=3 technical replicates.
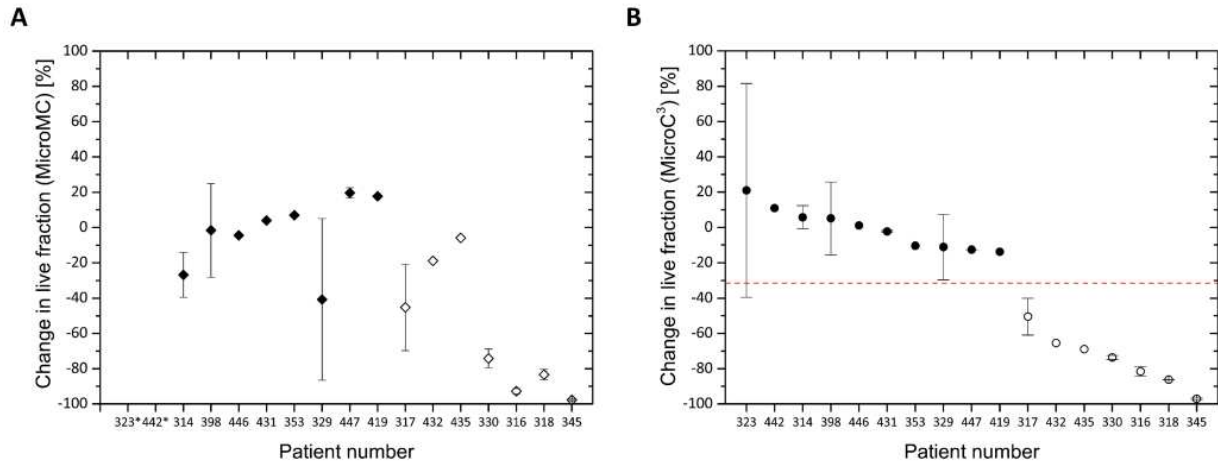
Figure S2. Patient MM tumor cell mean live fraction at 100 nM. The mean live fraction of patient MM tumor cells's *ex vivo* response to 100 nM bortezomib is shown for MicroMC (A) and MicroC^3 (B) in descending order of the change in live fraction according to MicroC^3. Range bars are shown for those patients for whom technical replicates were/were able to be performed (n=2). Open symbols denote clinically responsive patients whereas solid symbols indicate clinically non-responsive patients. The patients with an asterisk denote those omitted from MicroMC analysis (Pt's 323 and 442). The red line marks the Otsu threshold.
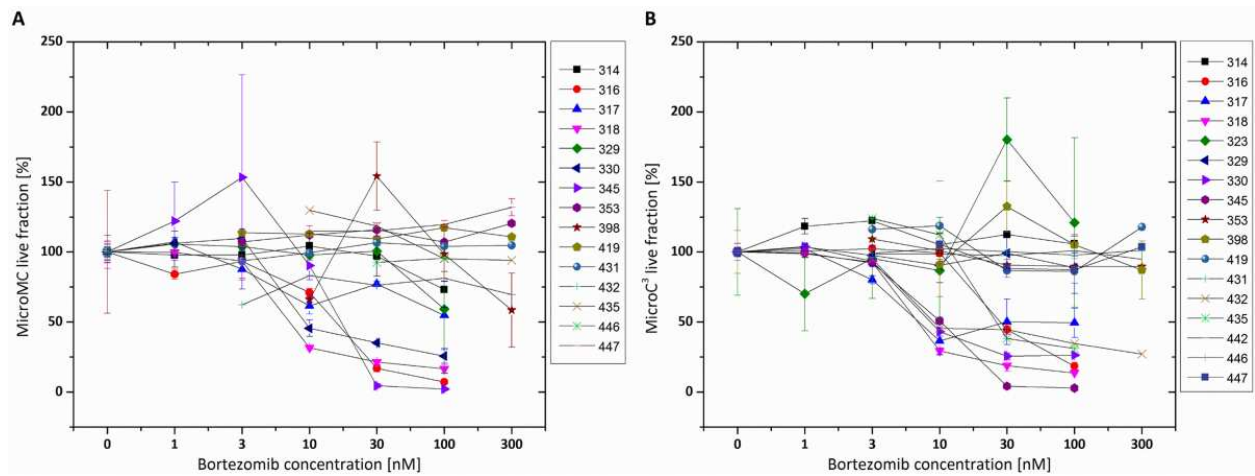
Figure S3. *Ex vivo* **responses of patient MM tumor cells to bortezomib.** *Ex vivo* responses patients' MM cells in MicroMC (A) and MicroC^3(B) to bortezomib are shown. Range bars are shown for those patients for whom technical replicates were/were able to be performed (n=2).

Figure S4. *K*-means clustered *ex vivo* responses of MM patient tumor cells in MicroMC to bortezomib. Box plots of patient *ex vivo* responses in MicroMC (MC) to bortezomib clustered by k-means clustering shown in blue. Open symbols denote clinically responsive patients whereas solid symbols indicate clinically non-responsive patients.
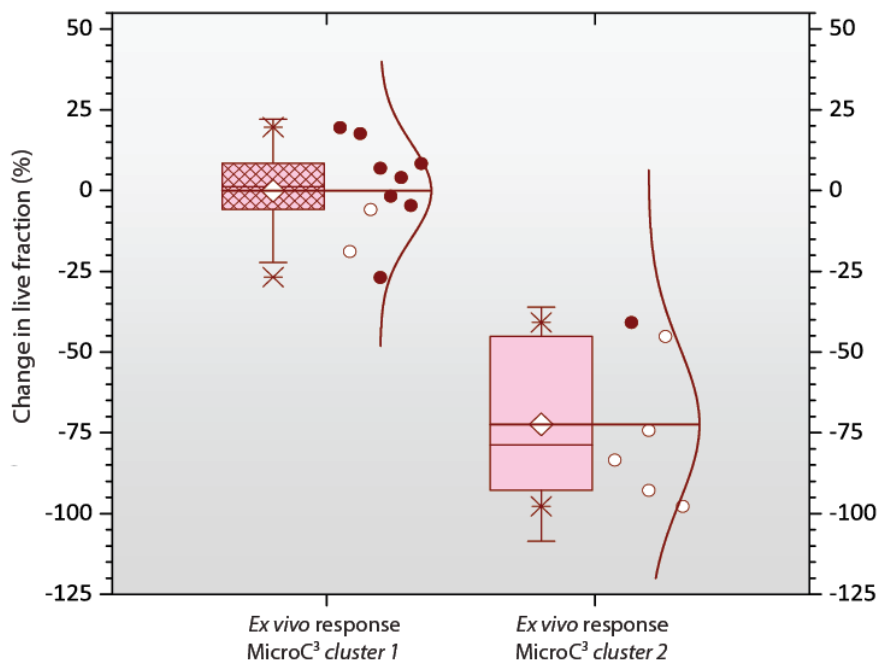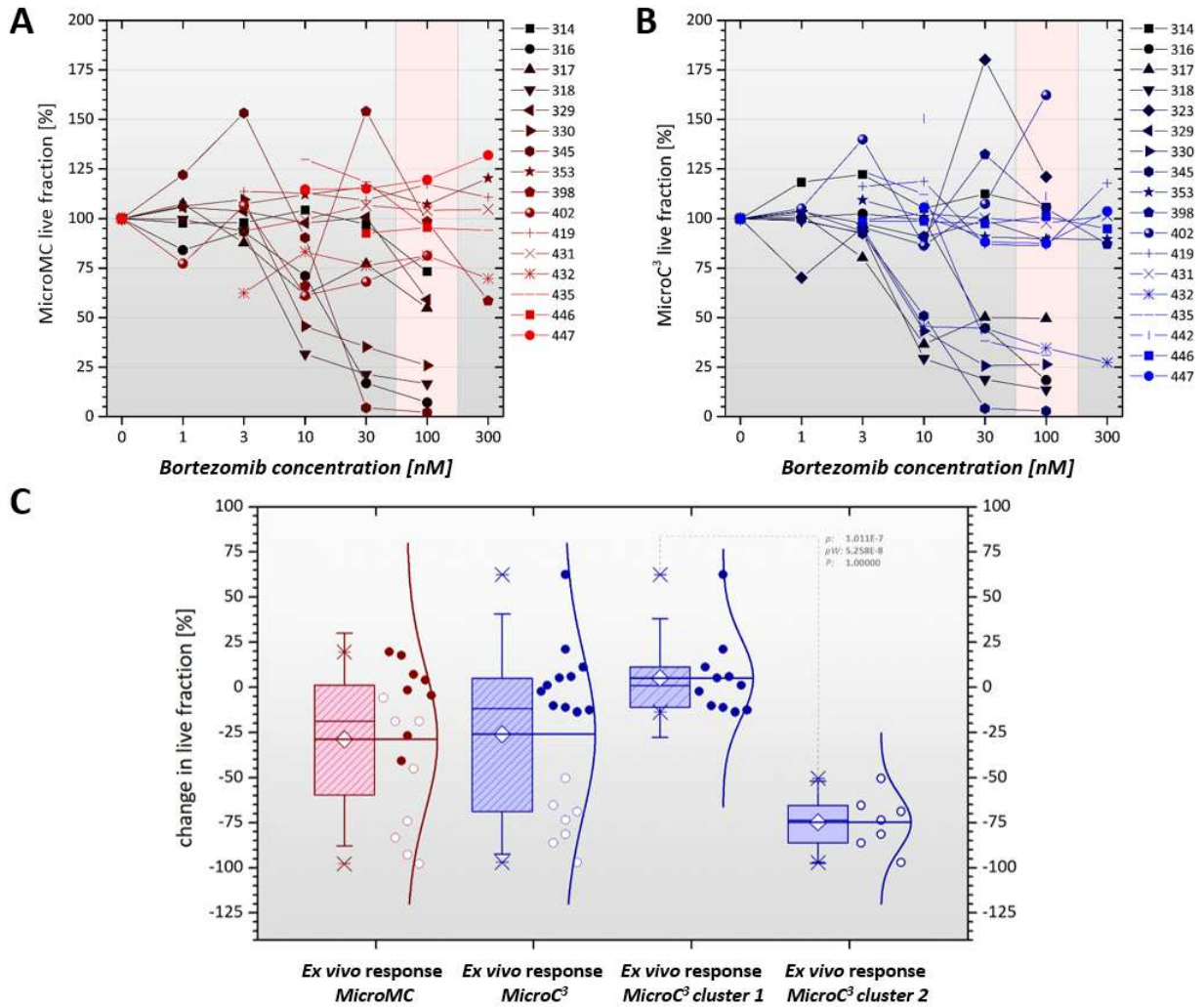
Figure S5. *Ex vivo* **responses of patient MM tumor cells to bortezomib including Pt 402.** (A) *Ex vivo* responses patients' MM cells in MicroMC to bortezomib are shown. (B) *Ex vivo* responses of patients' MM cells in MicroC^3 to bortezomib are shown. C) The first two box plots show patient MM tumor cells' *ex vivo* responses to bortezomib compared between MicroMC (MC, shown in red) and MicroC^3 (shown in blue) (x-axis). The live fraction change is compared between the 0 dose and 100 nM dose of bortezomib (y-axis). K-means and Gaussian clustering methods were applied to MicroC^3, resulting in two clusters of the *ex vivo cis*-cocultured patient MM tumor cells' responses to bortezomib (Cluster 1 and Cluster 2). The same clustering methods applied to MicroMC resulted in one cluster. The two clusters for MicroC^3 are shown in blue as the two box plots on the right.

Patient number	Mononuclear cell count before cryo	Mononuclear cell count after cryo	% alive after cryo	Number of CD138+ cells
142	1,200,000	150,000	12.5%	0
154	1,000,000	200,000	20%	0
321	15,600,000	5,040,000	32.3%	800,000
333	12,800,000	180,000	1.4%	0
334	14,200,000	2,800,000	19.7%	400,000
335	7,840,000	2,000,000	25.5%	80,000
337	3,830,000	1,500,000	39.2%	50,000
345	27,000,000	9,900,000	36.7%	320,000
345 (F)	27,000,000			1,500,000
348	1,900,000	400,000	21.1%	0
378	24,000,000	8,700,000	36.3%	200,000
Average	10,937,000	3,087,000	24.5%	185,000
F, freshly sort/no cryopreservation; cryo, cryopreservation				

Table S1. Patient MM tumor cell counts after cryopreservation.

Time [hr]	Fraction proteasome activity	Bort [nM]	Bort [ng/mL]
0	0.15719	10	38.424
0.25	0.40456	7.69312	29.56
0.5	0.58288	2.86845	11.02
1	0.65536	0.90736	3.48
2	0.53691	4.11238	15.8
4	0.64557	1.17227	4.5
6	0.5382	4.07738	15.67
8	0.5967	2.49447	9.58
10	0.63714	1.40053	5.39
12	1.00111	-8.44731	0
14	0.85956	-4.61743	0
16	1.08216	-10.6402	0
24	1.17081	-13.0387	0
	AUC	112.9155	

Table S2. Extrapolation of the concentrations of 100 nM bortezomib over 24 hours within MicroC[3]

100 nM results:

MicroMC

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	-26.8	1	0.642	2
	316	responder	-92.8	2	0.873	2
	317	responder	-45.2	2	0.299	2
	318	responder	-83.4	2	0.894	2
	323	non-responder	n/a	n/a	n/a	n/a
	345	responder	-97.8	2	0.856	2
	402	non-responder	n/a	n/a	n/a	n/a
	442	non-responder	n/a	n/a	n/a	n/a
BMBX post bortezomib therapy	329	non-responder	-40.8	2	-0.022	2
	330	responder	-74.2	2	0.892	2
	353	non-responder	7.0	1	0.954	1
	398	non-responder	-1.6	1	0.959	1
	419	non-responder	17.7	1	0.927	1
	431	non-responder	4.0	1	0.959	1
	432	responder	-18.8	1	0.837	1
	435	responder	-5.9	1	0.953	1
	446	non-responder	-4.5	1	0.954	1
	447	non-responder	19.6	1	0.919	1

AIC unimodal (k=1)	156.681
AIC bimodal (k=2)	156.591
AIC trimodal (k=3)	157.407
BIC unimodal (k=1)	158.097
BIC bimodal (k=2)	160.131
BIC trimodal (k=3)	163.071
Mean Silhouette (k=2)	0.818

MicroC³

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	5.8	1	0.935	1
	316	responder	-81.5	2	0.964	2
	317	responder	-50.5	2	0.736	2
	318	responder	-86.3	2	0.956	2
	323	non-responder	21.0	1	0.923	1
	345	responder	-97.1	2	0.925	2
	402	non-responder	62.4	n/a	n/a	n/a
	442	non-responder	11.0	1	0.937	1
BMBX post bortezomib therapy	329	non-responder	-11.1	1	0.831	1
	330	responder	-73.6	2	0.965	2
	353	non-responder	-10.3	1	0.841	1
	398	non-responder	5.1	1	0.933	1
	419	non-responder	-13.7	1	0.791	1
	431	non-responder	-2.3	1	0.909	1
	432	responder	-65.4	2	0.938	2
	435	responder	-68.9	2	0.954	2
	446	non-responder	1.0	1	0.924	1
	447	non-responder	-12.6	1	0.809	1

AIC unimodal (k=1)	176.397
AIC bimodal (k=2)	164.746
AIC trimodal (k=3)	168.091
BIC unimodal (k=1)	178.064
BIC bimodal (k=2)	168.079
BIC trimodal (k=3)	173.091
Mean Silhouette (k=2)	0.892

30 nM results:

MicroMC

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	-3.0	1	0.913	1
	316	responder	-83.1	2	0.978	2
	317	responder	-22.9	1	0.650	2
	318	responder	-78.5	2	0.977	2
	323	non-responder	n/a	n/a	n/a	n/a
	345	responder	-95.5	2	0.954	2
	402	non-responder	-32.0	n/a	n/a	n/a
	442	non-responder	n/a	n/a	n/a	n/a
BMBX post bortezomib therapy	329	non-responder	0.6	1	0.925	1
	330	responder	-64.9	2	0.903	2
	353	non-responder	15.8	1	0.927	1
	398	non-responder	54.1	1	0.815	2
	419	non-responder	9.2	1	0.933	1
	431	non-responder	6.6	1	0.933	1
	432	responder	-23.8	1	0.623	2
	435	responder	18.5	1	0.922	1
	446	non-responder	-7.4	1	0.889	2
	447	non-responder	15.0	1	0.928	1

AIC unimodal (k=1)	158.971
AIC bimodal (k=2)	159.090
AIC trimodal (k=3)	160.333
BIC unimodal (k=1)	160.387
BIC bimodal (k=2)	162.630
BIC trimodal (k=3)	165.998
Mean Silhouette (k=2)	0.882

MicroC³

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	12.4	1	0.878	1
	316	responder	-55.3	2	0.907	2
	317	responder	-49.8	2	0.847	2
	318	responder	-81.2	2	0.945	2
	323	non-responder	80.2	1	0.713	1
	345	responder	-95.8	2	0.898	2
	402	non-responder	7.5	n/a	n/a	n/a
	442	non-responder	n/a	n/a	n/a	n/a
BMBX post bortezomib therapy	329	non-responder	-0.9	1	0.804	1
	330	responder	-74.3	2	0.957	2
	353	non-responder	-9.3	1	0.674	1
	398	non-responder	32.4	1	0.865	1
	419	non-responder	-13.2	1	0.573	1
	431	non-responder	0.2	1	0.815	1
	432	responder	-55.4	2	0.908	2
	435	responder	-61.8	2	0.945	2
	446	non-responder	-2.5	1	0.786	1
	447	non-responder	-11.7	1	0.614	1

AIC unimodal (k=1)	161.495
AIC bimodal (k=2)	164.844
AIC trimodal (k=3)	168.844
BIC unimodal (k=1)	162.911
BIC bimodal (k=2)	167.676
BIC trimodal (k=3)	173.092
Mean Silhouette (k=2)	0.819

kM, k-means clustering; GM, Gaussian mixture clustering; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table S3. *K*-means and Gaussian mixture model clustering analysis of *ex vivo* bortezomib sensitivities.

100 nM results:

MicroMC

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	-26.8	1	0.642	1
	316	responder	-92.8	2	0.873	2
	317	responder	-45.2	2	0.299	1
	318	responder	-83.4	2	0.894	2
	323	non-responder	n/a	n/a	n/a	n/a
	345	responder	-97.8	2	0.856	2
	402	non-responder	-18.8	1	0.838	1
	442	non-responder	n/a	n/a	n/a	n/a
BMBX post bortezomib therapy	329	non-responder	-40.8	2	-0.022	1
	330	responder	-74.2	2	0.892	2
	353	non-responder	7.0	1	0.954	1
	398	non-responder	-1.6	1	0.959	1
	419	non-responder	17.7	1	0.927	1
	431	non-responder	4.0	1	0.959	1
	432	responder	-18.8	1	0.837	1
	435	responder	-5.9	1	0.953	1
	446	non-responder	-4.5	1	0.954	1
	447	non-responder	19.6	1	0.919	1

MicroC³

Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index	kM cluster (k=3) index	kM Silhouette value	GM cluster (k=3) index
314	non-responder	5.8	1	0.935	1	1	0.944	1
316	responder	-81.5	2	0.964	2	2	0.957	2
317	responder	-50.5	2	0.736	2	2	0.648	2
318	responder	-86.3	2	0.956	2	2	0.948	2
323	non-responder	21.0	1	0.923	1	1	0.620	1
345	responder	-97.1	2	0.925	2	2	0.914	2
402	non-responder	62.4	1	0.788	1	3	[unclear]	3
442	non-responder	11.0	1	0.937	1	1	0.890	1
329	non-responder	-11.1	1	0.831	1	1	0.940	1
330	responder	-73.6	2	0.965	2	2	0.957	2
353	non-responder	-10.3	1	0.841	1	1	0.945	1
398	non-responder	5.1	1	0.933	1	1	0.948	1
419	non-responder	-13.7	1	0.791	1	1	0.917	1
431	non-responder	-2.3	1	0.909	1	1	0.967	1
432	responder	-65.4	2	0.938	2	2	0.923	2
435	responder	-68.9	2	0.954	2	2	0.943	2
446	non-responder	1.0	1	0.924	1	1	0.964	1
447	non-responder	-12.6	1	0.809	1	1	0.928	1

AIC unimodal (k=1)	165.902
AIC bimodal (k=2)	162.990
AIC trimodal (k=3)	168.990
BIC unimodal (k=1)	167.447
BIC bimodal (k=2)	166.853
BIC trimodal (k=3)	175.170
Mean Silhouette (k=2)	0.784

	Analysis *with* pt 402	Analysis *without* pt 402
AIC unimodal (k=1)	190.606	176.397
AIC bimodal (k=2)	188.176	164.746
AIC trimodal (k=3)	183.306	168.091
BIC unimodal (k=1)	192.387	178.064
BIC bimodal (k=2)	191.737	168.079
BIC trimodal (k=3)	188.648	173.091
Mean Silhouette (k=2)	0.892	Mean Silhouette (k=3) 0.909

30 nM results:

MicroMC

	Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
BMBX pre bortezomib therapy	314	non-responder	-3.0	1	0.913	1
	316	responder	-83.1	2	0.978	2
	317	responder	-22.9	1	0.650	2
	318	responder	-78.5	2	0.977	2
	323	non-responder	n/a	n/a	n/a	n/a
	345	responder	-95.5	2	0.954	2
	402	non-responder	-32.0	1	0.275	2
	442	non-responder	n/a	n/a	n/a	n/a
BMBX post bortezomib therapy	329	non-responder	0.6	1	0.925	1
	330	responder	-64.9	2	0.903	2
	353	non-responder	15.8	1	0.927	1
	398	non-responder	54.1	1	0.815	2
	419	non-responder	9.2	1	0.933	1
	431	non-responder	6.6	1	0.933	1
	432	responder	-23.8	1	0.623	2
	435	responder	18.5	1	0.922	1
	446	non-responder	-7.4	1	0.889	2
	447	non-responder	15.0	1	0.928	1

MicroC³

Patient ID	Clinical response to Bortezomib	Ex vivo response [%]	kM cluster (k=2) index	kM Silhouette value	GM cluster (k=2) index
314	non-responder	12.4	1	0.878	1
316	responder	-55.3	2	0.907	2
317	responder	-49.8	2	0.847	2
318	responder	-81.2	2	0.945	2
323	non-responder	80.2	1	0.713	1
345	responder	-95.8	2	0.898	2
402	non-responder	7.5	1	0.864	1
442	non-responder	n/a	n/a	n/a	n/a
329	non-responder	-0.9	1	0.804	1
330	responder	-74.3	2	0.957	2
353	non-responder	-9.3	1	0.674	1
398	non-responder	32.4	1	0.865	1
419	non-responder	-13.2	1	0.573	1
431	non-responder	0.2	1	0.815	1
432	responder	-55.4	2	0.908	2
435	responder	-61.8	2	0.945	2
446	non-responder	-2.5	1	0.786	1
447	non-responder	-11.7	1	0.614	1

AIC unimodal (k=1)	168.390
AIC bimodal (k=2)	169.500
AIC trimodal (k=3)	171.339
BIC unimodal (k=1)	169.935
BIC bimodal (k=2)	173.363
BIC trimodal (k=3)	177.519
Mean Silhouette (k=2)	0.821

AIC unimodal (k=1)	181.150
AIC bimodal (k=2)	182.817
AIC trimodal (k=3)	185.150
BIC unimodal (k=1)	188.483
BIC bimodal (k=2)	179.405
BIC trimodal (k=3)	184.404
Mean Silhouette (k=2)	0.823

kM, k-means clustering; GM, Gaussian mixture clustering; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table S4. *K*-means and Gaussian mixture model clustering analysis of *ex vivo* bortezomib sensitivities, including Pt 402.