**Supplementary Figure legends**

Supplementary Figure 1, related to Figure 2CRecombinant USP1/UAF1 complex was incubated with DMSO control, USP1 inhibitor SJB, ML323 or proteasome inhibitor marizomib for 30 mins at 37°C, followed by the assessment of DUB activity using Ub-AMC assay (mean ± SE; p < 0.05 for USP1 activity in control verses SJB treated samples, n=3).

Supplementary Figure 2, related to Figure 3AMM.1S cells were treated with DMSO or SJB for 3h; protein lysates were incubated with HA-Ub-VS probe for 30 mins, followed by western blot analysis using anti-HA Ab.

Supplementary Figure 3, related to Figure 3BUb chain disassembly reactions of Ub tetramers by purified recombinant USP2 or USP7 enzymes after 30 min incubation with DMSO or SJB. Immunoblot analysis was performed using anti-Ub Abs.

Supplementary Figure 4, related to Figure 4AMM.1S, RPMI-8226 or normal PBMCs were treated with DMSO, ML323, SJB2-043, Pimozide or GW7647 for 72h, followed by measurement of cell viability with WST-1 assay (mean ± SE; p < 0.05 for all cell lines; n=3).

Supplementary Figure 5(A) Dox-40 cells were treated with SJB for 15h, and then analyzed for apoptosis using Annexin V/PI staining (mean ± SD; n = 3; p < 0.005). (B) Dox-40 cells were treated with DMSO control or SJB for 12h; protein lysates were subjected to immunoblot analysis using antibodies directed against USP1, ID1, ID2, ID3, ID4 or GAPDH.

Supplementary Figure 6, related to Figure 6A GEP analysis of ID proteins showed an inverse correlation with survival in MM patients. Kaplan-Meier plots: Red line show patient group with higher ID protein expression, and blue line indicates patients with lower ID expression.

Supplementary Figure 7Synergistic anti-MM activity of SJB with other agents **(A)** MM.1S cells were treated with SJB, bortezomib or SJB plus bortezomib for 24h, and then analyzed for viability. The graph shows values from the the tables. Confidence interval (CI) <1 indicates synergy. **(B)** MM.1S cells were treated with SJB, ACY-1215 or SJB plus ACY-1215 for 24h, and then assessed for viability using WST assay. Synergistic activity was analyzed as in (A). **(C)** MM.1S cells were treated with SJB, lenalidomide or SJB plus lenalidomide for 24h, and then examined for viability. Synergy was analyzed as in panel (A). **(D)** MM.1S cells were treated with SJB, pomalidomide or SJB plus pomalidomide for 24h, and then analyzed for viability. Synergy was analyzed as in panel (A).

Supplementary Figure 8Synergistic anti-MM activity of SJB with other agents **(A)** CD138+ patient MM cells were treated with SJB, bortezomib or SJB plus bortezomib for 24h, and then analyzed for viability using Cell Titer-Glo assay. The graph shows values from the the tables. Confidence interval (CI) <1 indicates synergy. **(B)** CD138+ patient MM cells were treated with SJB, ACY-1215 or SJB plus ACY-1215 for 24h, and then assessed for viability using WST assay. Synergistic activity was analyzed as in (A). **(C)** CD138+ patient MM cells were treated with SJB, lenalidomide or SJB plus lenalidomide for 24h, and then examined for viability. Synergy was analyzed as in panel (A). **(D)** CD138+ patient MM cells were treated with SJB, pomalidomide or SJB plus pomalidomide for 24h, and then analyzed for viability. Synergy was analyzed as in panel (A).