**Supplementary Figure 1.**

The cell viability assay with different order of drug treatment. (A, B) HCT116 and RKO cells were treated with Bortezomib and KPT330 at different order for 72h. Cell viability was measured by CCK8. Combination 1: Both drugs were given concurrently; Combination 2: Bortezomib were given after KPT330 preceding treatment for 3h; Combination 3: Bortezomib were given after KPT330 preceding treatment for 6h; Combination 4: KPT330 were given after Bortezomib preceding treatment for 3h; Combination 5: KPT330 were given after Bortezomib preceding treatment for 6h. (p<0.01, \*\*).

**Supplementary Figure 2.**

Carfilzomib and KPT330 exhibited synergistic cytotoxicity in HCT116 cells. (A, B) HCT116 and SW480 cells were treated concurrently with Carfilzomib and KPT330 at the indicated concentrations for 72h. Cell viability was measured by CCK8. The synergistic cytotoxicity was quantitatively analyzed by Combination Index (CI) using the Calcusyn software program. (C) Immunofluorescence with p53 antibody in HCT116 after treatment with Carfilzomib (2 nM) or KPT330 (100 nM) for 12 h. Bars represent 10 μm. (D) After knocking downing the expression of p53, HCT116 cells were treated with Carfilzomib (2 nM) or KPT330 (100 nM) for 72h. Scrambled siRNA served as negative control. CCK8 assay was performed to detect cell viability in different groups. The bars represent the mean ± SEM of triplicates in one experiment. (p<0.01, \*\*).

**Supplementary Figure 3.**

Bortezomib induced nuclear export of p53 in SW480 and SW620 cells. (A, B) Immunofluorescence with p53 antibody in SW480 and SW620 cells after treatment with Bortezomib (5nM) or KPT330 (100nM) for 12 h. Bars represent 10 μm.

**Supplementary Figure 4.**

Nuclear p53 plays a critical role in synergistic cytotoxic effect in RKO cells. (A) RKO cells were treated with Bortezomib (5nM) or KPT330 (100nM) for 12h. Nuclear (N) and cytoplasmic (C) Extracts were separated and subjected to western blotting using p53 antibody. (B) RKO cells were treated with Bortezomib (5nM) or KPT330 (100nM) for 12h and subjected to western blotting using various antibodies as indicated. (C) Band densities of results in Fig. S4B were measured. (D) The knockdown efficiency of siRNA of p53 was confirmed by real-time PCR analysis. (E) After knocking downing the expression of p53, RKO cells were treated with Bortezomib (5nM) or KPT330 (100nM) for 72h. Scrambled siRNA served as negative control. CCK8 assay was performed to detect cell viability in different groups. The bars represent the mean ± SEM of triplicates in one experiment. (p<0.01, \*\*).

**Supplementary Figure 5.**

Bortezomib and KPT330 co-treatment inhibit patients-derived xenografts in nude mice. (A) A representative PDX model used in this study. (B) Representative H&E stained sections of the original tumors and of xenografts both at an early passage (Px1) and the passage used for the experiments (Px3). Bars represent 100 μm. (C) The tumor reduction rate of 5 PDXs treated with various therapeutics. (n=6 per group).