Supplement Figure legends:

<u>Supplement Figure 1:</u> (A) Dose response curves to compare IC50 of Bortezomib in CRC cell lines. Six CRC cell lines were treated with various doses of Bortezomib for 48 hours and IC50 was determined by annexinV/PI dual staining. (B) Table of IC50 in six CRC cell lines. At-least three independent experiments were used to calculate the IC50 of CRC cell lines.

<u>Supplement Figure 2:</u> (A) Bortezomib-induced apoptosis in CRC cell lines. HCT-116, LOVO and DLD-1 cells were treated with various doses of Bortezomib (as indicated) for 48 hours and cells were subsequently stained with flourescein-conjugated annexin-V and propidium iodide (PI). (B) Effect of Bortezomib treatment on expression of SKP2 and p27Kip1. HCT-116, LOVO and DLD-1 cells were treated with and without 100 and 500nm Bortezomib for 48 hours. After cell lysis, equal amounts of proteins were separated by SDS-PAGE, transferred to immobilon membrane, and immuno-blotted with antibodies against SKP2, p27Kip1 and beta actin as indicated.

<u>Supplement Figure 3:</u> (A) Combination of Bortezomib and 5-Fluorouracil induced apoptosis. HCT-15 cells were treated with indicated doses of Bortezomib and 5-Fluorouracil for 48 hours and cells were subsequently stained with flourescein-conjugated annexin-V and propidium iodide (PI). (B) Bar graph depicting apoptosis induced in HCT-15 cells after combination treatment with

Bortezomib and 5-Fluorouracil as detected by flourescein-conjugated annexin-V and propidium iodide (PI) staining and analysis with flow cytometry.

Supplement Figure 4: Bortezomib induced activation of the mitochondrial apoptotic pathway in CRC cell lines. (**A**) Bortezomib -induced activation of caspase-8 and BID cleavage. Colo-320, and SW480 cells were treated with 100 and 500nM Bortezomib for 48 hours. Cells were lysed and 20μg of protein were separated by SDS-PAGE, transferred to immobilon membrane, and immuno-blotted with antibodies against caspase-8, Bid and beta-actin. (**B**) Loss of mitochondrial membrane potential by Bortezomib treatment in CRC cells. Colo320 and SW-480 cells were treated with and without Bortezomib for 48 hours. Cells with intact mitochondrial membrane potential (red bar) and with lost mitochondrial membrane potential (green bar) was measured by JC-1 staining and analyzed by flow cytometry as described in Materials and Methods. (**C**) Bortezomib-induced release of cytochrome c. Colo320 cells were treated with and without Bortezomib for 48 hours. Mitochondrial and cytoplasmic fractions were isolated as described in Materials and Methods. Cell extracts were separated on SDS-PAGE, transferred to PVDF membrane, and immuno-blotted with an antibody against cytochrome c and beta-actin.