**Supplementary Figure 1 and 2. Effects of cetuximab in combination with regorafenib in a panel of CRC cell lines with primary and acquired resistance to anti-EGFR inhibitor *in vitro*.**

The indicated CRC cell lines were treated every day with different concentrations of cetuximab (range, 0.01 to 20 g/ml) and/or regorafenib (range, 0.05 to 5 M) for 96 hours at a fixed drug ratio of 1:1 and cell proliferation was evaluated by MTT assay. Combination Index (CI) values were calculated according to the Chou and Talalay mathematical model for drug interactions using the Calcusyn software, as described in Materials and Methods. For each cell line, it is shown in the left panel the percent of cell growth inhibition determined by treatment with cetuximab, with regorafenib or with their combination. For each cell line, in the right panel it is shown the combination index for the combination of cetuximab plus regorafenib. Results represent the median of three separate experiments, each performed in quadruplicate.

**Supplementary Figure 3. Pro-apoptotic effects of cetuximab in combination with regorafenib in SW620 CRC cell line with primary resistance to anti-EGFR inhibitor.**

SW620 cells were treated for 48 hours with the same doses of drugs as Western blot assay. Apoptosis was evaluated with Annexin V staining, as described in Materials and Methods.

**Supplementary Figure 4.** **Effects of cetuximab in combination with regorafenib on mice body weight.**

NudeMice injected into the cecal wall with HCT116 cancer cells and treated with cetuximab and or regorafenib, were weighed twice weekly for the entire period of treatment. \*\* = *P*<0.005 (combination versus control).