Supplementary Figure Legends

Supplementary Figure 1. (A-B) Cells transduced with control or two independent KRAS (KRAS-1 or KRAS-2) targeting inducible shRNA were grown in the absence or presence of dox (10ng/ml) for 72 hours. Knockdown of KRAS transcript in all lines were confirmed by qRT-PCR. (C) Immunoblot analysis of pERK levels upon KRAS-1 and KRAS-2 knockdown.

Supplementary Figure 2. (A-B) Colony formation of HCT116 cells in a semi-solid medium was assessed upon knockdown of *PIK3CA* or *KRAS*. Colonies were visualized by Hoechst 33342 and quantitated. (C-D) Colony formation assay of HCT116 cells upon knockdown of a second KRAS targeting shRNA (KRAS-2). Colonies were visualized by Hoechst 33342 and quantitated.

Supplementary Figure 3. (A) Proliferation of HCT116 cells containing control or PIK3CA-1 inducible shRNA grown in the presence or absence of dox and PD0325901 was monitored by CellTiterGlo. (B) HCT116 cells containing a shRNA targeting *PIK3CA* (PIK3CA-2) were grown in the presence or absence of dox (50ng/ml) for 72 hours and harvested for immunoblot analysis with the indicated antibodies. (C) HCT116 cells containing control or two independent *PIK3CA* inducible shRNAs were grown in the presence or absence of dox and varying concentrations of PD0325901. Cell proliferation was assessed after 72 hours of treatment by CellTiterGlo.

Supplementary Figure 4. (A) PC3 cells containing a shRNA targeting PIK3CB were grown in the presence or absence of dox (10ng/ml) for 72 hours and harvested for immunoblot analysis with the indicated antibodies. (B) PC3 harboring PIK3CB shRNA were grown in the presence or absence of dox and varying concentration of Etoposide or PD0325901. Cell proliferation was assessed after 72 hours of treatment by CellTiterGlo.