Supplementary Information

PP2AC Level Determines Differential Programing of p38-TSC-mTOR Signaling and Therapeutic Response to p38-Targeted Therapy in Colorectal Cancer

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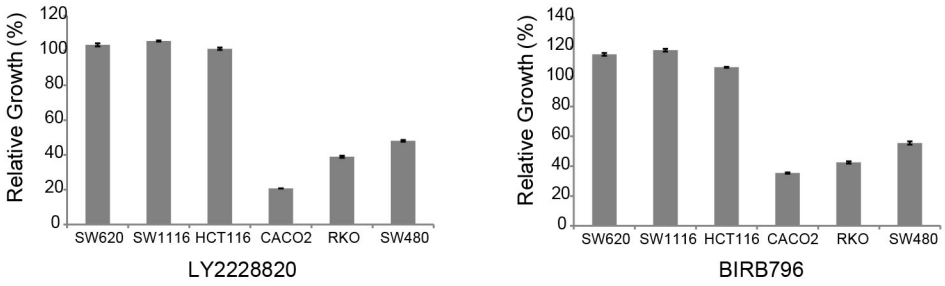

Fig. S1. LY2228820 and BIRB796 inhibit growth of CACO2, SW480 and RKO cells, but enhances growth of HCT116, SW620 and SW1116 cells. CRC cells were treated with LY2228820 4 μM or BIRB796 10 μM for 48 hours and cell growth was measured by SRB assay. Data represent means ± SD from three independent triplicate experiments.

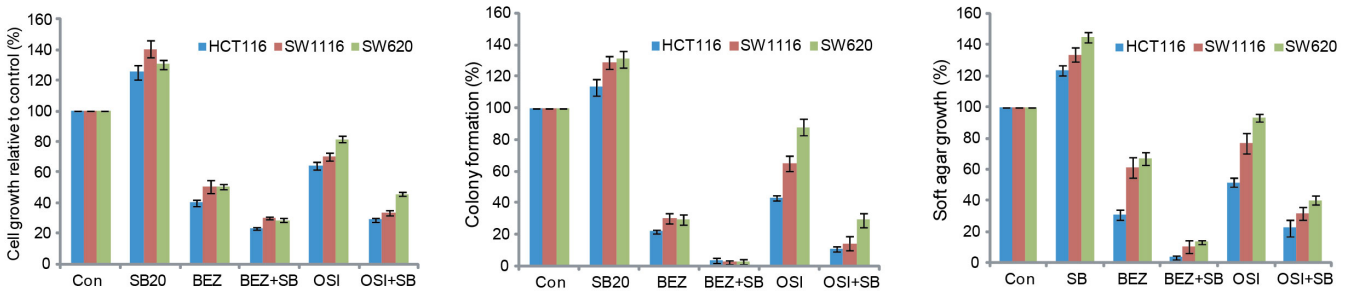

Fig. S2. mTOR kinase inhibitors blunt SB202190-stimulated growth of CRC cells. HCT116, SW620 and SW1116 cells were treated with 10 μM SB202190 with or without mTOR kinase inhibitor 30 nM BEZ235 or 6 μM OSI027. Cell growth was measured by SRB, colony formation and soft agar growth assays. Data represent means ± SD from three independent triplicate experiments.

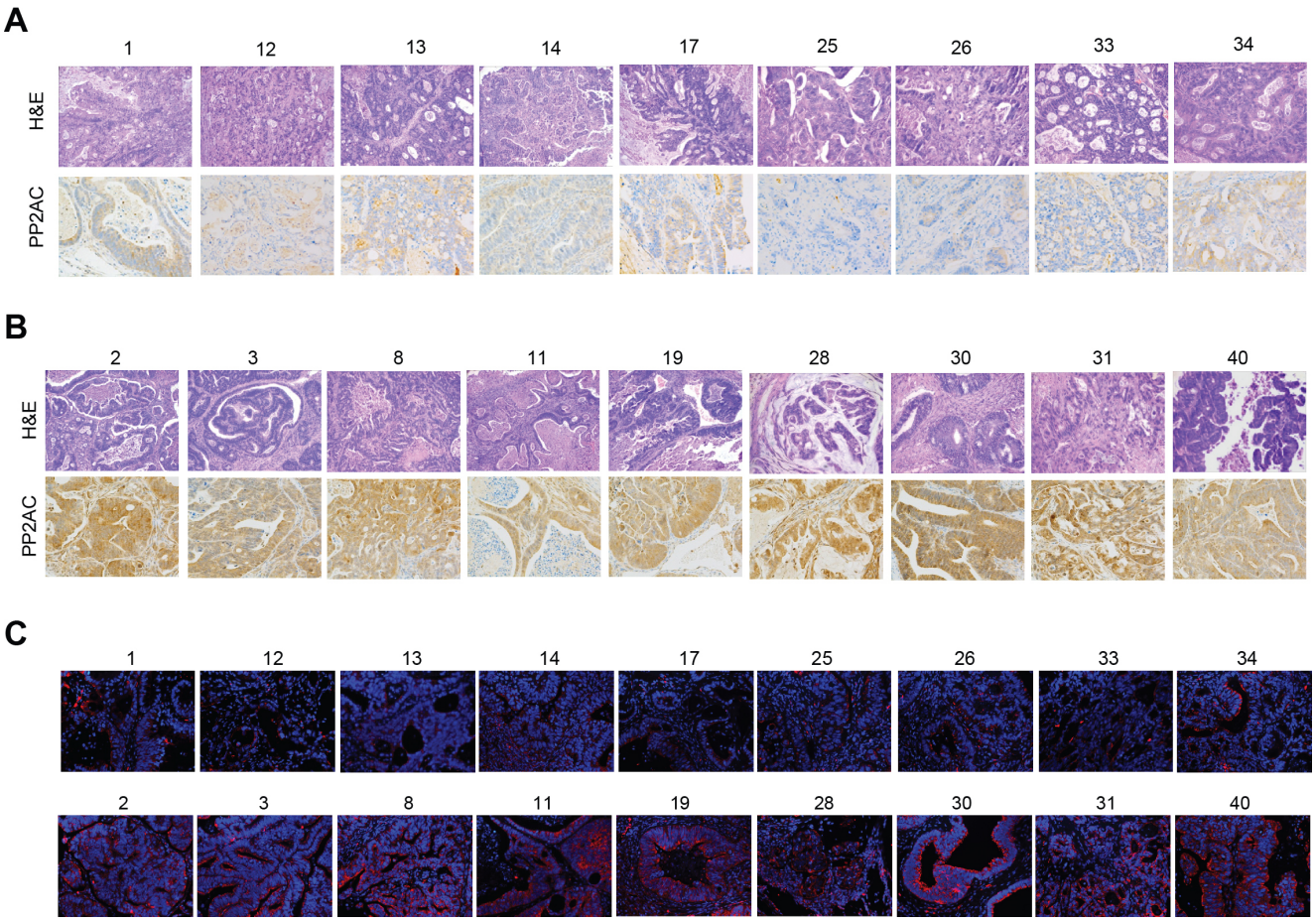

Fig. S3. PP2AC expression in patient-derived xenograft (PDX) CRC models**. A.** Histological features and low PP2AC expression in a subgroup of 9 PDX CRCs. Shown are H&E staining and PP2AC IHC staining of 9 PDX CRC tumors (1, 12, 13, 14, 17, 25, 26, 33, 34) with low PP2AC expression. **B.** Histological features and high PP2AC expression in a subgroup of 9 PDX CRCs. Shown are H&E staining and PP2AC IHC staining of 9 PDX CRC tumors (2, 3, 8, 11, 19, 28, 30, 31, 40) with high PP2AC expression. **C.** Immunohistochemistry staining of PP2AC in both subgroups of PDX CRCs.

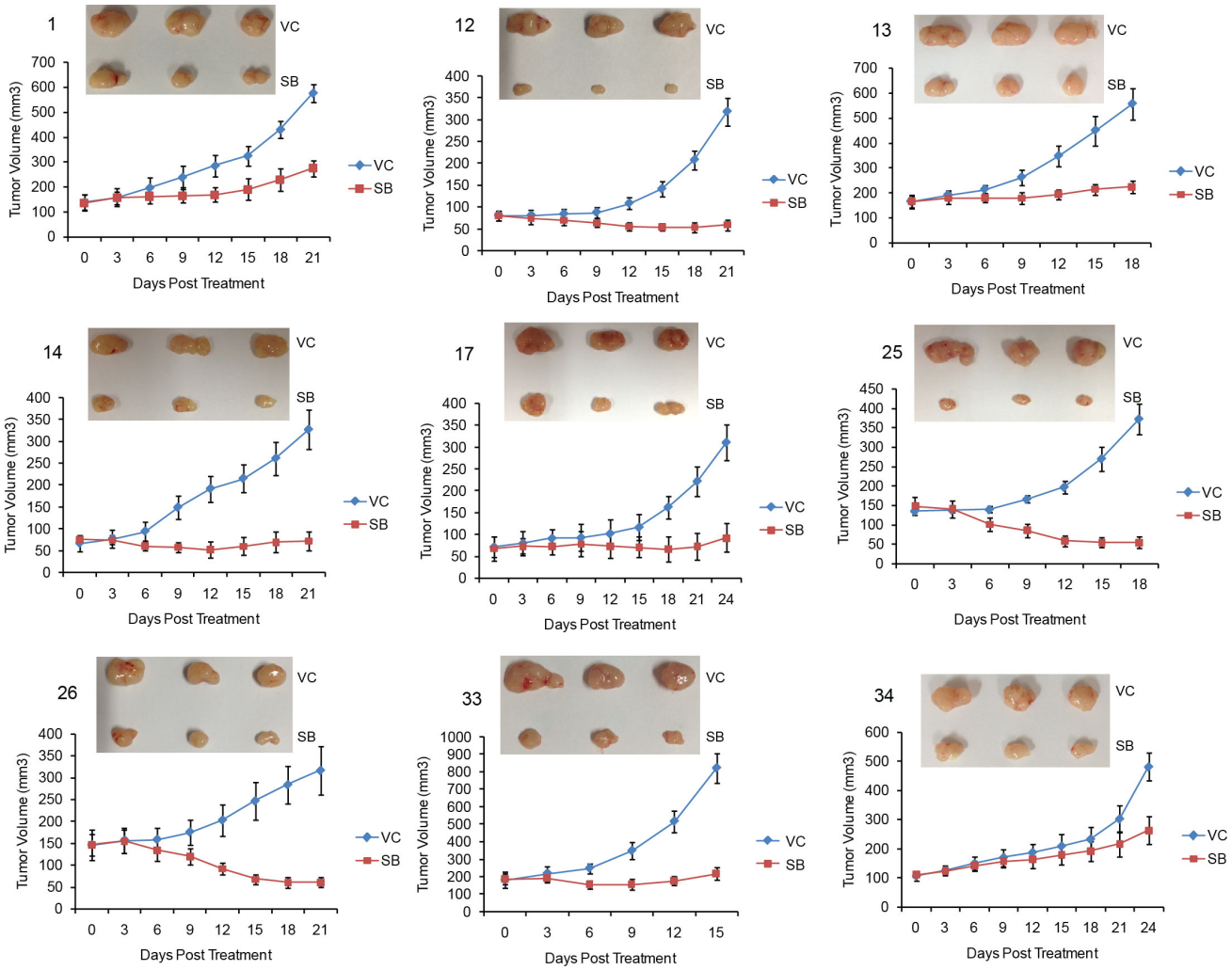

Fig. S4. PDX tumors with low PP2AC expression are sensitive to SB202190. Mice bearing PDX tumors 1, 12, 13, 14, 17, 25, 26, 33, 34 were treated with SB202190 (5 mg/kg/day) or drug vehicle (VC). Data are presented as means ± SD (n = 6).

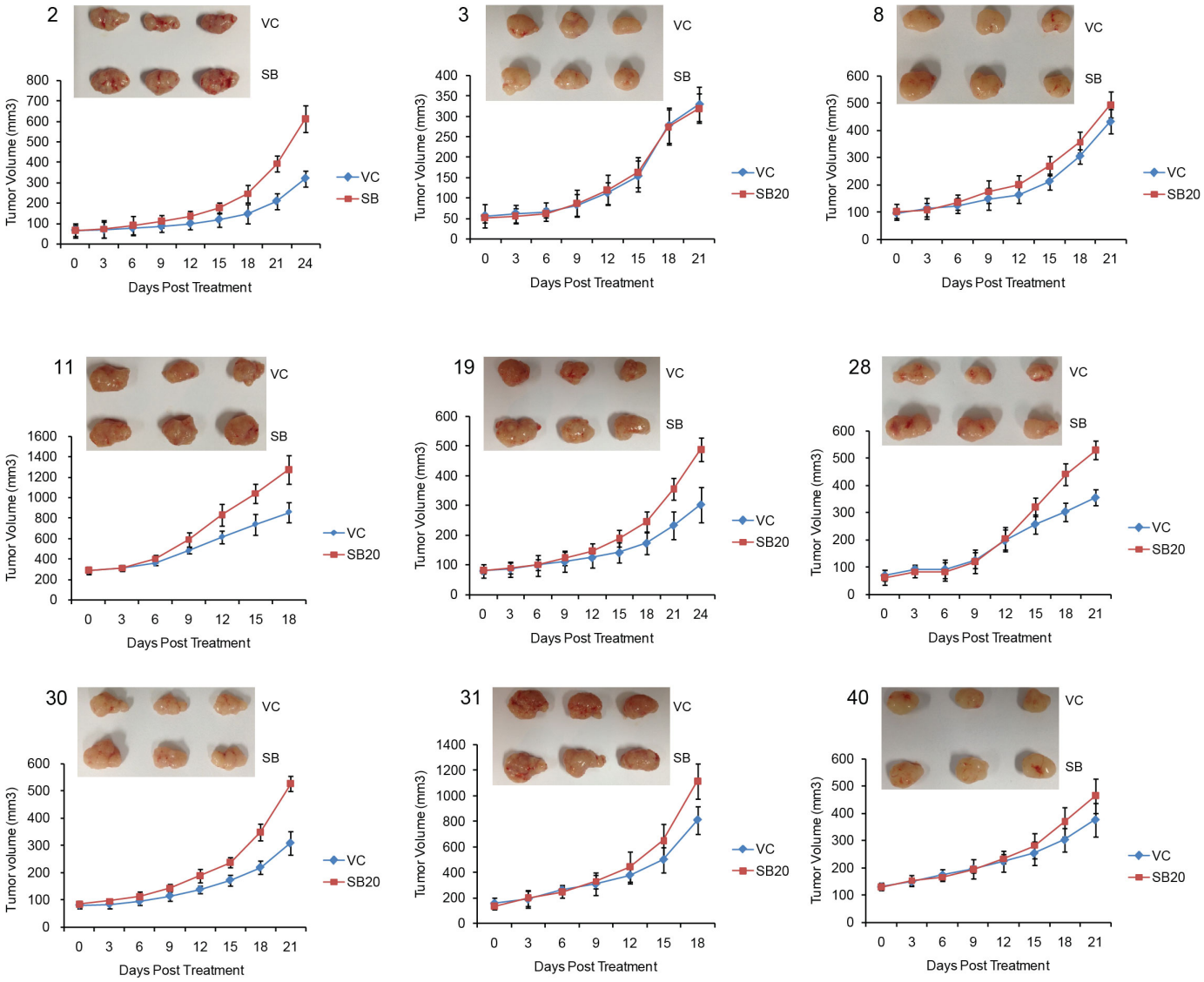

Fig. S5. SB202190 enhances growth of PDX tumors with high PP2AC expression. Mice bearing PDX tumors 2, 3, 8, 11, 19, 28, 30, 31, 40 were treated with SB202190 (5 mg/kg/day) or drug vehicle (VC). Data are presented as means ± SD (n = 6).

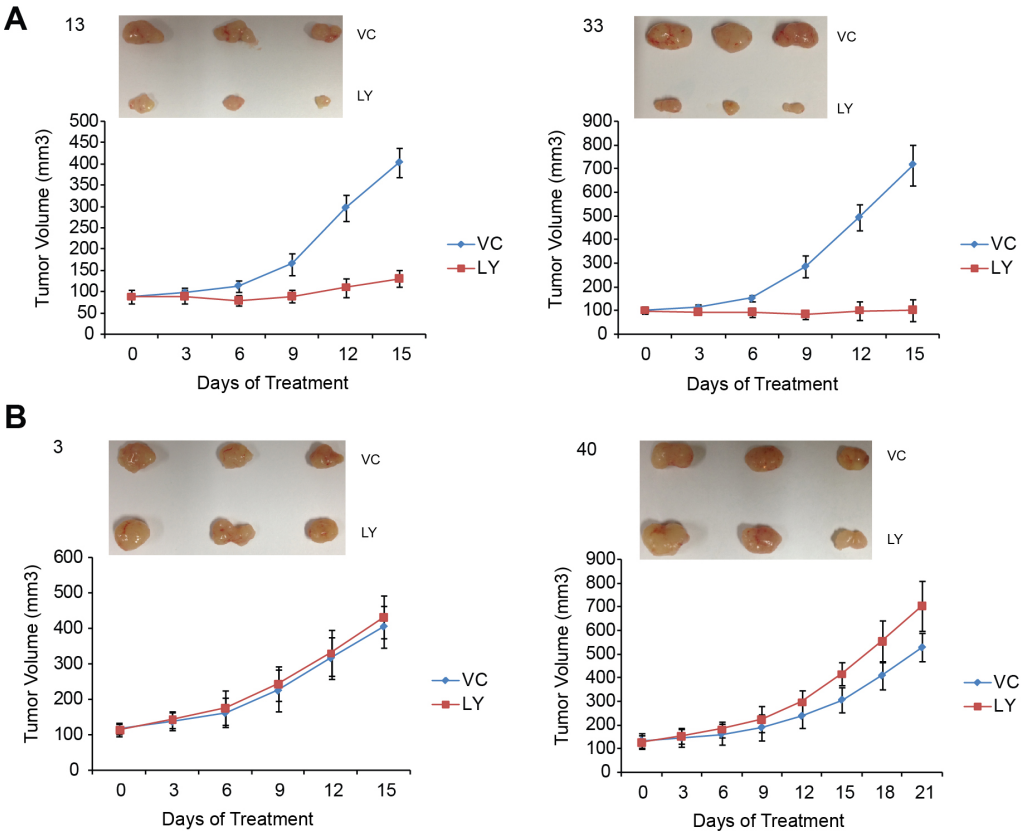
A
13
VC
LY
Tumor Volume (mm3)
Days of Treatment
33
B
3
40
C
13
33
VC
LY2228820
Ki67
P-MK2
P-S6
D
3
40

Fig. S6. PP2AC expression level predicts therapeutic outcome of LY2228820 in PDX CRC models**. A.** PDX tumors with low PP2AC expression are sensitive to LY2228820. Mice bearing PDX tumors 13 and 33 were treated with LY2228820 (10 mg/kg/day) or drug vehicle (VC). Data are presented as means ± s.d. (n = 6). **B.** LY2228820 enhances growth of PDX tumors with high PP2AC expression. Mice bearing PDX tumors 3 and 40 were treated with LY2228820 (10 mg/kg/day) or drug vehicle (VC). Data are presented as means ± s.d. (n = 6). **C.** LY2228820 inhibits mTORC1 and growth of PDX tumors with low PP2AC expression. Shown is IHC staining of Ki67, P-MK2 and P-S6 in PDX tumors 13 and 33 treated with LY2228820. **D.** LY2228820 enhances mTORC1 signaling and growth of PDX tumors with high PP2AC expression. Shown is IHC staining of Ki67, P-MK2 and P-S6 in PDX tumors 3 and 40 treated with LY2228820.