Supplementary Figure Legends:

Supplemental Figure 1: Characterization of a new, syngeneic, orthotopic mouse model of PDA. Representative images of either the autochthonous KRas driven model (KPC_p48^{cre}, left column), a syngeneic, orthotopic model in FVBn host (p53 2.1.1 $^{syn\_Luc}$ middle column) or the human PDA cell line Panc_2.13 orthotopically implanted in a nude mouse (right column). Note that the syngeneic model lacks p53 protein, whereas KPC p48^{cre} and Panc2.13 express (mutant) p53. Both the autochthonous and syngeneic models recruit activated stromal cells (as evidenced by smooth muscle actin staining), whereas the human PDA cell line in a nude mouse host does not. Scale bar is 50um.

Supplemental Figure 2: MEK inhibitor PD325901 inhibits MEK *in vivo*. Immunostaining for phosphorylated ERK1/2 in p53 2.1.1 $^{syn\_Luc}$ implanted mice six hours after A) Vehicle or B) 3mg/kg PD325901 by gavage.

Supplementary Figure 3: A: Dose response curves of either RAF inhibitor GDC-0879 (red), MEK inhibitor PD325901 (green), or a 2:1 molar ratio of GDC0874:PD325901 (blue). X axis is drug concentration in M. Y axis is percent growth inhibition at 72 hours. B: Western blot analysis demonstrating biochemical antagonism of MEK inhibition with GDC0879, as evidenced by increased phosphorlyated ERK (pERK) in Suit2 cells co treated with the indicated amounts of GDC-0879 (GDC) and PD325901 (PD) as compared to Suit2 cells treated with the same dose of PD325901 alone. Actin is loading control.

Supplementary Figure 4: MEK inhibition induces AKT activation. Indicated human PDA cell lines were treated with either DMSO or 1uM PD325901 for 24 hours in low serum

conditions followed by EGF (10nM) stimulation. pERK is phosphorylated ERK1/2, tAKT is total AKT, pAKT is AKT phosphorylated at s473.

Supplementary Figure 5: A: Dose response curves of human PDA cell lines treated with either MEK inhibitor GSK1120212 (red), AKT inhibitor GSK690693 (green), or a 5:1 fixed dose ratio of GSK1120212:GSK2141795, plotted as the dose of GSK1120212 (blue). X axis is drug concentration in M. Y axis is percent growth inhibition at 72 hours.

Supplementary Table 1: Human pancreatic cell lines used in this study and their publically available genotype information from Sanger Centre/CGP.

Supplementary Table 2: Drug Interaction matrix of GSK1120212 and GSK690693 across all dose combinations of all cell lines in figure 4a. Drug interactions with statistically significant synergy (interaction index and 95% confidence intervals all less than one) are denoted in green.