Supplemental Materials and Methods

Mouse Strains: All experiments were approved by the UCSF animal safety monitoring committee. *BRaf*^{CA} (1), *KRas*^{LSL} (2), *Trp53*$^{LSL\text{-}R270H}$ (3), *Pdx1::CreER*^{T2} (4), *Pik3ca*$^{lat\text{-}H1047R}$ (5) mice and their genotyping protocols have been described. Tamoxifen was dissolved in peanut oil and delivered in one IP injection on day 14 of life. Derivation of the p53 2.1.1 and INK4.1 lines from FVBn mice have been described (6). These cells were transduced *in vitro* with a lentiviral vector encoding a firefly luciferase and mCherry (pLV406G) and selected in 400ug/mL of G418 to give rise to INK4.1^{syn_Luc} and p53 2.1.1^{syn_Luc}. One thousand cells were orthotopically implanted in 6-8 week old FVBn mice in 20µl comprised of 50% Matrigel using a 28.5 gauge needle. Bioluminescent imaging on day seven allowed equal assignment of mice based of total luminescence into treatment and control groups. Mice were treated with 3mg/kg of MEK inhibitor PD325901 or vehicle control (0.5% hydroxypropyl methyl cellulose, 0.2% Tween80) by daily gavage for 14 days. Mice were monitored as described (7) and were euthanized when distressed. The survival package in GenePattern was used to calculate survival statistics.

Cell lines: HCG25, Capan1, and T3M4 were from S.K. Batra (Univ of Nebraska). YAPC and Sw1990 were from J. Settleman, (Massachusetts General Hospital). 3.27, 5.04, 2.03 2.13 and 6.03 were from E. Jaffee, (Johns Hopkins). BxPC3, Hs766T, were from P. Kirschmeier, (Schering Plough). DanG, PA-TU8902, PA-TU8988S, PA-TU8988T and ASPC-1 were from Lynda Chin, (MD Anderson). CfPac1, HPAC, and Panc1 are from ATCC. All cell lines were genotyped by Affymetrix SNP6.0 for definitive future disambiguation of provenance. No additional authentication was done by the authors. All cells were adapted to growth in DMEM with 10% FBS with L-Glutamine and Pen/Strep (all from Invitrogen).

Sensitivity Screens: PD325901 was obtained from Hansun International Trading, GDC0879 was provided by Genentech (South San Francisco, CA), GSK1120212 and GSK690693 were from ChemieTek (Indianapolis, IN). All were dissolved in DMSO. PDA cell lines were plated at 2.5X10^3 cells per well in white-walled 96 well plates on day 0, treated in triplicate with nine, two-fold dilutions of single drug or 1:1M (PD325901:GDC0879) or 5:1M (GSK690693:GSK1120212) ratio combinations of drugs on day 1, and read on a luminometer using CTG reagent (Promega) on Day 4. IC_{50} and synergy assessments were performed using the SYNERGY program (8) in the R environment.

Immunoblotting: Cells were grown to 70% confluence and then either treated with GSK690693 1uM or GSK1120212 200nM for 24 hours. Cells were lysed using ice cold RIPA buffer. Lysates were clarified, quantified and loaded onto NuPage Bis-Tris SDS gels. Antisera included anti-: phosphoERK1/2, ERK1, phosphoAKT (S473), panAkt, phosphor PRAS40, phosphoS6RP and phospho4EBP1 from Cell Signaling Technology and Beta Actin from Santa Cruz. The LiCor Oddessy system was used to visualize western blots.

Immunohistochemistry and Immunofluorescence: Pancreata were fixed overnight in zinc-containing neutral-buffered formalin (Anatech Ltd.), embedded in paraffin, cut into 5µm sections and placed on Superfrost Plus slides (Fisher Scientific). Following citrate mediated antigen retrieval, slides were incubated with monoclonal rabbit antibodies against Ki67 (Abcam), pERK1/2 (Cell Signaling Technology) or rat anti-CK19 (Hybridoma Bank at the University of Iowa), p53 sc6243 (Santa Cruz), and anti smooth muscle actin A2547 (Sigma) overnight followed by incubation with biotinylated goat anti-rabbit or goat anti Rat IgG and horseradish peroxidase (Vector). Detection was performed using the DAB chromogen system (Dako). Primary cilia were stained as described (9).

Methods References:

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