**SUPPLEMENTARY METHODS**

**Cell Lines and Reagents**

HCC1954, MDA-MB-468, SW527, CAL85-1, HCC70, MDA-MB-231, SUM149PT, HCC1143, SUM159PT, CAL120, HDQP1, MB-157, SKBR7, HS578T, BT20, CAL51, MACSL2, HCC1806, MX1, MDA-MB-436, HCC3153, HCC1937, HCC1569, MDA-MB-157 and HCC38 are from laboratory stocks, obtained as described previously (30). AsPC1, CFPAC-1, DAN-G, ES-2 Hs766T, HuPT3, Panc02.03, Panc02.13, Panc04.03, Panc08.13, Panc10.05, PSN-1, and SU.86.86 were purchased from ATCC (October 2017). Capan-2, CFPAC-1, HPAC, HPAF-II, HuPT4, MIAPaCa-2, Panc03.27, PATU8902, and SW1990 cells were obtained from Dr. Alec Kimmelman (NYU School of Medicine; July 2017). Caov3 cells were obtained from Dr. Douglas Levine (NYU School of Medicine; July 2017). KURAMOCHI, OAW28, OVSAHO, OV17R and TYKnu cells were obtained from Dr. Gottfried Konecny (UCLA; 2013). COV318, COV362, COV504, OV90, OVCAR3, OVCAR8, PEO1, TOV1369TR and TOV3133G cells were obtained from Dr. Robert Rottapel (Princess Margaret Cancer Center; 2013). KPA, KPC, CALU-1, H23 and H358 lung cancer cell lines were obtained from Dr. Kwok-Kin Wong (NYU School of Medicine; July 2017).

The NYU 16, 53 and 59 primary low passage human pancreatic cancer cell lines were generated according to Institutional Review Board (IRB) guidelines from invasive pancreatic adenocarcinoma samples from patients who underwent surgical resection at University of Michigan Hospital and NYU Langone Health (obtained July 2017). In brief, cell lines were generated by xenotransplantation of human PDA into immune deficient mice, and tumor cells were isolated by using MACS technology (Miltenyi Biotech). Cells were then plated and sub-cloned in RPMI 1640 medium, supplemented with 10% heat-inactivated FCS (Gibco), 2 mM L-glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin (Invitrogen) in 5% CO2 at 37 °C. Cultures were subsequently purified of mouse cell stroma by using a cell depletion kit (Miltenyi Biotech). Purity confirmed by flow cytometry.

The reconstituted RASless MEFs (WT, G12C, G12D, Q61R) were obtained from the NCI RAS Initiative (NIH) under an MTA (April 2018).

Every line was kept in culture for no longer than 3 months. Each cell line was tested for mycoplasma contamination by PCR 5-7 days after each thawing. Cells obtained from collaborators were genotyped by STR analysis at IDEXX Bioresearch (December 2017).

**Plasmids, Retroviruses and Lentiviruses**

A human SHP2 cDNA was cloned into pMSCV-IRES-GFP or pCW57.1 (pCW57.1 was a gift from David Root, Addgene plasmid #41393). Mutations were introduced by using the QuikChange II site-directed mutagenesis kit (Agilent Technologies). The IPTG inducible lentiviral shRNA plasmid vector pLKO.1-901 was obtained from Dr. Jason Moffat (University of Toronto), and shRNA against human *PTPN11* (shSHP2) (5'CGCTAAGAGAACTTAAACTTT 3') and a control shRNA against GFP (5' TGCCCGACAACCACTACCTGA 3') were introduced into this vector. The *SOS1* B1 (catalytic domain of SOS fused with a C-terminal CAAX T7 tag) construct was a gift from Dr. Dafna Bar-Sagi (NYU School of Medicine).

Viruses were produced by co-transfecting HEK293T cells with lentiviral or retroviral constructs and packaging vectors (pVSV-G + pvPac for retroviruses; pVSV-G + dR8.91 for lentiviruses). After 48h, culture media were passed through a 0.45 mm filter, and viral supernatants, supplemented with 8 g/ml of polybrene (Sigma), were used to infect 70% confluent cells in six-well plates for 16h at 37 °C.

**PrestoBlue Assays**

Cancer cells were seeded in 96-well tissue culture plates (500-3,000 cells/well). Following incubation with DMSO, 1 μM AZD6244, 10 μM SHP099 or both drugs, cell viability was assayed at 0, 1, 3 and 7 d (n=3) using the PrestoBlue cytotoxicity assay (Thermo Fisher), according to the manufacturer’s protocol. Media (including drugs) were refreshed every 48h. All data represent at least three biological independent experiments.

**Clonogenic Survival Assays**

Cells (100-500) were seeded in six-well plates one day before treatment with DMSO, 1 μM AZD6244, 10 μM SHP099 or the drug combination, allowed to grow until they formed colonies (7-14 days), rinsed twice with PBS to remove floating cells, fixed in 4% formaldehyde in PBS for 15 minutes, and stained in 0.1% crystal violet/10% ethanol for 20 minutes. Staining solution was aspirated, and colonies were washed with water 3x, air-dried and visualized with. At least three biological replicates were performed.

**RAS Activity Measurements**

One ml of lysis buffer (25 mM Tris-HCl, pH 7.2, 150 mM NaCl, 5 mM MgCl2, 5% glycerol, 1% NP40) containing protease inhibitors was added to treated cells for 15 minutes on ice, and lysates were scraped from the plate and centrifuged at 14,000 rpm for 15 minutes at 4°C. Clarified lysates (0.25-3 mg) were added to pre-washed GST-tagged RBD glutathione agarose beads (30 μL) for 1h at 4 °C under constant rocking. Beads were then centrifuged, washed once, and eluted in 30 μL of 2x SDS-PAGE sample buffer. Immunodetection of RAS proteins was carried out with KRAS (sc-30; Santa Cruz Biotechnology; 1:250), NRAS (sc3-1; Santa Cruz Biotechnology; 1:250) or pan-RAS (Ab-3; Calbiochem; 1:1,000) antibodies, with ERK-2 (sc-1647; Santa Cruz Biotechnology; 1:1000) used as a loading control.

**Immunoblotting**

Whole cell lysates were generated in modified radioimmunoprecipitation (RIPA) buffer (50mM Tris-HCl pH 8.0, 150mM NaCl, 2mM EDTA, 1% NP-40, and 0.1% SDS), supplemented with protease (40µg/ml PMSF, 2µg/ml antipain, 2µg/ml pepstatin A, 20µg/ml leupeptin, and 20µg/ml aprotinin) and phosphatase (10mM NaF, 1mM Na3VO4, 10mM β-glycerophosphate, and 10mM sodium pyrophosphate) inhibitors. Total lysate protein was resolved by standard SDS-PAGE, and transferred in 1X transfer buffer and 15% methanol. Membranes were incubated with their respective primary and secondary antibodies labeled with IRDye (680nm/800nm) and visualized by using a LICOR. Antibodies against p-p42/44 MAPK (#9101; 1:1000), p-MEK 1/2 (#9121; 1:1000), MEK1 (61B12; #2352; 1:1000), T7-tag (#13246), p-AKT (Thr308) (#4056; 1:1000), p-AKT (Ser473) (#9271; 1:1000), AKT (pan) (#2920; 1:1000), p-S6 Ribosomal Protein (Ser240/244) (#5364; 1:1000), S6 Ribosomal Protein (#2317; 1:1000), p-STAT3 (Tyr705) (#9145; 1:1000), p-SAPK/JNK (Thr183/Tyr185) (#4668; 1:1000), SAPK/JNK Antibody; (#9252), P-p38 MAPK (Thr180/Tyr182) (#4511), p38 MAPK (#8690), were obtained from Cell Signaling. p-PRAS40 (Thr246) (#07-888; 1:1000), PRAS40 Antibody, (#05-988; 1:1000), were obtained from Millipore. SHP2 (sc-280; 1:1000) and ERK2 (sc-1647; 1:1000) antibodies were purchased from Santa Cruz Biotechnology. SOS1 antibody (#MA5-17234) was purchased from Invitrogen. DUSP6 antibody (ab76310) was purchased from Abcam. STAT1 Antibody (#NB500-514) was purchased from Novus.

**Cell Cycle and Apoptosis Analyses**

Cells were fixed in cold 70% ethanol overnight, washed with PBS, and then stained with buffer containing 20L 7AAD (BD) and RNase (final concentration 0.5ug/mL) for 30 minutes at room temperature. Stained cells were analyzed by flow cytometry on an LSR II (BD). Data were analyzed by ModFit LT software (Versity Software House) to determine the fraction of cells in each cell cycle stage. For apoptosis assessment, cells were stained with the PE Annexin V Apoptosis Detection Kit I, according to the manufacturer’s protocol (BD), subjected to flow cytometry on an LSR II, and analyzed by using FlowJo software (BD).

**Xenograft Experiments**

All animal experiments were approved by the NYU Langone Institutional Animal Care and Use Committee (IACUC). MIAPaCa-2, Capan-2 and H358 xenografts were established by sub-cutaneous injection of 5 × 106 cells in 50% Matrigel (Corning) into the right flank of nude mice (*nu/nu*, #088 Charles River) when animals were 8-10 weeks of age. MDA-MB-468 xenografts were established by injecting 5 × 106 cells in 50% Matrigel into the right lower mammary pad. Ovarian PDXs were established by injecting 5 × 105 cells in 50% Matrigel into the right lower mammary pad of NSG mice (Jackson Lab) when animals were 6-8 weeks of age.

Each treatment group contained 8-10 mice. When tumors reached 100-500 mm3, as measured by calipers (volume=length\*width2\*0.5), mice were randomized to four groups (10 mice/group) for each model, and treated with: (i) vehicle, (ii) SHP099, (iii) trametinib, or (iv) SHP099/trametinib through oral garage. Investigators were not blinded to group allocation. The following oral gavage dosing regimens were employed: SHP099 75mg/kg QD, trametinib 0.25mg/kg QD, and trametinib 0.25mg/kg QD, SHP099 75mg/kg QOD. SHP099 was resuspended in 0.6% methylcellulose, 0.5% Tween80 in 0.9% saline. Trametinib was dissolved in DMSO before adding to the carrier. Caliper and weight measurements were performed every other day and continued until termination of the experiments.

**Syngeneic Orthotopic Pancreatic Cancer Models**

KPC 1203 cells were generated in the Bar-Sagi lab (NYU School of Medicine; obtained April 2018) from a pancreas tumor in an LSL-*Kras*G12D; LSL-*Trp53*R172H; Pdx1-Cre (KPC) mouse on C57BL/6 background, as described (15). Cells (1 x 105) were suspended in Matrigel, implanted into the pancreata of 6-8 week-old syngeneic male mice. Vehicle, trametinib (0.25mg/kg QD), SHP099 (75mg/kg QD), or trametinib 0.25 mg/kg QD, SHP099 75 mg/kg QOD was administered for 5 or 15 days, as indicated.

**Bliss Analysis**

Potential synergistic effects of SHP099 and AZD6244 were determined by Bliss analysis as: *Yab,P* = *Ya* + *Yb* – *YaYb*, where *Ya* stands for percentage inhibition of drug *a* and *Yb* stands for percentage inhibition of drug *b* (49). Synergistic effects were defined as % of observed effect greater than *Yab,P*.