**SUPPLEMENTARY TABLE LEGENDS**

**Supplementary Table S1: Bliss Index for Effect of MEK-I/SHP099 Combination on Cancer Cell Proliferation**

**Supplementary Table S2**:  **Primer Sequences for qRT-PCR**

**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary Figure S1: Combined SHP2/MEK inhibition prevents adaptive resistance in PDAC and NSCLC lines A,** Growth curves (PrestoBlue) of PDAC lines treated with DMSO, SHP099 10 μM, AZD6244 1 μM, or both (COMBO) for the indicated times. **B,** Effects of trametinib (10, 25 and 50 nM), SHP099 (10 μM) or both on PDAC lines after 1 week of treatment, measured by PrestoBlue. Red asterisks indicate synergistic effect of the two drugs by BLISS independent analysis**. C,** Effects of AZD6244 (1 μM), SHP099 (10 μM) or drug combination on pancreas PDX-derived cell lines after 1 week of treatment, measured by PrestoBlue. **D-E**, NSCLC lines were treated as indicated. Viability was quantified by PrestoBlue (D) after one week, and colony formation (E) was assayed at two weeks (\*P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001, two-sided t test). **F,** Cell cycle (upper panel), measured after 48h, and cell death (lower panel), measured after 6 days, of drug treatment, quantified by Annexin V/7AAD staining and flow cytometry. Representative results from a minimum of three biological replicates per condition are shown.

**Supplementary Figure S2: SHP2 inhibition abrogates MEK-I-evoked reactivation of the ERK MAPK pathway A,** Immunoblots of lysates from PDAC lines treated with DMSO, SHP099 (10 μM), AZD6244 (1 μM) or both for the indicated times. **B,** Immunoblots of lysates from PDAC lines treated with DMSO, SHP099 (10 μM), trametinib (10, 25, or 50 nM) or both drugs for the indicated times. For comparison, AZD6244 (1 μM) alone or in combination with SHP099 (10 μM) is also shown. **C,** ERK-dependent gene expression (*ETV1,4, 5* and *FOSL1*), assessed by qRT-PCR, in PDAC cells treated for the indicated times**. D,** Immunoblots of lysates from PDAC lines treated with DMSO, SHP099 (10 μM), AZD6244 (1 μM) or both for the indicated times. **E,** Immunoblots of lysates from H358 cells ectopically expressing wild-type SHP2 (WT) or an SHP099-resistant mutant (TM/QL), treated with single agents or the drug combination, as indicated. **F,** Immunoblots of lysates from KPC 1203 cells ectopically-expressing wild-type SHP2 (WT) or an SHP099 resistant-mutant (P491Q),treated as indicated. Numbers under blots indicate relative intensities, compared with untreated controls, quantified by LICOR.

**Supplementary Figure S3: Distinct mechanisms of resistance to MEK-I/SHP099 combination in PDAC lines A**, Immunoblots of whole cell lysates or GST-RBD pulldowns (RAS-GTP) from PSN1 cells treated with DMSO, SHP099 10 μM, AZD6244 1 μM, or both for times indicated. **B,** ERK-dependent gene expression (*ETV1, 4, 5* and *FOSL1*), assessed by qRT-PCR, in PSN1 cells, treated as above. **C,** Immunoblots of whole cell lysates from SU86.86 cells, treated as in **A**. **D,** ERK-dependent gene expression, assessed by qRT-PCR, in SU86.86 cells, treated as in **B**. Numbers under blots indicate relative intensities, compared with untreated controls, quantified by LICOR.

**Supplementary Figure S4: Development of tolerable SHP099/trametinib regimen A,** Upper GI bleeding in mice treated with daily combination of trametinib 1mg/kg; SHP099 75mg/kg. **B,** Histological analysis reveals multifocal ulcerations in lower esophagus, stomach, duodenum and Ileum. Blunting of villi in duodenum is also present. **C**, Histology of major organs in mice treated with revised combination regime (trametinib 0.25mg/kg QD; SHP099 75mg/kg QOD). **D-E,** Revised combination regime is well tolerated in all mouse models tested, with no significant decrease in body weight even after long term (>40 days) treatment. **F**, Full tumor growth curves for MIAPaCa-2, H358, MDA-MB-468 and PDX-2555 xenografts. **G**, p-ERK levels in MIAPaCa-2 tumors following 19 days of drug treatment, as shown by immunoblotting. **H**, qRT-PCR of lineage-specific genes in normal pancreatic epithelium of treated (15 days) KPC tumors.

**Supplementary Figure S5: Combination decreases tumor cell proliferation and promotes programmed cell death (PDAC and NSCLC) A,** Ki67 and cleaved Caspase 3 staining of sections from treated Capan-2, MIAPaCa-2 and H358 tumors.

**Supplementary Figure S6: Combination decreases tumor cell proliferation and promotes programmed cell death (PDAC, TNBC and HGSC) A,** Ki67 and cleaved Caspase 3 staining of sections from treated KPC, MDA-MB-468 and PDX-2555 tumors.

**Supplementary Figure S7: RTKs/RTK ligand expression and Annexin V/cell cycle analysis of TNBC and HGSC lines. A,** TNBC lines were treated with DMSO, SHP099 10 μM, UO126 10 μM, or both (Combo). PrestoBlue assay was performed at one week. Representative results from a minimum of three biological replicates are shown per condition (\*P < 0.05, \*\*P < 0.01, \*\*\**P* < 0.001, two-tailed t test). Red asterisks indicates synergistic interactions by BLISS independent analysis. **B,** Time-dependent increase in RTK (**A**) and RTK ligand (**B**) gene expression in TNBC (MDA-MB-468 and CAL-120) and HGSC (OVCAR8 and KURAMOCHI) cell lines after DMSO, SHP099, AZD6244, or combination treatment, monitored by qRT-PCR. **C-D,** Cell cycle distribution after 48h treatment (**C**), and cell death analysis after 6 days of treatment (**D**), with DMSO, SHP099 10 μM, AZD6244 1 μM or both drugs, assessed by flow cytometry.