Supplemental Table 1. Calculated IC₅₀ doses and combination index (CI) values for constant ratio dose combinations of FOLFOX and JNK-IN-8 in four PDAC cell lines as determined by CompuSyn software (45) (n=3).

Cell line	Drug/Combo	Calculated IC50 (µM)	CI at 1 µM	CI at 10 µM
P411-T1	JNK-IN-8	58.9	-	-
	FOLFOX	61.9	-	-
	COMBO 10:1:5	5.79	0.41	0.070
	COMBO 10:1:10	5.25	0.13	0.074
CFPAC-1	JNK-IN-8	47.7	-	-
	FOLFOX	13.7	-	-
	COMBO 10:1:5	2.30	0.077	0.043
	COMBO 10:1:10	2.25	0.038	0.031
P422-T1	JNK-IN-8	111	-	-
	FOLFOX	31800	-	-
	COMBO 10:1:5	17.4	0.037	0.085
	COMBO 10:1:10	16.2	0.046	0.15
MIA PaCa-2	JNK-IN-8	8.06	-	-
	FOLFOX	10.7	-	-
	COMBO 10:1:5	18.0	7.9	0.47
	COMBO 10:1:10	7.42	6.2	0.12



Supplemental Figure 1. p-value profiles and expression distributions for survival analyses. (A) p-value profiles for survival analyses for *JNK1* (top), *JNK2* (middle), and the JUN signature (bottom) as described for Figure 2. Samples were ordered by expression (*JNK1* or *JNK2*) or by mean ranked expression (JUN signature). Survival analysis for each possible binary classification of samples into high and low expressing groups and associated p-values were plotted. Horizontal dashed lines show p-values of 0.01 and 0.05. Vertical dashed lines show the minimum p-value sample cut-off as well as the top 10% (*JNK1* and *JNK2*) or median expression (JUN signature). (B) Normalized expression distribution for *JNK1* (top) and *JNK2* (bottom). Dotted vertical lines show potential cut-offs at the 10th percentile and at the geometric inflection point for each expression curve.



Supplemental Figure 2. Dose-response data for JNK-IN-8 with 5-FU (left) or OX (right) in P411-T1 PDX-CL. Dose-response curves for JNK-IN-8 (red), 5-FU or OX alone (blue), and constant ratio combinations (purple), shown as mean±SEM normalized % viability (n=2).



Supplemental Figure 3. Tolerance and kinetics data from in vivo tumor studies. (A) Average weights of NSG mice before and after treatments with 30 mg/kg twice weekly JNK-IN-8 alone (left) and in combination with FOLFOX (100 mg/mL LEU, 50 mg/mL 5-FU, and 5 mg/mL OX once weekly) (right). Mean±SEM with range shown, along with significance by one-way ANOVA with Kruskal-Wallis multiple comparisons test shown (n.s. non-specific; **** p<0.0001). (B) Immunoblots in matched tumors before treatment (Pre-tx) and after 8 d JNK-IN-8 (JNKi) in 411-T1 PDX tumors. (C) in vivo tumor growth depicted as box plots of log₂(tumor volume fold change at 28 d endpoint vs. treatment initiation) and as Kaplan-Meier survival plots with a tumor volume cutoff of 800 mm³ in CFPAC-1 (left) and Mia-PaCa-2 (right) cell line xenografts treated for 28 d with indicated treatments. Each group contained at least 7 mice. Significance determined by ANOVA with Tukey multiple-comparison's tests. (D) Individual tumor growth kinetics across designated 28 d treatment regimens. * p<0.05; ** p < 0.01, **** p < 0.0001.



Supplemental Figure 4. Immunoblot images from in vivo tumor studies. (A) Immunoblots in matched 319-T1 (top) and 411-T1 (bottom) PDX tumors before (-) and after (+) respective 28 d treatments. All tumors were harvested 4 h after final treatment. ACTB used as loading control.



Supplemental Figure 5. Additional data for cell lines with dox inducible expression of JUN, JNK1, and JNK2. (A) Immunoblots after inducible expression of JUN (left), JNK1 (middle), and JNK2 (right) in lentiviral-infected CFPAC-1 cells. ACTB used as loading control. (B) Effects of overexpression on sensitivity to FOLFOX and FOLFOX+JNK-IN-8 in MIA PaCa-2 cells overexpressing JUN (left), JNK1 (middle), and JNK2 (right) transgenes (n=2).