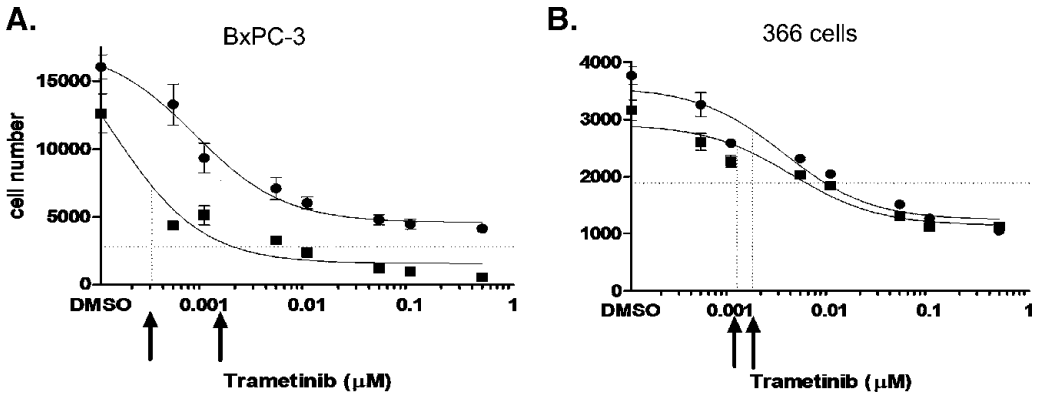

Figure W1. Dose-response curves for BxPC-3 (A), an established pancreatic cancer cell line, and 366 (B), a patient-derived cell line. Circles represent trametinib (GSK1120212) alone, and squares are trametinib (GSK1120212) in combination with 1.0 μM lapatinib. Horizontal dotted line indicates cell number initially plated. Vertical dotted lines indicate IC_{50} for each treatment.

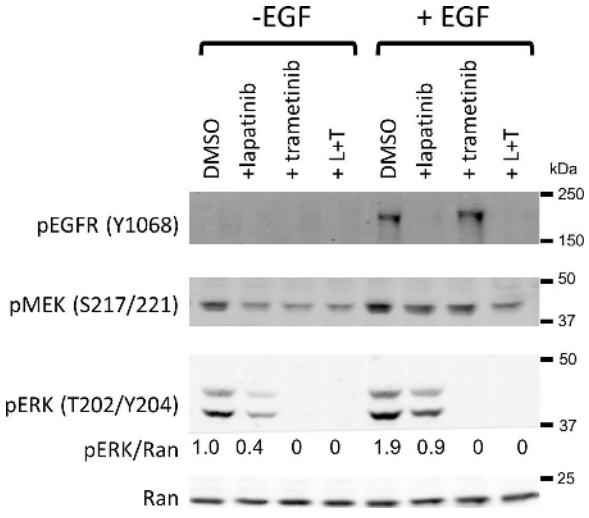

Figure W2. (A) 366 Cells were serum starved for 4 hours and then treated with either 1 μM lapatinib, 0.3 μM trametinib, or the combination (+L+T) for 1 hour before being stimulated with 100 ng/ml EGF for 30 minutes. pERK and Ran were quantitated and pERK was divided by Ran to determine changes in phosphorylation. Phosphorylated protein level was divided by total protein level to yield quantitative values.

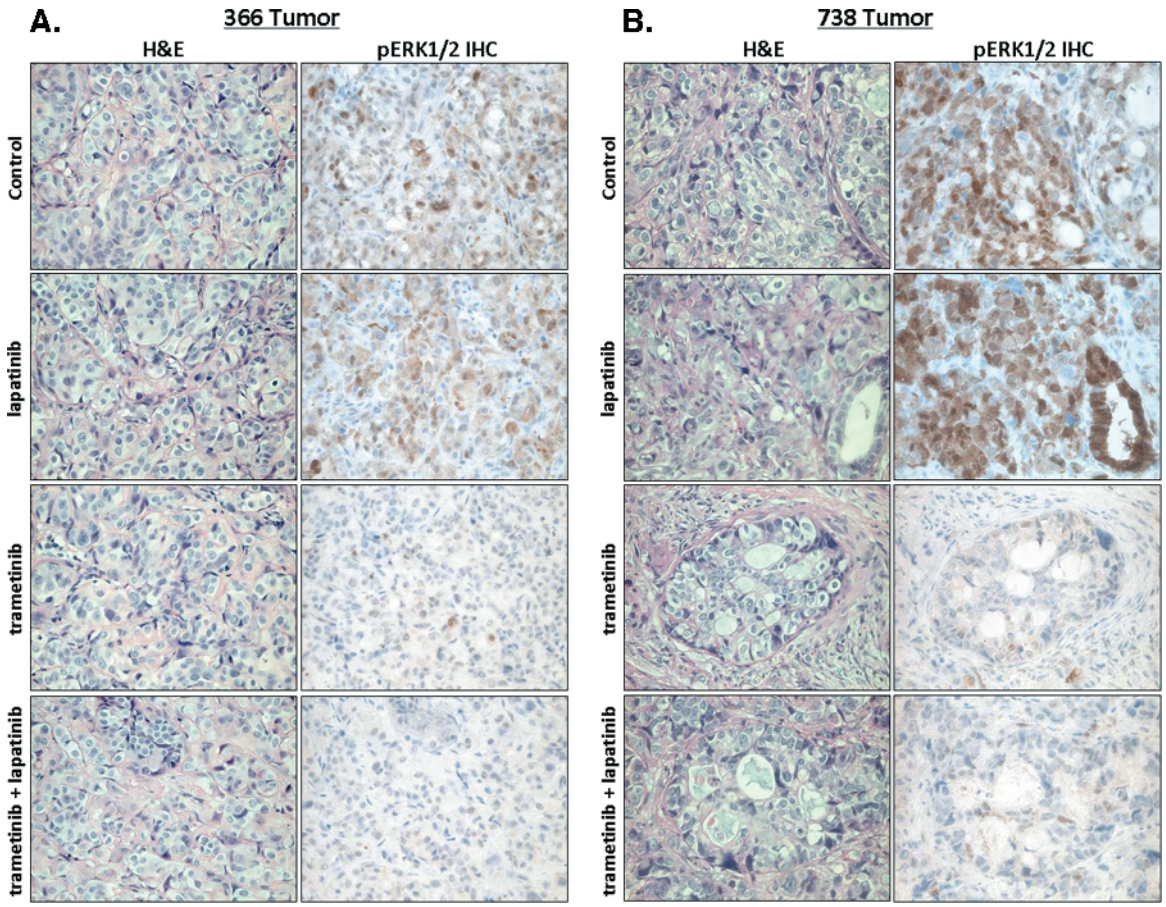

Figure W3. *In vivo* effect of lapatinib and trametinib on ERK1/2 phosphorylation measured by immunohistochemistry. Representative micrographs (original magnification, ×40) from patient-derived orthotopic tumor xenografts [(A) 366 tumor and (B) 738 tumor] treated for 24 hours with vehicle control, lapatinib (65 mg/kg, twice daily), trametinib (3 mg/kg, daily), or combination therapy. Phospho-ERK1/2 most intensely stains the pancreatic ductal adenocarcinoma cells in the control and lapatinib-treated mice, while limited or no staining is observed in trametinib- and combination-treated mice.

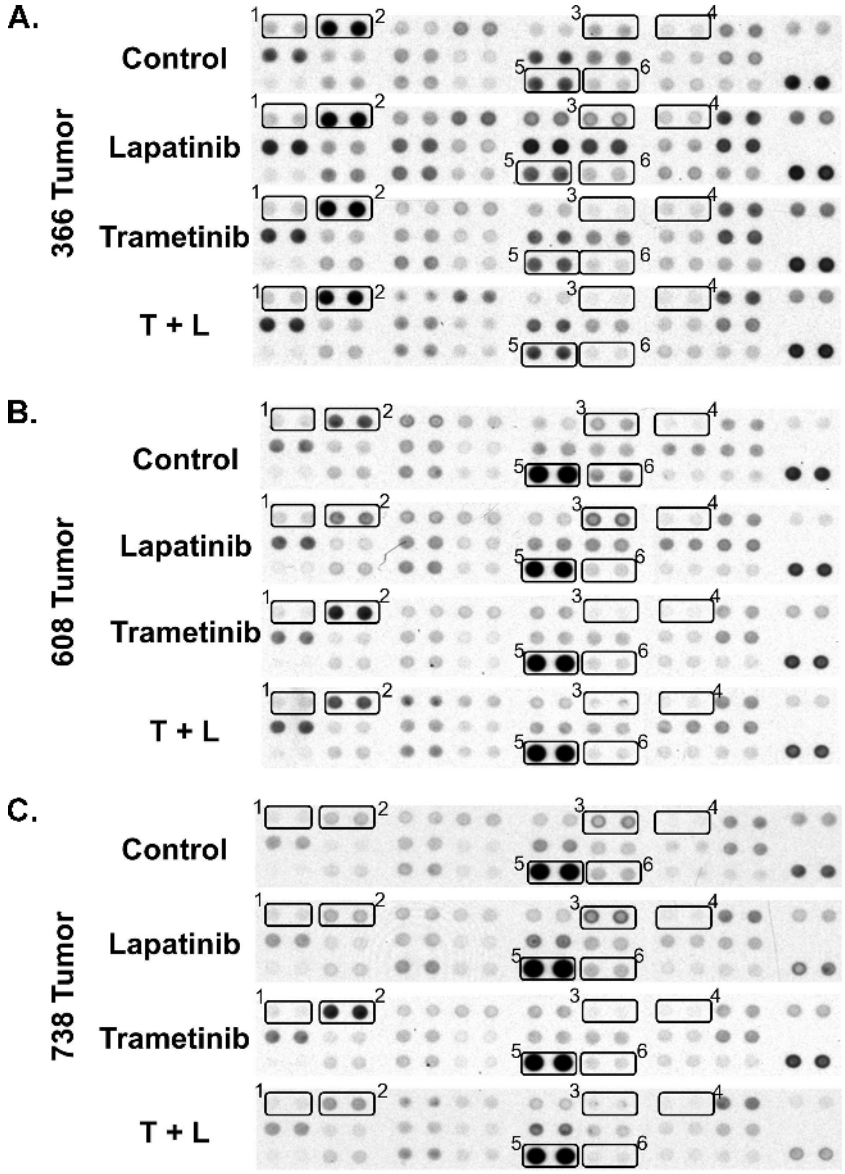

Figure W4. Relative phosphorylation of 366 tumor (*KRAS* mut), 608 tumor (*KRAS* mut), and 738 tumor (*KRAS* wt) xenografts treated with vehicle control, lapatinib (65 mg/kg, orally, twice daily), trametinib (3 mg/kg, orally, daily), or combination of trametinib and lapatinib (T + L). (A–C) Representative images of pMAPK arrays of whole tumor lysates from 366 tumor (A), 608 tumor (B), and 738 tumor (C) xenografts under the above treatment conditions. Relative pAkt1 (1), pAkt2 (2), pErk1 (3), pErk2 (4), p53 (5), and p70S6 kinase (6) levels are highlighted.