Supplementary Figures

Figure S1. Mismatched RTK capacity and pathway dependency fail to provide bypass resistance. (A) Absolute abundance of RTKs as measured by ELISA in four cancer cell lines with known dependencies on EGFR or HER2. Error bars indicate the SEM of biological triplicate. (B) Normalized receptor expression in PC9 cells after the indicated period of cell starvation in the presence or absence of 1 μM erlotinib. Inset: Normalized ErbB3 receptor abundance after treatment with 1 μM GSK690693, an Akt inhibitor. Error bars indicate the SEM of biological replicates (N = 2).

Figure S2. Validation of RTK overexpression. Quantification of GFP and receptor overexpression correspondence in PC9 cells transiently transfected with each indicated construct. FSC, SSC, and GFP indicate forward scatter, side scatter, and GFP fluorescence values respectively. Lines on each graph are shown for ease of comparison.

Figure S3. Parameter outputs of regression model in Figure 3C. Only parameters that were significantly nonzero in at least one cell line are included. Parameter values were obtained by sampling the posterior distribution of each model. Boxes indicate the interquartile range, and whiskers 1.5 times the interquartile range.

Figure S4. JNK pathway activation modulates bypass resistance. (A) pcJun measured in either PC9 or HCC827 cells after treatment with an Akt (GSK690693), Mek (U0126) or JNK (SP600125)

inhibitor for 4 hours. This was additionally performed in the presence or absence of 1 uM erlotinib and 50 ng/mL HGF. Error bars indicate SEM (N = 3). (B) Viability measurement in PC9 and HCC827 cells for a range of U0126 and SP600125; U0126 and JNK-IN-7; or U0126, JNK-IN-7, and erlotinib for 72 hours. Error bars indicate SEM (N = 2). (C) Viability measurement in four other lung cancer cell lines for a range of U0126 and JNK-IN-7; or U0126, JNK-IN-7, and erlotinib for 72 hours. Error bars indicate SEM (N = 2). (D-E) Viability measurement in PC9 cells after treatment with dasatinib, SP600125, erlotinib, U0126, and/or HGF for 72 hours. Error bars indicate SEM (N = 5).

Figure S5. Quantification of cJun abundance. Western blot of paxillin (as a loading control) and total cJun in each cell line after 4 hours of treatment with the indicated growth factors and inhibitors. Quantification is presented on the right. Bar colors match those used in Figure 1A-B. Grey indicates growth factors for which resistance was not quantified in Figure 1A. Error bars indicate SEM (N = 2).

Figure S6. Determination of interaction between Mek and JNK inhibition on viability. (A) The measured percent change in viability, predicted percent change assuming Bliss independence, and residual between the measured and predicted values. All individual viability measurements are presented with experimental error in Figures S4B and S4C. (B) Pearson correlation between the prediction given Bliss independence and measured viability with different combinations of JNK and Mek inhibitor. (C) Variance in the difference between the predicted and measured viability normalized to the variance in measured viability.

Table S1. Cell line data used to generate Figure 1G. Probe values for gene expression were measured previously (18). Each cell line was binned into whether resistance occurred with cognate ligand treatment by (6).