**Supplementary Figure 1**. Histograms of log-transformed SILAC ratio of phosphorylation. (A) Histograms for each individual cell line. (B) Histogram of the complete data set from all the cell lines. Top and bottom panels show data from experiments in complete medium and serum starved condition, respectively.

**Supplementary Figure 2**. Correlation of the SILAC phosphorylation ratios between biological replicates. (A-B) Correlation of the log 2 ratio of erlotinib (A) or afatinib (B) to DMSO in H1975 cells in complete medium between SILAC media-swapping experiments. (C-D) Correlation of the Log 2 ratio of (C) erlotinib or (D) afatinib to DMSO in H3255 cells in complete medium. (E-F) Correlation of the Log 2 ratio of (E) erlotinib or (F) afatinib to DMSO in 11-18 cells in complete medium.

**Supplementary Figure 3**. Functional analysis of the targets of each inhibitor among sensitive and resistant cell lines. DAVID analysis shows enrichment of (A) Gene Ontology molecular function terms and (B) KEGG Pathways among phosphoproteins in which at least one phosphosite is dephosphorylated upon erlotinib or afatinib treatment in TKI sensitive cells (H3255, PC9, 11-18) or TKI-resistant cells (H1975). Significance was determined by Fisher's exact test, and is represented as the –log (P value); the significance threshold is –log (P = 0.05) = 1.301.

**Supplementary Figure 4**. Networks of EGFR substrates whose phosphorylation was inhibited by erlotinib, afatinib or both in H3255 (A), PC9 (B), 11-18 (C) and H1975 (D) cells following serum starvation. Blue, both erlotinib and afatinib, green, erlotinib only and red, afatinib only.

**Supplementary Figure 5**. Label-free quantitation of the phosphotyrosine sites validated in doxycycline-inducible $EGFR^{L858R}$ transgenic mouse lung tumors, untreated or treated with erlotinib. (A) Hierarchical clustering of all phosphotyrosine sites identified in the mice based on label-free quantitation. Columns represent different mice of the same genotype ($EGFR^{L858R}$)

with/without erlotinib treatment; rows represent quantified phosphotyrosine sites. Expression is based on the log2 intensity of the phosphopeptide.

**Supplementary Figure 6**. Potential phosphatases downstream of EGFR or RTK-dependent parallel pathways affecting phosphosites whose phosphorylation was inhibited upon EGF stimulation and activated or remain unchanged upon TKI inhibition. (A) Phosphosites hypophosphorylated with EGF stimulation and hyperphosphorylated on erlotinib inhibition and the potential upstream phosphatases that are also downstream of EGFR in H3255 cells. (B) Phosphosites hypophosphorylated upon EGF stimulation, but remain unchanged upon erlotinib inhibition and the potential upstream phosphatases that are also downstream of EGFR in H1975 cells. (C) Phosphosites hypophosphorylated upon EGF stimulation and hyperphosphorylated upon erlotinib inhibition, along with the potential upstream phosphatases and kinases in H1975 cells.

**Supplementary Figure 7**. MS and MS/MS spectra of MST1R peptide with Y1238/Y1239 phosphorylation. Phosphorylation of both sites decreased upon erlotinib or afatinib inhibition of H1975 cells in complete medium. In serum starved experiments, phosphorylation increased upon EGF stimulation, but remained unchanged upon erlotinib inhibition.

**Supplementary Figure 8**. MS and MS/MS spectra of MET peptide with Y1252/Y1253 phosphorylation. Phosphorylation of both sites decreased upon erlotinib or afatinib inhibition of H1975 cells in complete medium.