**SUPPLEMENTARY MATERIAL AND METHODS**

*Antibodies*

Phospho-EGFR (Y1068, cat no 3777), EGFRL858R(cat no. 3197), EGFRDEL (cat no. 2085), pERBB2 (Y1221/1222, cat no. 2243), pERBB3 (cat no. 4791), pMET (cat no. 3077), MET (cat no. 4560), GAB1 (cat no. 3232), pGAB1(Y627, cat no. 3233), pGAB2 (cat no. 3882), pSTAT3 (cat no. 9131 and 9134), pERK1/2(cat no. 4370), pAKT(S473, cat no. 3787), STAT3 (cat no. 9132), AKT (cat no. 2938), ERK1/2 (Cat no. 9102) and p85 (cat no. 4257 for IP) antibodies were purchased from Cell Signaling Technology (Danvers, MA). Total ERBB2 (cat no. 06-562), p85 (cat no. 06-497), GAB2 (cat no. 06-967), IRS1 (cat no. 06-248) and IRS2 (cat no. MABS15) antibodies were purchased from Millipore (Billerica, MA). Additional antibodies include: total ERBB3 (NanoTools, cat no. 0237), pY-HRP (R&D Systems, part no. 841403), surfactant protein C (SPC) (Abcam, cat no. Ab90716, Cambridge, MA) and ACTIN (Sigma-Aldrich Co. LLC, cat no. A20266, St. Louis, MO).

*siRNA knock-down experiments*

For siRNA knock-down experiments, a final concentration of 25nM of each siRNA was mixed with lipofectamine RNAi Max at room temperature for 15 minutes in Optimum medium (Invitrogen). Before transfection, cells were trypsinized and counted. Cells were seeded at 3-5 x 105 cells/well in 6-well plates with siRNAs and maintained in a 37°C incubator with 5% CO2 for 3 days. The levels of proteins were examined by immunoblotting. For viability assays, cells were seeded at 2000 cells/ well in 96 well plates one day before transfection. Viable cells were assessed using CellTiter blue (Promega) three days after.

*Co-immunoprecipitation*

 To check the interaction between EGFR and ERBB3, 293T cells were maintained with DMEM medium supplemented with 10% FCS and 10 μg/ml penicillin and streptomycin at 37°C in a water-saturated atmosphere with 5% CO2. 293T cells were seeded in T25 flask one day before transfection at 50% confluence. Cells were transfected with 1.5 μg of plasmid encoding either mutant EGFRL858R (pCDNA3-EGFRL858R) or ERBB3 (pExpress-1 mERBB3, OPEN Biosystems) or both using 0.3% Fugene HD transfection reagent (Promega, cat no. E2311, WI) in 3 ml medium. Two days after transfection, cells were lysed in 500 μl Co-IP lysis buffer (150 mM NaCl, 50 mM Tris HCl, 1% NP40) on ice for 30 min. After centrifugation at 14,000 g for 10 min at 4°C, 150 μg supernatant in 200 μl lysis buffer were precleared with 1 μg rabbit IgG on ice for 1 hour. Lysate was then incubated with 1 μg mutant EGFRL858R specific antibody or an antibody against ERBB3 overnight at 4 °C. Lysates were then incubated with 20 μl 50% protein A/G plus beads (Thermo Scientific, cat no. 20423) for 2 hours at 4°C. Beads were pelleted at 10,000 g for 10 min at 4°C and then washed 3 times in PBS. Beads were eluted with 15 ul 2x Laemmli buffer and heated at 95°C for 5 min. Western blotting was used to check the levels of proteins of interest.

Lung tissue was pulverized on dry ice and lysed in NP-40 lysis buffer: 150 mM NaCl, 50 mM Tris HCl, 1% NP40 and halt protease and phosphatase inhibitor cocktail (Thermo Fisher Scientific Inc. Rockford, IL) on ice for 30 min. For each sample, 500 g of protein lysate was used in immunoprecipitation. After pre-clearing with protein A/G plus beads, tumor lysates were incubated with 5 g of antibody (an anti-mutant EGFRL858R specific antibody, and an ERBB3 antibody or a p85 antibody as indicated in the figures) at 4°C overnight. The lysates were further incubated with 40 l of 50% protein A/G plus beads for 1 hour at 4°C, followed by 5 washes with lysis buffer. The beads were eluted with Laemmli buffer and the rest was same as those in 293T cells.

*Phospho-RTK arrays*

Whole lung lysates were prepared from the lungs of moribund mice (and controls) in lysis buffer supplemented with protease and phosphatase inhibitor (R&D systems, Inc. Danvers, MA). Two hundred micrograms of protein lysate for each sample were hybridized to phospho-RTK arrays overnight at 4°C. Arrays were washed and probed with an HRP-conjugated phospho-tyrosine antibody according to the manufacturer’s instructions. Arrays were visualized using chemiluminescence with the ECL plus reagent (Life Sciences).

*MRI scanning and tumor volume measurements*

Mouse MRI scanning was performed at Memorial Sloan-Kettering Cancer Center and the Yale University Magnetic Resonance Research Center as described previously ([9](#_ENREF_9)). Tumor areas, visible as lung opacities in each image sequence were measured using BioImage Suite 3.01 (<http://www.bioimagesuite.org>) and tumor volume for each mouse was calculated.

*Data analysis*

Each experiment was performed independently at least 3 times. Data are presented as mean ± standard error. All data analysis was performed using GraphPad Prism5. Mouse survival curves were compared using the log-rank (Mantel-Cox) test. RTK arrays were analyzed using a two-way ANOVA test. Data from immunoblots and cell viability assays were analyzed by one-way ANOVA. The significance of multiple comparison analysis was determined using Bonferroni’s correction.