**SUPPLEMENTARY INFORMATION**

**Supplementary Figure Legends**

**Supplementary Figure S1. Activation levels of Src (p-Src) are not correlated with mTOR pathway activation (p-S6) across multiple breast cancer subtypes.** Scatter plot depicting levels of Src activation (y-axis) and mTOR pathway activation (x-axis) from human breast tumors analyzed in Fig. 1A. Each point on the graph represents an individual tumor. The correlation coefficient from linear regression analysis for all 60 tumors examined is r=0.201. Estrogen receptor-positive/negative (ER+/-), progesterone receptor-positive/negative (PR+/-), human epidermal growth factor receptor 2-positive/negative (HER2+/-).

**Supplementary Figure S2. Rapamycin induction of p-AKT occurs within 1 hour and is not due to increased levels of p-Src. A,** Human breast cancer cell lines were treated with increasing concentrations (1-100nM) of rapamycin for 3 to 24 hours and western blot analysis was performed on cell lysates. **B,** Time course of rapamycin treatment demonstrates feedback activation of AKT occurs as early as 30 minutes and is maintained at 24 hours. While rapamycin induced phosphorylation of AKT at all doses and times, there was no concomitant increase in phosphorylation of Src.

**Supplementary Figure S3.** **Analysis of mTOR and AKT signaling in breast cancer cell lines treated with dasatinib and rapamycin**. Breast cancer cell lines were treated as in Fig. 2A with dasatinib [MCF7 and BT474 (1uM), MDA-MB-231 (100nM)], rapamycin [MCF7 and BT474 (1nM), MDA-MB-231 (100nM)] or in combination for 1 and 24 hours. Western blots were probed with indicated antibodies. Phosphorylation of FoxO1/3a, a direct target of AKT, confirms an increase in AKT activity with rapamycin treatment. Quantification of changes in the ratio of phospho- to total AKT at each time point is shown in the graphs below the blots.

**Supplementary Figure S4.** **Combination dasatinib and rapamycin does not increase apoptosis over single agent treatment. A,** Breast cancer cell lines were treated as in Fig. 2A, stained with propidium iodide (PI) and analyzed by flow cytometry for changes in the SubG1 population. **B,** MCF7 cells were further analyzed for apoptosis at 24 and 48 hours. Representative plots of annexin V and PI staining of MCF7 cells treated with indicated drugs.. **C,** The % of apoptotic cells represents the AV+/PI- population in the lower-right quadrant. Error bars: ±S.D., n=3.

**Supplementary Figure S5.** **Animal monitoring of mouse weight and ex-vivo tumor weights for drug toxicity**. Differences in body weights among all treatment groups in graph **A** can largely be attributed to differences in tumor weights in graph **B**. **A,** Graph of animal weights across experimental time course. Mice in all four treatment groups were weighed twice per week and monitored for signs of drug toxicity. Mice in the vehicle treated group were killed at day 15 due to tumor burden. All other treatment groups were monitored to 30 days. Statistical analysis was performed comparing all groups at day 15. Average mouse weight in all drug treatment groups (dasatinib, rapamycin, combination) was significantly less compared to 15 day vehicle treated group (\*\*P<0.0001). There was no difference in body weight among the dasatinib, rapamycin, and combination-treated groups at 15 days. At 30 days, the average mouse weight in the combination-treated group was slightly less than either the dasatinib-treated or rapamycin-treated groups (\*P<0.05). **B,** Graph of *ex-vivo* tumor weights for each treatment group at 30 days (vehicle, 15 days). Tumors from all treatment groups weighed significantly less than the vehicle treated group (\*\*P<0.005); rapamycin versus dasatinib (#P<0.05); combination versus dasatinib (^P<.01); combination versus rapamycin (\*P<0.005). Error bars indicate SD.

**Supplementary Figure S6. The combination of dasatinib and rapamycin induces tumor regression of MMTV-PyMT-induced mammary tumors.** Graphed is the percent change in individual tumor volume from baseline by treatment group for individual mammary tumors analyzed in two separate cohorts at **A,** 4 days and **B,** 30 days of treatment. MMTV-PyMT mice bearing primary mammary tumors of ~300mm3 were treated with vehicle, dasatinib, rapamycin or with combination dasatinib + rapamycin. Dotted lines delineate progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR). Complete regression is defined by 95% or greater decrease in tumor volume. Data was analyzed using a mixed linear regression model to identify differences in response among treatment groups (see Methods for details). Tumors from the 30 day cohort were collected from the vehicle-treated mice at day 15 due to excessive tumor burden while the remaining groups of mice were treated for an additional 15 days. For the 4 day treatment cohort: P<0.05, vehicle *versus* dasatinib; P<0.05, vehicle *versus* rapamycin; P<0.005, dasatinib *versus* combination and P<0.005, rapamycin *versus* combination.  There was no difference in treatment effect between dasatinib and rapamycin treated groups (P=0.82).For the 30 day treatment cohort: P<0.05, dasatinib *versus* combination and P<0.005, rapamycin *versus* combination. There was no difference in treatment effect between the dasatinib and rapamycin treated groups (P=0.50).

**Supplementary Figure S7. Immunohistochemical analysis of target inhibition by rapamycin (p-S6) and dasatinib (p-Src) in MMTV-PyMT tumor sections.** Representative Hematoxylin and Eosin (H&E) stained tumor sections from mice treated in Figure 2 for 15 days (vehicle) or 30 days (dasatinib alone, rapamycin alone and combination dasatinib + rapamycin). Immunohistochemistry using antibodies against p-Src (middle panels) and p-S6 (bottom panels) was performed on tumor sections to confirm inhibition of dasatinib and rapamycin targets, respectively. Images were acquired at 10x magnification.

**Supplemental Figure S8. Dasatinib inhibits pulmonary metastases in MMTV-PYMT tumor bearing mice.** Lung metastases were visualized and quantified using Hematoxylin and Eosin (H&E) stained lung sections (3 sections per lung) from PyMT tumor-bearing mice following treatment with vehicle (15 days), dasatinib, rapamycin or dasatinib plus rapamycin (combo) (30 days) (n=5-10 mice per group) \*P<0.0001 for dasatinib or combination *versus* vehicle or rapamycin. #P=0.039 for rapamycin *versus* vehicle.  There is no difference between dasatinib and combination-treated groups (P=0.07). Error bars indicate ±SD.