Supplementary material

Supplementary Figure 1 a-i. *Pik3ca* ^{e20H1047R} expressing mammary glands show excessive side branching and presence of tumor nodules. Carmine alum stained whole mount (a-d) of the third pair of thoracic mammary gland from 12 week old (a, c) or *Pik3ca*$^{e20H1047R/+}$ (b, d) mice. Higher magnification images of the boxed regions in (a) and (b) are shown in (c) and (d), respectively. e. Quantification of number ductal branch points in *Pik3ca*$^{e20H1047R/+}$ (n=6) and control group [MMTV-Cre (n=3), *p=0.003; *Pik3ca*$^{e20mwt/+}$(n=4), *p=0.001]. Data presented is an average of four independent fields (~8.0 mm^2 rectangular grid) for each mammary gland. f-i are Carmine alum stained whole mount (f, g) and H&E stained sections (h, i) of abdominal mammary gland from 50 week old MMTV-Cre (f, h) or *Pik3ca*$^{e20H1047R/+}$ (g, i) mice. Arrowhead (f) points to a tumor nodule. Inset shows normal duct (e) and abnormal duct (f).

Supplementary Figure 2 Tumor free survival of multiparous and nulliparous cohorts. Kaplan–Meier analysis of median tumor free survival in multiparous (465 days) and nulliparous (492 days) is statistically different (log-rank test p-value = 0.0002). Animals bearing mammary tumors at end point are shown in the plot.

Supplementary Figure 3 a-d. Histology of seminal vesicles (a, b) and salivary glands (c, d) from *Pik3ca*$^{e20mwt/+}$ (a, c) or *Pik3ca* $^{e20H1047R/+}$ (b, d) mice.

Supplementary Figure 4 Histological comparison of primary and passaged tumors. Fibroadenoma (a) when passaged resulted in adenocarcinoma (b). However, the spindle

cell tumor (c) when passaged maintained its spindle cell histology with invasive characteristics (d).

Supplementary Figure 5 A heatmap representation of the predicted somatic mutations by tumor type in the primary tumor and passaged tumors.

Supplementary Figure 6. Heatmap depiction of the copy number alterations in the different mammary tumor types.

Supplementary Figure 7 aCGH analysis reveals loss of *Nf1* in chromosome 11(a) and a large deletion in chromosome 12 (b) in spindle cell tumors.

Supplementary Figure 8 Kaplan-Meier analysis of time to progression of tumor bearing mice treated with PI3K inhibitor at the doses indicated.

Supplementary Figure 9 The vector engineered to provide unique restriction enzyme sites for cloning and other elements needed to generate the targeting vector.