**Supplementary Figure S1. Heregulin is expressed in MCF-7Ca and LTLT-Ca cells.** MCF-7Ca and LTLT-Ca cells were plated in 10 cm dishes. Once cells had reached ~70% confluence, media was replaced with serum-free media and cells were further incubated for 24 h at 37°C. Cell lysates and media were collected and HRG levels were analyzed by ELISA as specified in the Materials and Methods. Heregulin levels in cell lysates are normalized to total protein concentration, and levels in media are expressed per milliliter of media collected. There was no significant difference in expression between groups, *P* > 0.05.

**Supplementary Figure S2. Statistical analyses of tumor growth curves in mouse study 1 (Figure 3).** Tumor growth rates were estimated using a non-linear mixed effect model (see Materials and Methods). (A) Analysis of tumor growth rates in the first 14 weeks of the study. Co-treatment with seribantumab and letrozole (light blue) had an enhanced inhibitory effect on tumor growth compared to letrozole alone (green) up to 14 weeks, but this effect was not statistically significant (*P* > 0.05). Treatment with letrozole, alone or in combination with seribantumab, had a significantly improved anti-tumor effect compared to either control (purple) or seribantumab alone (black). (B) Analysis of tumor growth rates following re-randomization of letrozole-treated mice at week 14. For tumor growth rate comparisons from weeks 14-22, co-treatment with seribantumab and letrozole, either from the beginning of the study (light blue) or in letrozole-treated mice following re-randomization at week 14 (dark blue), had significant inhibitory effects on tumor growth rates compared to letrozole alone (green) or seribantumab alone following re-randomization of letrozole-treatment mice at week 14 (red; *P* < 0.05). ANOVA was used to evaluate statistical significance comparing the mean (horizontal green lines) growth rates of each treatment arm. Green triangles represent one standard deviation from the mean. The overall mean is represented by the solid horizontal grey line. Box plots (red) represent the quantiles. Black dots represent the tumor growth rates of each tumor on individual mice. Colored circles on the right relate to each treatment group, colored according to their respective treatments; the diameter of the circles represents 2 standard deviations. Intersecting circles indicate no significant differences between the growth rates of those treatment groups, whereas non-intersecting circles represent significant differences in growth rates for those groups (*P* < 0.05).

**Supplementary Figure S3. Pharmacodynamic analyses of HRG and ERBB3 expression in tumors harvested post-treatment.** Protein lysates were generated from MCF-7Ca xenograft tumors harvested from mice at 24 hours and 24 weeks post-treatment with PBS, letrozole or MM-121, alone or in combination, as outlined in Figure 3. HRG levels were quantified by ELISA (A). Levels of expression of phosphorylated and total ERBB3 were evaluated by immunoblotting. Quantified expression, normalized to -actin, is shown in the bar graphs (B).

**Supplementary Figure S4. Statistical analyses of tumor growth curves in mouse study 2 (Figure 5).** Tumor growth rates were estimated using a non-linear mixed effect model (see Materials and Methods). (A) Analysis of tumor growth rates in the first 16 weeks of the study. Co-treatment with seribantumab and letrozole (light blue) had a significantly enhanced inhibitory effect on tumor growth compared to letrozole alone (green) up to 16 weeks treatment (*P* < 0.05). (B) Analysis of tumor growth rates following re-randomization of letrozole-treated mice at week 16. For tumor growth rate comparisons from weeks 16-20, co-treatment with everolimus and letrozole (yellow), seribantumab and letrozole (dark blue), or seribantumab, letrozole, and everolimus (orange) had significant inhibitory effects on tumor growth rates compared to letrozole alone (green; *P* < 0.05). The lowest growth rates in order are seribantumab + letrozole + everolimus < seribantumab + letrozole < everolimus + letrozole < letrozole alone. ANOVA was used to evaluate statistical significance comparing the mean growth rates (horizontal green lines) of each treatment arm. Green triangles represent one standard deviation from the mean. The overall mean is represented by the solid horizontal grey line. Box plots (red) represent the quantiles. Black dots represent the tumor growth rates of each tumor on individual mice. Colored circles on the right relate to each treatment group, colored according to their respective treatments; the diameter of the circles represents 2 standard deviations. Intersecting circles indicate no significant differences between the growth rates of those treatment groups, whereas non-intersecting circles represent significant differences in growth rates for those groups (*P* < 0.05).

**Supplementary Figure S5. ERBB3 levels are significantly higher following co-treatment with letrozole and everolimus.** MCF-7Ca xenograft tumors (n = 2-5/treatment group) were harvested 24 h after the final dose of letrozole, letrozole + seribantumab, letrozole + everolimus, or seribantumab + everolimus + letrozole (week 20), as shown in Figure 5. Tumor lysates were generated and analyzed by immunoblotting with antibodies for total ERBB3. Anti--actin antibody was used as a loading control. Quantified band intensities, normalized to -actin, are represented in the dot plots. \**P* < 0.05 vs. all other groups.

**Supplementary Figure S6. Dosing everolimus in combination with** **letrozole and seribantumab causes weight loss in mice**. Following treatment with letrozole for 16 weeks, mice were re-randomized to receive either letrozole alone; letrozole in combination with seribantumab; letrozole in combination with everolimus; or letrozole in combination with seribantumab and everolimus. All agents were administered as described in Figure 5. Mouse body weights were recorded weekly at the same time of the day. Following four weeks of treatment, mice dosed with the triple combination of letrozole, seribantumab, and everolimus had significantly decreased body weight compared to the other treatment arms (\**P* < 0.05), at which point the study was ended.