Supplementary Figure Legends

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Supplementary Figure S1. **The chemical structures of SGX523 and erlotinib.**

Supplementary Figure S2. **The effect of erlotinib on basal tyrosine phosphorylation of EGFR.** The cells (H1373, H1993, and EBC-1) were treated with erlotinib (5 μM) for the indicated period of times (0, 1h, 3h or 6h), and the whole cell lysates were prepared for western blot analyses of p-EGFR and total EGFR levels. β-Actin was the loading control. Erlotinib reduces p-EGFR level in the H1373 cells starting from 1h post-treatment. However, it does not reduce basal EGFR phosphorylation in the H1993 and EBC-1 cells even after treatment for 6h.

Supplementary Figure S3. **Inhibition of MET, EGFR, and their downstream signaling by SGX523 and erlotinib in the absence of ligands.** The cells (H1373, H1993 and EBC-1) were serum-starved overnight, followed by treatment with DMSO, SGX523 (1 μM), and/or erlotinib (5 μM) for 1 h. The whole cell lysates were prepared and subjected to western blot analyses of MET, EGFR, and their downstream signaling ERK and AKT.

Supplementary Figure S4. Dose-dependent inhibition of H1373 and H1993 cell proliferation by SGX523 and/or erlotinib *in vitro*. A) H1373 and **B)** H1993 cells were treated with SGX523 (0, 1.6nM, 8nM, 40nM, 200nM, 1μM, and 5μM), erlotinib (0, 8nM, 40nM, 200nM, 1μM, 5μM, and 25μM), or the combination of the two (1:5 ratio), in the presence of HGF (200 U/mL) and EGF (50ng/mL) for 24 h. All assays were performed in triplicate; error bars represent standard deviation. C) Analyses of drug combinational effect by the Chou-Talalay Method. The combination with 1μM SGX523 plus 5μM erlotinib (the concentrations used for the study shown in Figure 3) was analyzed for both H1373 and

H1993. A synergistic effect is observed for both cell lines, while the synergism in H1993 cells is much stronger. *Note: CI (combination index) = 1, additive; CI < 1, synergism; CI > 1, antagonism.

Supplementary Figure S5. **SGX523 and erlotinib combination results in a stronger ERK inhibition in the H1373 tumors.** Two H1373 tumor samples from each treatment group (Vehicle, erlotinib, SGX523, and the combination of erlotinib and SGX523) derived from the HGF^{tg}-SCID mice were homogenized in RIPA buffer containing proteinase inhibitor cocktail (Roche). The tumor lysates were quantified and subjected to Western blot analyses for p-MET, MET, p-EGFR, EGFR, p-ERK, ERK, p-AKT and AKT. β-actin was used as a loading control.

Supplementary Figure S6. **The effects of SGX523 and/or erlotinib on cell viability of H358, H1373, H1993 and EBC-1.** The cells (5000 cells/well) were seeded in 96-well dish. After serum-starvation for overnight, the cells were treated with DMSO, SGX523 (1μM), erlotinib (5μM), or the combination of SGX523 and erlotinib, with or without HGF (200 U/mL) and EGF (50ng/mL). 48 hours after treatment, the CellTiter-Glo Luminescent Cell Viability Assay (Promega) was performed. The assay was performed in triplicate, and the error bars represent standard deviation.

Supplementary Figure S7. EBC1-Sg3-H62 and EBC1-Sg3-H71 cells are relatively less sensitive to SGX523, compared to the parental EBC-1 cells. The cells (5000 cells/well) were seeded in a 96-well dish, serum-starved for overnight, and treated with SGX523 (0, 1.6nM, 8nM, 40nM, 200nM, 1μM, or 5μM) for 48 hours. The cell viability was determined by the CellTiter-Glo Luminescent Cell Viability Assay (Promega). The assay was performed in triplicate, and the error bars represent standard deviation.

Supplementary Figure S8. The effect of SGX523 and/or erlotinib on MET and EGFR in the EBC-1 and its tumor derivatives. The serum-starved cells (EBC-1, EBC1-Sg3-H62, and EBC1-Sg3-H71) were treated with or without SGX523 and/or erlotinib for 1 hour, followed by stimulation with or without HGF

(200 U/mL) and EGF (50ng/mL) for 30 min. The whole cell lysates were prepared and subjected to Western blot analyses with the indicated antibodies. A relatively higher EGFR phosphorylation can be observed in the EBC1-Sg3-H62 and –H71 cells, compared to that in EBC-1 cells in the presence of ligands. Also in the presence of ligands, a stronger p-EGFR level is left in the two EBC-1 derivatives after erlotinib treatment, compared to the parental cells.

Supplementary Figure S9. Kaplan-Meier survival analyses of the mice in the drug studies. The survival analyses were performed using GraphPad Prism program. Although no mice died from the treatment for H1373 study, we observed several losses of mice in the erlotinib & SGX523 combination groups for both H1993 and EBC-1 studies. These data indicate that there is likelihood of enhanced toxicity or side effect as a result of the two drugs combination.