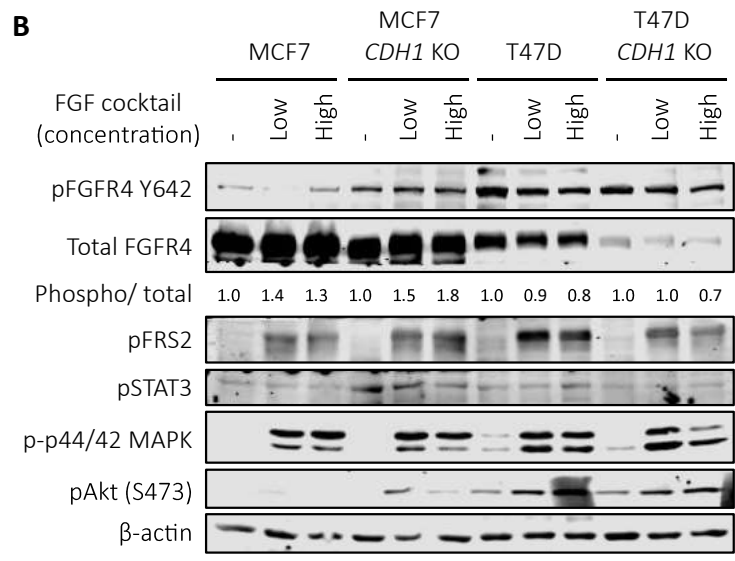
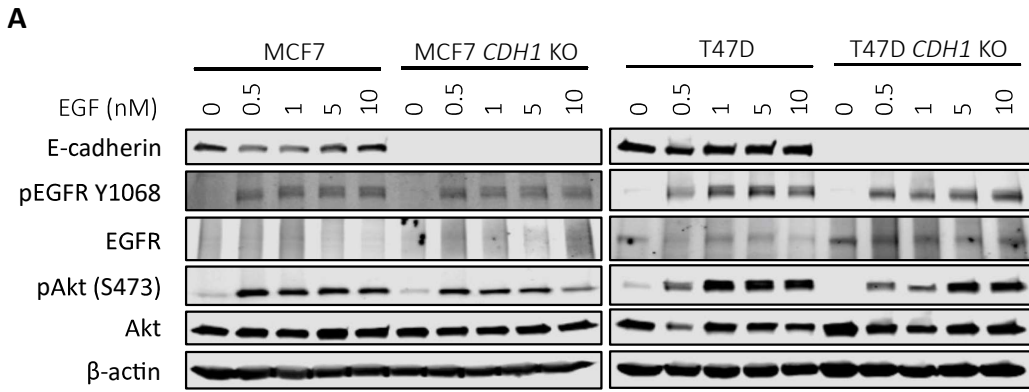
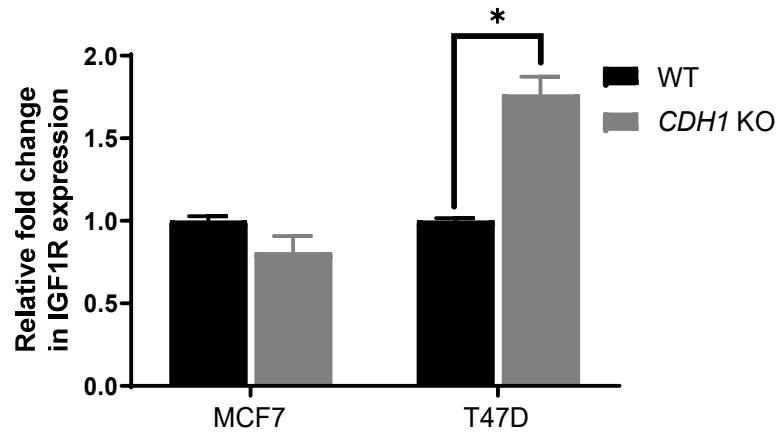


Supplementary Figure 1. (A) IDC cells (MCF7, T47D, ZR75.1) and ILC cells (MDA-MB-134-VI (MM134) and SUM44PE) were stimulated with doses of insulin or (B) EGF (0-5nM) for 15 minutes following an overnight serum starvation. IGF1R/IR, EGFR and Akt signaling was assessed by Western blotting. Phosphorylated protein levels were normalized over the corresponding total protein levels and loading control β-actin. Ligand treated samples values were further normalized to respective cell line's vehicle samples. (C) Cells were treated with GSK-3 inhibitor, CHIR 99021 for 24 hours and harvested for Western blotting. Total and active β-catenin protein levels were assessed. Representative experiment shown for all, n=2-3 for each experiment).

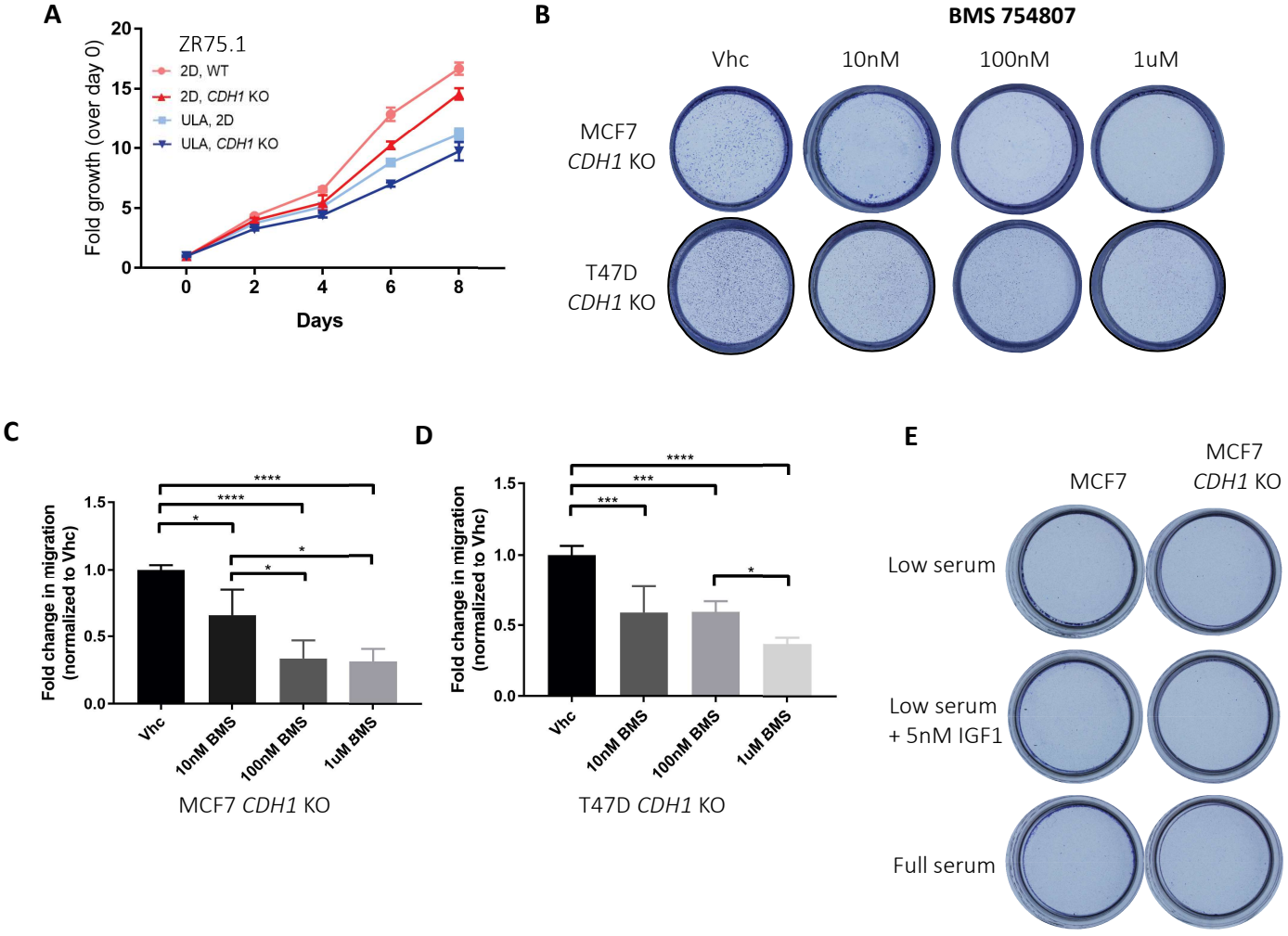


Supplementary Figure 2. Cells were serum starved overnight and stimulated with (A) EGF (0-10nM) and (B) cocktail of FGF ligands (10-50ng/mL) for 15 minutes. Cells were harvested for Western blot to assess downstream signaling. Representative experiment shown for all, n=2-3 for each experiment).



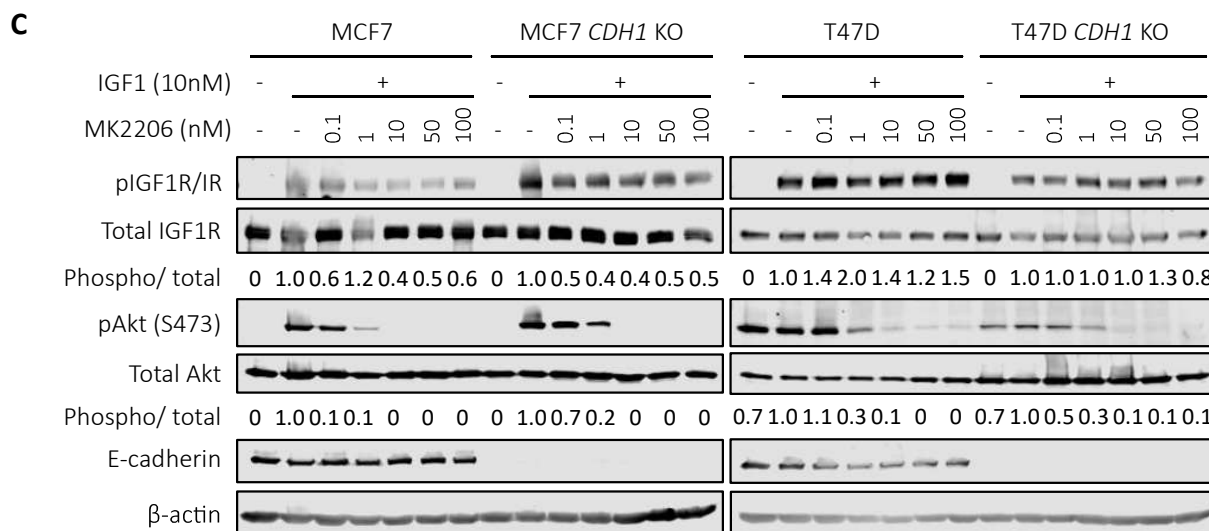
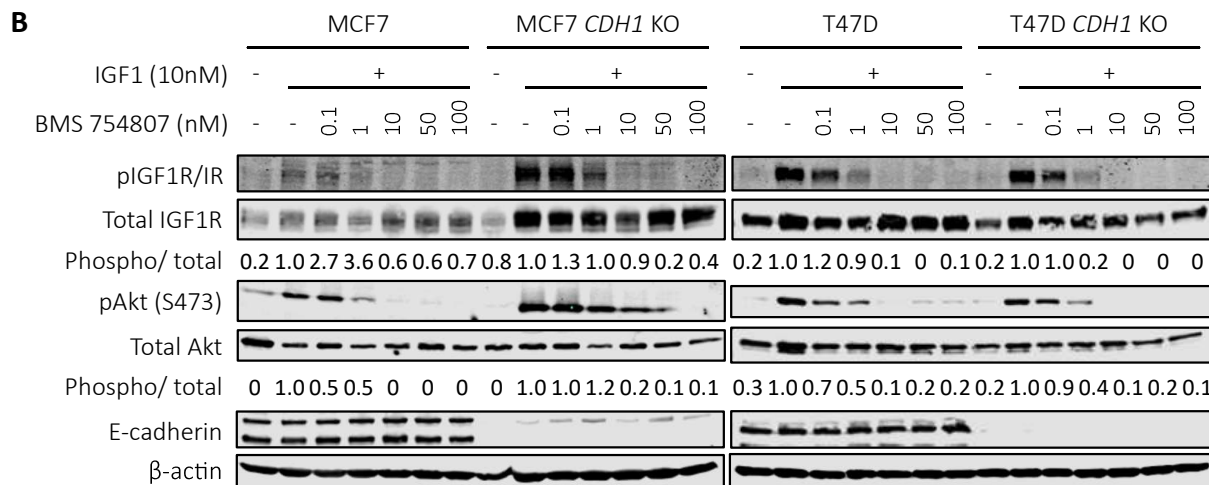
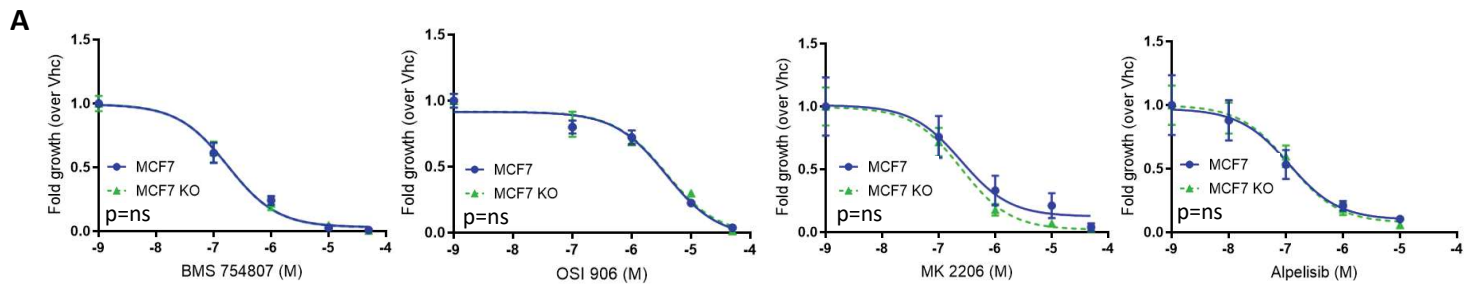
Supplementary Figure 3. qRT-PCR for IGF1R for the cell line models studied. Fold change in expression were calculated by normalizing delta Ct values to the respective WT values. Statistical differences were evaluated using paired t-test ($p=0.0105$ for T47D cell pair). Representative experiment shown, $n=2$ experiments with 2 biological and 3 technical repeats for each cell line.

Supplemental Figure 4



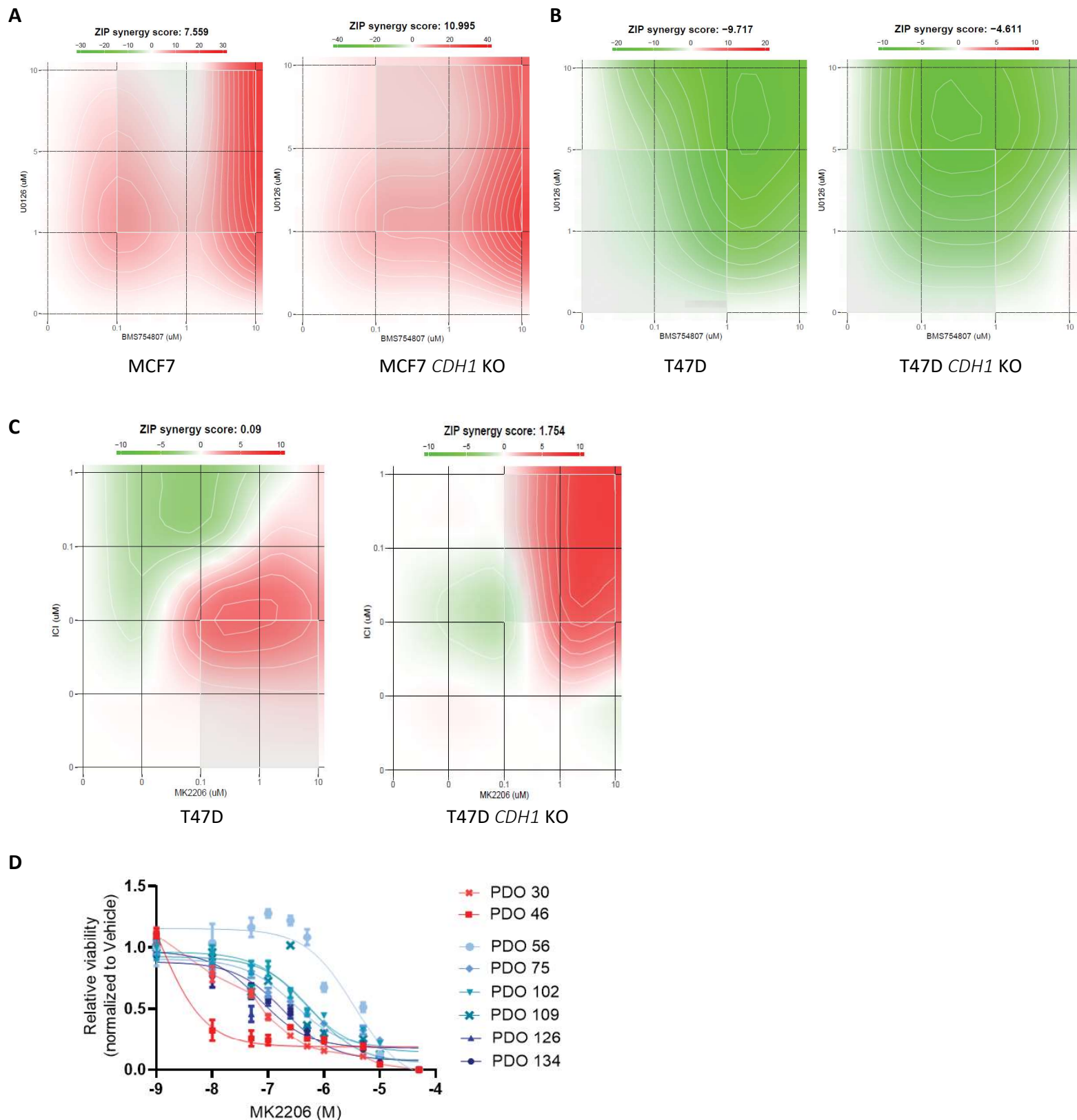
Supplemental Figure 4. (A) Representative 2D and ULA growth of ZR75.1 parental and *CDH1* KO cells quantified by CellTiter-Glo and normalized to Day 0. (B) Images and (C,D) quantification of crystal violet-stained Transwell inserts from migration assays towards low serum + 5nM IGF1 media after 72 hours. Cells were treated with increasing doses of BMS-754807 in the upper chamber to assess IGF1 specific migration. Graphs show representative data normalized to vehicle from two to three independent experiments (n=2 biological replicates). p-values are from one-way ANOVA. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001. (E) Images of crystal violet-stained collagen I inserts from invasion assays towards the indicated attractants after 72 hours.

Supplemental Figure 5



Supplementary Figure 5. (A) MCF7 parental and *CDH1* KO cells were treated with IGF1R inhibitor (OSI-906 or BMS-754807) or PI3K inhibitor (Alpelisib) or Akt inhibitor (MK2206) for 6 days. CellTiter Glo assay was used to assess cell viability (relative luminescence). IC50 values for viability were calculated by nonlinear regression and statistical differences evaluated using sum-of-squares Global f-test ($P < 0.05$; representative experiment shown; $n=3$ each with six biological replicates). Cells were treated with (B) BMS754807 and (C) MK2206 in increasing doses to assess signaling inhibition of the compounds used for cell viability assays. Representative experiment shown, $n=2$ for each experiment).

Supplemental Figure 6



Supplemental Figure 6. Results from (A) MCF7 WT and *CDH1* KO cells and (B) T47D WT and *CDH1* KO cells were treated with a combination of IGF1R inhibitor (BMS-754807) and MEK inhibitor (U0126) for 6 days. (C) T47D WT and *CDH1* KO cells were treated with a combination of a SERD (Fulvestrant) and Akt inhibitor (MK2206) for 6 days. CellTiter Glo assay was used to assess cell viability (relative luminescence). The viability values were input into the SynergyFinder platform and assessed for drug synergy effect. Synergy scores -10 to 10 signify an additive effect of the compounds being tested. (D) Complete dose response analysis of IDC and ILC organoids assayed for sensitivity to MK2206. Organoids were plated and treated in 96-well for 12 days. CellTiter Glo 3D assay was used to assess cell viability (relative luminescence) and data normalized to vehicle treated control. Representative experiment shown for all, n=2-3 for each experiment).