**Supplemental Methods**

**Western blotting**

Primary antibodies (rabbit anti-human AR, Santa Cruz (US), SC-816, dil. 1/1000; rabbit anti-human SGK3, Abcam (UK), ab153981, dil 1/1000; rabbit anti-human TBP, cell signalling (UK), 8515S dil. 1/1000, mouse anti-human ERα, Novocastra, Leica, Germany (NCL-L-ER 6F11, dil. 1/1000). All secondary antibodies were HRP conjugated (Dako, Den). For western blot analysis cells were treated with 4AD (10-7M) or ethanol vehicle (0.0001% (v/v)) for 48 hours. Cells were synchronized 96 hours prior to collection for AR basal level blots. For confirmation of AR, ER and SGK3 protein knockdown post siRNA, MCF7-Aro-LetR were transfected and protein was collected 24 hours post transfection.

**Sequenome massarray**

DNA was extracted from endocrine sensitive MCF7 and endocrine resistant MCF7-Aro-LetR using the DNeasy Kit (Qiagen Hilden, Germany). A minimum of 250ng of DNA/sample was isolated for MassArray analysis (RCSI, ERC Beaumont). Mass spectrometry-based single nucleotide polymorphism (SNP) genotyping technology (Agena Biosciences) was applied to DNA extracted from the cell lines to detect a total of 37 nonsynonymous somatic mutations in PIK3CA. Hotspot mutations in exon 1 (R88Q, K111N), exon 4 (N345K), exon 7 (C420R, E453K), exon 9 (E542V/G/K/Q, E545K/Q/D/A/G/V, Q546H/L/P/R/E/K),and exon 20 (Y1021H/N/C, R1023Q, T1025I/A/S, A1035V/T, M1043V/I, A1046V, H1047R/L/Y, G1049R) of PIK3CA were analysed. Matrix chips were analysed on an Agena MassArray MALDI-TOF system. Visual inspection and Typer Software were used to identify genotypes based on mass spectra. Reactions where >15% of the resultant mutant mass ran in the mutant site were scored as positive.

**Determination of optimal concentration (EC50) of pan-class PI3K/mTOR inhibitor BEZ235 and α/δ PI3K inhibitor pictilisib**.

MCF7, MCF7-Aro-LetR, ZR75.1 and ZR-Aro-LetR cell lines were treated with BEZ235 (NVPBEZ235; Selleck Chemicals, Germany) (2 µM to 0.02 nM) or pictilisib (Selleck Chemicals) (20 µM to 0.2 nM) for 48 hours [1, 2]. The level of cell viability was quantified using MTS assay as a measure of indirect metabolic activity. Using normalized, nonlinear regression, the EC50 for each cell line on treatment was determined. Relative Ec50 curves were transformed and normalized to 100% and 0% viability based on the lowest and highest drug concentrations using GraphPad Prism version 5.01 software. F test was used to determine the statistical difference between EC50 slopes.

**RNA-seq preprocessing:**  Raw sequencing data in the form of fastq files were aligned to human genome version 19 (hg19), using the sequence aligner subread [3] via the bioconductor R package Rsubread (https://bioconductor.org/packages/). Quality control was conducted using FASTQC. (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). The data was scale normalized using the TMM (trimmed mean of M values (TMM)) normalization method [4].

**Microarray preprocessing:** Raw data (.CEL files) files were downloaded from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo), accession number GSE41405. This experiment comprised 24 samples, 6 of which were of interest to us, specifically MCF7-Aro cells cultured in 4AD (1 nM, 6 days) versus vehicle [5]. The array platform used in this experiment was the Affymetrix Human Gene 1.0 ST Array. Probes were background corrected and quantile normalized using the robust multichip average preprocessing methodology using the R Bioconductor package “oligo” [6].

**RNA-seq validation**

Validation of RNA-seq was performed using primers for SGK3 (Forward (F): 5’-AGCTGCCCAAGTGTAAGCAT-3’, Reverse (R): 5’-CAGGAATCTTCAGGGCCATA-3’), GREB1 (F: 5’-GCCTGAAGGATGCTGTACC-3’, R: 5’- CTCTTGTCAACGGCGCACAC-3’), PKIB (F: 5’-TGTCACACCAGGATGTTGCT-3’, R: 5’-ATCTGAGGTTCCGTCTGTGG-3’) and MYBL (F: 5’-AATGGACAAGGGACGAGGA-3’, R: 5’-GATGCTGGCACTGAAAATCA-3’).

1. Kong D, Yamori T, Yamazaki K, Dan S: **In vitro multifaceted activities of a specific group of novel phosphatidylinositol 3-kinase inhibitors on hotspot mutant PIK3CA**. *Invest New Drugs* 2014, **32**(6):1134-1143.

2. Folkes AJ, Ahmadi K, Alderton WK, Alix S, Baker SJ, Box G, Chuckowree IS, Clarke PA, Depledge P, Eccles SA *et al*: **The Identification of 2-(1H-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as a Potent, Selective, Orally Bioavailable Inhibitor of Class I PI3 Kinase for the Treatment of Cancer**. *Journal of Medicinal Chemistry* 2008, **51**(18):5522-5532.

3. Liao Y, Smyth GK, Shi W: **The Subread aligner: fast, accurate and scalable read mapping by seed-and-vote**. *Nucleic acids research* 2013, **41**(10):e108.

4. Robinson MD, Oshlack A: **A scaling normalization method for differential expression analysis of RNA-seq data**. *Genome biology* 2010, **11**(3):R25.

5. Gattelli A, Nalvarte I, Boulay A, Roloff TC, Schreiber M, Carragher N, Macleod KK, Schlederer M, Lienhard S, Kenner L *et al*: **Ret inhibition decreases growth and metastatic potential of estrogen receptor positive breast cancer cells**. *EMBO Mol Med* 2013, **5**(9):1335-1350.

6. Carvalho B, Bengtsson H, Speed TP, Irizarry RA: **Exploration, normalization, and genotype calls of high-density oligonucleotide SNP array data**. *Biostatistics* 2007, **8**(2):485-499.