**Supplementary Figure 1. Degradation of ERα by AZD9496, fulvestrant and estradiol in MCF-7 cells.** MCF-7 cells were incubated with AZD9496, fulvestrant or estradiol at the indicated doses. Total protein was extracted after 48 hours incubation with compound and immunoblotting performed to detect effects on ERα. Images shown are representative of at least two independent experiments.

**Supplementary Figure 2. Rate of degradation of ERα peptide in the presence of**

**AZD9496, fulvestrant, tamoxifen and estradiol.** Cells were grown in steroid-free conditions in SILAC media containing 13C615N4 L-arginine for 48 hours and then switched to grow in media containing unlabelled L-arginine with 100 nM fulvestrant, 100 nM AZD9496, 300 nM tamoxifen, 0.3 nM estradiol or 0.1% DMSO for the times indicated. Protein lysates were prepared and spiked with internal standards (lysate from MCF-7 cells labelled with 13C6 lysine only) before immunoprecipitation overnight at 4oC using an anti-ERα monoclonal antibody coated on a Nunc Maxisorp Protein A/G coated plate. Wells were washed and then digested with 0.4 μg trypsin at 37oC overnight before analysing by mass spectrometry using relative peptide quantification by selected reaction monitoring (SRM). % Heavy ERα peptide was plotted over time as shown. Data enabled the calculation of the degradation half-life using the one-phase exponential decay equation in GraphPad PRISM (Y=Span.e-K.X+Plateau) where X is time and Y is response which starts out as Span+Plateau and decreases to Plateau with a rate constant K.

**Supplementary Figure 3. Degradation of ERα by AZD9496, fulvestrant and estradiol in the presence of protesomal inhibitor MG132.** MCF-7 cells were incubated with AZD9496, fulvestrant, tamoxifen or estradiol in the presence or absence of 10 μM of the 26S proteosomal inhibitor MG132 for 24 hours. ERα protein was detected by immunoblotting. Images shown are representative of at least two independent experiments.

**Supplementary Figure 4. Effect of AZD9496, fulvestrant and estradiol on ERα/PR levels in MCF-7 cells following compound removal.** (A)MCF-7 cells were treated with AZD9496, fulvestrant or estradiol for 0 - 48 hours. Concentrations of all compounds were based on five times higher than mean IC50 values as measured in an MCF-7 ERα down-regulation immunofluorescence assay *in vitro*. Total protein lyates were made and immunoblotting performed to detect ERα and GAPDH levels. Data shown is representative of n=2 experiments. (B) ERα levels were measured by chemiluminescent imaging of Western blots and plotted as a graphical representation of data in A with levels normalised to GAPDH control.

**Supplementary Figure 5. Estrogen levels in mice following estrogen pellet implants and effects on ER down-regulation in the present of SERD agents**

 (A) Estradiol levels were measured in mice plasma using a custom-made immunoassay kit (MSD) at various time points after implantation of two different concentration pellets. The mean concentration for each group of animals is shown.

**Supplementary Figure 6. Effect of fulvestrant, AZD9496 and tamoxifen on mRNA levels of estrogen-regulated gene transcripts in the MCF-7 *in vivo* model and MCF-7 cell line.** (A) Tumour samples dosed at 10 mg/kg for 3 days with AZD9496 or tamoxifen and fulvestrant given as a single dose 5 mg were taken 24 hours after the last dose of AZD9496 and tamoxifen and mRNA levels measured using a Human Transcriptome Array (HTA 2.0). A subset of known ER regulated genes are shown and coloured according to fold changes in mRNA levels detected (B - F) MCF-7 cells were treated with or without 1 nM estradiol and compound at doses ranging from 1 – 1000 nM for 48 hours. Cells were lysed, RNA extracted and measured using a Biomark FLUIDIGM system and software. Transcript data was normalised using house-keeping genes and visualised using TIBCO Spotfire software analysis. Fold changes were calculated by comparison with the 0 nM fulvestrant, no E2 samples with red horizontal lines depicting +2 and -2 fold changes. Graphs shown are representative of n=3 independent experiments.

**Supplementary Figure 7. ERα down-regulation by AZD9496 and fulvestrant in the HCC1428 LTED *in vivo* model.** HCC1428LTED xenografts were grown in ovariectomised NSG mice and were dosed daily with either PEG/captisol (vehicle control) or AZD9496 at doses shown. Tumours from treated mice were collected at the end of study (28 days) and analysed by Western blot for ER and vinculin proteins. Protein levels were measured by chemiluminescent and quantified using Syngene software. ER protein levels were normalised to vinculin as a loading control and plotted as shown.