## Supplemental Figure Legends

**Figure S1.** Sorafenib targets endometrial cancer cells with high specificity. (**A**) Distribution of EC cell lines among a total of 494 cancer cell lines across 12 different tyrosine kinase inhibitors. (**B**) Box plots illustrating sorafenib effects in all tissues represented in the study. Prostate was removed from the analysis due to low representation (n cell lines=2).

**Figure S2.** Sorafenib treatment increases autophagic markers in EC cells. Gene set enrichment analysis (GSEA) showing a negative correlation between sorafenib sensitivity and genes contained within the lytic vacuole (**A**), cellular catabolic process (**B**), catabolic process (**C**) and vacuole (**D**) gene ontology annotations. (**E**) Sorafenib treatment reduces lysosomal pH as observed by the increased intensity using a LysoSensor probe. Scale bar: 50 µm. Western blot and densitometry quantifications (n=3) showing increased LC3-II levels after increasing doses of sorafenib (**F**) and during a sorafenib time course (**G**) in Ishikawa cells. (**H**) Representative images of immunofluorescent LC3-II puncta in HEC-1A cells after 12 h of sorafenib treatment and sorafenib in combination with CQ. Scale bar: 50 µm. (**I**) Analysis of *SQSTM1* mRNA levels by qRT-PCR in Ishiwaka and HEC-1A cells treated with Sorafenib (20 µM). (**J**) Representative transmission electron microscopy images showing a cytoplasmic portion of untreated Ishikawa cells and 2 independent micrographs illustrating the increase in autophagic structures. Arrows indicate autophagosomes containing multivesicular and multilamellar structures. AP, autophagosomes. N, nucleous. RER, rough endoplasmic reticulum. G, Golgi. (**K**) Ishikawa cells were cultured in matrigel to form 3D organotypic structures. Organotypic cultures displayed typical cell-to-cell, cell-to-matrix contacts and apical localization of the Golgi apparatus as indicated by phalloidin, CDH1, GOLGA2/GM130 and LAM/laminin fluorescent stainings. Scale bar: 25 µm.

**Figure S3.** Sorafenib induces ER stress and MAPK8/9/10 activation. (**A**) TEM representative image magnification showing dilated ER in sorafenib-treated EC cells for 24 h. Asterisks indicate vacuolization and dilated ER cisternae. (**B**) Representative black and white images from Ishikawa cells treated with sorafenib. The endoplasmic reticulum was labelled with ER-Tracker Blue-White DPX and analyzed at 4 h post-treatment. Scale bar: 50 µm. (**C**) Western blot showing activation of MAPK8/9/10 and its target JUN after a time course treatment of sorafenib (20 µM) in KLE and HEC-1A EC cells. (**D**) Up, quantification of apoptotic nuclei after a sorafenib time-course treatment in Ishikawa cells infected with a FCIV (Flap C-ubiquitin promoter internal ribosome entry site (IRES) Venus) scrambled or BCL2L1-encoding lentiviral particles. Down, representative images of apoptotic nuclei after sorafenib treatment for 24 h. Scale bar: 50 µm. (**E**) Western blot showing inhibition of caspase activation by Sorafenib in FCIV-BCL2L1 cells. Cells were exposed to sorafenib (20 µM) for 24 h. (**F** and **G**) Western blots showing that increased expression of BCL2L1 and MCL1 are unable to revert activation of MAPK8/9/10 and JUN after sorafenib treatment in EC cells. (**H**) Targeted deletion of *Mapk8/9* impairs MAPK8/9 and JUN activation by western blot. Western blot against tubulin was performed to ensure equal protein loading amounts. (**I**) Analysis of *Sqstm1* mRNA levels by qRT-PCR in wild-type and *mapk8/9*-/- MEFs treated with sorafenib (20 µM).

**Figure S4.** BECN1 knockdown potentiates Sorafenib cytotoxicity. (**A**) Representative images of apoptotic nuclei of shRNA-Scrambled and shRNA-*BECN1* Ishikawa cells after sorafenib (10 µM and 20 µM treatment for 24 h. Scale bar: 100 µm.

**Figure S5.** Orthotopic PDXs recapitulate donor tissue architecture. (**A**) Representative hematoxylin and eosin (H&E) stainings reveal a high correlation between primary and paired engrafted tumors and show effects of sorafenib+choloquine treatment. (**B**) Representative images. At the time of sacrifice, liver tissues were resected for pathological analysis and no evident toxicity was detected by H&E staining in any of the mice used in the different drug treatments.