

Figure S1 – related to Figure 1: Foretinib is active in NSCLC cells independent of its cognate targets. Dose response curves of foretinib (FORE), cabozantinib (CABO), motesanib (MOTE) and PF-04217903 (PF) for inhibition of viability in NSCLC cells after 72 hours treatment and the respective IC_{50} values [μM], $n = 2$ (H1944, H460, HCC2935, H2122 and H661), $n = 3$ (A549, H2170, H1648, H157, H23, H3122, H358), Data are represented as mean \pm SD.

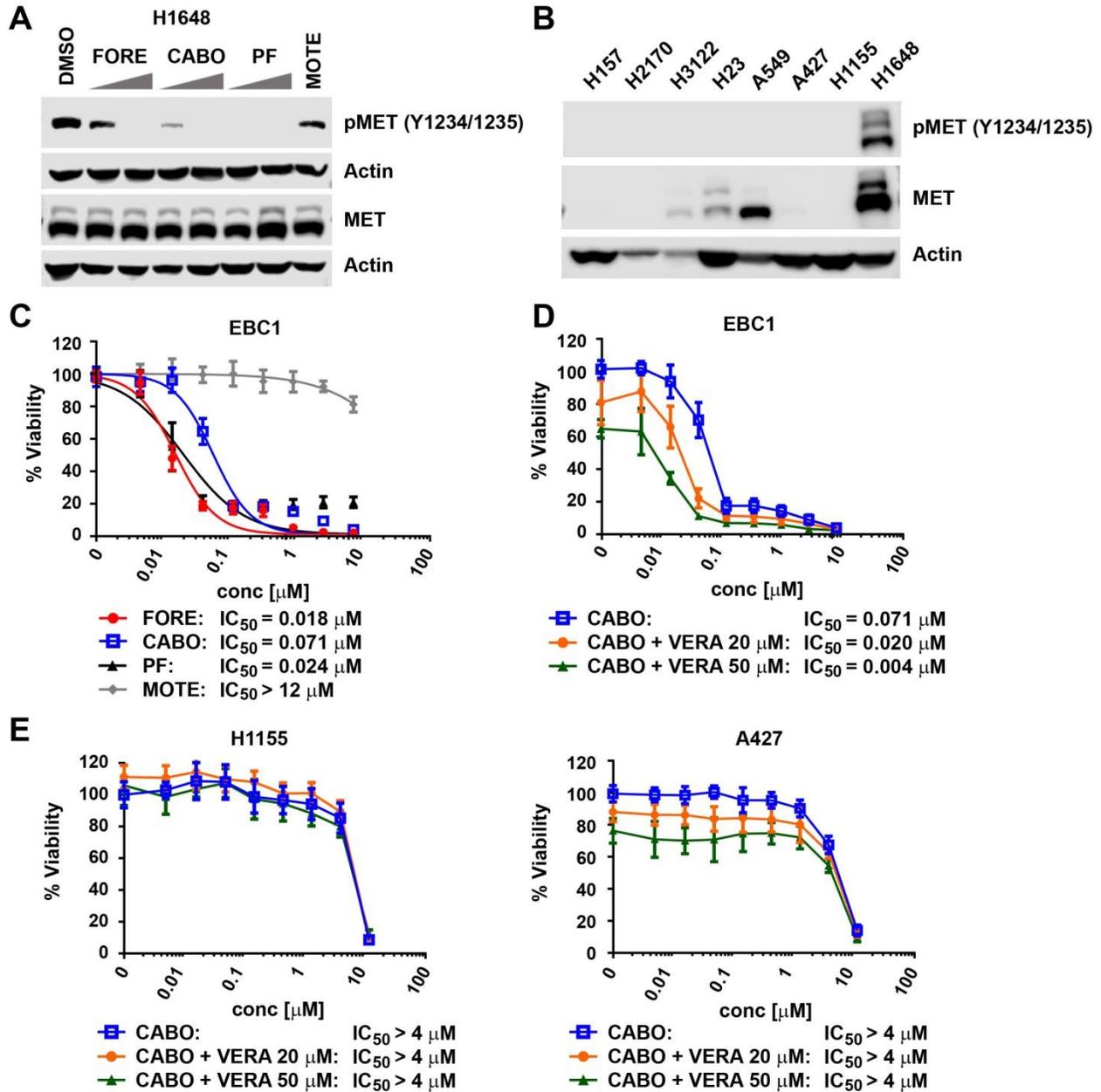


Figure S2 – related to Figure 1: Cellular validation of foretinib and cabozantinib:

(A) Western blot of pMET (Y1234/1235) after 1 hour treatment of H1648 cells with 0.01 μM and 0.1 μM of foretinib (FORE), cabozantinib (CABO) and PF-04217903 (PF- METi) and 0.1 μM of motesanib (MOTE - VEGFRi). Blots are representative of three independent experiments.

(B) Western blot of pMET (Y1234/1235) in several total cell lysates of NSCLC cells. H1648 is used as control since they express high levels of MET protein.

(C) Dose response curves of FORE, CABO, PF and MOTE for inhibition of viability of EBC1 cells (dependent on MET signaling) after 72 hours treatment and the respective IC_{50} values [μM], $n = 3$, Data are represented as mean \pm SD.

(D) Dose response curves of CABO alone and in combination with 20 μM or 50 μM of verapamil (VERA - efflux pump inhibitor) in the EBC1 cells after 72 hours treatment and the respective IC_{50} values [μM], $n = 3$, Data are represented as mean \pm SD.

(E) Dose response curves of CABO alone and in combination with 20 μM or 50 μM of verapamil (VERA - efflux pump inhibitor) in the H1155 (left) and A427 (right) cells after 72 hours treatment and the respective IC_{50} values [μM], $n = 3$, Data are represented as mean \pm SD.

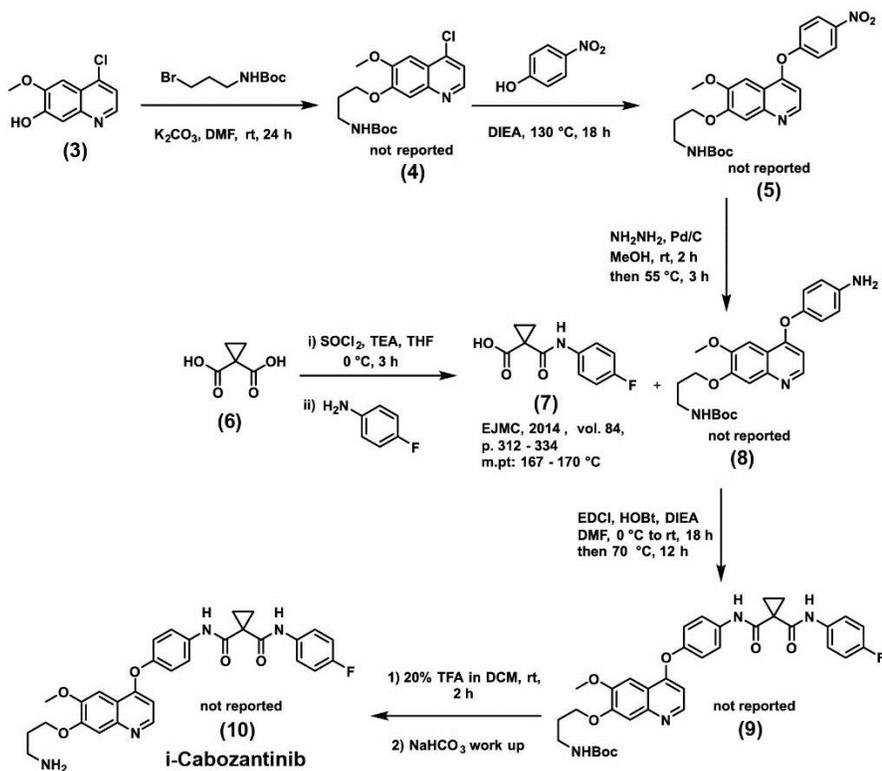
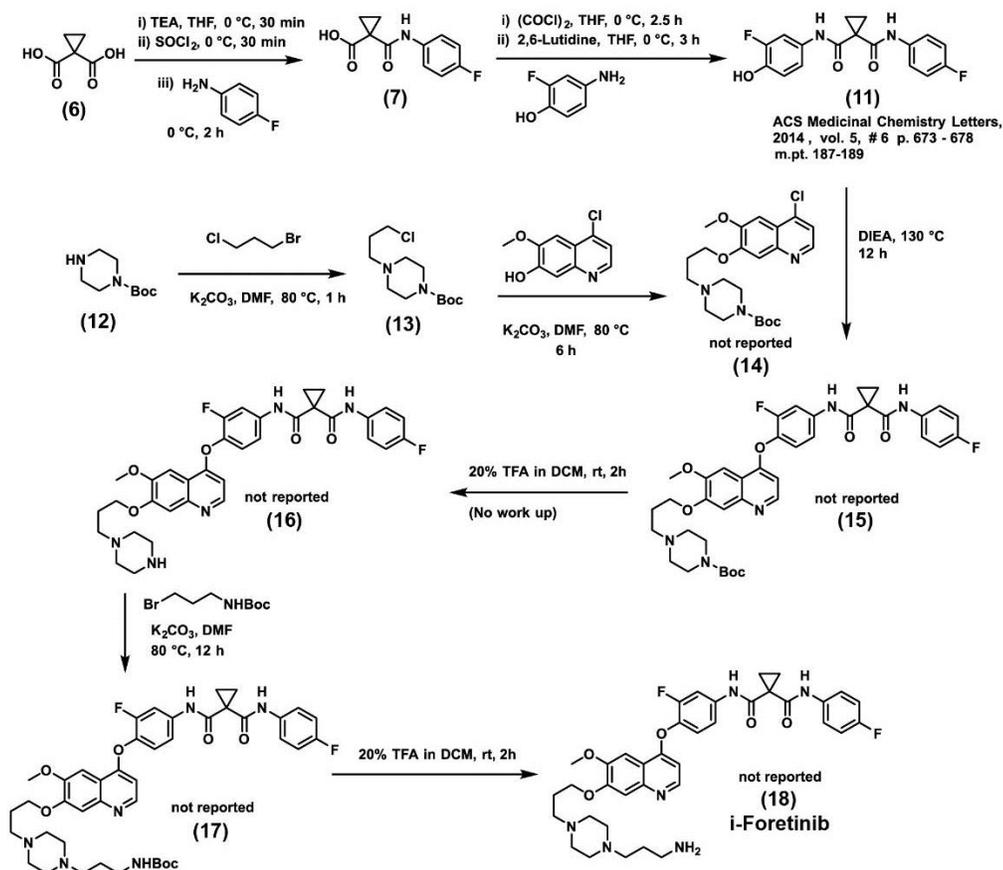
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Figure S3 – related to Figure 4: Synthetic scheme of tetherable compound analogues.

(A) Synthesis of immobilizable analogues of cabozantinib: i-cabozantinib.

(B) Synthesis of immobilizable analogues of foretinib: i-foretinib.

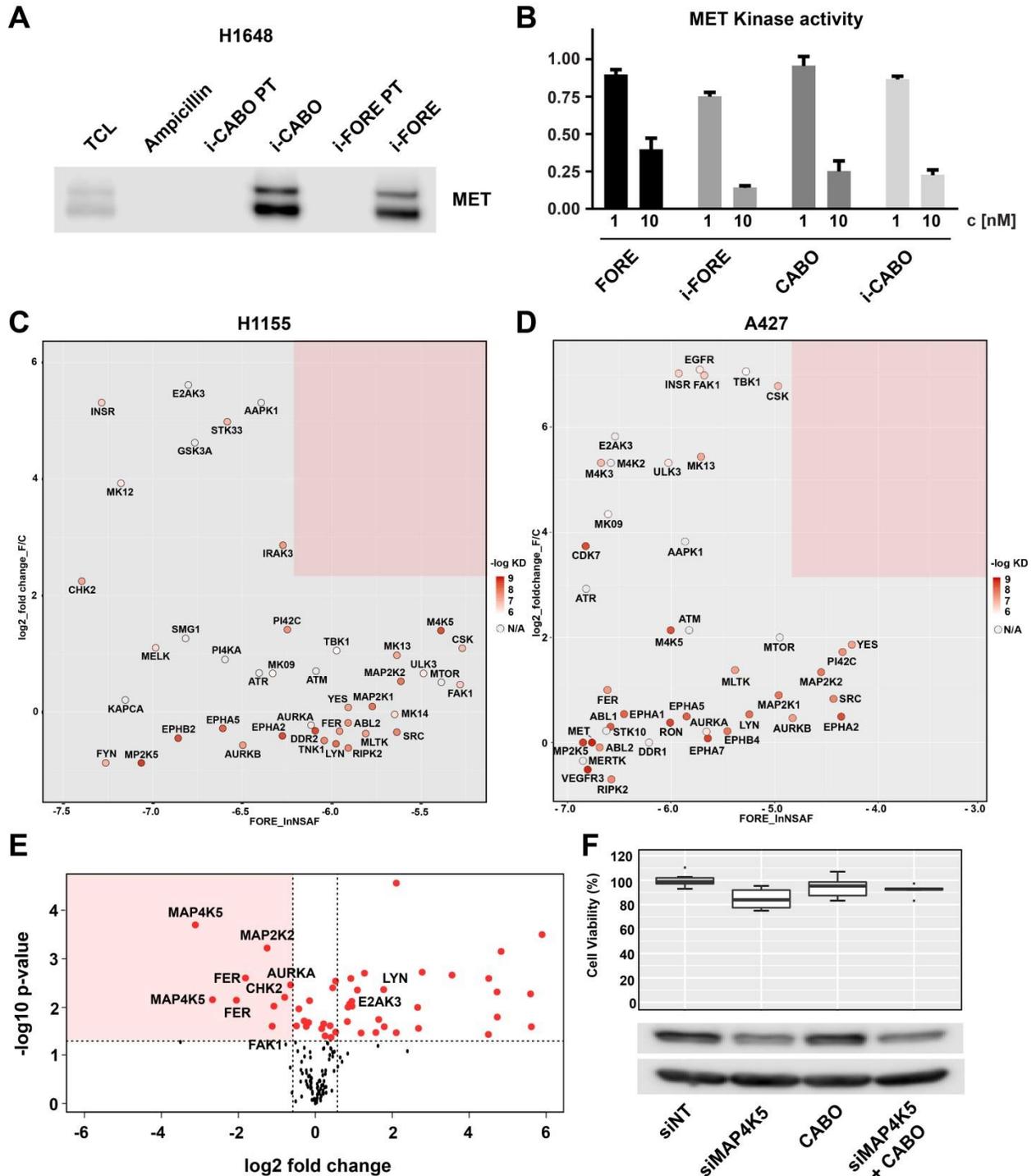


Figure S4 – related to Figure 4: Target profile of foretinib and cabozantinib.

(A) Western blotting for MET of drug affinity eluates using H1648 cells. Pulldowns were performed with immobilized cabozantinib (i-CABO) and immobilized foretinib (i-FORE). Lysates were also pre-treated with 20 μ M of foretinib (i-FORE PT) or cabozantinib (i-CABO PT). TCL: total cell lysate, AMP: ampicillin control.

(B) *In vitro* MET kinase assays for 1 and 10 nM of foretinib (FORE) and cabozantinib (CABO) and their respective immobilized analogues (i-FORE, i-CABO).

(C) Specificity plot of the chemical proteomics data in H1155 cells. The y axis indicates the log₂ fold change between foretinib and cabozantinib (F/C) and the x axis is the natural logarithm of NSAF (lnNSAF) for kinase proteins presenting NSAF > 0.0006 for foretinib (FORE) treatment. The highlighted pink area represents high NSAF values and high fold change for F/C.

(D) Specificity plot of the chemical proteomics data in A427 cells. The y axis indicates the log₂ fold change between foretinib and cabozantinib (F/C) and the x axis is the natural logarithm of NSAF (lnNSAF) for kinase proteins presenting NSAF > 0.001 for foretinib (FORE) treatment. The highlighted pink area represents high NSAF values and high fold change for F/C.

(E) Volcano plot for foretinib vs cabozantinib based on the activity-based probe profiling (ABPP) in H1155 cells. Kinases with more than 1.5-fold change and p-values < 0.05 in the ABPP experiment that also passed our cutoff in the chemical proteomics dataset are annotated. Highlighted area represents the significant changes of foretinib vs cabozantinib treatment.

(F) RNA interference of *MAP4K5* in combination with cabozantinib (1 μM) in H1155 cells. Cell viability was determined after 72 hours of treatment with DMSO or cabozantinib by trypan blue-based cell counting, n = 3, Data are represented as mean ± SD. Blots are representative of three independent experiments.

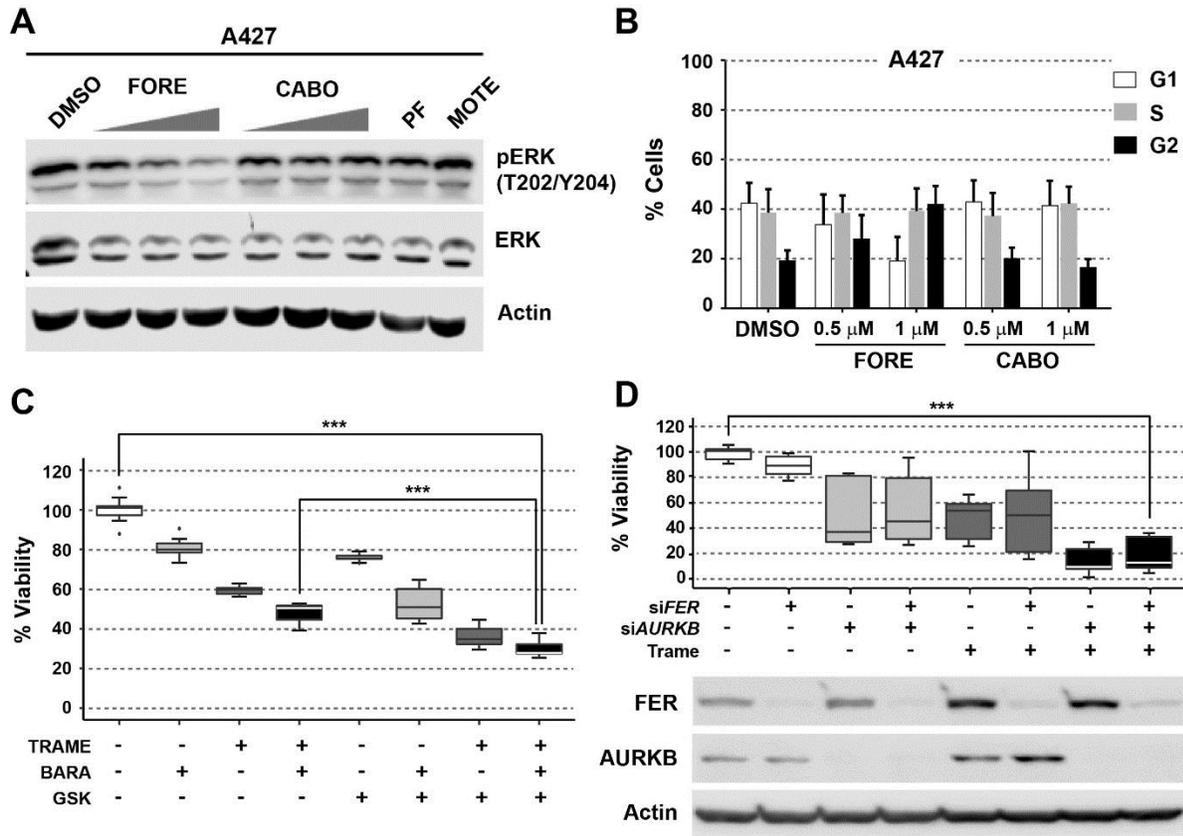


Figure S5 – related to Figure 5: Foretinib inhibits MEK, FER and AURKB simultaneously.

(A) Western blot of pERK (T202/Y204) after 1 hour treatment of A427 cells with 0.1, 0.5 and 1 μM foretinib (FORE) or cabozantinib (CABO), 0.1 μM of PF-04217903 (PF - METi) or 0.1 μM of motesanib (MOTE - VEGFRi). Blots are representative of three independent experiments.

(B) Cell cycle analysis of A427 cells after 6 hours of treatment with foretinib (FORE) and cabozantinib (CABO) at indicated concentrations, n = 3, Data are represented as mean + SD.

(C) A427 cell viability upon treatment with GSK1838705A (2.5 μM), barasertib (50 nM) and trametinib (35 nM) alone or in indicated combinations. Cell viability was determined by CellTiter-Glo assay after 72 hours of treatment and normalized to DMSO (first white bar), n = 3, Data are represented as mean ± SD.

(D) RNA interference of *FER* and *AURKB* in combination with trametinib (35 mM) in A427 cells. Cell viability was determined after 72 hours of treatment with DMSO or trametinib by trypan blue-based cell counting, n = 3, Data are represented as mean ± SD. Blots are representative of three independent experiments.

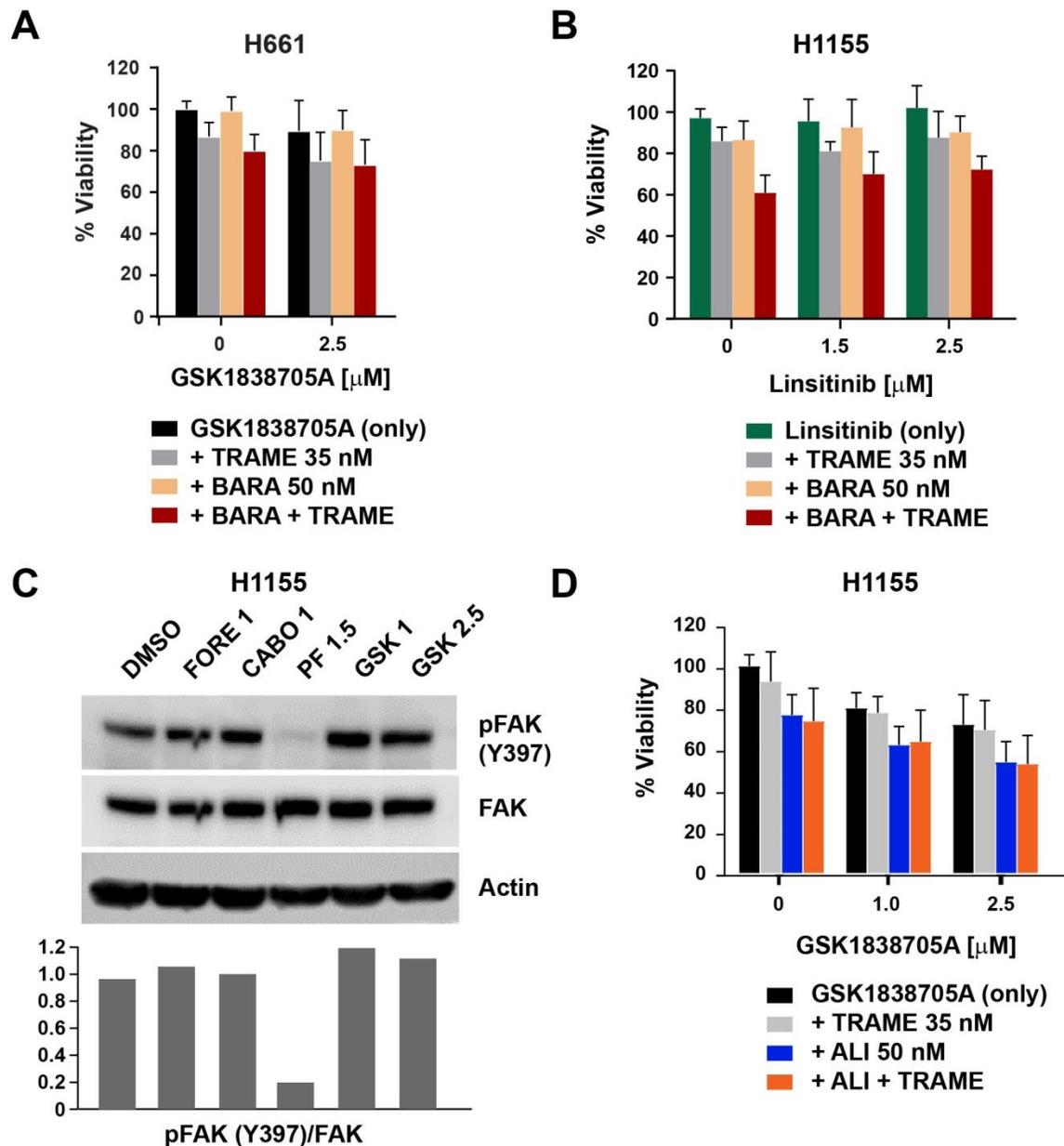


Figure S6 – related to Figure 5: Evaluation of co-target impact of utilized probe molecules.

(A) H661 cell viability upon treatment with GSK1838705A (2.5 μM), barasertib (50 nM) and trametinib (35 nM) alone or in indicated combinations. Cell viability was determined by CellTiter-Glo assay after 72 hours of treatment and normalized to DMSO (first black bar), n = 2, Data are represented as mean + SD.

(B) H1155 cell viability upon treatment with linsitinib (1.5 or 2.5 μM - IGF1R/INSRi), barasertib (50 nM) and trametinib (35 nM) alone or in indicated combinations. Cell viability was determined by CellTiter-Glo assay after 72 hours of treatment and normalized to DMSO (first green bar), n = 3, Data are represented as mean + SD.

(C) Western blot of pFAK (Y397) after 3 hours treatment of H1155 cells with 1 μ M foretinib (FORE) or cabozantinib (CABO), 1.5 μ M of PF-573228 (PF- FAKi) or 1 and 2.5 μ M of GSK1838705A. The bar graph shows the densitometric quantification of the western blot signals. Blots are representative of three independent experiments.

(D) H1155 cell viability upon treatment with GSK1838705A (1.0 and 2.5 μ M), alisertib (50 nM - AURKAi) and trametinib (35 nM) alone or in indicated combinations. Cell viability was determined by CellTiter-Glo assay after 72 hours of treatment and normalized to DMSO (first black bar), n = 3, Data are represented as mean + SD.

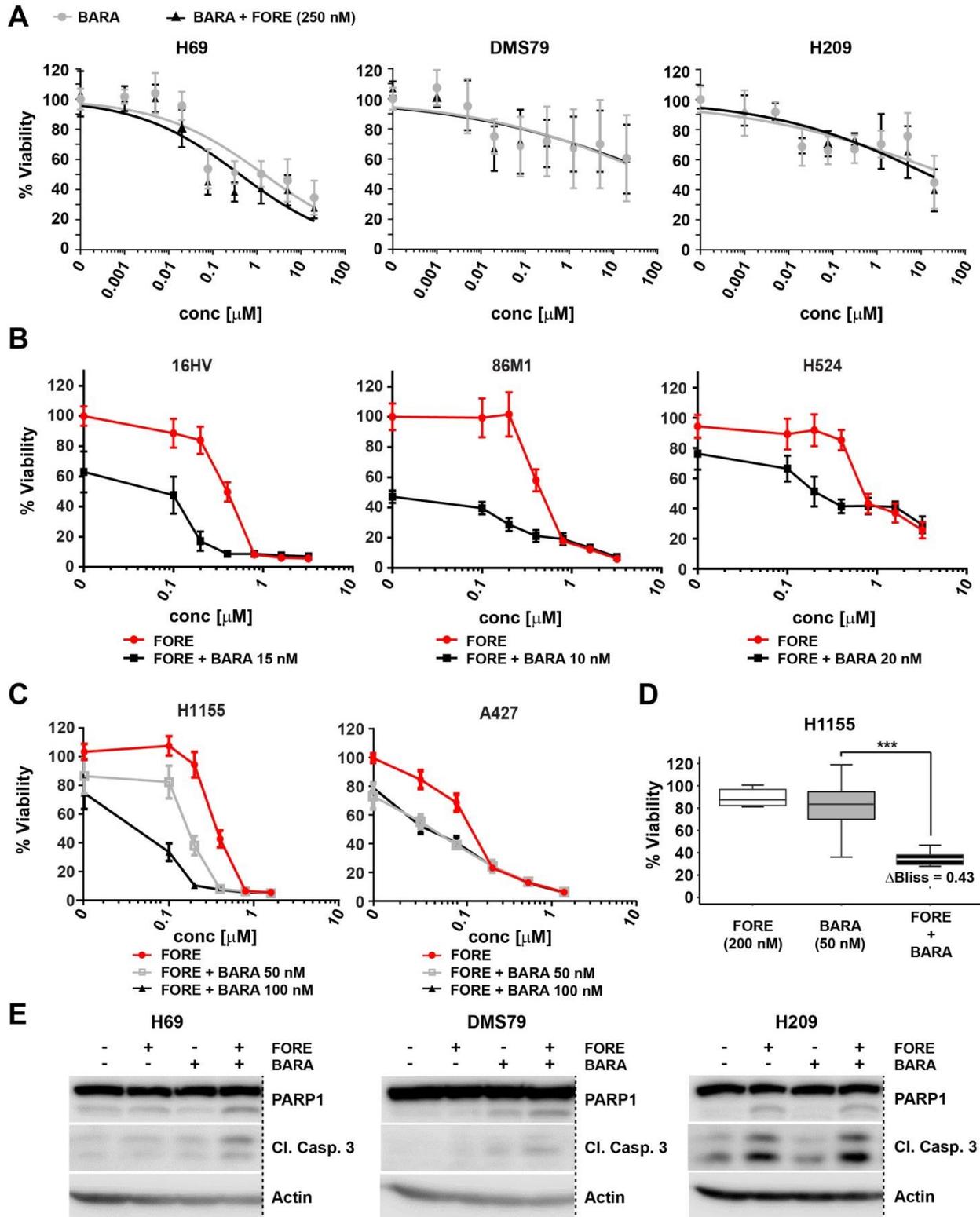


Figure S7 – related to Figure 7: Foretinib synergizes with barasertib specifically in *MYC*-amplified SCLC cells.

(A) Dose response curves for inhibition of viability of non-*MYC*-amplified SCLC cells after 72 hours treatment with barasertib (BARA) alone or in combination with 250 nM of foretinib (FORE), $n = 3$, Data are represented as mean \pm SD.

(B) Dose response curves for inhibition of viability of *MYC*-amplified SCLC cells after 72 hours treatment with FORE alone or in combination with BARA at the indicated concentrations, $n = 3$, Data are represented as mean \pm SD.

(C) Dose response curves for inhibition of viability of H1155 (left) and A427 (right) cells after 72 hours treatment with FORE alone or in combination with 50 and 100 nM of BARA, $n = 3$, Data are represented as mean \pm SD.

(D) Analysis of synergistic effects on cell viability of H1155 cells upon combination of 200 nM of FORE and 50 nM of BARA. Synergy was determined using the Bliss model of independence. Δ Bliss indicates the difference of observed inhibition of viability to the theoretically calculated additive effect. *** indicates p value < 0.001 as determined using Student's t -test, $n = 3$, Data are represented as mean \pm SD.

(E) Western blot analysis for PARP1 and caspase-3 cleavage in non-*MYC*-amplified SCLC cells after 24 hours of treatment with BARA (15 nM), FORE (250 nM) or their combination. Dashed lines indicate deletion of additional lanes. Blots are representative of three independent experiments.