Supplemental Methods:

Lentivirus preparation: Virus-containing media was prepared using standard methods (1). For the genome-wide screen, the HIV based GeneNet Lentiviral Human 50K library was used (pSIH1-H1-Puro, System Biosciences, Mountain View, CA) with minor modifications to the manufacturer's recommendations as described below. For validation experiments, TRC HIV-based (pLKO.1) lentiviral vectors were used.

Cell culture: 293FT cells were cultured in IMDM supplemented with 10% FBS and penicillin/streptomycin/amphotericin-B (Invitrogen). H322C, HCC4006, H3122, Calu3 and H3255 cell lines were cultured in RPMI supplemented with 10% FBS and penicillin/streptomycin/amphotericin-B. HCC4006 cells expressing vector (MSCV-Puro) or activated β-catenin (S33A/S37A/T41A/S45A mutant (2); Addgene plasmid 24313) were generated by retroviral transduction and selection in puromycin. HFF cells were grown in IMDM supplemented with 10% FBS.

Cell Viability Assays: Cells were seeded at 1x10^4/ml in triplicate in 48-well tissue culture plates (Greiner Bio-One). 24 hours after seeding, cells were treated with drug for a period of 96 hr. After treatment, cells were trypsinized and either re-seeded at 1/5 density without drugs or stained with propidium iodine (PI, 10 mg/ml) for cell viability assays. Viable cells (PI-negative) were counted with a flow cytometer (Quanta SC, Beckman Coulter). 3-4 days after re-seeding, live cells were again counted.

Colony forming assays: Different percentages of the treated culture were seeded in 10cm tissue culture dishes, grown for 10 days, and then stained with crystal violet for counting (>1cm^2 in size).

Cell cycle profile: Cells were stained with saponin/PI (25 μg/mL PI, 0.3 % saponin, 0.1 mM EDTA, and 2 U/mL RNase) overnight at 4°C and analyzed by flow cytometry. Modfit LT (Verity Software) was used for cell cycle and apoptotic peak modeling.

MTT Assay: Inhibition of cell growth by gefitinib was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, as previously described (3). Combination Indices (CI values) were calculated using the Chou-Talalay isobologram CI (4) and CalcuSyn software to determine additivity (CI=1), synergism (CI<1) and antagonism (CI>1).

Apoptosis and senescence staining: Cells were stained with AnnexinV-FITC and PI for 20 minutes at 37°C and analyzed by flow cytometry, or stained for β-galactosidase using the Senescence β-Galactosidase Staining Kit (#9860) from Cell Signaling Technology (Boston, MA).
**Western Blotting:** Preparation of whole cell lysates and western blotting were performed as described (5). See Table S2 for antibodies used.

**Quantitative Real-Time RT-PCR:** qPCR was performed using the TaqMan method, following manufacturer's directions (Roche). Primer and probe sequences are provided in Table S2. Oligonucleotides were purchased from IDT (Coralville, IA).

**Chemicals:** Gefitinib was supplied by AstraZeneca (London, United Kingdom). XAV939, endo-IWR1 and PNU74654 were purchased from Tocris (Ellisville, MO). Erlotinib was obtained from the National Cancer Institute. Puromycin and pyrvinium pamoate were purchased from Sigma (St. Louis, MO). All drugs were dissolved in DMSO. Paclitaxel was obtained from Bedford Laboratories (Bedford, OH).

**Animal welfare:** Mice were maintained in accordance with University of Colorado institutional guidelines, and all experiments were approved by the Institutional Animal Care and Use Committee.

**Experimental replicates:** Error (standard error) represents biological replicates (independent cultures or mice).