**Supplementary methods**

**Generation of Cas9 expressing cells and drug sensitivity assay**

To optimize Blasticidin and puromycin concentrations, PC9 cell and HCC827 cell were treated with different concentrations of drugs for 4 days (puromycin) or 7 days (blasticidin). The lowest concentration of drug that killed all cells was used in the screens. To produce Cas9-expressing cell lines, 1.5 x 10^6 cells with 4 g/ml polybrene were seeded in one well of a 12-well plate. Then add 750 l pLX311-Cas9 virus and add enough media to bring the total volume in each well to 2mL. Cells were spun for 2 hr at 2000 rpm at 30°C. 24 hr after infection, cells were selected with blasticidin for 7 days. To determine Cas9 activity, we performed Cas9 activity assay. Briefly, parental cell lines and Cas9-expressing cell lines were infected with pXPR\_011, a Cas9 activity reporter which expresses eGFP as well as a guide RNA targeting eGFP (Doench JG, Hartenian E, Graham DB, Tothova Z, Hegde M, Smith I, et al. Rational design of highly active sgRNAs for CRISPR-Cas9-mediated gene inactivation. Nature biotechnology. 2014;32:1262-7.). Then measure the percentage of eGFP positive population of the cells by flow cytometry to see the efficiency of Cas9 in each cell line. To optimize inhibitor concentrations, Cas9-expressing cells were infected with EGFP expressing virus (to mimic sgRNA plasmid infection) and were selected with puromycin. After 4 days of puromycin selection, cells were treated with different concentration of inhibitors to determine the optimal drug concentration for the screens.

**Optimization of infection conditions for CRISPR pooled screen**

To determine the optimal concentration of the Avana sgRNA library virus in Cas9-expressing cells to achieve 30-50% infection efficiency, 3x10^6 cells were seeded per well in a 12-well plate and were infected with different amounts of virus for sgRNA library (0, 10, 25, 50, 75, 100 uL), with a final concentration of 4 g/mL polybrene. Cells were spun for 2 hr at 2000 rpm at 30°C. Approximately 24 hours after infection, cells were trypsinized and seeded 2 wells of a 6-well plate, each with complete medium, one supplemented with the appropriate concentration of puromycin. Cells were counted 4 d post selection to determine the infection efficiency, comparing survival with and without puromycin selection. Volume of virus that yielded ~30 - 50% infection efficiency (40 uL) was used for screening.

**Follow-up CRISPR screen**

For customized mini-screen, we made smaller scale sgRNA library (supplementary table S4). We followed almost same protocol we used in initial genome wide-screen, except for we used 10 x 10^6 of Cas9-expressing for infection to achieve 1000 cells per sgRNA after selection (10 x 10^6 surviving cells containing 10,000 sgRNAs). After antibiotic selection, cells were treated with DMSO, 100 nM erlotinib or 100 nM erlotinib plus 50 nM THZ1.

In both screens, STARS algorithm (Doench JG, Fusi N, Sullender M, Hegde M, Vaimberg EW, Donovan KF, et al. Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9. Nature biotechnology. 2016;34:184-91.) was used to analyze enrichment or depletion of each sgRNA.

**Elisa assay**

Supernatants of PC9 cell culture treated with vehicle, 100 nM erlotinib, 100 nM THZ1, or THZ1 in combination with erlotinib were collected at 72 h. IL6 was assayed in cell culture supernatants using the Quantikine IL6 ELISA kit (R&D Systems) as per the manufacturer’s protocol.

**Antibodies for Immunobloting**

Following are the information of primary antibodies used in this study. S473 pAKT (#4060), AKT (#9272), Bcl-xL (#2762), Bcl-2 (#2876), Bim (#2933), Y1068 pEGFR (#2234), EGFR (#2232), pERK1/2 (#4370), ERK1/2 (#9107), IRE1α (#3294), IRF3 (#11904), S396 pIRF3 (#4947), tPERK (#5683), tRelA (#8242), S536 pRelA (#3033), p62 (#5114), STAT3 (#9132), Y705 pSTAT3 (#9145), STING (#13647) are from Cell Signaling Technologies. ATF4 (ab184909), CDK5RAP3 (ab168353), tEIF2α (ab169528), S51 pEIF2α (ab32157), S724 pIRE1α (ab124945), T982 pPERK (ab192591), UFM1 (ab109305), UBA5 (ab177478), UFC1 (ab189252), UFSP2 (ab192597), MCL1 (ab32087) are from Abcam. Actin (A5441) and Vinculin (V9131) are from Sigma-Aldrich (St. Louis, MO). UFL1 (A303-456A) is from Bethyllaboratories. DDRGK1 (21445-1-AP) is from Proteintech. E-cadherin (sc-8426) and N-cadherin (sc-7939) are from Santacruz Biotechnologies.

**Vectors**

pLX311(Cas9), pXPR-011, lentiCRISPRv2, lentiGuide-Puro, psPAX2 and VSVG-PMD2.G plasmids were obtained from Broad institute.

**Reagents**

THZ1 was synthesized by Gray lab as previously described (Kwiatkowski N, Zhang T, Rahl PB, Abraham BJ, Reddy J, Ficarro SB, et al. Targeting transcription regulation in cancer with a covalent CDK7 inhibitor. Nature. 2014;511:616-20., Zhang T, Kwiatkowski N, Olson CM, Dixon-Clarke SE, Abraham BJ, Greifenberg AK, et al. Covalent targeting of remote cysteine residues to develop CDK12 and CDK13 inhibitors. Nature chemical biology. 2016;12:876-84.) Erlotinib was purchased from Selleck Chemicals. KIRA6 and GSK2606414 were purchased from Millipore Sigma. Puromycin, polybrene and Brefeldin A were purchased from Santa Cruz Biotechnology. A133185, ABT-263 and ABT-199 were purchased from Chemietek. S63845 was gifted from Wei lab. Tunicamycin, SGC-CBP30 were purchased from Sigma Aldrich. Blasticidin was purchased from Life Technologies. Poly (I:C) and Poly (dA:dT) were purchased from InvivoGen.