Supplemental Information

Supplemental Materials and Methods

Druggable Genome and Validated Kinase siRNA screen

The Validated Kinase screen (vKinv4, Qiagen, Hilden, Germany) consisted of a library of siRNAs targeted to the human kinome (711 genes) and a custom library targeting 80 genes of interest including previously proposed drug targets, SWI/SNF genes, ATPases of the DEAD/H helicase family (in addition to SMARCA4 and SMARCA2), and other candidate synthetic lethal targets derived from the literature or RNA-seq-based identification of overexpressed genes in four SCCOHT tumors compared to normal ovaries. The druggable genome screen (DGv3, Qiagen) additionally targeted over 6,992 druggable genes with 4 siRNAs per gene. In total, each gene was targeted by 4-8 distinct siRNAs between the two screens. We performed the screen using optimized conditions in BIN67 with a cell viability endpoint (CellTiter Glo). Assay plates were prepared in advance by dispensing 1μL/well siRNA (667nM) from the corresponding library as well as positive and negative controls (AllStars Positive and Negative controls, Qiagen, and additional non-silencing and GFP controls), to each well of 384-well, white, solid-bottom, tissue culture treated microplates using a Biomek FX Laboratory Automation Workstation to achieve a final assay concentration of 13nM. A solution of transfection reagent (RNAiMax, Thermo Fisher Scientific) and serum-free DMEM/F12 was dispensed to the assay plates containing the siRNA at a volume of 25μL/well (67nL/well of RNAiMax) using a BIO-TEK μFill liquid dispenser and allowed to incubate at room temperature for 30 minutes to allow for complexing of siRNA and transfection reagent. 750 cells/well were then dispensed to the assay plates using a BIO-TEK μFill liquid dispenser. Cell viability was assayed after 96 hours

using Cell Titer Glo luminescence assay (Promega) on a Molecular Devices Analyst GT Microplate Reader.

Screening data analysis

Normalization: Normalization was applied to data output from the plate reader to remove plate effects. The signals of negative siRNA controls and untreated controls (non-transfected controls and controls without compound treatment, respectively) were assumed to remain stable across plates for use in plate-to-plate normalization. We observed the relative signal strength among the above five types of controls to be stable from plate to plate. Denoting c_i the relative signal strength of control i and p_j the effect coefficient of plate j, we model the observed median signal x_{ij} of control i on plate j as a product of p_j and c_i, where index j ranges from 1 to 180 (90 plates in 2 replicates) and i ranges from 1 to 5. Let X denote the matrix consisting of elements x_{ij}, let c denote the vector of relative signal in each of the controls and let p denote the vector of plate effects. Then X can be approximated as $\hat{X} = c^T p$. Unknown vectors c and p were found based on the optimization formulation introduced in (1) using algorithm of alternating minimizations (2). Finally, the estimated vector of plate effects was used for data normalization by dividing all measurements from plate j by the corresponding plate effect p_j.

Quality control: To characterize assay quality, key HTS quality measures were calculated using wells transfected with positive-control (all-star positive and UBBs1) and negative-control (GFP) siRNAs from each plate. The percent decrease of median signal from negative-controls to positive-controls was 99.4%, indicating high transfection efficiency. The coefficient of variation across the negative controls was as low as 12% indicating the robustness of the assay. Finally, a good separation between positive and negative controls was confirmed by a Z-factor (3) around 0.8.

Hit identification: To obtain an activity score for each gene, two strategies were used to combine multiple silencing activities of individual siRNAs targeting the same gene. In the first, the redundant siRNA activity (RSA) (4) method was used to assign a p-value for each gene that indicates statistical significance of all siRNAs corresponding to the gene being distributed unusually higher in the ranking than would be expected by chance. In the second strategy, individual siRNA activities were collapsed to the gene-level by calculating the mean signal of the top 75% siRNAs for the gene. Genes were ranked according to the above two methods independently in each replicate, and a final rank of genes was calculated by combining four individual ranks using another iteration of the RSA algorithm. We prioritized the genes with a p-value less than 0.05.

Screen validation: siRNA sequences were obtained from Qiagen with 4 siRNA sequences represented for each of the 232 out of 246 gene hits from the initial screen, as well as positive and negative controls. Assay plates are prepared by dispensing 1µL/well siRNA (667nM) to each well of a 384-well, white, solid-bottom, tissue culture treated microplate to achieve a final assay concentration of 13nM. A solution of transfection reagent (RNAiMax) and serum free DMEM/F12 is dispensed to the assay plates containing the siRNA at a volume of 25µL/well (67nL/well of RNAiMax) and allowed to incubate at room temperature for 30 minutes to allow for complexing of siRNA and transfection reagent. Cells are then harvested using 0.25% Trypsin, counted, and re-suspended in DMEM/F12 with 20% FBS and then dispensed to the assay plates at 25µL/well and a concentration of 750 cells/well. Assay plates are then incubated for 96 hours at 37°C. Cell viability is then measured using Cell Titer Glo luminescence assay (Promega) on a Molecular Devices Analyst GT Microplate Reader. Validated genes were defined as those with at least 2 out of 4 siRNAs inhibiting viability by >50%.

Pathway analysis

Pathway enrichment analysis of the selected hits in the siRNA screen was performed using the ReactomeFIPlugIn (5) (http://bit.ly/2rap1M7) cytoscape application (version 3.0). Enrichment was performed using the reactome pathways gene set. The Gene Set/Mutation Analysis utility was accessed for building the protein-protein interaction network with linker genes.

Protein interaction network constructed for RNAi validated screen hits using ReactomeFI network resource (6). The ReactomeFI network is constructed from publicly available protein-protein interaction resources and curated pathways. Additionally, computational predicted edge associations were generated based on PPI data.

Additionally, ClueGO (7) cytoscape application was utilized to perform additional enrichment analysis. Enrichment was performed with the following gene sets: GO_BiologicalProcess-GOA, Rectome_Pathways, Kegg, WikiPathways, and Kegg_Compound. Advanced Term/Pathway selection options were set at GO Tree Interval Minimum level 3 and Max level and minium number of genes at 3. The kappa score was set at 0.4. A two-sided hypergeometric test was used with Bonferroni step down correction. Common genes for each enriched term were projected onto enriched network figure using the CluePedia (v1.3.2).

LOPAC/Prestwick compound screen

The LOPAC^{1280} (Sigma-Aldrich, St. Louis, MO, USA) and Prestwick (Prestwick Chemical, Illkirch, France) chemical libraries each include 1,280 small molecules with ~20% overlap in compounds between libraries. LOPAC^{1280} includes pharmacologically active compounds targeting diverse signaling pathways and includes marketed drugs. The Prestwick Chemical

Library is entirely comprised of clinically approved compounds (FDA, EMA, etc.). Two screening runs were completed in BIN67 cells with duplicates at concentrations of 5μM and 10μM. Cells were harvested with 0.25% Trypsin (Thermo Fisher Scientific) and re-suspended in DMEM/F12 media with 10% FBS at a concentration of 15,000 cells/mL. Cells were subsequently dispensed at 50μL/well (750 cells/well) into 384-well, white, solid-bottom, tissue culture treated microplates (Corning, Corning, NY, USA) using a BIO-TEK μFill liquid dispenser. After 24 hours, LOPAC and Prestwick small molecule compound libraries were dispensed at 25 or 50 nL/well (5μM or 10 μM final concentrations) using an EDC Biosystems ATS-100 acoustic liquid dispenser. Cell viability was assayed after 72 hours using the CellTiter Glo luminescence assay (Promega, Madison, WI, USA) on a Molecular Devices Analyst GT Microplate Reader. Initial hits were defined as those compounds that reduced viability of BIN67 cells by >50% relative to controls. Amongst the two libraries, 110 initial hits at 10μM and 74 initial hits at 5μM were identified. No appropriate SCCOHT comparator cell line exists by which to eliminate non-selective hits given that SCCOHT's cell of origin remains unknown and that re-expression of SMARCA4 in SCCOHT cells to generate isogenic comparators precludes cell growth (8). Instead, SMARCA4-wildtype HepG2 hepatocellular carcinoma cells were used as a conservative option for eliminating those hits that were widely cytotoxic, an approach commonly used in HT drug screens (9). Out of 74 initial hits at 5μM, 64 (86%) were confirmed to selectively target BIN67 cells and not HepG2 cells (Supplemental Table 1). These filtered hits were tested through dose-dependent response (DDR) assays in BIN67 cells, as well as HepG2 controls, SCCOHT cell lines SCCOHT-1 and COV434, and the SVOG3e granulosa cell line, in order to determine respective IC_{50} values. DDR assays included 20-points and viability was measured 72 hours after dosing. For COV434 SMARCA4-inducible DDRs, doxycycline was

added 24 hours before drug dosing to allow induction, and viability was measured at 48 hours after dosing with ponatinib. Viability was measured using CellTiterGlo and IC_{50}s were determined using GraphPad Prism software.

Chemical Network Visualization

The chemical screen hits of interest were annotated to targets and biological concepts associated with each entity. The targets were mined from vendor sites and manual literature annotation. Biological concepts were also annotated to chemicals through database terms via MESH and domain expert annotation. A bipartite graph was constructed using cytoscape application, which is an open source software used for network visualization and bioinformatics analysis (www.cytoscape.org). The visualization of the network was manually edited for a more orderly visualization of the results.

Multiplexed Inhibitor Bead-Mass Spectrometry (MIB-MS)

Cells were treated with DMSO or 2μM ponatinib for 1 hr in biological triplicate, washed twice with cold PBS, and lysed in MIB lysis buffer (0.5% Triton X-100, 10% glycerol, 50mM Hepes-NaOH [pH 8.0], 150mM NaCl, 2mM EDTA, 2mM DTT). Five mg of protein lysate was brought to 1M NaCl and added to gravity flow columns containing 100μl of packed sepharose beads. The flowthrough was then passed over columns containing 175μl of packed MIBs (22% V/V of VI16832 and CTx-0294885; 14% V/V of Purvalanol B, PP58, UNC21474, and Shokat) at 4˚C with nutation for 15 min (10-14). Protein-bound MIBs were washed once each with MIB low salt buffer (0.5% Triton X-100, 50mM Hepes-NaOH [pH 8.0], 150mM NaCl, 1mM EDTA, and 1mM EGTA), MIB high salt buffer (0.5% Triton X-100, 50mM Hepes-NaOH [pH 8.0], 1M

NaCl, 1mM EDTA, and 1mM EGTA), and low salt buffer containing 0.1% SDS. Proteins were eluted from MIBs by boiling in elution buffer (0.5% SDS, 1% β-mercaptoethanol, and 100mM Tris-HCl [pH 6.8]). Samples were then reduced with DTT, alkylated with chloroacetamide, and concentrated prior to precipitation of proteins by methanol-chloroform extraction. Proteins were trypsinized overnight, desalted via a C18 spin column, and finally extracted 3 times with ethyl acetate to remove detergents.

Activity-Based Protein Profiling (ABPP)

ABPP experiments were carried out using Pierce® Kinase Enrichment Kits and ActivX® ATP Probes (ThermoFisher Scientific), according to the manufacturers' instructions and as previously published (15,16). Briefly, cells were resuspended in 400 µL of lysis buffer and 4 µL of Halt™ phosphatase and protease inhibitor cocktail (ThermoFisher Scientific). Samples were sonicated thrice at 1 minute intervals using a pulse of 50% duty cycle for 30 seconds (VCX130 Vibra-Cell™, Sonics). Cell lysates were cleared by centrifugation at 14,000 x g at 4 °C for 20 minutes and the supernatant was buffer exchanged using Zeba Spin Desalting Columns (ThermoFisher Scientific). Protein concentrations were estimated using BCA assays, and a total of 1mg of protein from each lysate was prepared for labeling, enrichment, and mass analysis. Cell lysates were first incubated with 20mM $MnCl_2$ (BIN67) or 20 mM $MgCl_2$ (SCCOHT-1) followed by incubation with 10µM of DesThioBiotinylated (DBT) ATP probes for 10 minutes. Following labeling, proteins were denatured in 10M urea and reduced with 5 mM DTT. Samples were alkylated by incubation with 40mM iodoacetamide in the dark for 30 minutes at room temperature. Following a second round of buffer exchange by Zeba Spin Desalting Columns, proteins were digested using trypsin (1:50 enzyme-to-substrate ratio) overnight at 37°C. DBT-

labeled peptides were captured by incubating the digests with 50 µL of high capacity streptavidin beads for 1 hour. The beads were sequentially washed with lysis buffer, PBS, and HPLC water. Bound peptides were eluted by addition of aqueous 50% acetonitrile with 0.1% trifluoroacetic acid (TFA). The eluted peptides were vacuum-concentrated and resuspended in aqueous 0.1% formic acid solvent for LC-MS/MS analysis.

Liquid Chromatography and Mass Spectrometry

LC-MS/MS data were acquired on a tribrid quadrupole-ion trap-Orbitrap instrument (Orbitrap Fusion Lumos, Thermo Scientific, San Jose, CA) interfaced with a nanoAcquity UPLC system (Waters, Millford, MA). Samples were first loaded on a trapping column (Acclaim PepMap 100 C18, 75µm ID * 2cm, 3µm particle size, 100 Å pore size) and washed for 10 minutes with 99.5% Solvent A (0.1% formic acid in water) and 0.5% Solvent B (0.1% formic acid in acetonitrile) at a flow rate of 4µL/min. The trapped peptides were transferred to an analytical column (PepMap RSLC C18, 50 µm ID * 15 cm, 2 µm particle size, 100 Å pore size) and eluted at a flow rate of 300nL/min using the following gradient: 3% to 30% B in 103 minutes, 30 to 90% B in 1 minutes, 90% B for 2 minutes, 3% B in 1 minute and re-equilibration for 13 minutes. Data-dependent acquisition was performed in Top Speed mode with a duty cycle of 3 seconds and following parameters: spray voltage of 1900V, ion transfer tube temperature of 275°C, survey scan in the Orbitrap at a resolution of 120K at 200 m/z, scan range of 400-1500 m/z, AGC target of 2E5 and maximum ion injection time of 50 ms. Every parent scan was followed by a daughter scan using High Energy Collision (HCD) dissociation of top abundant peaks and detection in the iontrap with following settings: quadrupole isolation mode, isolation window at 1.4 m/z, AGC target of 5E3 with maximum ion injection time of 35 ms and HCD collision energy of 35%.

Dynamic exclusion was set to 60 seconds. The same MS parameters were used as for MIB-MS runs except the RP separation was done on a 25 cm analytical column (PepMap RSLC C18, 50µm ID, 2µm particle size, 100 Å pore size) with a 205 min method using following gradient: 2% to 25% B in 180 minutes, 25 to 90% B in 3 minutes, 90% B for 8 minutes, 2% B in 0.5 minute and re-equilibration for 13.5 minutes.

Proteomics protein identification and quantification

Protein identification and label-free relative quantification was performed using the Andromeda search engine of MaxQuant (1.5.2.8) on a human UniProt/SwissProt database (release: July 2015) for both ABPP and MIB-MS experiments (17). ABPP runs were searched with the following parameters: trypsin cleavage rules, up to 3 missed cleavages, cysteine carbamidomethylation set as fixed modification, desthiobiotinylation of lysine residues, methionine oxidation and N-terminal acetylation set as dynamic modifications. Searches used MaxQuant's "match between runs" feature with a time window of 4 minutes. MaxQuant output was filtered to <2% FDR by retaining only those DBT-peptides matching following criteria: PEP <0.05 and non-zero intensity. DBT-peptides only observed once in either control DMSO or ponatinib-treated samples as well as DBT-peptides marked as contaminants and reverse-hits were discarded from the analysis. Intensity values were $\log_2$ transformed after averaging across technical replicates and $\log_2$ ratios were calculated between the DMSO control and ponatinib-treated cells. Only DBT-peptides mapping to kinases were considered for further analysis. Significantly different DBT-peptides were marked as those with a $\log_2$ ratio of 1.5 standard deviation from the mean $\log_2$ ratio of the entire dataset. Raw MIB-MS data was searched using the following parameters: trypsin cleavage rules, up to 2 missed cleavages, cysteine

carbamidomethylation set as fixed modification, methionine oxidation, N-terminal acetylation and Serine, Threonine and Tyrosine phosphorylation set as dynamic modifications. Searches used MaxQuant's "match between runs" feature with a time window of 0.7 minutes and the results were filtered at 1% protein FDR. Similar to ABPP MS data analysis, proteins identified only once in either condition as well as proteins mapping to contaminants or reverse hits were discarded from analysis. Protein intensity values were averaged across technical and biological replicates and $\log_2$-transformed. A $\log_2$ ratio was then computed between the DMSO and ponatinib-treated cells. A Kruskal-Wallis test was applied to determine significantly differently abundant proteins (p-value <0.05), of which significant kinases between the two conditions were filtered by $\log_2$ ratio above 1.5 standard deviation from the mean $\log_2$ ratio of the entire dataset, or uniquely identified in either DMSO or ponatinib treatments. Confirmed kinases from both ABPP and MIB-MS experiments were mapped to the known kinome tree using Kinmap (18).

RNA-seq Library Preparation

RNA was harvested from four SCCOHT tumors using the Qiagen RNeasy Mini Kit. 10ng of total RNA for each sample was used to generate whole transcriptome libraries for RNA sequencing. Using the Nugen Ovation RNA-Seq System v2, 10ng of total RNA for each sample was used to generate double stranded cDNA, which was subsequently amplified using Nugen's SPIA linear amplification process. Amplified products were cleaned using Qiagen's QIAquick PCR Purification Kit and quantitated using Invitrogen's Quant-iT Picogreen. 1µg of amplified cDNA was fragmented on the Covaris E210 to a target size of 300bp and Illumina's TruSeq DNA Library Preparation Kit with the manufacturer's gel-free protocol was used to generate

libraries. Final libraries were evaluated on the Agilent Bioanalyzer, quantitated using the Life Technologies/Invitrogen Qubit, and equimolarly pooled.

Paired End Sequencing

The library pool with a 1% phiX spike-in was used to generate clusters on a HiSeq Paired End v3 flowcell on the Illumina cBot using Illumina's TruSeq PE Cluster Kit v3. Clustered flowcells were sequenced by synthesis on the Illumina HiSeq 2000 using paired-end technology and Illumina's TruSeq SBS Kit, extending to 83bp for each of two reads and a 7bp index read.

RNA-seq Data Analysis

BCL conversion was performed using Illumina's Bcl Converter tool and parsed by barcode into independent FASTQ files. Alignment of FASTQ files against the GRCh37 human reference genome was performed using TopHat (19,20) to generate single BAM files. Cufflinks/Cuffdiff (20) was used to identify differentially expressed transcripts. This tool normalizes aligned reads to calculate a FPKM (fragments per kilobase of exon per million fragments mapped) value for all genes and transcripts. Gene annotations were performed using Ensembl version 74. RNA sequencing data has been uploaded to dbGaP (accession phs001528.v1.p1) and GEO (GSE109919).

Supplementary Figures and Table legends

Supplemental Figure 1. COV434-pIND20-Brg1 SMARCA4 induction optimization.

COV434 parental cells and subclones 1.2.1 and 1.2.7 were treated with 200ng/mL doxycycline and collected at 0, 24, 48, and 72 hours treatment. Western blots were probed for SMARCA4

(Brg1) and β-actin served as a loading control. HAP-1 cell lysates serve as a positive control for SMARCA4.

Supplemental Figure 2. Kinase hits from siRNA screen mapped to kinome dendrogram. Kinases identified in the validation set from the siRNA screen are displayed as red circles on the kinase dendrogram using KinMap. The full gene set is listed on the right and color-coded based on corresponding kinase family in the dendrogram. Atypical protein kinases are listed in black.

Supplemental Figure 3. ClueGo analysis of validated siRNA screen hits. Validated siRNA hits were run through ClueGO to identify clusters of genes based on common functional annotation. Edges connect genes to associated functional clusters, where size indicates the degree of enrichment for each cluster.

Supplemental Table 1. List of validated siRNA screen hits. Four siRNAs per candidate gene (232 total) identified in initial siRNA screen were repeated in three independent runs for validation in BIN67 cells. Confirmed siRNA hits from second screen are listed (N=109).

Supplemental Table 2. List of high-throughput drug screen hits. 64 validated drug hits from LOPAC and Prestwick libraries. Redundant hits between screens are bold-faced, and are counted only once in hit number.

Supplemental Table 3. IC_{50} summary of validated drug hits in SCCOHT cell lines. DDR assays were run for 51 drug hits from validated screen in SCCOHT cell lines. Compounds are listed in order of increasing average IC_{50} for SCCOHT cell lines BIN67, SCCOHT-1, and COV434, and are highlighted in gray if IC_{50} in BIN67 cells was <10-fold lower than in HepG2.

Supplemental Table 4. MIB-MS data. (A) List of proteins identified in MIB-MS experiment following MaxQuant search. (B) MaxQuant search parameters for MIB-MS SCCOHT-1 experiment.

Supplemental Table 5. SCCOHT-1 ABPP data. (A) List of identified desthiobiotinylated-peptides from MaxQuant search and the calculated log_2 ratios. (B) MaxQuant search parameters for ABPP SCCOHT-1 experiment.

Supplemental Table 6. BIN67 ABPP data. (A) List of identified desthiobiotinylated-peptides from MaxQuant search and the calculated log_2 ratios. (B) MaxQuant search parameters for ABPP BIN67 experiment.

Supplemental Table 7. Summary of hits from ponatinib analyses and target expression. Experimental method and the SCCOHT model they were tested in are represented by columns, and kinases are represented in rows. For RTK profiler arrays, MIB-MS, and ABPP data, kinases identified as hits are marked in orange, and kinases not tested by the experimental method are in black. RNA-Seq FPKMs that are above the median FPKM over all transcripts are also represented. Overlap between methods and cell models are summarized in the far right columns. Only kinases identified as a positive hit by at least one method and at least one cell line were included in the table.

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