## Supplementary Material & Methods

### Cell lines

B cell lymphomas cell lines were purchased from the DSMZ (Braunschweig, GER), or obtained from Dr. Günter Krause (Department I of Internal Medicine; University Hospital of Cologne; CECAD; Cologne; GER) or Prof. Dr. Hamid Kashkar (Institute of Medical Microbiology, Immunology and Hygiene (IMMIH); University of Cologne; Cologne; GER). The cell lines were grown at 37°C and 5% $CO_2$ and maintained in the medium specified for each cell line supplemented with FBS and other additives (Supplementary Table S1). Whole exome sequencing was used for cell lines authentification.

### Cell death assays

VEN sensitive and resistant B cell lymphoma cell lines as well as OSU wild-type cells and BAX knockout clones (100,000 cells per well) were plated in 100 µl medium per well in 96-well plates and treated with increasing drug concentrations. Cells were cultured for 24 h or 48 h at 37°C, 5% $CO_2$. Apoptosis was determined by flow cytometry using annexin V-FITC (Immuno Tools)/7-AAD (eBioscience) staining in annexin-V Binding Buffer (BD). Double negatives were considered as viable. Measurement was carried out by fluorescence-activated cell sorting (FACS) MACSQuant VYB (Miltenyi Biotech). Data was analyzed by Kaluza Analysis Software 2.0 (Beckman Coulter). Cell viability was determined using the CellTiter-Glo® Luminescent Cell Viability ATP Assay Kit (Promega). For these assays VEN sensitive and resistant B cell lymphoma cell lines were plated in triplicate into white 96-well plates at 100,000 cells per well in 100 µl medium and treated with increasing drug concentrations for 48 h. MEF wild-type and *Puma*$^{-/-}$ cells were plated in triplicates into white 96-well plates at 100,000 cells per well in 100 µl medium. After treatment with DMSO or 20 µM VEN for 24 h, 20 µl of the CellTiter-Glo® reagent was added per well. The mixture was shaken on a rocking platform for 2 min, incubated for further 10 min in the dark at room temperature. The luminescence signal, proportional to the amount of ATP present, was quantified using a multiplate reader (FLUOstar OPTIMA, BMG LABTECH). Data were normalized to the vehicle control and reported as percentage of viable cells.

### Cell Cycle Analysis

5x10^5 cells were incubated for 48 hours. Afte washing with PBS, cells were fixated in ethanol 70% for 48 hours. After rehydration with PBS, cells were stained in 0.1 % Triton X100 (Sigma Aldrich), 100 µg/ml RNase A (Promega) and 20 µg/ml Propodium Iodide (ThermoFisher) and

analyzed by flow cytometry (MACS Quant Vyb, Miltenyi; Kaluza software) in technical replicates after 24 hours.

**CRISPR Cas9 Screening**

Cells were retrovirally transduced with a *pMSCV-eSpCas9* expressing vector containing a hygromycin b resistance insert. After hygromycin b selection, cells were transduced with a retroviral mouse genome-wide CRISPR knockout library which was a gift from Sarah Teichmann (Addgene #104861). After transduction, the cells were selected with puromycin for 7 days. After selection, a sample for acquiring the initial library-representation was collected. The population was then split into two samples, one of which was treated with ABT-199 (10 nM) and the other with DMSO (0,0002 %). During all steps, a multiplicity of at least 500x was maintained and selection with puromycin and hygromycin b was continued. After 28 days of cultivation, DNA was extracted from both samples as well as the initial representation sample using a commercial kit (Qiagen, Cat. No. 158388). A total of 175 µg genomic DNA per sample was used for PCR amplification, which was performed using Q5 high-fidelity polymerase (New England Biolabs, Cat. No. M0491). PCR cycling conditions: an initial 30 s at 98 °C; followed by 10 s at 98 °C, 15 s at 61 °C and 20 s at 72 °C, for 35 cycles; and a final 2 min extension at 72 °C. Samples were purified using a commercial PCR-cleanup kit (Macherey-Nagel, Cat. No. 740609) and pooled. The amplicon was then sequenced at a multiplicity of 500x (2 x 100 bp, NovaSeq, Illumina).

The raw FASTQ-files were first stripped of their sequencing adapters. Then, every read was simultaneously checked for the presence of the PCR priming-site and the sgRNA sequence. The sgRNA sequence was then mapped to its individual gRNA-vector and counted. Afterwards, counts of every sample were normalized to its mean number of reads to account for variances in sequencing depth. Then, the mean fold change of the 5 different gRNAs per gene from the VEN treated sample in comparison to the control sample as well as the initial representation was calculated.

**MeDIP-sequencing**

In brief, 1.3 µg genomic DNA in 65 µl TE were sheared to a size range of 100 to 300 bp by focused ultrasonication in microTube-15 AFA Beads Screw-Caps using a Covaris E220 (Covaris Ltd.) with the settings: peak incident power: 75%, Duty factor 20 %, number of cycles per burst: 200, 8°C for 6 min. Size was evaluated using a 1% agarose gel and samples that did not have the required size range were sheared for an additional 2 min. Subsequently, libraries were prepared using the TrueSeq DNA Sample Preparation Kit (Illumina) with

unmethylated TrueSeq indexed adaptors and purified using the AMPure XP beads (Beckman Coulter GmbH). 5 µg of a monoclonal antibody targeting 5-methylcytidine (clone 33D3, #BI-MECY-1000, Lot: vt150601, Eurogentec) were coupled over night at 4°C to Dynabeads M-280 sheep anti mouse IgG (Bethyl Cat# A300-140A, RRID:AB_2149790) in 0.05 % BSA/PBS, washed two times with 0.5 % BSA/PBS and one time with immunoprecipitation buffer (IP-buffer, 10 mM sodium phosphate buffer (pH 7.0), 140 mM NaCl, 0.25% Triton X100). Prior to MeDIP, libraries were denatured for 10 min at 95 °C and immediately cooled in ice water. Denatured libraries and antibody coupled to Dynabeads were incubated at 4°C for 4h in IP-buffer with gentle rotation. Reactions were washed three times in IP-buffer and DNA was eluted from the beads using 50 mM Tris-HCl (pH 7.5), 10 mM EDTA, 1% SDS at 65 °C for 15 min followed by separation using a magnetic rack. The eluted DNA was diluted 1 to 1 with 10 mM Tris pH 8.0, 1 mM EDTA and treated with proteinase K (0.2 µg/µl) for 2 h at 55 °C. DNA was purified using the QiaQuick PCR purification kit (Qiagen). Following MeDIP enrichment, libraries were amplified using 10 PCR cycles and size selection was performed on a 2% agarose gel. DNA was purified using the QiaQuick gel extraction kit (Qiagen) and quantified using the Quant-iT dsDNA HS Assay Kit and a Qubit 1.0 Fluorometer (Thermo Fisher Scientific). 50 bp paired end reads were generated using a HiSeq2000 at the Sequencing core facility of the Max Planck Institute for Molecular Genetics, Berlin, Germany.

**MeDIP-analysis**

MeDIP sequencing reads were aligned to the GRCh38 reference genome using bwa Version 0.7.15-r1140 [1], and analyzed in 250 base windows using the R/bioconductor package QSEA[2] with standard parameters. Within QSEA, the MeDIP enrichment was calibrated using fully methylated regions in all respective cell lines from[3].

Genomic locations of the array probes were mapped from GRCh37 to GRCh38 using the UCSC liftOver command line tool[4], and probes within 250 base windows were averaged. Only invariant regions with beta values > 80% methylation in all calibration cell lines were considered fully methylated and used for calibration. Copy number variations of the cell lines were computed in QSEA from the MeDIP-seq data (based on sequencing fragments without CpG dinucleotides) and used for normalization in subsequent differential methylation analysis. DMRs obtained from QSEA (FDR 10%) were annotated with gene, exon, and promoter (transcription start site +/- 2 kilobases) information from RefSeq (RefSeq, RRID:SCR_003496), RepeatMaseker repeats, ENCODE TFBS and model based CpG islands, all obtained via the UCSC table browser. Since ENCODE TFBS are not available for GRCh38, genomic locations were mapped from GRCh37 using the liftOver tool (liftOver, RRID:SCR_018160).

**Pyrosequencing**

Targeted methylation analysis was performed using bisulfite conversion followed by pyrosequencing. In brief, 200 ng DNA were bisulfite converted using the EpiTect Bisulfite Kit (Qiagen) according to the manufacturer's recommendations. For the enzymatic conversion, 50 ng of DNA were converted employing the NEBNext Enzymatic Methyl-seq Conversion Module (New England Biolabs) according to the manufacturer's protocol. Subsequently, 20 ng of the BS-converted DNA was amplified with the Pyromark PCR kit (Qiagen).
Oligos used for methylation detection of the cytosine (hg38; chr19:47,231,698) in the first intron/promoter region of BBC3 were:

forward: Btn-5' TTATATTATGGATAGGGGTATGAG 3'; reverse: 5' CCAAAAAACCCTATTAATAAATCT 3'; sequencing: 5' TTAATAAATCTATACATTTC 3'.

hg38; chr19:47,231,337: forward: 5' TTATTATAAATTTGGTAGGGGATT 3'; reverse: Btn-5' CCAAATACCCAAAACTACTTCCA 3'; sequencing: 5' AATTTGGTAGGGGATT 3';

hg38; chr19:47,231,442: forward: Btn-5' TTTAGTTTAAGGTAAGGAGGATTT 3' ; reverse: 5' CATCCTCTAAACTCTACCTACA 3'; sequencing: 5' ATCTCCCCACACCCC 3'.

**Metabolic flux assays**

In brief, the day prior the assay Seahorse 96-well plates were coated with 15 µg/ml Human Plasma Fibronectin in PBS (FC010, Merck Millipore) and XFe96 sensor cartridges hydrated with 200 µl of Seahorse Calibrant were put in a non-$CO_2$ 37°C incubator overnight.

On the day of the assay, after washing the coated plate with PBS, 200000 cells/well were added in XF Base medium (Seahorse Bioscience, Agilent) supplemented with either 1 mM sodium pyruvate, 2 mM L-glutamine, and 10 mM glucose or 2 mM L-glutamine only (pH 7.4 for both). After centrifugation (1', 1500 rpm) the plate was incubated in a non-$CO_2$ 37°C incubator for 1h. The assay (5-8 wells per condition) was set as follows: 4 measurements (3' mixing plus 3' measuring each) for basal respiration, 3 measurements after oligomycin injection (1 µM), 3 measurements after FCCP injection (1 µM) and 3 measurements after rotenone/antimycin A injection (0,5 µM each). All injected compounds (Sigma Aldrich) were dissolved in DMSO. Oligomycin treatment allowed quantification of ATP production via inhibiting ATP synthase (complex V), FCCP (Carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone) uncoupler caused maximal cellular respiration and rotenone/antimycin A treatment revealed the amount of non-mitochondrial respiration via inhibiting complex I/III of the mitochondrial electron transport chain.

**DNA extraction for WES**

In detail, DNA was extracted with DNeasy® Blood and Tissue Kit (Cat No./ID: 69504; Qiagen) following the instructions. Whole-exome sequencing was performed using the SureSelect Human All Exon V6 (Agilent) target enrichment according to the manufacturer's instructions. Obtained exome libraries were paired-end sequenced on a HiSeq4000 platform (Illumina). Raw sequencing reads were aligned to the human reference genome (NCBI build 37/hg19) using the aligner BWA mem (BWA, RRID:SCR_010910, version 0.7.13-r1126). Concordant read pairs were masked as possible PCR duplicates. In addition, areas of overlapping read pairs were excluded from analysis in one read. Substitutions, insertions, and deletions were determined by our in-house cancer genome analysis pipeline.

**Targeted amplicon sequencing**

Obtained DNA-libraries were paired-end sequenced on a MiniSeq (2 × 150 bp) platform (Illumina). Bioinformatic processing of sequencing reads and variant analysis were conducted using Archer Analysis version 5.1.7 (ArcherDX) and Sequence Pilot Software version 4.4 (SeqNext module; JSI Medical Systems). Regions of interest coverage was at least 200x.

**DNA preparation for Pyrosequencing**

Targeted methylation analysis was performed using bisulfite conversion followed by pyrosequencing. In brief, 200 ng DNA were bisulfite converted using the EpiTect Bisulfite Kit (Qiagen) according to the manufacturer's recommendations. For the enzymatic conversion, 50 ng of DNA were converted employing the NEBNext Enzymatic Methyl-seq Conversion Module (New England Biolabs) according to the manufacturer's protocol. Subsequently, 20 ng of the BS-converted DNA was amplified with the Pyromark PCR kit (Qiagen).

**Western blot and immunodetection**

After harvesting, cells were washed in PBS, subsequently cells were lysed with RIPA III buffer (50 mM TRIS-HCl pH 7.5, 0.1% sodium dodecyl sulfate (SDS), 150 mM NaCl, 0.5% DOC, 1% NP-40, $H_2O$) supplemented with protease inhibitor (#P8340, Sigma-Aldrich) and phosphatase inhibitor cocktail (#04906845001, Roche). Protein content was determined by Roti-Quant (#K015.1, Roth). Cell lysates were mixed with SDS-loading buffer (60 mM Tris-HCl pH 6.8, 3.3% SDS, 20 mM Dithiothreitol (DTT), 0.01% bromphenol blue, 50% glycerol), the mixture was heated to 95°C for 5 min. In the following protein samples were loaded on a NuPAGE 4-

12% Bis-Tris gel (Thermo Fisher Scientific), separated by gel electrophoresis at 160V for 1 hour and then transferred to a Protran nitrocellulose membrane (0.45 µm pore size, Amersham Bioscience) by tank blotting at 80 V for 1 h. Afterwards the blotting membrane was blocked with 5% non-fat dry milk in Tris-buffered saline for 1 h.

Blots were probed with the following antibodies against: BAK1 (Sigma-Aldrich Cat # B5897, RRID:AB_258581), BAX (D2E11) (#5023S, Cell Signaling), BCL-2 (Millipore Cat# OP91, RRID:AB_2259054), $Bcl_XL$ (#2764S , Cell Signaling) , BFL1/A1 (#14093, Cell Signaling), BID (#2002S , Cell Signaling), BIM (#2819S, Cell Signaling), cleaved caspase-3 (Asp 175, 5A1E) (#9664, Cell Signaling), Caspase-8 (1C12) (#9746, Cell Signaling), MCL-1 (#4572S, Cell Signaling), NOXA (#3665, Biovision), PARP (#9542S, Cell Signaling) and PUMA (#4976S, Cell Signaling). β-actin (MAB1501, Merck/Millipore) or GAPDH (#CB1001, Calbiochem) was used as loading control. Detection of primary antibodies was achieved via specific IRDye secondary antibodies (LI-COR Biosciences). Protein bands were detected by LI-COR reader (LI-COR) and quantified by Image Studio Light Software (LI-COR).

**RNA isolation, reverse transcription, real-time PCR**

RNA isolation from cell pellets was performed by using TRIzol (Invitrogen) according to the manufacturer´s instructions. All of the preparation and handling steps of RNA took place in a laminar flow hood, under RNA-free conditions. The isolated RNA was dissolved in 21 µl RNAse-/DNAse-free water and stored at -80°C until used. RNA concentrations and ratios were determined photometrically (NanoDrop 1000, peqlab).

Of the isolated total RNA, 1 µg was used for cDNA generation by the Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics). Reactions were set up and run according to the manufacturer´s instructions; thereafter, samples were kept at -20°C until use in RT-qPCR and reverse-transcriptase PCR.

Real-time RT-PCR was performed using the LightCycler system (Roche Diagnostics). The primers and the used hybridization probes were designed by ProbeFinder (ProbeFinder, RRID:SCR_014490; Roche Diagnostics) and synthesized by Sigma-Aldrich. Real-time RT-PCR was performed in a total volume of 20 µl in the LightCycler glass capillaries. For the PCR, 5 µl cDNA were placed into a 15-µl reaction volume containing 0.2 µl of the sense primer (1 µM), 0.2 µl of the antisense primer (1 µM), 4 µl of the LightCycler TaqMan Master Mix (5x concentration), 0.2 µl of the probe (1 µM), and $H_2O_{dd}$ was added to the final volume. PCR reaction was initiated with a 10-min denaturation at 95°C and terminated with a 30-s cooling step at 40°C. The cycling protocol consisted of denaturation step at 95°C for 10 s, annealing

at 60°C for 10 s, and extension at 72°C for 20 s, and repeated for 50 times. Fluorescence detection was performed at the end of each annealing step for 1 s.

The following Universal Probe Libraries (Roche Diagnostics), were used: probe #64 (REF 04 688 635 001) and probe #68 (REF 04 688 678 001). The primer sequences for real-time PCR were as follows: *BBC3*-specific primers (5´ GACCTCAACGCACAGTACGA 3´ [forward] and 5´ GAGATTGTACAGGACCCTCCA 3´ [reverse]), and *β-ACTIN*-specific primers (5´ AGAAAATCTGGCACCACACC 3´ [forward] and 5´ AGAGGCGTACAGGGGATAGCA 3´ [reverse]) amplified fragments of the full-length transcripts. Results were normalized to β-ACTIN.

For reverse-transcriptase PCR the primer sequences were as follows: murine *Bax* specific primers (5´ TCTCCGGCGAATTGGAGATG 3´ [forward] and 5´ CTCACGGAGGAAGTCCAGTG 3´ [reverse]), and murine GAPDH-specific primers (5´ TGTCCGTCGTGGATCTGAC 3´ [forward] and 5´ CCTGCTTGACCACCTTCTTG 3´ [reverse]) amplified fragments of the full-length transcripts.

**Lentivirus production and transduction**

The lenticCRISPR v2 inserted with single-guide RNA, together with psPAX2 packaging plasmid (RRID:Addgene_12260, Addgene, Cat. #12260) and pMD2.G envelope plasmid (Addgene Cat. #12259). DNA were combined together and transfected into HEK293 cells using the Lipofectamine 2000 reagent (Cat. #11668-019, Invitrogen, Thermo Fisher Scientific). The transfection solution was added dropwise to the cells and incubated for 6 h at 37°C in a humidified 5% $CO_2$ cell culture incubator. Six hours post transfection the medium was replaced by adding DMEM supplemented with 5% FCS and 1% penicillin-streptomycin and incubated for 24 h. Eighteen hours post medium replacement, sodium butyrate (Cat. #B5887; Sigma Aldrich) was added to the culture medium at a final concentration of 1 mM. The viral harvest was performed for two times in 24-h intervals. After each collection, the virus-containing medium was cleared by centrifugation at 300 x *g* for 5 min at 4°C, sterile filtered through a 0.45 µm filter unit (Cat. #10462100; Whatman, GE, Healthcare Life Sciences) and stored at -80°C until use. Lentivirus-containing medium was used to infect OSU cells. For this purpose, $10^7$ cells were resuspended in viral supernatant supplemented with 2 µg/mL polybrene and centrifuged at 800 x *g* for 2 h and 32°C. After spinoculation the cell pellet was resuspended and cells were incubated for further 24 h under viral containing conditions at 37°C in a humidified 5% $CO_2$ atmosphere. After incubations, cells were washed in PBS, centrifuged and resuspended in cell culture growing medium. Cells were cultivated for 4 to 5 days until start of selection by 0.5 µg/mL puromycin (Cat. #ant-pr-1; InvivoGen) for 72 h. Subsequently 85 cells

were resuspended in 20 mL of medium and distributed by pipetting 200 µl of this cell suspension into 96 wells. After outgrowth of single-cell clones, these clones were lysed and prepared for western blotting.

**Luciferase reporter assays**

The plasmid containing the BBC3 insert was purchased from BioCat (BioCAT, RRID:SCR_001440). Following linearization of the pCpGL-basic vector with *BamHI* and *HindIII* (New England BioLabs), we ligated the synthesized fragment to the linearized pCpGL-basic backbone using Quick Ligation Kit (New England BioLabs). The resulting plasmid DNA was chemically transformed into competent *E. coli* GT115 cells (InvivoGen), selected and grown on LB agar plates in the presence of Zeocin, and purified using the QIAprep Spin Miniprep Kit (QIAGEN). We subjected the purified plasmid DNA (containing the pCpGL-basic backbone and the human BBC3 sequence insert) to two treatments: (i) *in vitro* methylation by *M.SssI* methyltransferase in the presence of the methyl donor S-adenosylmethionine (SAM), which results in methylation of all CpGs; or (ii) a mock treatment using only SAM and no methyltransferase. We transfected each methylated or unmethylated plasmid construct, as well as the pCpGL-basic (negative control) and pCpGL-CMV (positive control) plasmid into HEK293 cells. Specifically, when cells were approximately 70% confluent, we washed and seeded them in pools of 0.5 x $10^6$ cells/well in a 12-well plate. Transient transfection was performed by adding 200 µl of OptiMEM I Reduced Serum Media (Gibco) containing the following reagents: (i) 1.6 µg of methylated or unmethylated vector; (ii) 10 ng of *Renilla* control vector; and (iii) 4 µl of Lipofectamine 2000 (Invitrogen). Cells were incubated for 24 hr following transfection, and subsequently assayed for transgene luciferase expression with the Dual-Glo® Luciferase Assay Kit (Promega). We quantified enhancer activity by first normalizing firefly luciferase activity against *Renilla* luciferase activity to control for variation in transfection efficiency or cell number.

**References**

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**Supplementary figure legends**

**Supplementary Figure 1| Downregulation of BAX and PUMA and up-regulation of MCL-1 *in vitro* and *in vivo*.** (**A, B**) Western blot analysis of MCL1, PUMA, and BAX protein level were determined in ten sensitive (black) and VEN resistant (red) B cell lymphoma cell lines. GAPDH or β-ACTIN was used as a loading control. (**C**) *Left panel*: VEN resistant cells were cultured for 3 months without VEN (green). Afterwards these cells, as well as sensitive (blue) and VEN resistant (orange) cells that were kept under continuously VEN pressure, were incubated with VEN. Apoptosis was determined by flow cytometry (annexin-V/7-AAD positive fraction) after 48 hours. Data represent the mean ± SD of at least three independent experiments. *Right panel*: Cleavage of PARP was determined by Western blotting of cells treated with 10 *μM* of VEN for 6 h. (**D**) Western blot analysis of BCL-xL, BCL2, BID, BAK1, BFL1, NOXA and BIM in sensitive (black) and VEN resistant (red) B cell lymphoma cell lines. GAPDH or β-ACTIN was used as a loading control. (**E**) Correlation analysis of the MSI status and the change in the relative BAX protein level of the VEN resistant cell lines. Data are illustrated as mean ± SD of at least three independent experiments. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.001, compared with parental (blue) cells, using Students *t*-test.

**Supplementary Figure 2| Generation of S63845 resistance in B cell lymphoma cell lines.** (**A**) Confirmation of S63845 resistance in three B-NHL cell lines. Viability determined by flow cytometry (annexin-V/7AAD) after 48 h treatment with S63845. Sensitive (blue) and S63845 resistant (magenta) cell lines. Data represent the mean ± SD of at least three independent experiments. (**B**) *Left panel*: Viability assay in sensitive and S63845 resistant WSU-NHL and KARPAS-422 cell lines as described for A. *Right panel*: Cleavage of PARP and caspase-3 were determined by Western blotting of WSU-NHL and KARPAS-422 cells treated with 10 μM of the MCL1 inhibitor S63845 for 6 h. (**C**) Densitometric analyses of immunoblots from WSU-NHL and KARPAS-422 cell lines against MCL1, BAK1, PUMA, and BAX are shown. Data are illustrated as mean ± SD of at least three independent experiments. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.001, compared with parental (dashed blue line) (S63845 sensitive) cells, using Students *t*-test. (**D**) Results from whole-exome sequencing are shown, including cancer related gene mutations. Genomic alterations are annotated according to the colour panel below the image. (**E**) *PUMA/BBC3* promoter methylation in sensitive and S63845 resistant cell lines (n=3).

**Supplementary Figure 3| Effect of VEN on the expression of *BBC3* in B cell lymphoma cell lines and primary CLL cells.** (**A**) RNA was extracted from parental and VEN resistant cells and the fold change for *BBC3/PUMA* was determined by quantitative real-time PCR.

Transcript level of control cell lines (VEN sensitive) were set to 1 (blue dashed line). (**B**) Principal component analysis (PCA) from MeDip-seq data of the CpG island methylation (left panel) and the *BBC3* promoter methylation (right panel) in parental (blue) and VEN resistant (orange) B cell lymphoma cell lines. (**C**) Western blot analysis of PUMA level in sensitive and VEN resistant KARPAS-422 cells treated with or without 5'AZA (0.1 µM) for five passages. (**D**) Western blot analysis of PUMA protein in whole-cell extracts of wildtype and Puma$^{-/-}$ MEFs. (**E**) Viability of wildtype and Puma$^{-/-}$ MEFs was determined after 24 h exposure to 20 µM VEN by an MTT assay. Data represent the mean ± SD of at least three independent experiments. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, normalized to vehicle-treated cells, using Students *t*-test. (**F**) Western blot analysis of PUMA protein in whole-cell extracts of wildtype and three clones with *PUMA*$^{-/-}$ in KARPAS-422 cells. β-ACTIN served as loading control. (**G**) Viability assay of empty vector control (e.v.; dark blue) and three *PUMA*$^{-/-}$ KARPAS-422 clones (red, green, purple) and respective $IC_{50}$. The viability was determined after 48 h exposure to 100 nM VEN by an MTT assay. **P* < 0.05, ***P* < 0.01, *****P* < 0.0001, normalized to empty vector control, using One-Way-ANOVA. (**H**) Western blot analysis of PUMA protein in whole-cell extracts of wildtype and three *PUMA*$^{-/-}$ OSU cell line clones. β-ACTIN served as loading control. (**I**) Viability of *PUMA*$^{-/-}$ KARPAS-422 clones after VEN treatment determined by flow cytometry (annexin-V/7AAD) after 48 hours. Mean + SD, n=3. (**J**) Example of PI cell cycle analysis. (**K**) Cell cycle analysis by PI staining in *PUMA*$^{-/-}$ OSU and *PUMA*$^{-/-}$ KARPAS-422 clones. Mean + SD, n=3.

**Supplementary Figure 4| VEN resistance and loss of PUMA increase metabolic output of leukemic cells.** (**A**) Mitochondrial respiration in sensitive *vs* VEN resistant DOHH-2, KARPAS-422 and OSU cells, with or without glucose in the media, upon injection of the Seahorse Mito Stress test drugs, indicating changes in basal respiration (*top right*), maximal respiration (*bottom left*) and ATP production (*bottom right*). Data are shown as floating bars (min. to max.) and are representative of 3 to 4 independent experiments. Significance was determined by 2-way ANOVA (2WA, factor "resistance" as *, factor "media composition" as #) with Sidak multiple comparisons. (**B**) Glycolysis in sensitive *vs* VEN resistant DOHH-2, KARPAS-422 and OSU cells, with or without glucose in the media, upon injection of oligomycin indicating changes in basal ECAR (*left*) and glycolytic capacity (*right*). Data are shown as floating bars (min. to max.) and are representative of 3 to 4 independent experiments. Significance was determined by 2-way ANOVA (2WA, factor "resistance" as *, factor "media composition" as #) with Sidak multiple comparisons. (**C**) Mitochondrial respiration and glycolysis were measured in PUMA-depleted MEFs cells upon injection of the Seahorse Mito Stress test drugs indicating changes in basal respiration, maximal respiration, ATP production, basal ECAR and glycolytic capacity. Data are shown as floating bars (min. to max.) and are representative of 5 independent experiments. Paired two-tailed Student´s *t*-test was used to

assess statistical significance. ∗ $P$<0.05, ∗∗ $P$<0.01, #### $P$<0.0001. (**D-G**) Seahorse Mito Stress test was performed in sensitive *vs* VEN resistant KARPAS-422 cells after 2 h treatment with VEN (1 µM/well). (**D**) OCR in the presence (*left*, 10 mM) or absence of glucose (*right*) in the media. ECAR values from both media conditions are reported in (**G**). Data are representative of 3 independent experiments as mean ± SD. Individual floating bars (min. to max.) were extrapolated from (**D**) to represent VEN acute effect on OCR (**E**) and maximal respiration (**F**). (**H-K**) Seahorse Mito Stress test was performed in sensitive *vs* VEN resistant DOHH-2 cells (OCR, **H-I**; ECAR, **K**) after 2 h treatment with VEN (1 µM/well). OCR values are reported in the presence (**H** *left*, 10 mM) or absence of glucose (**H** *right*) in the media, as well as ECAR values (**K**). Data are representative of 2-3 independent experiments as mean ± SD. Individual floating bars (min. to max.) were extrapolated from (**H**) to represent VEN acute effect on OCR (**I**) and maximal respiration (**J**). OCR, oxygen consumption rate; ECAR, extracellular acidification rate.

**Supplementary Figure 5| *Bax* loss impacts on drug-resistance but not on disease kinetics *in vivo*.** (**A**) Mean $IC_{50}$ values for S63845 in naïve and VEN resistant cell lines determined by flow cytometry (48 hours). (**B**) Localization of the mutations in *BAX* and *TP53* identified in a treatment naïve CLL-patient. Scale: length of the protein in amino acids (aa). Blue boxes represent functional relevant domains of each protein (modified according to Pfam version 33.1). (**C**) Reverse-transcriptase PCR analysis for the *Bax* transcript. RNA was isolated from purified malignant, splenic B cells isolated from *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$* (blue), *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/wt}$* (orange) and *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/fl}$* (magenta) mice. The expected band sizes are 253 bp for murine *Bax* and 90 bp for murine GAPDH. M, molecular marker. (**D-F**) Results from the blood analyses of 32 weeks old *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$* (blue; n=10), *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/wt}$* (orange; n=11) and *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/fl}$* (magenta; n=6) mice. White blood count (**D**), red blood count (**E**) and platelets (**F**) in the blood of 32 weeks old *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$* (blue), *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/wt}$* (orange) and *Eμ-TCL1$^{tg}$; Cd19Cre$^{+/wt}$; Bax$^{fl/fl}$* (magenta) mice *$P$ < 0.05 compared with *Bax$^{wt/wt}$* mice, using Student´s *t*-test. (**G**) Spleen weight and length of *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$* (light blue; n=3; 59-83 weeks), *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{fl/wt}$* (light orange; n=3; 70-74 weeks) and *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{fl/fl}$* (pink; n=3; 65-83 weeks) mice. Data are illustrated as mean ± SD of three mice each. (**H**) Amount of $Cd5^+/Cd19^+$ positive cells in splenocytes of *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$* (light blue; n=3; 59-83 weeks), *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{fl/wt}$* (light orange; n=3; 70-74 weeks) and *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{fl/fl}$* (pink; n=3; 65-83 weeks) mice. **(I)** Amount of follicular cells ($Cd45^+$; $Cd19^+$; $CD93^-$; $Cd23^+$; $Cd21/35^+$) in splenocytes of *Eμ-TCL1$^{wt/wt}$; Cd19Cre$^{+/wt}$; Bax$^{wt/wt}$*

(light blue; n=3; 59-83 weeks), *Eμ-TCL1*$^{wt/wt}$*; Cd19Cre*$^{+/wt}$*; Bax*$^{fl/wt}$ (light orange; n=3; 70-74 weeks) and *Eμ-TCL1*$^{wt/wt}$*; Cd19Cre*$^{+/wt}$*; Bax*$^{fl/fl}$ (pink; n=3; 65-83 weeks) mice. **(J)** Immunophenotyping of splenocytes of a 69-week-old *Eμ-TCL1*$^{wt/wt}$*; Cd19Cre*$^{+/wt}$*; Bax*$^{wt/wt}$ (*upper panel*; light blue), a 71 weeks old *Eμ-TCL1*$^{wt/wt}$*; Cd19Cre*$^{+/wt}$*; Bax*$^{fl/wt}$ (*middle panel*; light orange) and a 74 weeks old *Eμ-TCL1*$^{wt/wt}$*; Cd19Cre*$^{+/wt}$*; Bax*$^{fl/fl}$ (*lower panel*; pink) mice. Depicted is the gating strategy on a FSC vs. SSC dot-plot. Viable cells were further gated to remove possible doublet cells on a dot-plot for FSC-area vs. -height. Viable cells were then analysed for Cd45, Cd19, Igm and Igd expression.

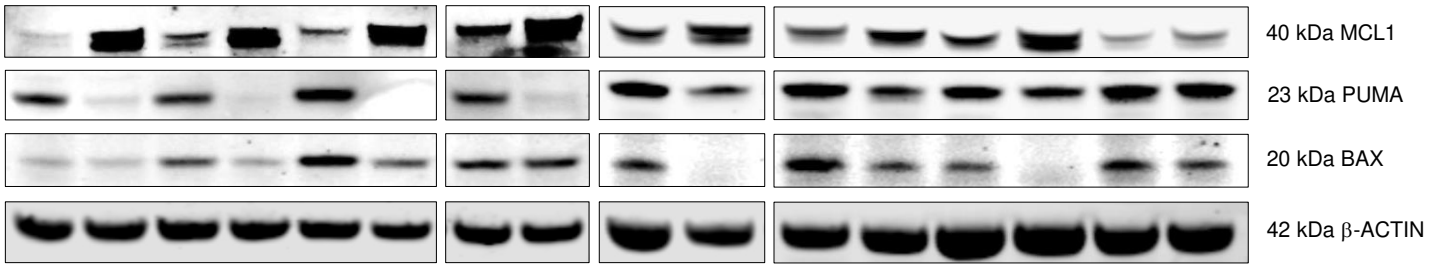
**Supplementary Figure 6| VEN resistance is mainly overcome by induction of extrinsic apoptosis.** (**A**) Compound Screen in sensitive and VEN resistant OSU (left) and DB cell line (right) according to their mean $IC_{50}$ (n=3) in μM (red: high IC 50, green: low IC 50) For TRAIL concentration is given in ng/ml. (**B**) $IC_{50}$ values for TRAIL in BAX deficient (red-orange) and BAX proficient (yellow-green) sensitive or VEN resistant B cell lymphoma cell lines. Cell death was determined by flow cytometry by annexin-V/7-AAD staining after 48 hours. Values represent the mean ± SD of three independent experiments. *p*-values were calculated by Student´s *t*-test. (**C**) Sensitive and VEN resistant P30-OH-KUBO cells were treated with 50 ng/mL TRAIL in the presence or absence of 25 μM Z-VAD-FMK for 16 h. Analysis of cleaved PARP and cleaved caspase-3 by Western blot. β-ACTIN was used as a loading control. (**D**) Viability of two (P30-OH-KUBO and WSU-NHL) B cell lymphoma cell lines after 48 hours treatment with TRAIL assessed by flow cytometry. Values represent the mean ± SD of three independent experiments. (**E**) Treatment of OSU *BAX* knockout clones (**Figure 3 B-C**) and parental/empty vector controls with 400 ng/mL TRAIL for 24 h. The cell viability was determined by MTT assays. The blue dashed line shows the viability of the parental cells. (**F**) Kinetics of caspase-8 activity after TRAIL treatment (400 ng/mL) in OSU *BAX* knockout clones and parental/empty vector control cells. (**G**) $IC_{50}$ values for TRAIL in BAX deficient (red-orange) and BAX proficient (yellow-green) sensitive or S63845 resistant B cell lymphoma cell lines. Cell death was determined by flow cytometry by annexin-V/7-AAD staining after 48 hours. (**H**) IC50 for YM155 for five different B cell lymphoma cell lines and their BAX expression level. Viability was determined by flow cytometry (7AAD/Annexin V) after 24 hours and normalized to DMSO. (**I**): Corresponding dose-response curve for YM155 in sensitive (blue) and VEN resistant (orange) cell lines including mean ± SD, n=3. (**J**): Immunoblot of P30-OH-KUBO cells (sensitive and VEN resistant) after treatment with YM-155 (100 nM, 16 hours) with or without Z-VAD-FMK (25 μM).

**Supplementary Figure 7| VEN resistance is mainly overcome by induction of apoptosis but not necroptosis.** Nalm6 (*upper part*) and DOHH-2 (*lower part*) cells were treated with 100

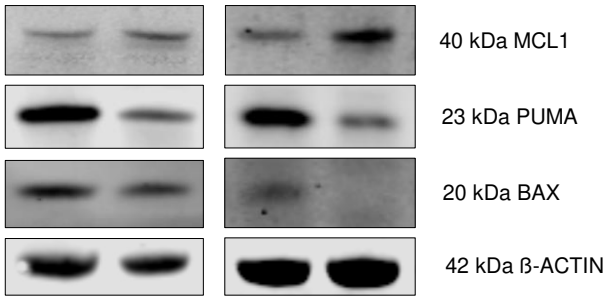
ng/mL TRAIL or TNF-alpha mono or in combination with the below mentioned substances (100 nM RIPKi; 250 nM birinapant; 1 µM IDN-6556/emricasan). Cell viability was determined after 24 h byMTT assays.

**Thomalla *et al.*, Supplementary Figure 1**

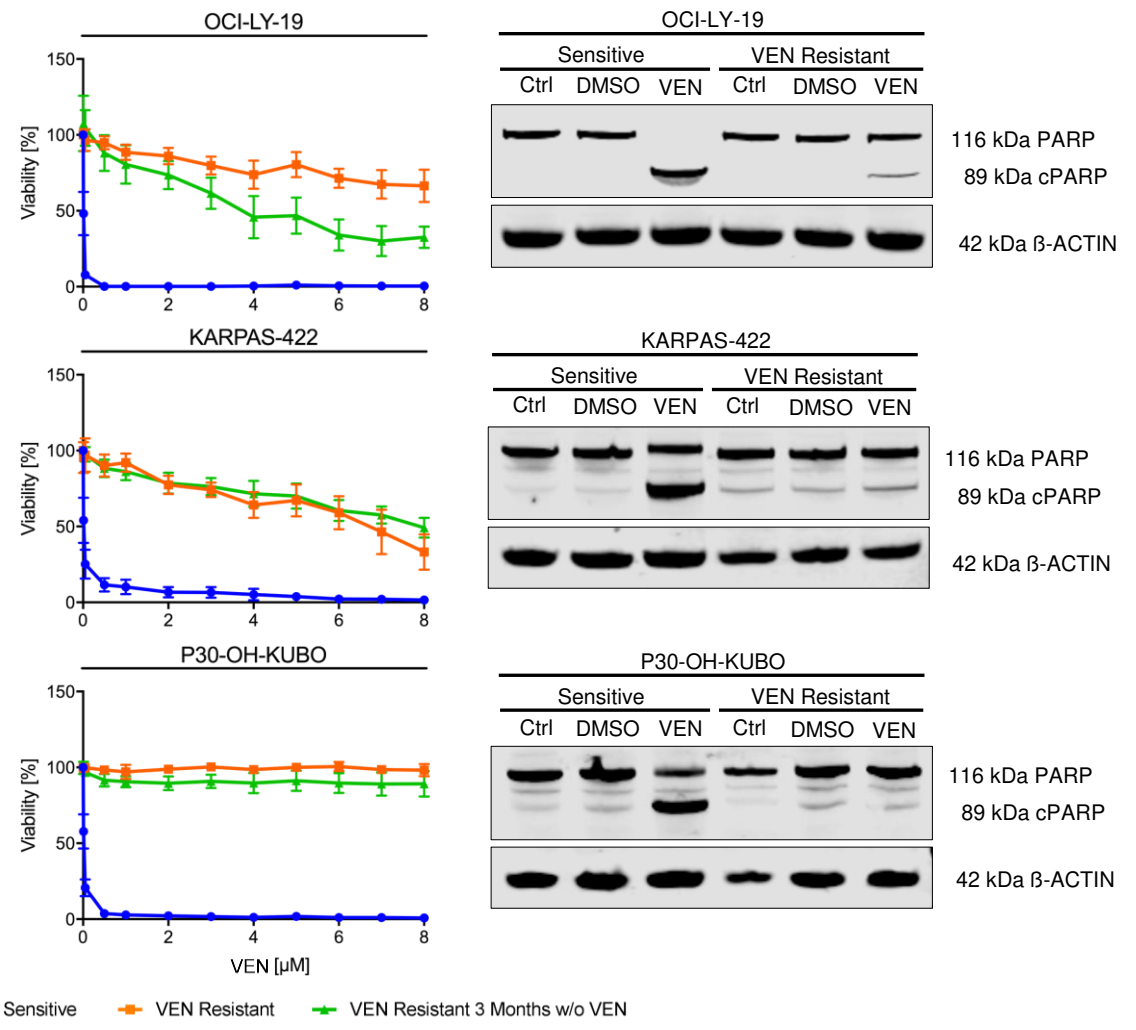
**A**




**B**

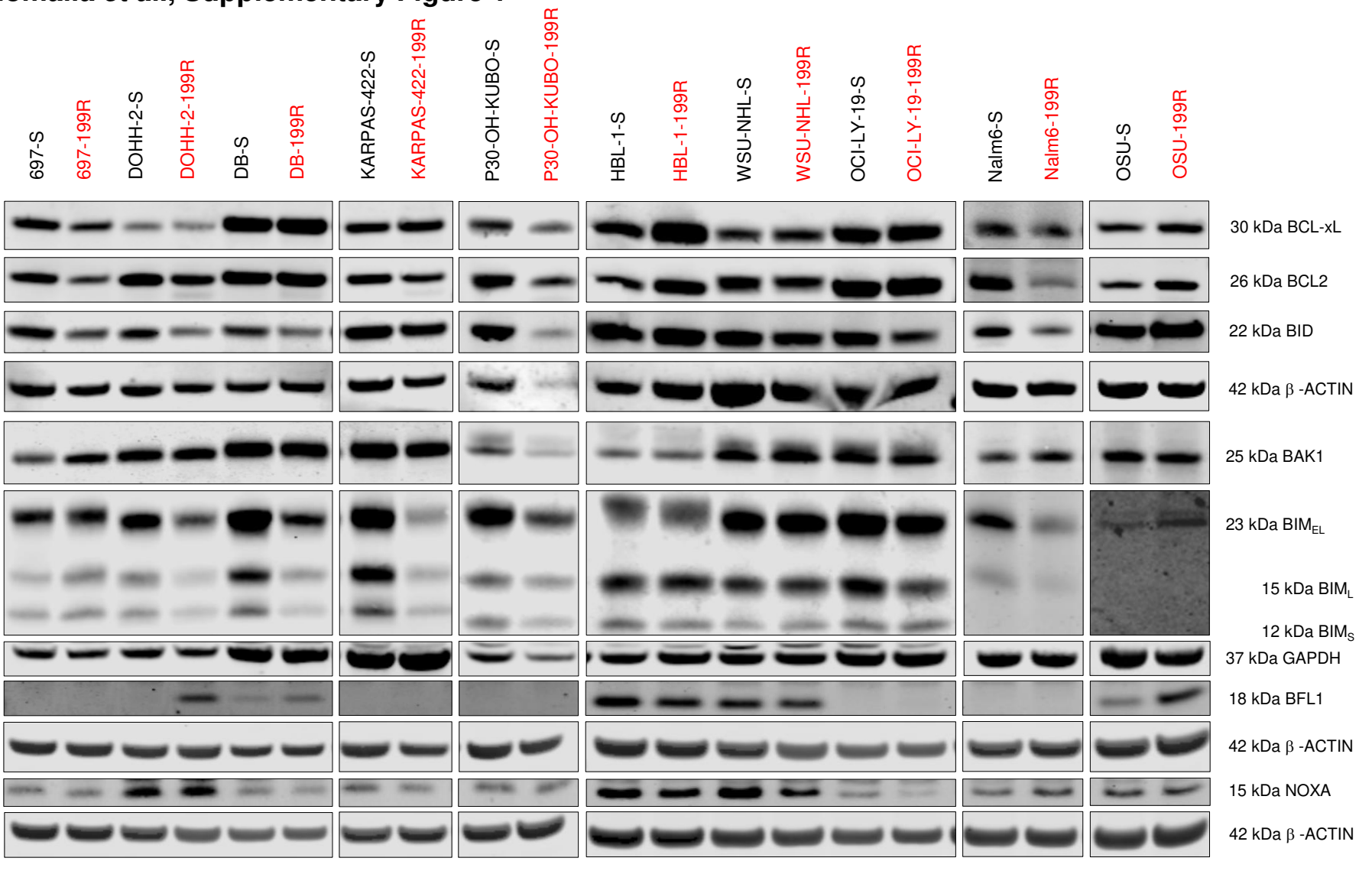



**C**



**Thomalla *et al.*, Supplementary Figure 1**

**D**

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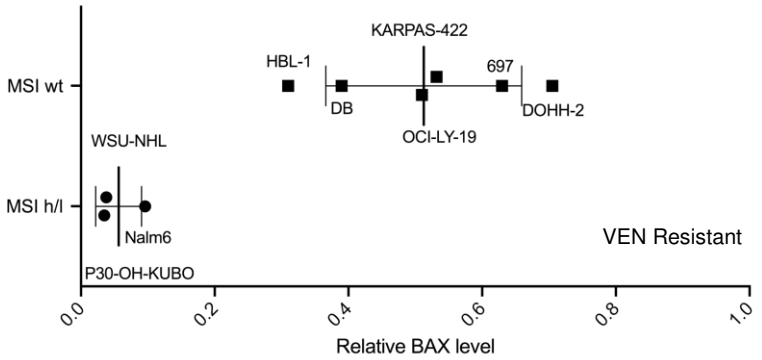
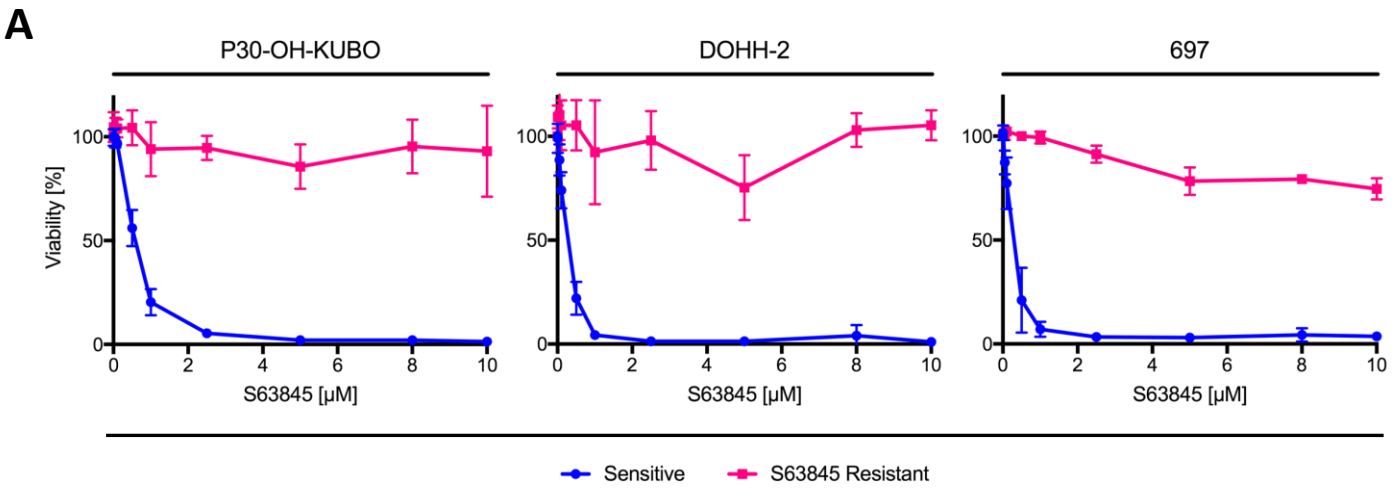
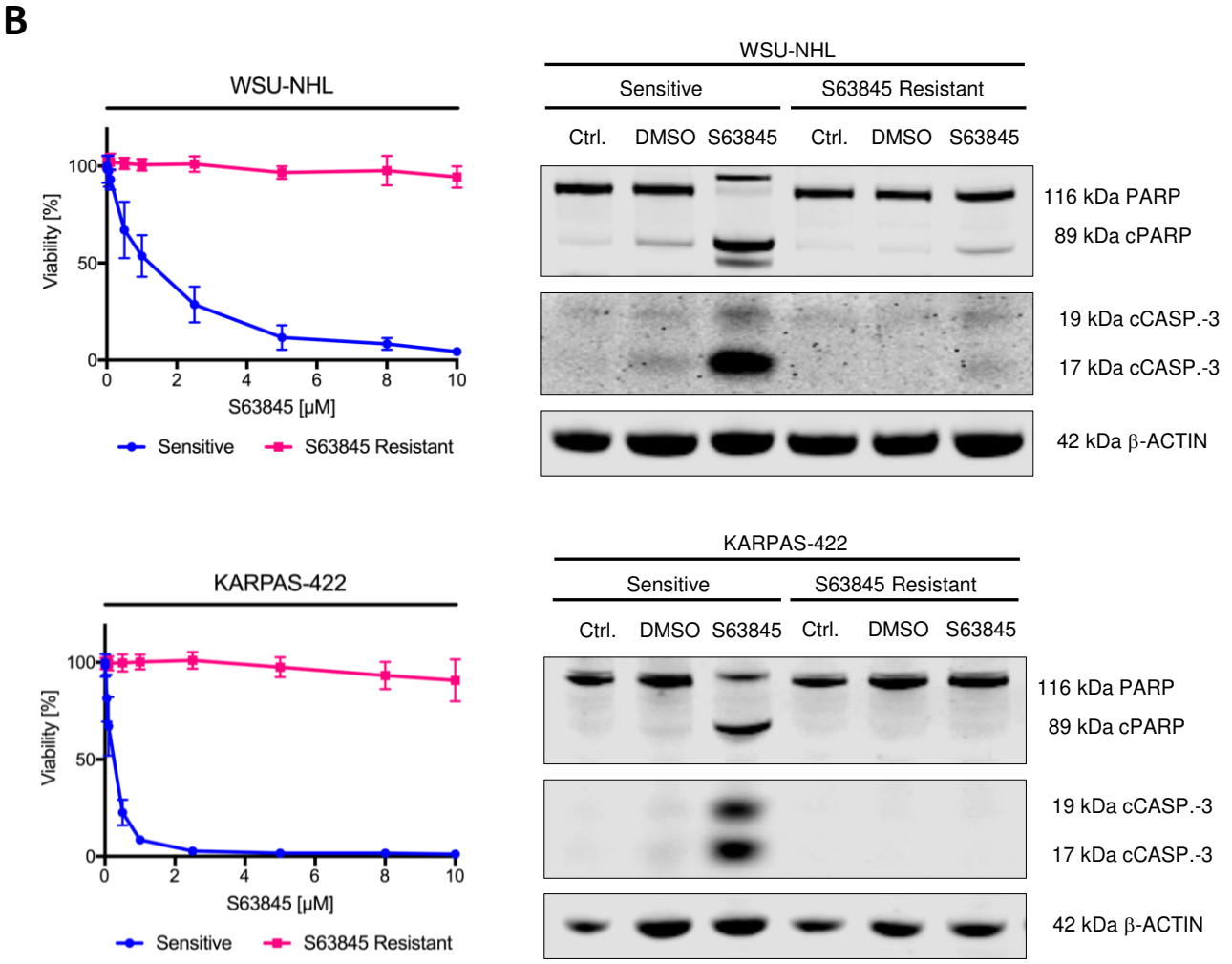
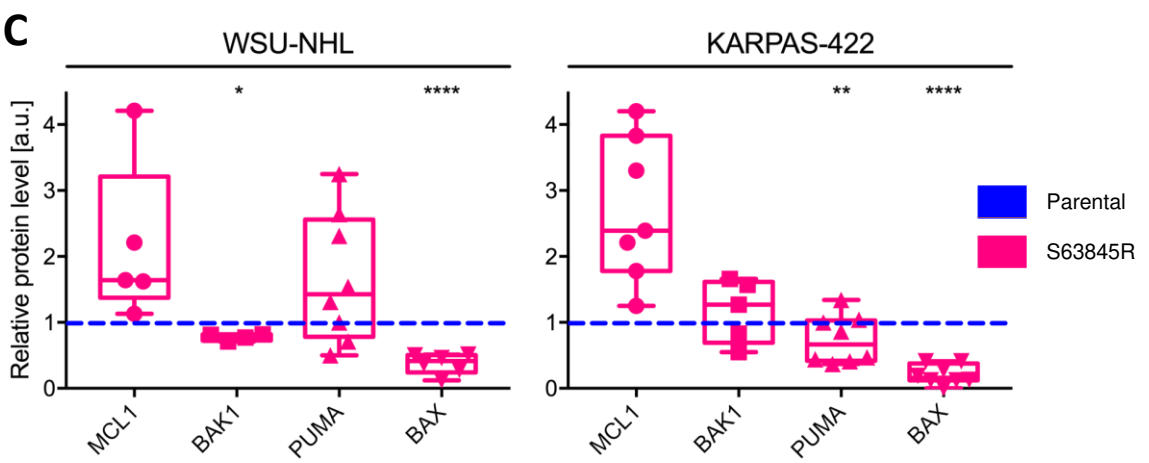
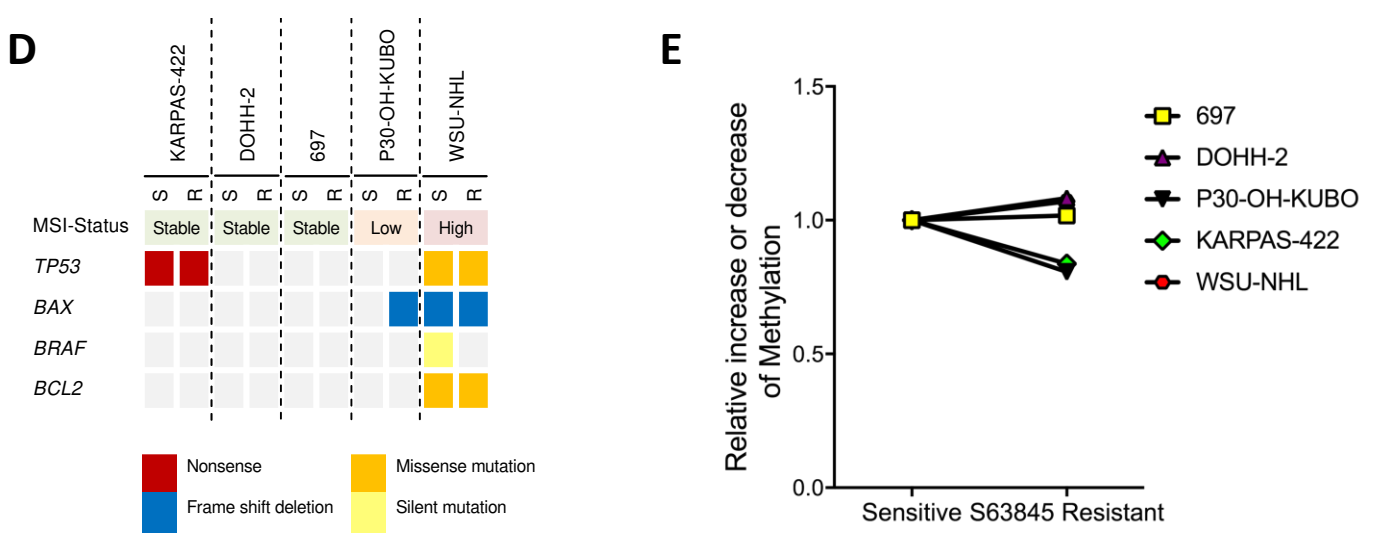


# Thomalla *et al.*, Supplementary Figure 2

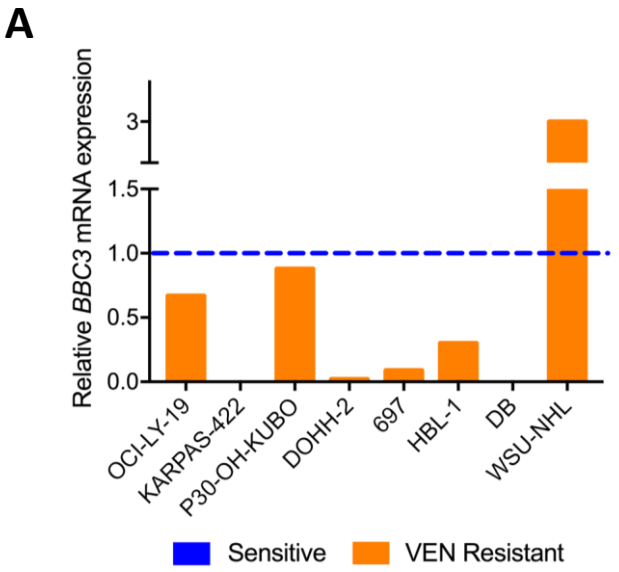


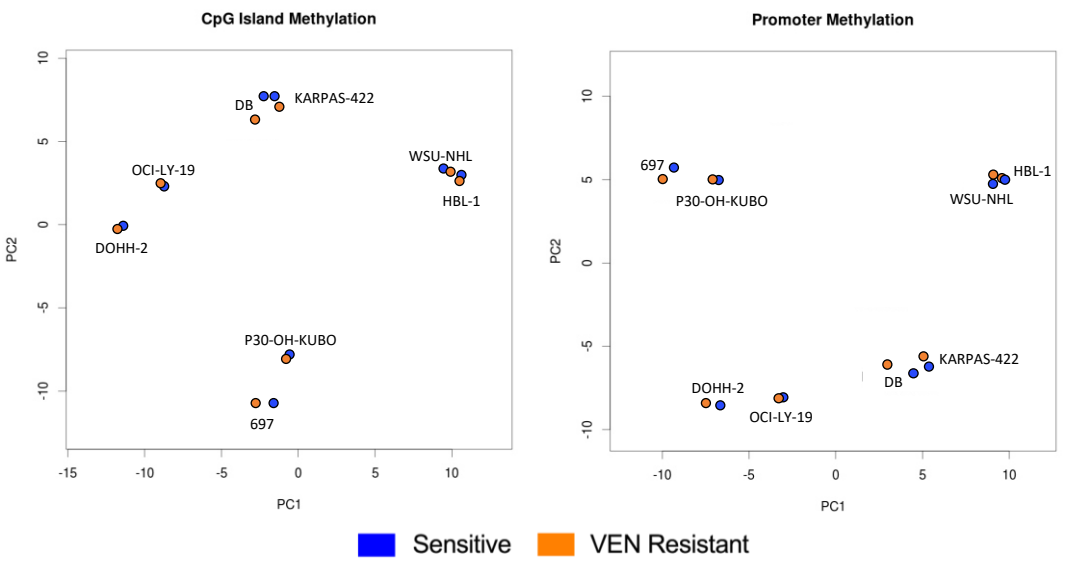



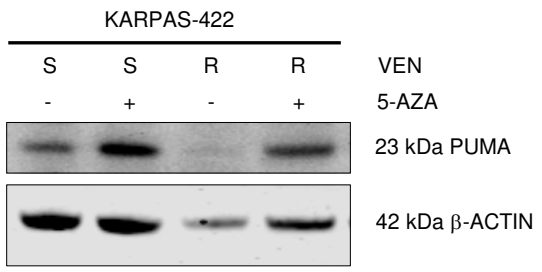



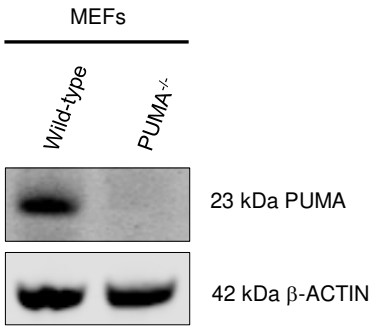



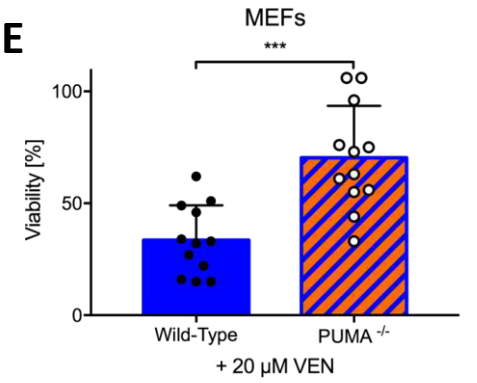
# Thomalla *et al.*, Supplementary Figure 3

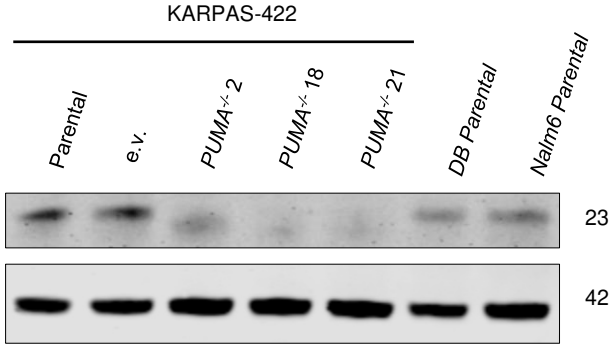


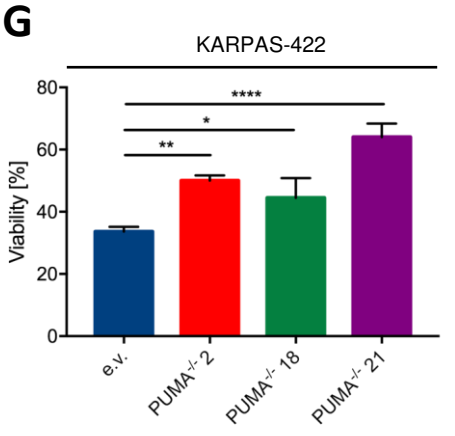



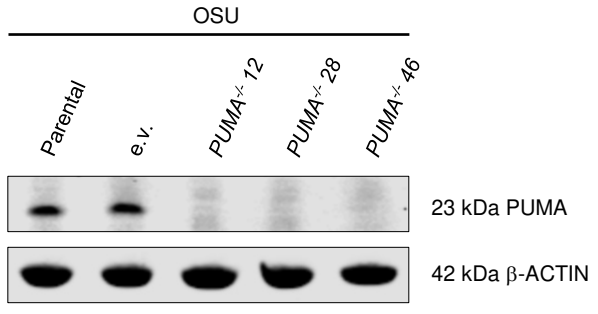



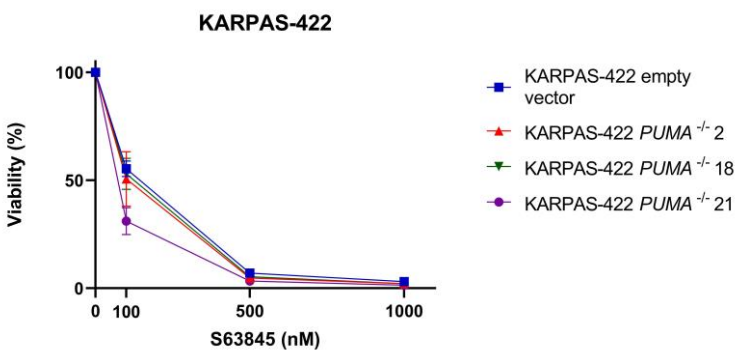



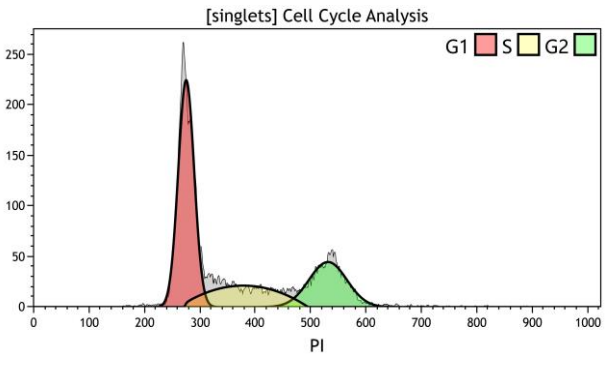



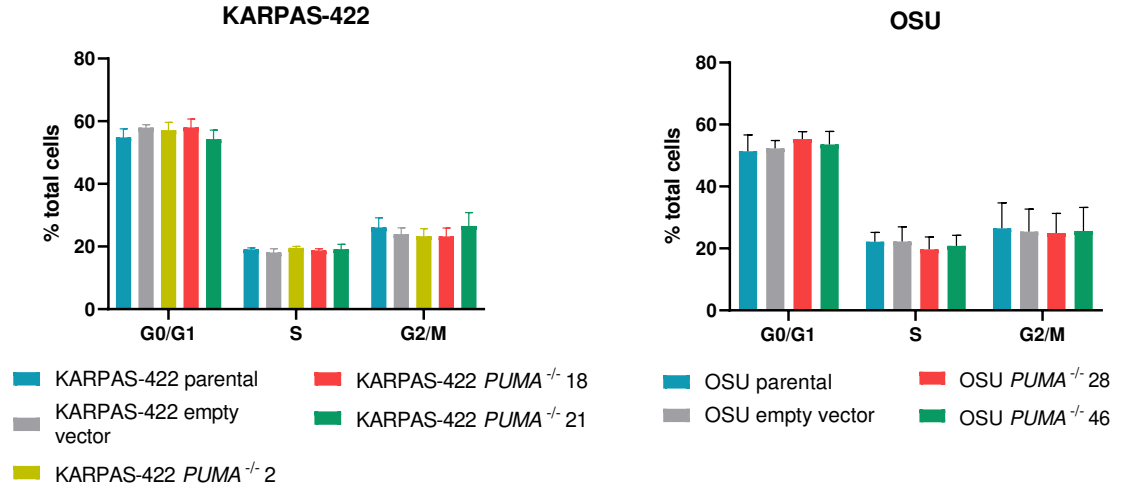




| Cell line | $IC_{50}$ [nM] VEN |
|---|---|
| e.v. | 30.08 |
| *PUMA*$^{-/-}$ 2 | 100 |
| *PUMA*$^{-/-}$ 18 | 44.30 |
| *PUMA*$^{-/-}$ 21 | 240.50 |

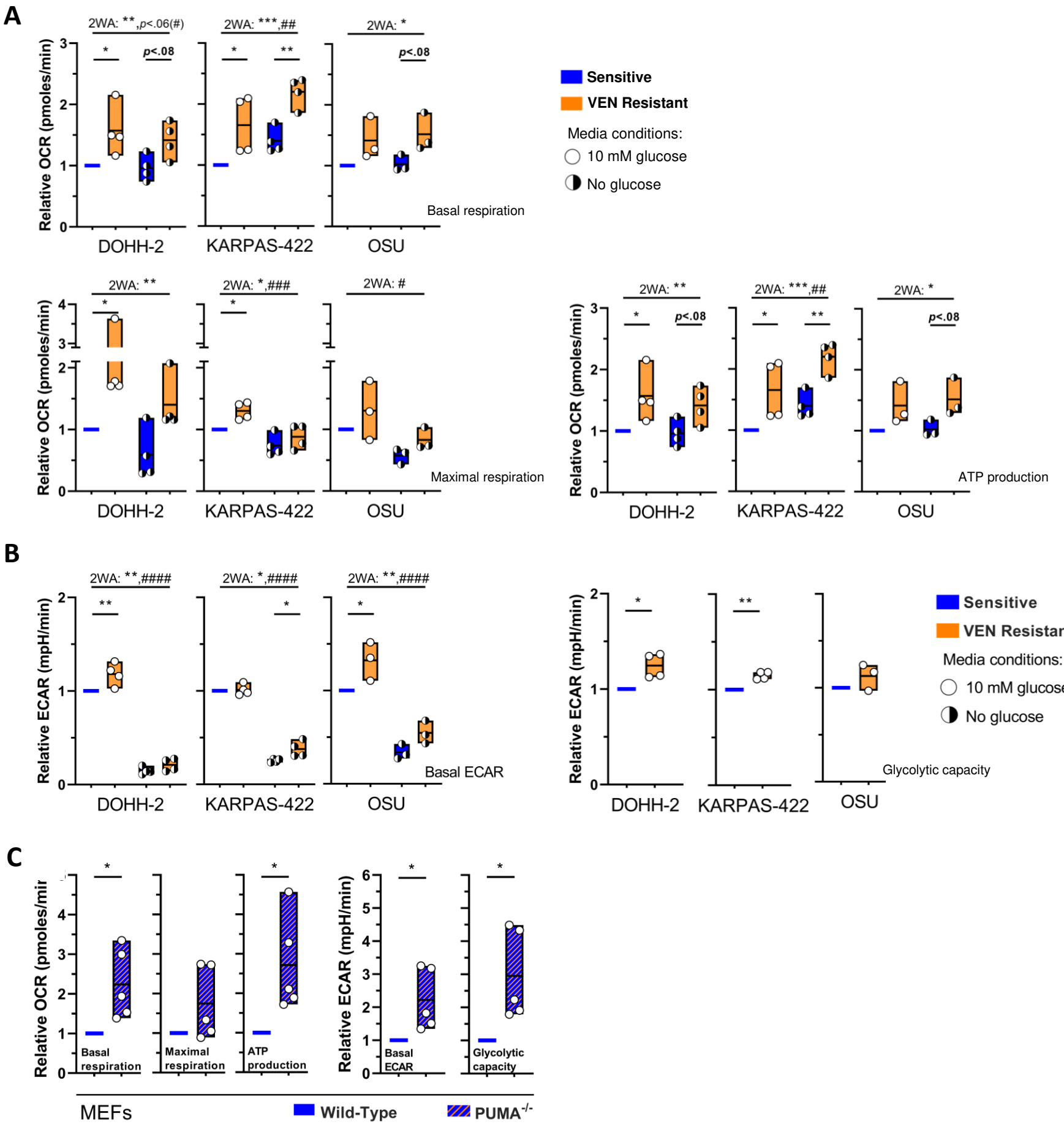


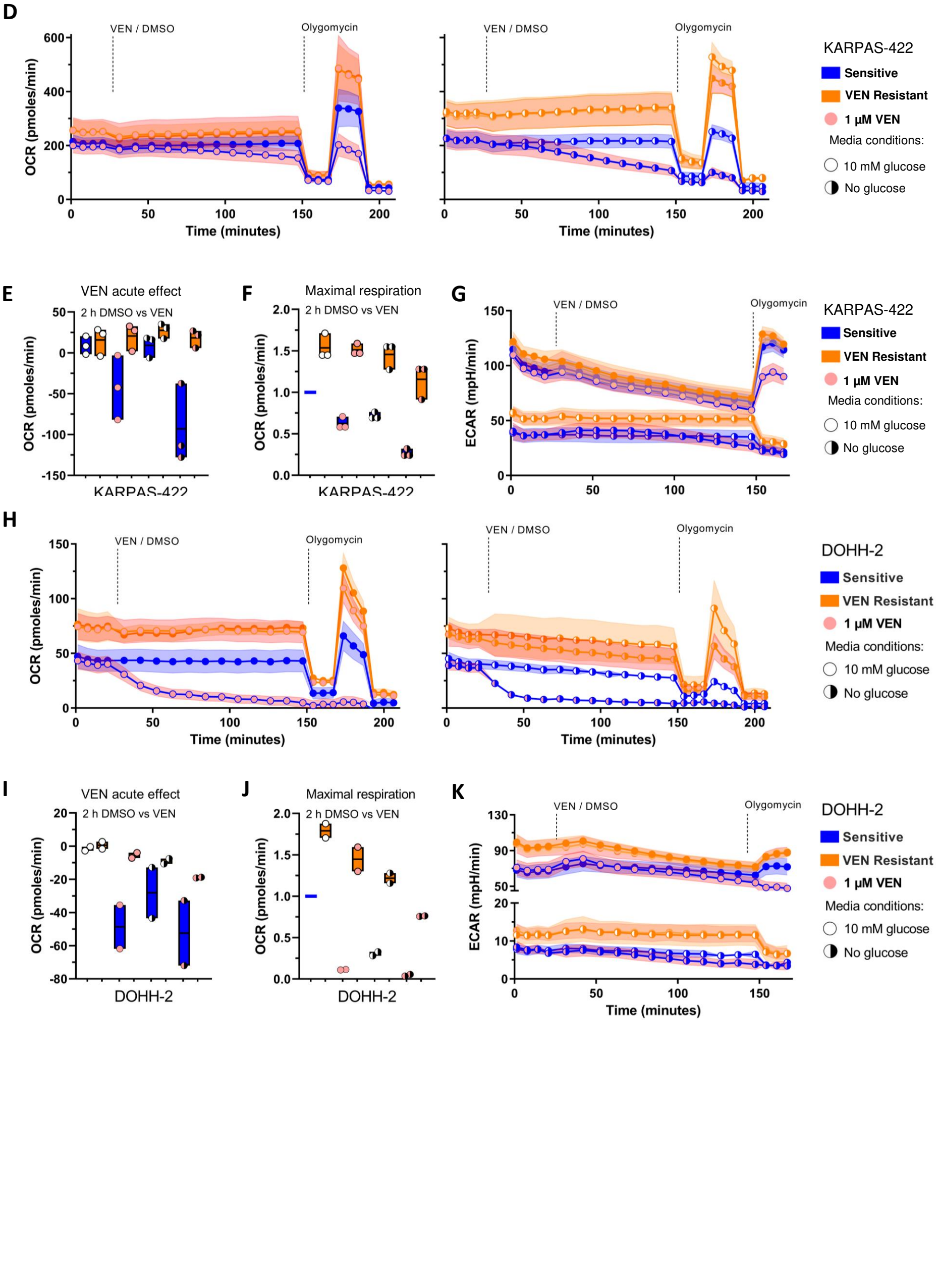



**Thomalla *et al.*, Supplementary Figure 4**



**Thomalla *et al.*, Supplementary Figure 4**

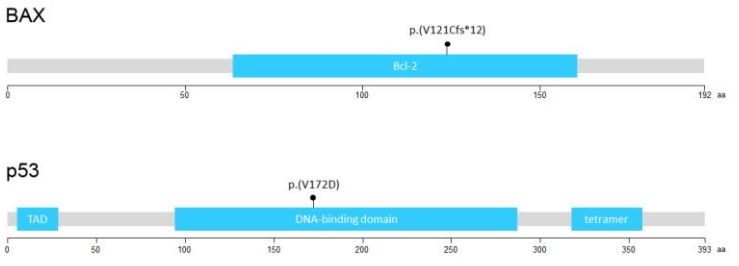


# Thomalla *et al.*, Supplementary Figure 5

**A**

| Cell line | $IC_{50}$ [nM] Sensitive | $IC_{50}$ [nM] VEN Resistant | *p*-Value |
|---|---|---|---|
| DB | 944.7 | 37.98 | 0.0024 |
| KARPAS-422 | 731.3 | 41.34 | 0.0006 |
| 697 | 254.0 | 115.6 | 0.1492 |
| DOHH-2 | 236.3 | 233.4 | 0.5361 |
| HBL-1 | >10,000 | 3842 | <0.0001 |
| WSU-NHL | 2071.0 | 2483 | ns |
| P30-OH-KUBO | 705.7 | 9380 | <0.0001 |
| Nalm6 | 8344.0 | >10,000 | ns |
| OCI-LY-19 | >10,000 | >10,000 | ns |

**B**

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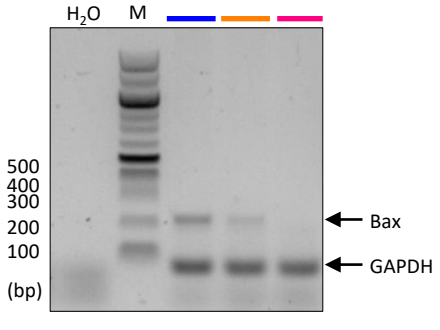
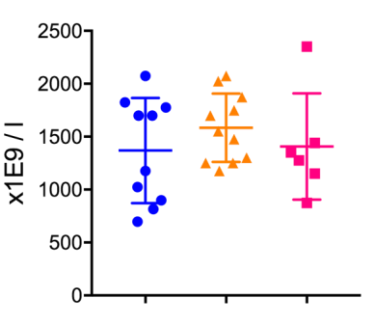



**D**

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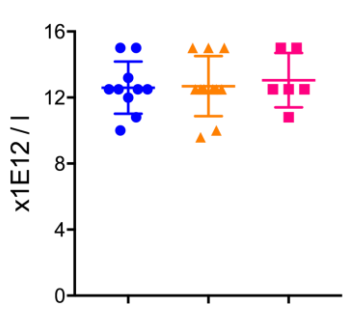
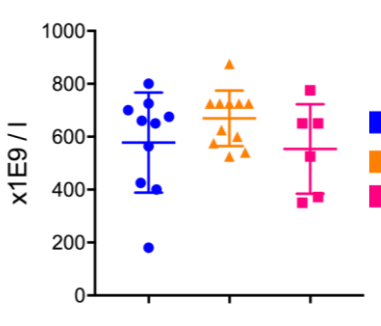
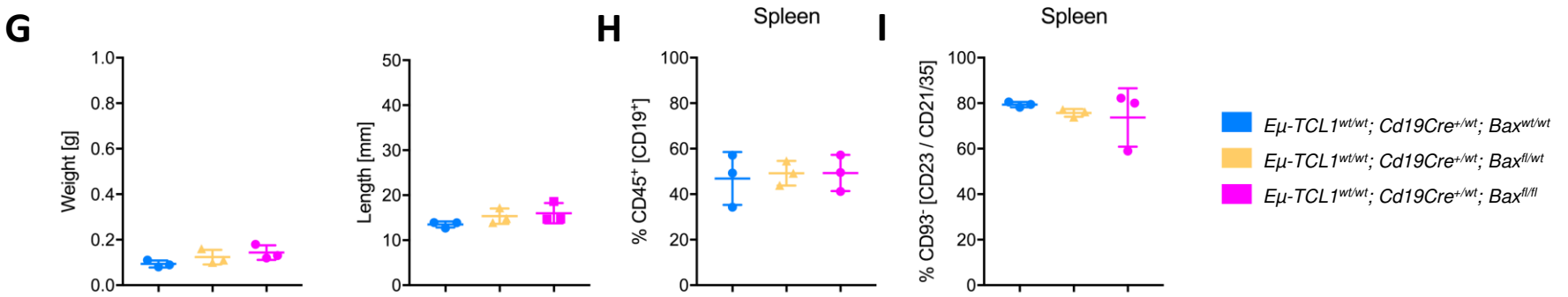
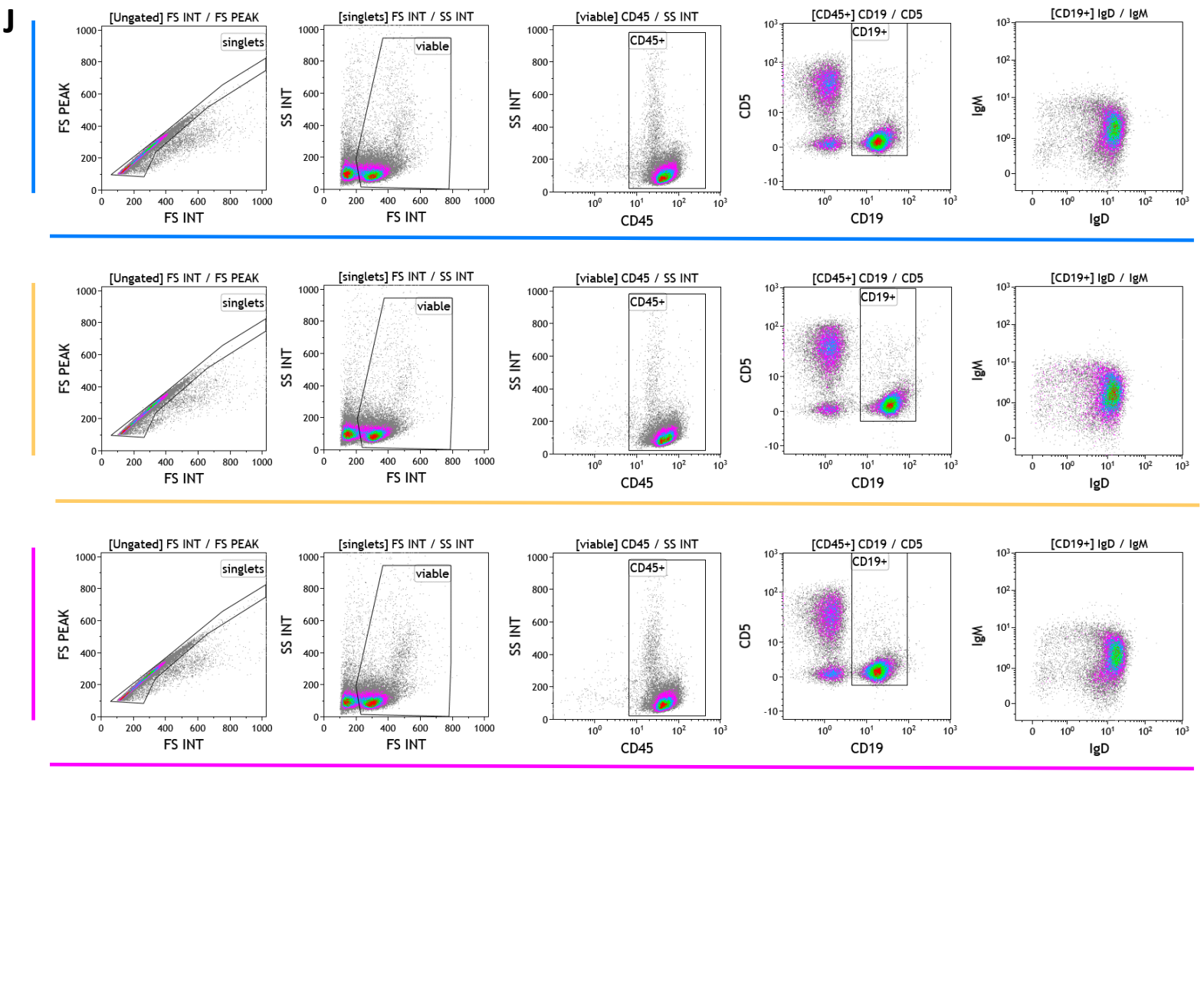



**F**

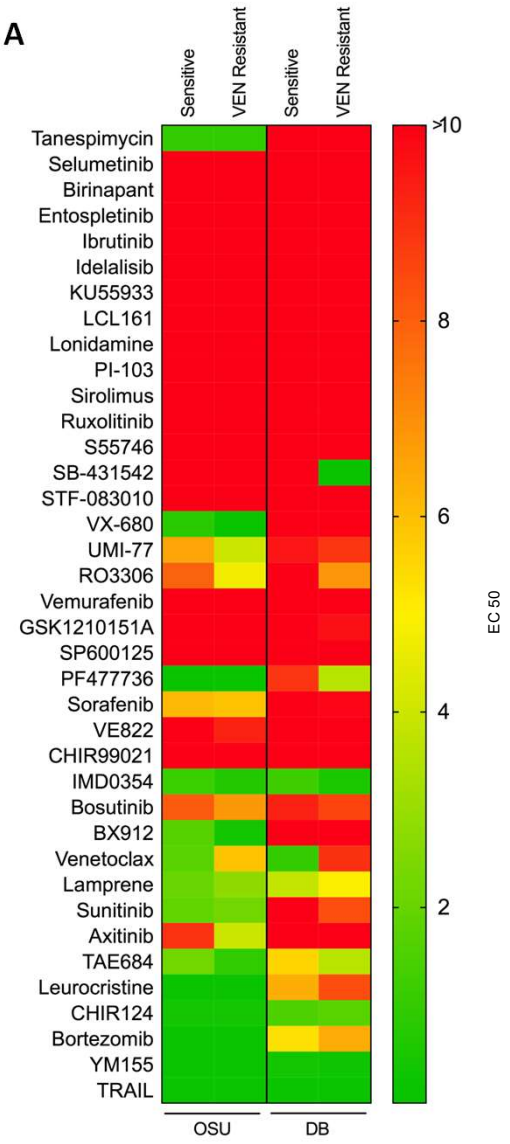


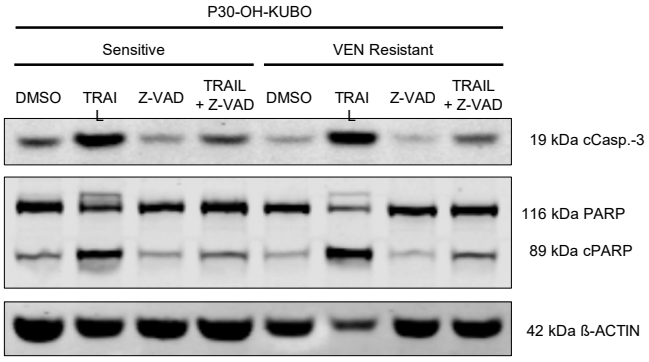
# Thomalla *et al.*, Supplementary Figure 5

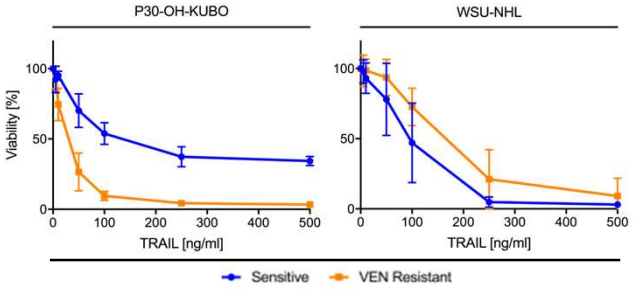


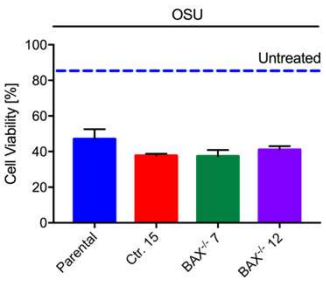



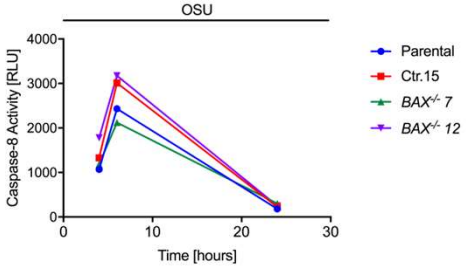
**Thomalla *et al.*, Supplementary Figure 6**



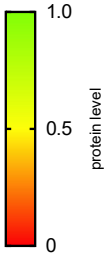



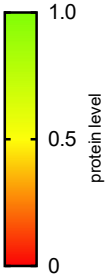

**B**

| Cell line | $IC_{50}$ [ng/mL] Sensitive | $IC_{50}$ [ng/mL] VEN Resistant | *p*-value | BAX |
|---|---|---|---|---|
| P30-OH-KUBO | 75.7 | 22.8 | 0.0023 | |
| WSU-NHL | 98.9 | 171.0 | 0.1788 | |
| Nalm6 | 58.0 | 47.8 | 0.0953 | |
| OSU *BAX* KO | >500.00 | ~ 400.00 | ns | |
| HBL-1 | 417.4 | >500.00 | 0.9979 | |
| DB | 134.8 | >500.00 | <0.0001 | |
| KARPAS-422 | 39.4 | 159.6 | 0.0002 | |
| 697 | 155.9 | 218.5 | 0.1339 | |
| OCI-LY-19 | 93.6 | >500.00 | <0.0001 | |
| DOHH-2 | 63.7 | >500.00 | 0.0011 | |
| OSU | >500.00 | >500.00 | ns | |



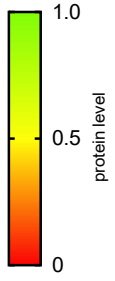

**G**

| Cell line | $IC_{50}$ [ng/mL] Sensitive | $IC_{50}$ [ng/mL] S63845 Resistant | *p*-value | BAX |
|---|---|---|---|---|
| P30-OH-KUBO | 60.44 | 29.99 | 0.0681 | |
| DOHH-2 | 55.90 | >500.00 | <0.0001 | |
| KARPAS-422 | 44.81 | 65.28 | 0.2700 | |
| 697 | 152.3 | >500.00 | <0.0001 | |
| WSU-NHL | 85.89 | 137.47 | 0.2092 | |

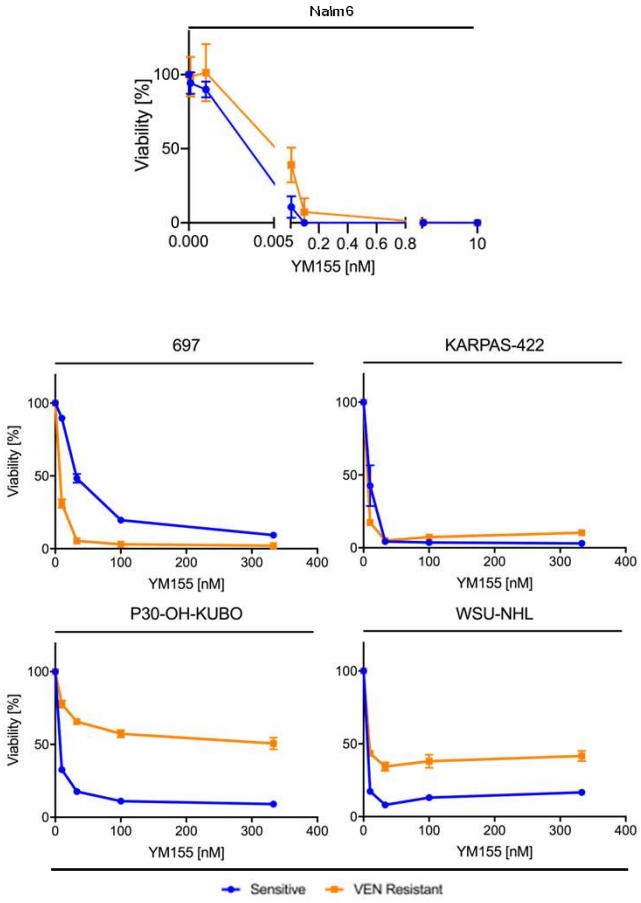


**H**

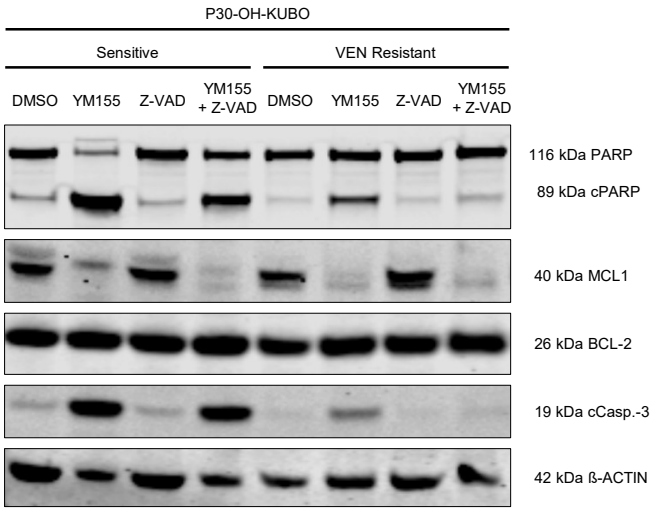
| Cell line | $IC_{50}$ [nM] Sensitive | $IC_{50}$ [nM] VEN Resistant | *p*-value | BAX |
|---|---|---|---|---|
| 697 | 35.42 | 3.97 | <0.0001 | |
| KARPAS-422 | 5.78 | 0.83 | 0.0052 | |
| P30-OH-KUBO | 3.69 | >330 | 0.021 | |
| Nalm6 | 3.21 | 7.76 | 0.1281 | |
| WSU-NHL | <0.2 | 0.3 | 0.4226 | |




**I**




**J**



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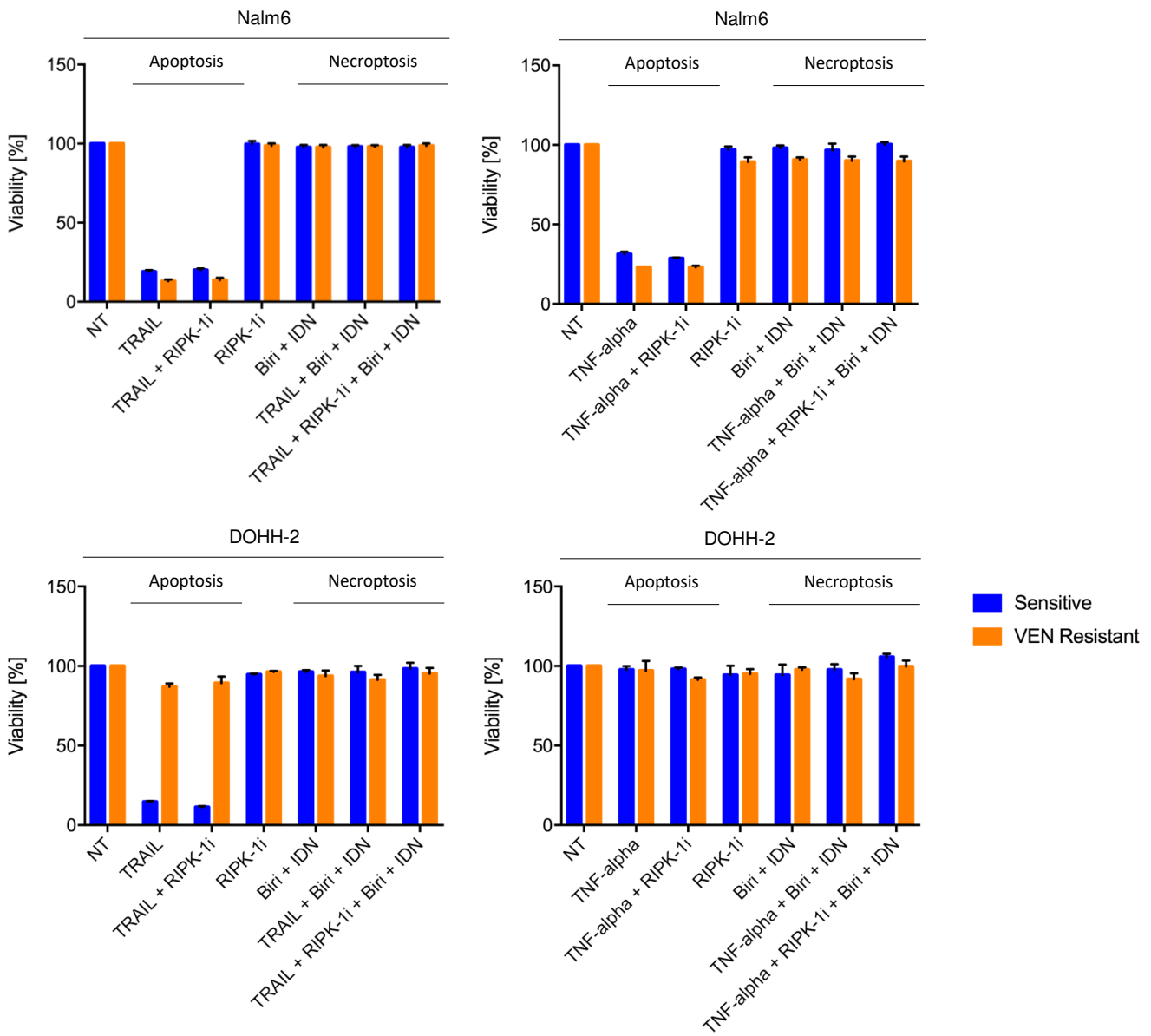

## Supplementary information

**Supplementary Table 1|** B cell lymphoma cell lines, growth medium and supplements.

| | Cell line | Initial Source | Type | Media type |
|---|---|---|---|---|
| 1 | 697 | DSMZ (No. ACC 42) | Acute lymphoblastic leukemia (ALL) | RPMI 1640 20% FBS 1% PenStrep |
| 2 | DOHH-2 | DSMZ (No. ACC 47) | Diffuse large B cell lymphoma (DLBCL) | RPMI 1640 10% FBS 1% PenStrep |
| 3 | WSU-NHL | DSMZ (No. ACC 58) | Follicular lymphoma | RPMI 1640 10% FBS 1% PenStrep |
| 4 | Nalm6 | DSMZ (No. ACC 128) | Acute lymphoblastic B cell leukemia | RPMI 1640 10% FBS 1% PenStrep |
| 5 | OCI-LY-19 | DSMZ (No. ACC 528) | B cell lymphoma unspecified | IMDM 10% FBS 1% PenStrep 50 µM β-Mercaptoethanol |
| 6 | DB | DSMZ (No. ACC 539) | Diffuse large B cell lymphoma (DLBCL) | RPMI 1640 10% FBS 1% PenStrep |
| 7 | P30-OH-KUBO | DSMZ (No. ACC 727) | Diffuse large B cell lymphoma (DLBCL) | RPMI 1640 10% FBS 1% PenStrep |
| 8 | HBL-1 | UhoC-Dr. Krause | Diffuse large B cell lymphoma (DLBCL) | RPMI 1640 20% FBS 1% PenStrep 1% GlutaMAX 50 µM β-Mercaptoethanol |
| 9 | OSU-CLL | UhoC-Dr. Krause | Chronic B cell leukemia | RPMI 1640 10% FBS 1% PenStrep |
| 10 | OSU-CLL BAX KO | UhoC-Lab of Dr. Frenzel | Chronic B cell leukemia | RPMI 1640 20% FBS 1% PenStrep |
| 11 | KARPAS-422 | Sigma-Aldrich (No. 06101702) | Diffuse large B cell lymphoma (DLBCL) | RPMI 1640 20% FBS 1% PenStrep 1% GlutaMAX |
| 12 | MEF wild-type | UoC-Prof. Dr. Hamid Kashkar | Mouse Embryonic Fibroblast (MEF) | DMEM 10% FBS 1% PenStrep 1% |

| | | | | |
|---|---|---|---|---|
| | | | | NAA 50 µM β-Mercaptoethanol |
| 13 | MEF PUMA$^{-/-}$ | UoC-Prof. Dr. Hamid Kashkar | Mouse Embryonic Fibroblast (MEF) | DMEM 10% FBS 1% PenStrep 1% NAA 50 µM β-Mercaptoethanol |
| 14 | HEK293 | DSMZ (No. ACC 305) | Embryonal kidney | DMEM 10% FBS 1% PenStrep |
| 15 | HeLa | DSMZ (No. ACC 57) | Cervix carcinoma | RPMI 1640 10% FBS 1% PenStrep |

**Supplementary Table 2|** Compounds screened in B cell lymphoma cell lines.

| **Name** | **Other Name** | **Drug Target** | **Company** | **Catalog No.** |
|---|---|---|---|---|
| 17-AAG | Tanespimycin, CP127374, NSC-330507 | HSP90 | Selleckchem | S1141 |
| ABT-199 | VEN, GDC-0199 | BCL2 | Abbvie/Selleckchem | S8048 |
| Axitinib | AG 013736 | PDGFR | Selleckchem | S1005 |
| Bortezomib | PS-341, LDP-341, MLM341 | 20S proteasome | Selleckchem | S1013 |
| Bosutinib | SKI-606 | Src | Selleckchem | S1014 |
| BX-912 | CAS702674-56-4 | PDK1 | Selleckchem | S1275 |
| CHIR-124 | CAS 405168-58-3 | Chk1 | Selleckchem | S2683 |
| CHIR-99021 | CT99021 | GSK-3α/β | Selleckchem | S2924 |
| Clofazimine | Lamprene, ATC J04BA01 | Potassium Channel KV1.3 | Selleckchem | S4107 |
| Etoposide | VP-16, VP-16213 | Topoisomerase II | Selleckchem | S1225 |
| GSK1210151A | I-BET151 | BRD 2,3,4 (BET) | Selleckchem | S2780 |
| Ibrutinib | PCIU-32765, | BTK | Selleckchem | S2680 |

| | | | | |
|---|---|---|---|---|
| | PCI-32765 | | | |
| Idelalisib | CAL-101, GS-1101 | p110δ | Selleckchem | S2226 |
| IMD0354 | CAS 978-62-1 | NF-κB | Selleckchem | S2864 |
| KU-55933 | CAS 587871-26-9 | ATM Kinase | Selleckchem | S1092 |
| LCL161 | CAS 1005342-46-0 | IAPs (i.e. XIAP, c-IAP) | Selleckchem | S7009 |
| Lonidamine | CAS 50264-69-2, AF1890 | Hexokinase | Selleckchem | S2610 |
| OSI-906 | Linsitinib | IGF-1R | Selleckchem | S1091 |
| PF477736 | PF-736, PF-00477736 | Chk1 (and Chk2 with lower affinity) | Selleckchem | S2904 |
| RO3306 | CAS 872573-93-8 | CDK1 | Selleckchem | S7747 |
| SB-431542 | CAS 301836-41-9 | ALK5 | Selleckchem | S1067 |
| Sorafenib | Bay 43-9006 | Raf-1, B-Raf, VEGFR-2 | Selleckchem | S1040 |
| SP600125 | CAS 129-56-6 | JNK (1,2,3) | Selleckchem | S1460 |
| Sunitinib | SU11248 | PDGFRβ, VEGFR-2 (Flk-1) | Selleckchem | S7781 |
| TAE684 | NVP-TAE684 | ALK | Selleckchem | S1108 |
| Trabectedin | Ecteinascidin 743, ET-743 | FUS-CHOP DNA Binding Blocker | Pharma Mar S.A. Colmenar Viejo, Spain | 5704993 |
| VE-822 | CAS 1232416-25-9 | ATR | Selleckchem | S7102 |
| Vemurafenib | PLX4032, RG7204, RO5185426 | B-Raf$^{V600E}$ | Selleckchem | S1267 |
| Vincristine | Leurocristine | Tubulin | Selleckchem | S1241 |
| VX-680 | Tozasertib, MK-0457 | pan-Aurora (mostly Aurora-A) | Selleckchem | S1048 |
| YM155 | Sepantronium Bromide | Survivin | Selleckchem | S1130 |
| STF-083010 | CAS 307543-71-1 | IRE | Sigma | SML0409 |

| | | | | |
|---|---|---|---|---|
| A-1210477 | CAS 1668553-26-1 | Mcl-1 | Selleckchem | S7790 |
| UMI-77 | CAS 518303-20-3 | Mcl-1 | Selleckchem | S7531 |
| Rapamycin | Sirolimus | mTOR | Selleckchem | S1039 |
| ABT-737 | CAS 724741-75-7 | Bcl-2 | Selleckchem | S1002 |
| AZD6244 | Selumetinib | MEK1 | Selleckchem | S1008 |
| Birinapant | TL32711 | cIAP1 | Selleckchem | S7015 |
| Entospletinib | GS-9973 | Syk | Selleckchem | S7523 |
| PI-103 | CAS 371935-74-9 | PI3K | Selleckchem | S1038 |
| Ruxolitinib | INCB018424 | JAK1/2 | Selleckchem | S1378 |
| SGX-523 | CAS 1022150-57-7 | c-Met | Selleckchem | S1112 |
| TRAIL | TRAIL | TRAIL Ligand | Enzo Life Sciences | ALX-201-115 |
| S63845 | CAS 1799633-27-4 | Mcl-1 | APExBIO | A8737 |

**Supplementary Table 3|** Calibration data set for MeDIP-seq analysis:

| **No** | **Accession cell line** |
|---|---|
| **1** | GSM1669740 DOHH-2 |
| **2** | GSM1669727 DB |
| **3** | GSM1669976 KARPAS-422 |
| **4** | GSM1670327 P30-OH-KUBO |
| **5** | GSM1670583 WSU-NHL |
| **6** | GSM1669562 697 |
| **7** | GSM1670298 OCI-LY-19 |

**Supplementary Table 4: Results from WES VEN sensitive and resistant cell lines**

| PAT_ID | Mut_ID | Target_Name | Gene_ Hugo | Chromo some | Strand | Transcript | CCDS_ID | Wild type | Mutant | Type_1 | Type_ 2 | Change_cDNA | Change_ Protein | Allelic_ Fraction_ Tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DB-S | DB-S_chr17:7577538_DNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | CG | TA | nonsense | DNM | c.742_743delins TA | p.R248* | 0.510656 |
| DB-R | DB-R_chr17:7577538_DNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | CG | TA | nonsense | DNM | c.742_743delins TA | p.R248* | 0.509218 |
| HBL-1-S | HBL-1-S_chr17:7578460_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | A | G | missense | SNM | c.470T>C | p.V157A | 0.985915 |
| HBL-1-R | HBL-1-R_chr17:7578460_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | A | G | missense | SNM | c.470T>C | p.V157A | 1 |
| Oci-Ly-19-R | Oci-Ly-19-R_chr18:60985514_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | C | A | missense | SNM | c.386G>T | p.R129L | 0.236893 |
| Oci-Ly-19-R | Oci-Ly-19-R_chr18:60985588_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | G | C | missense | SNM | c.312C>G | p.F104L | 0.49 |
| Oci-Ly-19-R | Oci-Ly-19-R_chr18:60985591_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | G | T | missense | SNM | c.309C>A | p.D103E | 0.484746 |
| Karpas-422-S | Karpas-422-S_chr17:7576891_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | T | A | nonsense | SNM | c.955A>T | p.K319* | 0.978723 |
| Karpas-422-R | Karpas-422-R_chr17:7576891_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | T | A | nonsense | SNM | c.955A>T | p.K319* | 1 |
| HBL-1-R | HBL-1-R_chr19:49458844_DEL | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | T | - | frameshift_del | DEL | c.74delT | p.L25fs | 0.15625 |
| P30-OH-KUBO-R | P30-OH-KUBO-R_chr19:49458971_INS | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | - | G | frameshift_ins | INS | c.113_114insG | p.M38fs | 0.424658 |
| WSU-NHL-S | WSU-NHL-S_chr19:49458971_DEL | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frameshift_del | DEL | c.114delG | p.M38fs | 0.435233 |
| WSU-NHL-R | WSU-NHL-R_chr19:49458971_DEL | entg\|BAX:ccds\|CCDS12742.1 | CLDN6 | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frameshift_del | DEL | c.114delG | p.M38fs | 0.478673 |
| WSU-NHL-R | WSU-NHL-R_chr1:150551568_SNM | entg\|MCL1:ccds\|CCDS956.1 | MCL1 | chr1 | - | NM_021960 | CCDS957.1 | C | T | missense | SNM | c.439G>A | p.V147I | 0.449495 |
| WSU-NHL-S | WSU-NHL-S_chr18:60985890_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | C | T | missense | SNM | c.10G>A | p.A4T | 0.497006 |
| WSU-NHL-R | WSU-NHL-R_chr18:60985890_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | C | T | missense | SNM | c.10G>A | p.A4T | 0.537736 |
| WSU-NHL-S | WSU-NHL-S_chr17:7577538_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | C | T | missense | SNM | c.743G>A | p.R248Q | 1 |
| WSU-NHL-R | WSU-NHL-R_chr17:7577538_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | C | T | missense | SNM | c.743G>A | p.R248Q | 1 |
| Nalm6-R | NAL2_chr6:33541962_SNM | entg\|BAK1:ccds\|CCDS4781.1 | BAK1 | chr6 | - | NM_001188 | CCDS4781.1 | C | T | missense | SNM | c.380G>A | p.R127H | 0.585366 |
| Nalm6 -S | NAL2_chr6:33541962_SNM | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frame_shift_del | DEL | c.114delG | p.M38fs | 0,4 |
| Nalm6-R | NAL2_chr6:33541962_SNM | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frame_shift_del | DEL | c.114delG | p.M38fs | 0,88 |

**Supplementary Table 5: Results from WES S63845 sensitive and resistant cell lines**

| ID | Mut_ID | Target_Name | Gene_ Hugo | Chromo some | Strand | Transcript | CCDS_ID | Wild type | Mutant | Type_1 | Type_ 2 | Change_cDNA | Change_ Protein | Allelic_ Fraction_ Tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P30 OH KUBO-R | DT-MR4_chr19:49458971_DEL | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frame_shift_del | DEL | c.114delG | p.M38fs | 0.508621 |
| Karpas422-R | DT-MR6_chr17:7576891_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | T | A | nonsense | SNM | c.955A>T | p.K319* | 1 |
| Karpas422-S | DT-S6_chr17:7576891_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | T | A | nonsense | SNM | c.955A>T | p.K319* | 1 |
| WSU NHL-R | DT-MR5_chr17:7577538_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | C | T | missense | SNM | c.743G>A | p.R248Q | 0.980769 |
| WSU NHL-R | DT-MR5_chr18:60985890_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | C | T | missense | SNM | c.10G>A | p.A4T | 0.410072 |
| WSU NHL-R | DT-MR5_chr19:49458971_DEL | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frame_shift_del | DEL | c.114delG | p.M38fs | 0.806283 |
| WSU NHL-S | DT-S5_chr17:7577538_SNM | entg\|TP53:ccds\|CCDS11118.1 | TP53 | chr17 | - | NM_000546 | CCDS11118.1 | C | T | missense | SNM | c.743G>A | p.R248Q | 1 |
| WSU NHL-S | DT-S5_chr18:60985890_SNM | entg\|BCL2:ccds\|CCDS11981.1 | BCL2 | chr18 | - | NM_000633 | CCDS11981.1 | C | T | missense | SNM | c.10G>A | p.A4T | 0.553846 |
| WSU NHL-S | DT-S5_chr19:49458971_DEL | entg\|BAX:ccds\|CCDS12742.1 | BAX | chr19 | + | NM_004324 | CCDS12744.1 | G | - | frame_shift_del | DEL | c.114delG | p.M38fs | 0.458333 |
| WSU NHL-S | DT-S5_chr7:140487358_SNM | entg\|BRAF:ccds\|CCDS5863.1 | BRAF | chr7 | - | NM_004333 | CCDS5863.1 | A | G | silent | SNM | c.1167T>C | p.R389R | 0.243902 |