## Supplementary Methods:

### Collection and processing of primary normal CD34$^+$ and DLBCL cells

Normal human bone marrow mononuclear cells were obtained with informed consent from the bone marrow of patients undergoing routine bone marrow aspirations for non-myeloid hematologic disorders. These studies have been approved by the Investigational Review Board of Virginia Commonwealth University (IRB #HM-12443). CD34$^+$ cells were isolated using an immunomagnetic bead separation technique. CD34$^+$ cells were then suspended in RPMI1640 medium containing 10% FCS and exposed to agents as in the case of continuously cultured cell lines. Parallel studies were performed in primary DLBCL cells obtained from the bone marrow of 2 patients with DLBCL and extensive marrow infiltration (>70%) (IRB #MCC-03340).

### Generation of bortezomib resistant DLBCL Cells

Bortezomib-resistant SUDHL16-10BR (GC) and OCI-LY10-40BR (ABC), were generated by exposing the respective parental cells to progressively increasing concentrations of bortezomib starting at 1.0 nM. Once cells developed resistance to bortezomib, they were cultured in the absence of drug for two weeks prior to experiments. Multiple studies documented the persistence of drug resistance under these conditions.

### Transient transfection

Transient transfection of SUDHL4 cells employed an Amaxa Nucleofector shuttle apparatus (Cologne, Germany) using DN-100 protocols using transfection kit SG (from Amaxa, Germany). Briefly, cells were cultured for 2 days prior to transfection but not allowed to grow beyond a concentration of 5 x $10^5$ cells/ml before transfection. One

million cells were pelleted by centrifugation and resuspended in 20 ul of transfection reagent SG after which 1.0 ug of DNA was added. Resuspended cells in medium containing DNA were transferred to a 96-well nucleo-cuvette module and transfected as per protocol DN-100 using the Amaxa shuttle instrument. To transfected cells, 80µl of fresh media was added, following by incubation for 15mins. Cells were then transferred to 12 well plates, resuspended in 2.0 ml medium, and subjected to drug treatment after 48 hrs

**Detection of Bax/BAK conformational change**

Drug treated cells were subjected to cellular fractionation as previously described [26]. Mitochondria-rich fractions were prepared, washed with $Ca^{2+}$/$Mg^{2+}$ free PBS, lysed with Chaps lysis buffer (10mM Hepes, pH 7.4, 150 mM NaCl, 1% chaps, 1mM DTT), and supplemented with protease and phosphatase inhibitors. Two miligrams of anti–Bax (6A7) monoclonal antibody were pre-incubated with 30ul of Dynabeads for 2 hrs. at $4^0$C on a rotor. A total of 500-1000µg of protein was then added to the anti-Bax antibody loaded with dynabeads and maintained on a rotor for overnight at $4^0$C. Dynabeads were then collected utilizing a Dynal Magnetic Particle concentrator and washed four times with Chaps lysis buffer. Conformationally changed Bax protein was eluted from the dynabeads by heating with 4x protein gel loading buffer (Invitrogen) and subjected to Western blotting.

**Detection of Bax oligomerization**

Cells were treated with various agents for the indicated interval and then pelleted by centrifugation at 600g. The mitochondria-rich fragment was prepared and re-suspended with 2mM of DSP cross-linker prepared in DMSO and incubated for 0.5-1 hr. at room temperature to allow cross-linking to take place. The cross-linking reaction was terminated by adding Tris –HCl to a final concentration of 20mM and further incubated for 15 min. at room temperature. The mitochondrial pellet was separated by centrifugation at 10000g for 30 min and re-dissolved in Chaps lysis buffer and subjected to western blotting [26].

**NF-κB Activity**

Nuclear protein was extracted using a Nuclear Extract Kit (Active Motif, CA). NF-κB activity was determined by enzyme linked immunosorbent assay (ELISA) Kit TransAM NF-κB p65 Transcription Factor Assay Kit (Active Motif), according to the manufacturer's instructions.

**Formulation and dosing of drugs *in vivo***

Stock carfilzomib was dissolved in 10% sulfobutylether betacyclodextrin in 10mM citrate buffer pH 3.5. Stocks were stored in -80$^0$C in small aliquots and diluted before injection by IV route BIW as described earlier [13]. Obatoclax was prepared by adding 5 mL of 5% dextrose solution to the 30 mg bottle, which was vortexed until drug was dissolved, after which 5 mL of the supplied diluent was added to the bottle and vortexed again until mixed. Final stock solutions were 3 mg/mL. Volumes for injection were 60 uL, and the drug stock was further diluted with 5% dextrose to attain the desired dose before injection by the intramuscular route TIW.

**WBC counts**

10 uL of blood was collected and mixed with 950 uL of the Nerl Diluent 2 (Coulter Counter diluent). 4 drops of Zap-oglobin were added and cells were enumerated using Profile C (set to count 10 uL of blood between 4 and 8 microns).