**Supplementary Materials and Methods**

*Cell cycle analysis, viability determination, and annexin V staining*

Following compound treatment, cells were fixed, permeablized, and stained with propidium iodide as described ([1](#_ENREF_1)). Viable cells (cells in G0/G1, S, and G2/M) were counted and normalized as indicated to obtain % growth. Apoptosis was assessed by counting cells with sub G1 DNA content or staining with fluorescently labeled Annexin V/PI (Trevagen) according to the manufacturer’s instructions.

*Gene expression profiling*

Total RNA was prepared from treated cells using a Qiagen RNEasy mini kit with on column DNAse digestion. RNA sequencing and alignments were performed at Ocean Ridge Biosciences. For q-RTPCR, first strand cDNA was prepared using SuperScript III RT according to manufacturer’s instructions, and qPCR was performed using UPL primer/probe combinations from Roche. Primer sequences are available upon request.

For quantification of the effect of CPI203 treatment on the expression of apoptotic genes, each cell line received a score of 1 for each pro-apoptotic gene that was up-regulated at least 2-fold and for each anti-apoptotic gene that was down-regulated at least two fold. The sum across all of the genes was defined as the composite gene score for each cell line.

*Lentiviral shRNA transduction*

Lentiviral shRNA constructs targeting *BCL2L1* and *BCL2* were obtained from Sigma. *BCL2L1* shRNA1 and shRNA2 correspond to Sigma TRC numbers TRCN0000033499 and TRCN0000033500 (target sequences available at Sigma website). *BCL2* shRNA1 and shRNA2 correspond to TRC numbers TRCN0000286223 and TRCN0000293675. Generation of virus particles and transduction were performed according to manufacturer’s instructions.

*Comparison of apoptotic and cell cycle arrest response with GI50*

Cell lines were treated with CPI203 for 4 d, and viability was assessed using resazurin (Sigma). GI50 values were calculated as the concentration at which fluorescence reached 50% of the DMSO control. Cell lines were classified as sensitive if they had a GI50 value of less than or equal to 0.25 M, and insensitive if they had a GI50 of greater than 0.25 M. Following cell cycle analysis, the percentage of cells with subG1 or G0/G1 DNA content in DMSO was subtracted from the value at 0.25 M to obtain the % subG1 and % G1 increase for each cell line. The median of the values across all of the cell lines was calculated, and the number of standard deviations of the values in each cell line were determined as Z subG1 and Z G1 increase. Data were plotted and analyzed with GraphPad Prism.

*BH3 profiling*

BH3 profiling using JC-1 fluorescence was performed as described ([2](#_ENREF_2)). BH3 only peptides were obtained from Anaspec (BIM:cat#62439, BAD: cat#64082) or Abgent (HRK: cat#SP1016a). Fluorescence readings were acquired at 0, 30, 60, 90, 120, 180, and 240 minutes, and total fluorescence was calculated using the AUC function in GraphPad Prism. Calculations of % depolarization were carried out as described previously ([2](#_ENREF_2)).

*Western blotting*

Cells were lysed in RIPA buffer + EDTA (Boston Bioproducts) with protease inhibitor cocktail (Roche), or were boiled in 2x SDS PAGE sample buffer. Lysates were subjected to SDS PAGE and Western blotting with anti-BCL2L1 (Abcam), anti-BCL2 (Sigma), anti-GAPDH (Ambion), or anti-beta-actin (Ambion). For the determination of BCL2 and BCL2L1 levels in a panel of cell lines, 50 g of lysate for each cell line was subjected to SDS-PAGE, with recombinant C-terminally truncated BCL2 (Sigma, 10 or 50 ng) or BCL2L1 (Sigma, 0.5 ng and 2 ng) on the same gel for normalization. Expression levels (ng per g of lysate) from normalization with the two amounts of recombinant protein were averaged to obtain a final value.

*Compounds*

Cytarabine and doxorubicin were obtained from Sigma. (+)-JQ1 was obtained from Selleck Chemicals.

**References**

1. Mertz JA*, et al.* (2011) Targeting MYC dependence in cancer by inhibiting BET bromodomains. *Proceedings of the National Academy of Sciences of the United States of America* 108(40):16669-16674.

2. Ryan J & Letai A (2013) BH3 profiling in whole cells by fluorimeter or FACS. *Methods* 61(2):156-164.