

## Description of Additional Supplementary Files

**File Name:** Supplementary Data 1

**Details:** List of all cell lines used in study

**File Name:** Supplementary Data 2

**Details:** Linear regression analysis to determine if tissue of origin or mutation status better predicts BCL-2 gene dependencies.

**File Name:** Supplementary Data 3

**Details:** BCL-2 family gene expression correlates of BCL-2, BCL-X<sub>L</sub>, or MCL-1 dependency. A linear regression analysis was performed to compare the BCL-2 gene expression data to BCL-2, BCL-X<sub>L</sub>, or MCL-1 dependencies. The effect size and p-values are plotted here.

**File Name:** Supplementary Data 4

**Details:** Results from a pooled negative-selection CRISPR screen for sensitizers to BCL-X<sub>L</sub> + MCL-1 co-inhibition in the resistant cell line TYKNU. The CRISPR library is shown, as well as the depletion scores (based on the 3-scores) for each replicate. Genes are then ranked based on average depletion scores from the 2 replicates, and the genes shown in red were selected for further validation.

**File Name:** Supplementary Data 5

**Details:** Phenotypic outlier cell lines have outlying expression levels of response modifying BCL-2 genes. Fifteen cell lines from 9 different tissue types were noted to have BCL-2 gene dependency data that stood out as unique compared to the other cell lines from the same tissue. In addition, the expression levels of certain BCL-2 genes from these cell lines were also unique compared to the average expression levels from the same tissues. The unique phenotypes and possible molecular explanations are included in the table.

**File Name:** Supplementary Data 6

**Details:** List of all shRNA and CRISPR sequences used in study.