

Supplemental Information

Venetoclax is effective in small cell lung cancers with high BCL-2 expression

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Supplemental Figure 1. Venetoclax sensitivity and BCL-2 mRNA correlation analysis.

(A) LN IC₅₀ waterfall plot of 26 tumor types from Fig. 1A. (B) Correlation analysis of *BCL2* mRNA expression from the GDSC compared to venetoclax sensitivity, plotted as AUC vs *BCL2* mRNA (left panel) or LN IC₅₀ vs *BCL2* mRNA (right panel). Linear regression is plotted as a red line. Correlation was determined using Spearman's correlation.

Supplemental Figure 2. Cell viability assays of border line venetoclax-sensitive and -resistant SCLC cell lines and combination of venetoclax with chemotherapy.

5-day CellTiter-Glo assays were performed on the sensitive (AUC=0.965) NCI-H187 cell line (A), and the resistant (AUC=0.987) NCI-H525 cell line (B). Error bars are plotted as standard error. (C) A dose matrix of Venetoclax and the combination of Cisplatin and Etoposide was performed on the venetoclax-sensitive DMS-53 cell line, venetoclax-resistant, low BCL-2 NCI-H2171 and NCI-H82 cell lines, and the venetoclax-resistant high BCL-2 NCI-H1048, NCI-H1688, and NCI-H211 cell lines (displayed concentrations are μ M). Percent of the excess over the Bliss at each dose of the drug is presented. Bliss scores greater than zero, close to zero, and less than zero represent synergy, additivity, and antagonism, respectively.

Supplemental Figure 3. Correlation analysis of BCL-2 family members to venetoclax sensitivity in SCLC cell lines.

Correlation analysis of *PMAIP1* (encodes NOXA, top left), *BCL2L1* (encodes BCL-X_L, top right), *MCL1* (bottom left), or *BCL2L11* (encodes BIM, bottom right) mRNA expression from GDSC compared to venetoclax sensitivity, plotted as AUC vs *BCL2* mRNA (A) or LN IC₅₀ vs *BCL2* mRNA (B). Linear regression is plotted as a red line. Correlation was determined using Spearman's correlation.

Supplemental Figure 4. Comparison of BCL-2 family members to venetoclax sensitivity in SCLC cell lines.

(A) Top and bottom quartiles were determined for *PMAIP1* (encodes NOXA, top left), *BCL2L1* (encodes BCL-X_L top right), *MCL1* (bottom left), or *BCL2L11* (encodes BIM, bottom right). The AUC to venetoclax was plotted for each quartile. (B) Top and bottom quartiles were determined for *BCL2* and *PMAIP1* (top left), *BCL2* and *BCL2L1* (top right), *BCL2* and *MCL1* (bottom left), or *BCL2* and *BCL2L11* (bottom right). The AUC to venetoclax was plotted for each quartile. The Mann-Whitney U test was used to determine *p*-values.

Supplemental Figure 5. BCL-2 mRNA expression is increased in SCLC compared to other cancer types.

(A) Left panel shows *BCL2* mRNA expression of SCLC, NSCLC, and other solid tumors from the GDSC RNA expression database. Right panel is a *BCL2* mRNA comparison with data from the CCLE RNA expression database. (B and C) Comparison of *BCL2* mRNA expression in NSCLC versus SCLC. Determination of *p*-values was performed using the Mann-Whitney U test.

Supplemental Figure 6. Cell viability of venetoclax-sensitive and -resistant SCLC cell lines.

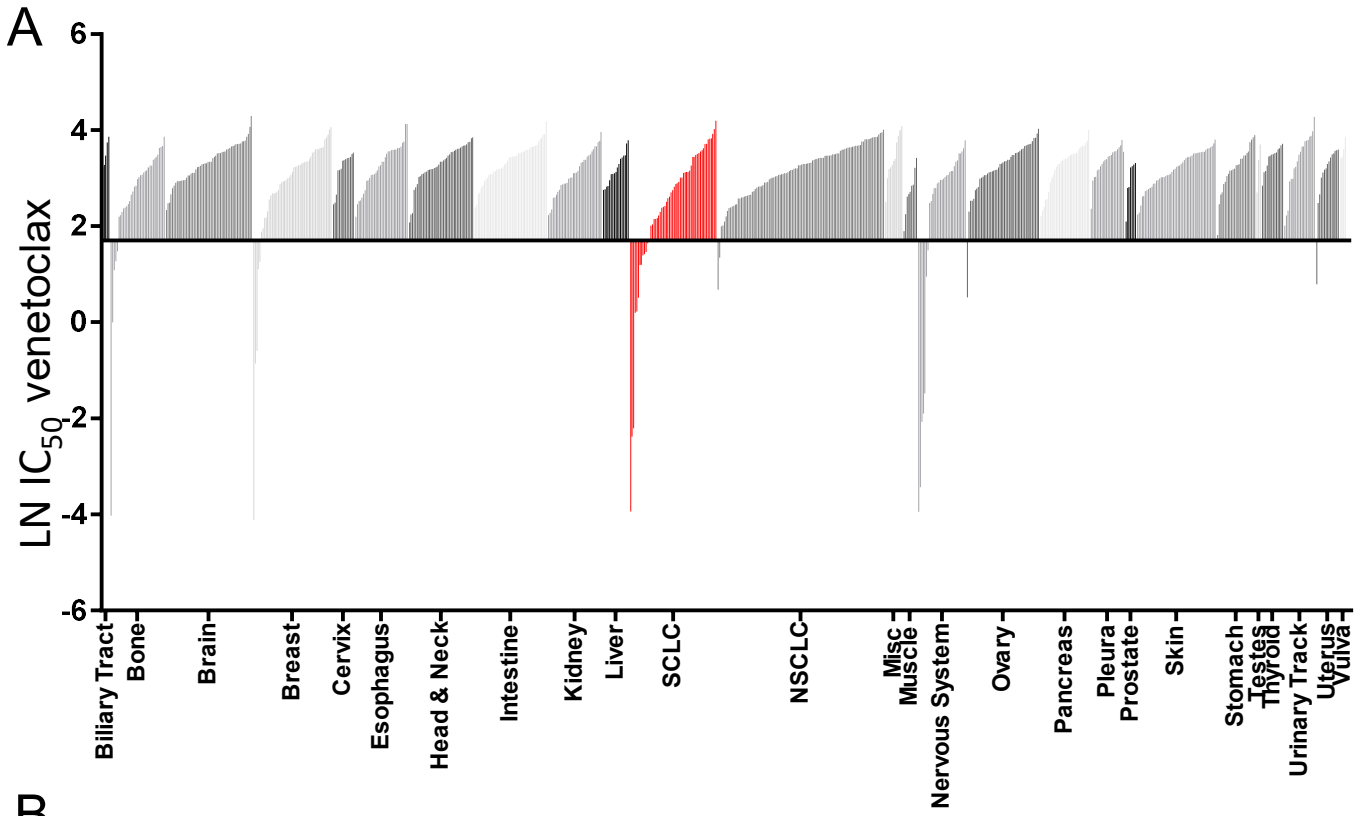
3-day CellTiter-Glo assays were performed on venetoclax-sensitive DMS-53 (A) and NCI-H510A (B) cell lines, -resistant NCI-H82 (C) cell line and an *ex vivo* cell culture of the LU5263 PDX model (D). Error bars are plotted as standard error.

Supplemental Figure 7. Weight profiles of xenograft and PDX models treated with venetoclax.

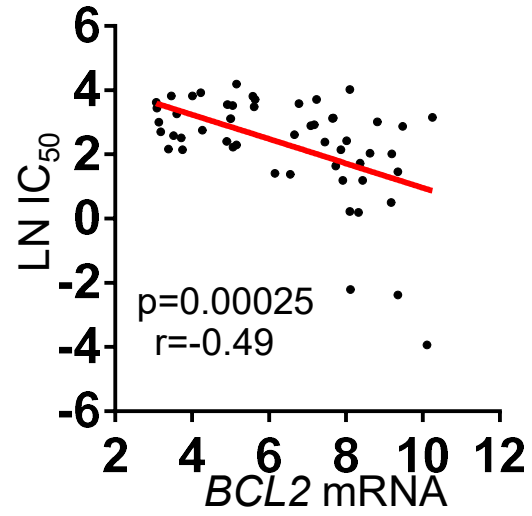
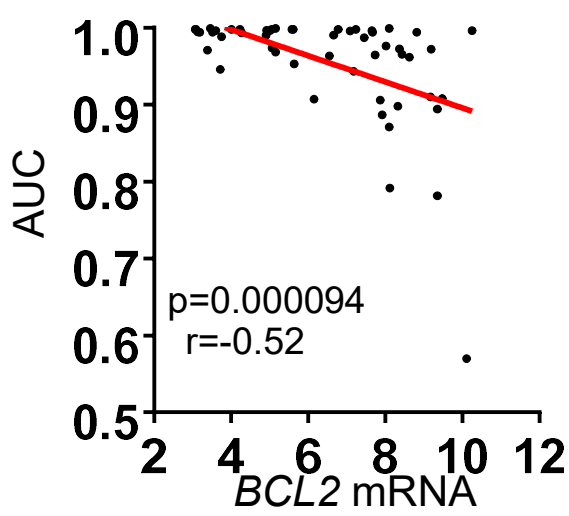
Weight is expressed as a percentage of initial weight in DMS-53 (A), LU5263 (B), LU86 (C), and LU95 (D) mouse models during venetoclax treatment.

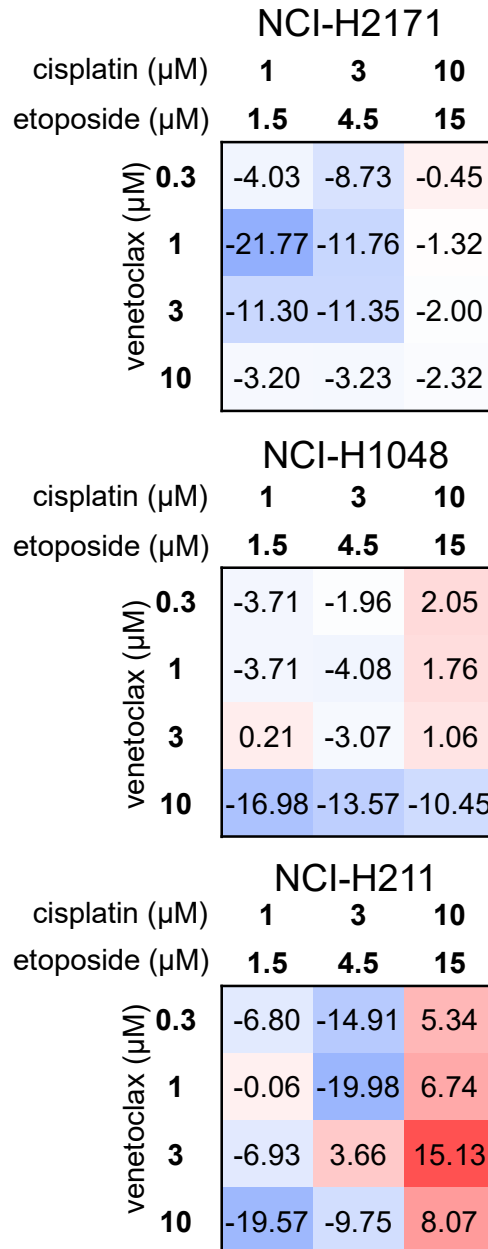
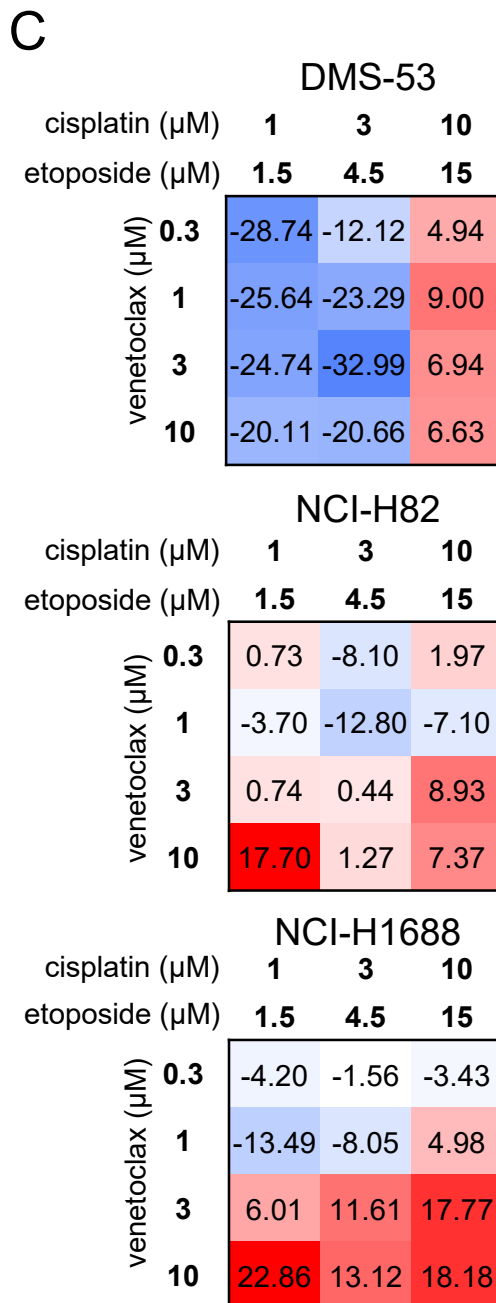
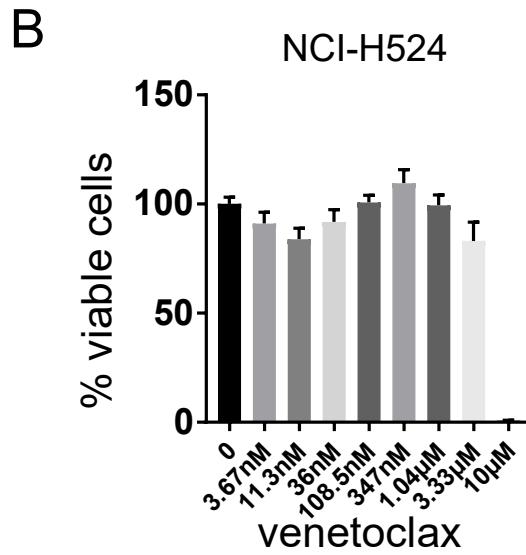
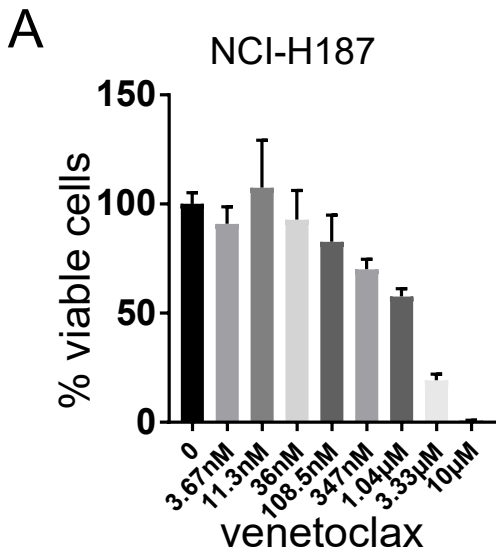
Supplemental Figure 8. The PDX models from this study express high levels of BCL-2.

Western blot of the high BCL-2 expressing PDX model tumors compared to venetoclax-sensitive (NCI-H510A) and -resistant (NCI-H82 and NCI-H2171) cell lines. Expression of the BCL-2 family proteins in SCLC cell lines was determined by Western blot analyses using the indicated antibodies.

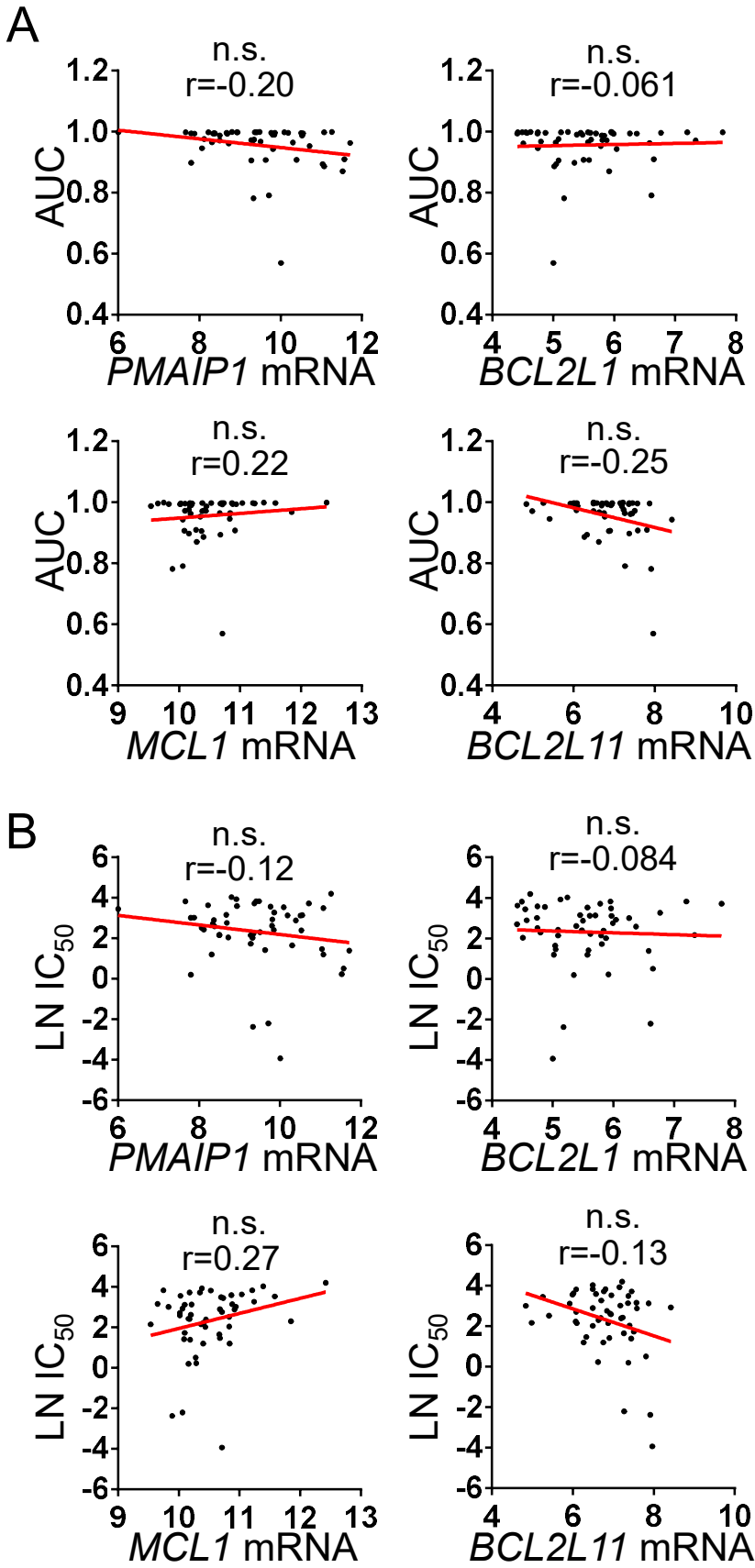


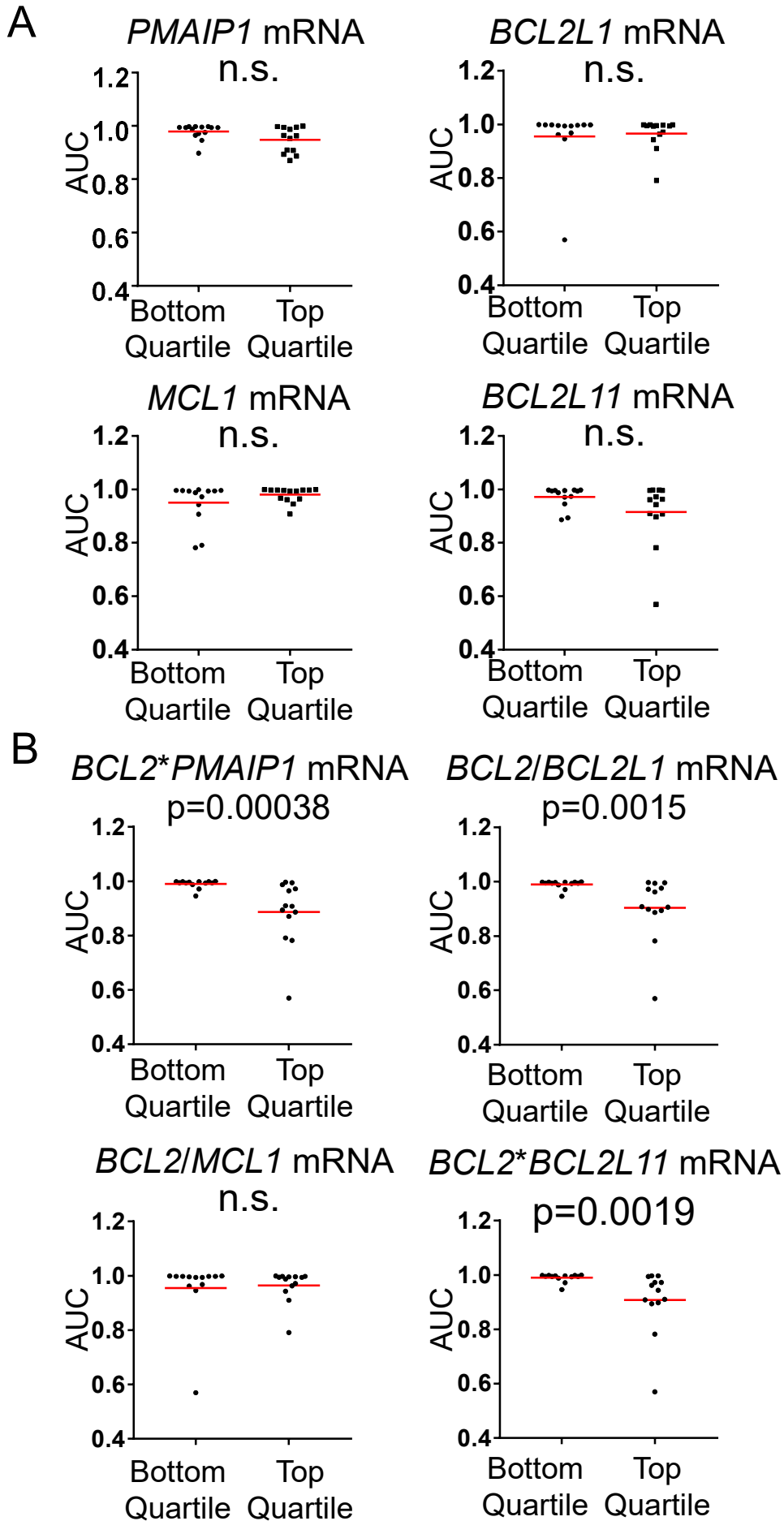
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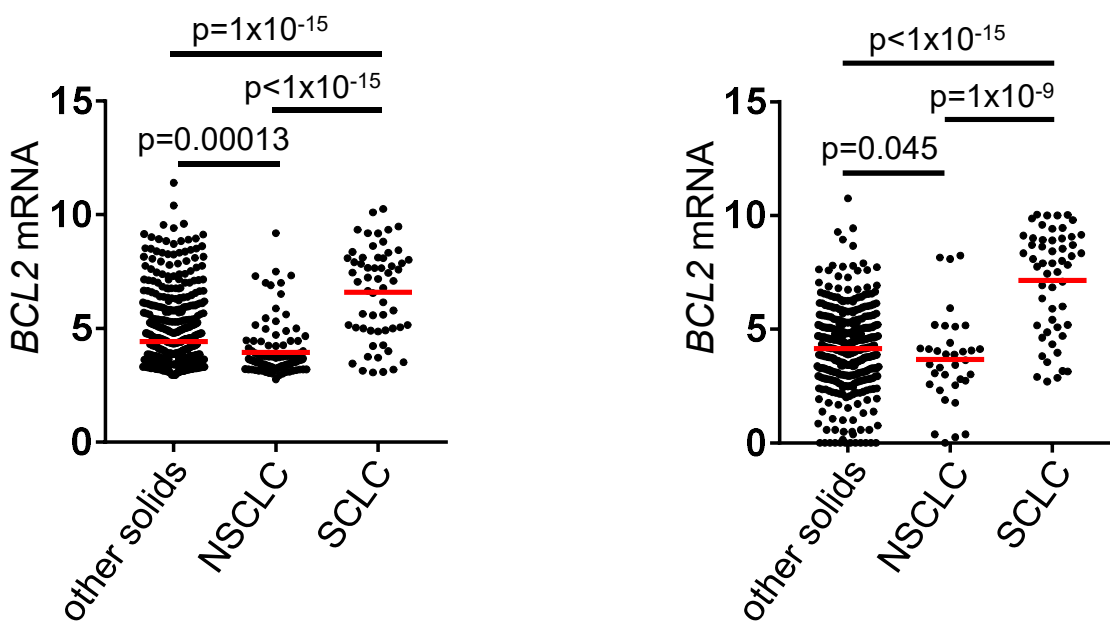


Sup Fig. 2

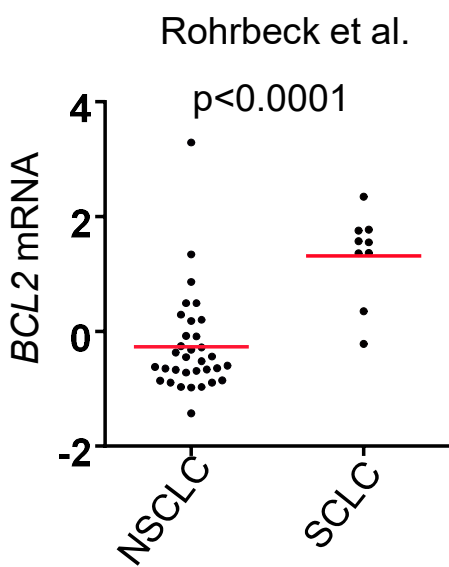




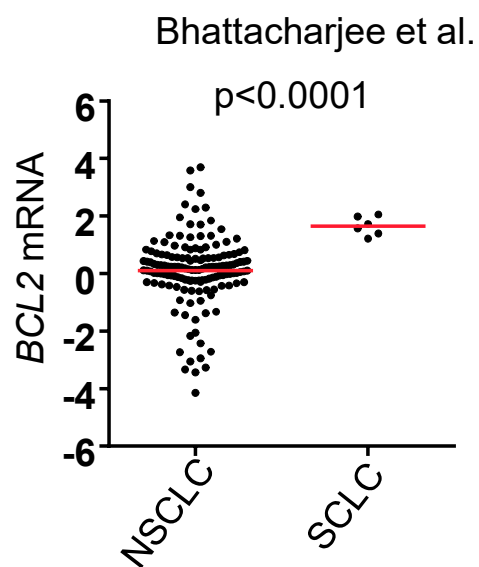
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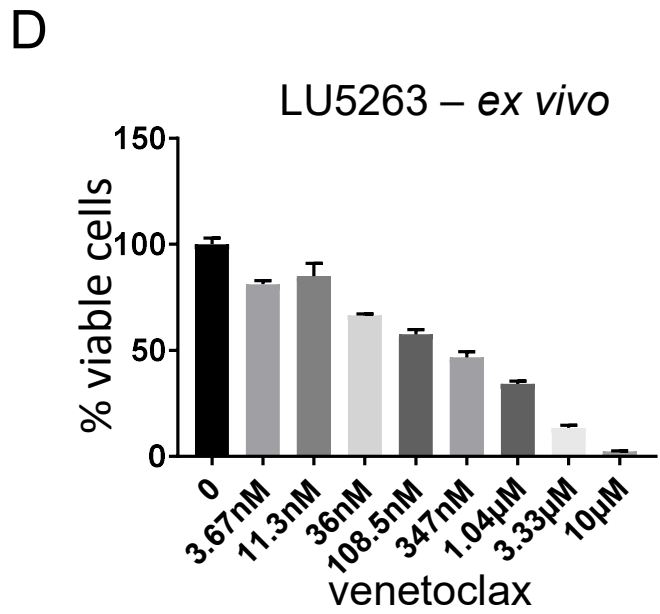
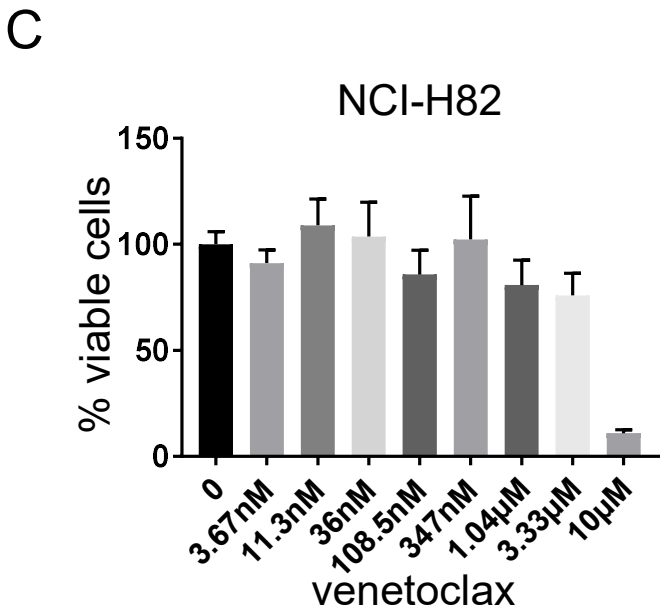
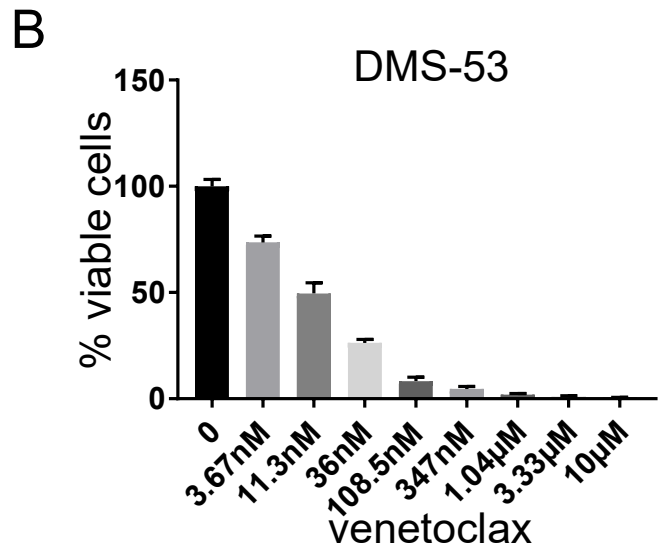
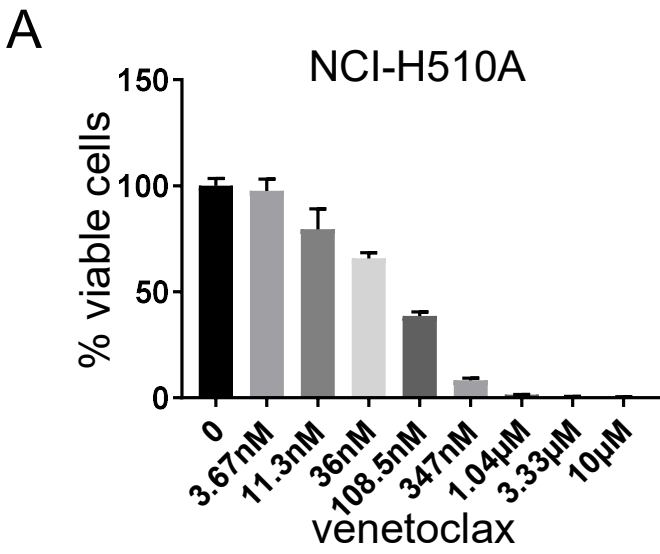


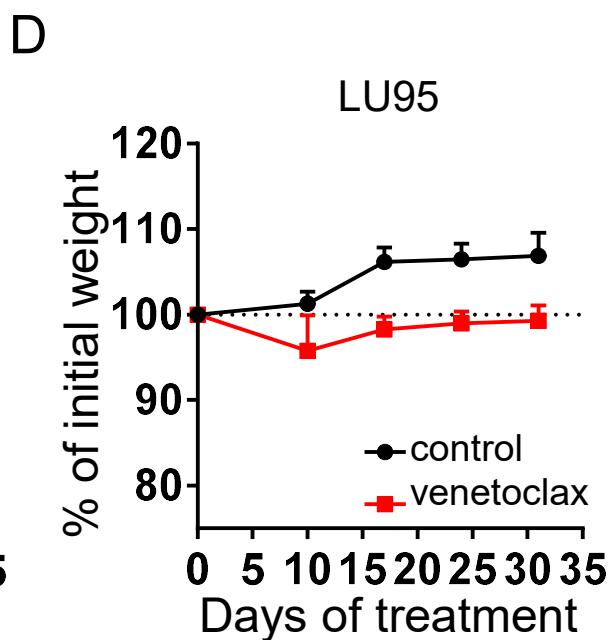
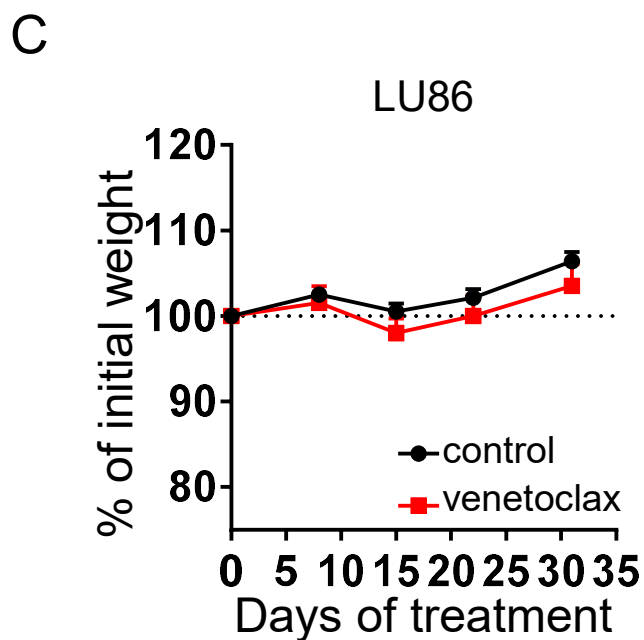
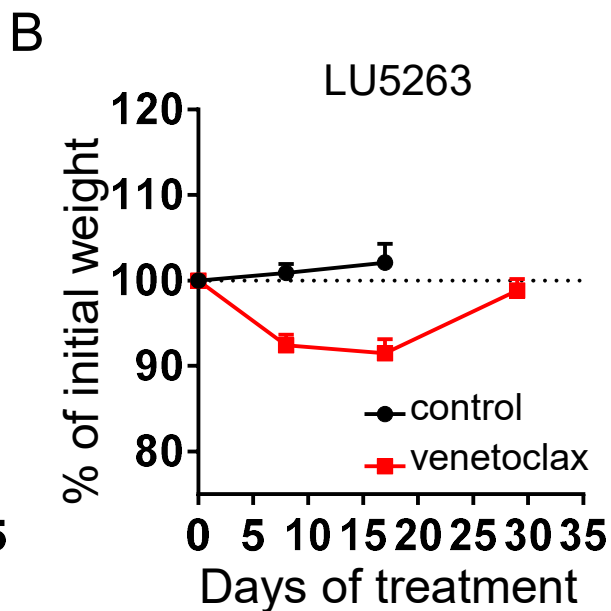
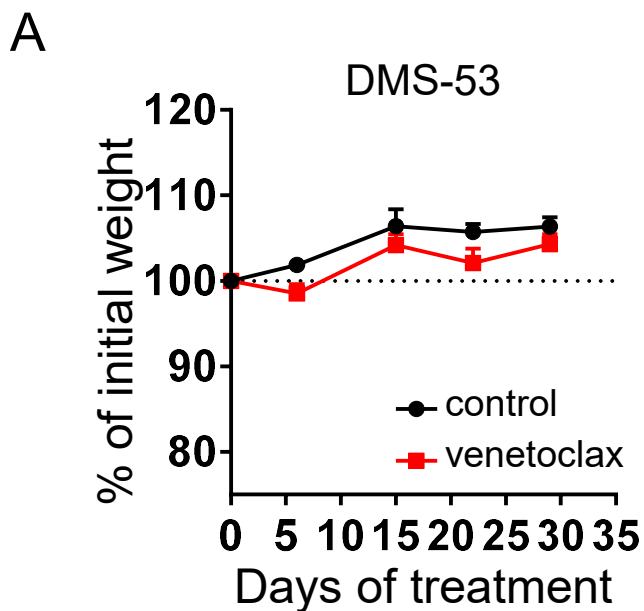
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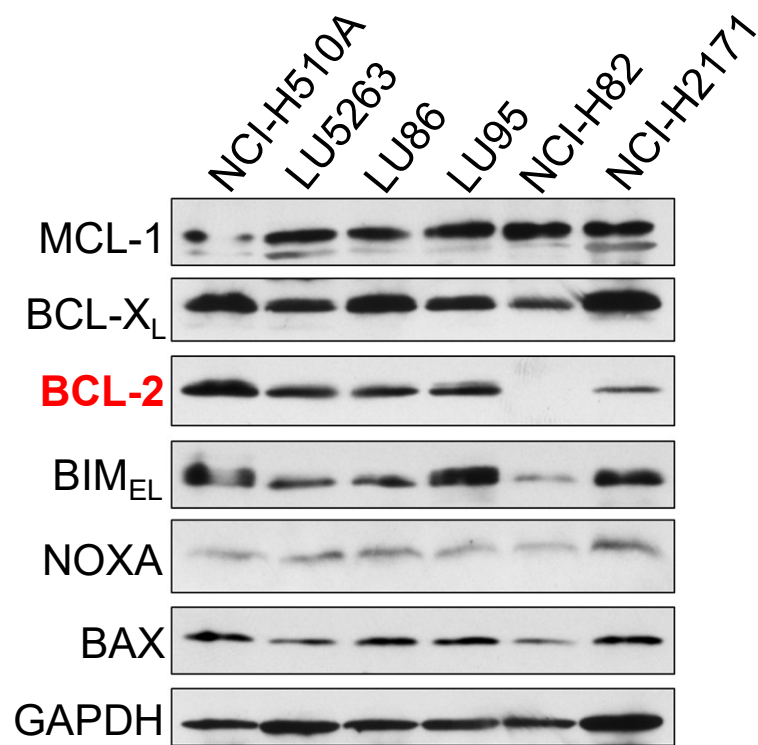


C









Sup Fig. 8