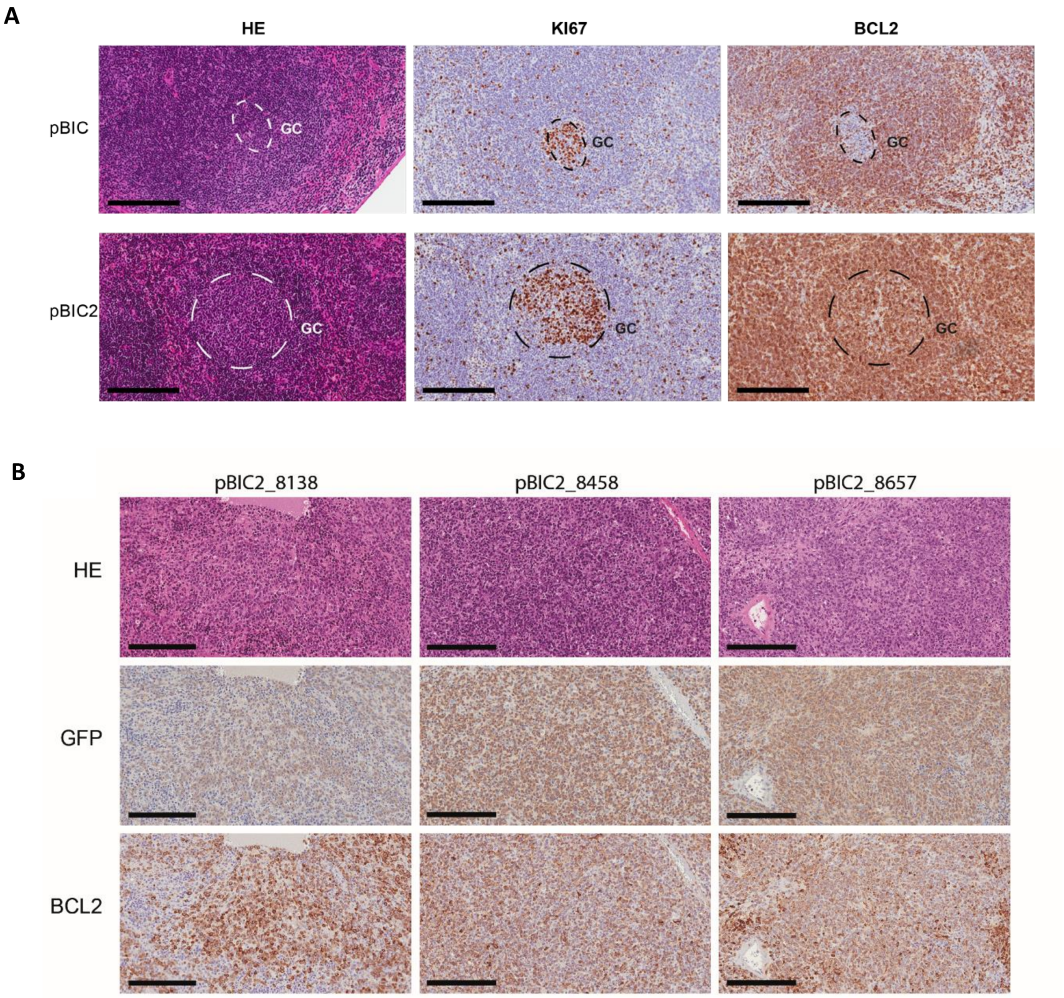
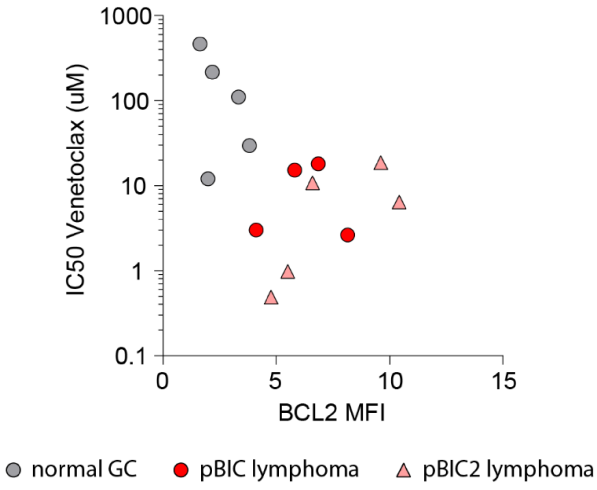
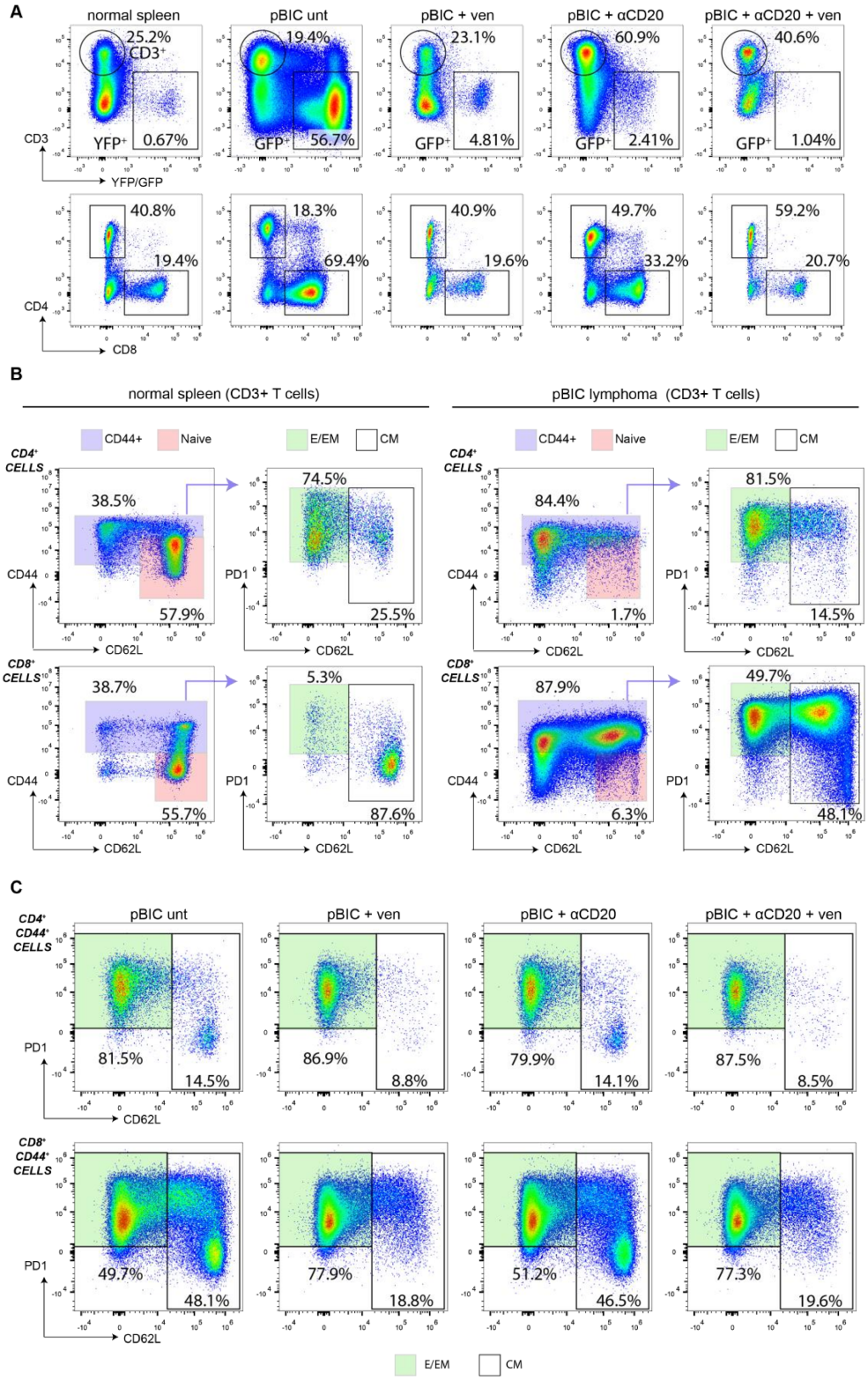
SUPPLEMENTAL MATERIAL



Supplementary Figure S1. (A) Representative Hematoxylin-Eosin (HE) and IHC staining of Ki67 and BCL2 of splenic sections from young pBIC and pBIC2 mice during secondary immune response to SRBC immunizations (i.e. 100 days of life), supporting that BCL2 is normally downregulated in germinal centers ($Ki67^+$ GC, dotted circles) while it remains expressed in pBIC2. The BCL2 antibody recognizes both human and murine BCL2 (see methods). Scale bar 200 µm. (**B**) Representative IHC photos of three pBIC2 tumors (identified by different ear tag numbers). Histologic examinations by an expert pathologist in the field (O.B.) showed morphological features of high-grade B cell lymphomas compatible with human DLBCL characteristics and $GFP^+/BCL2^+$ expression. Scale bar 200 µm.

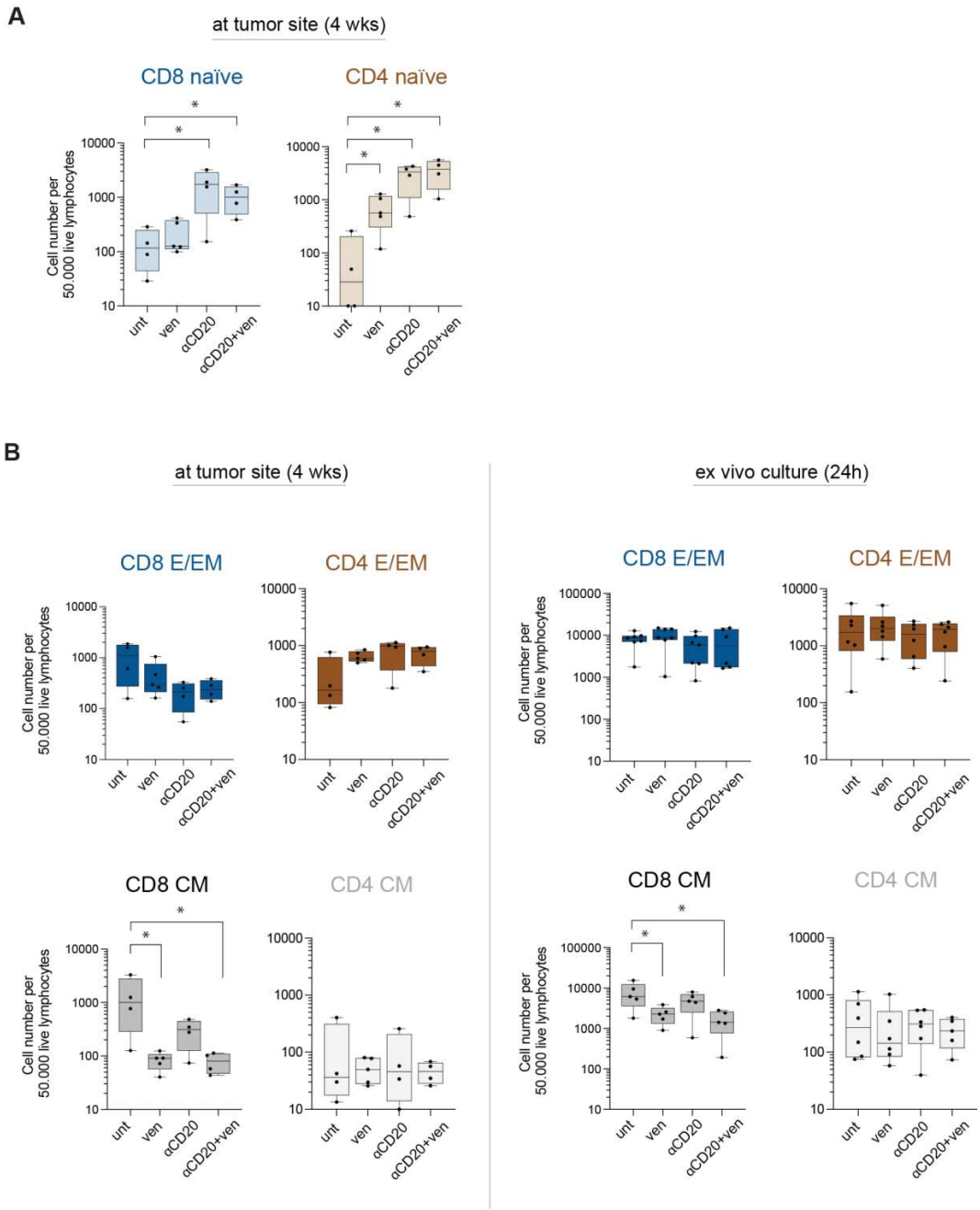


Supplementary Figure S2. Data supporting that BCL2 expression within tumor cells correlates with sensitivity to venetoclax. Grey dots represent YFP^+ GC B cells from YC control mice, dark red dots represent GFP^+ tumor cells from pBIC mice at advanced stages of the disease and light red triangles represent GFP^+ tumor cells from pBIC2 mice at advanced stages of the disease. IC50 was calculated following 24-hour treatment with escalating doses of venetoclax as described in Supplemental Methods. The sum of both mBCL2 and hBCL2 MFI values was normalized to the corresponding MFI observed in normal GC B cells from YC mice. Pearson's correlation, r = -0.5482 p= 0.0424. MFI, median fluorescence intensity.



Supplementary Figure S3. (**A**) Representative flow cytometry data supporting that untreated pBIC lymphomas have an inflamed tumor microenvironment enriched in

$CD3^+CD8^+$ T cells with a high percentage of GFP^+ tumor cells, as opposed to normal spleen YC control mice and mice treated with venetoclax or αCD20, alone or in combination, where $CD3^+CD4^+$ T cells predominate and GFP^+ tumor cells appear significantly depleted after 4 weeks of treatment (half-time of overall treatment duration). (**B**) Representative flow cytometry data supporting that, compared to normal spleen YC mice (left), where Naïve ($CD44^-CD62L^+$, highlighted in red) T cells predominate; untreated pBIC lymphomas (right) have a tumor microenvironment enriched in $CD44^+$ cells (highlighted in purple), consisting mainly in effector/effector memory (E/EM, $CD44^+CD62L^-$, highlighted in green) and central memory (CM, $CD44^+CD62L^+$, highlighted in white rectangles) T cells, with almost complete absence of Naïve T cells. (**C**) Representative flow cytometry data supporting that both CD4 (top) and CD8 (bottom) central memory (CM, $CD44^+CD62L^+PD1^{+/-}$, highlighted in white rectangles) intratumoral T cells in pBIC lymphomas are more sensitive to treatment regimens involving venetoclax than effector/effector memory (E/EM, $CD44^+CD62L^-PD1^+$, highlighted in green) T cells, which is not evidenced in the anti-CD20 alone immunotherapy group.



Supplementary Figure S4. Venetoclax treatment differentially affects cell numbers of murine T-cell subsets both *in vivo* and *ex vivo*. (**A**) Normalized absolute cell counts of naïve ($CD44^{-}CD62L^{+}PD\text{-}1^{-}$) T cells within the CD8 and CD4 compartments of pBIC lymphomas (n≥ 4) after 4 weeks of treatment. (**B**) Normalized absolute cell counts of Effector/Effector Memory (E/EM, $CD44^{+}CD62L^{-}PD\text{-}1^{+}$) and Central Memory (CM, $CD44^{+}CD62L^{+}PD\text{-}1^{+/-}$) T cells after *in vivo* treatment of pBIC lymphomas for 4 weeks (n≥ 4, left panels), or as measured *ex vivo* after exposing primary pBIC tumour tissues to the different treatments for 24h (n≥ 4, right panels). Nonparametric Mann-Whitney tests were used for statistical analysis: *, p≤0.05. Unt, untreated; ven, venetoclax; αCD20, anti-mouse CD20 monoclonal antibody.

Supplementary Table 1. List of flow cytometry antibodies used in this study.

Antigen	Channel	Clone	Provider
B220	APC	RA3-6B2	BioLegend
CD95/Fas	PE	Jo2	BD Biosciences
CD38	PE-Cy7	90	BioLegend
CD19	BUV-661	eBio1D3	BD Biosciences
CD138	BV-785	281-2	BioLegend
CD3	PE-Cy7	17A2	BioLegend
CD4	BV-650	RM4-5	BioLegend
CD8	BV-510	53-6.7	BioLegend
CD44	BUV-395	IM7	BD Biosciences
CD62L	PE	MEL-14	BioLegend
PD1	BV-421	29F.1A12	BioLegend
PDL1	PE	MIH5	BD Biosciences
IFN-γ	FITC	XMG1.2	Biolegend
TCF-1	PE	S33-966	BD Biosciences
Zombie NIR	APC/Cy7	N/A	Biolegend
7AAD	PE-Cy5	N/A	Thermo Fisher
Annexin-V	APC	A35110	Thermo Fisher
γH2AX	BV-421	N1-431	BD Biosciences
mBCL2	PE	BCL/10C4X	BioLegend
hBCL2	BV-421	100	BioLegend
Active Casp3	PE	C92-605.1	BD Biosciences
GFP	FITC	FM264G	BioLegend
Rab α-mMYC	N/A	Y69	Abcam
Goat α-rab IgG	APC		Invitrogen
Fc receptor block	N/A	2.4G2	BD Biosciences

BUV: Brillant Ultra Violet. UV: Ultra Violet. m: murine. h: human. rab: rabbit. All antibodies were used at a dilution 1:100 except for secondary antibody goat α-rabbit IgG (APC) that was used at 1:2000.

Supplementary Table 2. List of qRT-PCR Primers used in this study.

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
h/mBCL2*	CACCTGACGCCCTTCACC	ACACACATGACCCCACCG
Trp53	CTCTCCCCCGCAAAAGAAAAA	CGGAACATCTCGAAGCGTTTA
Myc	GTGCTGCATGAGGAGACACC	AGGGGTTTGCCTCTTCTCC
Bcl-xl	AACATCCCAGCTTCACATAACCCC	GCGACCCCAGTTTACTCCATCC

*: *BCL2* primers recognize both human and murine *BCL2* cDNA sequences and amplify both genes with the same efficiency.