Supplemental Table 1 Patients' clinical information

No	Age	Diagnose	Left ventricular ejection fraction （LVEF）	Pro-BNP （pg/ml）	Complication
1	>80	DLBCL（GCB）-IV A	42%	5607.00	Chronic heart failure
2	>65	DLBCL（ABC）-IV B relapse	50%	4256.00	Chronic cardiac insufficiency after chemotherapy
3	>65	DLBCL（GCB）-II A	43%	1407.00	Chronic heart failure, arhythmia

Supplemental Table 2 Genesets used for ssGSEA

Geneset	Gene
cGAS_STING	*CGAS TMEM173 IRF1 IRF5 IRF7 ISG15 USP18 IFNB1 OAS1 OASL TLR4 IFI6 IFI35 IFI44 IFIT1 IFIT2 IFIT3 IFITM1 IFITM2*
Pyroptosis	*IRF1 ZBP1 NLRP1 GSDMD CASP1 AIM2 NLRP3 NLRP6 IL18 NLRC4 CASP6 DHX9 GSDME CASP3 CASP8 TP63 IRF2 CASP5 PYCARD CASP4 BAX DPP9 TP53 IL1A MEFV BAK1 GSDMA*

Supplemental Table 3 Geneset targeted by BR

Subtype	Gene
cGAS_STING	*CGAS TMEM173 (STING1)*
Pyroptosis	*GSDMD CASP1 NLRP1*
Inflammatory factor	*IFNB1 TNF CXCL10*
MHC molecule	*HLA-A HLA-B HLA-C*

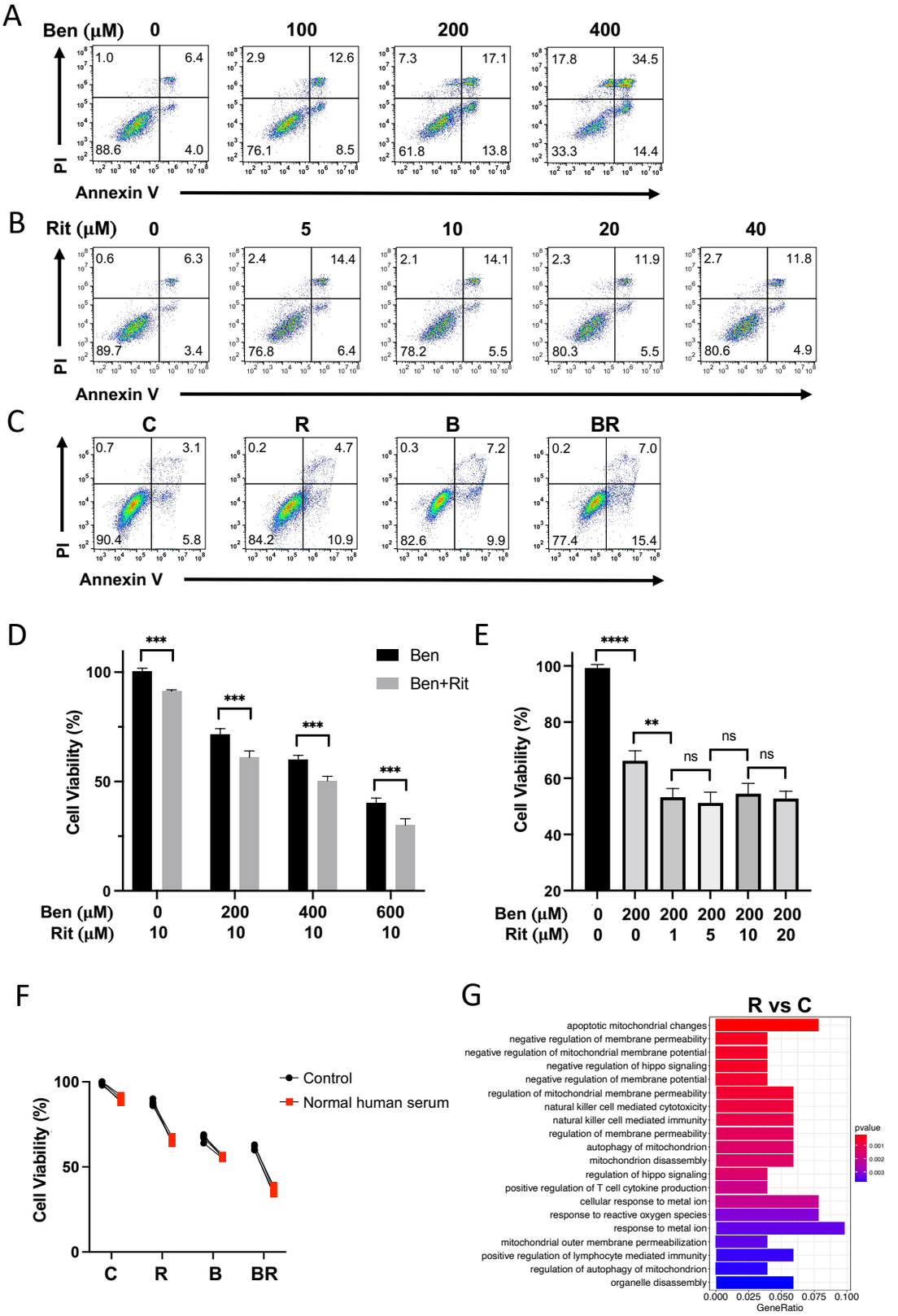
A
Ben (μM) 0 100 200 400
1.0 6.4 88.6 4.0
2.9 12.6 76.1 8.5
7.3 17.1 61.8 13.8
17.8 34.5 33.3 14.4
PI
Annexin V
B
Rit (μM) 0 5 10 20 40
0.6 6.3 89.7 3.4
2.4 14.4 76.8 6.4
2.1 14.1 78.2 5.5
2.3 11.9 80.3 5.5
2.7 11.8 80.6 4.9
PI
Annexin V
C
C R B BR
0.7 3.1 90.4 5.8
0.2 4.7 84.2 10.9
0.3 7.2 82.6 9.9
0.2 7.0 77.4 15.4
PI
Annexin V
D
Ben
Ben+Rit
Cell Viability (%)
100
50
0
***
Ben (μM) 0 200 400 600
Rit (μM) 10 10 10 10
E
Cell Viability (%)
100
80
60
40
20
****
**
ns
Ben (μM) 0 200 200 200 200 200
Rit (μM) 0 0 1 5 10 20
F
Control
Normal human serum
Cell Viability (%)
100
50
0
C R B BR
G
R vs C
apoptotic mitochondrial changes
negative regulation of membrane permeability
negative regulation of mitochondrial membrane potential
negative regulation of hippo signaling
negative regulation of membrane potential
regulation of mitochondrial membrane permeability
natural killer cell mediated cytotoxicity
natural killer cell mediated immunity
regulation of membrane permeability
autophagy of mitochondrion
mitochondrion disassembly
regulation of hippo signaling
positive regulation of T cell cytokine production
cellular response to metal ion
response to reactive oxygen species
response to metal ion
mitochondrial outer membrane permeabilization
positive regulation of lymphocyte mediated immunity
regulation of autophagy of mitochondrion
organelle disassembly
pvalue
0.001
0.002
0.003
0.000 0.025 0.050 0.075 0.100
GeneRatio

Figure S1, related to Figure 1. **Bendamustine and Rituximab Elicit Cytotoxic Effects on DLBCL Cells In Vitro.**

A, B. Annexin V-PI assay for cell apoptosis. Apoptosis status of SU-DHL2 cell line after treatment with different concentrations of bendamustine (A) or rituximab (B) for 12 hours. C. Annexin V-PI assay for cell apoptosis. Apoptosis status of KARPAS-422 cells after treatment with C, R, B and BR for 12 hours. D, E. Annexin V-PI assay for cell apoptosis. (D) Apoptosis status of OCI-LY1 cells after combined treatment with rituximab at a concentration of 0 or 10 μM and different concentrations of bendamustine for 12 hours. (E) Apoptosis status of OCI-LY1 cells after combined treatment with bendamustine at a concentration of 0 or 200 μM and different concentrations of rituximab for 12 hours. F. Cell Counting Kit-8 assay for cell viability: Cell viability of OCI-LY1 cells after treatment with or without normal human serum for 36 hours. G. Gene ontology (GO) enrichment analysis of DEG between Rituximab group and control group.

C&CTRL: control group, R&Rit: rituximab group, B&Ben: bendamustine group, BR&Ben+Rit: bendamustine + rituximab. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$

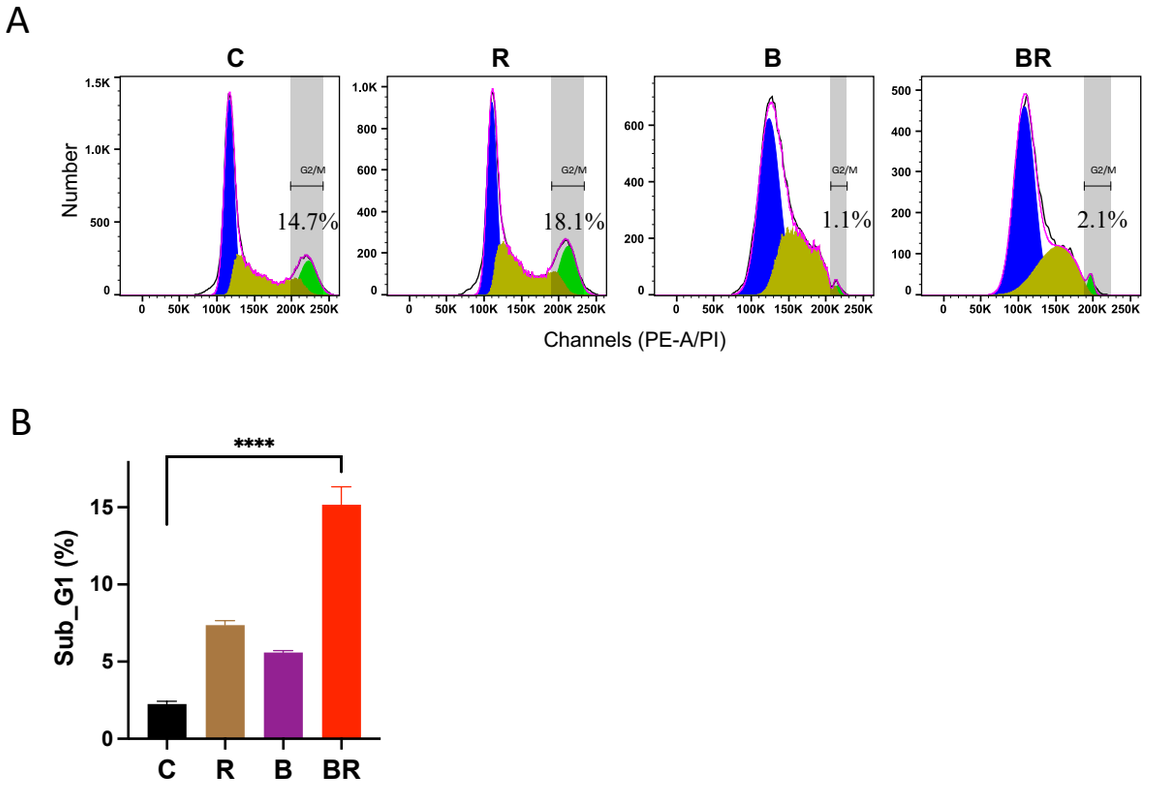

Figure S2, related to Figure 2. **Impact of BR Therapy on Cell Cycle of SU-DHL2 Cells.**

A. PI cell cycle staining: Assessment of cell cycle status in SU-DHL2 cell line after 36 hours of treatment with C, R, B and BR. B. Proportion of SU-DHL2 cells in sub-apoptotic phase after different treatments. C: control group, R: rituximab group, B: bendamustine group, BR: bendamustine + rituximab. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$

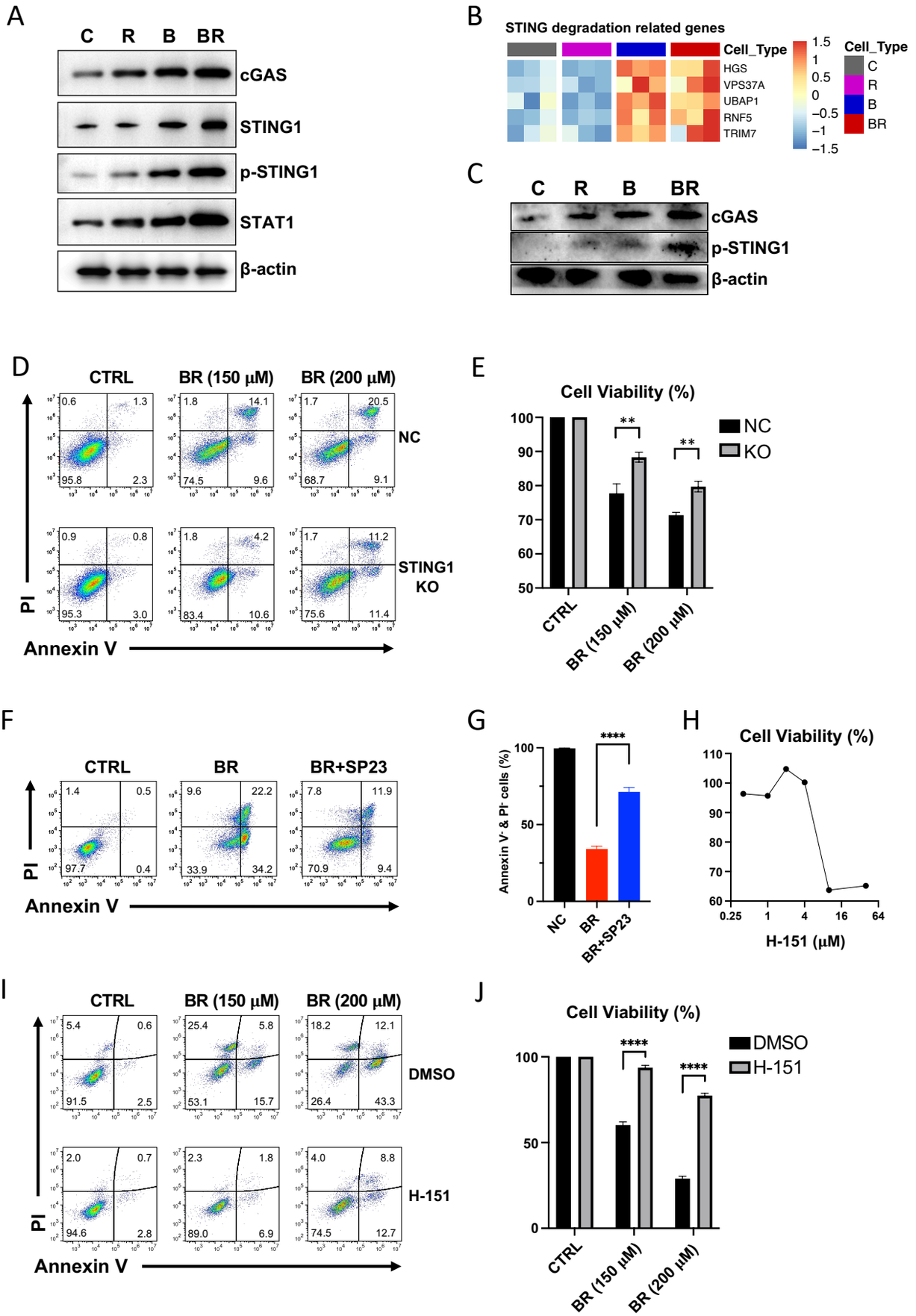
A
C R B BR
cGAS
STING1
p-STING1
STAT1
β-actin
B
STING degradation related genes
Cell_Type
HGS
VPS37A
UBAP1
RNF5
TRIM7
1.5
1
0.5
0
−0.5
−1
−1.5
Cell_Type
C
R
B
BR
C
C R B BR
cGAS
p-STING1
β-actin
D
CTRL
BR (150 μM)
BR (200 μM)
NC
STING1 KO
PI
Annexin V
0.6 1.3 95.8 2.3
1.8 14.1 74.5 9.6
1.7 20.5 68.7 9.1
0.9 0.8 95.3 3.0
1.8 4.2 83.4 10.6
1.7 11.2 75.6 11.4
E
Cell Viability (%)
NC
KO
**
**
100
90
80
70
60
50
CTRL
BR (150 μM)
BR (200 μM)
F
CTRL
BR
BR+SP23
PI
Annexin V
1.4 0.5 97.7 0.4
9.6 22.2 33.9 34.2
7.8 11.9 70.9 9.4
G
Annexin V- & PI- cells (%)
****
100
50
0
NC
BR
BR+SP23
H
Cell Viability (%)
110
100
90
80
70
60
0.25
1
4
16
64
H-151 (μM)
I
CTRL
BR (150 μM)
BR (200 μM)
DMSO
H-151
PI
Annexin V
5.4 0.6 91.5 2.5
25.4 5.8 53.1 15.7
18.2 12.1 26.4 43.3
2.0 0.7 94.6 2.8
2.3 1.8 89.0 6.9
4.0 8.8 74.5 12.7
J
Cell Viability (%)
DMSO
H-151
****
****
100
50
0
CTRL
BR (150 μM)
BR (200 μM)

Fig S3, related to Figure 3. **Contribution of cGAS-STING Pathway to Toxicity of BR Therapy.**

A. Western blot analysis of cGAS, STING1, p-STING1, STAT1 expression levels in the OCI-LY1 cells with C, R, B, BR treated for 20 hours. β-actin was used as a control. B. Heatmap shows the variations in genes linked to STING degradation in OCI-LY1 cells given C, R, B, BR treatment. C. Western blot analysis of cGAS and p-STING1 expression levels in the SU-DHL2 cell line. β-actin was used as a control. D, E. Flow cytometry analysis of apoptosis levels in NC SU-DHL2 and STING1 KO SU-DHL2 in different treatment groups (D) and the corresponding statistics (E). F, G. Flow cytometry analysis of apoptosis levels in OCI-LY1 treated with C, BR and BR+SP23 (F) and the corresponding statistics (G). H. Toxicity of different concentrations of H-151 to OCI-LY1 cells. I, J. Flow cytometry analysis of apoptosis levels in DMOS and H-151 treated OCI-LY1 cells in different treatment groups (I) and the corresponding statistics (J). NC: SU-DHL2 with empty vector, STING1 KO: STING1 Knockout SU-DHL2, BR (150 μM): Bendamustine 150 μM + Rituximab 10 μM; BR (200 μM): Bendamustine 200 μM + Rituximab 10 μM, CTRL: untreated, BR: Bendamustine 150 μM + Rituximab 10 μM, BR+SP23: Bendamustine combined with Rituximab and the STING ubiquitin E3 ligase inhibitor SP23. C, untreated. R, rituximab monotherapy. B, bendamustine monotherapy. BR, bendamustine plus rituximab combination therapy. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$

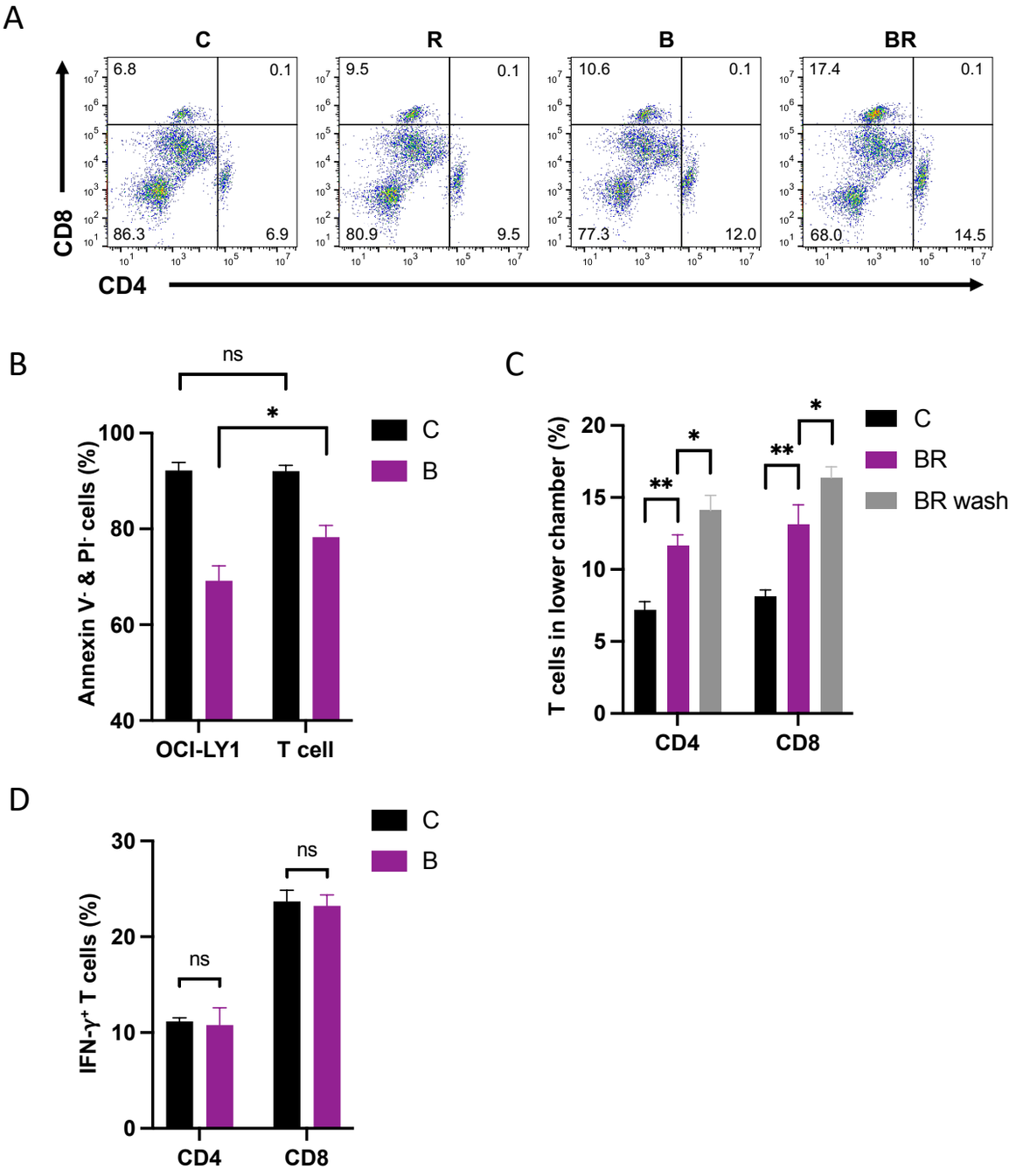
A
C
R
B
BR
6.8
0.1
86.3
6.9
9.5
0.1
80.9
9.5
10.6
0.1
77.3
12.0
17.4
0.1
68.0
14.5
CD8
CD4
B
ns
*
C
B
Annexin V- & PI- cells (%)
100
80
60
40
OCI-LY1
T cell
C
ns
*
**
**
*
C
BR
BR wash
T cells in lower chamber (%)
20
15
10
5
0
CD4
CD8
D
C
B
IFN-γ+ T cells (%)
30
20
10
0
ns
ns
CD4
CD8

Fig S4, related to Figure 5, 6. **Enhanced T Cell Migration Induced by BR Therapy-Treated Tumor Cells and Direct Impact of BR Therapy on T Cells.**
A. Flow cytometry detected the proportion of $CD4^+$ and $CD8^+$ T cells migrating downward in a transwell experiment. KARPAS-422 cells treated with C, R, B and BR as the lower chamber. B. Annexin V-PI assay for cell apoptosis. Apoptosis status of OCI-LY1 cell line and T cell after treatment with bendamustine for 36 hours. C. Flow cytometry detected the proportion of $CD4^+$ and $CD8^+$ T cells migrating downward in a transwell experiment. OCI-LY1 cells pretreated with C, BR were seeded to the lower chamber. T cells were seeded into the upper wells. In BR group: BR was added to the medium during transwell assay. In BR wash group: OCI-LY1 cell was washed twice to remove BR and there is no BR in the medium. D. Flow cytometry was used to assess the expression levels of IFN-γ in $CD4^+$ and $CD8^+$ T cells treated with C or B for 36 hours. Control: control group, Rit: rituximab group, Ben: bendamustine group, Ben+Rit: bendamustine + rituximab. C, untreated. R, rituximab monotherapy. B, bendamustine monotherapy. BR, bendamustine plus rituximab combination therapy. ns: no significant difference, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$

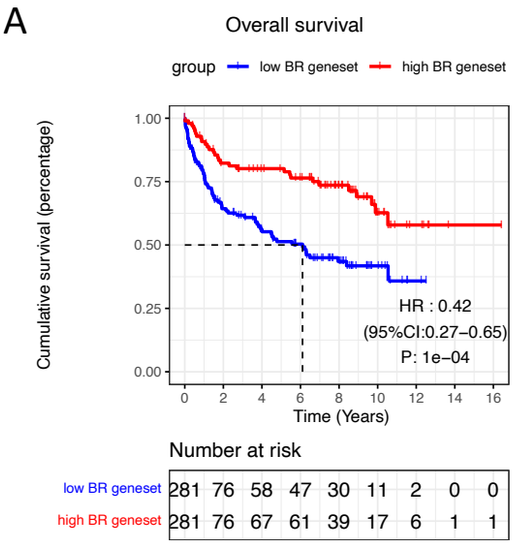

Fig S5, related to Figure 6. **Gene Set Targeted by Bendamustine-Rituximab Therapy Predicts Patient Prognosis.**

A. Kaplan-Meier (KM) survival curve displaying prognosis of high and low score of gene set targeted by BR therapy (Supplemental Table 3). The p-value was generated using the Mantel-Cox log-rank test. HR, hazard ratio.