ARTICLE - Non-Hodgkin Lymphoma

Characterization and clinical impact of the tumor microenvironment in post-transplant aggressive B-cell lymphomas

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Supplementary Data

Characterization and clinical impact of the tumor microenvironment in post-transplant aggressive B-cell lymphoma

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Supplementary Methods

Patients and samples

The PTLD cohort consisted of aggressive B-cell lymphomas (PT-ABCLs), including DLBCL, high-grade B-cell lymphoma, Burkitt lymphoma and primary central nervous system lymphoma (PCNSL), classified according to the WHO classification of the lymphoid neoplasms (2016 revision)[1]. Precise classification according to the newest version of the WHO 5th edition[2] or International Consensus Classification[3] would require genetic analysis. However, in many cases material was limited, and these studies could not be performed.

Of the PT-ABCL patients, 53 were treated with rituximab, comprising ten patients with rituximab monotherapy, one with rituximab in combination with radiotherapy, and 42 with a combination of rituximab and cytotoxic treatment. Thirteen patients were treated with different combinations of cytotoxic therapy with or without radiotherapy (in some cases in combination with surgery). Five patients died of PTLD before the treatment started. One patient had a spontaneous regression on reduction of immunosuppression and did not receive any further treatment. One patient was treated with graftectomy followed by re-transplantation (PT-ABCL allocated only to the transplanted organ). One patient received antiviral treatment and intravenous immunoglobulin along with tapering of immunosuppression. No information was available concerning the treatment of one patient.

Gene expression profiling

For RNA isolation, either two to three 20 µm sections or two 1 mm punches from formalin-fixed paraffin-embedded (FFPE) lymphoma blocks were processed with RecoverAll™ Total Nucleic Acid Isolation Kit for FFPE (Life Technologies, Thermo Fisher Inc., Waltham, MA) according to manufacturer's instructions. Thereafter, a total of 100 ng of RNA was hybridized with the 770-gene Human PanCancer Immunoprofiling Panel codeset (XT-CSO-HIP1-12, NanoString Technologies, Seattle, WA) and analyzed with the nCounter Digital Analyzer system (Nanostring Technologies). The quality of the data was confirmed by using the default quality control settings in nSolver 4.0 software (NanoString Technologies). Thereafter, the data were normalized using the geNorm algorithm [4] and log2 transformed for subsequent analyzes, which were performed by R version 4.0.2. Genes expressed in <15% of the samples, based on negative control geometric mean thresholding, were filtered out from the analyzes. This resulted in a final dataset of 616 genes.

Multiplex immunohistochemistry

Tissue microarray (TMA) was available for seven PT-ABCL patient samples included in this study. Multiplex immunohistochemistry (mIHC) staining and imaging were done as previously described[5, 6]. To profile the main immune cell types we used primary antibodies for CD3 (MA5-14482, Thermo Fisher Scientific, Madison,WI), CD4 (ab133616, Abcam, Cambridge, UK), CD8 (M7103, Dako, Agilent Technologies, Santa Clara, CA), CD68 (M0876, Dako), and CD20 (MS340, Thermo Fisher Scientific) coupled with Alexa-647 and Alexa-750 labeled secondary antibodies. Nuclei were counterstained with DAPI. Quantification of the fluorescent images was done using Ilastik v.1.3.3 and CellProfiler v.3.1.8 softwares.

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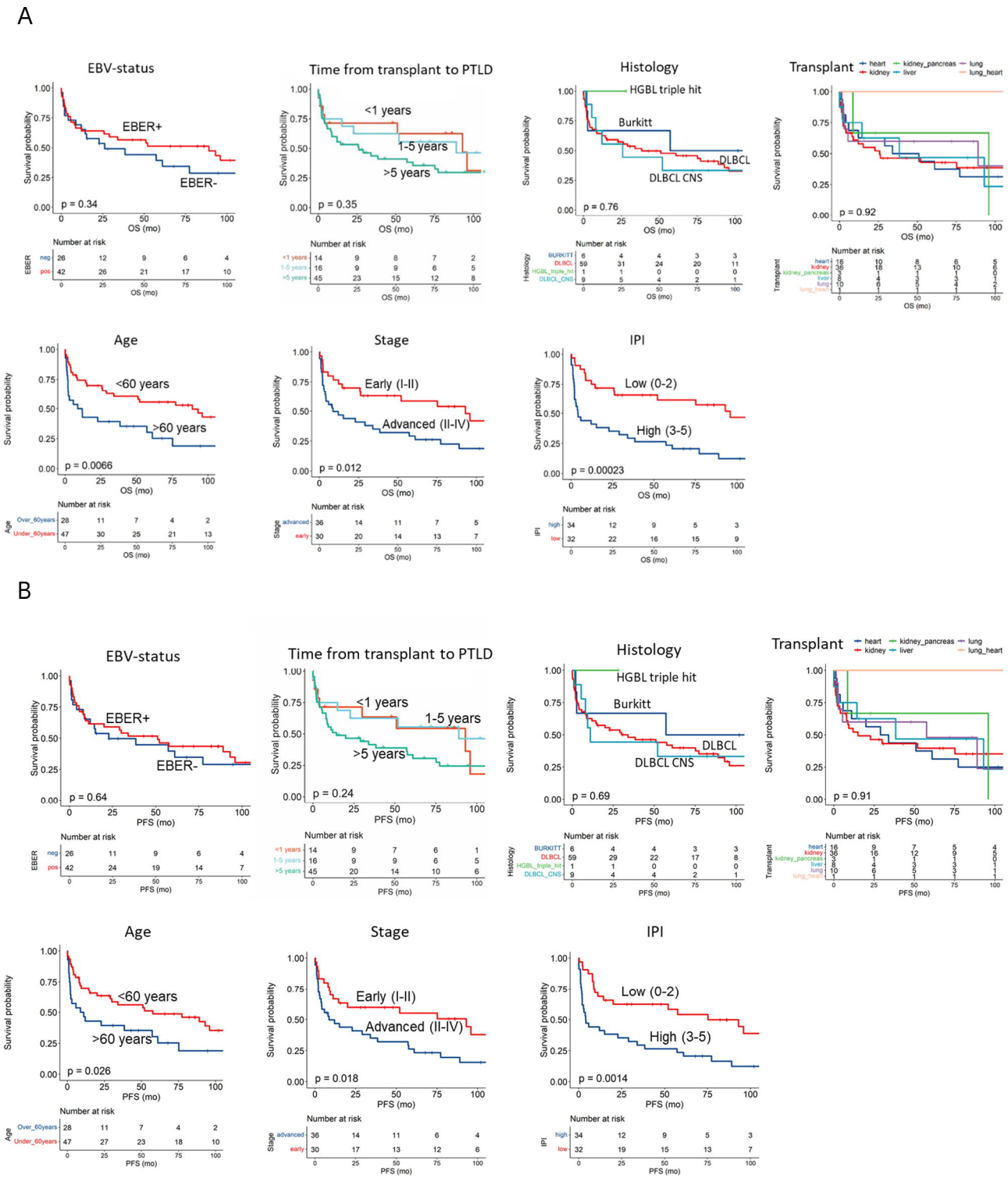
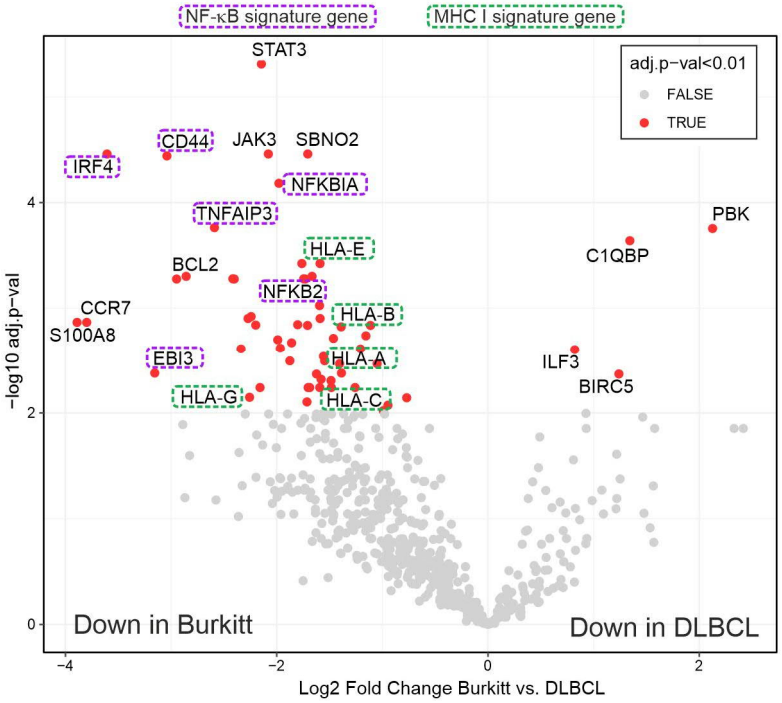
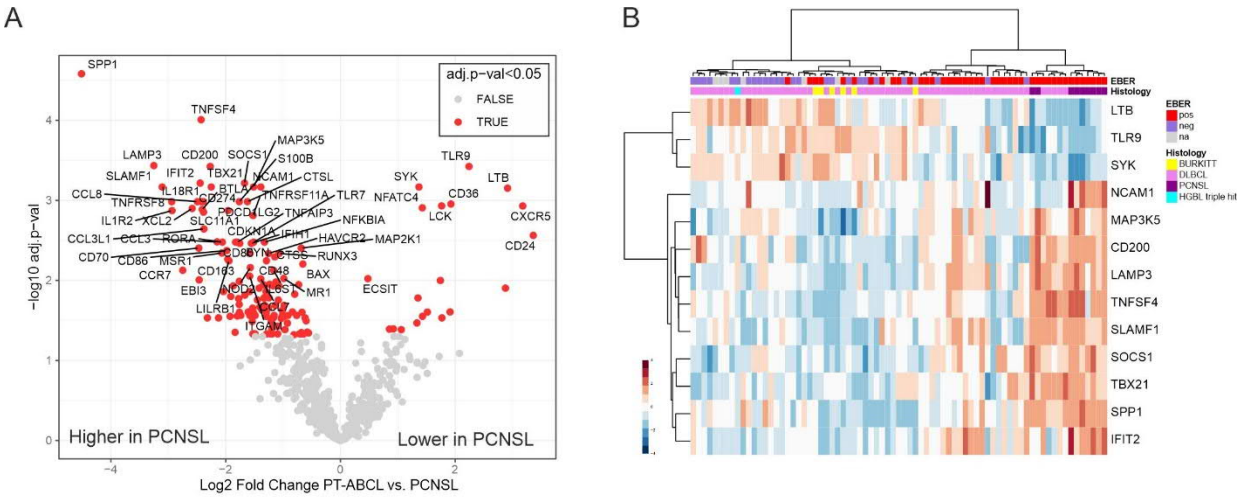
Supplementary Figures



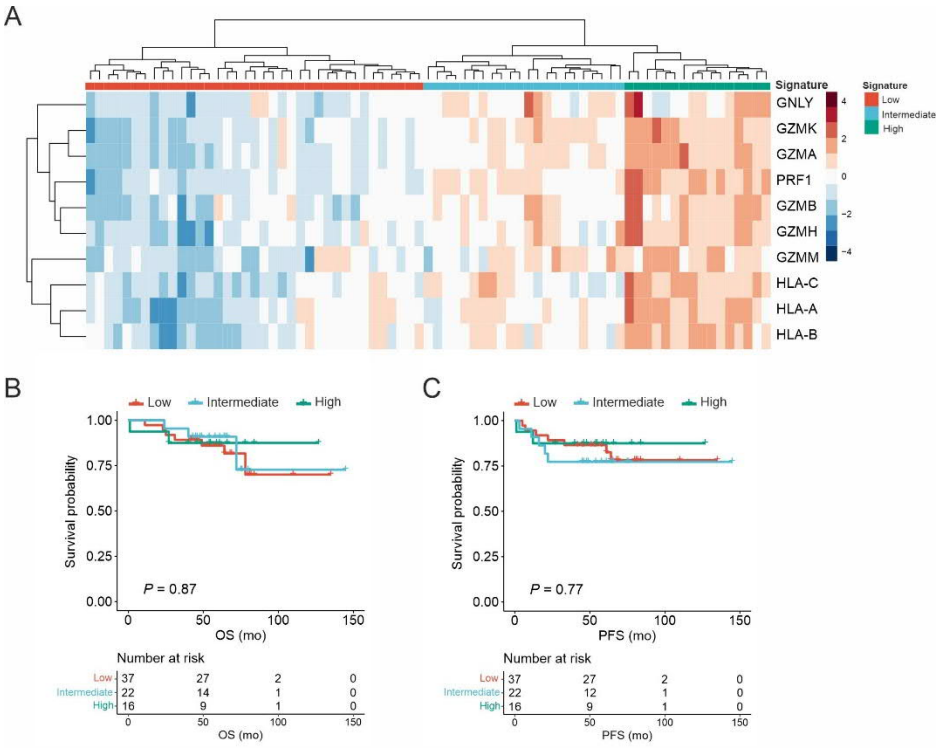
Supplementary Figure S1. Kaplan-Meier plots visualizing the effect of distinct clinical parameters on the A) overall survival (OS) and B) progression-free survival (PFS) of PT-ABCL patients.



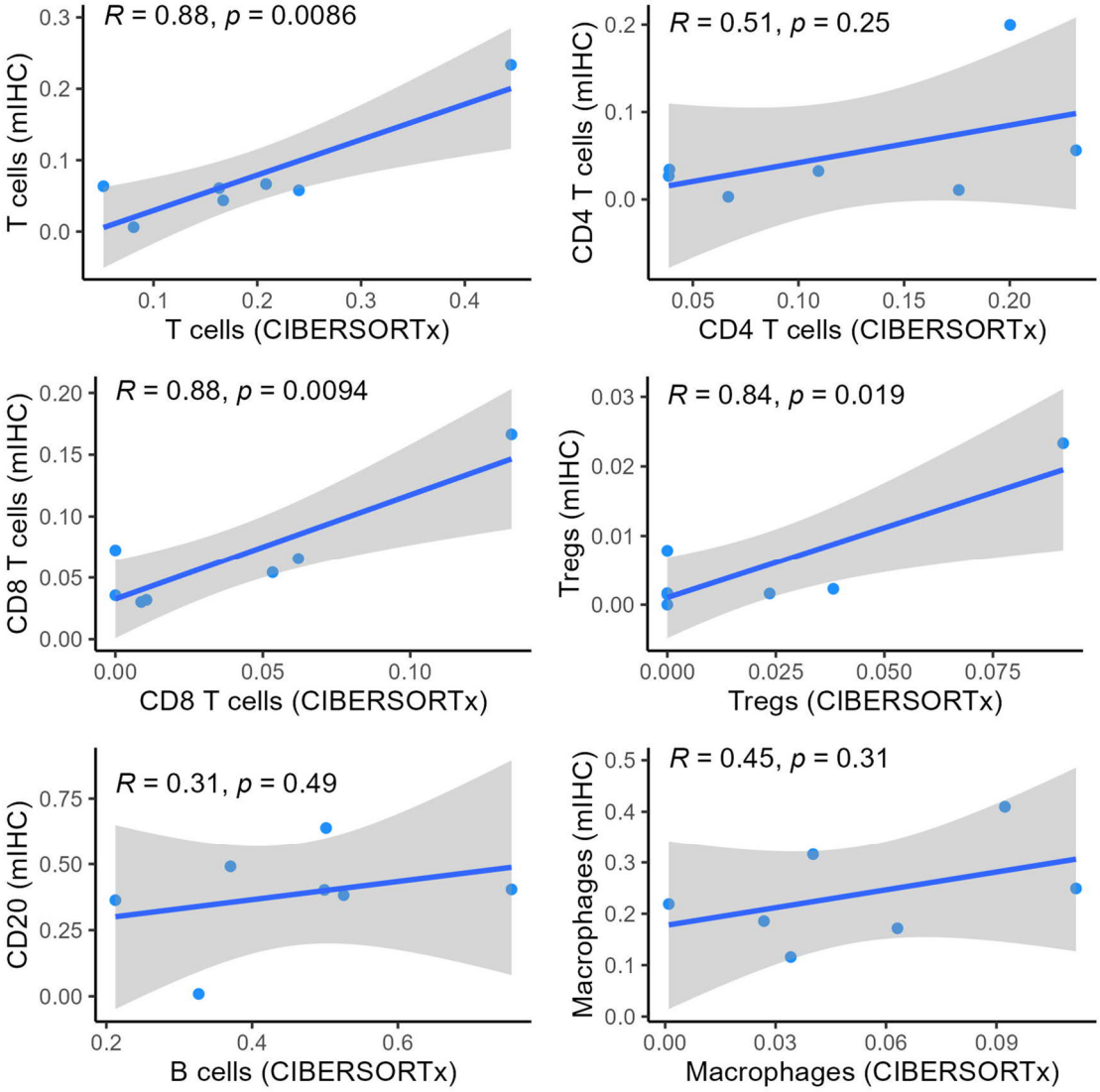
Supplementary Figure S2. Differentially expressed genes between Burkitt-PTLD and DLBCL-PTLD. A volcano plot showing differentially expressed genes in Burkitt-PTLDs as compared to DLBCL-PTLDs. The genes with log2 fold change <0 have lower expression in Burkitt-PTLD, whereas the genes with log2 fold change >0 have higher expression in Burkitt-PTLD. Genes belonging to the NF-kB target gene signature, or MHC I signature are highlighted in the plot.



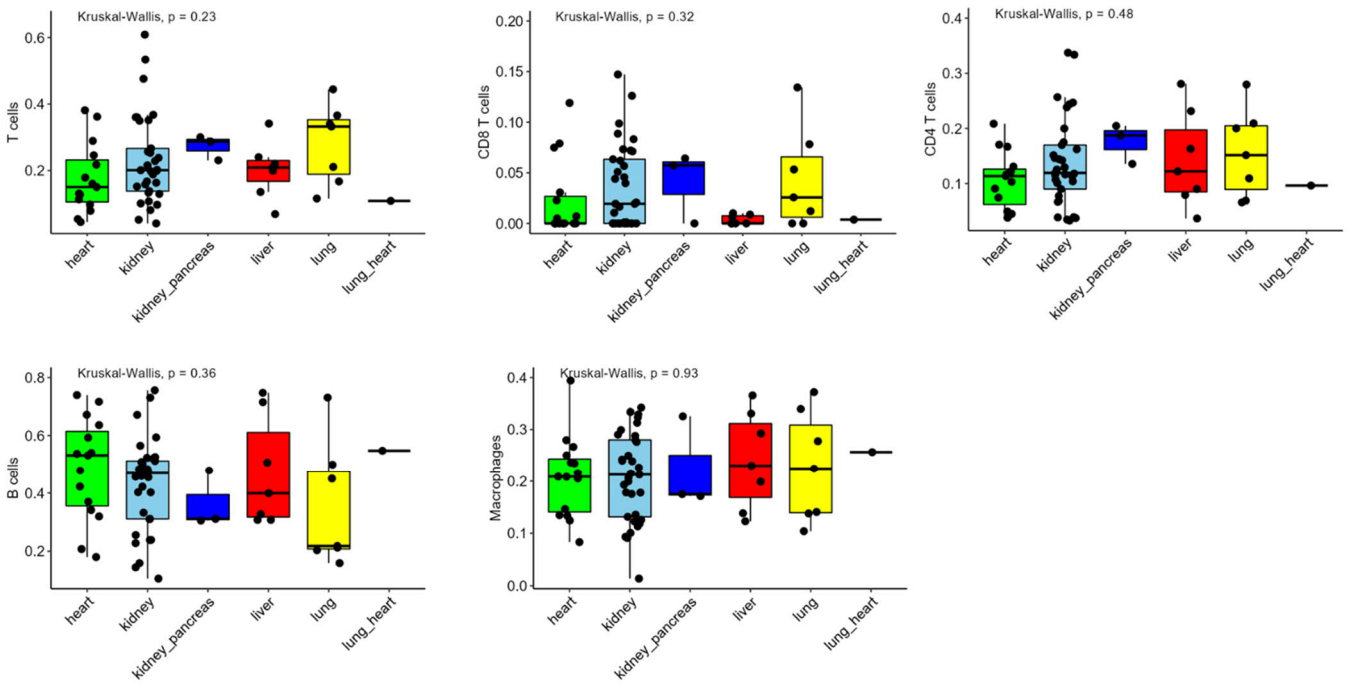
Supplementary Figure S3. Differentially expressed genes between PT-PCNSL and systemic PT-ABCL. A) A volcano plot showing differentially expressed genes in PCNSL-PTLDs as compared to systemic PT-ABCLs. The genes with log2 fold change >0 have lower expression in PCNSL-PTLD, whereas the genes with log2 fold change <0 have higher expression in PCNSL-PTLD. B) Unsupervised hierarchical clustering of the differentially expressed genes (adj.*P*<0.001).



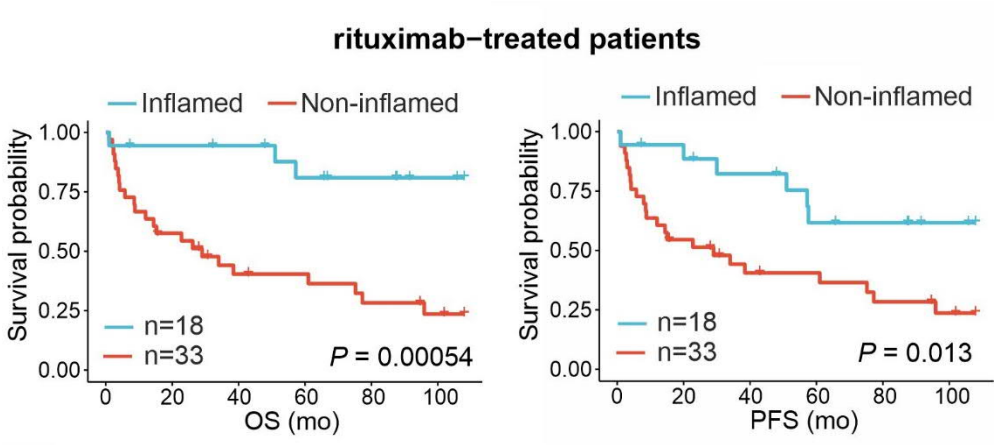
Supplementary Figure S4. Cytotoxicity signature in immunocompetent host DLBCL. A) Heatmap showing unsupervised hierarchical clustering of genes associated with cytotoxicity. B-C) Kaplan-Meier plots with the overall survival (B) and progression-free survival (C) estimates of high, intermediate, and low expression of the cytotoxic signature. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.



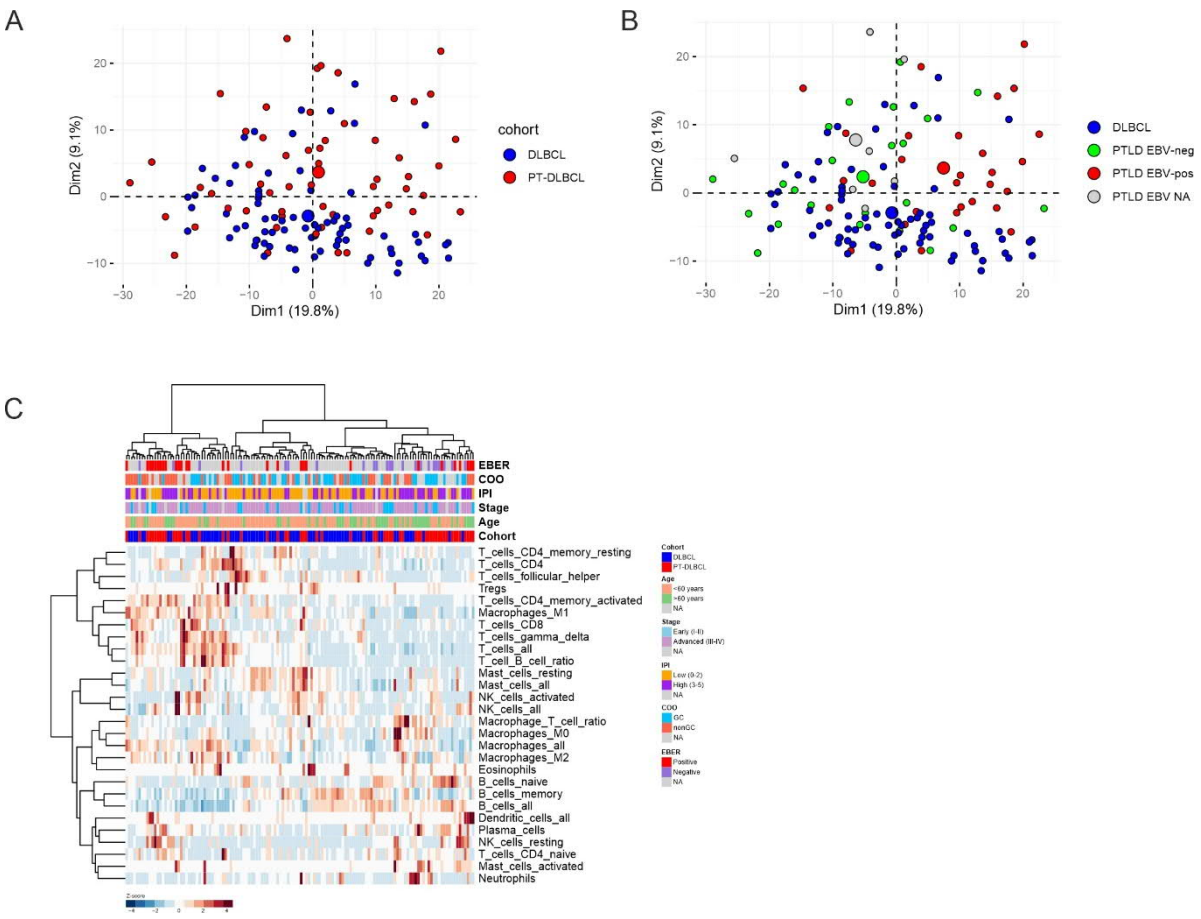
Supplementary Figure S5. Correlation between multiplex immunohistochemistry and CIBERSORTx -based immune cell proportions. Relative cell proportions determined by mIHC were correlated with the corresponding CIBERSORTx-deconvoluted cell proportions.



Supplementary Figure S6. Main immune cell types by the transplant organ. The boxplots visualize the proportions of CIBERSORTx estimates of the distinct immune cells by the transplant organ.



Supplementary Figure S7. The association of inflamed TME with survival in rituximab-treated PT-ABCL patients. Kaplan-Meier overall survival (OS) and progression-free survival (PFS) estimates of the inflamed and non-inflamed TME subclusters of the rituximab-treated patient subset.



Supplementary Figure S8. Comparison of PT-DLBCL and DLBCLs of immunocompetent patients. A-B) Principal component analysis (PCA) showing clustering of PT-DLBCL and DLBCL samples coloured by the cohort (A) or EBV-status (B). C) Unsupervised clustering of the CIBERSORTx deconvoluted immune cells in PT-DLBCL and DLBCL.

Supplementary Tables

Supplementary Table S1: Differentially expressed genes between EBER-positive vs. EBER-negative PT-ABCLs (limma analysis results, adj. *P*<0.05)

Gene	log2FC	AveExpr	t	*P*.Value	adj.*P*.Val	B
CXCR5	-2.82309	8.469658	-6.58303	1.22E-08	7.54E-06	9.634178
CD83	-1.94813	10.44396	-5.95977	1.39E-07	4.27E-05	7.32568
CD79B	-1.71024	11.42287	-5.17797	2.69E-06	0.000552	4.512649
NFATC1	-1.54794	8.317799	-5.03621	4.54E-06	0.000699	4.016779
ISG15	1.683606	9.247582	4.86865	8.37E-06	0.001032	3.437712
BCL6	-1.23485	9.003415	-4.62425	2.02E-05	0.002046	2.608127
IL18	-1.19222	7.912856	-4.58449	2.32E-05	0.002046	2.474996
TNFRSF17	1.676808	8.46528	4.446591	3.78E-05	0.002912	2.017485
LTB	-1.8569	9.421435	-4.41042	4.29E-05	0.002938	1.898618
PAX5	-1.21033	9.209441	-4.29103	6.50E-05	0.00365	1.509715
PSMB10	0.562185	10.0861	4.289132	6.54E-05	0.00365	1.503582
TNFRSF8	1.993954	6.819551	4.254971	7.36E-05	0.00365	1.393348
CXCL11	1.681631	7.758169	4.210773	8.56E-05	0.00365	1.251415
HLA-DMB	-0.78388	10.28192	-4.20863	8.62E-05	0.00365	1.244544
SYK	-0.85082	9.996212	-4.19979	8.89E-05	0.00365	1.216255
CARD11	-1.16178	9.148729	-4.06179	0.000142	0.005464	0.77889
CD97	1.028701	9.333952	4.013552	0.000167	0.006045	0.627941
CCR1	1.154155	7.412718	3.993082	0.000179	0.006114	0.564186
TNFRSF13C	-1.47241	9.341966	-3.87123	0.000267	0.008452	0.188584
CCL3	1.435381	8.637186	3.863389	0.000274	0.008452	0.164647
SIGLEC1	1.365929	8.425686	3.783421	0.000356	0.009782	-0.07781
ITGA4	0.848106	9.091056	3.783266	0.000356	0.009782	-0.07828
CD1C	-1.35804	5.846901	-3.77356	0.000368	0.009782	-0.1075
MX1	1.592679	10.19926	3.761987	0.000382	0.009782	-0.14228
MIF	0.617414	12.05824	3.750025	0.000397	0.009782	-0.17816
TNF	-1.14312	7.207071	-3.71071	0.000451	0.010677	-0.29558
CD37	-0.90686	9.090525	-3.6597	0.000531	0.011963	-0.4468
CD70	1.664535	8.735203	3.652047	0.000544	0.011963	-0.46938
CDKN1A	1.238002	8.794884	3.605469	0.000631	0.013393	-0.60613
BST2	0.721698	10.04958	3.59032	0.000661	0.013582	-0.65036
HLA-C	0.86659	12.73288	3.54505	0.000763	0.015076	-0.78185
DUSP4	1.354783	7.674472	3.536637	0.000783	0.015076	-0.80616
SLAMF7	1.477628	8.610701	3.511083	0.000848	0.015762	-0.87979
GPI	0.485063	10.23215	3.483706	0.000924	0.015762	-0.95828
RORA	1.34863	7.434088	3.471511	0.00096	0.015762	-0.99311
REL	-0.97411	9.359927	-3.4653	0.000978	0.015762	-1.01083
CCL3L1	1.385916	8.429212	3.463273	0.000984	0.015762	-1.0166
HLA-DMA	-0.64662	10.90741	-3.46138	0.00099	0.015762	-1.02198
HLA-DOB	-1.14577	8.504511	-3.45885	0.000998	0.015762	-1.02919
GZMH	1.359828	7.190774	3.414264	0.001145	0.017299	-1.15556
IDO1	1.775507	8.679523	3.408475	0.001166	0.017299	-1.17188
ITGAL	0.7711	9.56037	3.403179	0.001185	0.017299	-1.1868

INPP5D	-0.5427	9.541458	-3.39696	0.001208	0.017299	-1.20431
IL4R	-0.67607	9.314088	-3.38734	0.001244	0.017411	-1.23133
PNMA1	0.493716	7.613415	3.354058	0.001377	0.01883	-1.32444
IFI35	0.969382	8.010754	3.347083	0.001406	0.01883	-1.34388
OAS3	1.189584	8.26013	3.261993	0.001818	0.023826	-1.57874
CD48	0.79922	9.842579	3.251322	0.001877	0.024087	-1.6079
IFIT2	1.118952	6.988297	3.234844	0.001972	0.024559	-1.65279
IL2RB	1.374052	9.049576	3.23114	0.001993	0.024559	-1.66286
TBX21	1.12226	7.157147	3.205701	0.00215	0.025758	-1.73181
IL12RB1	0.673816	8.378842	3.201907	0.002174	0.025758	-1.74206
FCGR3A	1.292972	9.446034	3.175966	0.002348	0.027287	-1.81191
CD38	0.920631	9.094814	3.136361	0.002638	0.030088	-1.91777
IL15	0.760107	6.711356	3.128191	0.002701	0.030256	-1.9395
KLRD1	0.793256	6.115051	3.092462	0.002998	0.032977	-2.03401
BLK	-1.1766	7.975364	-3.08489	0.003065	0.033118	-2.05393
CCL8	1.219528	7.055763	3.052255	0.003368	0.035769	-2.13944
ISG20	0.717247	10.11517	3.031408	0.003576	0.037101	-2.19371
PRKCE	-0.82587	5.887342	-3.02331	0.00366	0.037101	-2.21471
GZMB	1.547385	8.59741	3.021992	0.003674	0.037101	-2.21813
SELPLG	0.880511	7.908201	3.003457	0.003874	0.038001	-2.26604
CD24	-1.77376	8.772551	-2.9986	0.003928	0.038001	-2.27855
C1QA	1.018479	10.47323	2.996811	0.003948	0.038001	-2.28317
MS4A1	-1.36074	11.28421	-2.9654	0.004317	0.040551	-2.36372
RUNX3	0.636533	10.07637	2.963128	0.004345	0.040551	-2.36954
IFI27	1.283336	10.29536	2.944762	0.004576	0.041909	-2.41633
RELB	-0.71671	8.288034	-2.93626	0.004687	0.041909	-2.43791
IRF7	0.922442	8.860884	2.935733	0.004694	0.041909	-2.43925
IFIH1	0.781991	8.047404	2.916398	0.004957	0.043618	-2.48817
TAP1	0.684132	9.619054	2.895132	0.005261	0.044892	-2.54169
IRF1	0.706484	8.913441	2.890092	0.005335	0.044892	-2.55433
HLA-A	0.670886	13.23759	2.887023	0.005381	0.044892	-2.56202
PSMB9	0.543429	11.01555	2.882298	0.005452	0.044892	-2.57384
GZMA	1.027166	8.617305	2.880291	0.005483	0.044892	-2.57886
IL1R2	1.469087	6.675616	2.876288	0.005544	0.044892	-2.58887
TAP2	0.431886	10.07051	2.871959	0.005612	0.044892	-2.59967
MAGEB2	-1.22169	5.567949	-2.86425	0.005733	0.045276	-2.61888
TLR10	-0.93771	8.071251	-2.85306	0.005914	0.046112	-2.64671
CCR2	1.021202	6.453989	2.839041	0.006147	0.047334	-2.68143

Supplementary Table S2. Patient characteristics in the low, intermediate, and high cytotoxicity signature groups.

		Low	Intermediate	High	*P*-value (Fisher's exact)
Number of patients		24 (100)	23 (100)	19 (100)	
Gender	Female	5 (21)	8 (35)	7 (37)	0.444
	Male	19 (79)	15 (65)	12 (63)	
Age	<60 years	13 (54)	12 (52)	15 (79)	0.155
	≥60 years	11 (46)	11 (48)	4 (21)	
Stage	Early (I-II)	8 (33)	8 (35)	7 (37)	0.698
	Advanced (III-IV)	15 (63)	12 (52)	7 (37)	
	NA	1 (4)	3 (13)	5 (26)	
IPI	Low (0-2)	8 (33)	8 (35)	9 (47)	0.202
	High (3-5)	15 (63)	12 (52)	5 (26)	
	NA	1 (4)	3 (13)	5 (26)	
EBV-status (EBER)	Neg	14 (58)	9 (39)	3 (16)	**0.002**
	Pos	6 (25)	11 (48)	16 (84)	
	NA	4 (17)	3 (13)	0	
Histology	DLBCL	19 (79)	22 (96)	18 (95)	**0.046**
	BURKITT	5 (21)	0	1 (5)	
	HGBL triple hit	0	1 (4)	0	
Time to PTLD	<1 years	0	3 (13)	11 (57.5)	**<0.001**
	1-5 years	5 (21)	5 (22)	3 (16)	
	5-10 years	4 (17)	2 (9)	2 (10.5)	
	≥10 years	15 (63)	13 (57)	3 (16)	
Transplant	Kidney	12 (50)	13 (57)	7 (37)	0.570
	Liver	2 (8)	4 (17)	1 (5)	
	Heart	7 (29)	4 (17)	4 (21)	
	Lung	2 (8)	1 (4)	4 (21)	
	Multiorgan	1 (1)	1 (4)	2 (11)	
	NA	0	0	1 (5)	
Rituximab	Yes	19 (79)	17 (74)	15 (79)	0.974
	No	5 (21)	5 (22)	4 (21)	
	NA	0	1 (4)	0	
Response	CR	13 (54)	12 (52)	15 (79)	0.329
	PR	1 (4)	3 (13)	0	
	PD	4 (17)	2 (9)	0	
	No	1 (4)	1 (4)	2 (10.5)	
	NA	5 (21)	5 (22)	2 (10.5)	

NA, not assigned; IPI, international Prognostic Index; EBER, Epstein-virus-encoded small RNA; DLBCL, Diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Supplementary Table S3. A-B) Cox univariable regression analysis for CIBERSORTx-estimated immune cell types in the PT-ABCL. C) Cox multivariable analysis of CIBERSORTx-estimated cell types together with IPI and rituximab-containing treatment.

A)

Overall survival (OS)		
Cell type	**HR (95% CI for HR)**	***P*-value**
Mast cells activated	5.35 (1.8-16)	0.002
Dendritic cells resting	2.66 (1.3-5.5)	0.009
Tregs	0.0494 (0.003-0.81)	0.035
T cell/B cell ratio	0.946 (0.89-1)	0.048
T cells gamma delta	0.505 (0.25-1)	0.062
T cells CD8	0.467 (0.19-1.1)	0.096
T cells all	0.79 (0.6-1)	0.099
Macrophages M2	0.51 (0.23-1.1)	0.099

B)

Progression-free survival (PFS)		
Cell type	**HR (95% CI for HR)**	***P*-value**
Mast cells activated	4.84 (1.7-14)	0.004
Dendritic cells resting	2.52 (1.2-5.2)	0.013
Tregs	0.0931 (0.009-0.96)	0.046
T cell/B cell ratio	0.964 (0.92-1)	0.102

C)

	OS			PFS	
	HR (95% CI for HR)	*P*-value		HR (95% CI for HR)	*P*-value
Mast cells activated	5.09 (1.53-16.90)	0.008		4.91 (1.52-15.86)	0.008
IPI (3-5)	3.42 (1.60-7.33)	0.002		2.68 (1.31-5.47)	0.007
Rituximab treatment	0.24 (0.12-0.48)	<0.001		0.28 (0.14-0.56)	<0.001
Tregs	0.02 (0.00-0.49)	0.017		0.05 (0.00-0.84)	0.038
IPI (3-5)	4.55 (2.09-9.91)	<0.001		3.38 (1.65-6.92)	0.001
Rituximab treatment	0.25 (0.12-0.51)	<0.001		0.30 (0.15-0.61)	0.001
Dendritic cells resting	1.39 (0.66-2.94)	0.382		1.42 (0.68-2.98)	0.353
IPI (3-5)	3.72 (1.75-7.92)	0.001		2.93 (1.45-5.95)	0.003
Rituximab treatment	0.28 (0.14-0.56)	<0.001		0.32 (0.16-0.64)	0.001

Supplementary Table S4. Characteristics of the patients in the sporadic DLBCL and post-transplant (PT) DLBCL cohorts.

	DLBCL N (%)	PT-DLBCL N (%)	*P*-value
Number of patients	75 (100)	59 (100)	
Age			0.590
<60 years	49 (65)	35 (59)	
≥60 years	22 (35)	24 (41)	
Stage			<0.001
Early (I-II)	8 (11)	20 (34)	
Advanced (III-IV)	67 (89)	30 (51)	
NA	0	9 (15)	
IPI			0.068
Low (0-2)	46 (61)	22 (37)	
High (3-5)	29 (39)	28 (47)	
NA	0	9 (15)	

Supplementary Table S5: Differentially expressed genes between PT-DLBCL and DLBCL of immunocompetent patients (limma analysis results, adj. *P*<0.05)

	log2FC	AveExpr	t	P.Value	adj.P.Val	B
CXCR1	-1.61963	5.60808	-8.60019	1.71E-14	1.17E-11	22.47868
IGLL1	1.274375	4.283295	7.836025	1.20E-12	4.10E-10	18.36093
MAPK8	0.651261	7.270443	7.286958	2.35E-11	5.32E-09	15.48835
IL22RA1	1.088494	3.987124	6.848737	2.36E-10	4.01E-08	13.2599
ITGAE	-0.74666	6.602746	-6.59592	8.66E-10	1.18E-07	12.00406
IFIT1	1.362703	5.851753	6.394428	2.40E-09	2.70E-07	11.02029
HLA.G	-1.13889	8.555458	-6.32507	3.40E-09	2.70E-07	10.68535
IL19	0.831684	3.812963	6.284409	4.17E-09	2.70E-07	10.48991
CCL7	1.014138	4.146597	6.278325	4.30E-09	2.70E-07	10.46073
KLRC1	1.114315	5.309969	6.277689	4.31E-09	2.70E-07	10.45768
DMBT1	2.270163	5.648084	6.275389	4.36E-09	2.70E-07	10.44665
ARG2	0.942949	4.649597	6.128469	9.03E-09	5.12E-07	9.746742
CD4	-0.92524	8.302418	-6.09307	1.07E-08	5.63E-07	9.579499
MEFV	-1.21328	6.042202	-5.99714	1.72E-08	8.35E-07	9.128972
IL7	-1.0465	5.192143	-5.96967	1.96E-08	8.91E-07	9.000727
IL18	-1.06924	8.014538	-5.91073	2.61E-08	1.11E-06	8.72669
YTHDF2	-0.36413	7.759383	-5.7445	5.79E-08	2.32E-06	7.962428
VEGFA	1.209316	7.638523	5.466096	2.13E-07	8.07E-06	6.712226
CD84	-0.77418	8.891452	-5.40625	2.81E-07	1.01E-05	6.448567
CCL20	1.33287	4.9182	5.385254	3.09E-07	1.05E-05	6.356503
PLA2G1B	0.68974	3.755841	5.375996	3.23E-07	1.05E-05	6.315984
TICAM2	-0.64167	7.002253	-5.34231	3.77E-07	1.17E-05	6.16891
SMAD2	-0.44383	8.48017	-5.31935	4.18E-07	1.24E-05	6.06904
IL22RA2	1.219972	5.298521	5.234069	6.15E-07	1.74E-05	5.70045
RELB	-0.58839	7.641631	-5.193	7.39E-07	2.01E-05	5.524341
FOXP3	-1.10725	4.908931	-5.11278	1.06E-06	2.77E-05	5.183027
CD37	-0.79863	9.238307	-5.06025	1.33E-06	3.29E-05	4.961475
IFNL1	-0.90822	5.594024	-5.05738	1.35E-06	3.29E-05	4.949403
MAGEA3	1.148681	4.579706	4.941714	2.24E-06	5.26E-05	4.467201
RORC	0.858507	4.130893	4.844451	3.41E-06	7.75E-05	4.067686
GAGE1	-0.57724	3.791749	-4.76731	4.74E-06	0.000103	3.754776
IL12A	0.727308	4.834142	4.763454	4.82E-06	0.000103	3.739234
CDKN1A	0.972487	7.957458	4.685064	6.72E-06	0.000139	3.425095
ISG15	1.115501	7.221302	4.672791	7.07E-06	0.000142	3.376249
KLRD1	0.816664	5.162785	4.628718	8.50E-06	0.000165	3.201601
EPCAM	1.374291	5.943112	4.608841	9.23E-06	0.000175	3.123225
TLR1	-0.4898	8.368345	-4.54104	1.22E-05	0.000225	2.857751
TNFAIP3	0.814771	8.942367	4.507748	1.40E-05	0.000251	2.728423
IL1R2	1.316792	5.098427	4.491491	1.50E-05	0.000262	2.66553
CD34	0.66487	5.509905	4.443708	1.82E-05	0.00031	2.48165
RAG1	0.607246	3.958914	4.428974	1.93E-05	0.000315	2.425247
ABCB1	0.971582	6.062306	4.421534	1.99E-05	0.000315	2.396817
GPI	0.411446	10.06904	4.421402	1.99E-05	0.000315	2.396312
TLR5	-0.57391	4.470455	-4.38934	2.27E-05	0.000343	2.274195

IL26	0.745543	4.804447	4.389142	2.27E-05	0.000343	2.273457
IRF4	1.142972	9.757452	4.267571	3.68E-05	0.000545	1.816553
BID	-0.49089	5.375727	-4.22296	4.39E-05	0.000636	1.651315
BST2	0.555732	9.113475	4.213808	4.55E-05	0.000644	1.617597
CYFIP2	-0.42728	9.352199	-4.20412	4.73E-05	0.000644	1.581966
OSM	0.79316	5.309042	4.204032	4.73E-05	0.000644	1.581627
INPP5D	-0.4151	9.589336	-4.17916	5.21E-05	0.000691	1.49041
KIT	0.635313	4.034821	4.169325	5.41E-05	0.000691	1.454444
CD70	1.221022	7.365061	4.167191	5.46E-05	0.000691	1.446649
CCL11	1.128568	5.074409	4.166299	5.48E-05	0.000691	1.443392
MASP2	0.673196	4.147214	4.115678	6.66E-05	0.000825	1.25945
ATG12	0.517102	4.742278	4.082066	7.58E-05	0.000922	1.138277
EGR2	-0.75547	6.91755	-4.06993	7.94E-05	0.000949	1.094722
CD1A	0.618044	4.131099	4.031874	9.18E-05	0.001078	0.958771
CX3CR1	-0.68904	5.519371	-3.98426	0.00011	0.001269	0.790089
CD3EAP	0.446736	6.829585	3.9758	0.000113	0.001288	0.760285
TNFRSF8	1.059712	5.944635	3.970439	0.000116	0.001293	0.741423
CHUK	0.264126	8.02744	3.959398	0.000121	0.001307	0.70264
APOE	-0.7947	11.40726	-3.95476	0.000123	0.001307	0.686391
IL6	1.085286	4.828561	3.954696	0.000123	0.001307	0.68615
VCAM1	-0.71286	8.056794	-3.94359	0.000128	0.001341	0.647255
LILRA5	0.94809	5.496124	3.907008	0.000147	0.001504	0.519779
CCR7	1.18285	7.109149	3.904792	0.000148	0.001504	0.512087
HLA.DRA	-0.6377	13.70485	-3.86661	0.00017	0.001707	0.38011
TNFRSF11A	0.714557	4.089909	3.849142	0.000182	0.001794	0.320056
CASP3	-0.3871	8.538872	-3.82597	0.000198	0.001898	0.240751
IL1RAPL2	0.571791	4.420812	3.825966	0.000198	0.001898	0.240733
TNFRSF12A	0.651231	4.697028	3.790727	0.000225	0.002129	0.12086
TFE3	-0.39646	5.910247	-3.7599	0.000252	0.002348	0.016737
AMICA1	-0.64501	8.050964	-3.73394	0.000276	0.002544	-0.07043
IRF2	-0.35637	8.785483	-3.72967	0.000281	0.002549	-0.08473
SPA17	0.529873	6.100022	3.705588	0.000306	0.002742	-0.16506
CD1C	-1.12287	5.627282	-3.67767	0.000338	0.002974	-0.25767
TGFB1	0.389366	10.16323	3.675574	0.000341	0.002974	-0.2646
IL16	-0.5452	10.09741	-3.67202	0.000345	0.002974	-0.27633
RRAD	0.734741	4.10673	3.655173	0.000366	0.003118	-0.33188
HLA.DMB	-0.51305	10.28734	-3.62702	0.000405	0.003361	-0.42422
CD247	-0.73584	7.687275	-3.62695	0.000405	0.003361	-0.42444
CTCFL	0.587335	4.044996	3.612036	0.000427	0.003477	-0.47313
LAMP3	1.040515	5.977611	3.608926	0.000431	0.003477	-0.48326
IRF8	-0.62883	8.988371	-3.60712	0.000434	0.003477	-0.48915
CD53	-0.43679	11.64335	-3.59771	0.000449	0.003539	-0.51974
BIRC5	0.490745	8.60892	3.595468	0.000452	0.003539	-0.52702
TIGIT	-0.76017	7.676906	-3.5887	0.000463	0.003583	-0.54897
IRF7	0.609593	8.428186	3.583121	0.000472	0.003612	-0.56704
RORA	0.760678	6.883321	3.564613	0.000504	0.00381	-0.62683
CD200	-0.7234	6.468784	-3.55671	0.000518	0.003853	-0.65227
RUNX1	-0.40388	7.175897	-3.55043	0.000529	0.003853	-0.67248

CTSH	-0.59029	10.11345	-3.54977	0.00053	0.003853	-0.67459
CCL22	1.345655	6.81964	3.548881	0.000532	0.003853	-0.67744
MICB	0.317821	8.158276	3.526049	0.000576	0.00409	-0.75057
TNFRSF9	-0.75176	6.631332	-3.52563	0.000577	0.00409	-0.75191
IL3	0.493825	3.858987	3.51468	0.000599	0.004203	-0.78684
HLA.DPB1	-0.60832	11.68307	-3.50354	0.000622	0.004323	-0.82227
MNX1	0.448594	3.870545	3.475925	0.000684	0.004658	-0.90974
MR1	-0.38182	6.169821	-3.47592	0.000684	0.004658	-0.90974
PIK3CD	-0.43005	8.926989	-3.46527	0.000709	0.004783	-0.94334
ICAM2	0.392159	7.142096	3.445373	0.000759	0.005021	-1.00583
IL8	1.623886	6.023109	3.445242	0.000759	0.005021	-1.00624
SPINK5	0.75915	4.720207	3.435328	0.000785	0.005119	-1.03726
ECSIT	-0.25854	6.816551	-3.43391	0.000789	0.005119	-1.04169
ITGAL	-0.54884	9.341493	-3.42029	0.000827	0.00531	-1.08419
PTGS2	0.770438	4.694355	3.414444	0.000843	0.005333	-1.10238
ZNF205	0.432083	4.043852	3.413449	0.000846	0.005333	-1.10547
BCL6	-0.62194	9.058603	-3.3931	0.000906	0.00566	-1.16856
PVR	0.531628	6.396148	3.36867	0.000983	0.006087	-1.24392
LY96	-0.5048	7.565407	-3.36487	0.000996	0.006109	-1.25559
CFB	0.764832	6.405705	3.354548	0.001031	0.006267	-1.28727
ICOSLG	0.779478	6.831672	3.349659	0.001048	0.006314	-1.30224
C9	0.604789	3.959499	3.315906	0.001172	0.007	-1.40508
RUNX3	0.418587	9.024241	3.30843	0.001201	0.007113	-1.42774
SYT17	-0.51665	3.839438	-3.29081	0.001273	0.007473	-1.48099
TLR10	-0.59698	7.855467	-3.28094	0.001315	0.007603	-1.51068
IL15	0.484307	6.100339	3.279722	0.00132	0.007603	-1.51436
IFI27	0.882054	9.330432	3.277814	0.001329	0.007603	-1.52009
C1QBP	0.360723	10.06959	3.260482	0.001406	0.00798	-1.57204
MAVS	-0.20155	8.773937	-3.24835	0.001463	0.008167	-1.60828
CCL3	0.719169	7.711545	3.248293	0.001463	0.008167	-1.60844
CLEC6A	0.53984	4.737828	3.244194	0.001483	0.008194	-1.62066
CHIT1	-1.15577	7.086752	-3.24228	0.001492	0.008194	-1.62636
ISG20	0.511509	9.426849	3.238927	0.001508	0.008218	-1.63633
PSEN1	0.286744	7.592947	3.220925	0.001599	0.008643	-1.68974
ADA	-0.47799	8.68003	-3.20326	0.001693	0.009079	-1.7419
ETS1	-0.35896	10.84622	-3.20005	0.001711	0.009102	-1.75135
CREBBP	0.371959	5.19502	3.19645	0.001731	0.009137	-1.76195
LY9	-0.63994	7.086066	-3.18863	0.001775	0.009297	-1.78491
SMPD3	0.710697	4.411578	3.181576	0.001816	0.009438	-1.80559
STAT5B	-0.36098	7.669106	-3.16712	0.001902	0.009811	-1.84785
TYK2	0.244853	8.900936	3.140945	0.002067	0.010585	-1.92394
CTSS	-0.51626	11.01662	-3.10807	0.002294	0.011659	-2.01874
CXCL6	0.871917	5.102942	3.105342	0.002314	0.011673	-2.02656
ATF1	-0.17267	7.359902	-3.09732	0.002373	0.011884	-2.04953
ITGB3	0.76361	4.906061	3.081429	0.002495	0.012339	-2.09492
BAGE	-0.52963	4.579279	-3.07853	0.002518	0.012339	-2.10317
CD33	0.474391	5.044556	3.078416	0.002518	0.012339	-2.1035
TIRAP	0.344309	5.880903	3.076043	0.002537	0.012342	-2.11026

CCL23	0.416973	3.853405	3.064657	0.002629	0.012699	-2.14259
CXCR5	-0.77562	8.396105	-3.05605	0.002701	0.012953	-2.16698
TTK	0.384649	6.869234	3.031368	0.002916	0.013888	-2.23654
PTGDR2	0.357141	3.689012	3.006557	0.003149	0.01476	-2.30598
AICDA	-1.18695	6.326367	-3.00572	0.003157	0.01476	-2.30832
KIR_Inhibiting_Subgroup_2	0.470364	3.786381	3.004945	0.003164	0.01476	-2.31048
DOCK9	0.42269	7.760928	2.993226	0.00328	0.015197	-2.34309
HLA.DRB4	1.569447	6.988282	2.961689	0.003613	0.016623	-2.43029
SAA1	0.990646	6.465814	2.938111	0.003881	0.017738	-2.49496
ITGB4	0.898775	6.204844	2.933157	0.00394	0.017886	-2.50849
GZMK	-0.88007	8.879993	-2.92952	0.003983	0.017905	-2.51842
CXCL5	0.973799	4.749429	2.92844	0.003996	0.017905	-2.52135
GNLY	0.888778	7.393798	2.920089	0.004098	0.018242	-2.54408
HMGB1	-0.33189	9.872018	-2.91654	0.004142	0.018318	-2.55371
LILRA1	0.477462	5.213331	2.908203	0.004248	0.018663	-2.57633
ITGB2	-0.50657	9.323242	-2.89558	0.004412	0.019169	-2.61045
ELK1	0.280784	7.34052	2.895023	0.004419	0.019169	-2.61196
CARD11	-0.48271	8.795557	-2.89171	0.004463	0.019238	-2.62089
SLC11A1	0.763324	6.459142	2.877017	0.004664	0.019975	-2.66041
CFD	0.655978	6.116879	2.874427	0.0047	0.020004	-2.66735
KLRC2	0.667653	4.716461	2.828268	0.005389	0.022796	-2.79022
JAM3	-0.46229	6.021773	-2.82202	0.005489	0.023075	-2.8067
MS4A1	-0.77024	11.03346	-2.80065	0.005845	0.024418	-2.86288
HLA.DPA1	-0.45736	11.92334	-2.7982	0.005887	0.024444	-2.86929
NFATC1	-0.49792	7.327519	-2.7769	0.006264	0.025853	-2.92488
FLT3	-0.40564	4.108547	-2.77274	0.00634	0.02601	-2.93567
TNFSF13B	-0.55334	7.83296	-2.76144	0.006551	0.026609	-2.96497
F2RL1	0.585121	4.146035	2.760759	0.006564	0.026609	-2.96673
CSF1	-0.50517	6.35934	-2.75626	0.00665	0.026798	-2.97835
SLAMF1	0.804838	6.05533	2.745802	0.006854	0.027458	-3.00532
LCN2	1.020271	5.077509	2.740731	0.006955	0.027699	-3.01836
IL11	0.749513	4.300776	2.73107	0.007151	0.028314	-3.04315
FCER2	0.804878	5.963774	2.696367	0.007898	0.031046	-3.13154
XCR1	0.452652	5.482949	2.694822	0.007932	0.031046	-3.13545
MAGEC2	0.498782	4.470441	2.685475	0.008146	0.031699	-3.15908
IL1B	0.840092	6.07609	2.671562	0.008473	0.032721	-3.1941
MAGEA4	0.549678	3.788539	2.670266	0.008505	0.032721	-3.19736
CD81	-0.28339	12.26134	-2.6597	0.008762	0.033339	-3.22383
CEACAM6	0.92515	4.605206	2.659658	0.008763	0.033339	-3.22394
DPP4	0.493147	4.580174	2.64705	0.00908	0.034351	-3.25541
IL18R1	0.573222	6.1948	2.638581	0.009298	0.034979	-3.27648
CR2	0.771144	7.22642	2.636654	0.009348	0.034979	-3.28126
APP	0.482721	9.027216	2.624818	0.009663	0.035861	-3.31058
PTPRC	-0.54721	9.594265	-2.62384	0.009689	0.035861	-3.313
SYCP1	0.377711	3.998369	2.609834	0.010075	0.037086	-3.34752
MSR1	0.683996	6.644257	2.601852	0.010301	0.037714	-3.36713
S100B	-0.44263	4.42827	-2.59646	0.010456	0.038077	-3.38033
CXCL3	0.785067	5.218978	2.588754	0.010681	0.038691	-3.39918

IL1RL1	0.467511	4.958901	2.584836	0.010797	0.038905	-3.40874
CXCL14	-0.97897	7.084406	-2.5762	0.011058	0.039633	-3.42975
SYK	-0.33038	9.940215	-2.56859	0.011292	0.040071	-3.44824
PPARG	0.456462	4.234922	2.568398	0.011298	0.040071	-3.4487
KLRB1	-0.69704	5.88666	-2.55329	0.011776	0.04155	-3.48521
OAS3	0.533633	7.709037	2.551407	0.011837	0.04155	-3.48976
RELA	0.189936	7.279545	2.544452	0.012064	0.04213	-3.50649
CCL13	0.693901	4.81195	2.539081	0.012242	0.0423	-3.51939
ADORA2A	0.27333	7.479124	2.538295	0.012268	0.0423	-3.52128
MAPK11	0.349831	5.981651	2.537376	0.012299	0.0423	-3.52348
IFI35	0.412447	6.959178	2.523073	0.012786	0.043757	-3.55768
RIPK2	0.306107	7.543115	2.521197	0.012852	0.04376	-3.56215
EGR1	0.569629	6.01685	2.518997	0.012929	0.043803	-3.5674
IL10RA	-0.37322	9.317465	-2.51338	0.013127	0.044253	-3.58075
PECAM1	-0.37837	9.04603	-2.50156	0.013553	0.045465	-3.6088
C5	0.402283	5.015763	2.497762	0.013692	0.045707	-3.61777
CMKLR1	-0.36885	8.808234	-2.48743	0.014078	0.046766	-3.64215
IRGM	0.278522	3.689515	2.469828	0.014758	0.048786	-3.68345
TNFSF14	0.470456	5.532055	2.467373	0.014855	0.04887	-3.68919
TLR4	-0.33526	8.0575	-2.46006	0.015147	0.049593	-3.70626
PAX5	-0.479	9.329547	-2.45724	0.015261	0.049728	-3.71283