Supplementary Table S1. List of 315 genes in a NGS panel

ABL1	*BRCA1*	*CRLF2*	*FANCA*	*GSK3B*	*KMT2C*	*NFE2L2*	*PRKAR1A*	*SOX9*
ABL2	*BRCA2*	*CSF1R*	*FANCC*	*H3F3A*	*KMT2D*	*NFKBIA*	*PRKDC*	*SPOP*
ACVR1B	*BRD4*	*CSF3R*	*FANCD2*	*HGF*	*KRAS*	*NKX2-1*	*PRSS1*	*SRC*
AKT1	*BRIP1*	*CTCF*	*FANCE*	*HIST1H3B*	*LMO1*	*NOTCH1*	*PTCH1*	*SRSF2*
AKT2	*BTG1*	*CTNNA1*	*FANCF*	*HNF1A*	*LRP1B*	*NOTCH2*	*PTEN*	*STAG2*
AKT3	*BTK*	*CTNNB1*	*FANCG*	*HOXB13*	*LYN*	*NOTCH3*	*PTPN11*	*STAT3*
ALK	*CALR*	*CUL3*	*FAS*	*HRAS*	*LZTR1*	*NPM1*	*RAC1*	*STK11*
AMER1	*CARD11*	*CUX1*	*FBXW7*	*HSD3B1*	*MAGI2*	*NRAS*	*RAD21*	*SUFU*
APC	*CBL*	*CXCR4*	*FGF4*	*HSP90AA1*	*MAP2K1*	*NSD1*	*RAD50*	*SUZ12*
AR	*CBLB*	*CYLD*	*FGF6*	*ID3*	*MAP2K2*	*NTRK1*	*RAD51*	*TAL1*
ARAF	*CBLC*	*DAXX*	*FGFR1*	*IDH1*	*MAP2K4*	*NTRK2*	*RAF1*	*TCF3*
ARFRP1	*CCND1*	*DDR2*	*FGFR2*	*IDH2*	*MAP3K1*	*NTRK3*	*RB1*	*TERT*
ARID1A	*CCND2*	*DICER1*	*FGFR3*	*IGF1R*	*MAP3K14*	*NUP93*	*RET*	*TET2*
ARID1B	*CCND3*	*DNM2*	*FGFR4*	*IGF2*	*MAPK1*	*PAK3*	*RHEB*	*TGFBR2*
ARID2	*CCNE1*	*DNMT3A*	*FH*	*IKBKE*	*MCL1*	*PALB2*	*RHOA*	*TNFAIP3*
ASXL1	*CD274*	*DOT1L*	*FLCN*	*IKZF1*	*MDM2*	*PAX5*	*RICTOR*	*TNFRSF14*
ATM	*CD79A*	*EED*	*FLT3*	*IKZF3*	*MDM4*	*PBRM1*	*RIT1*	*TOP2A*
ATR	*CD79B*	*EGFR*	*FLT4*	*IL7R*	*MED12*	*PDCD1LG2*	*RNF43*	*TP53*
ATRX	*CDC73*	*EGLN1*	*FOXL2*	*INHBA*	*MEF2B*	*PDGFRA*	*ROS1*	*TRAF3*
AURKA	*CDH1*	*EP300*	*FOXP1*	*INPP4B*	*MEN1*	*PDGFRB*	*RUNX1*	*TSC1*
AURKB	*CDK12*	*EPAS1*	*FRS2*	*IRF2*	*MET*	*PHF6*	*SDHB*	*TSC2*
AURKC	*CDK4*	*EPHA3*	*FUBP1*	*IRF4*	*MITF*	*PIK3C2B*	*SETBP1*	*TSHR*
AXIN1	*CDK6*	*EPHA5*	*GALNT12*	*JAK1*	*MLH1*	*PIK3CA*	*SETD2*	*U2AF1*
AXIN2	*CDK8*	*EPHA7*	*GATA1*	*JAK2*	*MPL*	*PIK3CB*	*SF3B1*	*U2AF2*
B2M	*CDKN2A*	*EPHB1*	*GATA2*	*JAK3*	*MRE11A*	*PIK3R1*	*SLIT2*	*VEGFA*
BAP1	*CDKN2B*	*ERBB2*	*GATA3*	*KAT6A*	*MSH2*	*PIK3R2*	*SMAD2*	*VHL*
BCL2	*CDKN2C*	*ERBB3*	*GATA4*	*KDM5A*	*MSH6*	*PIM1*	*SMAD3*	*WHSC1*
BCL2L1	*CEBPA*	*ERBB4*	*GEN1*	*KDM5C*	*MTOR*	*PLCG1*	*SMAD4*	*WISP3*
BCL6	*CHD2*	*ERG*	*GID4*	*KDM6A*	*MUTYH*	*PMS1*	*SMARCA4*	*WT1*
BCOR	*CHD4*	*ESR1*	*GNA11*	*KDR*	*MYC*	*PMS2*	*SMARCB1*	*XPO1*
BCORL1	*CHEK1*	*ETV6*	*GNA13*	*KEAP1*	*MYCL*	*POLD1*	*SMC1A*	*XRCC2*
BCR	*CHEK2*	*EXO1*	*GNAQ*	*KIT*	*MYCN*	*POLE*	*SMC3*	*XRCC3*
BIRC3	*CIC*	*EZH2*	*GNAS*	*KLHL6*	*MYD88*	*PPM1D*	*SMO*	*ZBTB2*
BLM	*CREBBP*	*FAM175A*	*GREM1*	*KMT2A*	*NF1*	*PPP2R1A*	*SOCS1*	*ZNF217*
BRAF	*CRKL*	*FAM46C*	*GRIN2A*	*KMT2B*	*NF2*	*PRDM1*	*SOX2*	*ZRSR2*

Supplementary Table S2. Clinical features of the distinct genetic subtypes classified by the LymphGen classifier in the study cohort

	EZB	MCD	BN2	ST2	A53
n	73	25	12	14	4
Characteristic					
Gender					
Male	38	18	3	8	4
Female	35	7	9	6	0
Age, years					
≤60	36	5	0	6	3
>60	37	20	12	8	1
Stage of disease					
I-II	21	12	4	7	3
III-IV	48	13	8	6	1
Serum LDH level					
Normal	23	10	2	2	1
Elevated	42	13	10	10	2
ECOG performance status					
0-1	56	19	9	11	3
≥2	9	5	2	1	0
No. of extranodal sites involved					
0-1	52	17	8	12	3
≥2	15	8	4	1	0
IPI risk group					
0-2	43	13	5	9	3
3-5	26	12	7	3	0
B-symptoms					
Absence	46	21	8	10	4
Presence	22	4	4	3	0
Tumor size					
<5 cm	30	8	6	9	3
≥5 cm	24	16	3	3	0
Cell-of-origin subtype					
GCB	61	3	2	10	1
ABC	10	22	10	4	3
$MYC^{inter/hi}BCL2^{hi}$					
No	40	10	6	12	2
Yes	28	14	6	2	2
$MYC^{hi}BCL2^{hi}$					
No	55	13	9	12	4
Yes	14	11	3	2	0

Abbreviations: ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; IPI: International Prognostic Index; GCB, germinal center B-cell–like; ABC, activated B-cell–like.

MYC^{hi}, ≥70% MYC^{+} expression; MYC^{inter}, 40-60% MYC^{+} expression.

Supplementary Table S3. Gene Oncology (GO) category enrichment analysis for gene-expression signatures of DLBCL genetic subtypes

	Enriched gene category of GO terms	
Comparison	**Downregulated**	**Upregulated**
MCD compared with EZB (FDR < 0.05)	EASE sore < 0.05: GO Biological Process: cellular process, morphogenesis, organogenesis, antigen presentation\, exogenous antigen, antigen processing\, exogenous antigen via MHC class II, cell adhesion, cell communication, positive regulation of cell proliferation, development, antigen processing, antigen presentation, negative regulation of cell cycle, regulation of cell proliferation, skeletal development, humoral immune response, cellular morphogenesis, regulation of cellular process, regulation of biological process, immune response. GO Cellular Component: cytoskeleton, cell-substrate adherens junction, focal adhesion. GO Molecular Function: cell adhesion molecule activity, actin binding, receptor signaling protein activity, MHC class II receptor activity, cytoskeletal protein binding, phosphotransferase activity\, alcohol group as acceptor, kinase activity, inositol/phosphatidylinositol kinase activity, transmembrane receptor protein tyrosine kinase signaling protein activity, 3'\,5'-cyclic-nucleotide phosphodiesterase activity, protein binding, cyclic-nucleotide phosphodiesterase activity, DNA binding, SH3/SH2 adaptor protein activity, ubiquitin thiolesterase activity, transmembrane receptor protein tyrosine kinase docking protein activity, extracellular matrix structural constituent conferring tensile strength.	EASE sore < 0.001: GO Biological Process: nucleosome assembly, mitotic cell cycle, RNA processing, RNA metabolism, chromatin assembly/disassembly, tRNA metabolism, DNA metabolism, mitosis, carboxylic acid metabolism, tRNA aminoacylation for protein translation, tRNA aminoacylation, amino acid activation, M phase of mitotic cell cycle, organic acid metabolism, metabolism, tRNA modification, mitotic checkpoint, cell cycle checkpoint, nucleobase\, nucleoside\, nucleotide and nucleic acid metabolism, chromatin, nuclear division. GO Cellular Component: chromosome, intracellular, nucleus, nucleosome, nucleolus, obsolete cellular component, nuclear membrane, pore complex, nuclear pore, chromatin. GO Molecular Function: purine nucleotide binding, nucleotide binding, ATP binding, adenyl nucleotide binding, helicase activity.
MCD compared with unsubtyped/'Other'	EASE sore < 0.05: GO Biological Process: cellular process, cell communication, cGMP biosynthesis, cGMP metabolism, signal transduction, cell adhesion,	EASE sore < 0.0001: GO Biological Process: metabolism, DNA metabolism, mitotic cell cycle, nucleobase\, nucleoside\, nucleotide and nucleic acid metabolism, RNA

genetic subtype (FDR < 0.10)	intracellular signaling cascade, muscle development, morphogenesis. GO Cellular Component: extracellular matrix, cytoskeleton, plasma membrane, protein binding, actin binding, cytoskeletal. GO Molecular Function: protein binding, actin binding, cytoskeletal protein binding, cell adhesion molecule activity, inositol/phosphatidylinositol kinase activity, guanylate cyclase activity, transcription factor binding, phosphorus-oxygen lyase activity, heparin-glucosamine 3-O-sulfotransferase activity.	metabolism, RNA processing, nucleosome assembly, cell cycle, DNA replication and chromosome cycle, S phase of mitotic cell cycle, mitosis, M phase of mitotic cell cycle, chromatin assembly/disassembly, DNA replication, nuclear division, regulation of mitosis, M phase, DNA packaging, DNA repair, DNA dependent DNA replication, establishment and/or maintenance of chromatin architecture, response to DNA damage stimulus, regulation of cell cycle, response to endogenous stimulus, RNA splicing. GO Cellular Component: intracellular, nucleus, nucleolus, chromosome, ribonucleoprotein complex, nucleosome, obsolete cellular component, chromatin. GO Molecular Function: nucleic acid binding, ATP binding, adenyl nucleotide binding, DNA binding, purine nucleotide binding, nucleotide binding, RNA binding.
EZB compared with unsubtyped/'Other' genetic subtype (FDR ≤ 0.01)	EASE sore < 0.05: GO Biological Process: protein amino acid phosphorylation, cell communication, phosphorylation. GO Molecular Function: protein serine/threonine kinase activity, transferase activity\, transferring phosphorus-containing groups.	EASE sore < 0.05: GO Biological Process: antigen presentation\, exogenous antigen, antigen processing\, exogenous antigen via MHC class II, phosphorylation, protein kinase cascade, phosphorus metabolism, phosphate metabolism, protein amino acid phosphorylation. GO Cellular Component: nucleus. GO Molecular Function: phosphotransferase activity\, alcohol group as acceptor, kinase activity, transferase activity\, transferring phosphorus-containing groups, receptor signaling protein activity, transmembrane receptor protein tyrosine kinase signaling protein activity, protein kinase activity, RNA polymerase II transcription factor activity, DNA binding, nucleic acid binding, transmembrane receptor protein tyrosine kinase docking protein activity, MHC class II receptor activity, protein serine/threonine kinase activity.

Abbreviations: FDR, false discovery rate; EASE: Expression Analysis Systematic Explorer (A desktop version of DAVID).

Supplementary Table S4. Clinical features of DLBCL patients stratified by MYC/BCL2 double-expression (DE) status and high-grade B-cell lymphoma patients with *MYC*/*BCL2* double-hit

MYC/BCL2	MYC^{hi} DE	MYC^{inter} DE	NonDE	Double-hit
n	73	68	262	6
Characteristic				
Gender				
Male	38	34	152	4
Female	35	34	110	2
Age, years				
≤60	21	22	125	3
>60	52	46	137	3
Stage of disease				
I-II	24	24	131	1
III-IV	45	41	123	4
Serum LDH level				
Normal	24	27	90	1
Elevated	43	36	158	4
ECOG performance status				
0-1	51	51	202	4
≥2	16	7	39	1
No. of extranodal sites involved				
0-1	47	46	193	2
≥2	22	18	57	3
IPI risk group				
0-2	31	37	170	3
3-5	39	29	85	2
B-symptoms				
Absence	42	40	170	5
Presence	27	26	81	0
Tumor size				
<5 cm	30	31	127	2
≥5 cm	31	17	77	2
Treatment response				
CR	47	62	238	3
Non-CR	26	6	24	3
Cell-of-origin by GEP				
GCB	16	17	124	6
ABC	46	36	80	0
Unclassified	4	6	25	0
Cell-of-origin by GEP and/or IHC				
GCB	22	22	149	6
ABC	61	46	109	0
Genetic subtypes				
EZB	11	14	39	4
MCD	11	3	10	0
ST2	2	0	12	0
BN2	3	3	6	0
A53	0	2	2	0
Other	47	46	193	2

Abbreviations: ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; IPI: International Prognostic Index; CR, complete response; GEP, gene expression profiling; GCB, germinal center B-cell–like; ABC, activated B-cell–like; IHC, immunohistochemistry.
MYC^{hi}, ≥70% MYC^{+} expression; MYC^{inter}, 40-60% MYC^{+} expression.

Supplementary Table S5. Multiple testing corrections for prognostic significance of immune microenvironment biomarkers on overall survival (OS) in LymphGen-unclassfied cases with the Benjamini-Hochberg method

Immune microenvironment biomarker	*P*-value for OS by Log-rank test	Benjamini-Hochberg significance FDR<0.05	Benjamini-Hochberg *P*-value
PD-L1$^+$ in T cells	0.0006	Significant	0.006
PD-1$^+$ in CD4 T cells	0.0011	Significant	0.006
PD-L1$^+$ in NK cells	0.0013	Significant	0.006
FN1$^+$	0.0026	Significant	0.0091
High CD8 T cell infiltration	0.0085	Significant	0.0233
PD-L1$^+$ in macrophages	0.01	Significant	0.0233
PD-L2$^+$ in B cells	0.02	Significant	0.04
Low Treg infiltration	0.024	Significant	0.042
Low NK cell infiltration	0.029	Significant	0.0451
High macrophage infiltration	0.034	Significant	0.0467
PD-L1$^+$ in B cells	0.039	Significant	0.0467
PD-1$^+$ in CD8 T cells	0.04	Significant	0.0467
CTLA-4$^+$ in T cells	0.047	Not significant	0.0506
PD-L2$^+$ in macrophages	0.21	Not significant	0.21

Abbreviations: FDR, false discovery rate; NK, natural killer; Treg, regulatory T cells.

Supplementary Table S6. Multiple testing corrections for prognostic impact of mutations on overall survival (OS) and progression-free survival (PFS) with the Benjamini-Hochberg method

Gene with mutation	*P*-value for OS by Log-rank test	Benjamini-Hochberg significance	Benjamini-Hochberg *P*-value
SMARCA4	0.025 (worse OS)	Significant	0.248
ARID1A	0.03 (worse OS)	Significant	0.248
KMT2D	0.031 (worse OS)	Significant	0.248
TET2	0.053 (worse OS)	Not significant	0.318
CDKN2A	0.077	Not significant	0.328
KRAS	0.082	Not significant	0.328
MYC	0.157	Not significant	0.538
NOTCH2	0.203	Not significant	0.609
CD79B	0.279	Not significant	0.713
TP53	0.297	Not significant	0.713
MYD88	0.371	Not significant	0.776
CARD11	0.422	Not significant	0.776
STAT3	0.449	Not significant	0.776
PRDM1	0.471	Not significant	0.776
PIM1	0.517	Not significant	0.776
ARID1B	0.517	Not significant	0.776
NFKBIA	0.649	Not significant	0.835
KMT2A	0.677	Not significant	0.835
FAS	0.687	Not significant	0.835
EZH2	0.696	Not significant	0.835
RB1	0.771	Not significant	0.881
ETV6	0.89	Not significant	0.927
APC	0.921	Not significant	0.927
CREBBP	0.927	Not significant	0.927
Gene with mutation	***P*-value for PFS by Log-rank test**	**Benjamini-Hochberg significance**	**Benjamini-Hochberg *P*-value**
SMARCA4	0.003 (worse PFS)	Significant	0.072
ARID1A	0.028 (worse PFS)	Significant	0.24
TET2	0.035 (worse PFS)	Significant	0.24
CDKN2A	0.04 (better PFS)	Significant	0.24
KMT2D	0.099	Not significant	0.451
KRAS	0.116	Not significant	0.451
PRDM1	0.157	Not significant	0.451
MYC	0.163	Not significant	0.451
CREBBP	0.169	Not significant	0.451
ARID1B	0.293	Not significant	0.703
CD79B	0.351	Not significant	0.766

EZH2	0.498	Not significant	0.84
NFKBIA	0.535	Not significant	0.84
PIM1	0.549	Not significant	0.84
STAT3	0.561	Not significant	0.84
TP53	0.587	Not significant	0.84
ETV6	0.671	Not significant	0.84
CARD11	0.695	Not significant	0.84
KMT2A	0.732	Not significant	0.84
FAS	0.736	Not significant	0.84
MYD88	0.77	Not significant	0.84
APC	0.77	Not significant	0.84
RB1	0.916	Not significant	0.919
NOTCH2	0.919	Not significant	0.919

Significant mutation factors at Benjamini-Hochberg false discovery rate of 0.25 are in bold.

Supplementary Table S7. Multiple testing corrections for prognostic significance of immune microenvironment biomarkers with the Benjamini-Hochberg method

(1), effect on overall survival (OS) in MYC/BCL2 double-high expressors

Biomarker	*P*-value for OS by Log-rank test	Benjamini-Hochberg significance FDR<0.05	Benjamini-Hochberg *P*-value
FN1 positive expression	0.0007	Significant	0.0098
T cell deficiency	0.012	Not significant	0.06
PD-L1^{+} in T cells	0.02	Not significant	0.06
NK cell deficiency	0.023	Not significant	0.06
PD-1^{+} high in CD8 T cells	0.023	Not significant	0.06
PD-1^{+} high in CD4 T cells	0.03	Not significant	0.06
CTLA-4^{+} in CD4 T cells	0.03	Not significant	0.06
PD-L2^{+} in macrophages	0.071	Not significant	0.071
PD-L1^{+} in B cells	0.085	Not significant	0.085
Macrophage infiltration	0.13	Not significant	0.13
PD-L2^{+} in B cells	0.16	Not significant	0.16
PD-L1^{+} in macrophages	0.32	Not significant	0.32
CTLA-4^{+} in CD8 T cells	0.4	Not significant	0.4
PD-L1^{+} in NK cells	0.65	Not significant	0.65

(2), effect on progression-free survival (PFS) in MYC^{intermdiate} BCL2^{hi} double expressors

Biomarker	*P* for PFS by Log-rank test	Benjamini-Hochberg significance FDR<0.05	Benjamini-Hochberg *P*-value
High FN1 expression	0.0037	Significant	0.048
PD-L1^{+} in NK cells	0.028	Not significant	0.18
PD-L1^{+} in T cells	0.056	Not significant	0.24
PD-L1^{+} in macrophages	0.089	Not significant	0.29
PD-L1^{+} in B cells	0.16	Not significant	0.42
PD-1^{+} in CD4 T cells	0.21	Not significant	0.455
CTLA-4^{+} in T cells	0.32	Not significant	0.52
PD-L2^{+} in B cells	0.32	Not significant	0.52
T cell infiltration	0.53	Not significant	0.63
PD-1^{+} high in CD8 T cells	0.53	Not significant	0.63
NK cell infiltration	0.58	Not significant	0.63
Macrophage infiltration	0.58	Not significant	0.63
PD-L2^{+} in macrophages	0.75	Not significant	0.75

(3), effect on OS in non-double expressors

Biomarker	*P* for PFS by Log-rank test	Benjamini-Hochberg significance FDR<0.05	Benjamini-Hochberg *P*-value
High FN1 expression	<0.0001	Significant	0.0011
PD-L2$^+$ in macrophages	0.0047	Significant	0.02567
PD-L2$^+$ in B cells	0.007	Significant	0.02567
NK cell infiltration	0.022	Not significant	0.0605
PD-L1$^+$ in T cells	0.036	Not significant	0.0644
PD-1$^+$ high in T cells	0.04	Not significant	0.0644
PD-L1$^+$ high in macrophages	0.041	Not significant	0.0644
CTLA-4$^+$ in T cells	0.069	Not significant	0.0949
Macrophage infiltration	0.098	Not significant	0.113
CD8 T cell infiltration	0.10	Not significant	0.11
PD-L1$^+$ in B cells	0.11	Not significant	0.11

Abbreviation: FDR, false discovery rate.

Supplementary Figure legends

Figure S1. Prognostic analysis for LymphGen genetic subtypes of DLBCL. (A) A pie chart showing the proportion of genetic subsets in the study cohort classified by the LymphGen classifier web tool. **(B)** Within the germinal center B-cell–like (GCB) cell-of-origin (COO) subtype of DLBCL, the EZB genetic subtype showed a non-significant unfavorable progression-free survival (PFS) compared with combined ST2, BN2, MCD, and A53 subtype cases. Within the activated B-cell–like (ABC) COO subtype of DLBCL, combined MCD and EZB subtype cases showed a non-significant unfavorable overall survival (OS) compared with combined ST2, BN2, and A53 subtype cases. **(C)** Patients with MCD subtype had non-significant poorer OS in overall DLBCL, DLBCL, not otherwise specified (NOS), and patients with *MYD88* mutations. The case plot above is for all cases with *MYD88* or *CD79B* mutations to show their overlaps with the MCD subtype. Abbreviations: Mut, mutation; *CD79B*-ITAM, *CD79B* mutations in the immunoreceptor tyrosine-based activation motif (ITAM) of CD79B.

Figure S2. Gene-expression profiling and immune profiling analysis for DLBCL genetic subtypes. ***(*****A)** Heatmaps for gene-expression signatures associated with EZB and MCD subtypes. **(B)** Top, a box plot to show the distribution and significant differences in absolute cell counts of immunophenotypes between MCD and EZB subtypes by two-sided Mann-Whitney U test. Significant differences are marked by asterisks. *: $P \leq 0.05$, **: $P \leq 0.01$. Bottom, two scatter plots comparing T cell percentages (CD4 and CD8 T cell numbers divided by total number of B cells, T cells, macrophages, and natural killer cells) between genetic subtypes. The two *P* values for each comparison are by unpaired *t* test and Mann-Whitney test, respectively. Statistically significant *P* values are in bold.

Figure S3. Prognostic analysis for MYC/BCL2 expression in DLBCL genetic subsets and immune microenvironment analysis in EZB and LymphGen-unsubtyped cases. (A) High

MYC expression (≥70%) was associated with significantly poorer overall survival (OS) in the EZB genetic subtype. With a ≥40% cutoff for MYC^+, MYC^+BCL2^+ double-expression (DE) was not significantly associated with poorer OS in the EZB subtype. **(B)** MYC/BCL2 double-high expression (DhE) was not associated with significant prognostic effects within the MCD and ST2 subtypes. **(C)** In genetically unsubtyped cases by the LymphGen algorithm, both DhE and DE were associated with significantly poorer OS and progression-free survival (PFS). However, single MYC-high expression was not associated with poorer survival ($MYC^{hi}BCL2^{low}$ compared with MYC^{low} cases) in LymphGen-unsubtyped cases. **(D)** Left, two scatter plots to show that DhE was significantly associated with lower T-cell PD-1 expression within the EZB subtype and lower CD4 T-cell infiltration in LymphGen-unsubtyped DLBCL cases. Right, *FN1* mRNA expression was significantly associated with favorable prognostic effects in overall DLBCL and the EZB subset.

Figure S4. Prognostic analysis for immune microenvironment biomarkers in DLBCL genetic subsets. (A) A clustermap to show clusters based on mean absolute cell counts of immunophenotypes in DLBCL genetic subtypes. **(B)** Left, a scatter plot to show that FN1 expression in the EZB subset of DLBCL was associated with a lower mean level of NK cell infiltration (assessed by percentage of NK cells). Each point represents one patient. Right, Kaplan-Meier curves to show that in EZB, FN1 expression and NK cell infiltration had significant adverse prognostic effects independent of MYC/BCL2 double-high expression (DhE) status. **(C)** In MCD cases with MYC/BCL2 DhE, CD8 T cell infiltration was significantly associated with better OS. High PD-L1 expression in macrophages (>50%) was associated with a non-significant better OS in MCD. High FN1 expression was significantly associated with poorer OS within MCD subtype with a >30% cutoff and within BN2 subtype with a >50 cutoff.

(D) In the ST2 genetic subset, high levels of T cell infiltration (≥25% of the total number of B/T/macrophage/NK cells in a DLBCL sample), positive macrophage/NK cell infiltration, and PD-L1 expression in B cells were associated with significantly poorer OS.

Figure S5. Significant prognostic effects of immune microenvironment biomarkers in genetically unsubtyped DLBCL subset. Most effects resembled those in overall DLBCL except for $CD68^{+}$ percentages and PD-L1 expression in B cells.

Figure S6. Comparisons of genetic features between DLBCL subgroups by Fisher's exact test. (A) DLBCL with MYC/BCL2 double-high expression (DhE) compared DLBCL without MYC/BCL2 double-expression (DE) more frequently had *MYD88* mutation, *CD79B* mutation, *PIM1* mutation and *PRDM1* mutation. **(B)** DhE-DLBCL compared with DLBCL with intermediate MYC expression (MYC^{inter}) and high BCL2 expression (double expressor, DE) more frequently had *CREBBP* mutation, *CD79B* mutation, and *PRDM1* mutation. **(C)** DhE-DLBCL compared with non-DE and MYC^{inter} DE-DLBCLs had a significantly higher frequency of MCD genetic subtype. Abbreviations: MUT, mutated; WT, wild-type.

Figure S7. CONSORT diagram for the studied cohort and the prognostic effects of the LymphGen genetic subtypes in DLBCL subgroups stratified by MYC/BCL2 expression. Abbreviations: HGBCL, high-grade B-cell lymphoma; DH, double-hit; DLBCL, NOS, diffuse large B-cell lymphoma, not otherwise specified; hi, high expression; inter, intermediate expression; OS, overall survival.

Figure S8. Prognostic analysis for genetic mutations in DLBCL, not otherwise specified (NOS) cases with MYC/BCL2 double-high expression (DhE). (A) In DhE-DLBCL-NOS, *SMARCA4*, *ARID1A*, and *TET2* mutations were significantly associated with poorer overall

survival (OS) or progression-free survival (PFS), whereas *CDKN2A* mutation was associated with better PFS. **(B)** *TET2* mutation status was associated with poorer OS significantly in non-DhE cases and with border-line significance in DhE DLBCL-NOS. In contrast, *KMT2D* mutations showed significant adverse effect on OS only in DhE but not non-DhE cases. The prognostic impact of DhE in DLBCL-NOS was independent of *TET2* and *KMT2D* mutations. **(C)** Case distribution plot for cases with DhE or *KMT2D* mutations. Each column represents one patient. *KMT2D* mutations were associated with the EZB subtype (in both DhE and nonDhE). **(D)** In the EZB genetic subset, DhE cases with *KMT2D* mutations but not those without *KMT2D* mutations had significantly poorer OS compared with non-DhE cases with or without *KMT2D* mutations. In contrast, the prognostic significance of DhE in LymphGen-unsubtyped cases was independent of *KMT2D* mutations.

Figure S9. Significant prognostic effects of MYC/BCL2 double expression (DE) in genetic subtypes and prognostic analysis for genetic subtype/mutations in DE cases in two validation cohorts. (A) In the BCCA cohort as a validation cohort, only in EZB and (especially) LymphGen-unsubtyped genetic subsets, DE showed significant prognostic impact on overall survival (OS, which was the disease specific survival [DSS] according to Wright et al, Cancer Cell 2020). **(B)** Left, MCD genetic subtype and ABC molecular subtype were enriched in DLBCL-NOS cases with DE in the BCCA cohort. Right, LymphGen-unsubtyped/'Other' genetic subset was associated with significantly poorer survival in $MYC^{+}BCL2^{+}$ DE cases of the BCCA cohort. *KMT2D* mutations were associated with significantly poorer survival in combined A53, composite EZB/A53, and LymphGen-unsubtyped DE cases. **(C)** In another validation cohort deposited by Reddy et al (PMID 28985567), *KMT2D* mutations were associated with significantly poorer survival in $MYC^{+}BCL2^{+}$-DE but not nonDE cases.

Figure S10. Significant prognostic effects of immune microenvironment biomarkers within DLBCL subgroups with or without MYC/BCL2 double expression (DE). (A) A clustermap based on mean absolute cell counts in DLBCL-NOS cases with MYC/BCL2 double-high expression (DhE, ≥70% cutoff), non-DhE, and high-grade B-cell lymphoma with *MYC*/*BCL2* double hit (DHL). **(B)** In DLBCL-NOS cases with DhE, PD-1-high expression in CD4/CD8 T cells and PD-L1 expression in T cells were associated with significantly poorer overall survival (OS). **(C)** In the DE-DLBCL-NOS subset with intermediate MYC expression (40-60%), FN1-high expression in stromal cells (≥50% cutoff) was associated with significantly poorer progression-free survival (PFS), and PD-L1 expression in T cells and NK cells was associated with significantly poorer OS. **(D)** In LDBCL-NOS with nonDE, FN1-high expression (≥30%), PD-1-high expression in T cells, and PD-L1-high expression in macrophages were associated with significantly poorer OS, whereas high levels of NK cell infiltration and PD-L2 expression were associated with significantly better OS.