

Supplemental File

Methods

The cell-of-origin subgroup was defined by immunohistochemistry using the Hans' algorithm¹. For the discovery set only, cell-of-origin molecular subtype was assigned using a modified RUO version of the NanoString Lymphoma Subtyping Test (LST) algorithm², as previously described³.

Table S1. Clinical and pathological characteristics

<i>Characteristics</i>	<i>Discovery set (n, 22)</i>		<i>Validation set (n, 53)</i>	
	<i>THRLBCL (n, 12)</i>	<i>DLBCL (n, 10)</i>	<i>THRLBCL (n, 20)</i>	<i>DLBCL (n, 33)</i>
Age				
Median (range), y	44 (27-55)	58 (28-62)	52 (34-59)	62.5 (28-82)
Sex, n (%)				
Female	4 (33)	4 (40)	5 (25)	12 (35)
Male	8 (67)	6 (60)	15 (75)	22 (65)
COO (Hans), n (%)				
GCB	0 (0)	5 (50)	0 (0)	11 (33)
Non-GC	12 (100)	5 (50)	6 (30)	19 (58)
n.a.	-	-	14 (70)	3 (9)
COO (GEP), n (%)				
GCB	9 (75)	7 (70)	4 (20)	4 (12)
Unclassifiable	2 (17)	2 (20)	1 (5)	0 (0)
ABC	1 (8)	1 (10)	0 (0)	1 (3)
n.a.	-	-	15 (75)	28 (85)
aaIPI, n (%)				
0-1	0 (0)	0 (0)	0 (0)	7 (21)
2-3	12 (100)	10 (100)	16 (80)	24 (73)
n.a.	-	-	4 (20)	2 (6)

Abbreviations: THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; COO, Cell of origin category; GCB, germinal centre like; ABC, activated B-cell like; GEP, gene expression profiling (Lymph2Cx); aaIPI, age-adjusted International Prognostic Index; n.a., information not available.

Table S2. Patient characteristics and TCF7/TCF1 expression in r/r THRLBCL treated with pembrolizumab (adapted from *Griffin et al, Blood 2021*)⁴

	Patients		
	"1"	"3"	"5"
Prior therapies, n	2	2	2
Prior anti-CD19 CAR-T cells	No	No	No
Cycles of pembrolizumab, n	32	14	5
Best radiographic response	CR (ongoing*)	PR	PD
TCF7/TCF1 (% of positive cells)	29	29	13

* CR > 2 years.

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease.

Identification of EOMES-upregulated genes in THRLBCL cases.

Table S3. Genes differentially expressed in control and *EOMES*-overexpressing OT-I cells according to Li⁵, selected with Fold Change ≥ 2 and FDR $\leq .01$.

GeneID	log2FoldChange	FDR	Symbol
22354	2.807354922	0.009982753	Vipr1
76491	0.650001622	0.009747917	Abhd14b
244668	0.614709844	0.009535607	Sipa112
73332	0.88810712	0.009454893	Ccdc30
319939	1.137503524	0.009101881	Tns3
14218	0.847996907	0.00883886	Sh3pxd2a
545651	5	0.00849083	Gm13278
241589	2	0.008488329	D430041D05Rik
100043468	0.840801405	0.008179099	Zfp955b
22173	1.109624491	0.007987613	Tyr
626854	1.072756342	0.007772314	Gm38396
114774	1.479167837	0.007291949	Pawr
71918	0.941897045	0.007128705	Zcchc24
57248	2.345774837	0.006796401	Ly6i
73852	0.898554736	0.006790665	D3Erd751e
633640	0.664815808	0.00592919	Tmem267
76681	0.770241749	0.005811766	Trim12a
545732	0.6631801	0.005734823	4933402N22Rik
317750	1.757429697	0.005496184	Slc24a5
20668	0.793549123	0.005414885	Sox13
74616	0.766902878	0.005034387	Scrn3
546644	5.906890596	0.004603557	Ly6g

14027	0.903784685	0.004526169	Evpl
75516	0.680754326	0.004497881	Ttc32
52855	0.835770604	0.004239074	Lair1
233878	2	0.004175487	Sez6l2
70892	3.321928095	0.004080626	Ttll7
72514	0.667424661	0.003916598	Fgfbp3
17096	0.614506776	0.0037109	Lyn
232491	0.61693489	0.003529171	Pyroxd1
72599	0.611253799	0.003345679	Pdia5
56274	0.773229138	0.003017889	Stk3
74185	0.62702656	0.002815919	Gbe1
72058	1.099535674	0.002795718	Igsf5
170772	0.649092838	0.002679024	Glcci1
93896	3.459431619	0.002488663	Glp2r
224585	0.902152677	0.002441604	Zfp160
66724	0.63005039	0.00230977	Tab3
320506	0.791413378	0.002256245	Lmbrd2
12514	0.776261153	0.00222111	Cd68
17067	2.560714954	0.002103441	Ly6c1
100039707	0.593764816	0.002020641	Mthfsl
60411	0.589932175	0.001711125	Cenpk
27355	1.154328146	0.001691239	Pald1
11555	1.392317423	0.00154531	Adrb2
224170	0.617383978	0.00151917	Dzip3
16409	4	0.001485554	Itgam
56217	0.658963082	0.001380702	Mpp5
545490	5.554588852	0.001336197	Zfp973
21990	0.9510904	0.001263273	Tph1
66689	0.894290559	0.001190818	Klhl28
79560	0.713529039	0.001145007	Ublcp1
282663	2.321928095	0.001077387	Serpinb1b
14191	0.764783538	0.001071293	Fgr
626848	0.816445658	0.001030568	Zfp971
224694	1.032061209	0.000903535	Zfp81
17436	0.880418384	0.00087823	Me1
407786	0.584962501	0.00070732	Taf9b
237759	1.337034987	0.000704494	Col23a1
245638	0.788495895	0.000670397	Tbc1d8b
67225	0.670760373	0.000663304	Rnpc3
171180	1.097847323	0.000523575	Syt12
19223	2.304854582	0.000424345	Ptgis
12286	0.768674454	0.000410175	Cacna1a
100041979	1.930737338	0.000403666	Gm3604
433801	1.222392421	0.000403625	Gm13212
11567	2.925999419	0.000311108	Avil
233987	0.853158612	0.000266968	Zfp958
94229	4.087462841	0.000257078	Slc4a10
100041677	0.725140159	0.00023606	Zfp984
50928	1.793549123	0.000215778	Klrg1
12753	0.656045599	0.000180942	Clock
268515	1.925999419	0.000151346	Bahcc1
12217	0.706268797	0.000138354	Bsn
56468	0.710493383	0.000127839	Socs5
66259	1.431339312	0.000110926	Camk2n1
320116	0.617181237	0.000110326	Fndc9
399510	2.152003093	0.000106294	Map4k5

28105	0.702095134	0.000105688	Trim36
22439	0.780034316	0.000103885	Xk
214763	0.672758105	9.66E-05	Mb21d1
71398	0.86318331	7.34E-05	5430427O19Rik
67246	0.719892081	5.09E-05	2810474O19Rik
84111	4.564784619	4.25E-05	Gpr87
170741	0.775205452	3.70E-05	Pilrb1
26904	2.526545814	3.65E-05	Sh2d1b1
214254	0.872888082	3.25E-05	Nudt15
217653	0.688871306	3.10E-05	Mis18bp1
380863	1.521050737	2.90E-05	Tmem171
30046	0.65838357	2.52E-05	Zfp292
71710	1.183221824	1.62E-05	Lrrcc1
105377	0.606885816	1.42E-05	Slf1
630579	1.371968777	1.41E-05	Zfp808
67030	0.582018224	1.31E-05	Fanc1
330938	2.152003093	1.04E-05	Dixdc1
224796	0.762500686	9.70E-06	Clic5
26386	1.234169589	8.71E-06	Hsf4
19212	0.721166884	7.22E-06	Pter
240641	0.68589141	4.56E-06	Kif20b
74513	0.662965013	4.01E-06	Neto2
18536	0.657718843	3.86E-06	Pcm1
627049	0.609415544	2.36E-06	Zfp800
93734	1.830074999	2.22E-06	Mpv171
14457	4.247927513	2.00E-06	Gas7
11852	0.581097792	1.48E-06	Rhob
19218	2.373458396	1.43E-06	Ptger3
18139	0.584962501	1.42E-06	Zfp638
26885	0.589669503	1.14E-06	Casp8ap2
57257	1.240314329	1.05E-06	Vav3
320940	0.717856771	8.38E-07	Atp11c
69590	1.319349551	7.18E-07	Gpx8
320916	1.238404739	2.58E-07	Wscd2
81703	0.819879231	1.28E-07	Jdp2
333789	0.694292258	9.65E-08	N4bp2
233529	0.902952227	9.48E-08	Kctd14
93759	0.583851453	7.37E-08	Sirt1
170439	0.629416099	6.54E-08	Elovl6
72640	0.968635829	6.51E-08	Mex3a
22601	0.740567831	5.33E-08	Yap1
76089	0.907881798	5.29E-08	Rapgef2
19877	0.633461018	4.93E-08	Rock1
381511	0.857127918	4.20E-08	Pdp1
140488	0.593502792	3.07E-08	Igf2bp3
76464	0.872125177	2.55E-08	Kn1
76131	0.833827133	2.32E-08	Depdc1a
677296	3.295455884	1.98E-08	Fcrl6
75339	0.626782676	1.37E-08	Mphosph8
21950	0.782825288	1.36E-08	Tnfsf9
22330	0.765965466	1.34E-08	Vcl
99003	0.847996907	1.25E-08	Qser1
21872	2.925999419	9.78E-09	Tjp1
239217	1.333423734	2.06E-09	Kctd12
71862	0.945469887	1.45E-09	Gpr160
229715	0.782408565	1.37E-09	Amigol

226551	0.719162772	1.21E-09	Suco
14537	0.648387881	1.02E-09	Gcnt1
320878	1.062060968	9.10E-10	Mical2
68725	0.619968951	4.27E-10	1110032F04Rik
171212	0.624112254	2.95E-10	Galnt10
22759	6.044394119	2.22E-10	Zfp97
268469	0.655385855	2.05E-10	Zfp652
241447	0.736965594	1.64E-10	Cers6
73288	0.657635151	1.32E-10	Vps50
237928	2.246311048	1.24E-10	Phospho1
78826	0.615177114	9.74E-11	P2ry10
263406	0.828087541	3.75E-11	Plekhg3
16468	0.633056789	2.19E-11	Jarid2
269643	2.201633861	1.99E-11	Ppp2r2c
72446	1.084064265	1.16E-11	Prr51
171170	0.666169816	1.05E-11	Mbnl3
27278	1.76213617	5.91E-12	Clnk
72258	1.079007874	5.16E-12	Kcnk10
19267	0.959358016	3.88E-12	Ptpre
17231	3.412598454	2.47E-12	Mcpt8
75317	0.708407983	1.56E-12	Parpbp
67241	0.596985029	1.49E-12	Smc6
353346	0.742951889	1.23E-12	Gpr141
16554	0.843790796	3.37E-13	Kif13b
22035	0.813148886	3.30E-13	Tnfsf10
21682	0.674253764	2.43E-13	Tec
19055	0.606360538	1.50E-13	Ppp3ca
68268	0.660403257	7.01E-14	Zdhhc21
71592	0.732519689	5.83E-14	Pogk
52055	1.009460329	4.18E-14	Rab11fip5
94185	0.997285615	2.73E-14	Tnfrsf21
244416	1.019808481	2.25E-14	Ppp1r3b
14127	1.253493639	7.07E-15	Fcer1g
18106	0.992569795	3.57E-16	Cd244
14064	0.946800433	1.68E-16	F2rl2
58250	0.679929851	9.46E-17	Chst11
69601	1.154471349	2.72E-17	Dab2ip
64008	1.163583475	2.64E-17	Aqp9
100041546	1.069554676	2.51E-17	Ly6c2
20688	1.035046947	1.27E-17	Sp4
83671	0.91478961	1.01E-18	Sytl2
276905	0.832890014	5.35E-19	Armc7
226090	0.615447775	3.26E-19	Ermp1
98582	4.708344916	1.62E-19	Khdc1b
269639	0.841412253	3.96E-20	Zfp512
171504	0.950860598	1.21E-20	Apobr
104215	0.659568898	8.29E-21	Rhoq
14284	0.682366557	1.80E-21	Fosl2
214230	0.69779831	9.99E-22	Pak6
74777	0.949478224	2.17E-22	Selenon
70788	2.568842835	7.52E-23	Klhl30
13025	0.754621263	6.92E-23	Ctla2b
15201	0.61265774	4.57E-23	Hells
18124	0.603568575	4.07E-23	Nr4a3
230863	1.005829079	2.39E-23	Sh2d5
22165	1.357450008	5.87E-24	Txk

14579	0.604319444	3.25E-24	Gem
107022	0.893344064	3.06E-25	Gramd3
67254	3.179323699	2.71E-25	2900011O08Rik
544963	0.732258591	9.69E-26	Iqgap2
70598	1.76957026	9.02E-26	Filip1
16154	0.853158612	1.31E-26	Il10ra
70350	0.775508002	1.88E-28	Baspl
70099	0.644328353	9.63E-29	Smc4
12484	1.234893925	1.36E-29	Cd24a
51869	0.976283931	2.83E-33	Rif1
14944	2.637182184	7.73E-35	Gzmg
14103	0.974137937	1.52E-36	Fasl
69981	0.642336008	1.44E-39	Tmem30a
71690	1.372520667	4.08E-40	Esml
226856	0.626854113	1.92E-41	Lpgat1
232406	1.48567158	5.91E-42	BC035044
17909	0.738290079	7.08E-43	Myo10
110052	0.739006266	1.71E-45	Dek
74340	0.762003791	4.97E-46	Ahcy12
233489	0.613769349	8.58E-47	Picalm
15007	2.685435294	2.13E-47	H2-Q10
67016	0.723325918	1.15E-48	Tbc1d2b
12495	1.133918073	8.02E-49	Entpd1
11881	0.9435709	2.54E-57	Arsb
13819	2.188661564	5.31E-58	Epas1
171285	0.644879884	2.24E-58	Havcr2
14062	0.911857931	2.38E-59	F2r
12774	1.033178599	2.17E-64	Ccr5
17059	4.210710616	7.86E-67	Klrb1c
20708	1.119443552	7.86E-67	Serpinb6b
13024	0.765888906	8.01E-69	Ctla2a
17999	0.829253184	3.20E-69	Nedd4
13449	0.792347377	1.23E-69	Dok2
12193	0.591955704	4.45E-70	Zfp3612
16905	1.771552406	1.90E-72	Lmna
18030	0.849764645	1.05E-72	Nfil3
433278	4.184835036	6.62E-85	Khdc1c
20351	0.674789963	1.20E-92	Sema4a
20750	1.035064774	2.71E-101	Sppl
233328	0.882114357	2.47E-102	Lrrk1
56336	0.608348773	4.08E-110	B4galt5
12772	2.096334335	1.48E-132	Ccr2
22234	0.888813967	1.61E-138	Ugeg
15902	1.134682503	2.39E-140	Id2
14945	4.9347052	1.06E-142	Gzmk
20723	1.321624657	4.33E-184	Serpinb9
368204	4.603022472	3.45E-191	Khdc1a
15519	0.588316118	4.24E-294	Hsp90aa1
13813	5.713856074	0	Eomes
14941	3.202311701	0	Gzmd
14942	3.120302187	0	Gzme
14938	1.165112117	0	Gzma

Identification of progenitor exhausted T-cell genes in THRLBCL cases.

Miller⁶ recognized a set of genes differentially expressed in the progenitor exhausted T-cells vs terminally exhausted T-cells, in (OVA)-expressing B16.F10 mouse melanoma tumors (B16-OVA tumors). From this set of genes, we selected 186 genes significantly overexpressed in progenitor exhausted T-cells vs terminally exhausted T cells, with a Log₂ Fold-Change ≥ 2 and an adjusted $P \leq .05$ (Table S4 below). We used Metascape tool⁷ to overlap this set of 186 genes with the genes overexpressed in THRLBCL vs DLBCL cases.

Table S4. Differentially expressed genes between progenitor exhausted vs terminally exhausted T-cells (Log₂FC ≥ 2 and an adjusted $P \leq .05$), according to Miller⁶.

GENE	LOG ₂ FOLD CHANGE	PADJ
CLDN10	4.305321308	0.058676
BDH2	2.692212601	0.057971
CHST15	4.731154397	0.056037
ADH4	4.57033954	0.053821
MCOLN3	2.036990688	0.053289
BMP7	2.26527244	0.051719
NCS1	2.256471669	0.051004
SLC15A1	3.689083606	0.048397
4932425I24RIK	2.031747344	0.048397
HEMGN	3.466855637	0.048234
CTSL	2.206122462	0.044094
TMEM121	2.902307496	0.043671
KCNMB1	5.243232244	0.043407
TNFRSF13B	4.755996188	0.040529
NAPB	3.541762024	0.039741
PLA2G4F	4.729639084	0.039397
PRSS2	4.017267482	0.039275
P2RX7	4.278572702	0.038518
CD40LG	5.118023344	0.036635
SLC1A2	3.146654273	0.028934
FAM160A1	4.645217596	0.028584
CXXC5	4.729946436	0.027225
SOSTDC1	5.50683234	0.026948
DZIP1	2.798507254	0.025939
ST8SIA1	4.917329578	0.022012
S1PR5	4.661026575	0.021079
LRRK2	2.199937395	0.020703
IMMP2L	2.021639366	0.020488
WNT10A	5.260384602	0.019265
DHRS3	5.006649622	0.019217
FAM109A	2.67652075	0.017898
DEGS2	2.645597302	0.017415
KLF3	4.676615477	0.017347

OAF	3.854592585	0.016728
FAM81A	4.183277554	0.01629
SPOCK2	2.130686863	0.015136
TMEM231	2.777593967	0.013419
GM11346	2.0562586	0.013195
ISPD	2.738640967	0.012194
GALNT14	4.1228251	0.011924
CCDC157	2.043516601	0.011815
AQP3	3.989249554	0.011346
MTMR7	2.978859799	0.009231
DTX1	5.035264799	0.008254
IL1RL1	3.501660638	0.00819
TNP2	4.278456632	0.008165
ARHGAP5	2.20203501	0.007884
PRKAB2	2.637827034	0.006777
COLQ	3.834954348	0.006251
TREML2	5.674933469	0.006074
KLF4	3.205037985	0.005411
HECTD2	6.291532646	0.004914
CYR61	4.68511129	0.004873
TERT	2.316535983	0.004873
P2RX4	2.131067175	0.004527
THA1	3.204074177	0.004027
SNX30	2.833792978	0.003822
AS3MT	2.078137877	0.003498
PGCP	5.689894001	0.003299
IL18	4.464621121	0.003105
DNASE1L3	3.293298553	0.002266
XCL1	4.705582532	0.002169
FAM84A	5.821553372	0.002166
TRPM1	2.124431532	0.002033
MTAP7	2.758627216	0.001918
PRNP	3.388795447	0.00189
PTER	2.451134637	0.001663
H60B	2.612256714	0.001661
LRIG1	4.514815951	0.001532
LAD1	2.385772952	0.001526
ST6GAL1	2.723706148	0.001423
BCL6	3.016983754	0.001406
VAT1L	6.691668187	0.00138
POU2F2	2.176875394	0.001073
ART3	6.120272386	0.001016
MAPK11	6.199552619	0.00098
PLD4	3.308962929	0.00083
TNFRSF25	6.70341181	0.000829
PDE2A	2.714170138	0.000692
ARHGEF4	2.156284652	0.000637
2610019F03RIK	6.329755455	0.000579
CPM	2.233168885	0.00056
ZFP467	4.189813712	0.000484
OTX1	6.901910625	0.000428
SSPO	4.456248355	0.00035
TRAT1	3.025871237	0.000239
BC048355	2.159101802	0.000214
ANGPTL2	3.420444904	0.000146
SEMA4F	2.068082961	0.00014
ITGAX	2.129234949	0.000122
CD22	6.8542726	0.000107
VCL	2.313701934	9.43E-05
ARMCX2	2.009940236	7.84E-05
SLC2A6	4.130884598	6.65E-05
KLF2	2.452540422	5.76E-05
SPRY1	2.074319012	4.13E-05
2610035D17RIK	2.149580715	2.84E-05
LIF	5.68309806	2.18E-05

GALNT9	2.874900943	0.000015
CARD6	2.015849665	1.14E-05
FAM178B	4.199738257	1.07E-05
CELSR1	2.129073632	7.22E-06
CCDC64	2.959801007	6.07E-06
MGAT5	2.016149713	5.75E-06
POU6F1	3.336501419	5.19E-06
ABCA3	2.261081764	3.59E-06
SELL	4.934806571	3.15E-06
RASGEF1A	2.342639896	2.28E-06
SLFN5	2.99079557	2.01E-06
ID3	8.18010505	1.18E-06
IGSF3	2.410341227	1.17E-06
F2RL1	3.867902825	4.58E-07
TLR1	2.96838709	4.27E-07
ZFP36L1	2.261449808	4.25E-07
AFF3	8.711353213	2.5E-07
ZHX2	3.240973323	1.95E-07
CD81	3.358957045	1.51E-07
CXCR5	8.634753692	1.27E-07
IRF2BP2	2.050014196	1.2E-07
FGFBP3	2.542386713	1.14E-07
CD9	2.126894657	1.12E-07
EGR2	2.76214632	1.07E-07
CLEC2I	2.801313294	7.48E-08
NSG2	4.461878484	5.09E-08
CMPK2	2.071575137	4.63E-08
EPHX1	2.26517035	1.51E-08
RAMP3	2.879371126	1.06E-08
SLC26A11	2.674792961	9.17E-09
GZMM	3.980980028	8.87E-09
CAR2	3.084499821	7E-09
ARL5C	2.525196713	5.58E-09
SESN3	3.022912075	3.06E-09
LTA	2.326401412	2.9E-09
SH3BP5	4.288656505	2.28E-09
TNFSF8	5.964896847	7.57E-10
RGS10	2.637389711	3.55E-10
ARC	3.452407919	1.56E-10
ACSS1	2.124102291	1.47E-10
PIK3IP1	2.512230755	9.77E-11
PACSL1	2.156579327	8.35E-11
DCLK1	2.870699539	3.68E-11
GUCY1A3	4.096054935	2.7E-11
JUB	3.285416068	1.82E-11
PDLIM1	2.849841414	8.7E-12
PLXNC1	2.2291593	7.8E-12
CCR6	11.05770392	4.71E-12
CD83	4.694271344	2.67E-12
BTLA	2.601556597	1.21E-12
GATSL3	3.119468897	9.59E-13
SH2B3	4.613057703	1.68E-13
TNFRSF26	3.70591315	5.73E-14
FGFR1OP	2.023457563	2.16E-14
ASAP1	2.171610912	1.15E-14
NTSE	2.927406444	5.66E-15
1700019D03RIK	2.530799983	5.66E-15
TNFSF14	5.970397382	2.79E-15
PLXDC2	2.896691986	2.49E-15
ARL4D	3.03775796	9.12E-16
ARHGAP26	2.334085895	8.22E-16
TNFSF11	3.765345064	6.65E-16
CXCR3	3.625689935	5.82E-16
CPNE3	2.631842922	1.55E-17
2310001H17RIK	2.38020185	1.02E-17

GPRIN3	2.694064495	4E-18
TCF7	10.09477177	6.46E-20
SSH2	2.321203043	2.03E-20
RAB37	3.231130195	9.39E-21
CMAH	3.089876356	7.13E-21
SYNPO	5.627270884	1.8E-21
BACH2	3.660523721	1.7E-21
S1PR1	5.830208482	1.63E-21
JUN	2.106636038	4.09E-24
SIDT1	2.658746414	8.75E-26
TBC1D4	4.293401692	7.08E-26
TAGAP	2.308201291	4.73E-27
TESPA1	4.540356785	1.82E-27
DAPL1	8.375458606	2.74E-28
ITGB1	2.198321522	3.41E-32
SAMD3	4.244483319	3.93E-33
FAM53B	2.966830545	9.91E-35
LAMP1	2.077575751	6.97E-35
GPR183	2.558663538	1.95E-35
CCR7	3.78866065	1.2E-40
SLAMF6	7.43295399	1.47E-50
CRTAM	3.339929255	6.81E-61
EMB	3.640607025	4E-99

Immunohistochemistry

Table S5. Antibody sources, dilutions, and detection systems

<i>Antibody</i>	<i>Source</i>	<i>Clone</i>	<i>Dilution</i>	<i>Detection</i>
CD3	Dako	F7.2.38	1:40	Fast red
CD20	Dako	L26	1:150	Fast red
CD10	Leica	56C6	1:40	Fast red
BCL6	Dako	PG-B6P	1:10	Fast red
IRF4	Courtesy of Prof Falini	MUM1	1:4	Fast red
CD4	Leica	1F6	1:30	Fast red
CD8	Dako	144B	1:100	Fast red
PD-L1	Cell Signaling	E1L3N	1:200	Fast red
PD-1	Abcam	NAT105	1:4	Fast red
LAG3	Cell Signaling	D2G40	1:200	Fast red
EOMES	Invitrogen	WD1928	1:100	DAB
TCF1/TCF7	CellSignaling	C63D9	1:50	Fast red
IDO	Merck Millipore	10.1	1:100	Fast red
STAT1	CellSignaling	9H2	1:60	Fast red

Abbreviations: DAB, 3,3'-diaminobenzidine; IDO, indoleamine 2,3-dioxygenase.

Table S6. Top 10 biological process enriched in genes upregulated in THRLBCL vs DLBCL cases of discovery set, sorted by p-value ranking. Gene Ontology enrichment analysis was performed by Enrichr bioinformatic tool.⁸

Term	Overlap	P-value	Adj P-value
cytokine-mediated signaling pathway (GO:0019221)	89/633	3.07E-72	5.41E-69
inflammatory response (GO:0006954)	47/252	6.36E-43	5.60E-40
cellular response to cytokine stimulus (GO:0071345)	56/456	6.60E-41	3.87E-38
regulation of immune response (GO:0050776)	43/251	1.38E-37	6.06E-35
response to lipopolysaccharide (GO:0032496)	31/155	2.15E-29	7.56E-27
chemokine-mediated signaling pathway (GO:0070098)	20/52	1.00E-25	2.93E-23
positive regulation of cytokine production (GO:0001819)	30/220	2.47E-23	5.45E-21
cellular response to interferon-gamma (GO:0071346)	24/116	2.48E-23	5.45E-21
positive regulation of T cell activation (GO:0050870)	20/68	5.53E-23	1.08E-20
cellular response to tumor necrosis factor (GO:0071356)	28/194	1.58E-22	2.78E-20

Table S7. Immunohistochemical evaluation of THRLBCL and DLBCL cases

Marker	% of positive cells, median		P
	THRLBCL (n, 20)	DLBCL (n, 33)	
CD3	64	10	.0001838
CD20	10	90	.0001624
CD4	25	1	.03
CD8	30	5	.03
PD-L1	35	5	7.834e-05
PD-1	30	2	7.138e-07
LAG3	20	2	2.829e-06
EOMES	35	5	2.232e-06
TCF1/TCF7	25	5	.0008734
IDO	10	0	.0006877
STAT1	35	5	.0137

Statistical comparison was calculated using the Mann–Whitney U test.

Table S8. Gene Ontology enrichment analysis results of each single MCODE module, recognized in the discovery set. GO enrichment analysis was applied to each MCODE component by Metascape bioinformatic tool⁷ with the following ontology sources: KEGG Pathway, GO Biological Processes, Reactome Gene Sets, Canonical Pathways and CORUM. The resulting top-three best p-value terms were retained. Results were ranked by Score value.

Network	Score	Annotation
Input ID_MCODE_1	11	R-HSA-380108 Chemokine receptors bind chemokines -51.9 R-HSA-375276 Peptide ligand-binding receptors -49.9 R-HSA-418594 G alpha (i) signalling events -45.1
Input ID_MCODE_3	6.5	R-HSA-909733 Interferon alpha/beta signaling -36.9 GO:0060337 type I interferon signaling pathway -35.0 GO:0071357 cellular response to type I interferon -35.0
Input ID_MCODE_4	3.2	R-HSA-389948 PD-1 signaling -20.0 R-HSA-388841 Costimulation by the CD28 family -16.3 ko04660 T cell receptor signaling pathway -15.1
Input ID_MCODE_5	3	R-HSA-6798695 Neutrophil degranulation -12.4 GO:0043312 neutrophil degranulation -12.4 GO:0002283 neutrophil activation involved in immune response -12.3
Input ID_MCODE_2	2.8	R-HSA-1280218 Adaptive Immune System -18.9 hsa04650 Natural killer cell mediated cytotoxicity -17.9 ko04650 Natural killer cell mediated cytotoxicity -17.9
Input ID_MCODE_6	2	R-HSA-5668541 TNFR2 non-canonical NF-kB pathway -12.2 R-HSA-5676594 TNF receptor superfamily (TNFSF) members mediating non-canonical NF-kB pathway -12.2 GO:0033209 tumor necrosis factor-mediated signaling pathway -11.1

Table S9. Gene Ontology enrichment analysis results of each single MCODE module, , recognized in the *in silico* set. GO enrichment analysis was applied to each MCODE component by Metascape bioinformatic tool⁷ with the following ontology sources: KEGG Pathway, GO Biological Processes, Reactome Gene Sets, Canonical Pathways and CORUM. The resulting top-three best p-value terms were retained. Results were ranked by Score value.

Network	Score	Annotation
Input ID_MCODE_1	3.8	R-HSA-375276 Peptide ligand-binding receptors -20.9; GO:0070098 chemokine-mediated signaling pathway -19.6; GO:1990869 cellular response to chemokine -19.2
Input ID_MCODE_2	3.8	R-HSA-389948 PD-1 signaling -23.9; WP4585 Cancer immunotherapy by PD-1 blockade -20.2; R-HSA-388841 Costimulation by the CD28 family -19.7
Input ID_MCODE_3	1.5	R-HSA-2029481 FCGR activation -13.8; R-HSA-9664323 FCGR3A-mediated IL10 synthesis -11.6; R-HSA-2029480 Fcgamma receptor (FCGR) dependent phagocytosis -10.2
Input ID_MCODE_4	1.5	R-HSA-909733 Interferon alpha/beta signaling -10.5; R-HSA-913531 Interferon Signaling -8.7; GO:0051607 defense response to virus -8.3
Input ID_MCODE_5	1.25	WP545 Complement activation -8.9; R-HSA-166663 Initial triggering of complement -8.8; WP3941 Oxidative damage response -8.0

Table S10. Exhausted T-cell related genes upregulated in THRLBCL versus DLBCL cases.

Immune Checkpoint genes	FC
CD160	4.72
CD209	2.54
CD27	1.53
CD274	2.09
CD28	3.81
CD96	2.99
CTLA4	3.43
HAVCR2	2.03
HLA-A	1.54
HLA-B	1.56
HLA-C	1.29
HLA-E	1.18
HLA-G	1.95
ICOS	3.17
IDO1	3.49
KIR2DS1	1.70
KIR2DL1	3.67
KIR2DL3	3.95
KIR3DL2	3.04
LAG3	3.93
PDCD1	2.91
PDCD1LG2	1.42
PVR	1.46
TIGIT	2.82
TNFRSF14	1.21
TNFRSF18	2.86
TNFRSF4	2.08
TNFRSF9	1.52
TNFSF14	1.28
EOMES - upregulated genes	FC
CCR2	2.90
CCR5	3.07
CD244	3.74
CD68	1.92
EOMES	3.81
FCER1G	2.48
GZMA	2.68
GZMK	3.42
HAVCR2	2.03
KLRG1	2.73
TNFSF10	2.63

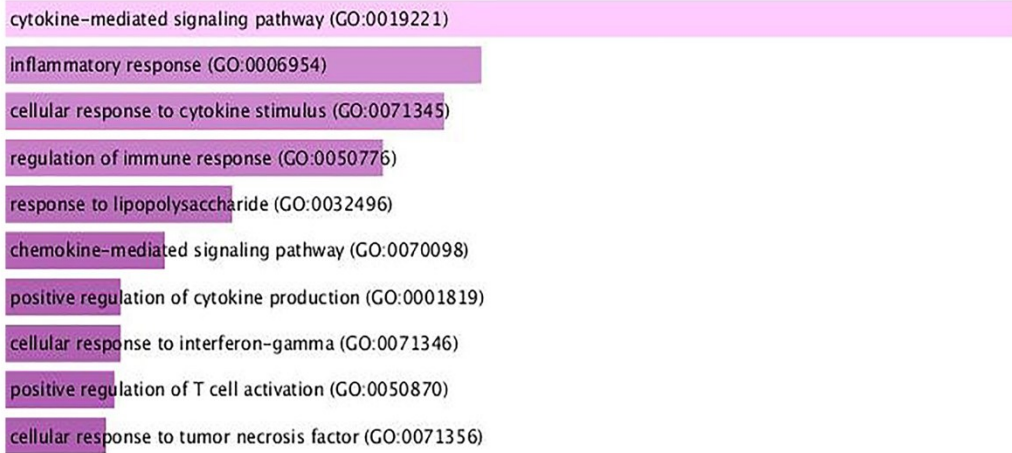
Exhausted Virus-induced genes**FC**

CCL5	2.35
CCR5	3.07
CCRL2	2.08
CD244	3.74
CSF1	1.79
CTLA4	3.43
CXCR3	2.80
EOMES	3.81
GZMB	3.78
IFNG	3.57
KLRK1	2.94
TNFRSF1A	1.42
TNFRSF9	1.52
TNFSF10	2.63
XCR1	2.48

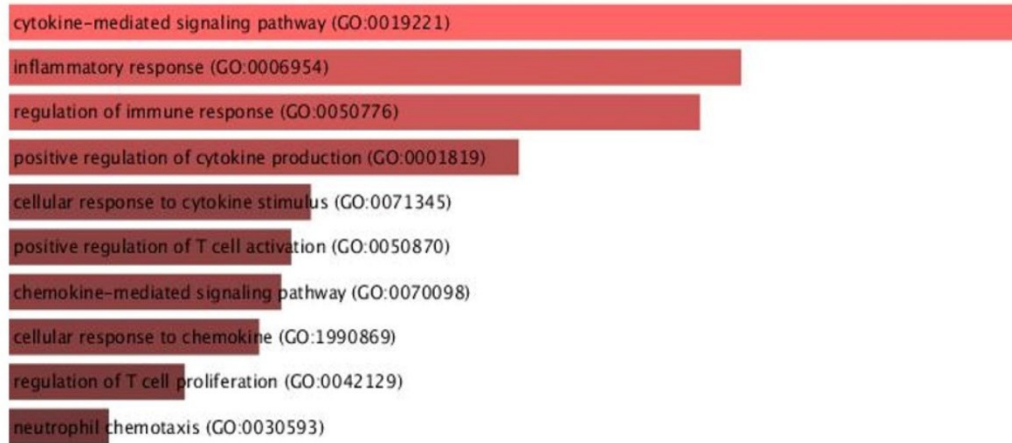
Supplemental Figures

Figure S1

A



B



C

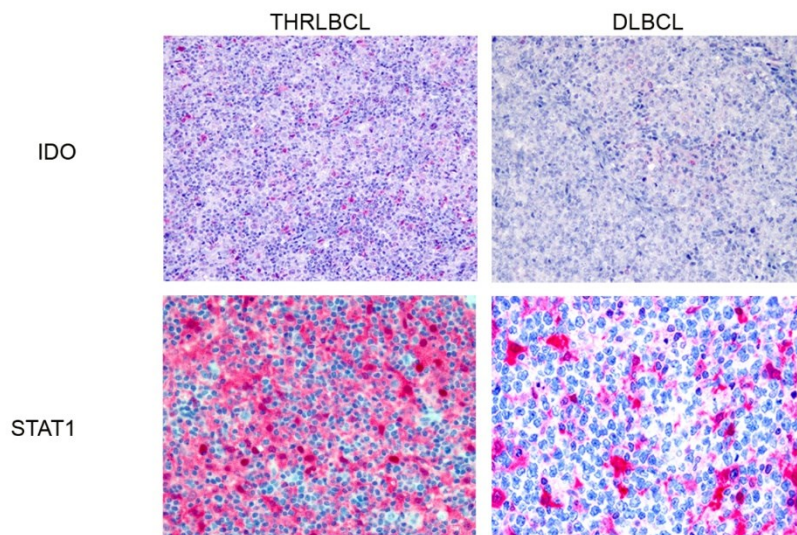


Figure S1. Enrichment analysis of genes upregulated in THRLBCL vs DLBCL. (A) Histogram plot of biological processes significantly enriched in the 235 genes upregulated in THRLBCL vs DLBCL cases of the discovery set, sorted by decreasing p-value ranking from the top to the bottom. (B) Histogram plot of biological processes significantly enriched in the 95 genes upregulated in THRLBCL vs DLBCL, *in silico* cases (GSE181063) sorted by decreasing p-value ranking from the top to the bottom. (C) Immunohistochemistry evaluation of IDO and STAT1 showing higher expression in THRLBCL vs DLBCL cases.

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