Clinicopathological features and survival in EBV-positive diffuse large B-cell lymphoma not otherwise specified

SUPPLEMENTARY FIGURES LEGENDS

Figure S1. Hans algorithm for EBV$^+$ DLBCL-NOS cell-of-origin, according to histological pattern. (A) Polymorphic EBV$^+$ DLBCL-NOS and (B) monomorphic EBV$^+$ DLBCL-NOS.

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; GCB: Germinal Center B; MUM1: multiple myeloma oncogene 1; non-GC: non-Germinal Center B.

Figure S2. Distribution of EBV$^+$ DLBCL-NOS cases per histological pattern. The age distribution of (A) EBV$^+$ DLBCL-NOS with polymorphic pattern (n=46) and (B) EBV$^+$ DLBCL-NOS with polymorphic pattern (n=21) follow a bimodal distribution.

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified.

Figure S3. Survival probabilities for the 70 EBV$^+$ DLBCL-NOS patients. (A) PFS and (B) OS for the 70 EBV$^+$ DLBCL-NOS. The survival curves plateau after 2 years. At 5 years, PFS is 52.7% [95% CI, 46.4-58.9] and OS is 54.8% [95% CI, 48.5-61.1].

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; OS: overall survival; PFS: progression free survival.

Figure S4. Survival probabilities of EBV$^+$ DLBCL-NOS according to clinicopathological characteristics (70 patients). PFS and OS for all 70 EBV$^+$ DLBCL-NOS according to (A-B) age group, (C-D) presence of HLH and (E-F) histological pattern.

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; HLH: hemophagocytic lymphohistiocytosis; OS: overall survival; PFS: progression free survival.

Figure S5. Survival probabilities of EBV$^+$ DLBCL-NOS according to clinicopathological characteristics (56 patients with curative-intent therapy). PFS and OS for the 56 EBV$^+$ DLBCL-NOS with intent-to-cure therapy according to (A-B) age group, (C-D) presence of HLH and (E-F) histological pattern.

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; HLH: hemophagocytic lymphohistiocytosis; OS: overall survival; PFS: progression free survival.

Figure S6. Flow chart for the EBV$^-$ DLBCL-NOS control cohort.

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; EBER: EBV-encoded small RNAs; ISH: in situ hybridation.

Figure S7. Distribution of EBV$^+$ DLBCL-NOS and EBV$^-$ DLBCL-NOS cases treated with curative intend per age group.

The age distribution of (A) EBV$^+$ DLBCL-NOS (n=56) peaks in the seventh decade of life, while distribution of (B) EBV$^-$ DLBCL-NOS follows a Gaussian curve (n=425).

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified.

Figure S8. Survival probabilities of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL with intend to cure therapy according to age group.

PFS and OS of EBV$^+$ DLBCL-NOS compared with EBV$^-$ DLBCL-NOS according to age group: (A-B) ≤ 50 years and (C-D) > 50 years. In young patient, PFS at 5 years of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL-NOS is 91.3% [95% CI, 85.4-97.2] and 69% [95% CI, 62-76] respectively (p = .066). OS of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL-NOS at 5 years is 91.3% [95% CI, 85.4-97.2] and 83.8% [95% CI, 78-89.6] respectively (p = .438). In elderly, PFS at 5 years of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL-NOS is 47.9% [95% CI, 33.7-68.7] and 45.8% [95% CI, 40-53.4] respectively (p = .405). OS of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL-NOS at 5 years is 53% [95% CI, 38.2-74] and 60.8% [95% CI, 55.4-69.3] respectively (p = .038).

DLBCL-NOS: diffuse large B-cell lymphoma not otherwise specified; OS: overall survival; PFS: progression free survival.

Figure S1.

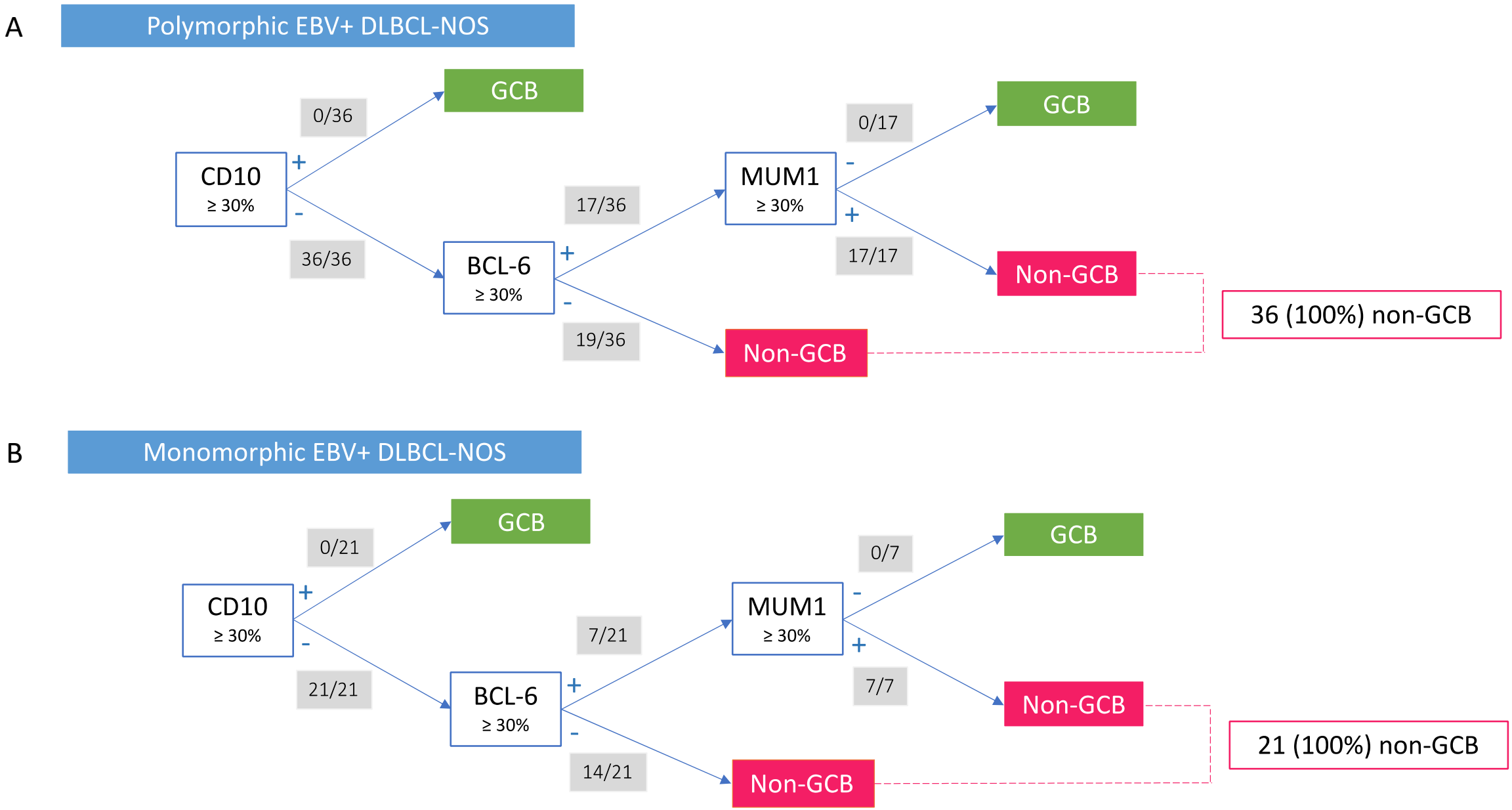
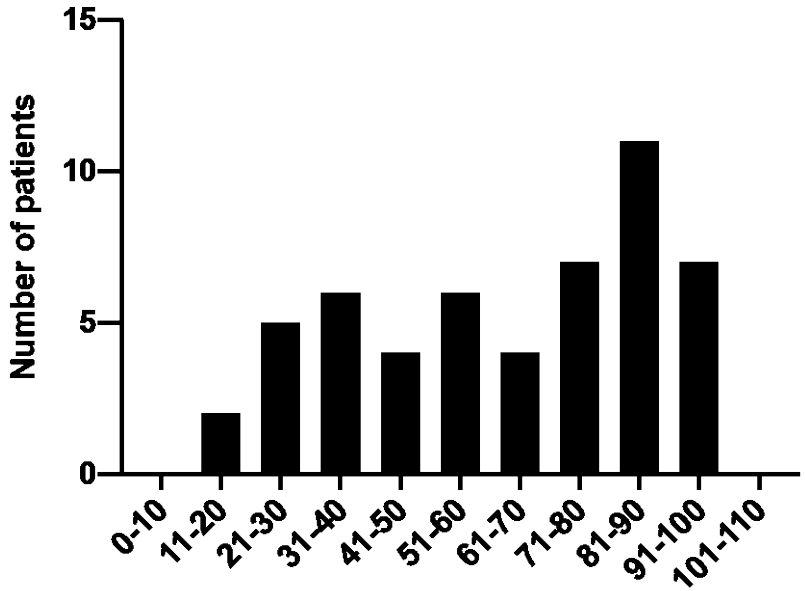

A
Polymorphic EBV+ DLBCL-NOS
CD10
≥ 30%
+
0/36
GCB
-
36/36
BCL-6
≥ 30%
+
17/36
MUM1
≥ 30%
-
0/17
GCB
+
17/17
Non-GCB
-
19/36
Non-GCB
36 (100%) non-GCB
B
Monomorphic EBV+ DLBCL-NOS
CD10
≥ 30%
+
0/21
GCB
-
21/21
BCL-6
≥ 30%
+
7/21
MUM1
≥ 30%
-
0/7
GCB
+
7/7
Non-GCB
-
14/21
Non-GCB
21 (100%) non-GCB

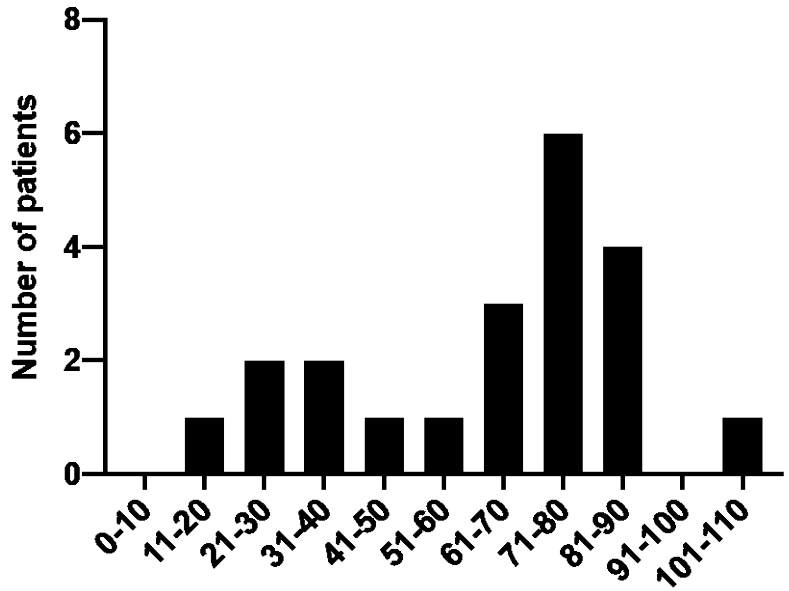
Figure S2.

A.



Age group in EBV+ DLBCL-NOS with polymorphic pattern (n=46)

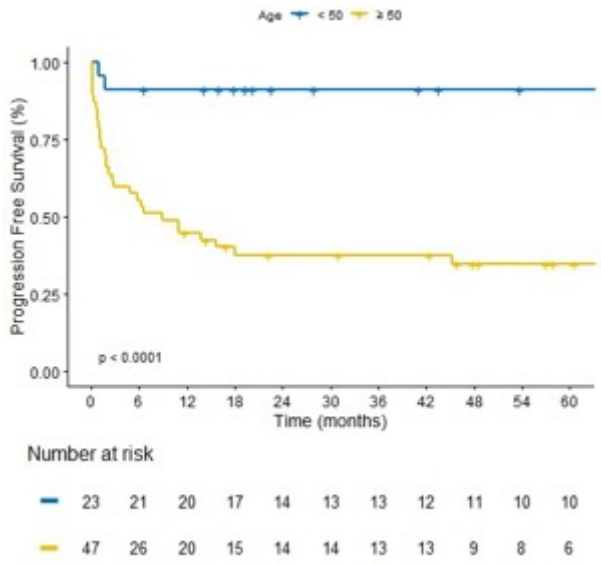
B.



Age group in EBV+ DLBCL-NOS with monomorphic pattern (n=21)

Figure S3.

A



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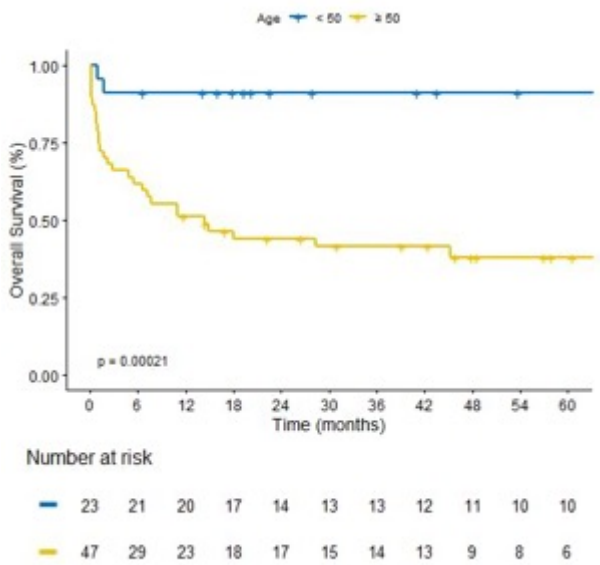

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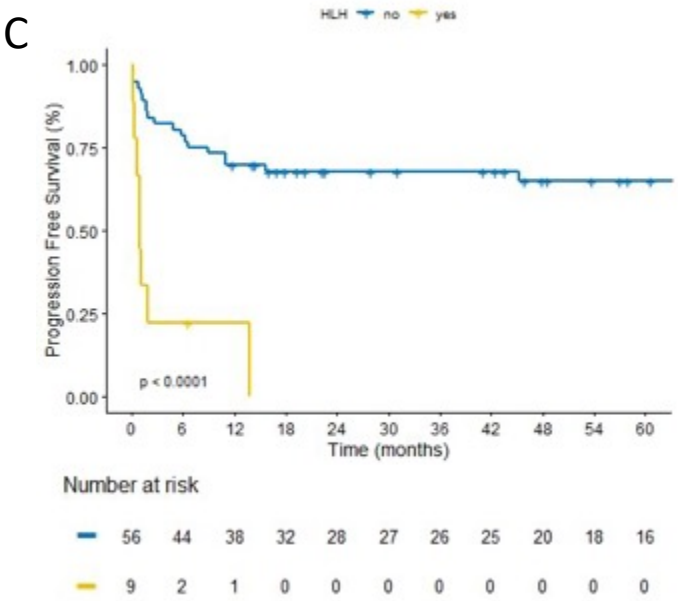

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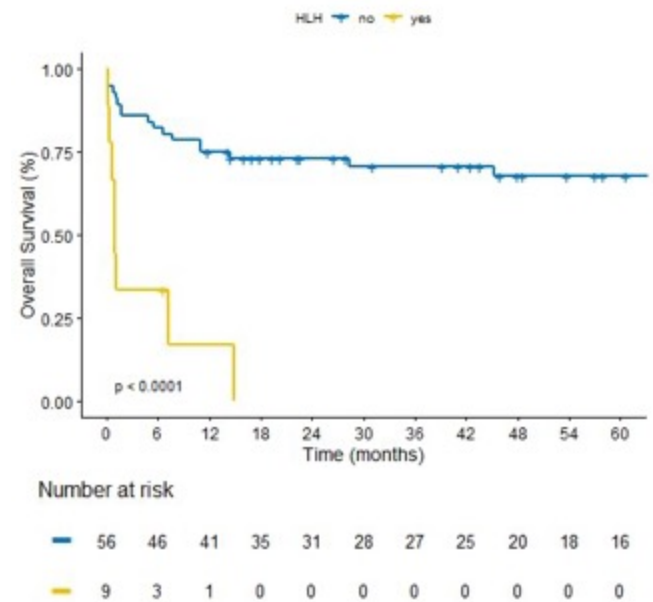

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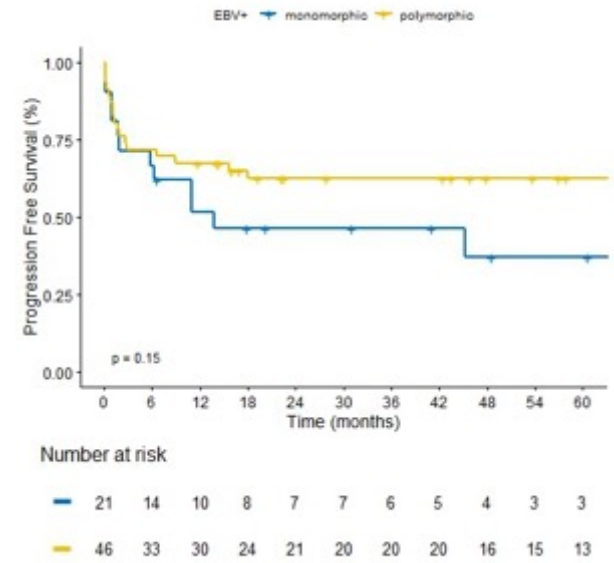

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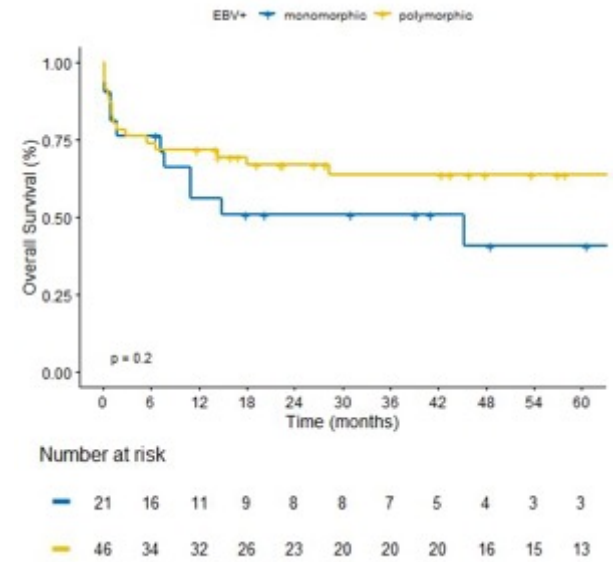
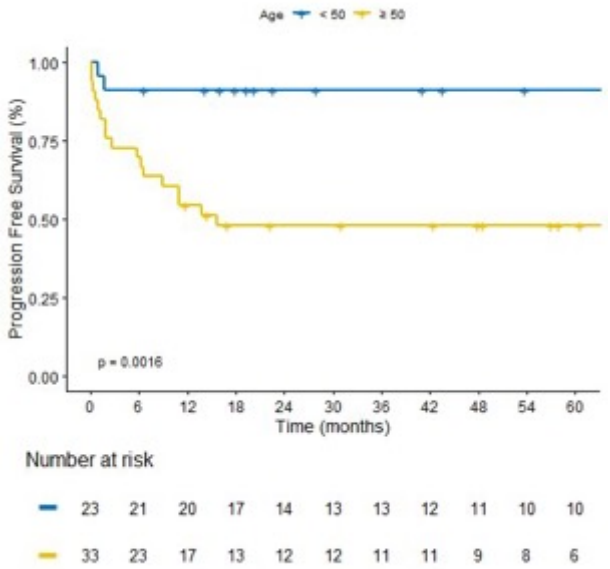


Figure S4.

A



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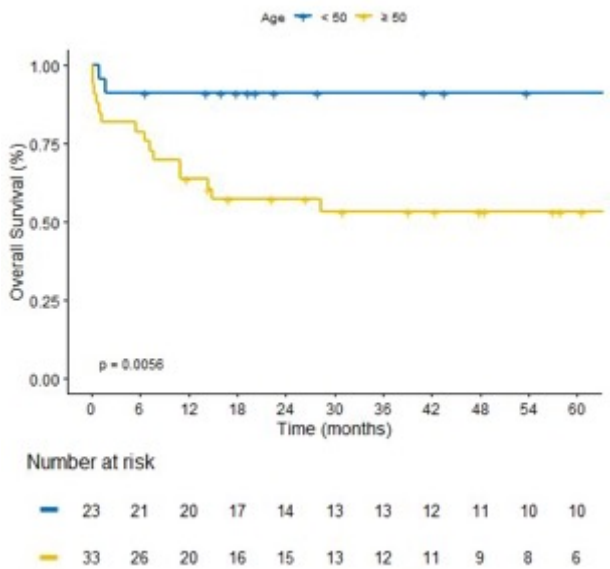

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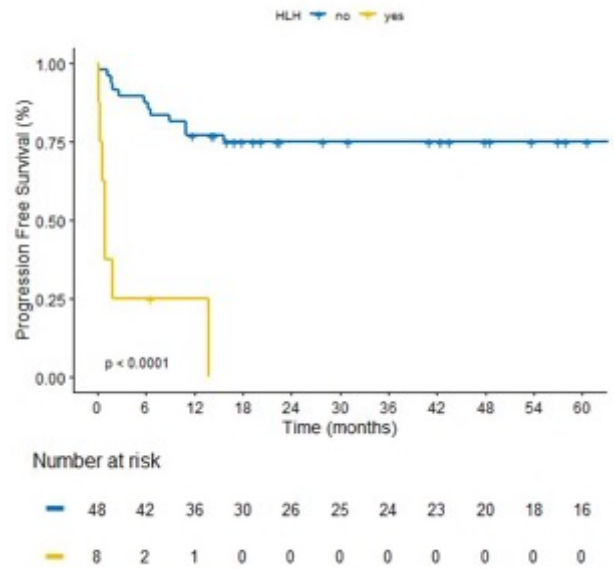

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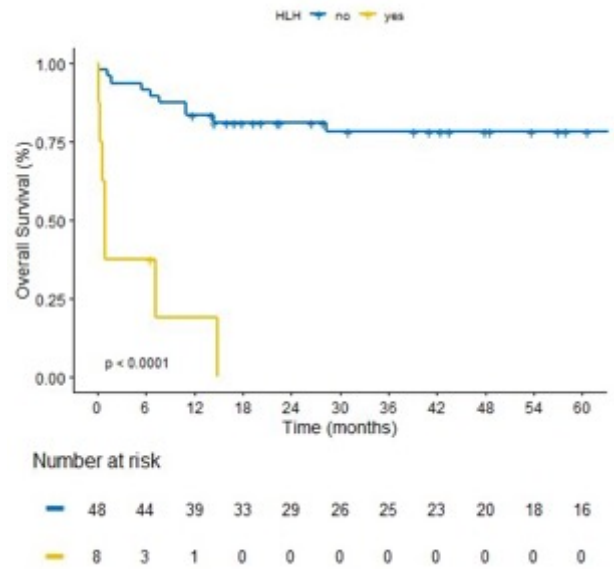

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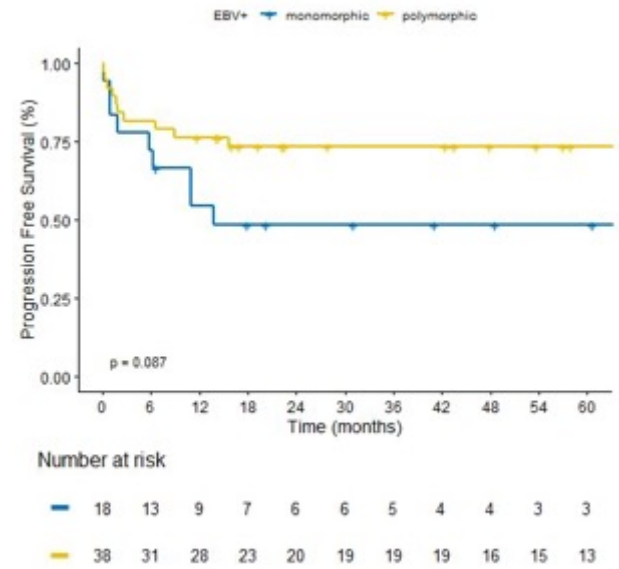

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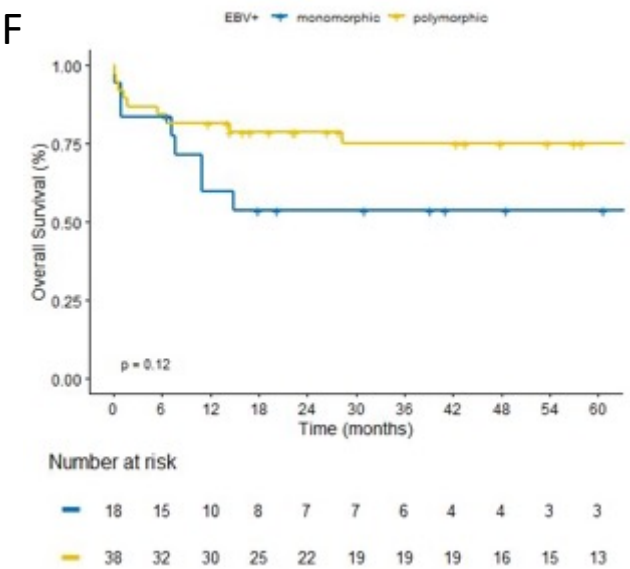


Figure S5.

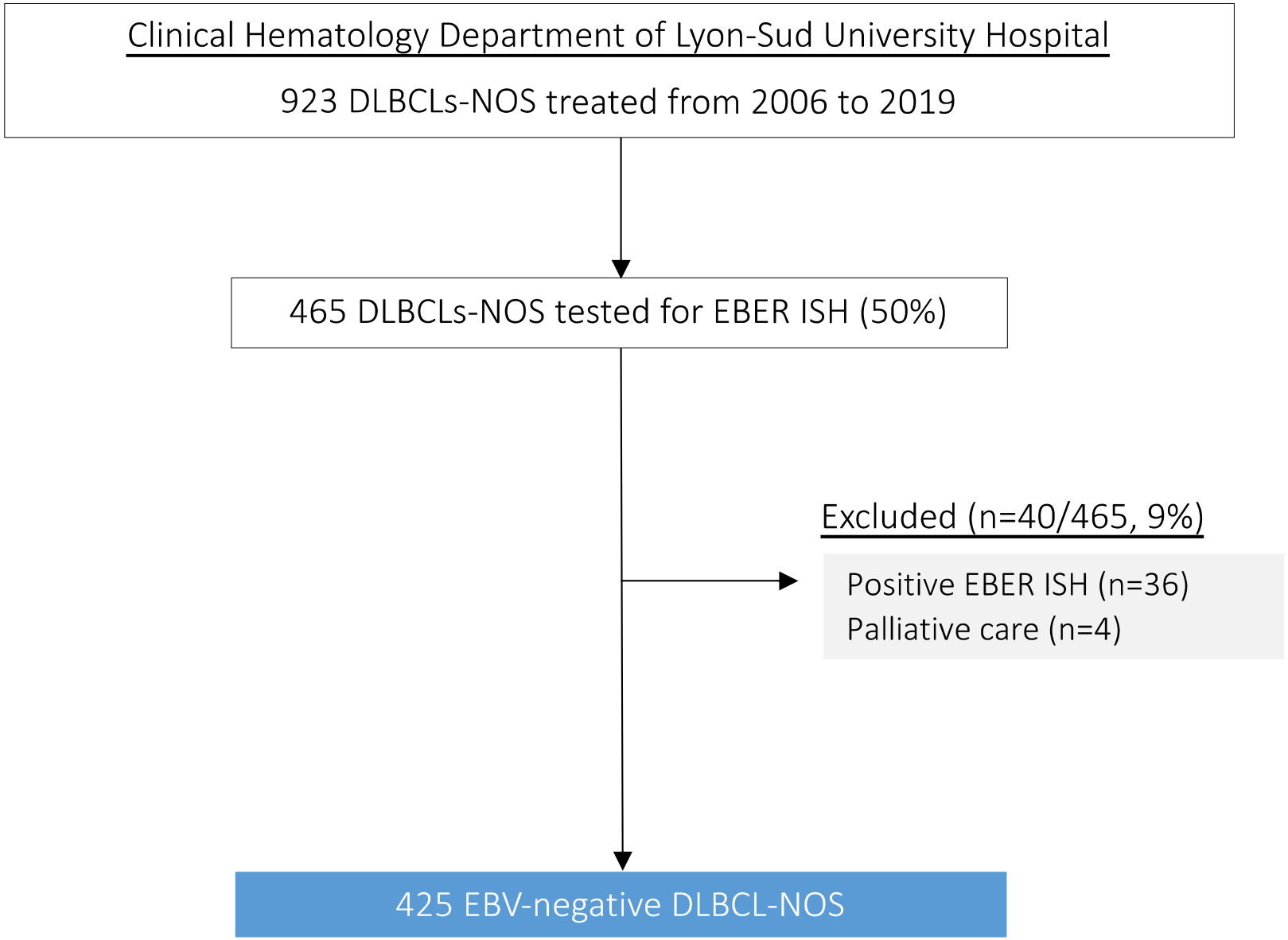

Clinical Hematology Department of Lyon-Sud University Hospital
923 DLBCLs-NOS treated from 2006 to 2019
465 DLBCLs-NOS tested for EBER ISH (50%)
Excluded (n=40/465, 9%)
Positive EBER ISH (n=36)
Palliative care (n=4)
425 EBV-negative DLBCL-NOS

Figure S6.

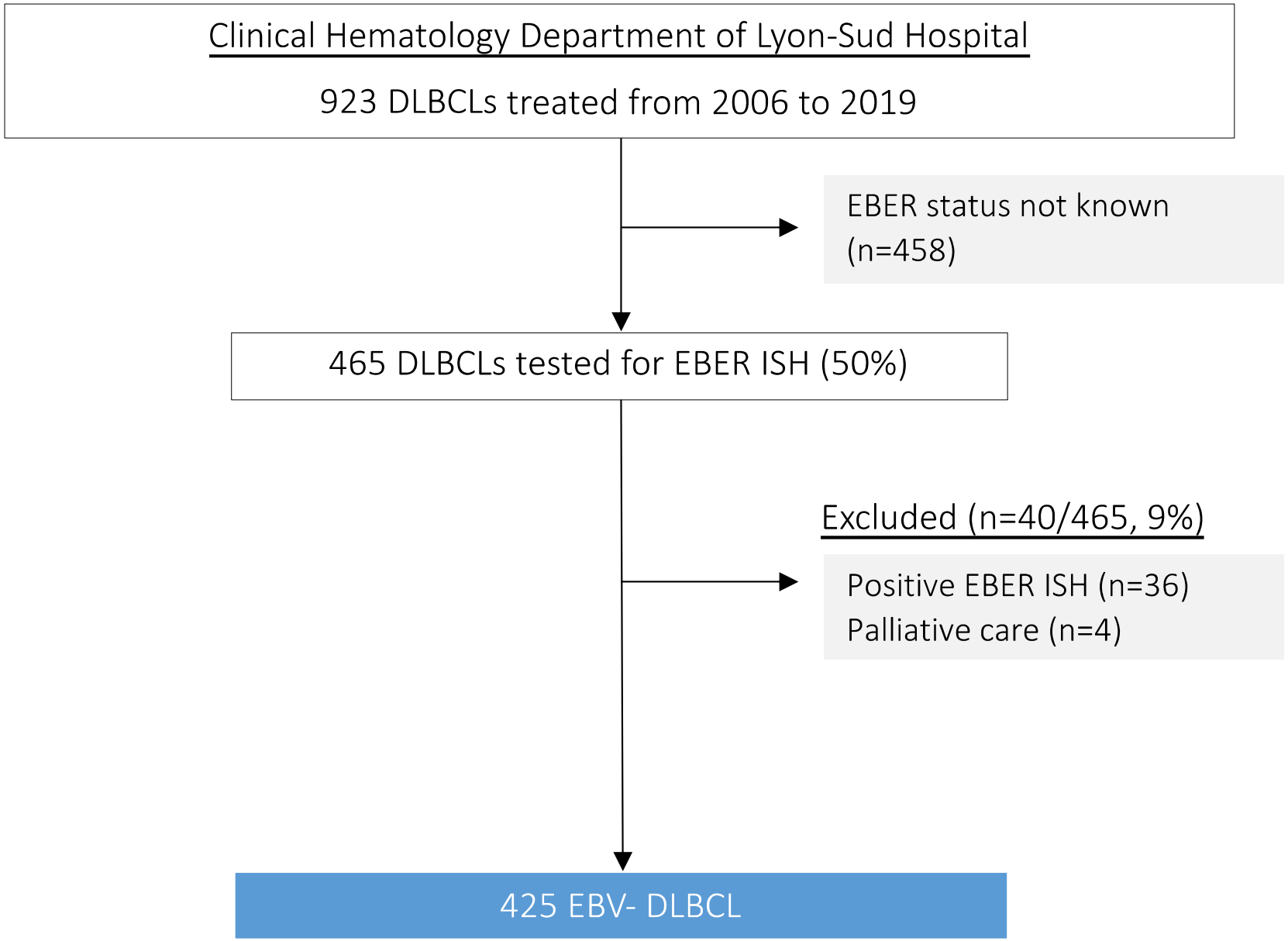
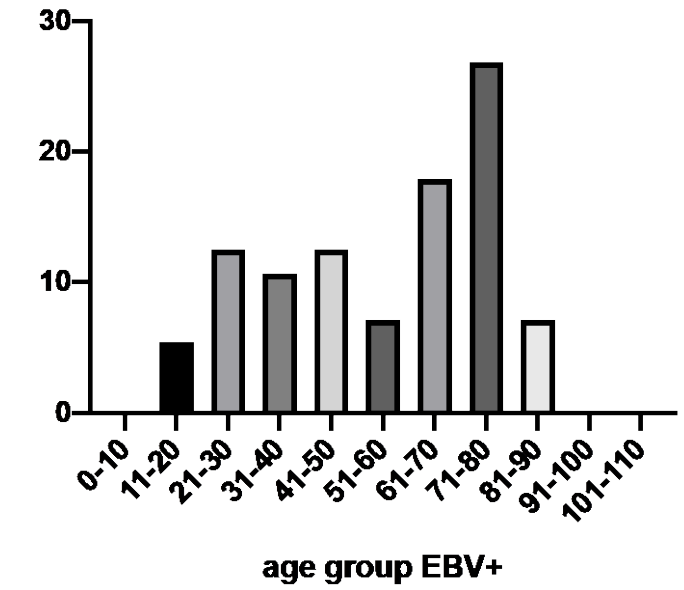

Clinical Hematology Department of Lyon-Sud Hospital
923 DLBCLs treated from 2006 to 2019
EBER status not known
(n=458)
465 DLBCLs tested for EBER ISH (50%)
Excluded (n=40/465, 9%)
Positive EBER ISH (n=36)
Palliative care (n=4)
425 EBV- DLBCL

Figure S7.

A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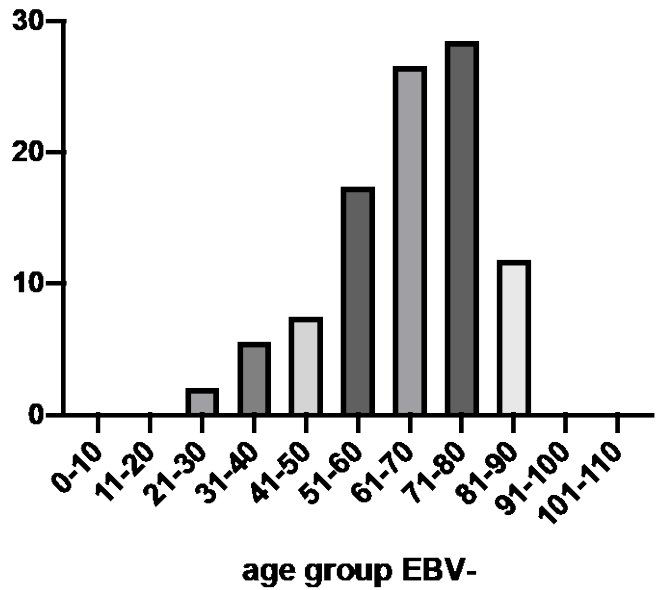
51-60
61-70
71-80
81-90
91-100
101-110
age group EBV+

B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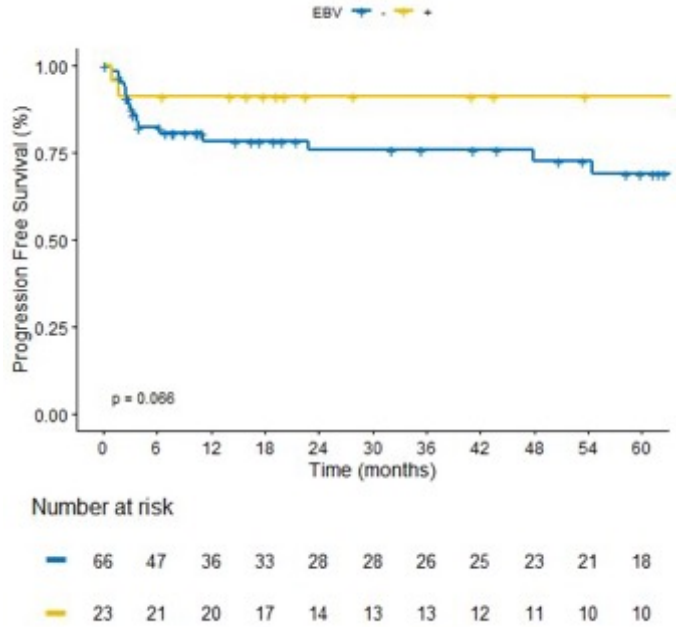
101-110
age group EBV-

Figure S8.

A



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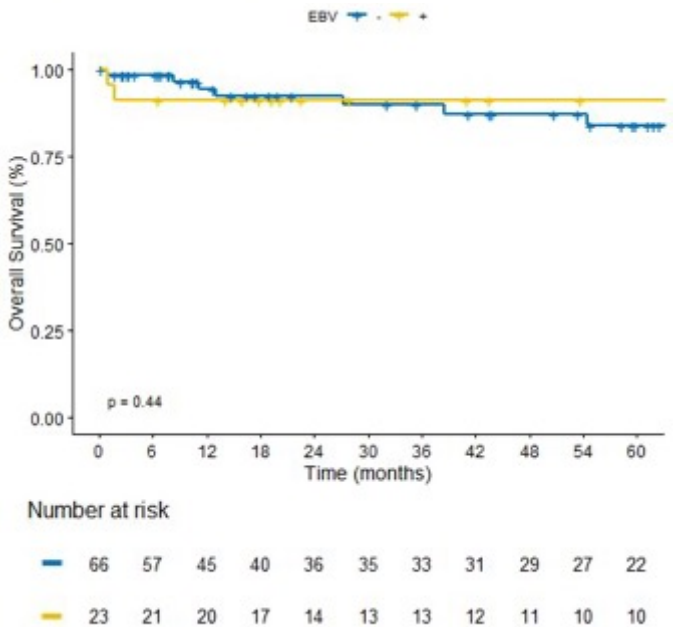

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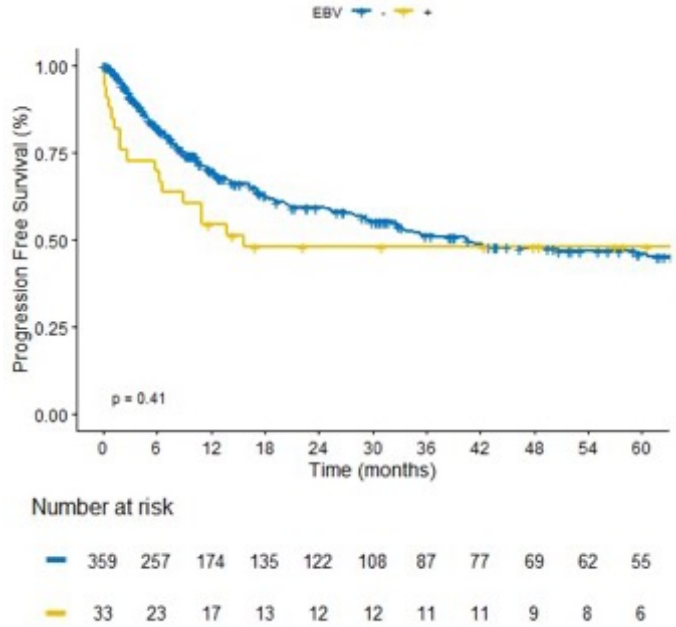

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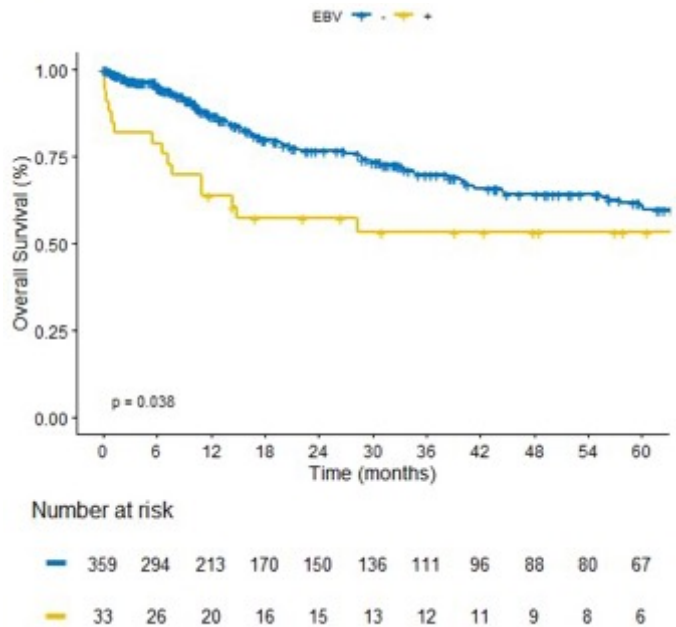

SUPPLEMENTARY TABLES

Table S1. Prevalence and comparative survival of EBV$^+$ DLBCL-NOS vs EBV$^-$ DLBCL-NOS, according to different geographical areas and EBER cutoffs.

AUTHORS	YEAR	COUNTRY	DLBCL EBV$^+$/EBV$^-$	PREVALENCE	AGE (year)	EBER CUTOFF	MEDIANE OS OF EBV$^+$ vs EBV$^-$ DLBCL-NOS (months)
ASIA							
KUZE	2000	Japan	13/101	11.4%	NS	NS	-
PARK	2007	Korea	34/346	8.9%	≥18	20%	35.8 vs NR, P = .026
OYAMA	2007	Japan	96/1696	5.4%	>40	50%	25 vs NR*, P < .001
WADA	2011	Japan	16/468	3.3%	NR	20%	-
AHN	2013	Korea	18/204	8.1%	≥50	10%	42 vs 74*, P = .627
PAN	2013	China	8/204	3.8%	>50	50%	-
CHANG	2014	Taiwan	15/317	4.5%	NS	10%	5 vs 39.3, P = .058
SATO	2014	Japan	14/225	5.9%	NS	30%	8.7 vs NR, P < .0001
LU CH	2014	Taiwan	15/74	16.9%	NS	20%	17.7 vs NR, P = .276
LIANG	2015	China	24/208	1.3%	NS	50%	26 vs NR *, P = .03
LU TX	2015	China	26/224	1.4%	NS	50%	37 vs NR, P < .0021
OKAMOTO	2015	Japan	8/115	6.5%	>18	20%	-
CHUANG	2015	Taiwan	10/164	5.7%	>60	10%	16 vs 30*, P = .00056
HONG JY	2015	Korea	48/523	8.4%	NS	20%	17.3 vs. 192.6, P < .001
OHASHI	2017	Japan	30/604	4.7%	NS	80%	100 vs NR, P < .01
OKAMOTO	2017	Japan	11/123	8.9%	NS	20%	NR for both, P = .001
KATAOKA	2019	Japan	27/48	-	NS	NS	-
NAN	2020	China	14/90	13.5	NS	50%	12 vs 20*, P = .039
LATIN AMERICA							
MORALES	2010	Peru	11/63	14.9%	>18	NS	7 vs 47, P = .001
HOFSCHEIER	2011	Mexico	9/127	6.6%	>50	majority	-
BELTRAN	2011	Peru	28/171	14%	>50	20%	-
BELTRAN	2011	Peru	3/134	2.2%	<50	10%	-
COHEN	2014	Argentina	7/68	9.3%	NS	20%	-
BELTRAN	2017	Peru	33/84	28%	>18	20%	-
WESTERN COUNTRIES							
HOELLER	2010	Switzerland and Italy	8/250	3.1%	≥50	10%	-
UNER	2011	Turkey	12/245	4.7%	>50	majority	8 vs 84*, P < .001
HOFSCHEIER	2011	Germany	4/165	2.4%	>50	majority	-
OK	2014	USA	28/675	4.1%	NS	10%	50 vs 92*, P = .189
SLACK	2014	USA	11/374	2.9%	>50	majority	-
NICOLAE	2015	USA	46	-	<45	90%	-
NAEINI	2016	USA	37/530	5.8%	NS	10%	-
TRACY	2018	USA	16/346	4.4%	NS	30%	129 vs 143, P = .97
WITTE	2020	Germany	80/314	-	NS	50%	NR for both, P = .116
AFRICA							
CASSIM	2020	South Africa	9/131	7%	NS	80%	-

DLBCL: diffuse large B-cell lymphoma; EBER: EBV-encoded small RNAs; NR: not reach; NS: not specified; OS: overall survival.

*estimated from Kaplan-Meier curves

Table S2. Geographical origin of the 70 EBV^{+} DLBCL-NOS cases included in the cohort.

CENTERS	NUMBER OF PATIENTS (n=70)
RHÔNE-ALPES REGION	**52 (74%)**
Lyon	29
Saint-Étienne	4
Chambery	4
Annecy	3
Grenoble	3
Valence	2
Bourgoin-Jallieu	2
Chalon-sur-Saône	1
Dijon	1
Villefranche-sur-Saône	1
Le Puy en Velay	1
Macon	1
OTHER REGIONS	**18 (26%)**
Lille	4
Bordeaux	2
Paris	2
Rennes	2
Pontoise	1
Nancy	1
Nantes	1
Liège	1
Strasbourg	1
Le Mans	1
Nimes	1
Martinique	1

Table S3. Panel of antibodies, clone and positivity cut-off used for EBV$^+$ DLBCL-NOS diagnosis.

Target	Antibody	Clone	Positivity cut-off (%)
Tumor cells	CD20	L26, Dako	10
	CD30	BerH2, Dako	10
	CD15	MMA, Ventana Roche	10
	PAX5	SP34, Ventana Roche	10
	OCT-2	MRQ2, Ventana Roche	10
	BOB1	SP92, Ventana Roche	10
	MUM1	MRQ43, Cell marq	30
	CD10	SP67, Ventana Roche	30
	BCL-2	124, Ventana Roche	50
	BCL-6	GI191E/A8, Cell marq	30
	c-MYC	Y69, Ventana Roche	40
	Ki67	Ki67, Dako	-
	CD138	BA38, Ventana Roche	30
	LMP1	CS1.4, Agilent	-
	EBNA-2	PE2, Abcam	-
	PD-L1	QR1, Quartet	5
	PD-L2	D7U8C, Cell Signaling	5
Tumor-microenvironment cells	CD3	polyclonal, Dako	-
	PD1	NAT105, Ventana Roche	5

EBNA-2: EBV-nuclear antigen 2; LMP1: latent membrane protein 1; MUM1: multiple myeloma oncogene 1; PD-L1/L2: programmed death ligand 1/2, PD1: programmed cell death 1.

Table S4. Immunophenotype of EBV$^+$ neoplastic cells according to histological subtype (n=67*).

ANTIBODY		**POLYMORPHIC** (n=46)	**MONOMORPHIC** (n=21)	*P*
CD20		46/46 (100%)	21/21 (100%)	> .99
	0-2	0	0	
	3	46/46 (100%)	21/21 (100%)	
PAX5		40/42 (95%)	17/17 (100%)	> .99
OCT-2		37/40 (93%)	15/16 (94%)	> .99
BOB1		32/39 (82%)	17/17 (100%)	.088
CD30		44/45 (98%)	21/21 (100%)	> .99
	0	1/45 (2%)	0	
	1	1/45 (2%)	0	
	2	14/45 (31%)	20/21 (95%)	
	3	30/45 (67%)	1/21 (5%)	
CD15		10/44 (23%)	0/17 (0%)	.049
MUM1		41/44 (93%)	19/21 (91%)	> .99
CD10		0/36 (0%)	0/21 (0%)	> .99
BCL-6		19/39 (49%)	7/21 (33%)	.287
COO (Hans *et al.*)		35	21	> .99
	GCB	0	0	
	Non-GCB	35 (100%)	21 (100%)	
BCL-2		12/36 (33%)	5/20 (25%)	> .99
c-MYC		26/35 (74%)	8/19 (42%)	.037
DOUBLE EXPRESSOR		9/35 (26%)	4/18 (22%)	> .99
PD-L1		37/40 (93%)	17/17 (100%)	> .99
PD-L2		7/40 (18%)	1/17 (6%)	.413
LMP1		40/40 (100%)	17/17 (100%)	> .99
EBNA-2		4/40 (10%)	3/17 (18%)	> .99

COO: cell of origin; EBNA2: EBV-nuclear antigen 2; GCB: germinal center B; LMP1: latent membrane protein 1; MUM1: multiple myeloma oncogene 1; non-GCB: non germinal center B; PD-L1/L2: programmed death-ligand 1/2.

*Missing data (for 3 patients, microbiopsy insufficient for histological classification)

Table S5. Baseline clinical and biological characteristics in EBV+ DLBCL-NOS patients according to the presence of an HLH (n=65*).

CHARACTERISTICS	HLH	NO HLH	*P*
TOTAL, n	9	56	
Median age, years	66.5	68.5	.733
Age ≤ 50 years	2	21	.474
Age > 50 years	7	35	
Male	8	34	.142
Female	1	22	
INVOLVED SITE, n	9	56	
Nodal, n (%)	9 (100%)	54 (96%)	>.99
Extra-nodal, n (%)	6 (67%)	25 (45%)	.291
1, n (%)	1 (11%)	13 (23%)	
≥ 2, n (%)	5 (56%)	12 (22%)	
CLINICAL STAGE, n	9	56	
I-II, n (%)	0	13	.185
III-IV, n (%)	9 (100%)	43	
aaIPI, n	9	49	
0-1, n (%)	0	16 (32%)	.052
2-3, n (%)	9 (100%)	33 (67%)	
ECOG, n	9	56	
0-1, n (%)	2 (22%)	28 (50%)	.161
2-5, n (%)	7 (78%)	28 (50%)	
B SYMPTOMS, n	9	55	
Absent, n (%)	0	15 (27%)	.101
Present, n (%)	9 (100%)	40 (73%)	
LDH, n	9	49	
Normal, n (%)	0	15 (31%)	.094
High, n (%)	9 (100%)	34 (69%)	
HYPOGAMMAGLOBULINEMIA, n	4	47	
Absent, n (%)	3 (75%)	16 (34%)	.140
Present, n (%)	1 (25%)	31 (66%)	
EBV LATENCY	8	47	
Type II (LMP1+/EBNA2-), n (%)	6 (75%)	43 (91%)	.206
Type III (LMP1+/EBNA2+), n (%)	2 (25%)	4 (9%)	

aaIPI: age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; EBNA2: EBV nuclear antigen 2; HLH: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; LMP1: latent membrane protein 1; RT: radiation therapy.
*Missing data (for 5 patients, clinical data were not sufficient)

Table S6. Baseline clinical and biological characteristics in EBV$^+$ DLBCL-NOS patients who underwent core needle biopsy vs those with an excisional biopsy.

CHARACTERISTICS	CORE NEEDLE BIOPSY	EXCISIONAL BIOPSY	*P*
TOTAL, n	20	50	
Median age, years	69	68.5	.004*
Age ≤ 50 years	4 (20%)	19 (38%)	.172
Age > 50 years	16 (80%)	31 (62%)	
Male	10 (50%)	34 (68%)	.181
Female	10 (50%)	16 (32%)	
INVOLVED SITE, n	18	49	
Nodal, n (%)	15 (83%)	49 (100%)	.017*
Extra-nodal, n (%)	13 (72%)	19 (39%)	.026*
CLINICAL STAGE, n	18	49	
I-II, n (%)	1 (6%)	13 (27%)	.090
III-IV, n (%)	17 (94%)	36 (73%)	
aaIPI, n	13	45	
0-1, n (%)	2 (15%)	14 (31%)	.318
2-3, n (%)	11 (85%)	31 (69%)	
ECOG, n	17	49	
0-1, n (%)	5 (29%)	25 (51%)	.162
2-5, n (%)	12 (71%)	24 (49%)	
B SYMPTOMS, n	17	48	
Absent, n (%)	3 (18%)	12 (25%)	.740
Present, n (%)	14 (82%)	36 (75%)	
LDH, n	13	45	
Normal, n (%)	2 (15%)	13 (29%)	.480
High, n (%)	11 (85%)	32 (71%)	
HLH, n	16	49	
Absent, n (%)	14 (88%)	42 (86%)	>.99
Present, n (%)	2 (12%)	7 (14%)	
HISTOLOGICAL PATTERN	17	50	
Monomorphic, n (%)	8 (47%)	13 (26%)	.135
Polymorphic, n (%)	9 (53%)	37 (74%)	
EBV LATENCY	7	50	
Type II (LMP1+/EBNA2-), n (%)	5 (71%)	45 (90%)	.202
Type III (LMP1+/EBNA2+), n (%)	2 (29%)	5 (10%)	

aaIPI: age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; EBNA2: EBV nuclear antigen 2; HLH: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; LMP1: latent membrane protein 1; RT: radiation therapy.

Table S7. Baseline clinical and biological characteristics in EBV+ DLBCL-NOS patients according to histological pattern (n=67*).

CHARACTERISTICS	POLYMORPHIC	MONOMORPHIC	*P*
TOTAL, n	46	21	
Median age, years	64.5	73	.327
Age ≤ 50 years	17 (37%)	6 (29%)	.587
Age > 50 years	29 (63%)	15 (71%)	
Male	30 (65%)	14 (67%)	> .99
Female	16 (35%)	7 (33%)	
INVOLVED SITE, n	43	21	
Nodal, n (%)	43 (100%)	19 (91%)	.104
Extra-nodal, n (%)	16 (37%)	13 (62%)	.108
1, n (%)	8 (19%)	5 (24%)	
≥ 2, n (%)	8 (19%)	8 (38%)	
CLINICAL STAGE, n	43	21	
I-II, n (%)	9 (21%)	5 (24%)	> .99
III-IV, n (%)	34 (79%)	16 (76%)	
aaIPI, n	38	18	
0-1, n (%)	11 (29%)	5 (28%)	> .99
2-3, n (%)	27 (71%)	13 (72%)	
ECOG, n	42	21	
0-1, n (%)	22 (52%)	8 (38%)	.423
2-5, n (%)	20 (48%)	13 (62%)	
B SYMPTOMS, n	42	20	
Absent, n (%)	12 (29%)	3 (15%)	.346
Present, n (%)	30 (71%)	17 (85%)	
LDH, n	38	18	
Normal, n (%)	9 (24%)	6 (33%)	.524
High, n (%)	29 (76%)	12 (67%)	
LYMPHOPENIA, n	35	15	
Absent, n (%)	13 (37%)	3 (20%)	.328
Present, n (%)	22 (63%)	12 (80%)	
HYPOGAMMAGLOBULINEMIA, n	17	11	
Absent, n (%)	14 (82%)	10 (91%)	> .99
Present, n (%)	3 (18%)	1 (9%)	
HLH, n	40	20	
Absent, n (%)	36 (90%)	15 (75%)	.253
Present, n (%)	4 (10%)	5 (25%)	
EBV LATENCY	40	17	
Type II (LMP1+/EBNA2-), n (%)	36 (90%)	14 (82%)	.415
Type III (LMP1+/EBNA2+), n (%)	4 (10%)	3 (18%)	

aaIPI: age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; EBNA2: EBV nuclear antigen 2; HLH: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; LMP1: latent membrane protein 1; RT: radiation therapy.
*Missing data (for 3 patients, microbiopsy was insufficient for histological classification)

Table S8. Baseline clinical and biological characteristics of EBV+ DLBCL-NOS patients treated with intent-to-cure regimen vs palliative care (n=69*).

CHARECTERISTICS	INTENT-TO-CURE	PALLIATIVE	*P*
TOTAL, n	56	13	
Median age, years	62.5	86	<.0001
Age ≤ 50 ans	23 (41%)	0	.003
Age > 50 ans	33 (59%)	13 (100%)	
Male	39 (70%)	4 (30%)	.013
Female	17 (30%)	9 (70%)	
INVOLVED SITE, n	56	10	
Nodal, n (%)	55 (98%)	8 (80%)	.058
Extra-nodal, n (%)	26 (46%)	6 (60%)	.505
1, n (%)	11 (42%)	4 (67%)	
≥ 2, n (%)	15 (58%)	2 (33%)	
CLINICAL STAGE, n	56	10	
I-II, n (%)	11 (20%)	2 (20%)	>.99
III-IV, n (%)	45 (80%)	8 (80%)	
aaIPI, n	50	7	
0-1, n (%)	14 (28%)	1 (14%)	.662
2-3, n (%)	36 (72%)	6 (86%)	
ECOG, n	56	9	
0-1, n (%)	29 (52%)	0	.003
2-5, n (%)	27 (48%)	9 (100%)	
B SYMPTOMS, n	55	9	
Absent, n (%)	12 (22%)	2 (22%)	>.99
Present, n (%)	43 (78%)	7 (78%)	
LDH, n	50	7	
Normal, n (%)	12 (24%)	2 (29%)	>.99
High, n (%)	38 (76%)	5 (71%)	
LYMPHOPENIA, n	44	7	
Absent, n (%)	15 (34%)	1 (14%)	.410
Present, n (%)	29 (66%)	6 (86%)	
HYPOGAMMAGLOBULINEMIA, n	34	3	
Absent, n (%)	14 (41%)	2 (67%)	.568
Present, n (%)	20 (59%)	1 (33%)	
HLH, n	56	8	
Absent, n (%)	48 (86%)	7 (88%)	>.99
Present, n (%)	8 (14%)	1 (12%)	
EBV LATENCY	49	7	
Type II (LMP1+/EBNA2-), n (%)	43 (88%)	6 (86%)	>.99
Type III (LMP1+/EBNA2+), n (%)	6 (12%)	1 (14%)	

aaIPI: age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; EBNA2: EBV nuclear antigen 2; HLH: hemophagocytic lymphohistiocytosis; LDH: lactate dehydrogenase; LMP1: latent membrane protein 1; RT: radiation therapy.
*Missing data (for 1 patient, treatment regimen not available)

Table S9. First-line regimen received by EBV$^+$ DLBCL-NOS patients treated with curative intent (n=56).

IMMUNOCHEMOTHERAPY ± RT, n (%)	41 (73%)
R-CHOP-like (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), n (%)	24 (59%)
R-ACVBP (rituximab, cyclophosphamide, doxorubicin, vindesine, bleomycine, prednisone), n (%)	13 (31%)
Others, n (%)	4 (10%)
R-BEACOPP (rituximab, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone)	1
R-ABVD (rituximab, bleomycin, dacarbazine, doxorubicin, vinblastine)	1
R-PVAG (rituximab, prednisone, vinblastine, doxorubicin, gemcitabine)	1
COP and R-anti-CD25 immunotoxin (LMB2)	1
CHEMOTHERAPY ± RT, n (%)	15 (27%)
BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), n (%)	5 (33%)
ABVD (bleomycin, dacarbazine, doxorubicin, vinblastine), n (%)	5 (33%)
COPDAC (cyclophosphamide, vincristine, prednisone et dacarbazine), n (%)	1 (7%)
COP (cyclophosphamide, vincristine, prednisone), n (%)	4 (27%)

RT: radiation therapy

Table S10. Salvage regimen and outcome for relapsed/refractory EBV$^+$ DLBCL-NOS treated with curative intend (n=56).

RELAPSED/REFRACTORY EBV$^+$ DLBCL-NOS (n=14)		OUTCOME	PFS (months)	OS (months)
Refractory to first-line therapy, n (%)		10 (71%)		
Patient 1	R-GEMOX	Death from lymphoma	1.93	5.41
Patient 2	R-GEMOX	Death from lymphoma	8.92	14.33
Patient 3	R-GEMOX	Death from lymphoma	2.69	26.49
Patient 4	R-GEMOX	Remission	5.80	39.10
Patient 5	R-ICE	Death from lymphoma	1.93	7.18
Patient 6	No treatment	Death from lymphoma	.56	.56
Patient 7	No treatment	Death from lymphoma	.16	.16
Patient 8	No treatment	Death from lymphoma	.30	.30
Patient 9	No treatment	Death from lymphoma	.95	.95
Patient 10	Missing data	Death from lymphoma	6.30	7.67
Relapse after first-line therapy, n (%)		4 (29%)		
Patient 11	R-DHAOx	Death from lymphoma	13.84	14.85
Patient 12	IVOX followed by ASCT	Remission	164.69	219.97
Patient 13	R-Holoxan VP16	Death from lymphoma	15.61	28.33
Patient 14	Missing data	Death from lymphoma	1.92	1.92

ASCT: autologous stem cell transplantation; IVOX: ifosfamide, etoposide, oxaliplatine; PFS: progression free survival, OS: overall survival; R-GEMOX: rituximab, gemcitabine, oxaliplatine; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine, oxaliplatine; R-ICE: rituximab, ifosfamide, carboplatine, etoposide.

Table S11. Univariate Cox proportional hazard regression in EBV⁺ DLBCL-NOS (n=56 with curative-intent regimen).

	PFS		OS	
VARIABLE	HR (IC 95%)	P	HR (IC 95%)	P
HLH	**1.58 (3.96,28.23)**	< .001	**14.01 (4.99,39.39)**	< .001
ECOG-PS ≥ 2	**11.78 (3.03, 45.73)**	< .001	**1.92 (2.49,47.81)**	.002
aaIPI ≥ 2	**9.23 (1.22,69.7)**	.031	-	> .99
Age > 50 ans	**7.29 (1.78,29.82)**	.006	**6.27 (1.43,27.42)**	.015
Extra nodal disease	**3.16 (1.21,8.28)**	.019	**3.20 (1.12,9.13)**	.030
Clinical stage III – IV	6.58 (.88,49.47)	.067	-	.999
LDH elevated	2.72 (.62,11.88)	.180	5.26 (.69,4.09)	.109
Lymphopenia	2.01 (.56,7.22)	.280	2.84 (.62,12.96)	.189
Latency type III	2.25 (.68,7.47)	.180	2.40 (.66,8.71)	.190
PD-L1 H-score > 150	.59 (.19,1.83)	.360	.48 (.15,1.54)	.220
Polymorphic	.47 (.19,1.16)	.100	.47 (.18,1.23)	.130
Female	.33 (.10,1.12)	.076	.4 (.11,1.39)	.150
B symptoms	-	>.99	-	.988

aaIPI: age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; HLH: hemophagocytic lymphohistiocytosis; HR: hazard ratio; H-score: histoscore; LDH: lactate dehydrogenase; PD-L1: programmed death ligand 1.

Table S12. Baseline clinical and biological characteristics in 56 EBV+ DLBCL-NOS patients compared with 425 EBV- DLBCL-NOS with intent-to-cure therapy.

CARACTERISTIC	DLBCL-NOS (n=481)		*P*	DLBCL-NOS > 50 years (n=392)		*P*	DLBCL-NOS ≤ 50 years (n=89)		*P*
	EBV+	**EBV-**		**EBV+**	**EBV-**		**EBV+**	**EBV-**	
TOTAL, n	56	425		33	359		23	66	
Median age (range), years	62.5 (16 – 86)	67 (20 – 97)	.008	73 (52 – 86)	70 (51 – 97)	.293	37 (16 – 50)	39.5 (20 – 50)	.051
Age ≤ 50 years, n (%)	23 (41%)	66 (16%)	<.0001	-	-		-	-	
Age > 50 years, n (%)	33 (59%)	359 (85%)		-	-		-	-	
Male, n (%)	39 (70%)	276 (65%)	.551	25 (76%)	229 (64%)	.187	14 (60%)	47 (71%)	.436
Female, n (%)	17 (30%)	149 (35%)		8 (24%)	130 (36%)		9 (40%)	19 (29%)	
CLINICAL STAGE, n	56	404		33	343		23	61	
I-II, n (%)	11 (20%)	90 (22%)	.733	4 (12%)	72 (21%)	.265	7 (30%)	18 (30%)	>.99
III-IV, n (%)	45 (80%)	314 (78%)		29 (88%)	271 (79%)		16 (70%)	43 (70%)	
aaIPI, n	50	315		28	276		22	39	
0-1, n (%)	14 (28%)	98 (31%)	.869	4 (14%)	83 (30%)	.084	10 (45%)	15 (38%)	.601
2-3, n (%)	36 (72%)	217 (69%)		24 (86%)	193 (70%)		12 (55%)	24 (62%)	
ECOG-PS, n	56	347		33	303		23	44	
0-1, n (%)	29 (52%)	242 (70%)	.013	10 (30%)	204 (67%)	<.0001	19 (83%)	38 (86%)	.726
2-5, n (%)	27 (48%)	105 (30%)		23 (70%)	99 (33%)		4 (17%)	6 (14%)	
B SYMPTOME, n	55	268		32	231		23	37	
Absent, n (%)	12 (22%)	181 (68%)	<.0001	6 (19%)	151 (65%)	<.0001	6 (26%)	30 (81%)	<.0001
Present, n (%)	43 (78%)	87 (32%)		26 (81%)	80 (35%)		17 (74%)	7 (19%)	
LDH, n	50	357		28	308		22	49	
Normal, n (%)	12 (24%)	74 (21%)	.582	6 (21%)	61 (20%)	.807	6 (27%)	13 (27%)	>.99
Elevated, n (%)	38 (76%)	283 (79%)		22 (79%)	247 (80%)		16 (73%)	36 (73%)	

aaIPI : age adjusted International Pronostic Index; ECOG-PS: Eastern Cooperative Oncology Group-Performans Status; LDH: lactate dehydrogenase.