BHS Educational Course on Hodgkin lymphoma & aggressive lymphoma

Diffuse Large B-cell Lymphoma

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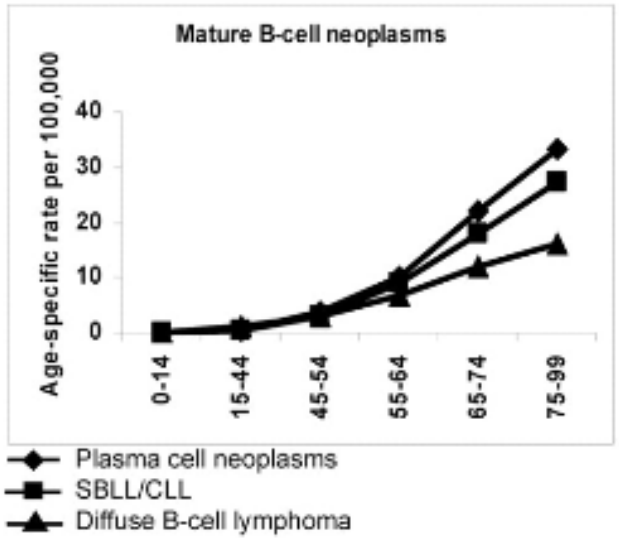
Incidence

Lymphoid malignancies

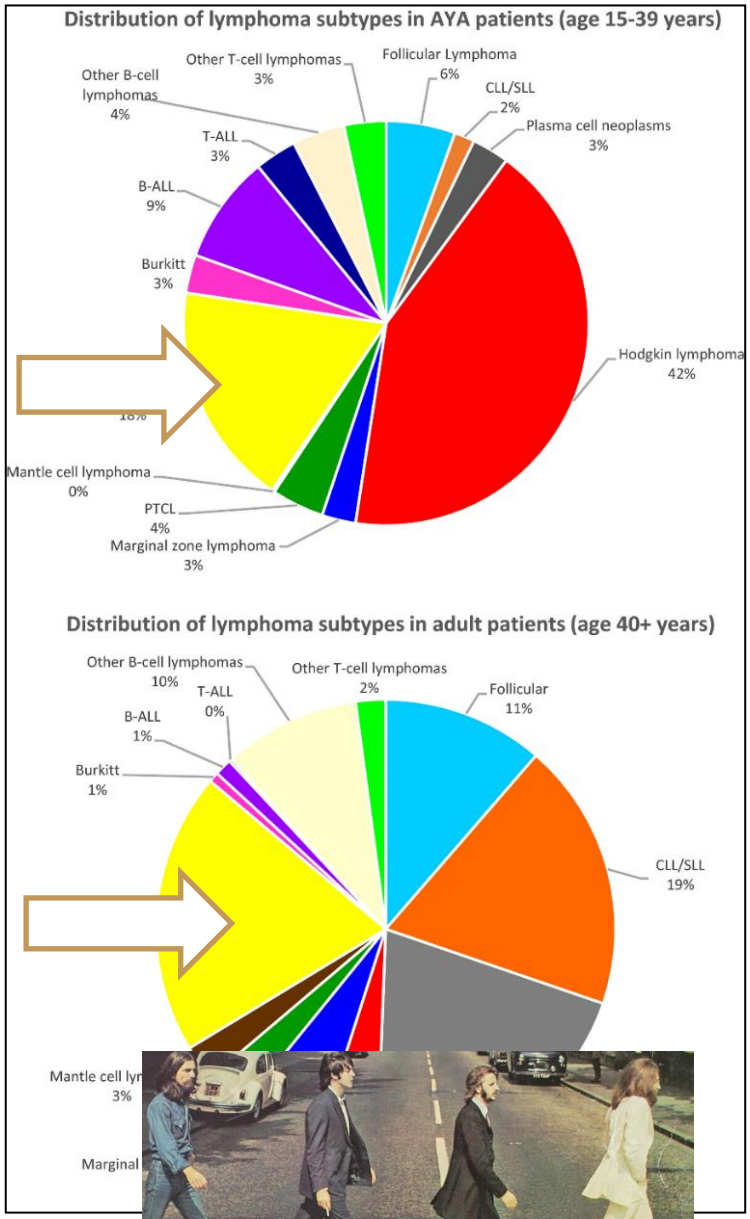


10%

Hodgkin lymphoma (HL)	Non-Hodgkin lymphoma (NHL)
Classical HL	B-cell NHL **80%**
Non-classical HL	T-cell NHL **10%**
(B-cell origin)	NK-cell NHL

Incidence 3.8/100.000/year

Sant M, et al. Blood 2010;116:3724-34
Blum KA, et al. Br J Haematol 2018;183:385-99
Flower A, et al. Br J Haematol 2019;185:418-35



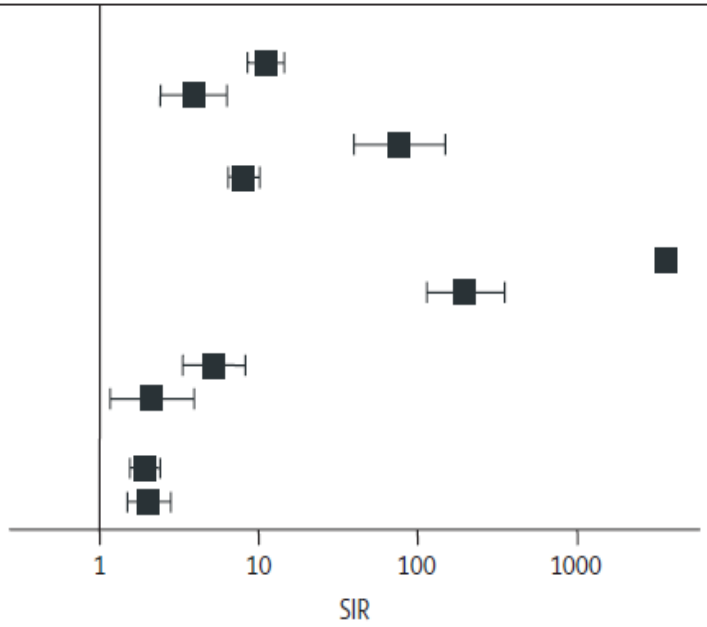
Etiological classification

- *de novo*
- Transformation
  - Richter transformation (CLL/SLL)
  - Transformed FL
  - Transformed HL
- Underlying immunodeficiency (viral)

Etiology

HIV

	Cohort	Meta-analysis SIR (95% CI)	Number of studies	Observed number of cancers	Heterogenity p value
EBV-related cancers					
Hodgkin's lymphoma	HIV/AIDS	11·03 (8·43–14·4)	7	802	0·00
	Transplant	3·89 (2·42–6·26)	4	21	0·65
Non-Hodgkin lymphoma	HIV/AIDS*	76·67 (39·4–149)	6	5295	0·00
	Transplant	8·07 (6·40–10·2)	4	333	0·02
HHV-8 related cancer					
Kaposi's sarcoma	HIV/AIDS*	3640·0 (3326–3976)	1	494	
	Transplant	208·0 (114–349)	1	14	-
HBV/HCV-related cancer					
Liver	HIV/AIDS	5·22 (3·32–8·20)	7	133	0·01
	Transplant	2·13 (1·16–3·91)	3	19	0·25
***Helicobacter pylori*-related cancer**					
Stomach	HIV/AIDS	1·90 (1·53–2·36)	7	89	0·49
	Transplant	2·04 (1·49–2·79)	3	44	0·85



Lymphoma type	CD4+ T-cell count (cells/mm³)
Plasmacytoid Burkitt lymphoma	Normal to low (>200)
DLBCL immunoblastic lymphoma	Very low (<100)
Plasmablastic lymphoma	Low
Classic PEL	Very low (<100)
Solid PEL	Low (<200)
Polyclonal lymphoma	Low (<200)

Gruhlich AE et al. Lancet 2007;370:59-67
Carbone A, et al. Nat Rev Clin Oncol 2014;11:223-38

Etiology

HIV

Cancer site or type (ICD10)	Period								
	Pre-HAART (1985–1996) 20615 PY			Early-HAART (1997–2001) 17690 PY			Late-HAART (2002–2006) 15410 PY		
	O/E	SIR	95% CI	O/E	SIR	95% CI	O/E	SIR	95% CI
AIDS-defining cancers									
Kaposi's sarcoma (C46)	272/1.1	246	218–277	25/0.7	47.8	33.3–66.6	14/0.6	22.9	12.5–38.5
Non-Hodgkin's lymphoma (C82-C88, C96)	191/1.9	103	88.8–119	52/1.9	26.7	19.9–35.1	32/2.0	16.2	11.1–22.9
Cervix uteri (C53)	4/0.5	8.4	2.2–21.8	2/0.5	3.7	0.3–13.6	0/0.5	—	—
All AIDS-defining cancers	467/3.4	136	124–149	89/3.2	27.7	22.2–34.1	46/3.1	14.7	10.8–19.6
Non-AIDS-defining cancers									
Head and neck (C00-C14, C30-C32)[a]	9/2.1	4.3	2.0–8.3	8/2.7	2.9	1.3–5.8	7/3.2	2.2	0.9–4.5
Stomach (C16)	1/0.7	1.5	0.0–8.5	1/0.9	1.2	0.0–6.7	1/1.0	1.0	0.0–5.6
Small intestine, colon, rectum and rectosigmoid junction (C17-C20)	2/1.8	1.1	0.1–4.0	2/2.8	0.7	0.1–2.6	1/3.5	0.3	0.0–1.6
Anus (C21)	2/0.1	25.7	2.4–94.5	12/0.1	112	57.8–197	6/0.1	49.9	18.0–109
Liver (C22)	2/0.4	5.5	0.5–20.2	7/0.7	10.7	4.2–22.2	5/0.8	6.1	1.9–14.3
Pancreas (C25)	0/0.4	—	—	2/0.6	3.4	0.3–12.4	1/0.7	1.4	0.0–7.8
Trachea, lung and bronchus (C33, C34)	8/2.4	3.3	1.4–6.6	10/3.6	2.8	1.3–5.1	12/4.6	2.6	1.3–4.6
Skin, melanomatous (C43)	3/2.5	1.2	0.2–3.5	2/3.1	0.6	0.1–2.4	6/3.1	2.0	0.7–4.3
Skin, non-melanomatous (C44)	7/4.0	1.7	0.7–3.6	23/6.5	3.5	2.2–5.3	23/7.0	3.3	2.1–4.9
Breast (C50)[b]	1/1.7	0.6	0.0–3.4	4/3.3	1.2	0.3–3.2	4/4.3	0.9	0.2–2.4
Ovary (C56)	2/0.3	6.4	0.6–23.5	0/0.4	—	—	0/0.5	—	—
Prostate (C61)	0/1.1	—	—	5/2.8	1.8	0.6–4.1	5/3.8	1.3	0.4–3.1
Testis (C62)	4/3.0	1.3	0.3–3.4	3/2.4	1.2	0.2–3.7	1/1.8	0.5	0.0–3.1
Kidney (C64)	1/0.5	1.9	0.0–10.6	1/0.8	1.3	0.0–7.2	3/1.0	3.1	0.6–9.2
Bladder (C67)	1/1.0	1.1	0.0–6.0	0/1.4	—	—	1/1.7	0.6	0.0–3.3
Brain, meninges and central nervous systems (C70-C72)	2/0.9	2.2	0.2–7.9	2/0.9	2.2	0.2–8.0	0/1.0	—	—
Thyroid (C73)	2/0.7	2.9	0.3–10.7	1/0.8	1.3	0.0–7.0	2/0.8		
Hodgkin's lymphoma (C81)	7/0.8	9.2	3.6–19.0	12/0.6	21.0	10.8–36.8	13/0.5	28.1	14.9–48.2
Multiple myeloma (C90)	3/0.2	14.8	2.8–43.9	1/0.3	3.2	0.0–18.1	2/0.4	5.1	0.5–18.9
Leukaemias (C91-C95)	1/0.7	1.5	0.0–8.3	2/0.8	2.4	0.2–8.8	1/0.9	1.1	0.0–6.5
All non-AIDS-defining cancers[c]	62/26.7	2.3	1.8–3.0	100/37.3	2.7	2.2–3.3	94/42.8	2.2	1.8–2.7
All cancers	529/30.1	17.6	16.1 –19.1	189/40.6	4.7	4.0–5.4	140/46.0	3.0	2.6–3.6

Franceschi S, et al. Br J Cancer 2010;103:416-22

Etiology

PTLD

	Kyllonen et al	Birkeland et al	Adami et al	Vajdic et al	Villeneuve et al
Non-AIDS-defining cancers					
Lip	22·95 (12·55–38·51)	13·02 (10·75–15·63)	53·33 (38·10–72·62)	47·09 (41·76–52·91)	31·76 (23·86–41·45)
Oral cavity and pharynx†	..	5·26 (2·27–10·37)	2·75 (1·50–4·61)	..	3·07 (2·02–4·46)
Oesophagus	..	..	3·21 (1·04–7·48)	3·82 (2·26–6·04)	1·56 (0·51–3·65)
Stomach	..	..	2·30 (1·19–4·02)	1·84 (1·07–2·94)	2·08 (1·17–3·44)
Small intestine	11·76 (3·21–30·12)	..	1·10 (0·03–6·12)	1·72 (0·21–6·23)	..
Colon	3·94 (2·10–6·74)	..	2·30 (1·49–3·40)	2·36 (1·87–2·92)	..
Rectum	..	..	1·90 (1·04–3·19)	0·63 (0·33–1·07)	..
Colon and rectum	..	..	2·14 (1·52–2·92)	1·71 (1·38–2·09)	1·35 (1·00–1·77)
Anus	..	..	10·26 (2·79–26·26)	2·77 (1·51–4·64)	..
Liver	..	..	1·10 (0·30–2·81)	3·19 (1·53–5·88)	1·85 (0·60–4·32)
Pancreas	..	..	0·90 (0·25–2·31)	1·21 (0·56–2·31)	1·08 (0·43–2·22)
Larynx	..	..	2·50 (0·52–7·31)	2·10 (0·96–3·98)	1·74 (0·75–3·43)
Trachea, bronchus, and lung	..	..	1·70 (1·09–2·53)	2·45 (2·00–2·97)	2·10 (1·72–2·53)
Melanoma	..	1·35 (0·28–3·93)	1·80 (0·98–3·02)	2·53 (2·08–3·05)	1·90 (1·16–2·94)
Non-melanoma skin‡	39·10 (29·20–51·27)	10·68 (8·84–12·79)	56·16 (49·75–63·17)	..	..
Breast	1·20 (0·64–2·05)	1·45 (0·72–2·59)	1·00 (0·64–1·49)	1·03 (0·78–1·34)	1·31 (0·98–1·72)
Vulva and vagina	..	..	23·91 (11·94–42·79)	22·22 (13·93–33·64)	..
Uterus	..	..	..	1·74 (0·92–2·97)	0·90 (0·33–1·95)
Ovary	..	..	2·00 (0·91–3·80)	1·15 (0·46–2·38)	1·49 (0·60–3·07)
Penis	..	..	..	15·79 (5·79–34·37)	..
Prostate	..	..	1·10 (0·67–1·70)	0·95 (0·68–1·29)	0·91 (0·64–1·26)
Testis	..	..	2·31 (0·48–6·74)	1·25 (0·34–3·19)	..
Kidney	7·97 (5·00–12·07)	4·08 (1·50–8·88)	4·90 (3·26–7·09)	7·3 (5·69–9·22)	7·32 (5·72–9·23)
Bladder	..	1·63 (0·53–3·81)	2·30 (1·40–3·55)	3·33 (2·40–4·50)	1·98 (1·27–2·95)
Eye	..	..	2·00 (0·05–11·14)	7·56 (3·46–14·36)	..
Brain	..	1·38 (0·28–4·02)	1·00 (0·40–2·06)	0·57 (0·16–1·46)	1·25 (0·54–2·46)
Thyroid	8·09 (4·04–14·47)	0·91 (0·02–5·09)	3·80 (1·39–8·27)	6·90 (4·69–9·80)	5·00 (3·17–7·50)
Hodgkin's lymphoma	..	8·00 (1·65–23·38)	2·20 (0·27–7·94)	3·74 (1·51–7·71)	3·60 (1·65–6·83)
Multiple myeloma	..	..	2·70 (0·99–5·88)	2·67 (1·38–4·67)	3·82 (2·04–6·54)
Leukaemia	..	..	2·36 (1·02–4·65)	2·46 (1·57–3·66)	2·27 (1·32–3·63)
All cancers	3·33 (2·92–3·79)	3·59 (3·12–4·11)	4·05 (3·75–4·36)	3·40 (3·22–3·59)	2·48 (2·31–2·66)
AIDS-defining cancers					
Kaposi's sarcoma	..	..	..	208·0 (113·7–349·0)	..
Cervix uteri	..	..	2·00 (0·65–4·67)	2·50 (1·33–4·27)	1·54 (0·56–3·35)
Non-Hodgkin lymphoma	..	5·48 (2·37–10·80)	6·00 (4·38–8·03)	9·86 (8·37–11·54)	8·87 (7·38–10·56)

Gruhlich AE et al. Lancet 2007;370:59-67

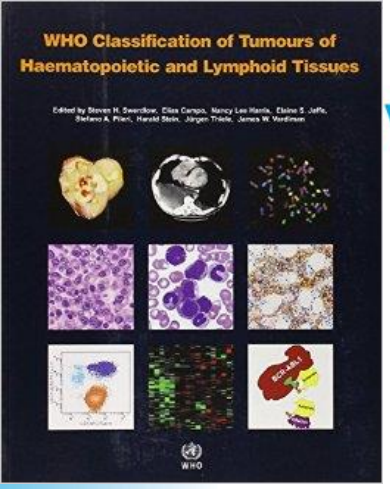
Etiology

PTLD

Table 1. Risk Factors for the Development of Post-Transplantation Lymphoproliferative Disorder.*

Variable	Risk after Solid-Organ Transplantation	Risk after Allogeneic HSCT
Established risk factors		
	Type of transplanted organ, relative risk: multiorgan and intestinal, 239.5; lung, 58.6; pancreas, 34.9; liver, 29.9; heart, 27.6; kidney, 12.6	Type of donor or donation, incidence: haploidentical, ≤20%; unrelated, 4–10%; umbilical cord blood, 4–5%; HLA-identical related, 1–3%
	EBV mismatch at time of transplantation (recipient EBV-negative, donor EBV-positive); relative risk, 10–75	
		Recipient age, >50 yr; relative risk, 5.1
	Intensity of induction immunosuppressive therapy and duration of maintenance therapy (including graft-rejection episodes); overall SIR, 10	Conditioning regimen (T-cell–depleting strategies, both in vivo and ex vivo; relative risk, 3.1–15.8); maintenance immunosuppressive medication (for chronic GVHD; relative risk, 2.0)
Strong evidence of risk		
	Increased risk associated with ATG, OKT3, tacrolimus, azathioprine, new agents (e.g., belatacept in EBV-negative transplant recipient)	
	Controversial degree of risk associated with alemtuzumab, cyclosporine, mTOR inhibitors	
	No increase in risk associated with mycophenolate mofetil, basiliximab, daclizumab	
Weak evidence of risk		
	Underlying disorder (HCV, cystic fibrosis, autoimmune hepatitis)	Underlying disorder (primary immunodeficiency, advanced Hodgkin's lymphoma)
	Race or ethnic group (risk in descending order): white, black, African	
		Prior splenectomy
	Monoclonal gammopathy of undetermined significance (in recipient)	Monoclonal gammopathy of undetermined significance (in recipient or donor)
	Non-EBV infection (HCV or CMV infection)	Non-EBV infection (CMV infection)
	Older donor age and younger recipient age	
	Cytokine gene polymorphisms	
	HLA alleles, haplotypes, mismatches, antibodies	HLA alleles, haplotypes, mismatches, antibodies

Dierickx D, Habermann TM. N Engl J Med 2018;378:549-62

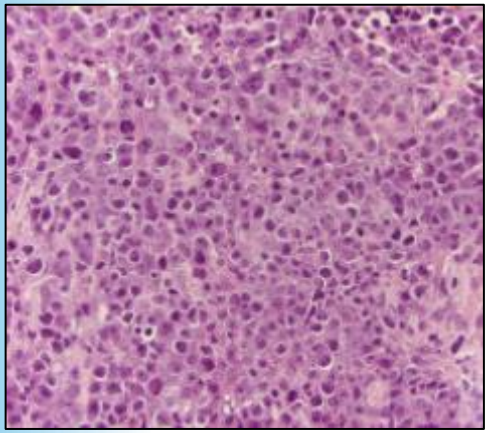


VEN

Classification

DLBCL

- Large cells (> nuclei benign histiocytes)
- Diffuse pattern
- B-cell



Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	*Not previously included*
Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with *IRF4* rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	*Not previously included* (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	*Not previously included*
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	*Not previously included*, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis*)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)
Burkitt lymphoma	
Burkitt lymphoma	(Same)
KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder

Testicular follicular lymphoma*
Large B-cell lymphoma with *IRF4* rearrangement*
Mantle cell lymphoma
- In situ mantle cell neoplasia
- Leukemic non-nodal mantle cell lymphoma

Diffuse large B-cell lymphoma, NOS
- Germinal center B-cell subtype
- Activated B-cell subtype

*Large B-cell lymphoma with 11q aberration**
Nodular lymphocyte predominant B-cell lymphoma*
T cell/histiocyte-rich large B-cell lymphoma
Primary diffuse large B-cell lymphoma of the central nervous system
Primary diffuse large B-cell lymphoma of the testis*
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
*HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma**
Epstein-Barr virus–positive mucocutaneous ulcer*
Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation
- Fibrin-associated diffuse large B-cell lymphoma

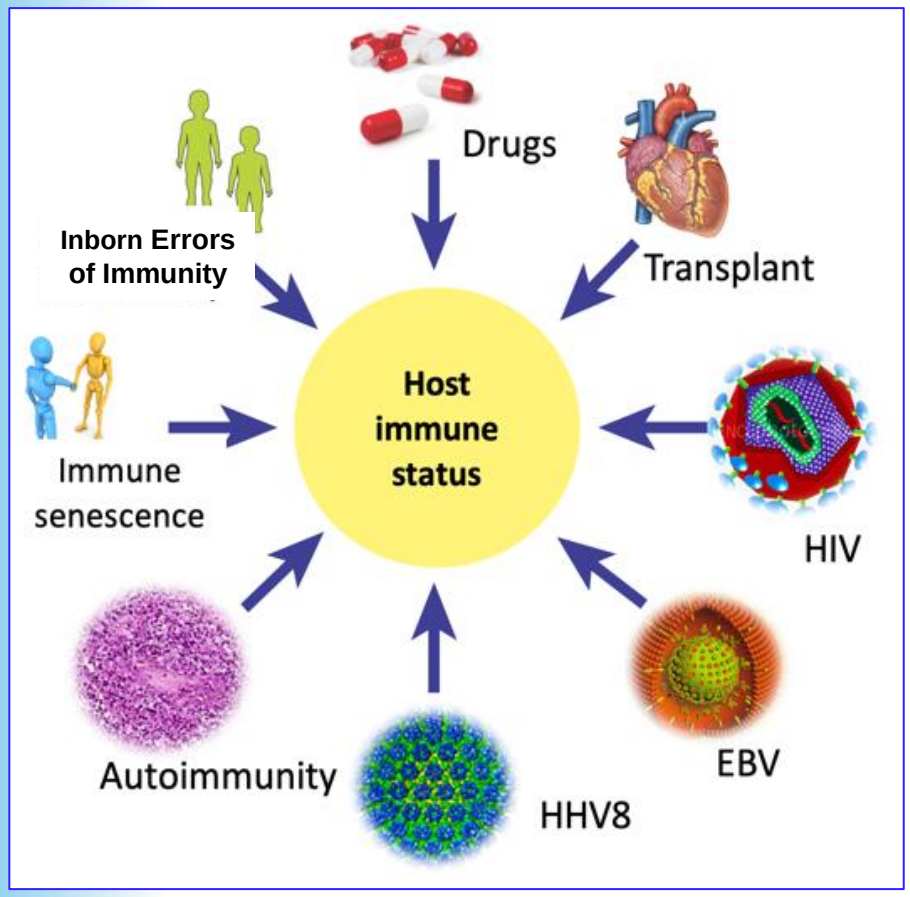
Lymphomatoid granulomatosis
Epstein-Barr virus–positive polymorphic B-cell lymphoproliferative disorder, NOS*
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
HHV-8–associated lymphoproliferative disorders
- Multicentric Castleman disease
- HHV-8–positive germinotropic lymphoproliferative disorder
- HHV-8–positive diffuse large B-cell lymphoma, NOS
- Primary effusion lymphoma

Burkitt lymphoma
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements*
*High-grade B-cell lymphoma with MYC and BCL6 rearrangements**
High-grade B-cell lymphoma, NOS
Primary mediastinal large B-cell lymphoma
Mediastinal gray-zone lymphoma*

DLBCL, NOS → **80-85%**

Gifford GK, et al. Pathology 2016;48:5-16
Campo E, et al. Blood 2022;140:1229-53
Alaggio R, et al. Leukemia 2022;36:1720-48

Classification



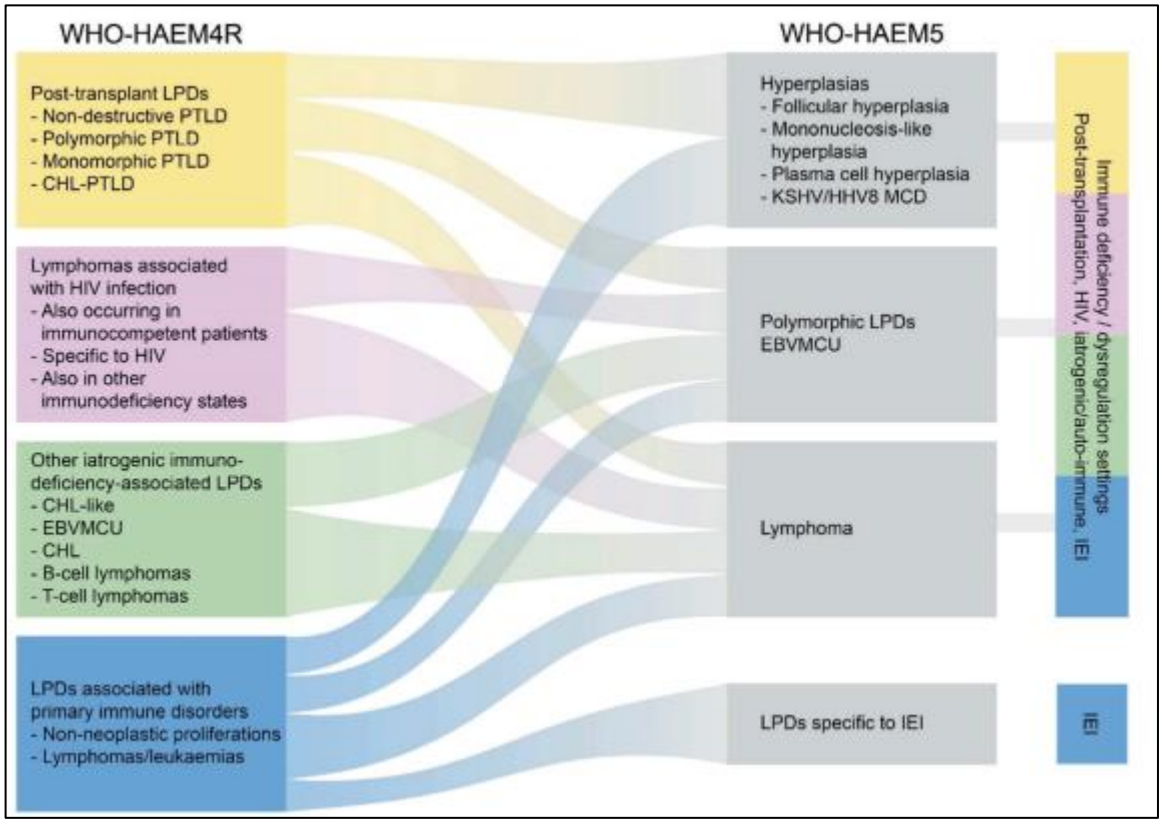
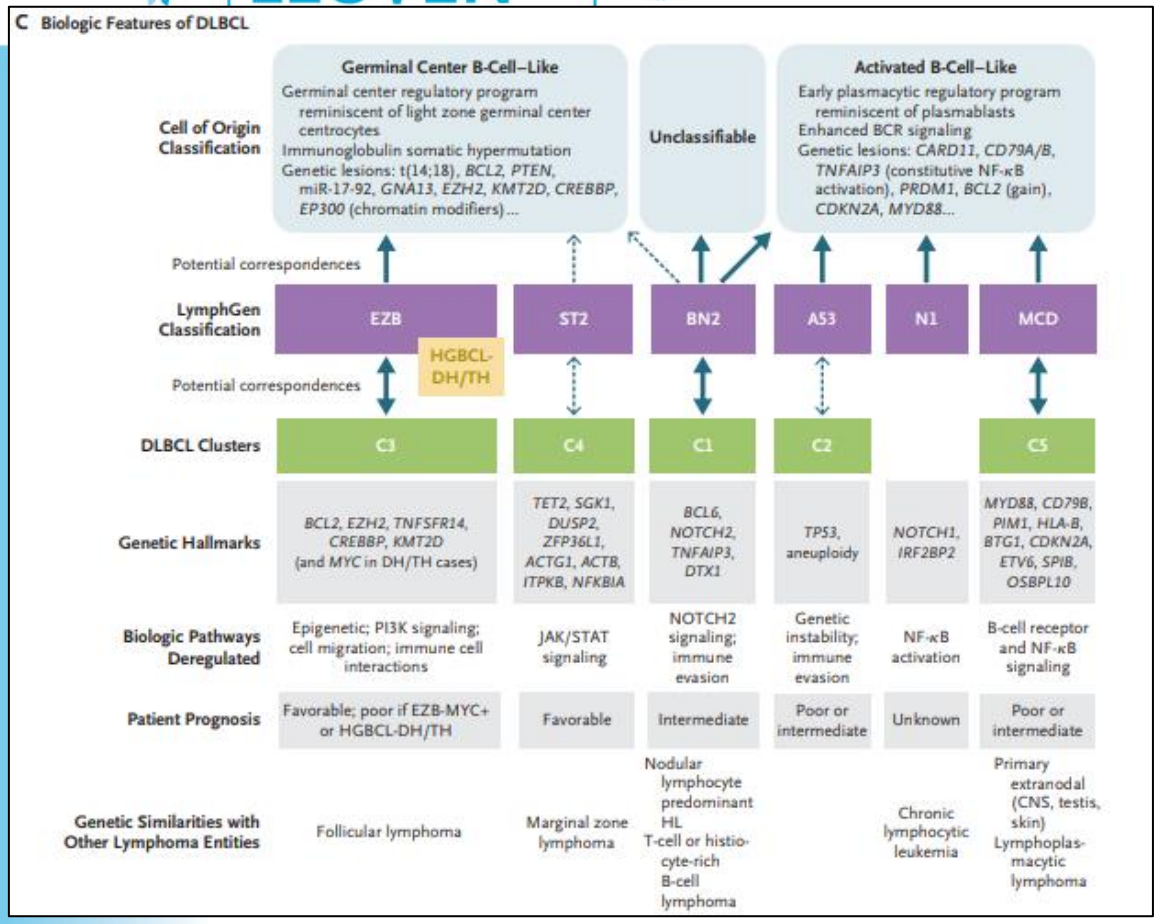


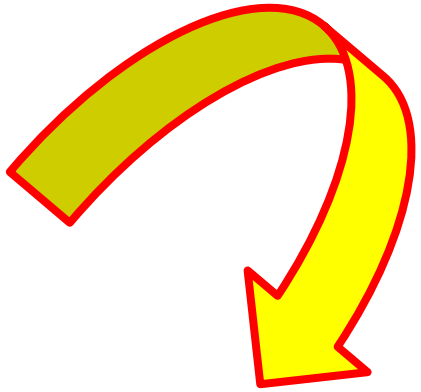
Table 5. Three-part nomenclature for lymphoid proliferations and lymphomas arising in the setting of immune deficiency/dysregulation.

Histological diagnosis	Viral association	Immune deficiency/dysregulation setting
◦ Hyperplasia (specify type) ◦ Polymorphic lymphoproliferative disorder ◦ Mucocutaneous ulcer ◦ Lymphoma (classify as for immunocompetent patients)	◦ EBV +/− ◦ KSHV/HHV8 +/−	◦ Inborn error of immunity (specify type) ◦ HIV infection ◦ Posttransplant (specify: solid organ/bone marrow) ◦ Autoimmune disease ◦ Iatrogenic/therapy-related (specify) ◦ Immune senescence

Natkunam Y, et al. Blood 2018;132:1871-8
Alaggio R, et al. Leukemia 2022;36:1720-48

Molecular classification





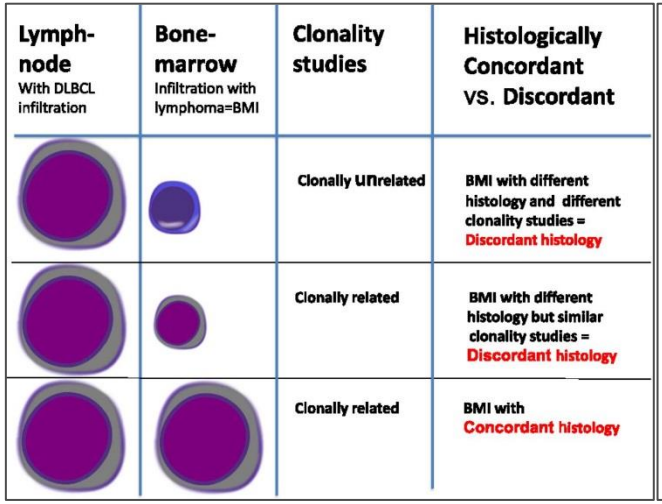
GCB (~60%, total) 5-year OS, 76%			**ABC** (~30%, total) 5-year OS, 16%		
Cluster 3 5-year PFS, ~50%	**Cluster 4** 5-year PFS, ~70%	**Cluster 2** 5-year PFS, ~60%	**Cluster 1** 5-year PFS, ~80%	**Cluster 5** 5-year PFS, ~60%	
EZB (88% GCB) 5-year PFS, ~60%		**BN2** (19% GCB, 41% ABC) 5-year PFS, ~60%	**N1** (95% ABC) 5-year PFS, ~20%	**MCD** (96% ABC) 5-year PFS, ~20%	
EZB, MYC+ (5.9%, total) 5-year OS, 48%	**EZB, MYC-** (17.8%, total) 5-year OS, 82%	**ST2** (6.4%, total) 5-year OS, 84%	**BN2** (13.3%, total) 5-year OS, 67%	**A53** (5.8%, total) 5-year, OS, 63%)	**MCD** (8.7%, total) 5-year OS, 40%	**N1** (1.7%, total) 5-year OS, 27%
MHG positive (~50% MYC+) 3-year PFS, 37%			**MHG negative** 3-year PFS, 72%		
DHITsig positive (50% DHT+; 27% of total GCB) 5-year PFS 57%			**DHITsig negative** 5-year PFS 81%		
GCB 1: DHIT+/TP53+ 2-year OS, ~45%	**GCB 2: DHIT+/TP53-** 2-year OS, ~75%		**GCB 3: EZB like** 2-year OS, >90%	**GCB 4: GCB, NOS** 2-year OS, >90%	

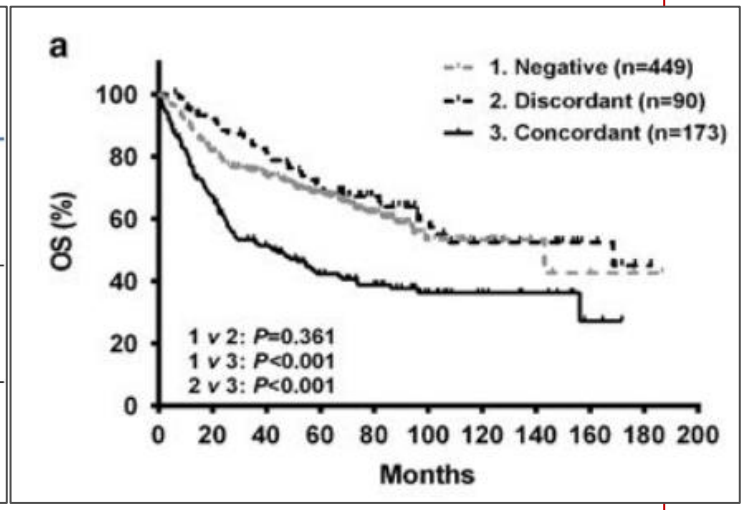
Favorable-risk ABC DLBCL
Poor-risk GCB DLBCL

Sehn L, Salles G. N Engl J Med 2021;384:842-58
Gordon MJ, Westin JR. Leuk Lymphoma 2022;63:1034-44
Nastoupil LJ, Barlett NL J Clin Oncol 2022;41:903-13

Symptoms

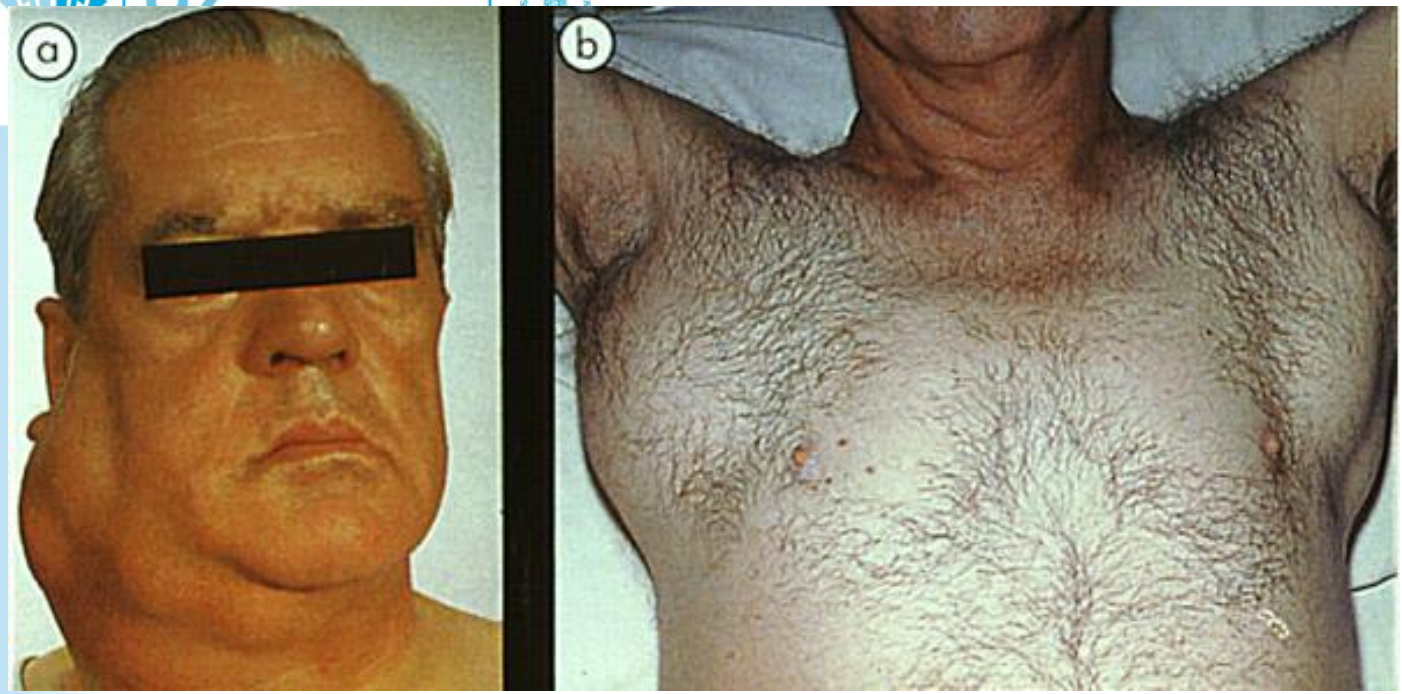
- Nodal masses
- 40%: extranodal involvement
- 1/3: B symptoms
- 50%: stage I-II, 50% stage III-IV
- 10-20%: bone marrow involvement
  - Concordant
  - Discordant

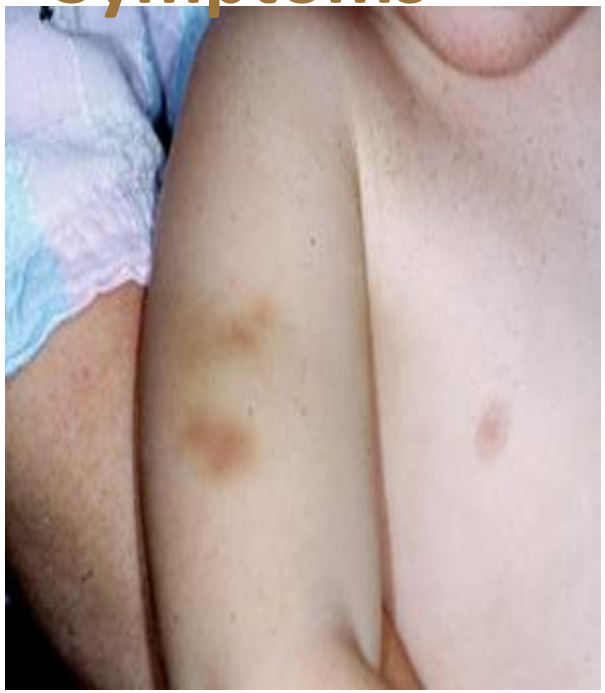


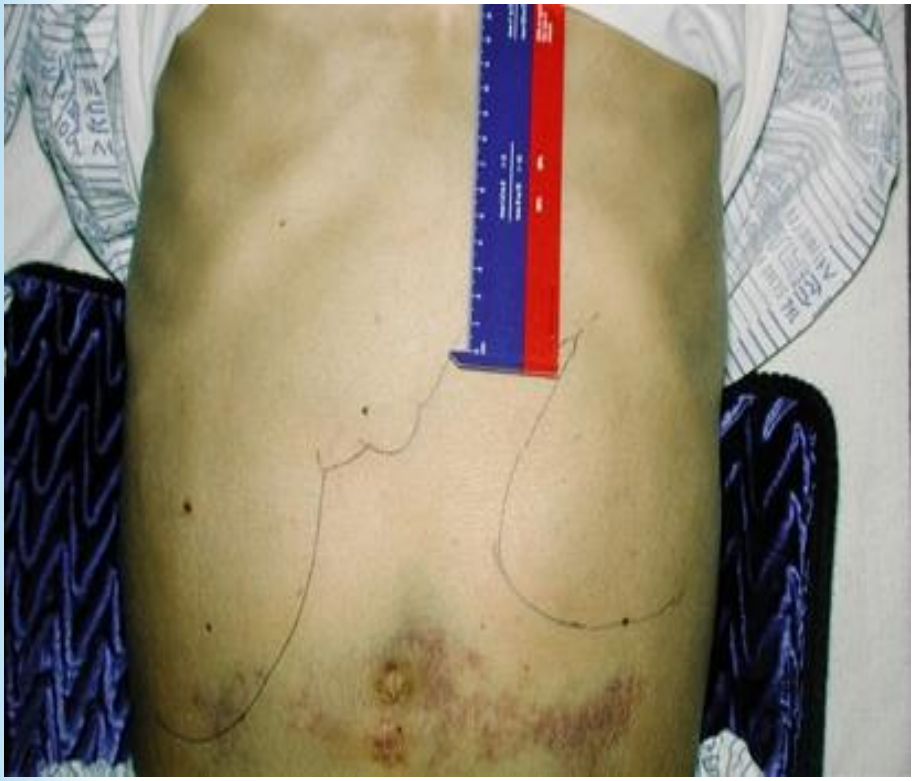


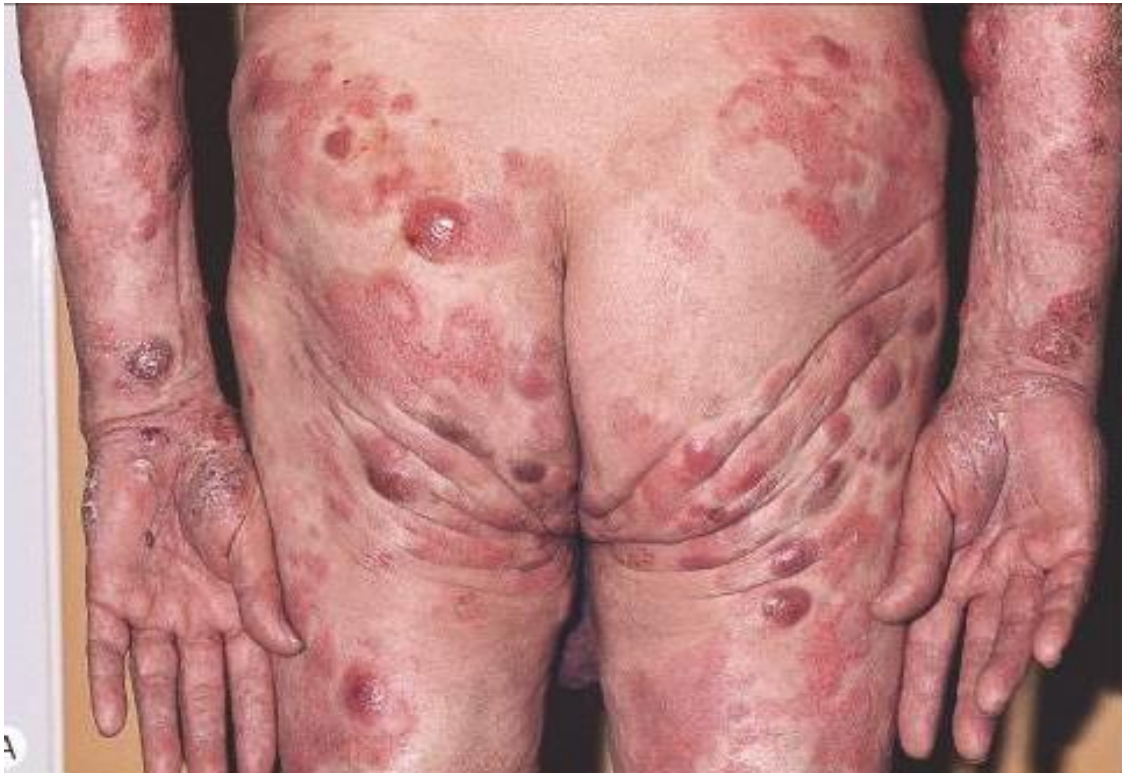
Brudno J, et al. Blood 2016;127:965-70
Li S, et al. Pathology 2018;50:74-87
Yao Z, et al. Leukemia 2018;32:353-63

Symptoms







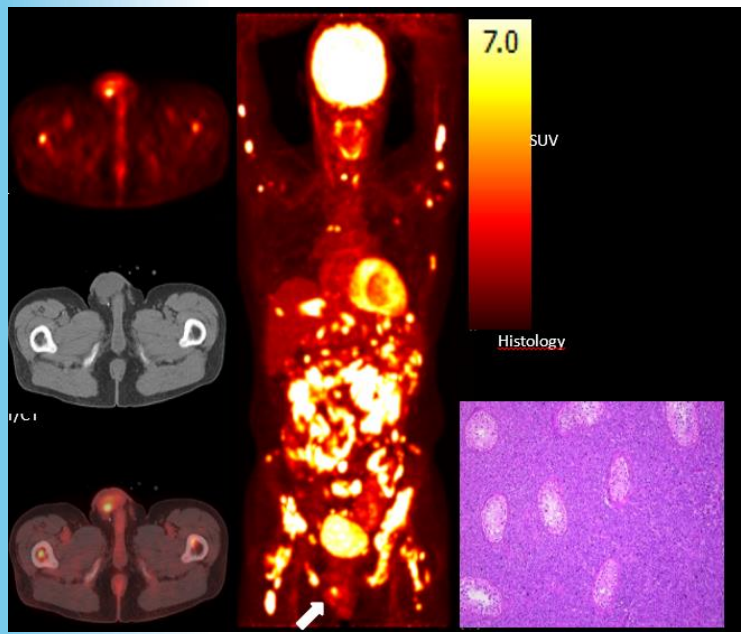


Staging

Ann Arbor/Lugano staging

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable



A: no B-symptoms
B: B-symptoms

Cheson BD, et al. J Clin Oncol 2014;32:3059-68
Courtesy to Prof Gheysens and Prof Tousseyn

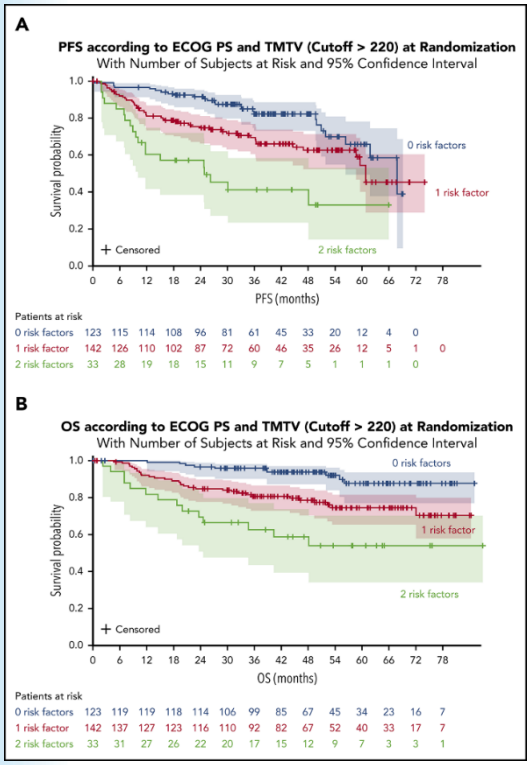
Staging

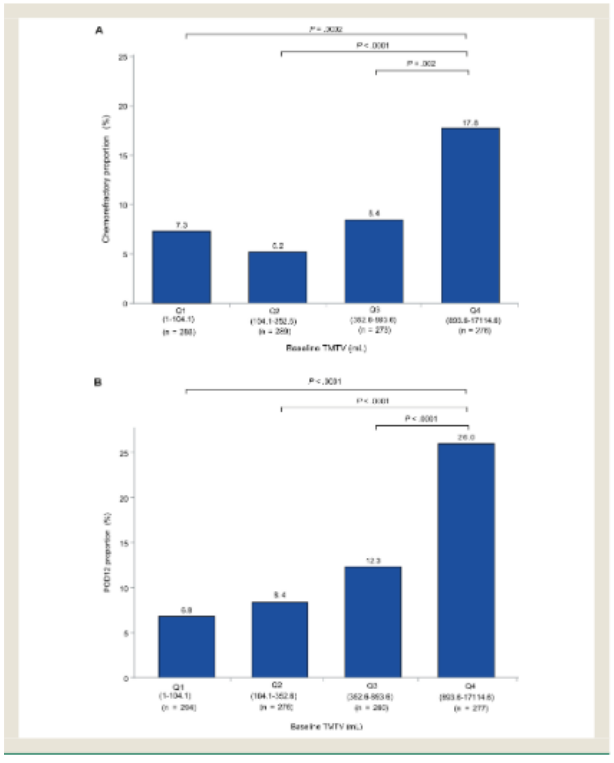
TABLE 1. ^{18}F-FDG Avidity of Lymphoma According to World Health Organization Histopathologic Classification

Histology	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Hodgkin disease	233	233	0	100
Burkitt lymphoma	18	18	0	100
Mantle cell lymphoma	14	14	0	100
Anaplastic large T-cell lymphoma	14	14	0	100
Marginal zone lymphoma, nodal	8	8	0	100
Lymphoblastic lymphoma	6	6	0	100
Angioimmunoblastic T-cell lymphoma	4	4	0	100
Plasmacytoma	3	3	0	100
Natural killer/T-cell lymphoma	2	2	0	100
Diffuse large B-cell lymphoma	222	216	6	97
Follicular lymphoma	140	133	7	95
Peripheral T-cell lymphoma	10	9	1	90
Small lymphocytic lymphoma	29	24	5	83
Enteropathy-type T-cell lymphoma	3	2	1	67
Marginal zone lymphoma, splenic	3	2	1	67
MALT marginal zone lymphoma	50	27	23	54
Lymphomatoid papulosis	2	1	1	50
Primary cutaneous anaplastic large T-cell lymphoma	5	2	3	40
All	766	718	48	94

TABLE 2. ^{18}F-FDG Avidity of NHL According to Clinical Classification

Clinical subtype	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Aggressive*	293	285	8	97
Indolent†	240	200	40	83

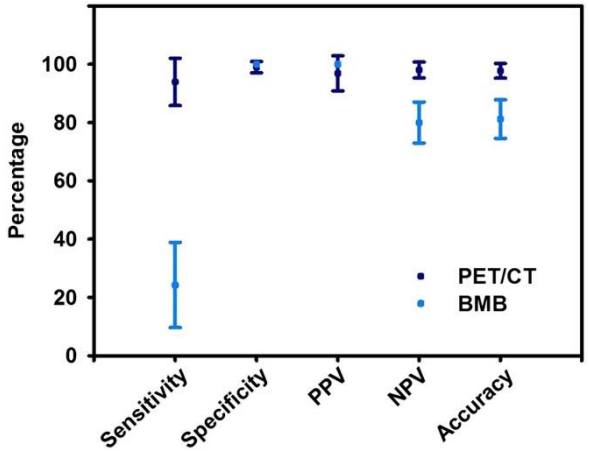




Weiler-Sagie M, et al. J Nucl Med 2010;51:25-30
Barrington SF, Trotman J. Lancet Hematol 2021;8:e80-e93
Vercellino L, et al. Blood 2020;135:1396-405
Canalez Riuz I, et al. Clin Lymphoma Myeloma Leuk 2022;22:e804-14

Bone marrow biopsy

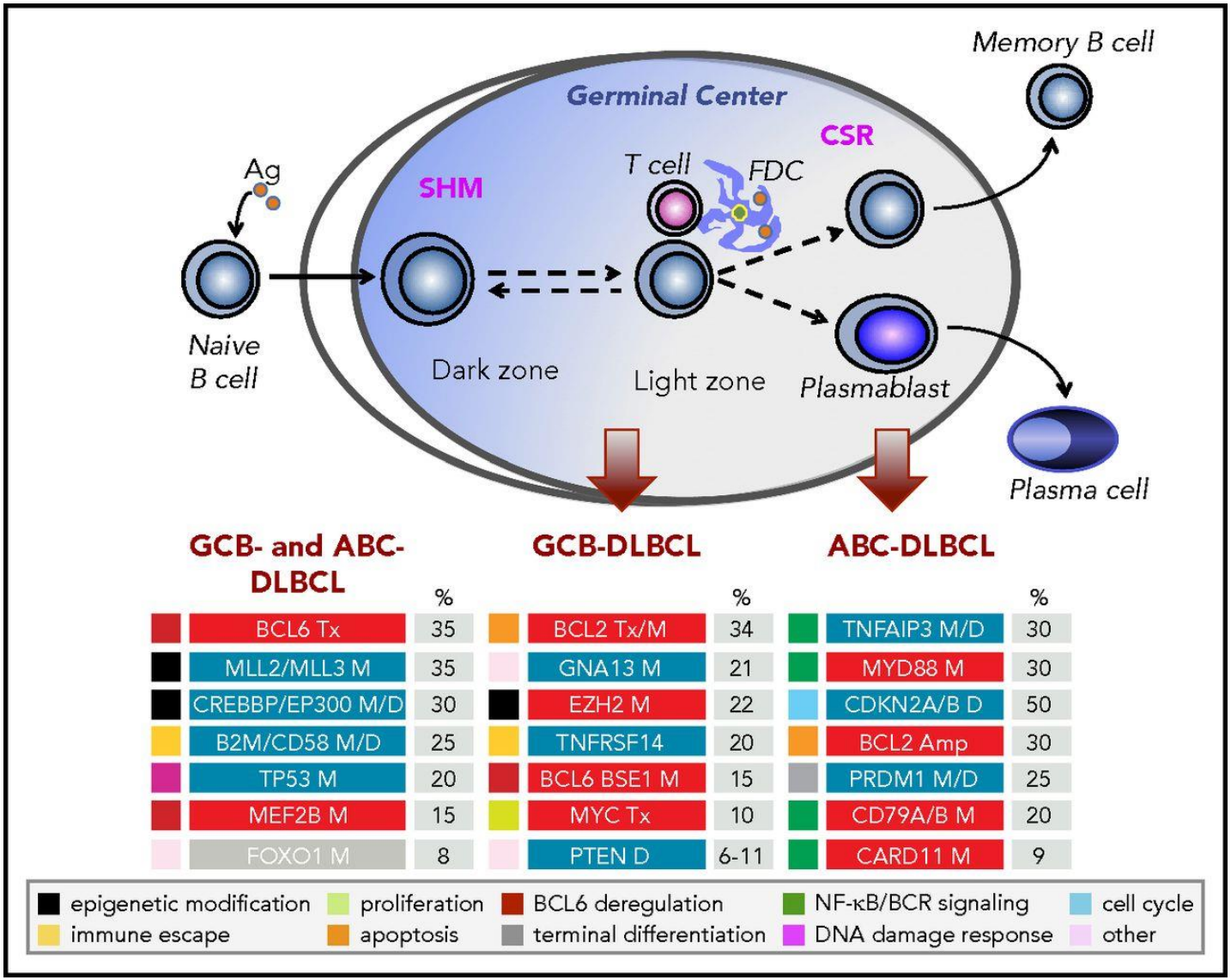
- PET-CT has demonstrated better sensitivity and specificity than bone marrow biopsy for detecting bone marrow involvement.



- Low volume involvement (< 10%-20%) and discordant lymphoma may be missed by PET/CT imaging.
- Bone marrow biopsy is no longer required when a PET-CT scan demonstrates bone or marrow involvement but may be appropriate in case of negative PET.

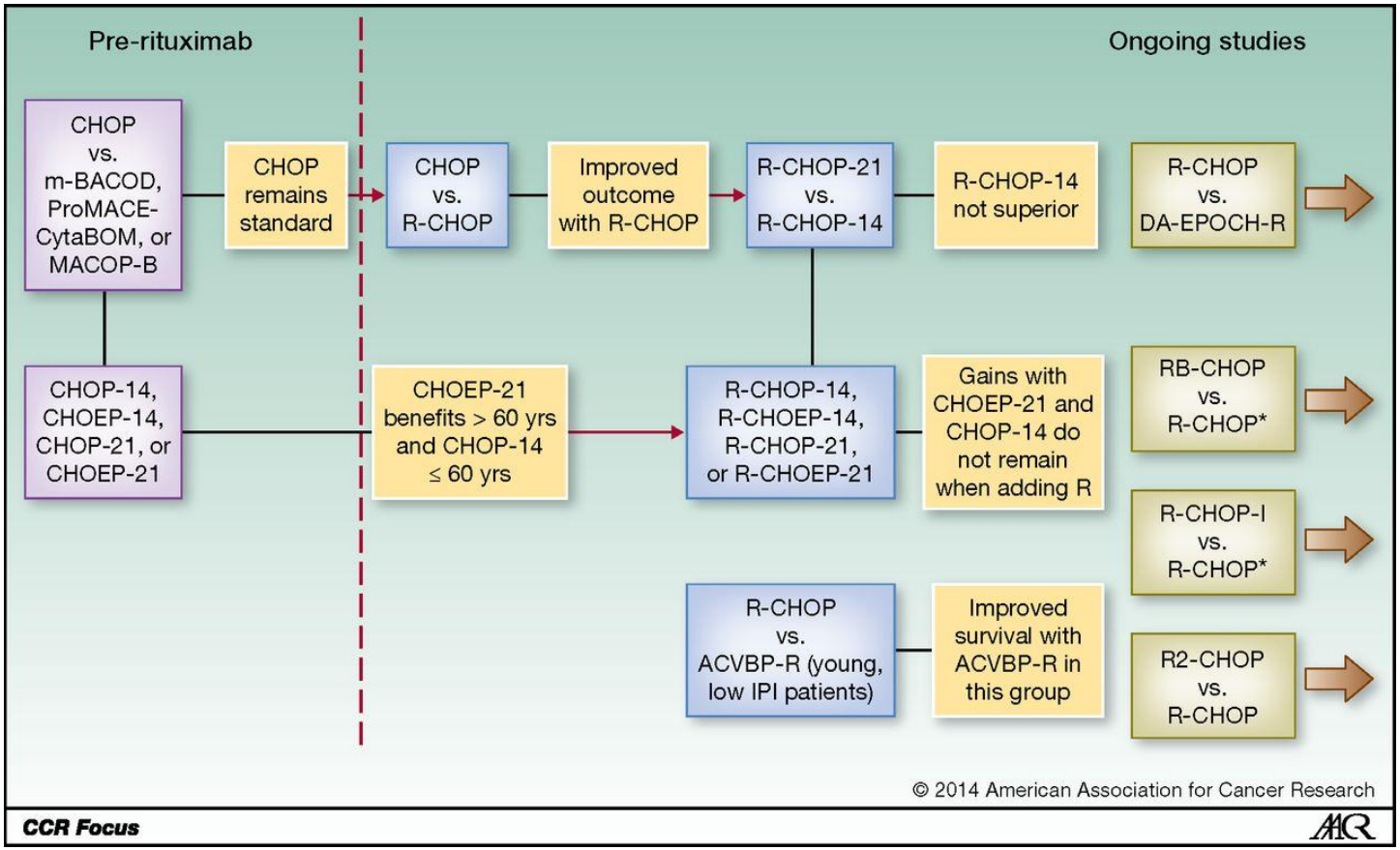
Berthet L, et al. J Nucl Med 2013;54:1244-50
Adams HJ, et al. Eur J Nucl Med Molec Imaging 2014;41:565-74
Barrington SF, et al. J Clin Oncol 2014;32:3048-58

Genetic landscape



Pasqualucci L, Dalla-Favera R. Blood 2018:131:2307-19

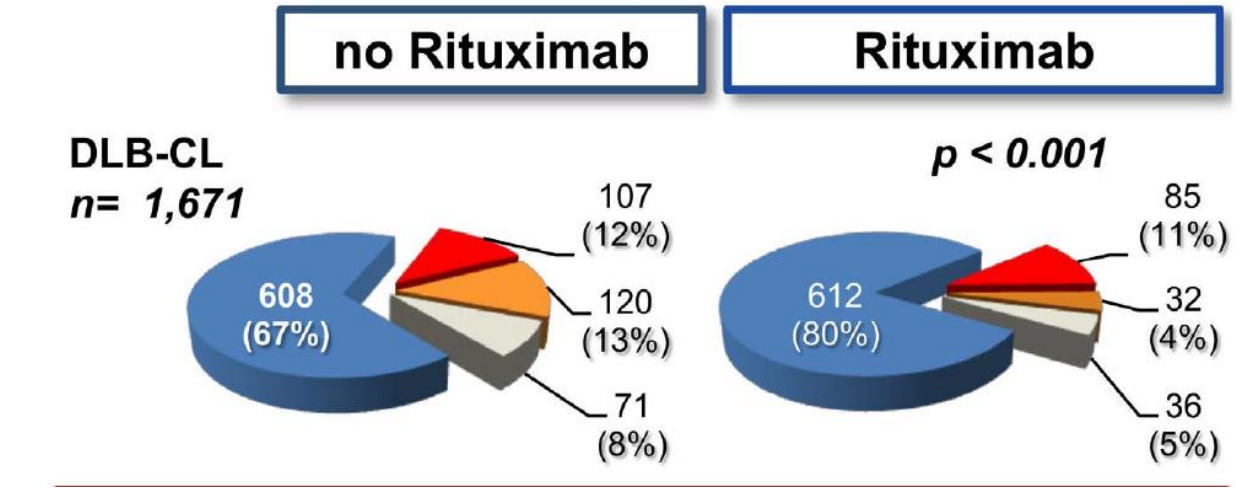
Treatment

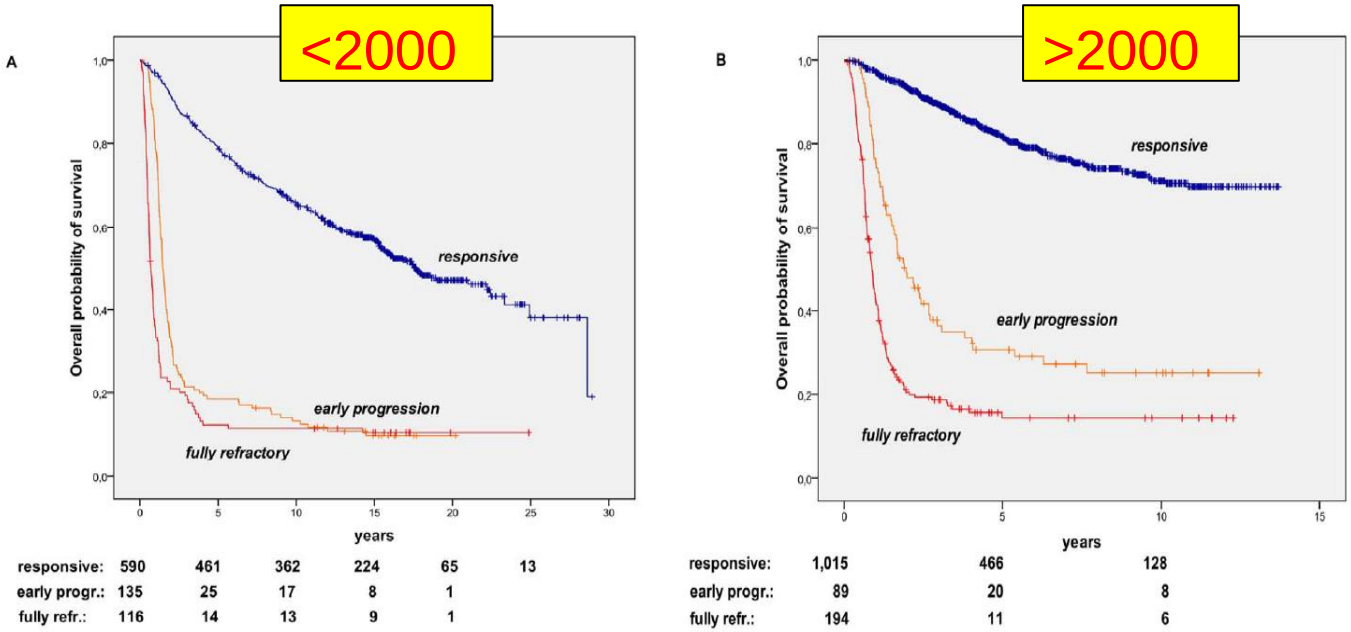


Rituximab
=
“the great equalizer”

Dunleavy K, et al. Clin Cancer Res 2014;20:5182-93

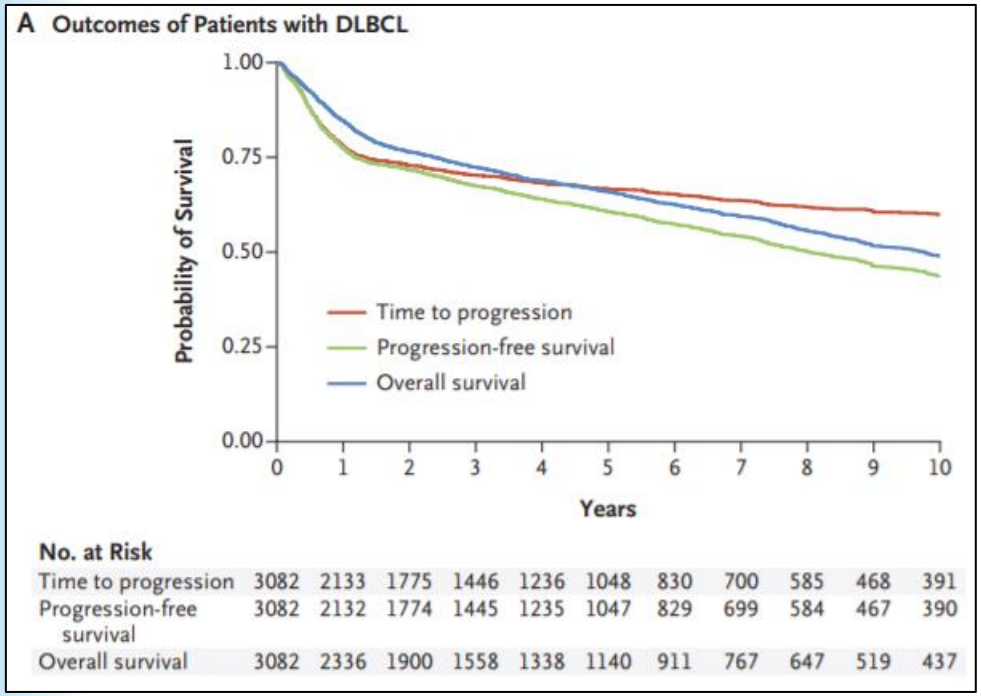
Treatment



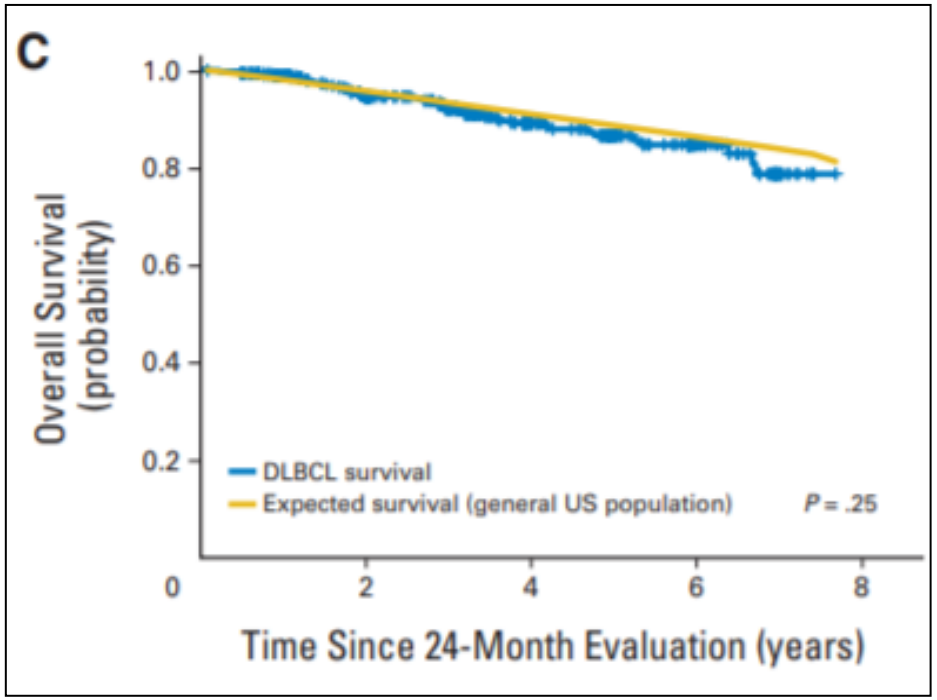


Tarella C, et al. PLoS One 2014;9:e106745

Treatment

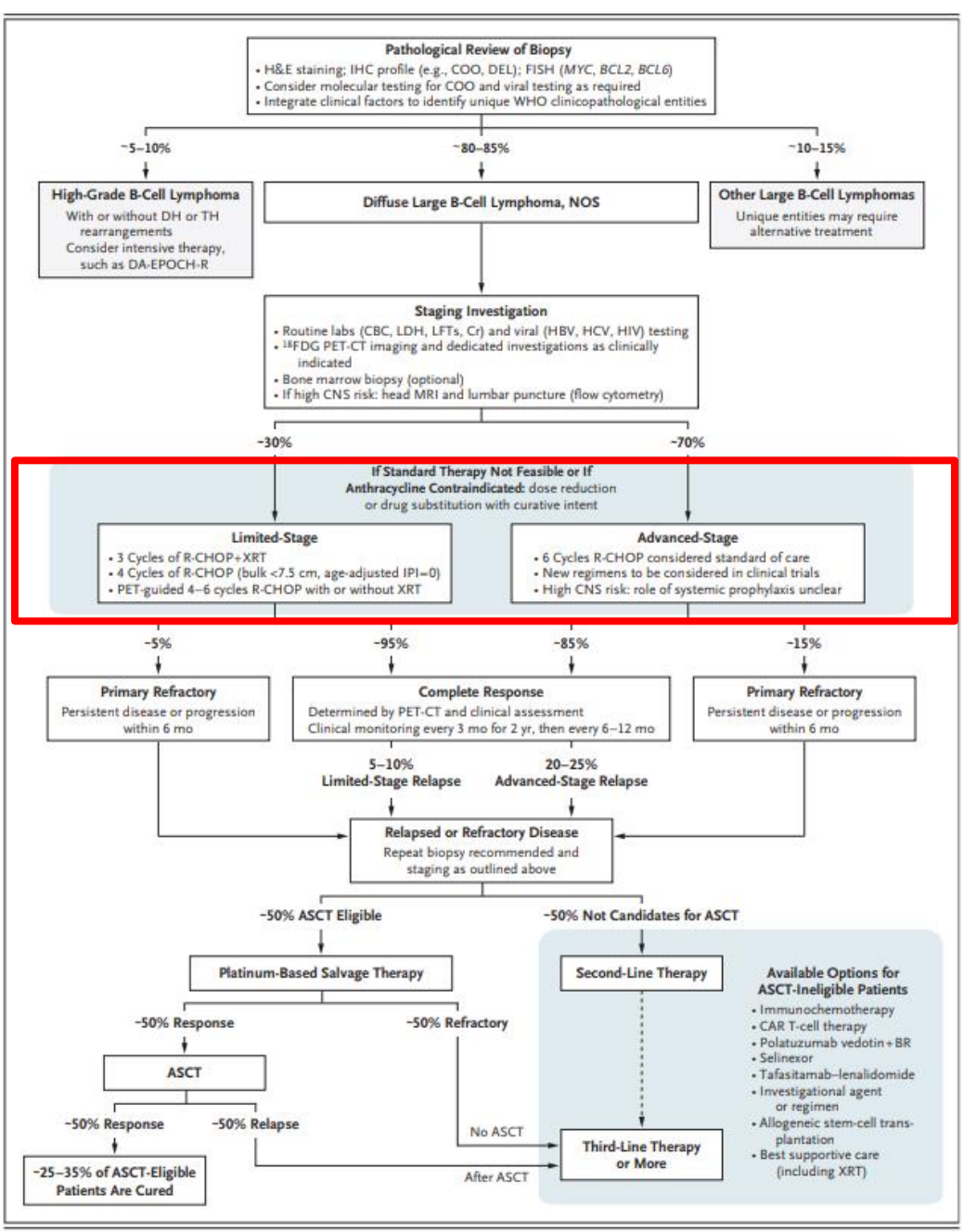


No. at Risk											
Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

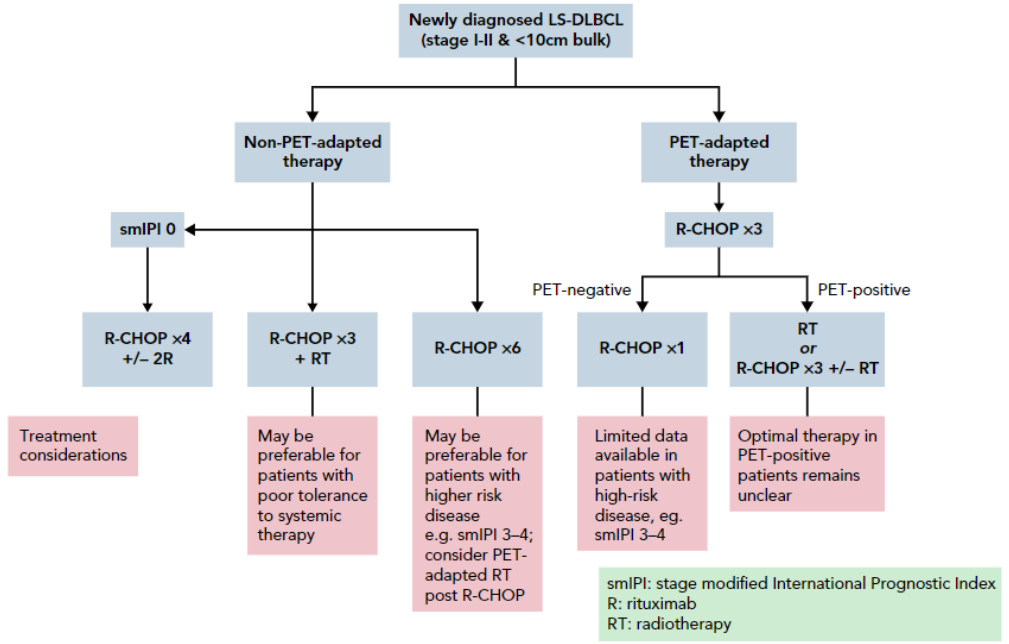


Maurer MJ, et al. J Clin Oncol 2014;32:1066-73
Sehn L, Salles G. N Engl J Med 2021;384:842-58

1L treatment



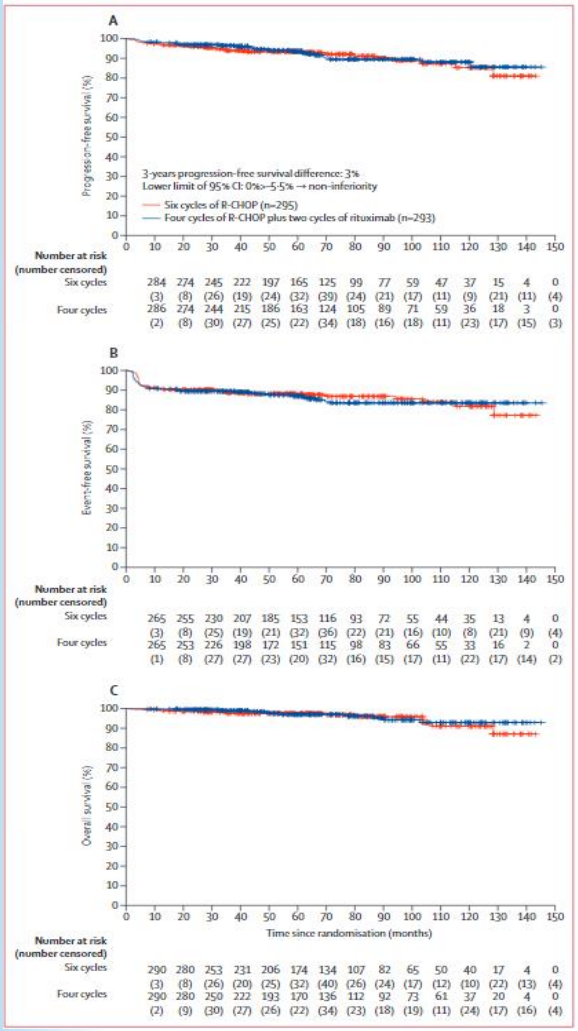
Strategy	Combined modality	Abbreviated chemo	PET-adapted			Standard chemo
Trial details	SWOG S0014[33] Phase II single arm n=60	GLA FLYER[12] Phase III RCT n=592	LYSA/GOELAMS 02–03[10] Ph III RCT n=334	SWOG S1001[11] Ph II n=132	LYSA LNH09-IB[58] Ph III RCT n=650	DHSNHL MiNT[9] Ph III RCT n=824
Population	Age>18 smIPI ≥1 Bulk >10cm permitted (for stage I only)	Age 18–60 aaIPI 0 Bulk >7.5cm not permitted	Age 18–75 Bulk >7cm not permitted	Age>18 ECOG 0–2 Bulk >10cm not permitted	Age 18–80 DLBCL/G3BFL aaIPI 0 Bulk >10cm permitted	Age18–60yrs Stage I-IV: 72% I-II aaIPI 0–1 Bulk permitted: >5, 7 or 10cm (per institution)
Treatment	RCHOP ×3 + RT 40–46Gy	RCHOP ×6* vs RCHOP ×4 + 2R	RCHOP14 ×4 then PET-neg: RT* vs nil. PET-pos or adverse features: RCHOP14 ×6 + RT*	RCHOP ×3 then PET-neg: RCHOP ×1 PET-pos: RT + RIT	RCHOP ×6* vs R-CHOP ×2 then PET-neg: RCHOP ×2 PET-pos: RCHOP ×4	CHOP-like ×6* vs R-CHOP-like ×6 Bulk received RT 30–40Gy



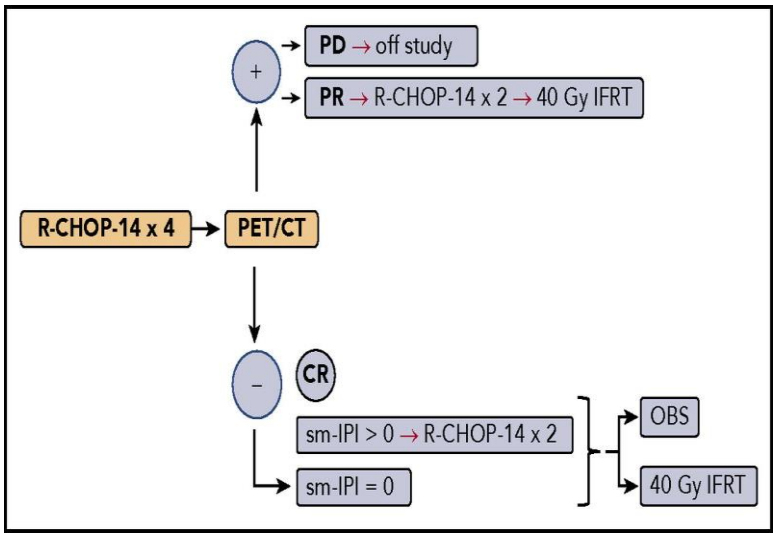
Sehn L, Salles G. N Engl J Med 2021;384:842-58
Hawkes EA, et al. Blood 2022;139:822-34

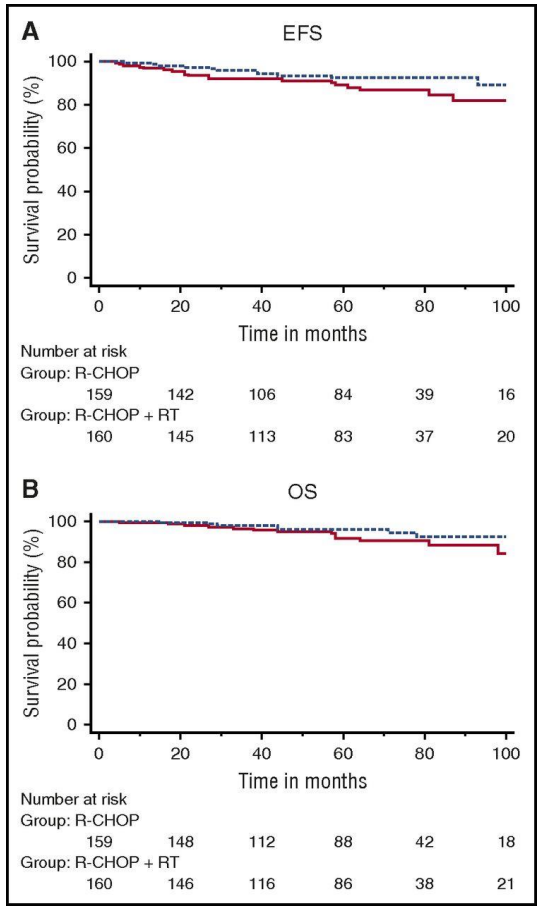
1L treatment

Phase III FLYER
n = 592
18 to 60 years, aaIPI = 0, no bulky disease
6 x R-CHOP21 *vs* 4 x R-CHOP21 + 2 x R



Phase III LYSA/GOELAMS
n = 334
Non-bulky limited stage
4-6 x R-CHOP14 +/- RT 40 Gy



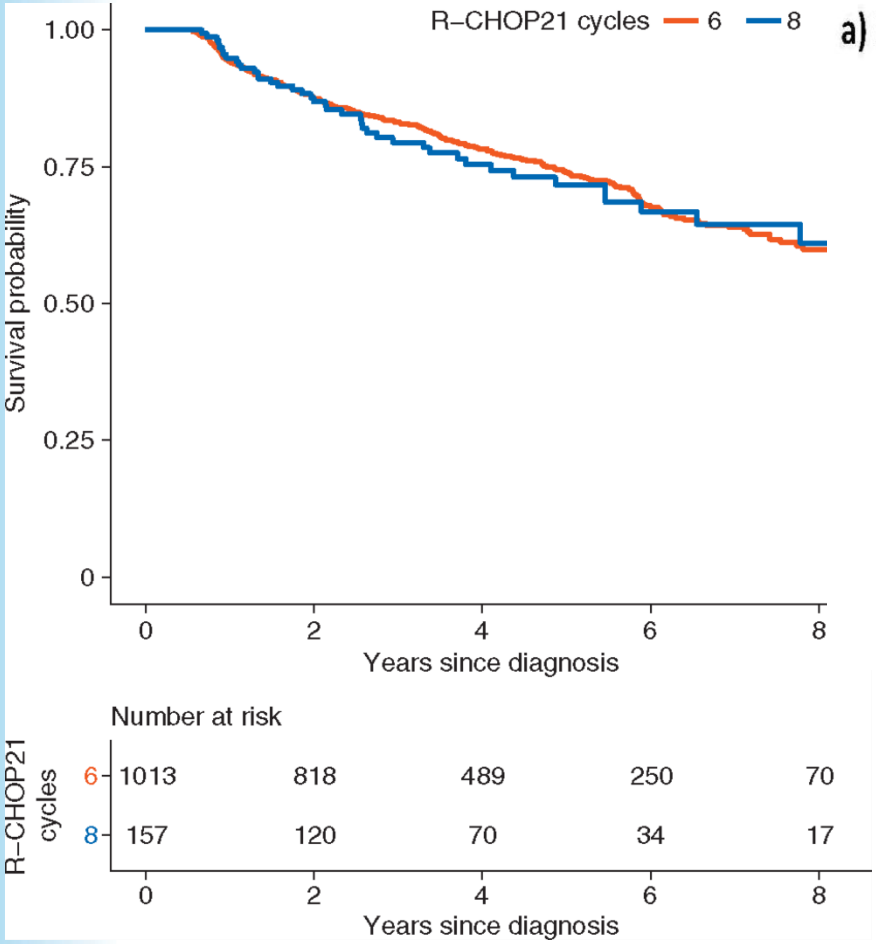


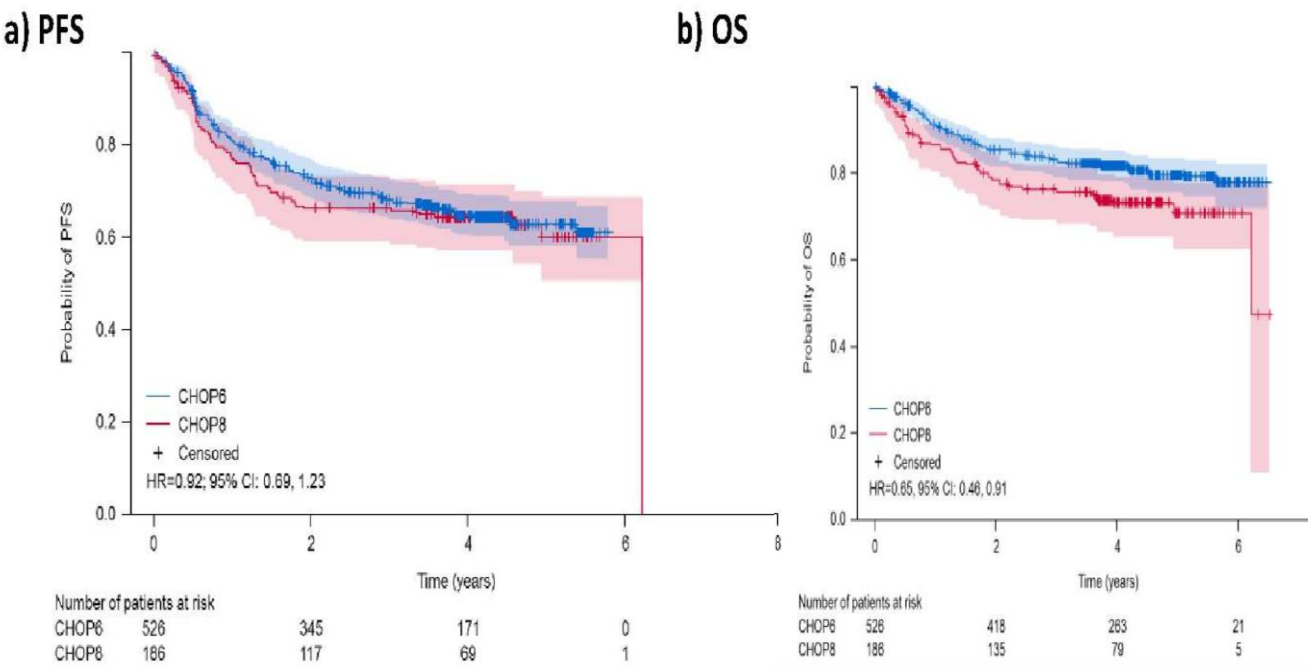
Lamy T, et al. Blood 2018;131:174-81
Persky DO. Blood 2018;131:155-6
Poeschel V, et al. Lancet 2019,394:2271-81

1L treatment

Nordic Lymphoma Group (registry)
n = 1170
6 x R-CHOP21 *vs* 8 x R-CHOP21

GOYA trial
n = 722
6 x R-CHOP21 + 2 x R *vs*
8 x R-CHOP21



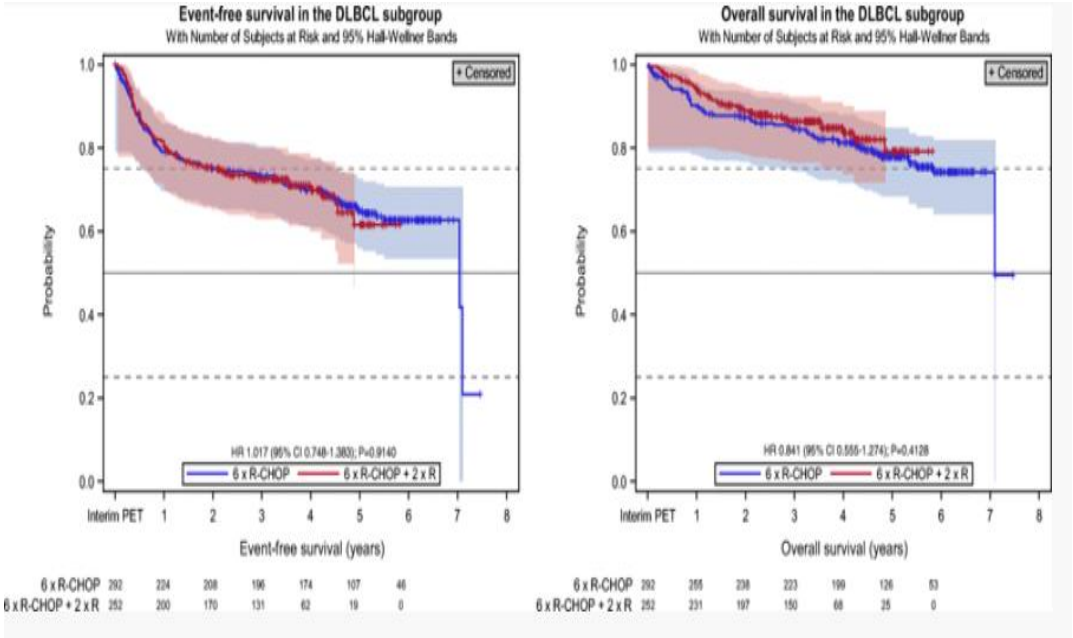


Wasterlid T, et al. Ann Oncol 2018;29:1882-3

Sehn L, et al. ASH 2018, abstract 783

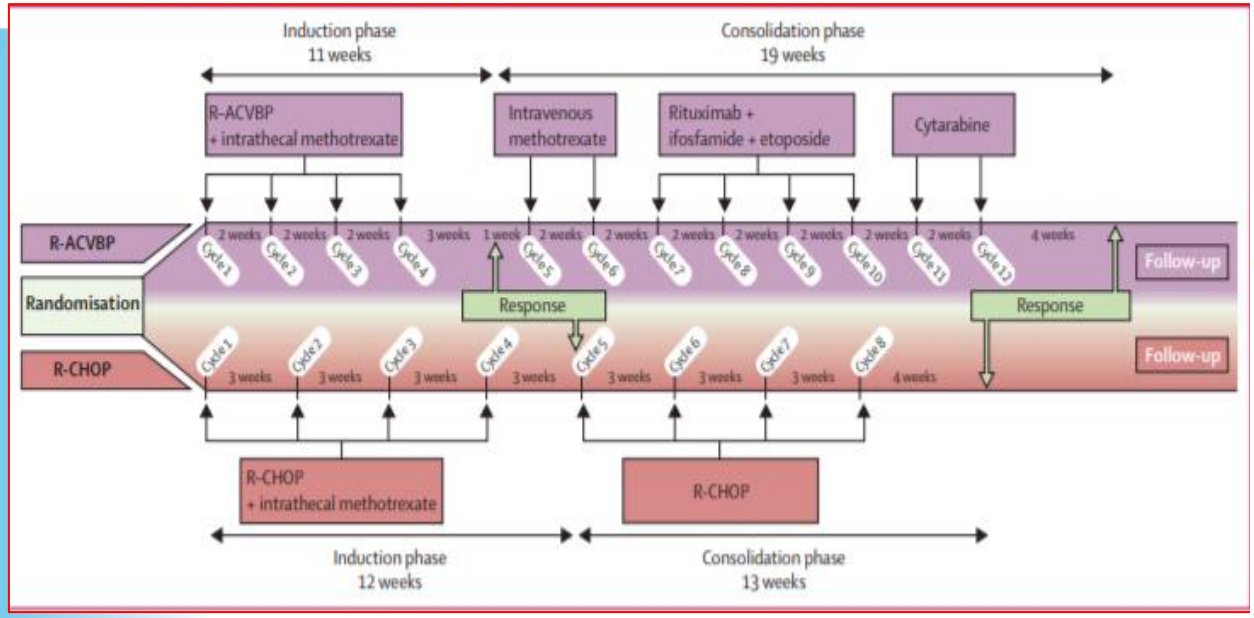
1L treatment

PETAL trial
n = 544 (DLBCL)
iPET negative patients: 2xR vs no R following 6 x R-CHOP



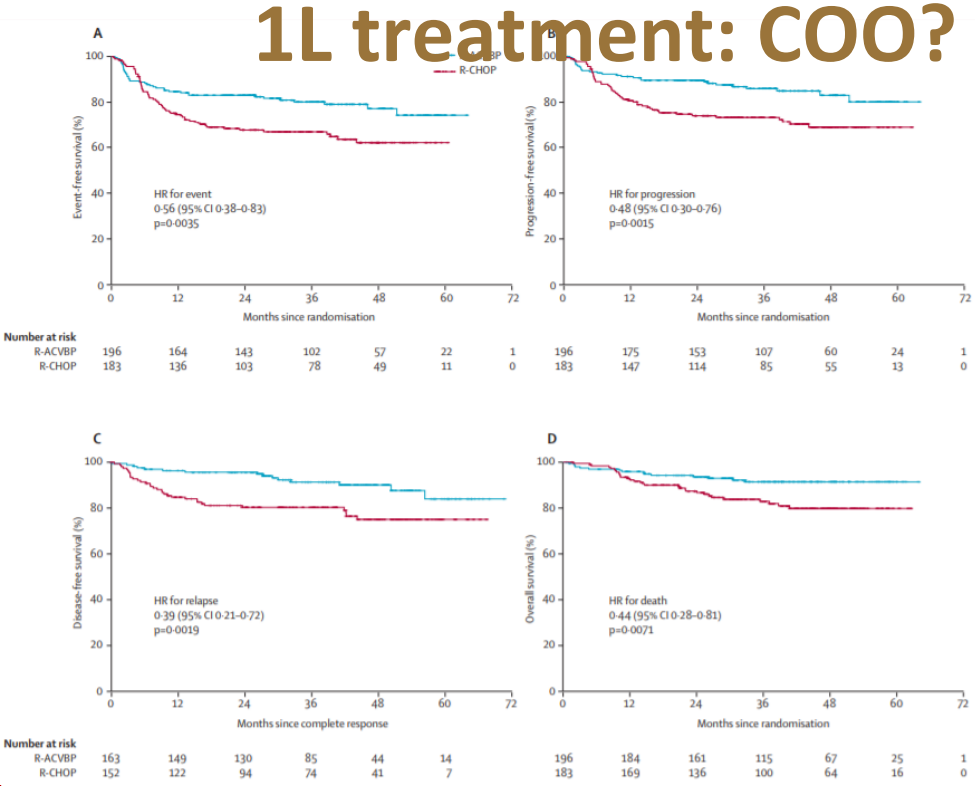
Hüttmann A, et al. Ann Hematol 2019;98:897-907

1L treatment: COO?

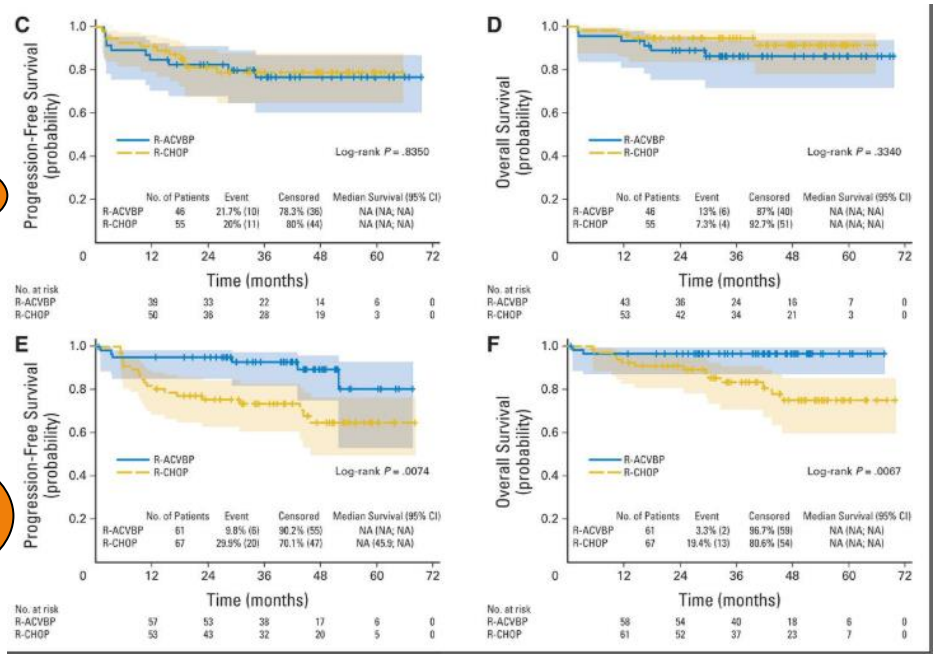


18–59 years, first line; age-adjusted international prognostic index equal = 1 (low intermediate)

Phase III: LNH 03-2B



GCB



non-GCB

Récher C, et al. Lancet 2011;378:1858-67
Molina T, et al. J Clin Oncol 2014;32:3996-4003

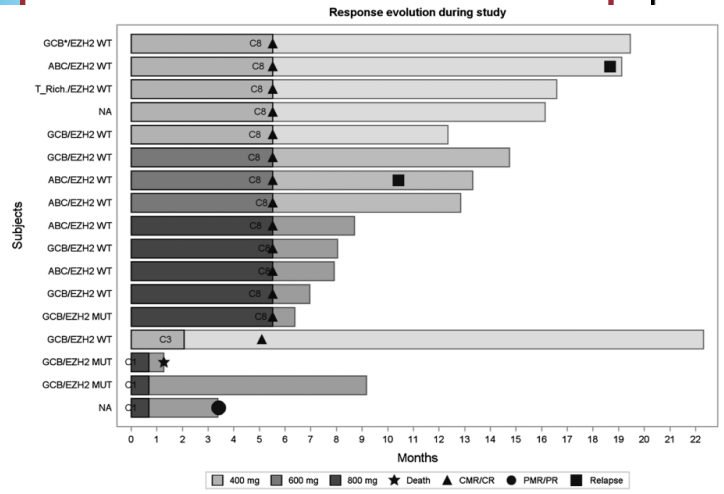
1L treatment: COO?

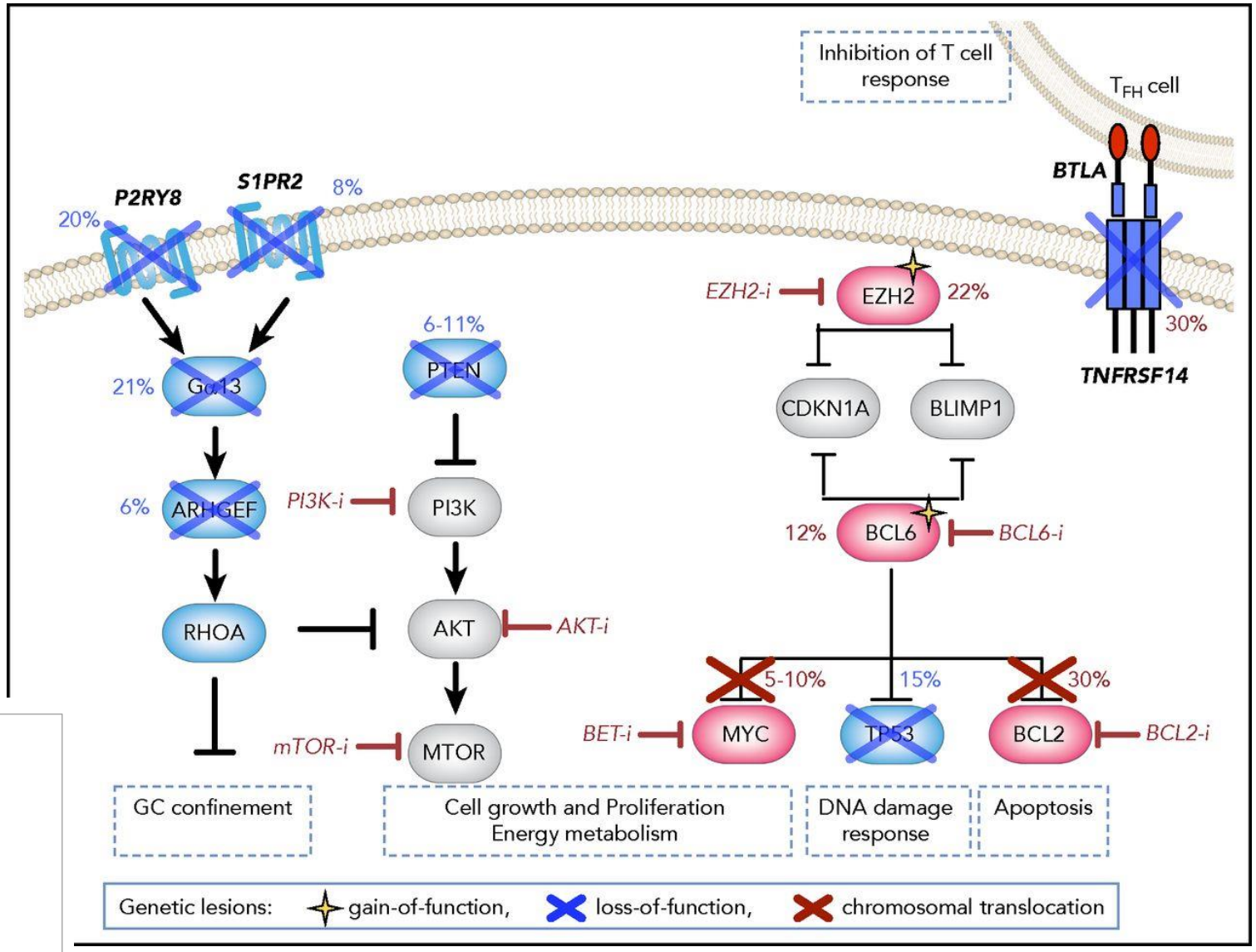
Tailored therapy in GCB?

Less focus compared to ABC:

- Better outcome
- Marked heterogeneity

- Tazemetostat (LYSA trial EPZ-6438)





Pasqualucci L, Dalla-Favera R. Blood 2018:131:2307-19
Sarkozy C, et al. Clin Cancer Res 2020;26:3145-53

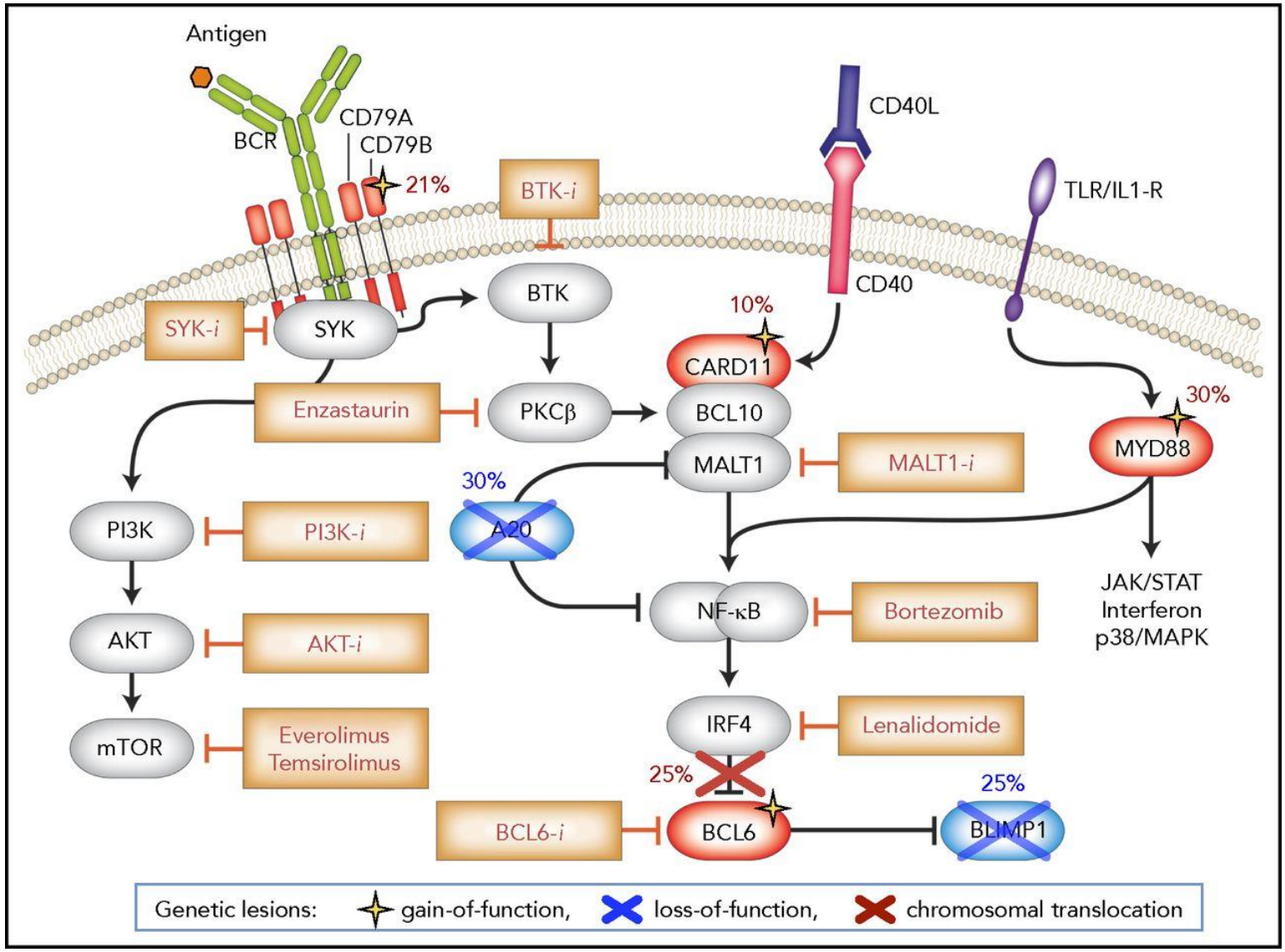
1L treatment: COO?

Targeted treatment in ABC?

More focus compared to ABC:

- Poor outcome
- Less heterogeneity

- Targeting NF-KB
- Targeting BCR signaling
- Immunomodulatory agents



Pasqualucci L, Dalla-Favera R. Blood 2018:131:2307-19

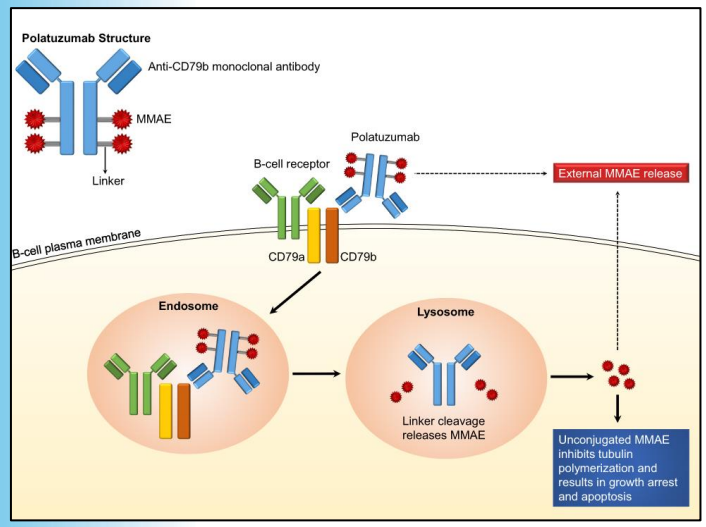
1L treatment

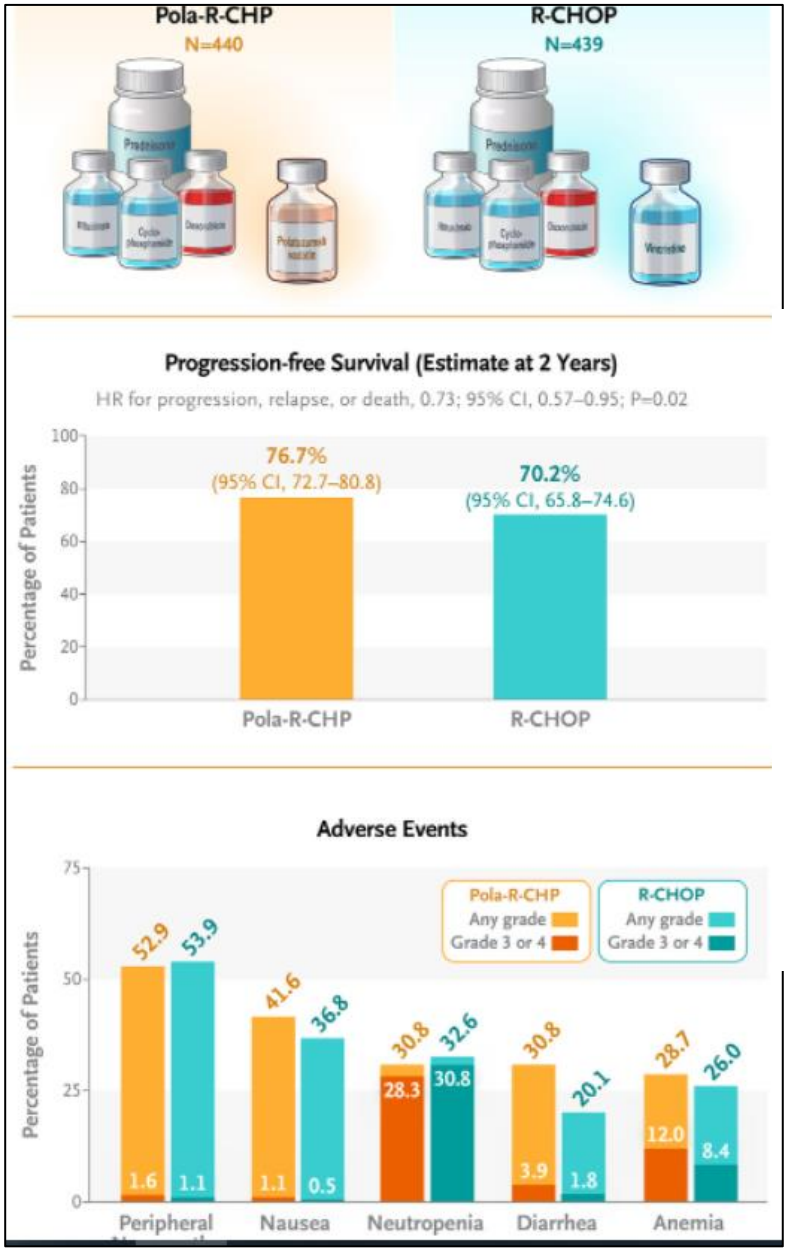
Therapy	DLBCL Subtype	Better compared to R-CHOP?	Study
R-CHP-bortezomib	All	No	REMoDL-B, 2019
Obinutuzumab-CHOP	All	No	GOYA, 2017
R-CHOP-ibrutinib	Non-GCB	< 60 year? MCD and N1 subtypes?	PHOENIX, 2019
R-CHOP-lenalidomide	ABC	No	ROBUST, 2021
R-CHOP-lenalidomide (Phase 2)	All	? Yes	ECOG-ACRIN E1412, 2021
Rituximab maintenance	All	No	US Interstudy Group, 2006
Lenalidomide maintenance	All	Elderly patients	REMARC, 2017

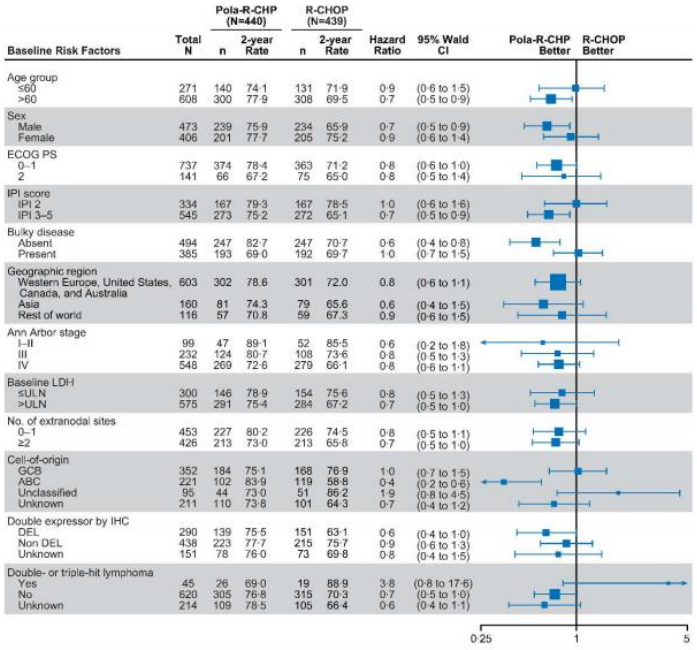
Davies A, et al. Lancet Oncol 2019;20;649-62
Vitolo U, et al. J Clin Oncol 2017;35:3529-37
Younes A, et al. J Clin Oncol 2019;37:1285-95
Nowakowski GS, et al. J Clin Oncol 2021;39:1317-28
Nowakowski GS, et al. J Clin Oncol 2021;39:1329-38
Habermann TM, et al. J Clin Oncol 2006;24:3121-7
Thieblemont C, et al. J Clin Oncol 2017;35:2473-81
Wilson WH, et al. Cancer Cell 2021;39:1643-53

1L treatment

Polatuzumab vedotin (CD79b)







Sawalha Y, Maddocks K. Onco Targets Ther 2020;13:5123-33
Tilly H, et al. N Engl J Med 2022;386:351-63

1L treatment PTLD

- No consensus/uniform guidelines on RIS:

STOP antimetabolites
Reduce CNI dose
Continue or increase steroids

- 1-4 weeks ➔ response rates: 0 - >50%

	Treatment	Overall response rate (CR)
Pennsylvania	RIS only	45% (37%)
Baltimore	Sequential therapy (RIS – IFNα – chemo)	6% (0%)

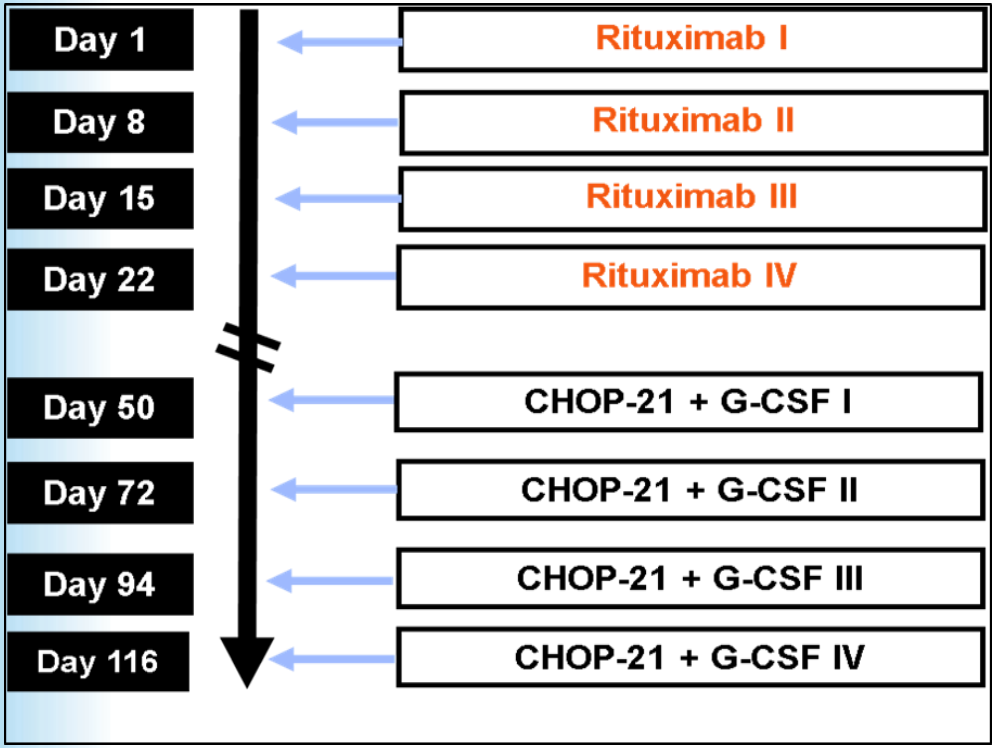
Organ dependent

Kidney: dialysis rescue
HSC: less efficacy
Heart: risk sudden death

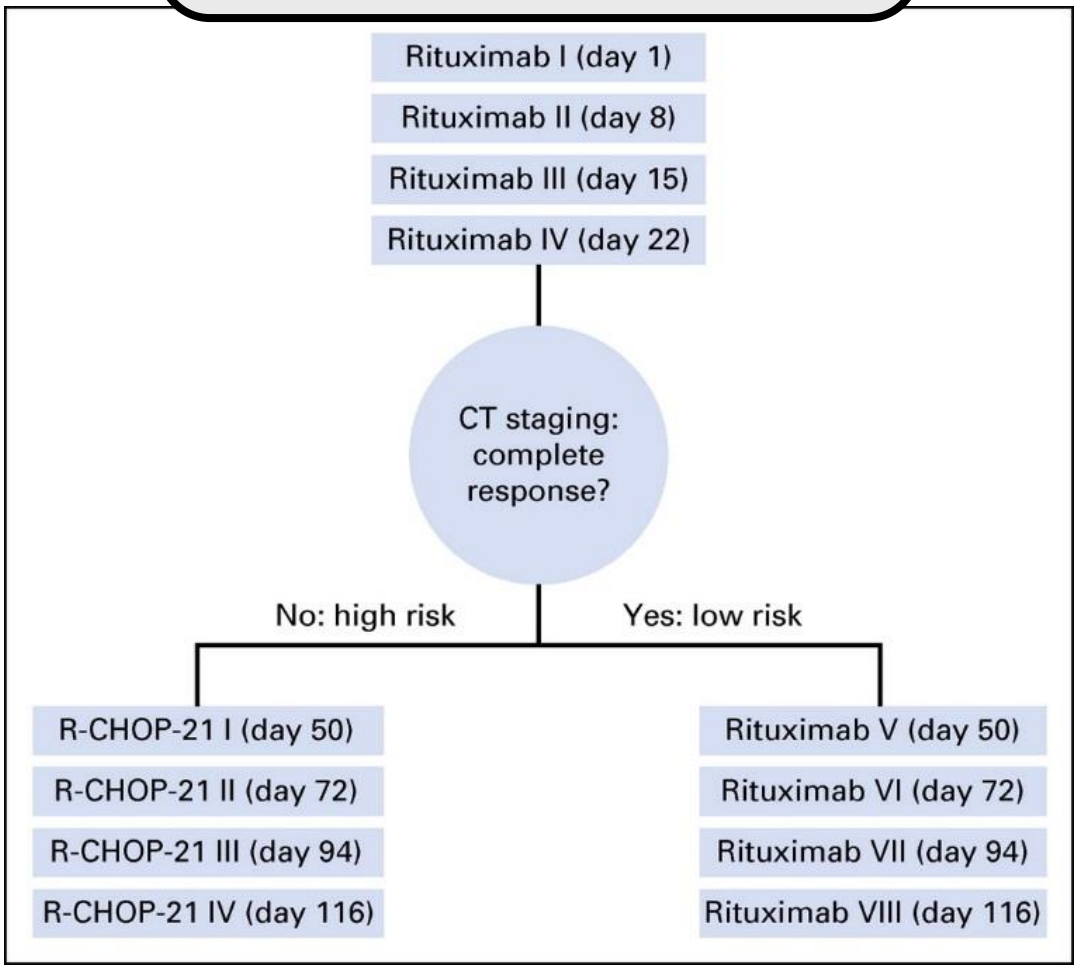
Swinnen LJ, et al. Transplantation 2008;86:215-22
Reshef R, et al. Am J Transplant 2011;11:336-47
Zimmermann H, et al. Transplantation 2018;102:1914-23

1L treatment PTLD

Sequential Treatment (ST)



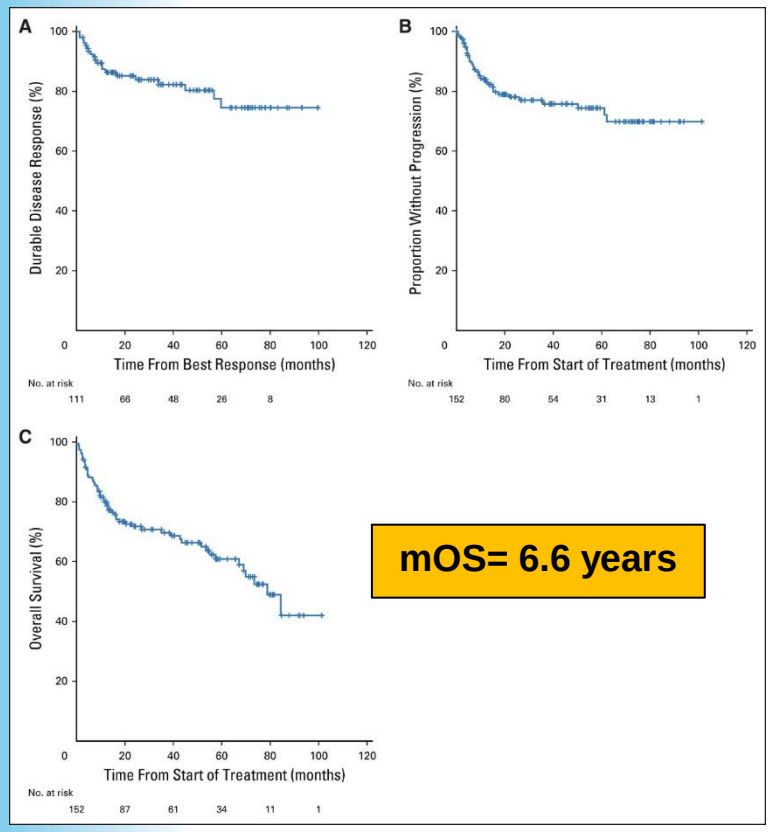
Risk Stratified Sequential Treatment (RSST)



PTLD1 trial

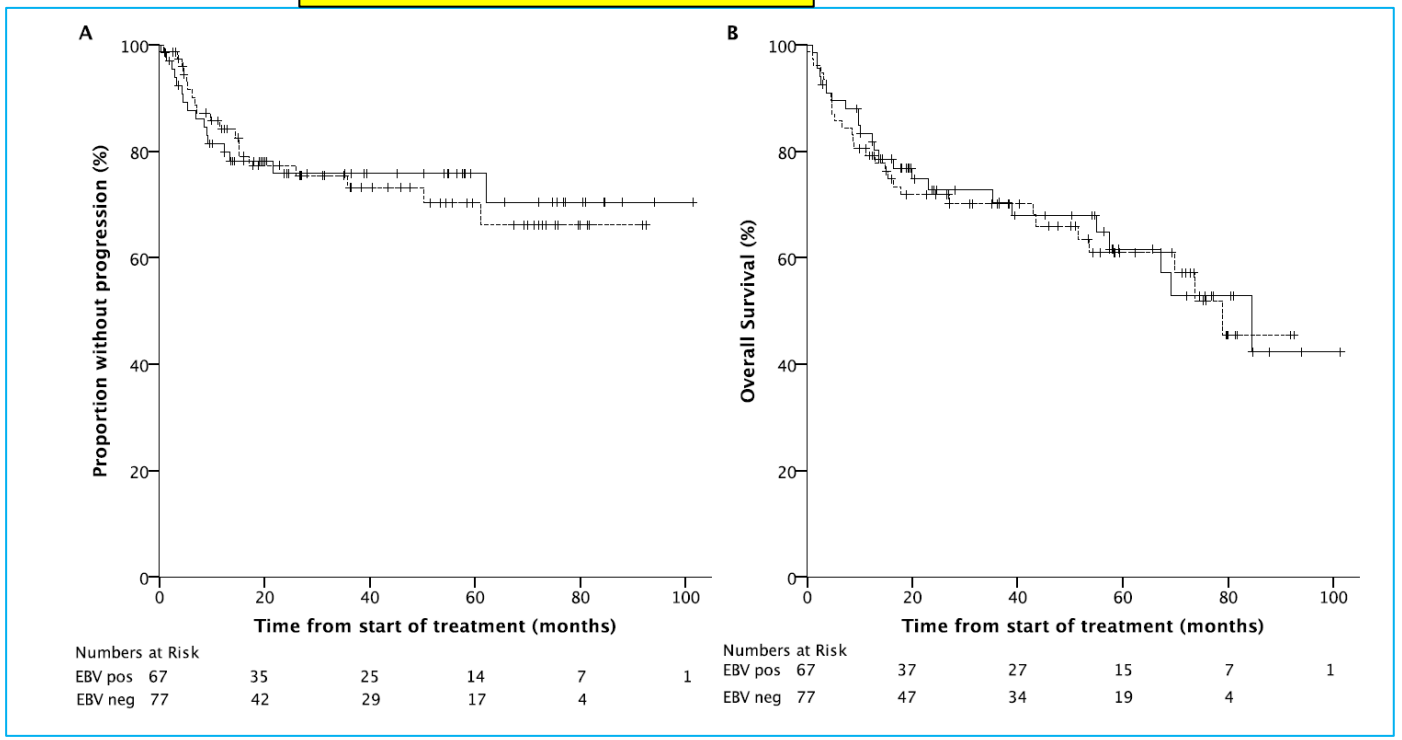
Trappe R, et al. Lancet Oncol 2012;13:196-206
Trappe RU, et al. J Clin Oncol 2017,35:536-43

1L treatment



mOS= 6.6 years

n = 152 (SOT)



25%: CR at interim staging

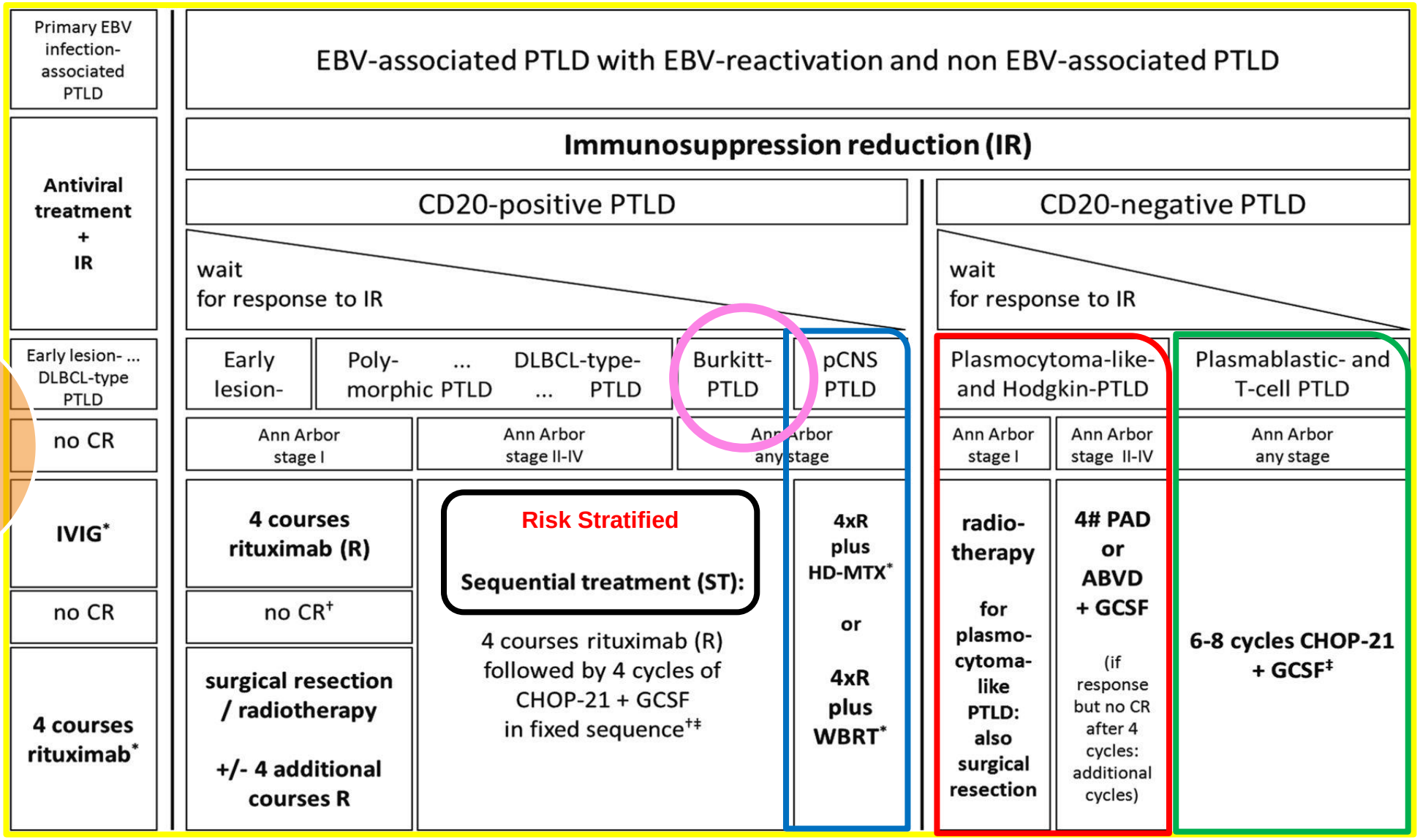
Risk factors predictive for OS:

- IPI score
- Response to rituximab at interim staging
- Type of transplant

Trappe RU, et al. Am J Transplant 2015;15;1091-100
Trappe RU, et al. J Clin Oncol 2017,35:536-43

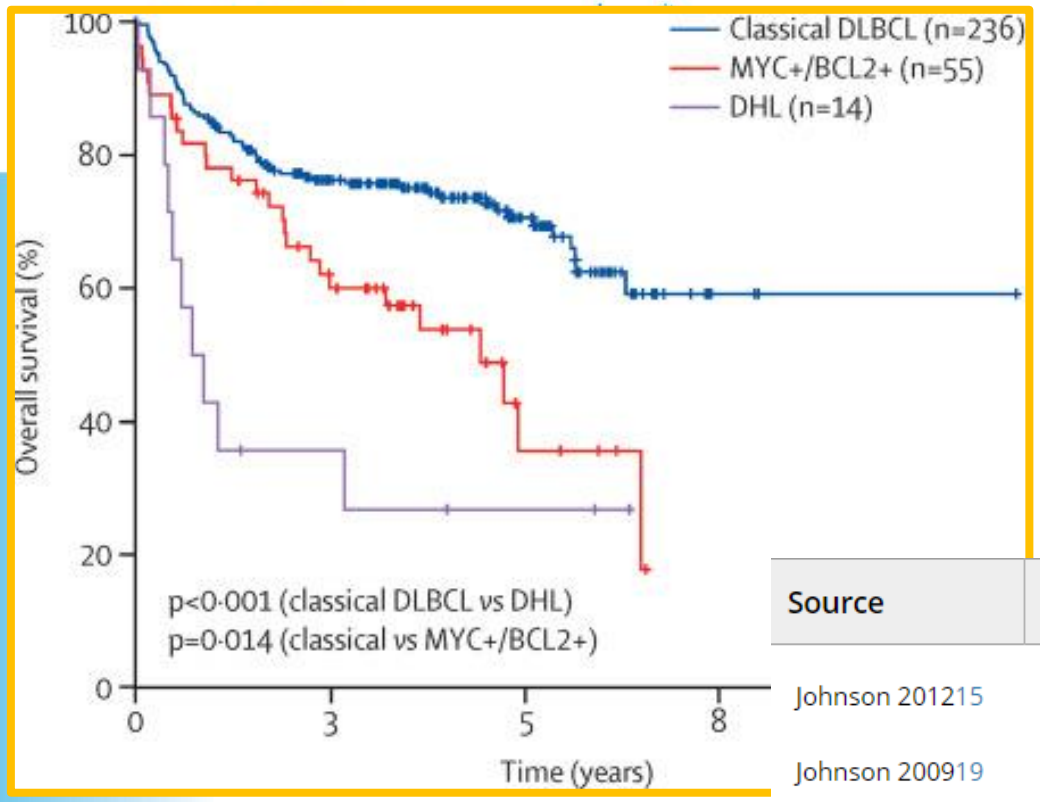
1L treatment PTLD

PTLD



Zimmermann H, Trappe R. Hematology Am Soc Hematol Educ Program 2013;2013:95-102
Trappe RU, et al. J Clin Oncol 2017;35;536-43

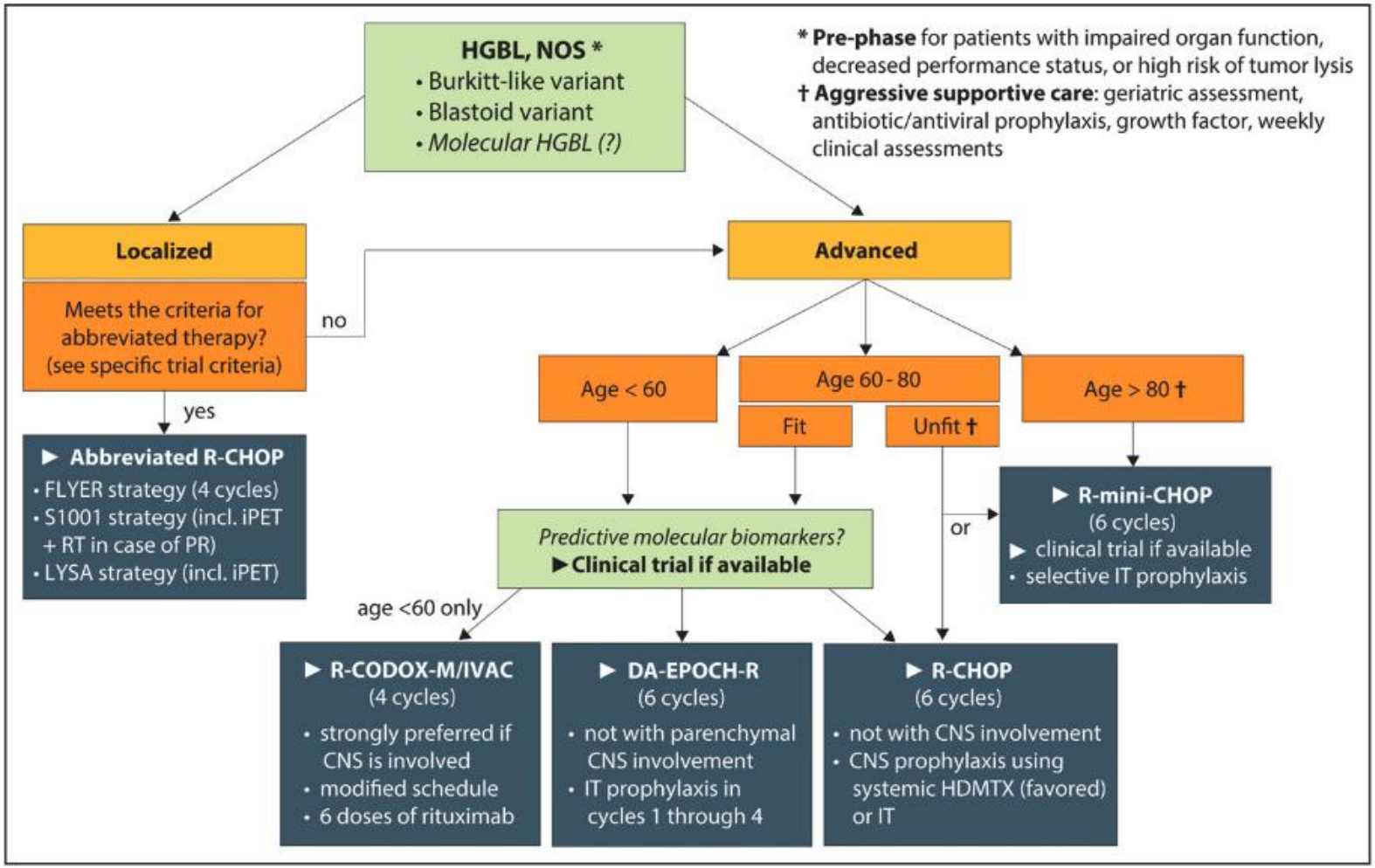
1L treatment HGBL



Source	Focus	Patients, No.	Treatment, No.	PFS/EFS	OS
Johnson 201215	DHL	14	R-CHOP: 14	PFS: 18% at 5 y	OS: 27% at 5 y
Johnson 200919	DHL	54	R-CHOP: 11	N/A	Median OS: 1.4 y
Petrich 201446	DHL	311	R-CHOP: 100	Median PFS: 7.8 mo	N/A
			R-EPOCH: 64	Median PFS: 21.6 mo	N/A
Oki 201451	DHL	129	R-CHOP: 57	EFS: 20% at 5 y	OS: 22% at 5 y
			R-EPOCH: 28	N/A	N/A
Johnson 201215	DEL	55	R-CHOP: 55	PFS: 32% at 5 y	OS: 36% at 5 y
Green 201243	DEL	54	R-CHOP: 54	PFS: 39% at 3 y	OS: 43% at 3 y
Hu 201344	DEL	157	R-CHOP: 157	PFS: 27% at 5 y	OS: 30% at 5 y

Johnson NA, et al. J Clin Oncol 2012;30:3452-9
Sarkozy C, et al. Lancet Oncol 2015;16:e555-67
Riedell PA, Smith SM. Cancer 2018;124:4622-32

1L treatment HGBL

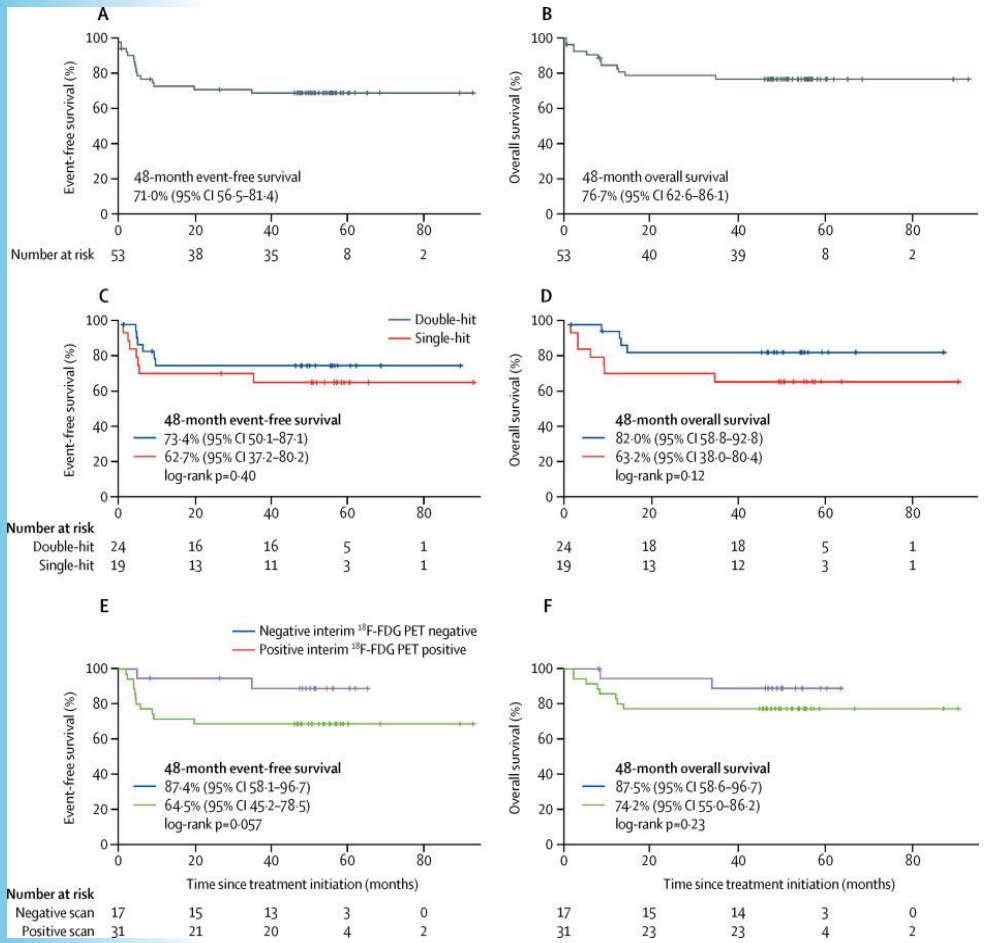


Olzewski AJ, et al. Blood 2022;140:943-54

MYC

1L treatment

DA-EPOCH-R



Phase II
NCT01092182

R²-CHOP

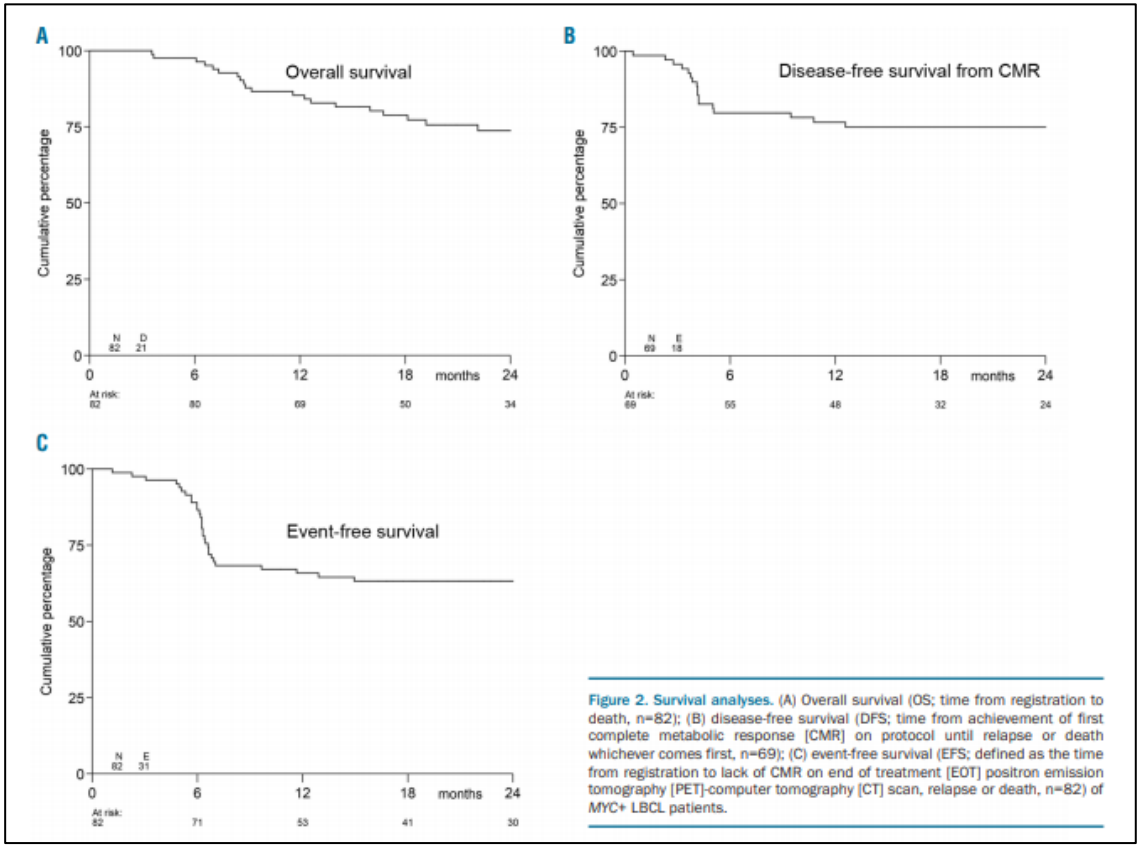


Figure 2. Survival analyses. (A) Overall survival (OS; time from registration to death, n=82); (B) disease-free survival (DFS; time from achievement of first complete metabolic response [CMR] on protocol until relapse or death whichever comes first, n=69); (C) event-free survival (EFS; defined as the time from registration to lack of CMR on end of treatment [EOT] positron emission tomography [PET]-computer tomography [CT] scan, relapse or death, n=82) of *MYC*+ LBCL patients.

Phase II
HOVON 130

Dunleavy K, et al. Lancet Hematol 2018;5:e609-17
Chamuleau ME, et al. Haematologica 2020;105;2805-12

BCL2

R-CHOP + Venetoclax

Phase II: CAVALLI

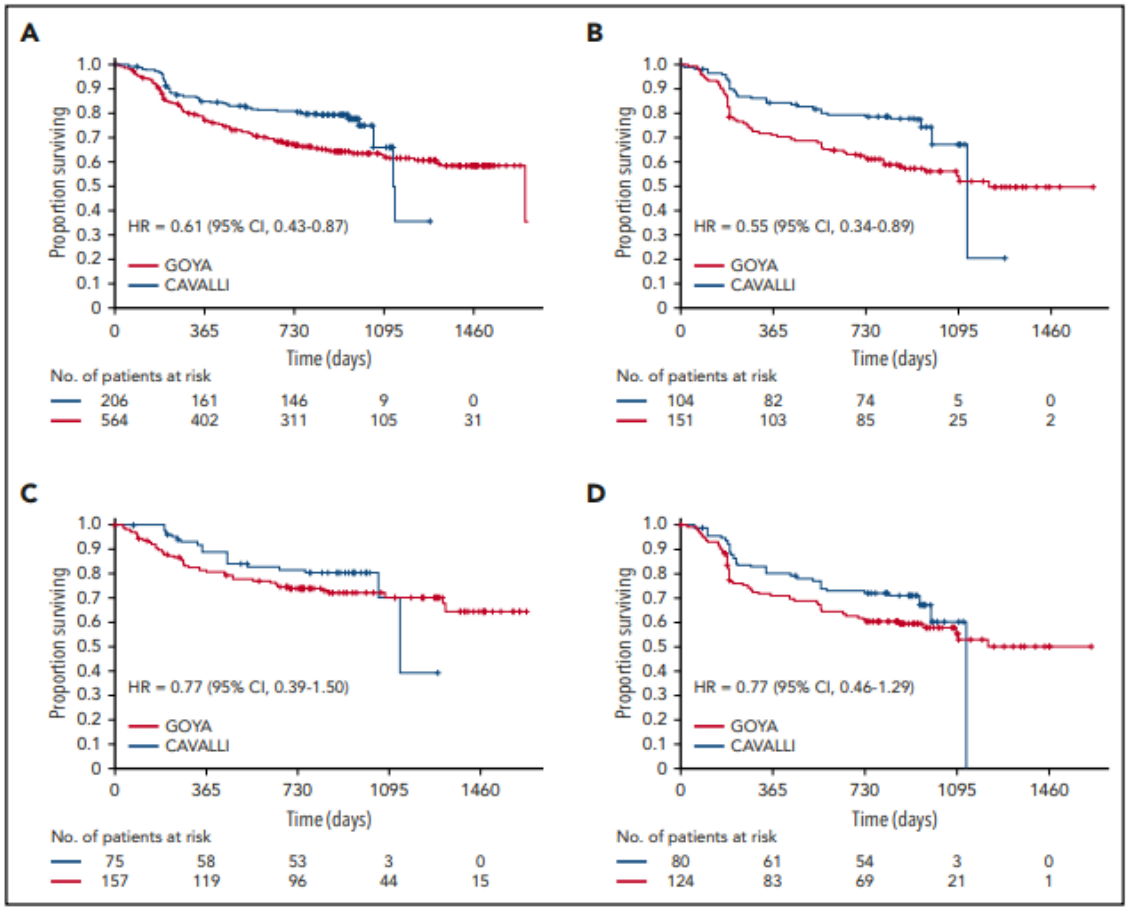


Figure 1. Investigator-assessed PFS in CAVALLI vs GOYA IPI 2 to 5. Kaplan-Meier curves for the overall population (A) and the Bcl-2 IHC$^+$ (B), Bcl-2 IHC$^-$ (C), and DEL (D) subgroups. The following covariates were adjusted: age, sex, ECOG PS, bone marrow involvement, IPI (high vs nonhigh), bulky disease (>7.5 cm), disease stage (IV vs I-III), LDH, and COO.

Morschhauser F, et al. Blood 2021;137:600-9

CNS prophylaxis

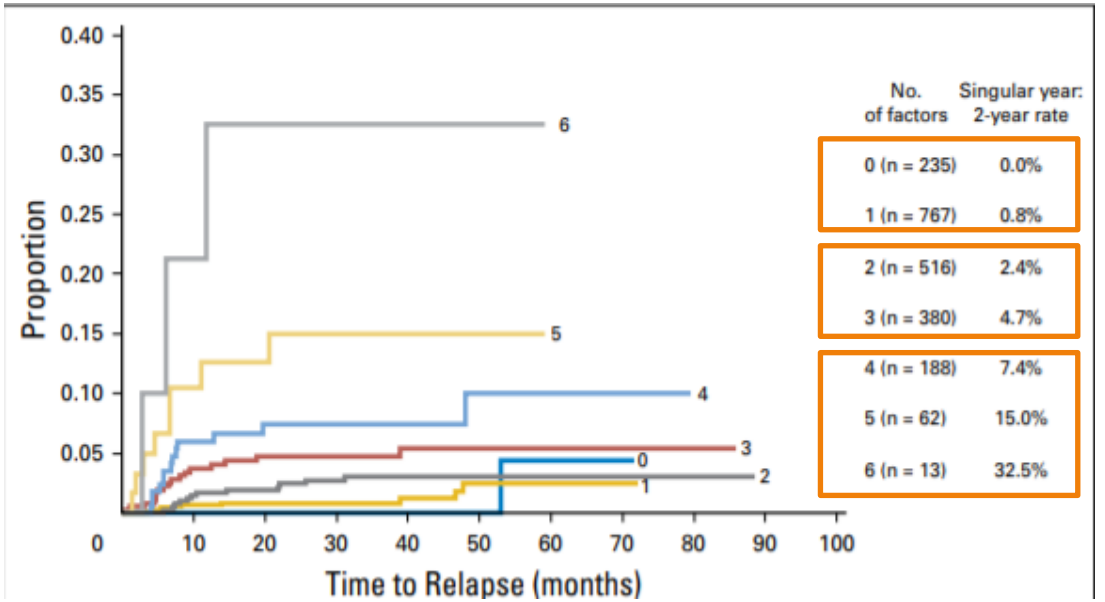
Table 2. Factors Defining the CNS International Prognostic Index: Results of Multivariable Analysis

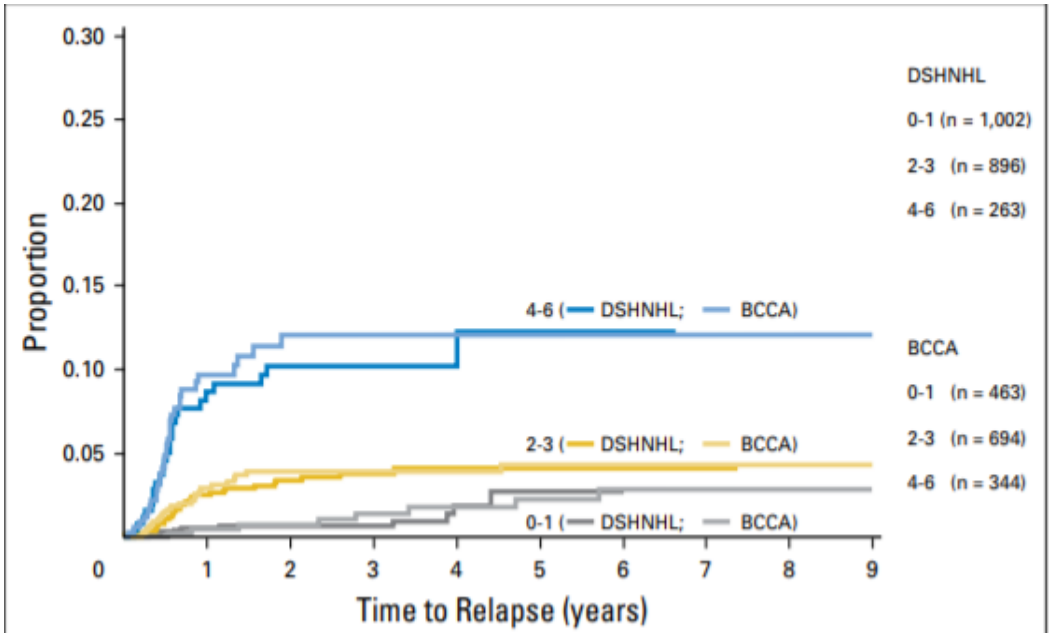
Factor	Hazard Ratio	95% CI	*P*
Kidney and/or adrenal glands involved	2.8	1.3 to 5.8	.006
Age > 60 years	2.5	1.3 to 4.5	.001
LDH > normal	2.4	1.3 to 4.5	.005
ECOG PS > 1	2.2	1.3 to 3.9	.006
Stage III/IV disease	2.0	1.0 to 3.8	.039
Extranodal involvement > 1	1.0	0.5 to 1.8	.935

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

Table 1. Risk stratification for secondary CNS involvement in non-Hodgkin lymphoma integrating histologic, clinical, and molecular factors

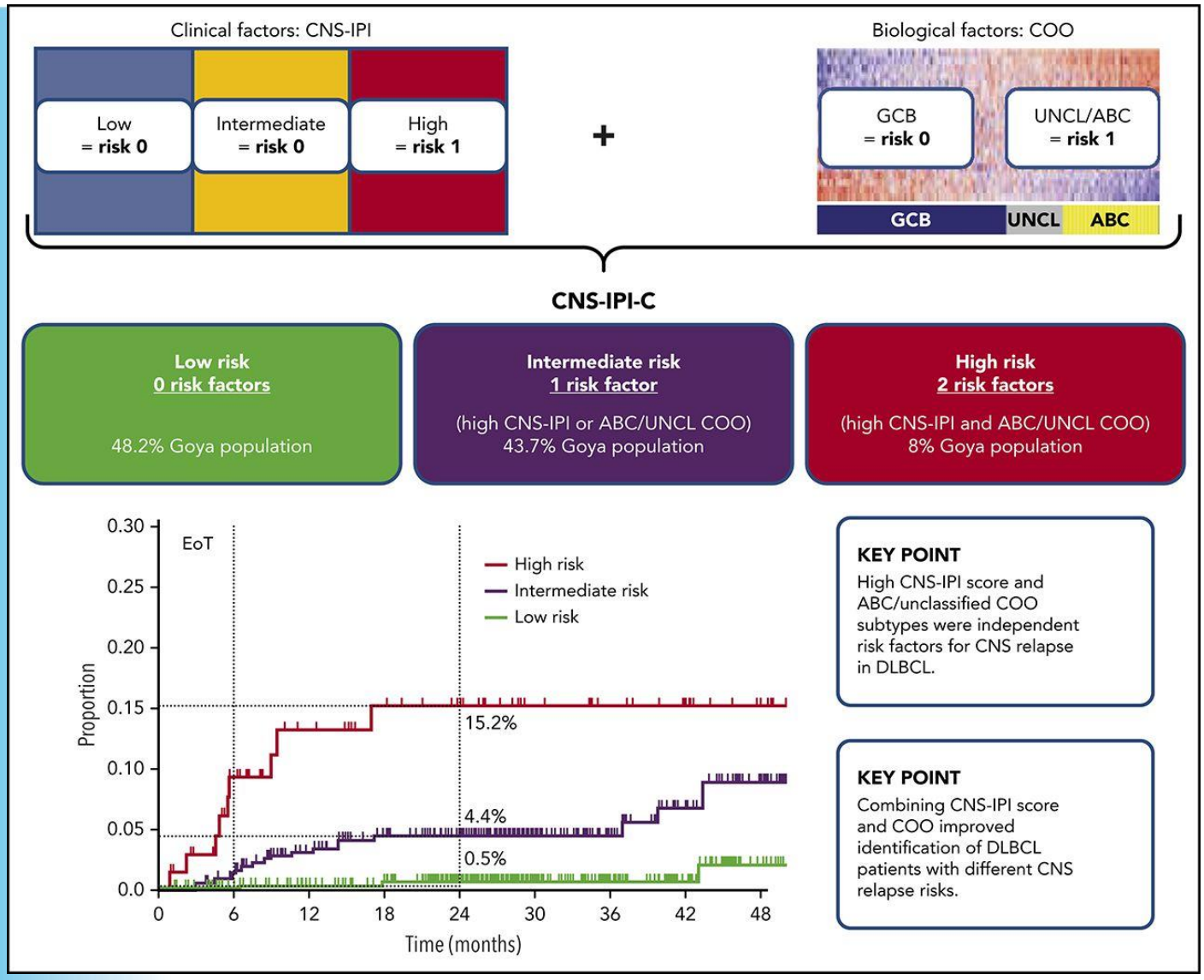
Histologic subtype	Histologic subtype-specific risk factors	Approximate CNS relapse risk
DLBCL	CNS-IPI ≥ 4[6]	10% at 2 y
	or involvement of breast,[17] testis,[18] uterus,[19] epidural,[20,21] kidney/ adrenals[6,16]	Varies by site
	MYC/BCL2 DE DLBCL, particularly if ABC subtype[22]	10% at 2 y (15% if ABC COO)
	CD5+ DLBCL[23]	12.7% at 2 y
	Intravascular large B-cell lymphoma[24]	25% at 3 y
	IgM-secreting DLBCL[25]	41% cumulative incidence (7 of 17)
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements[26]		13% at 3 y
MCL	Blastoid histology or Ki-67 ≥ 30%[27]	25.4% at 2 y
PTCL (PTCL-NOS, AITL, ALCL)	>1 extranodal site, skin or gastrointestinal involvement[28]	~10% at 2 y
ALK+ ALCL	>1 extranodal site[29]	1-y 15%

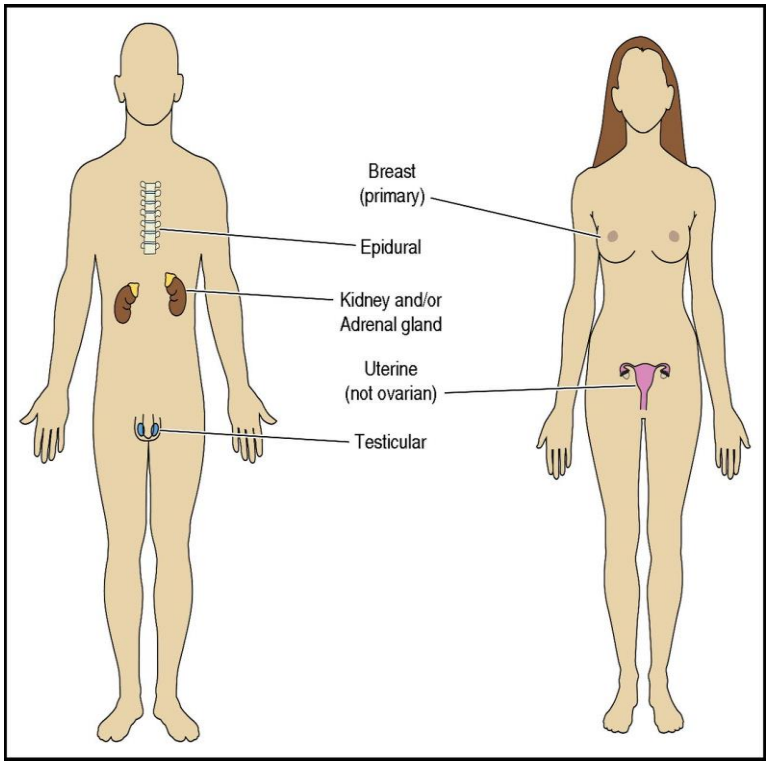




Schmitz N, et al. J Clin Oncol 201;34:3150-6
Chin CK, Cheah CY. Blood 2017;130:867-74

CNS prophylaxis





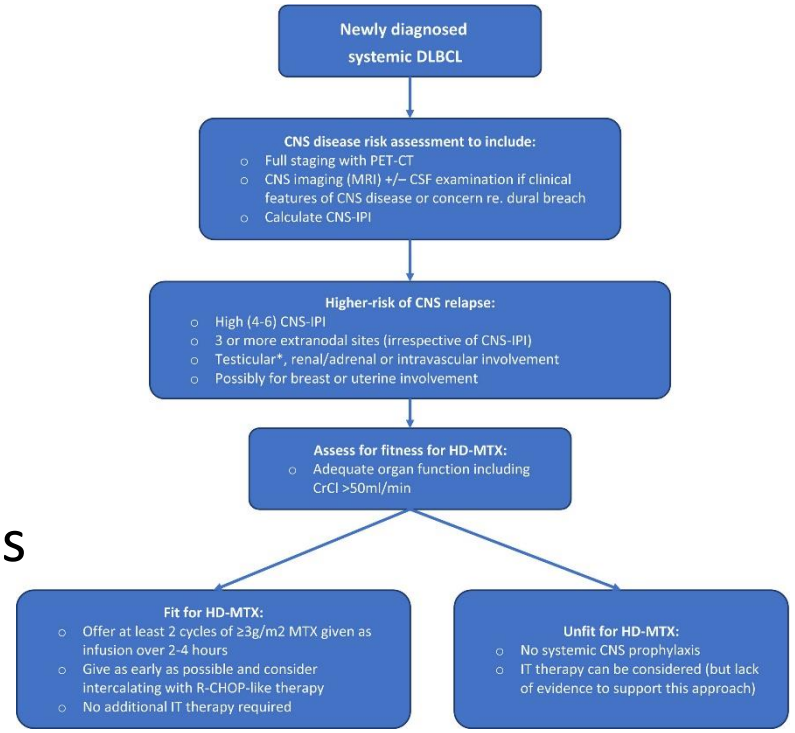
BCL2/MYC dual-expression status did not impact CNS relapse risk

Chin CK, Cheah CY. Blood 2017;130:867-74
Klanova M, et al. Blood 2019;133:919-26

Prophylactic strategies

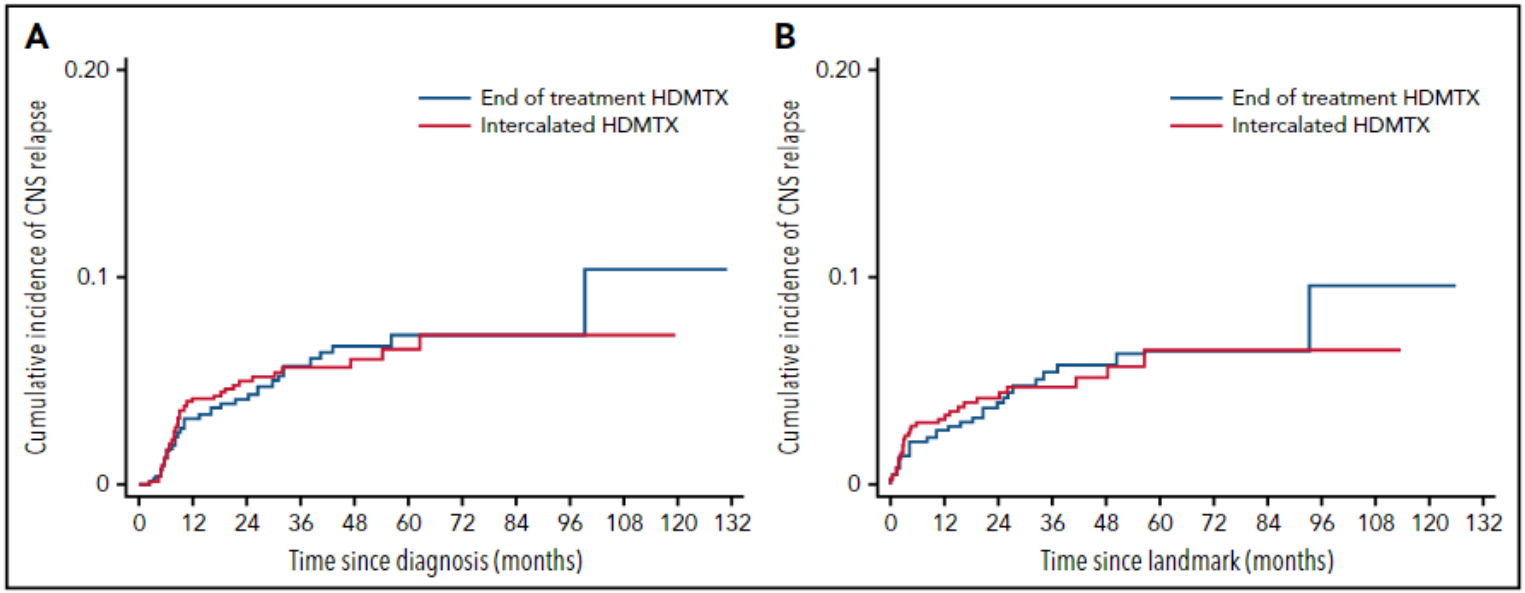
- Stand-alone IT chemotherapy (MTX, Ara-C, steroids): not recommended anymore based on a systematic review

- HD MTX
  - 2 cycles of MTX 3 gr/m²
  - MTX 3 gr/m² on day 15 (R-CHOP21) 2-4 cycles



Savage KJ. Hematology Am Soc Hematol Educ Program 2017;2017:578-86
Chin CK, Cheah CY. Blood 2017;130:867-74
Eyre TA, et al. Haematologica 2020;105:1914-24
McKay P, et al. Br J Haematol 2020;190:708-14

Prophylactic strategies



Single-route central nervous system prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions

Overall cohort N=1162

Switched route due to toxicity: N=32
Followed for toxicity only

Intravenous N=236

Intrathecal N=894

Study N, by CNS-IPI score:

Low	Moderate	High
196	546	321

Predicted baseline CNS relapse risk, weighted by CNS-IPI score: **5.8%**

Overall CNS relapse rate, after single-route prophylaxis: **5.7%**

5.4%	CNS relapse after **intrathecal** prophylaxis	**P=0.40**
6.8%	CNS relapse after **intravenous** prophylaxis	

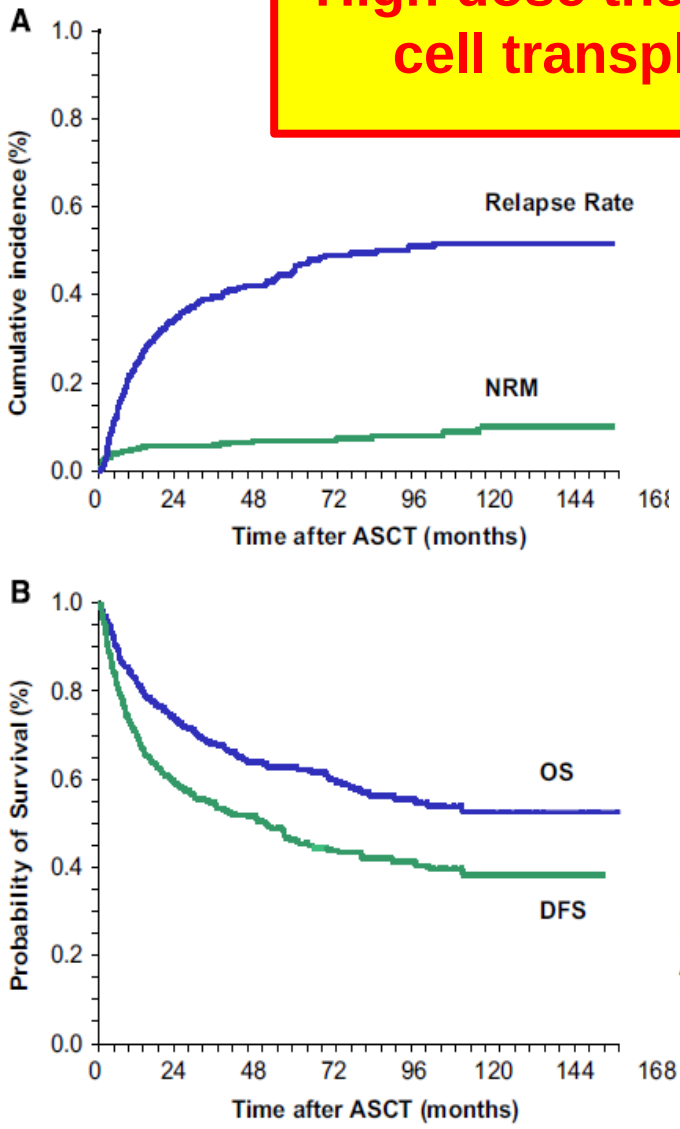
Key findings:

1. CNS relapse rates similar to CNS-IPI predictions, despite all patients receiving prophylaxis
2. PPx route did not significantly affect CNS relapse rate
3. Higher CNS relapse risk despite single-route PPx with:
   - Testicular involvement
   - Non-GCB subtype
   - Increased extranodal burden

Orellana VM, et al. Blood 2022;139:413-23
Wilson MR, et al. Blood 2022;139:2499-511
Eyre T, et al. Lancet Oncol 2022;23:e416-e426

2L treatment

High dose therapy and autologous stem cell transplantation in first relapse



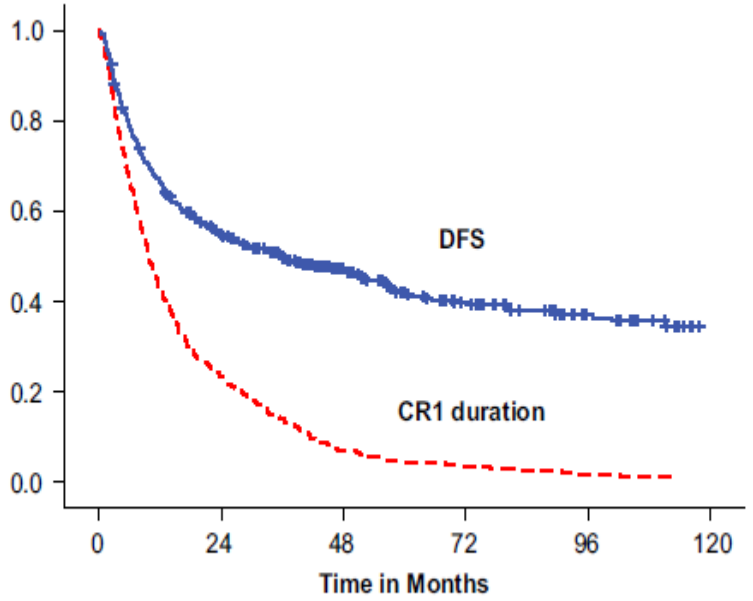
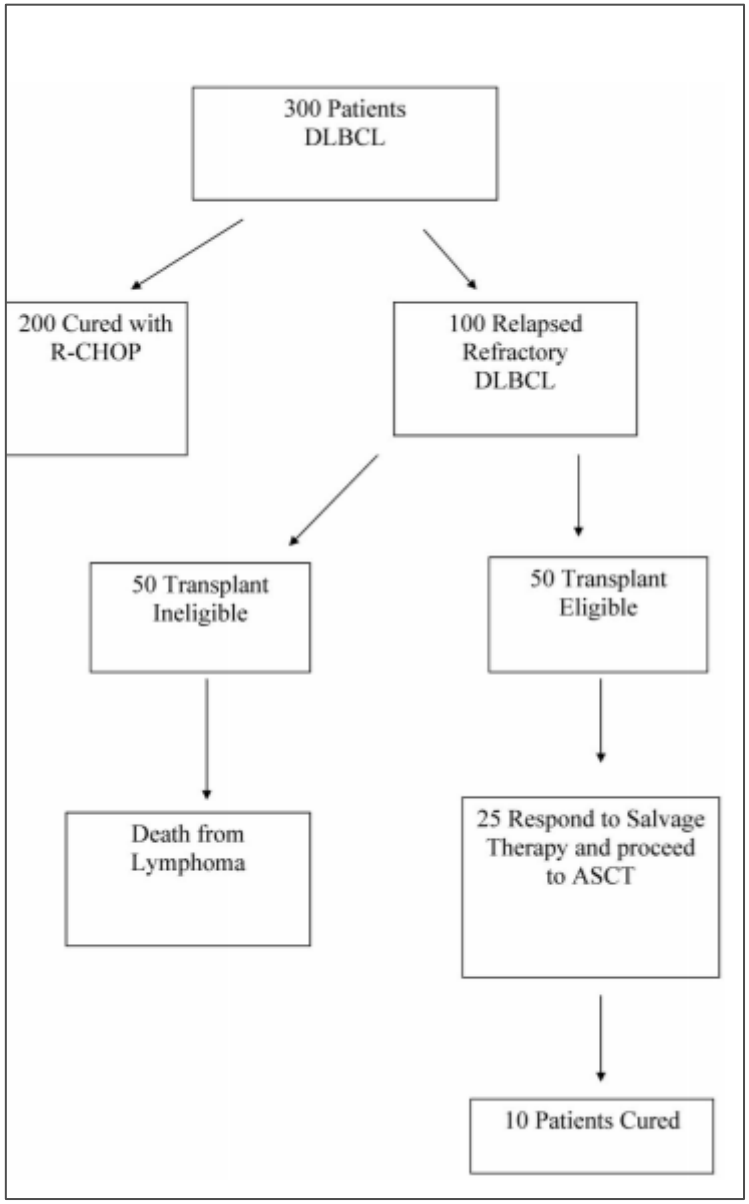


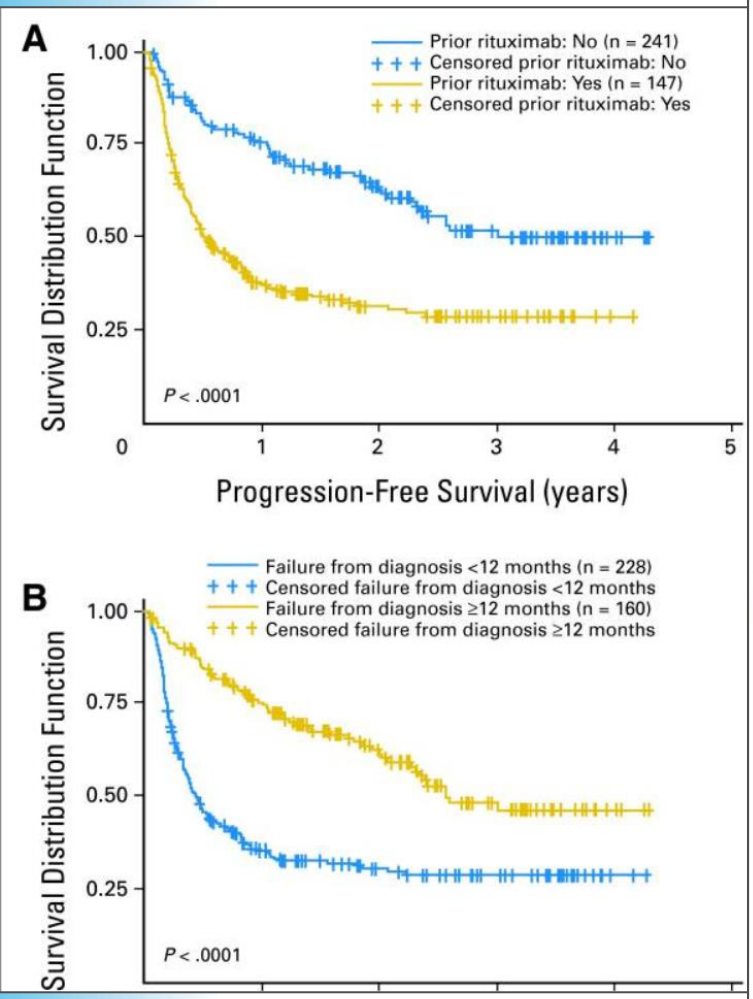
Figure 3. Duration of first complete remission and DFS after the ASCT for the entire series (n = 470).

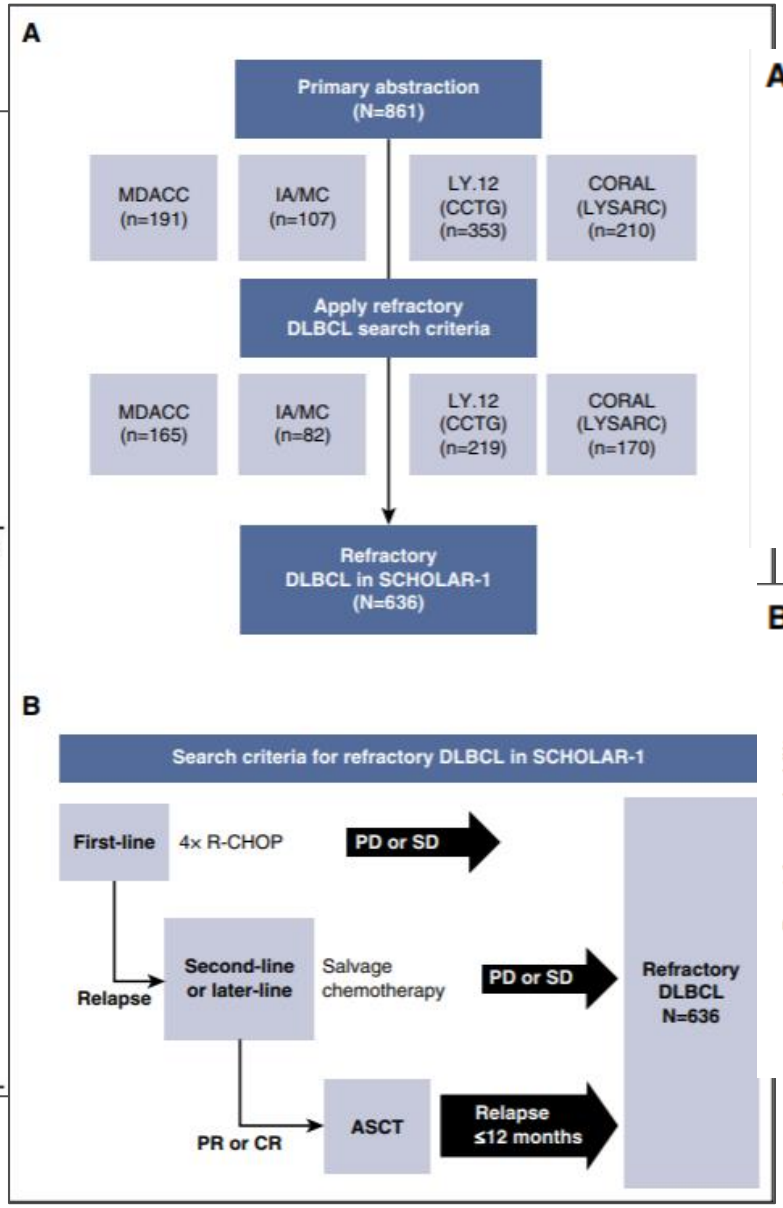
Figure 2. Overall outcome of the entire series (n = 470). (A) Relapse rate and nonrelapse mortality. (B) DFS and OS.

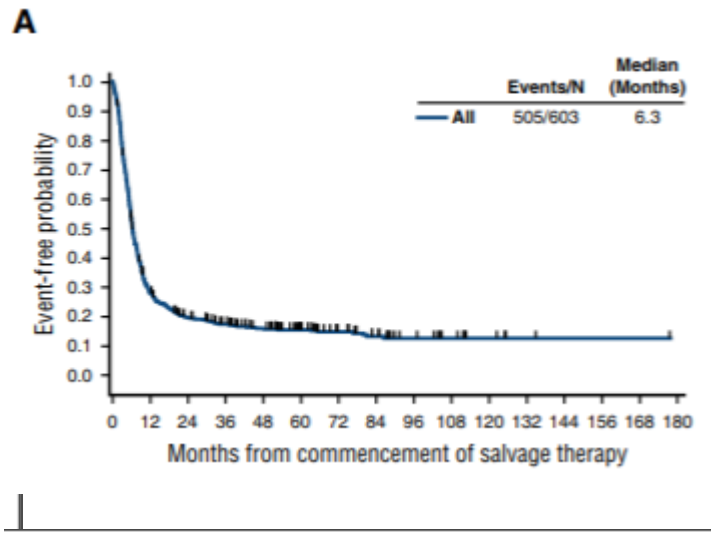


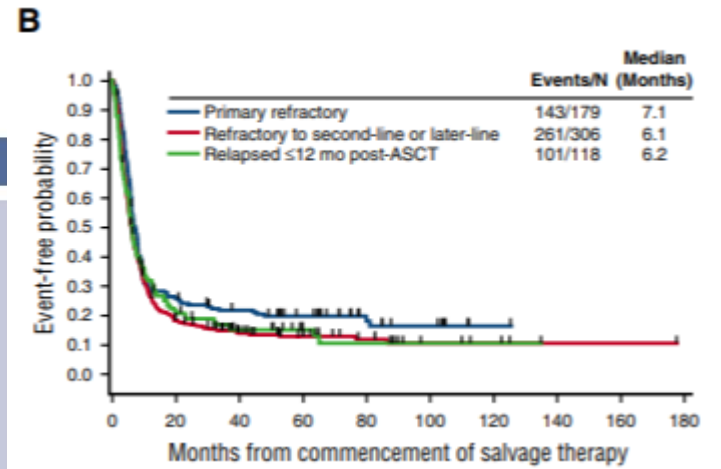
Friedberg JW. Hematology Am Soc Hematol Educ Program 2011;2011:498-505
Mounier N, et al. Biol Blood Marrow Transplant 2012;18:788-93

Treatment









SCHOLAR-1

Gisselbrecht C, et al. J Clin Oncol 2010;28:4184-90
Crump M, et al. Blood 2017;130:1800-8

2L treatment

Salvage chemotherapy (transplant ineligible)

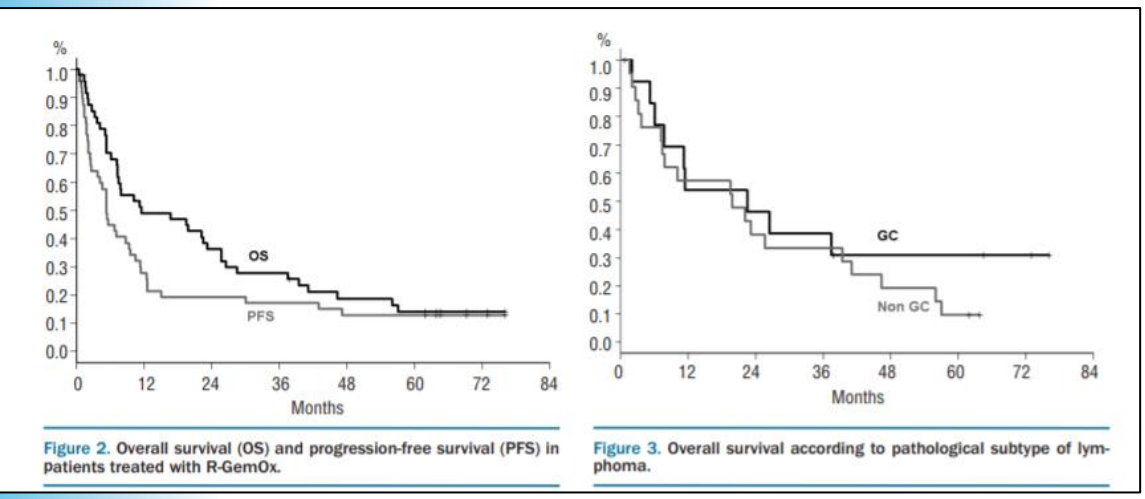


Figure 2. Overall survival (OS) and progression-free survival (PFS) in patients treated with R-GemOx.

Figure 3. Overall survival according to pathological subtype of lymphoma.

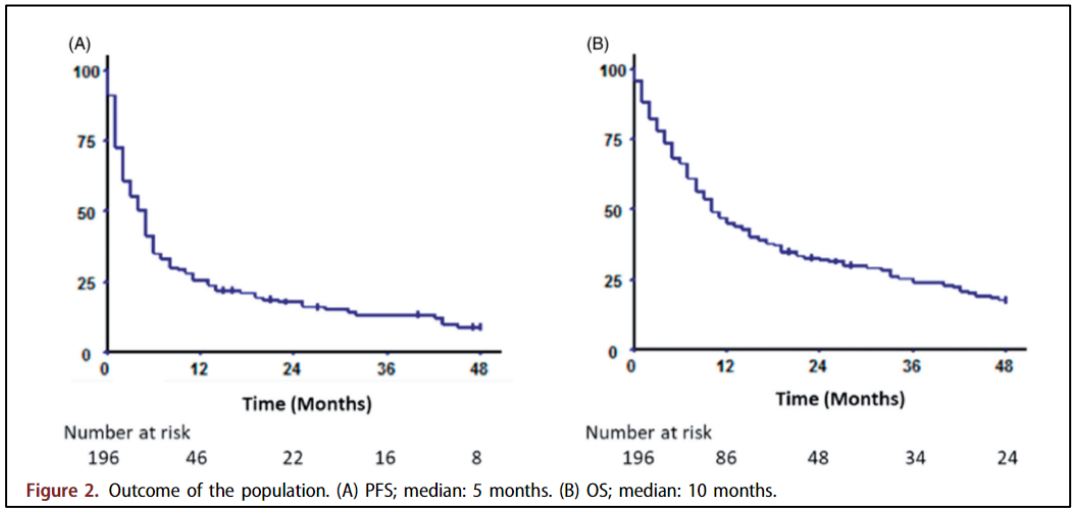


Figure 2. Outcome of the population. (A) PFS; median: 5 months. (B) OS; median: 10 months.

Mounier N, et al. Haematologica 2013;98:1726-31
Cazelles C, et al, Leuk Lymphoma 2021;62:2161-8

2L/RR treatment

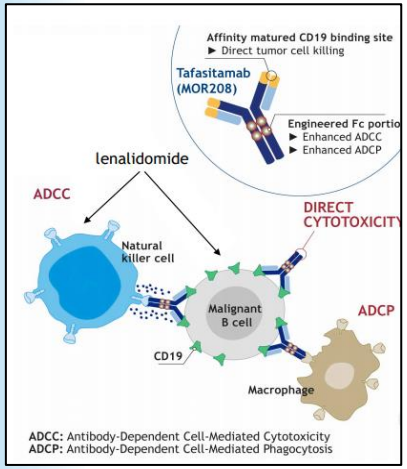
Table 4. Select Agents in Development for the Treatment of DLBCL.*

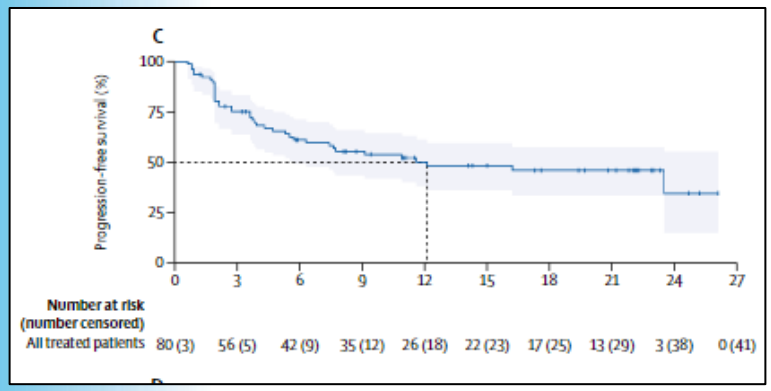
Class and Agent	Target	Clinical Trial Phase	Overall Response Rate	Complete Response Rate	Study
			percent		
CAR T-cell therapy†					
Axicabtagene ciloleucel	CD19	1	82	54	Neelapu et al.[68]
Tisagenlecleucel	CD19	2	52	40	Schuster et al.[69]
Lisocabtagene maraleucel	CD19	1	73	53	Abramson et al.[67]
Monoclonal antibodies					
Tafasitamab	CD19	2a	26	6	Jurczak et al.[70]
Tafasitamab plus lenalidomide	CD19	2	60	43	Salles et al.[71]
Antibody–drug conjugates					
Loncastuximab tesirine	CD19	1	42	23	Hamadani et al.[72]
Brentuximab vedotin	CD30	2	44	17	Jacobsen et al.[73]
Polatuzumab vedotin	CD79b	1	52‡	13‡	Palanca-Wessels et al.[74]
Polatuzumab vedotin plus BR vs. BR	CD79b	2, randomized	45 vs. 17.5	40 vs. 17.5	Sehn et al.[75]
Bispecific antibodies					
Blinatumomab	CD19–CD3	2	43	19	Viardot et al[76]
Mosunetuzumab	CD20–CD3	1/1b	35§	19§	Schuster et al.[77]
Glofitamab	CD20–CD3	1/1b	41	29	Hutchings et al.[78]
Odronextamab	CD20–CD3	1	42¶	35¶	Bannerji et al.[79]
Epcoritamab	CD20–CD3	1/2	76‖	32‖	Hutchings et al.[80]
NF-κB and BCR modifiers					
Ibrutinib	BTK	1/2	37 ABC, 5 GCB	16 ABC, 0 GCB	Wilson et al.[81]
Lenalidomide vs. investigator's choice	Multiple, NF-κB	2, randomized	28 vs. 12	10 vs. 2	Czuczman et al.[82]
Agents with other targets					
Venetoclax	BCL2	1	18	12	Davids et al.[83]
Selinexor	XPO1	2b	28	12	Kalakonda et al.[84]
Checkpoint inhibitors					
Nivolumab	PD-1	2	≤10	≤3	Ansell et al.[85]
Magrolimab	CD47	1b	40	33	Advani et al.[86]
Epigenetic modifiers					
Tazemetostat	EZH2	2	17 EZH2 mt, 17 EZH2 wt	3 EZH2 mt, 9 EZH2 wt	Ribrag et al.[87]

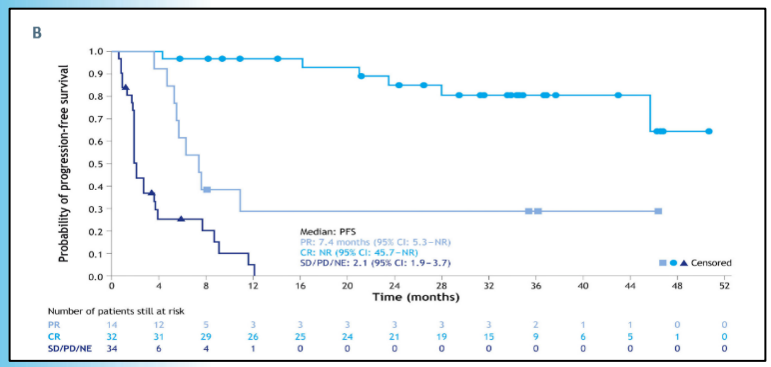
Sehn L, Salles G. N Engl J Med 2021;384:842-58

2L/3L/RR treatment: MAbs

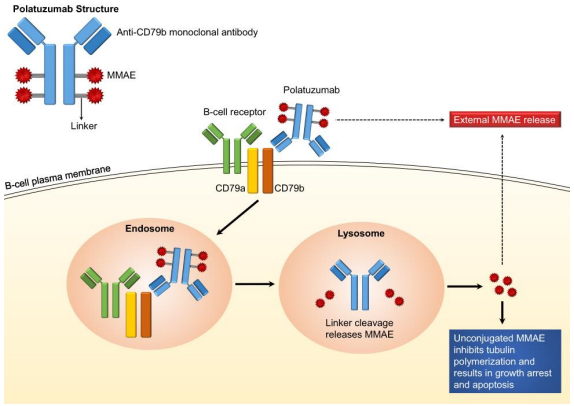
Tafasitamab (CD19)
Phase 2 L-Mind

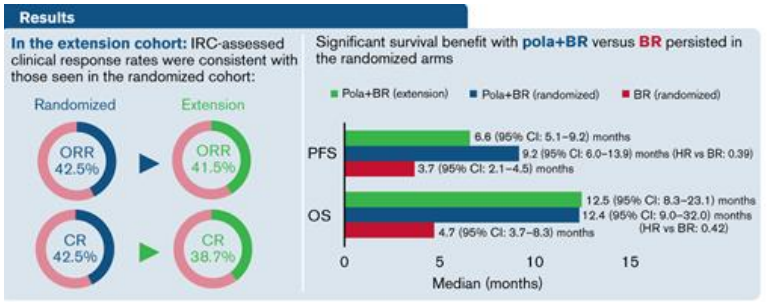




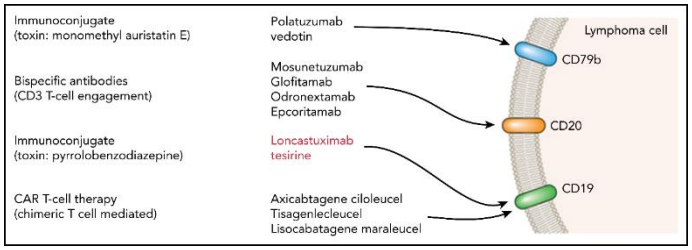


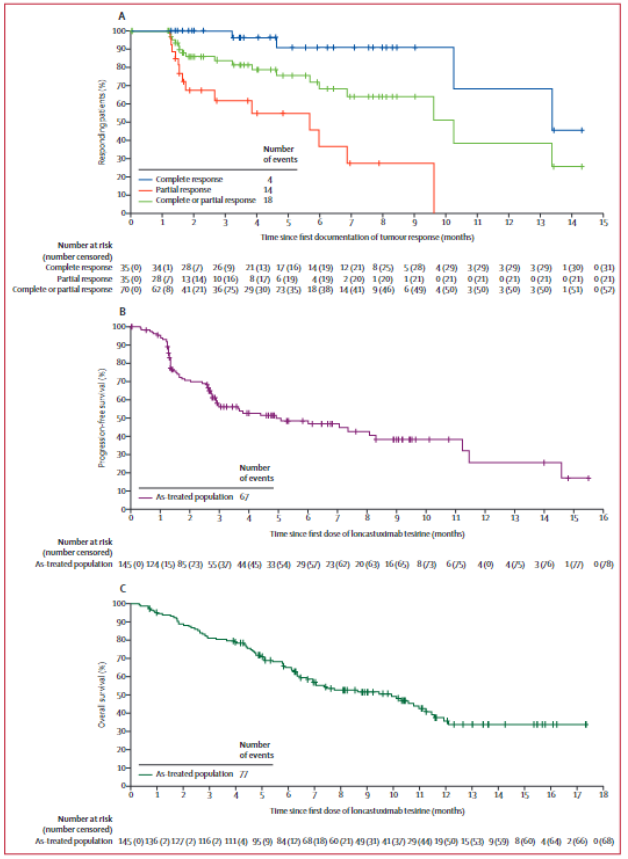
Polatuzumab vedotin (CD79b)





Loncastixumab tesirin (CD19)

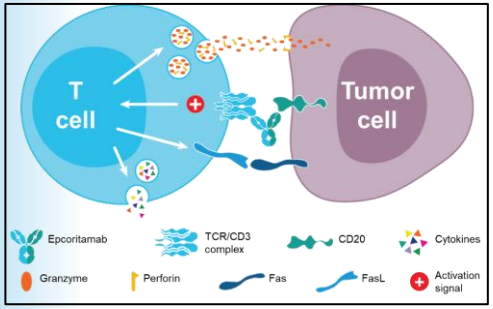




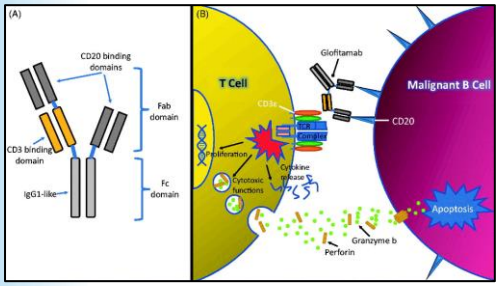
Salles G, et al. Lancet Oncol 2020;21:978-88
Duell J, et al. Haematologica 2021;106:2417-26
Zinzani PL, et al. Clin Cancer Res 2021;27:6124-34
Sehn L, et al. Blood Adv 2022:6:533-43
Kahl BS, et al. Blood 2021;137:2634-45
McMillan A. Blood 2021;137:2568-60
Caimi PF, et al. Lancet Oncol 2021;22:790-800

2L/3L/RR treatment: MAbs

Epcoritamab (CD3/CD20)

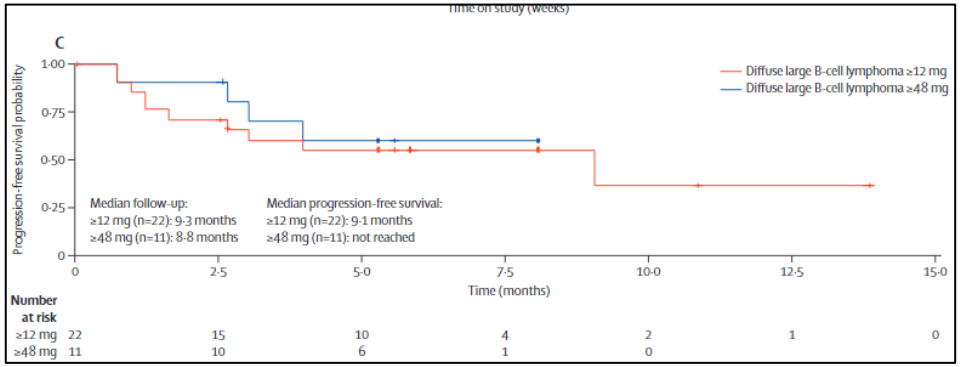


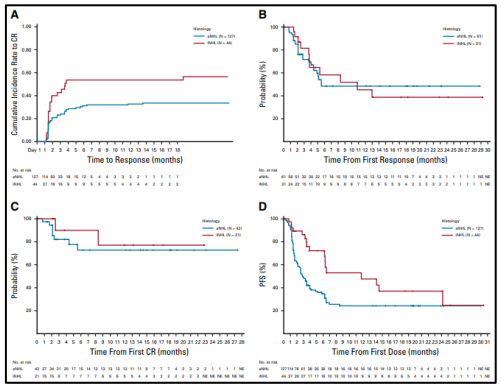
Glofitamab ($CD3/CD20_2$)

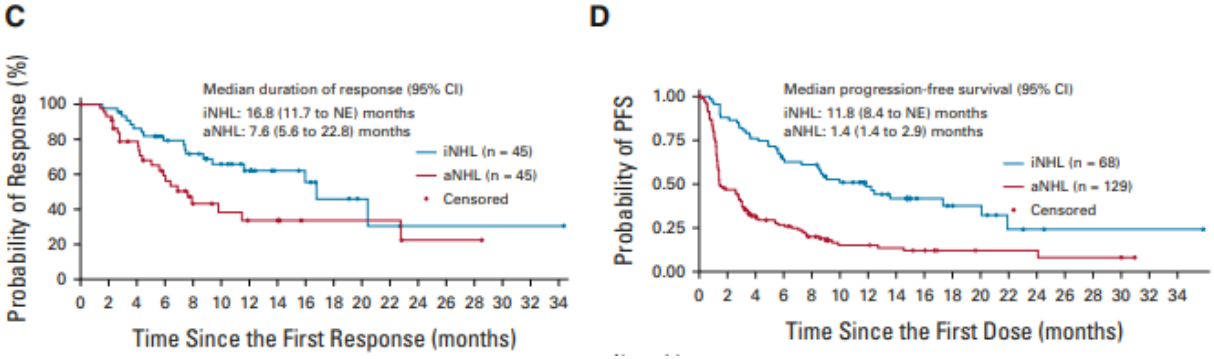


Mosunetuzumab (CD3/CD20)

Odronextamab (CD3/CD20)

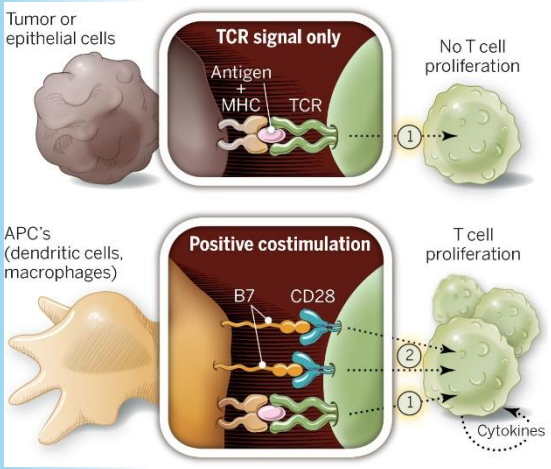


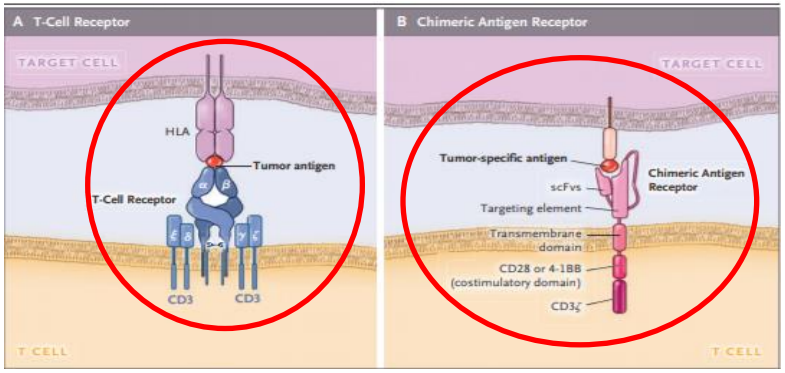


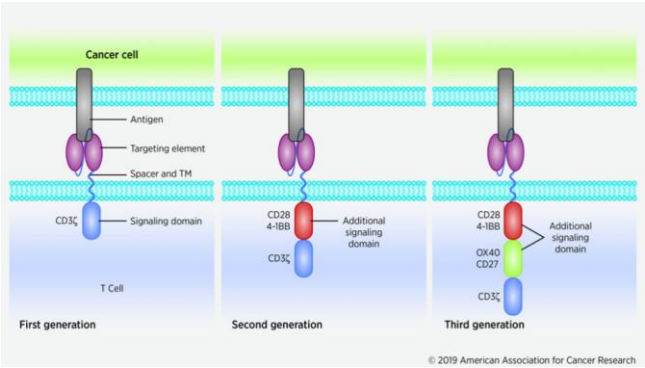


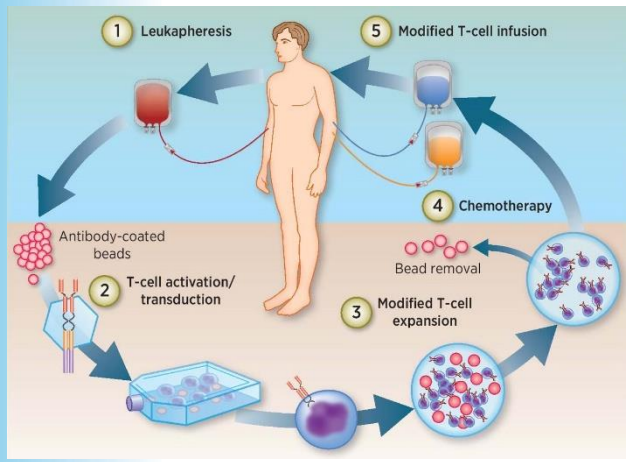
Hutchings M, et al. Lancet 2021;398:1157-9
Minson A, Dickinson M. Leuk Lymphoma 2021;62:3098-108
Hutchings M, et al. J Clin Oncol 2021;39:1959-70
Bannerji R, et al. Lancet Hematol 2022;9:e327-e339

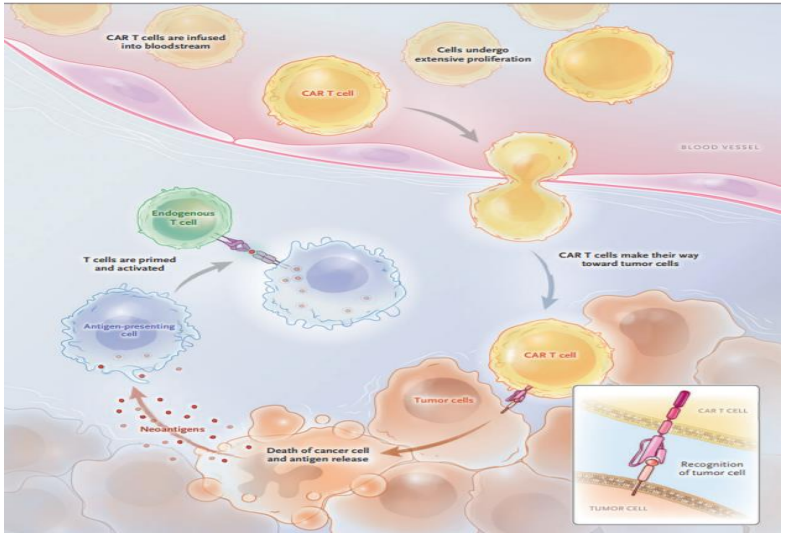
2L/3L/RR treatment: CARTs











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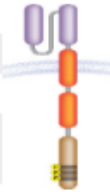
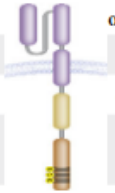
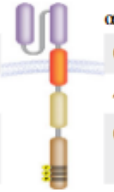
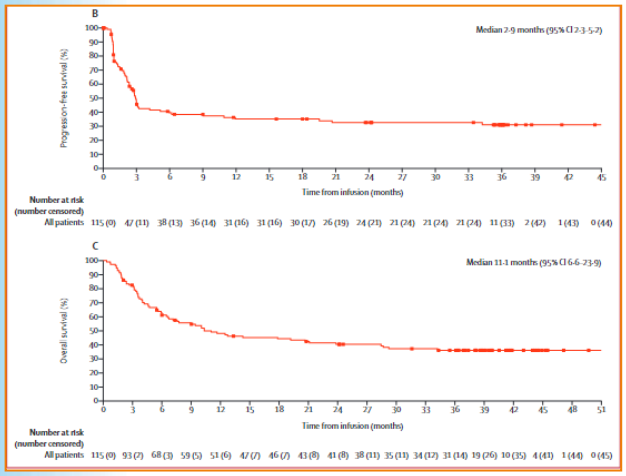
2L/3L/RR treatment: CARTs

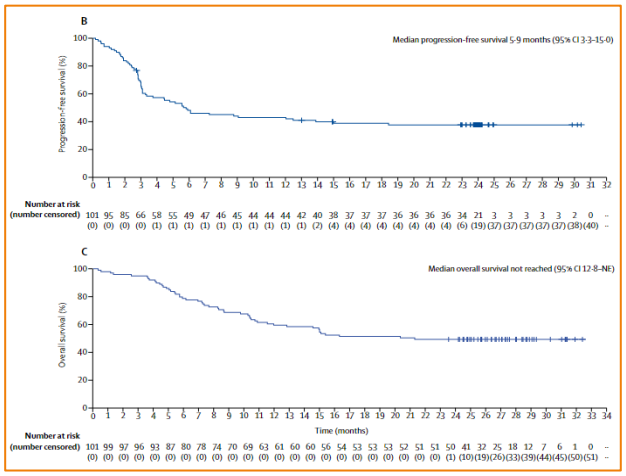
	Axicabtagene ciloleucel ZUMA-1[4]	Tisagenlecleucel JULIET[2,10,11]	Lisocabtagene maraleucel TRANSCEND[6]
CAR	 α CD19	 α CD19	 α CD19
Transmembrane domain	CD28	CD8	CD28
Co-stimulatory domain	CD28	4-1BB	4-1BB
T-cell activation domain	CD3ζ	CD3ζ	CD3ζ
Leukapheresis	Fresh product direct to manufacturing (within US)	Cryopreserved product (could be stored before manufacturing)	Fresh product direct to manufacturing (within US)
Conditioning therapy	Cyclophosphamide-fludarabine (500 mg/m^2, 30 mg/m^2 daily × 3 days)	Cyclophosphamide-fludarabine (250 mg/m^2, 25 mg/m^2 daily × 3 days) or Bendamustine (90 mg/m^2 daily × 2 days)[a]	Cyclophosphamide-fludarabine (300 mg/m^2, 30 mg/m^2 daily × 3 days)
CAR-T cell target dose	2 × 10^6/kg; max dose was 2 × 10^8/kg	0.1 × 10^8 to 6 × 10^8 flat dose	0.5 × 10^8 to 1.5 × 10^8 each of CD4+ and CD8+ CAR-T cells at 1:1 dose ratio
CNS disease	No history of, or active, CNS disease allowed	No active CNS disease allowed	Secondary CNS allowed
Prior anti-CD19 therapy	Not allowed	Not allowed	Allowed, if CD19+ tumor present
Bridging therapy	Not permitted	Permitted[b]	Permitted[b]
Outpatient administration	Not allowed	Allowed	Allowed
Patients enrolled, n	119	167	344
Patients infused, n	7 (phase 1) 101 (phase 2)	99 (main cohort) 16 (Cohort A)	294[c]
Manufacturing failure, n	1	12	2

Westin JR, et al. Am J Hematol 2021;96:1295-312

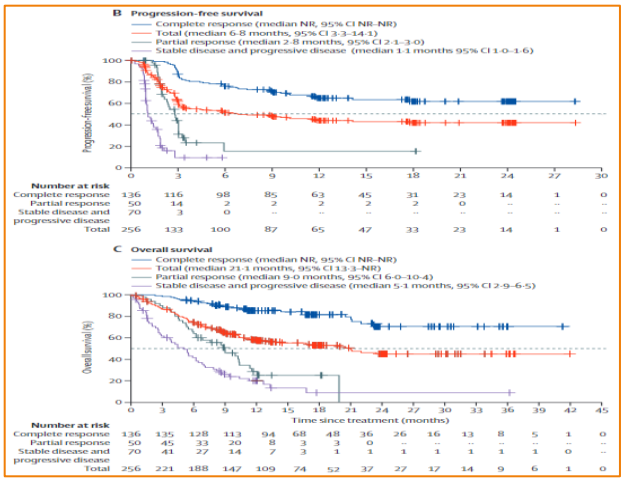
R/R treatment: CARTs



JULIET (Tisa-Cel)
(Schuster SJ, et al. Lancet Oncol 2021;22:1403-15)

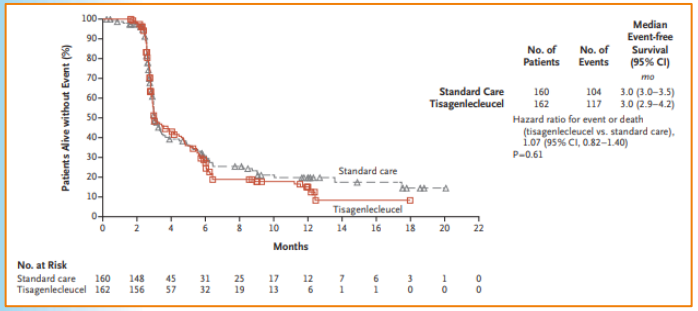


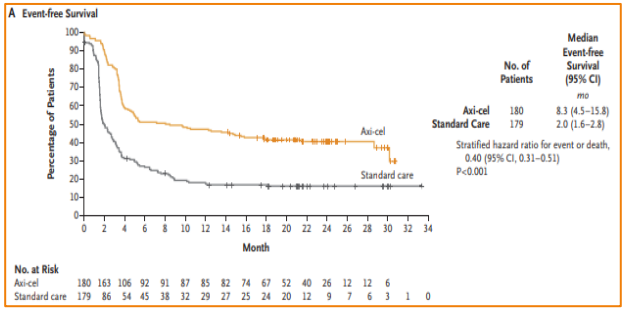
ZUMA-1 (Axi-Cel)
(Locke FL, et al. Lancet Oncol 2019;20:31-42)

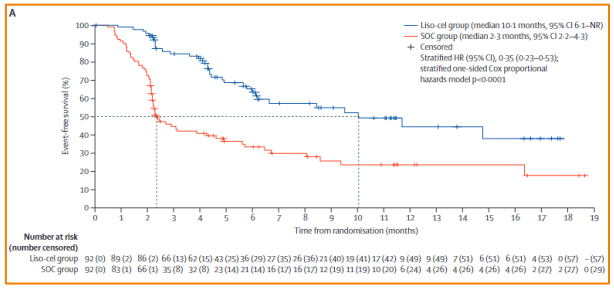


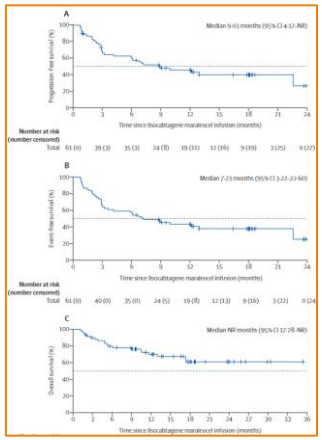
TRANSCEND NHL001 (Liso-Cel)
(Abramson JS, et al. Lancet 2020;396:839-52)

2L treatment: CARTs









BELINDA (Tisa-Cel)
(Bishop MR, et al. N Engl J Med 2022;386:629-39)

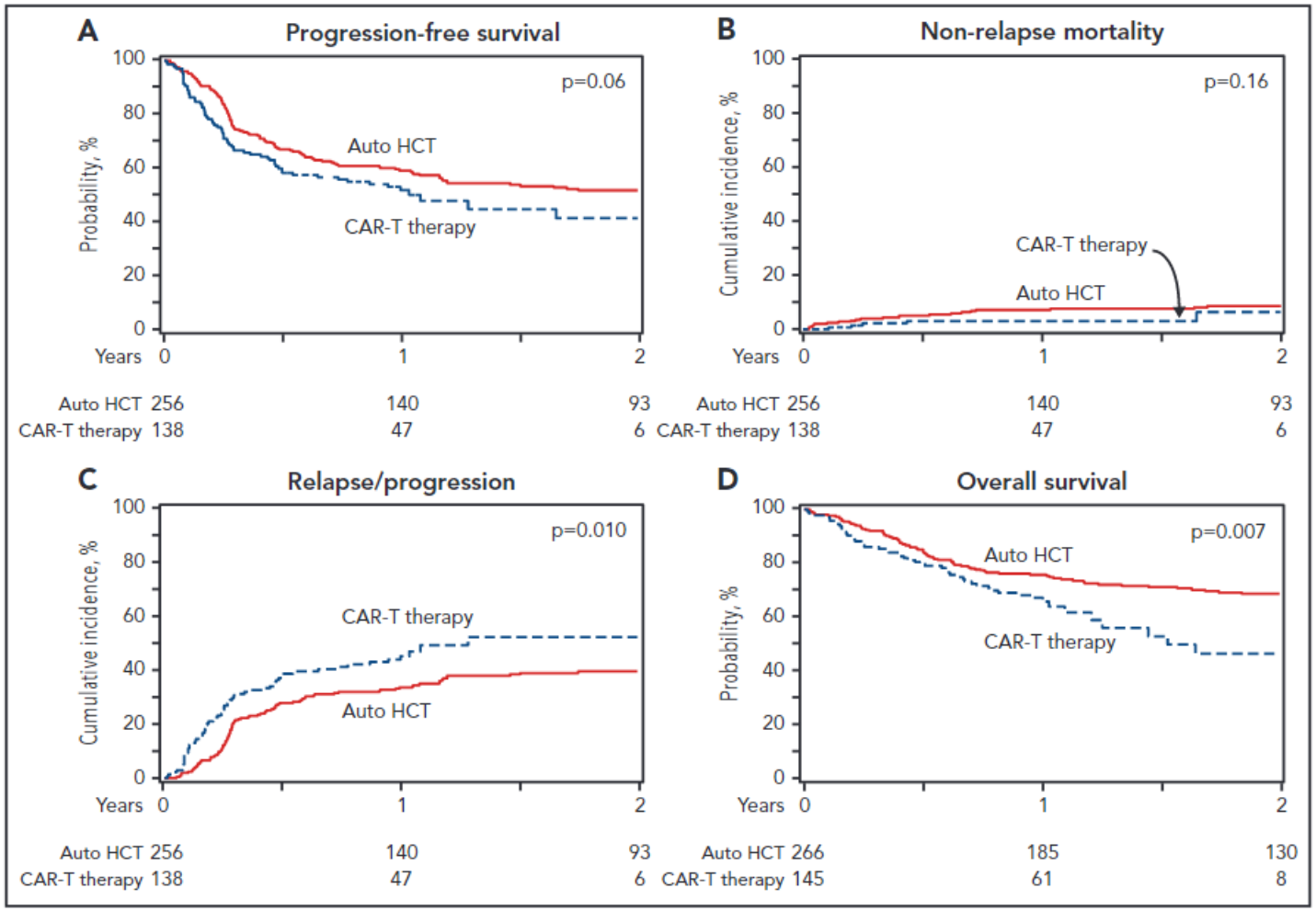
ZUMA-7 (Axi-Cel)
(Locke FL, et al. N Engl J Med 2022;386:640-54)

TRANSFORM (Liso-Cel)
(Kamdar M, et al. Lancet 2022;399:2294-308)
PILOT (Liso-Cel)
(Sehgal A, et al. Lancet Oncol 2022;23:1066-77)

2L/3L/RR treatment: CARTs

Center for International Blood & Marrow Transplant Research registry database

PR



Shadman M, et al. Blood 2022;139:1330-9

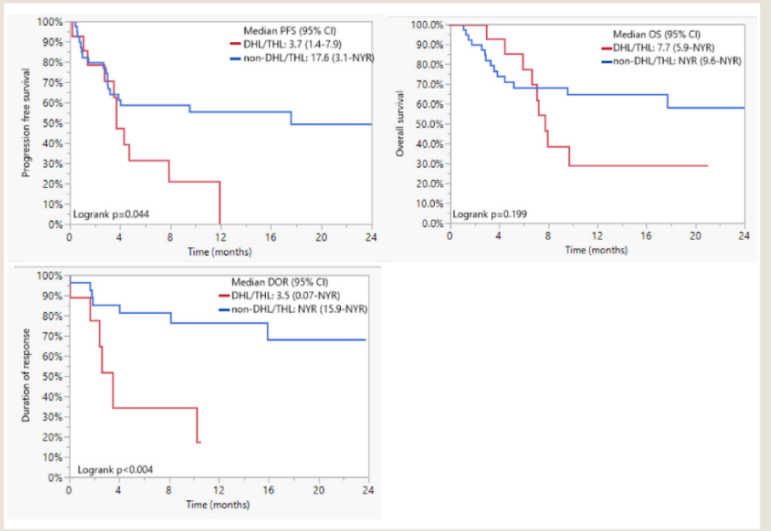
2L/3L/RR treatment

Table 1. Clinical trials in DLBCL included patients with double-hit or double expressor lymphoma.

Treatment type	Regimen	Trial design	Population	ORR/CR	PFS	OS	Trial
CAR T	Axi-cel	Phase 1/2	R/R DLBCL including DEL in 30 and DHL in 5 patients, 64% and 11% of total assessed, respectively	DEL: 91%/70%	-	-	ZUMA 1 [75]
	Axi-cel	Phase 2	High risk DLBCL with positive interim PET, DHL in 17 of 32 patients, 53%	85%/74%	-	-	ZUMA 12 [26]
	Tisa-cel	Phase 2	R/R DLBCL including DHL in 19 of 70, 27%	DHL: 50%/25%	-	-	Juliet [73]
	Liso-cel	Phase 2	R/R DLBCL including DHL in 36 of 269, 13%	DHL: 76%/61%	-	-	TRANSCEND [71]
	Axi-cel ($n = 94$) tisa-cel ($n = 36$)	Retrospective	R/R DLBCL, MYC rearranged in 32 of 130 and DHL in 22 of 130	-	MYC: HR = 0.96 (0.58–1.61) DHL: HR = 0.96 (0.55–1.69)	MYC: HR = 1.20 (0.66–2.19) DHL: HR = 1.05 (0.54–2.06)	[76]
	Axi-cel	Retrospective	R/R DLBCL, DHL in 64 (21%) and DEL in 98 (33%) of 298	-	DHL: 12-month, 39%	DHL: 12-month, 69%	[77]
Targeted therapy + chemo-/immunotherapy	R/G-CHP-polatuzumab	Phase 1/2	De novo DLBCL, DEL in 13 of 82 patients, 16%	DEL: 92%/69%	DEL: 12-month 92%	-	[78]
	Venetoclax + R-CHOP	Phase 2	De novo DLBCL, DEL in 80 of 206 patients, 39%	DEL: 84%/66%	24-month, 79%	24-month, 72%	CAVALI [79]
	Venetoclax + R-EPOCH	Phase 1	De novo DLBCL, DHL in 15 of 30 patients, 50%	DHL: 93%/80%	-	-	[80]
	Lenalidomide + R-EPOCH	Phase 1	De novo DLBCL, 10 of 15 DEL, 66% and 5 of 15 DHL, 3%	DEL: 100%/100% DHL: 80%/60%	DEL: 100% at 20 months DHL: 60% at 20 months	DEL: 100% at 20 months DHL: 60% at 20 months	[81]
Targeted therapy/ Chemo- free	Venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide	Phase 1/2	R/R NHL, DHL in 12 of 53 patients, 23%	DHL: 58%/50%	-	-	VIPOR [25]
	Venetoclax, polatuzumab, rituximab	Phase 1/2	R/R DLBCL, DEL in 20 of 57 patients, 34%	DEL: 40%/35%	-	-	GO29833 [82]
	Tafasitamab, lenalidomide	Phase 2	R/R DLBCL, MYC rearranged in 7 and DHL in 2 of 81 patients	MYC: 58%/50% DHL: 50%/50%	-	-	L-MIND [25]
	Mosunetuzumab	Phase 1/2	De novo DLBCL, elderly or unfit, DHL in 4 of 19 patients, 21%	DHL: 50%/50%	-	-	[83]

University of California, Los Angeles

Figure 2 Kaplan-Meier curve showing survival probability comparisons between the DHL and non-DHL cohorts after CAR-T, demonstrating (A) median PFS 3.7 months vs. NR for DHL and non-DHL, respectively, $P = .011$ by log-rank test. (B) median OS 7.7 months and NR for DHL and non-DHL, respectively, $P = .200$ by log-rank test. (C) median DOR 2.6 months and NR for DHL and non-DHL, respectively, $P = .029$ by log-rank test. CAR-T = CD19-directed chimeric antigen T-cell receptor; DHL = double hit lymphomas; DOR = duration of response; NR = not reached; OS = overall survival; PFS = progression free survival



Novel CART constructs
Maintenance strategies
(immunomodulators, allogeneic HSCTx)

Ghafouri S, et al. Clin Lymphoma Myeloma Leuk 2021;21:861-72
Gordon MJ, Westin JR. Leuk Lymphoma 2022;63:1034-44

1L treatment

Zuma-12:
Axicabtagene Ciloleucel

HIGH RISK DISEASE

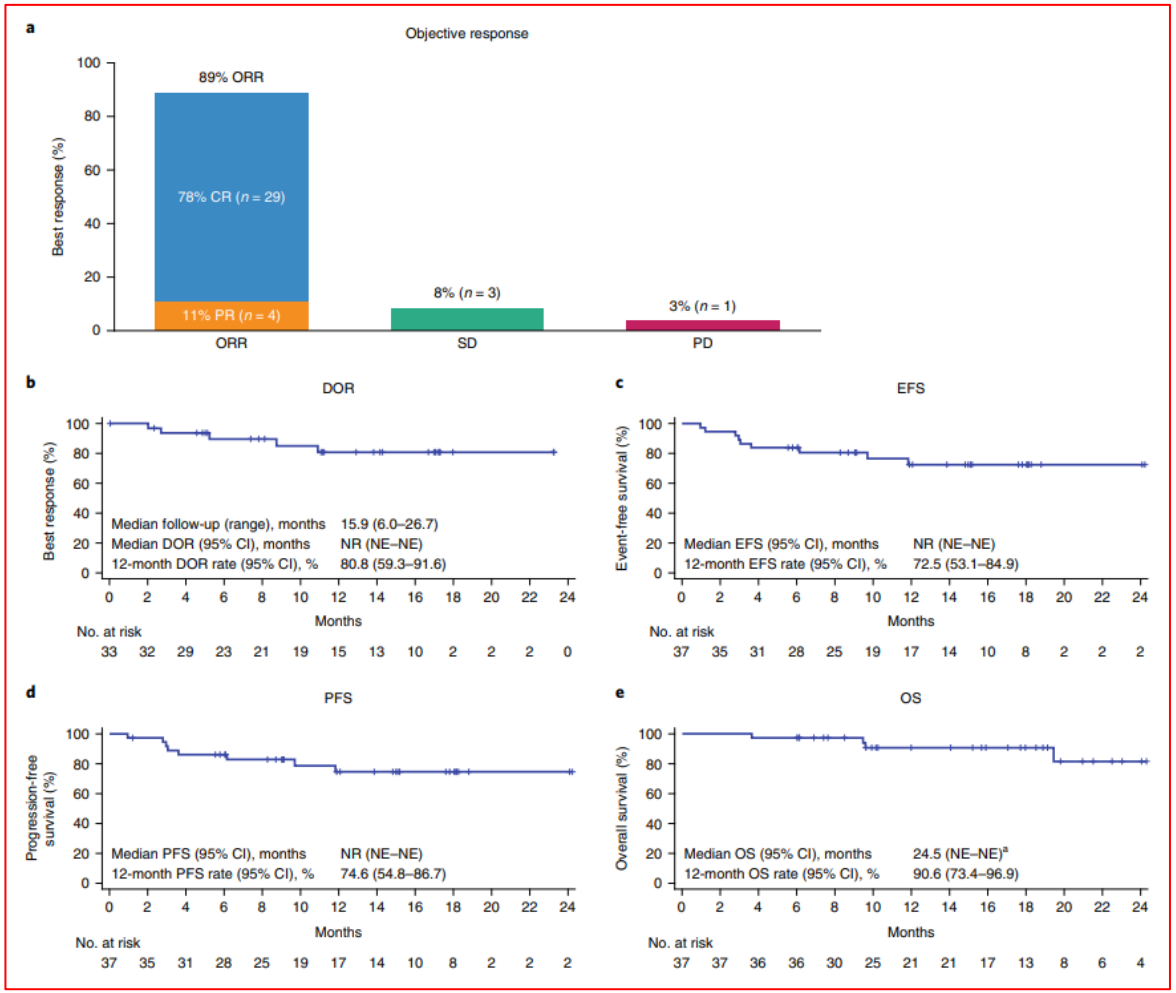
- double- or triple-hit lymphoma
- LBCL with IPI ≥3

+

PET2+ (DS 4-5) after two cycles of chemoimmunotherapy

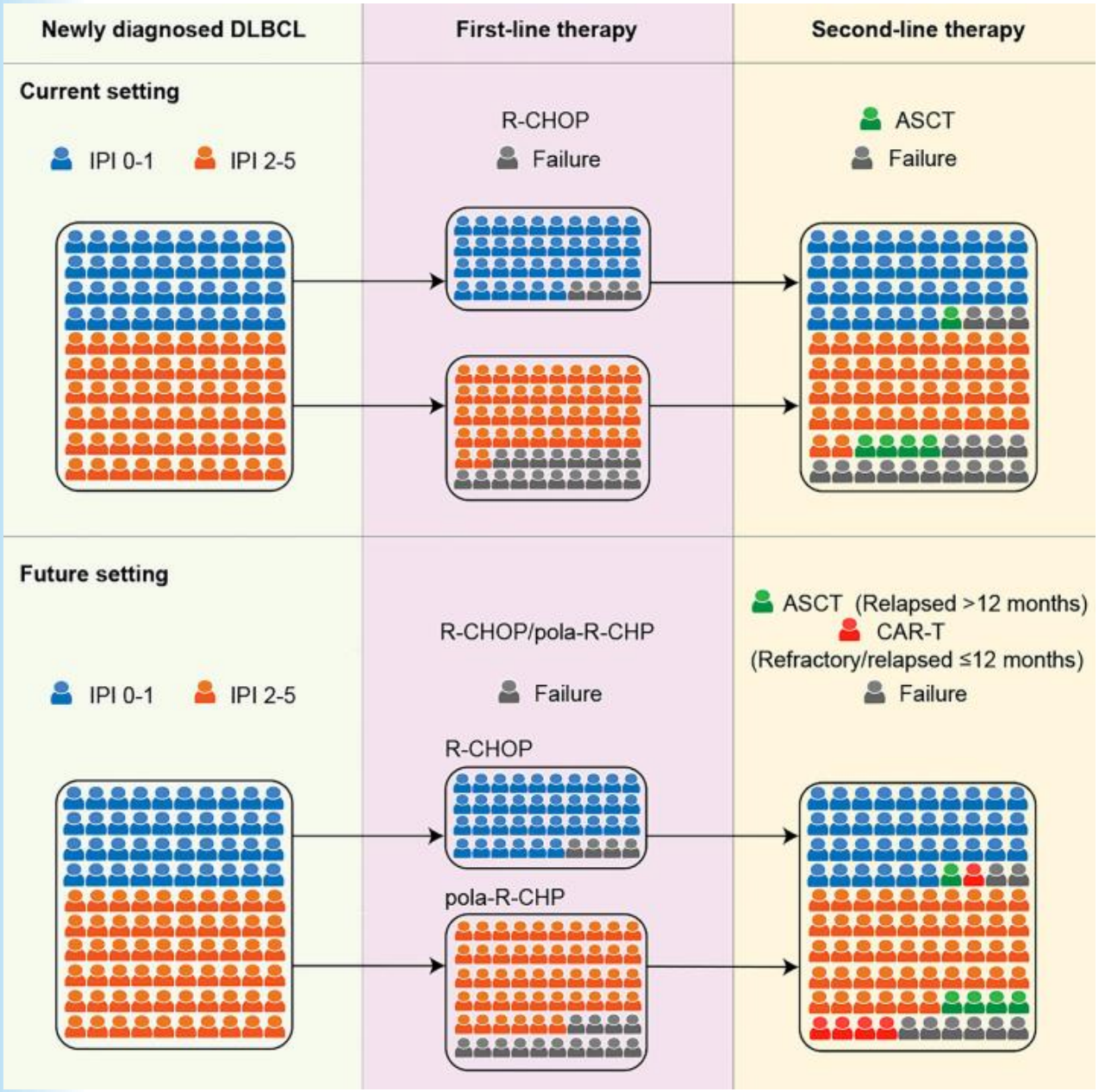
Table 3 | Adverse events of interest occurring in ≥15% of all treated patients, by worst grade

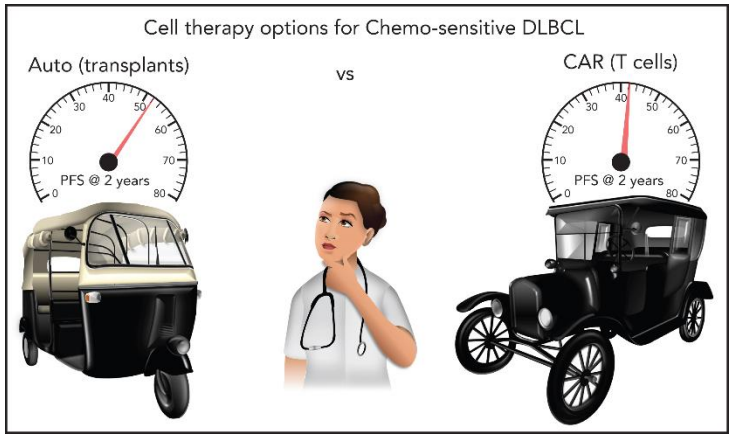
Adverse event[a], *n* (%)	Grade 1	Grade 2	Grade ≥3	Total
Subjects with any CRS[a]	27 (68)	10 (25)	3 (8)	40 (100)
Pyrexia	8 (20)	28 (70)	4 (10)	40 (100)
Hypotension	7 (18)	5 (13)	0 (0)	12 (30)
Chills	9 (23)	1 (3)	0 (0)	10 (25)
Hypoxia	2 (5)	2 (5)	5 (13)	9 (23)
Sinus tachycardia	6 (15)	0 (0)	0 (0)	6 (15)
Subjects with any neurologic events	14 (35)	6 (15)	9 (23)	29 (73)
Confusional state	7 (18)	2 (5)	2 (5)	11 (28)
Encephalopathy	2 (5)	2 (5)	6 (15)	10 (25)
Tremor	8 (20)	2 (5)	0 (0)	10 (25)

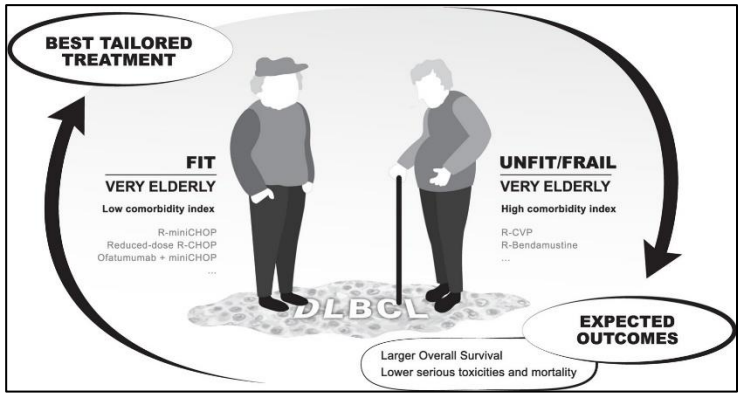


Neelapu SS, et al. Nat Med 2022;28:735-42

Treatment







Xu P-P, et al. Cancer Cell 2022;40:131-3
Tavares A, Moreira I. Crit Rev Oncol Hematol 2021;160:103294
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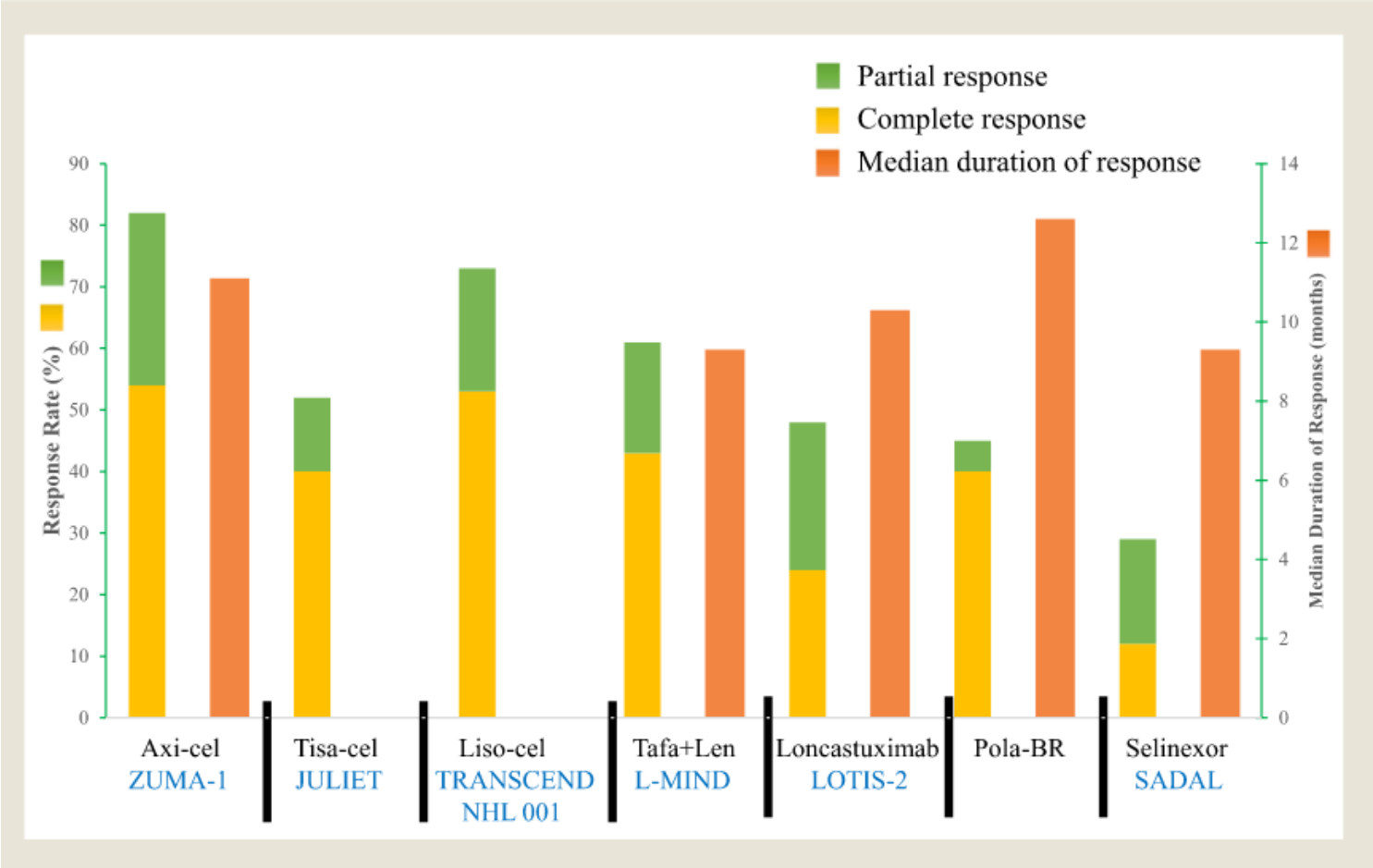
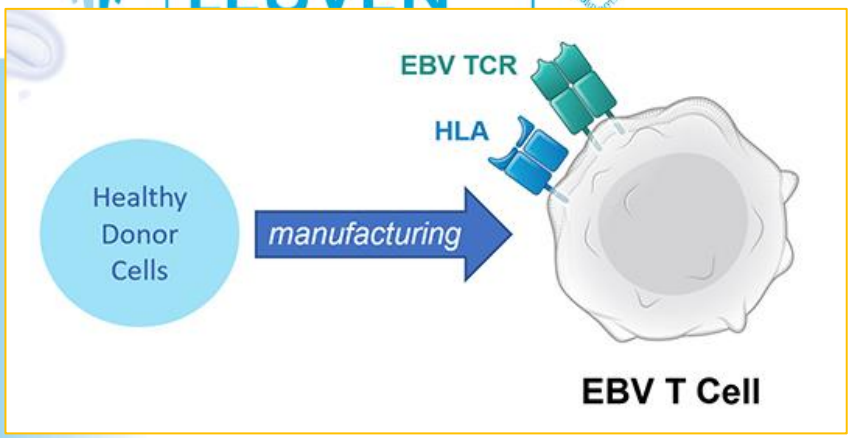
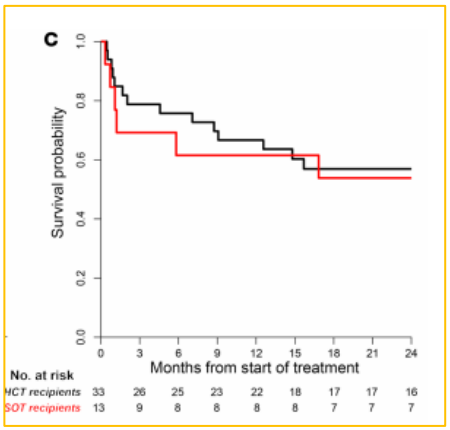
Treatment



Nuvvula S, et al. Clin Lymphoma Myeloma Leuk 2022;22:362-72

2L treatment PTLD

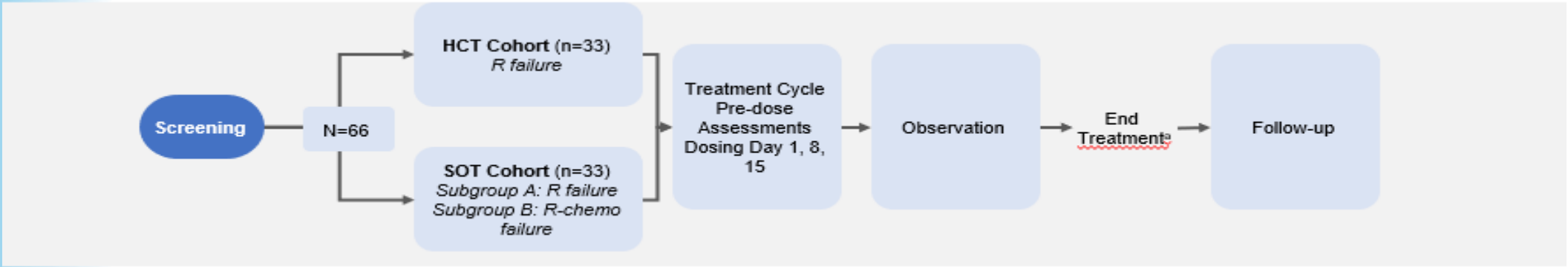


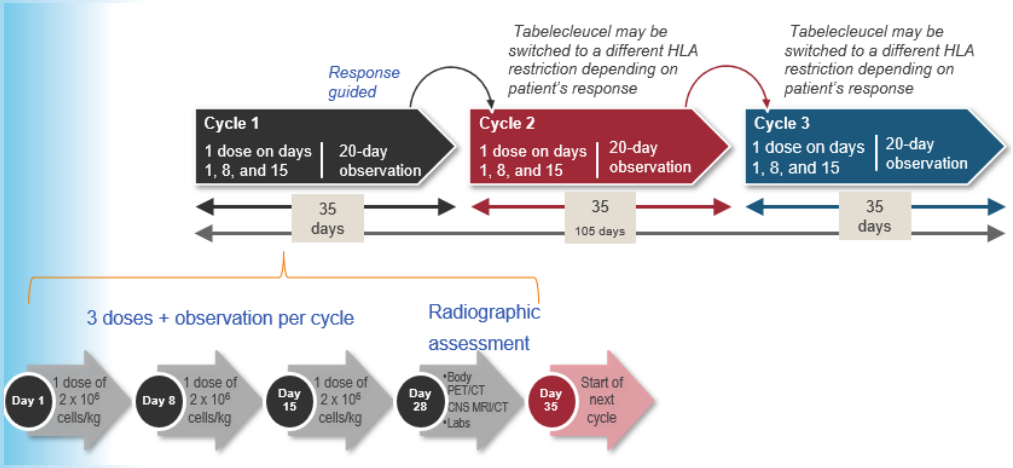


Ultimate response to treatment

Cohort	N	CR	PR	SD	POD	CR + PR
HCT recipients	33	19	3	1	9	68%
SOT recipients	13	2	5	1	5	54%

ATA129-302 ALLELE Study: Tabelecleucel Phase 3 Clinical Trial





Prockop S, et al. J Clin Invest 2020;130:733-47

Take home messages

1. DLBCL is a very heterogeneous lymphoma subtype, even within the COO subtypes.
2. Underlying immunodeficiency is a very important risk factor.
3. R-CHOP remains the first line treatment in DLBCL, NOS. Phase III trials with new therapeutic strategies combined with R-CHOP have been disappointing.
4. New immunotherapeutic options are changing the therapeutic landscape (in all lines) .
5. HGBL is associated with a poor prognosis and requires more intensive first line therapy.
6. The role of central nervous system prophylaxis in high risk patients remains controversial.

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DLBCL

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CNS prophylaxis

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HGBL

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PTLD

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