The Role of c-Myc and Bcl-2 in the Classification and Management of Aggressive B Cell Lymphoma

Double Hit/Expressor and Burkitt's Lymphomas

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2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

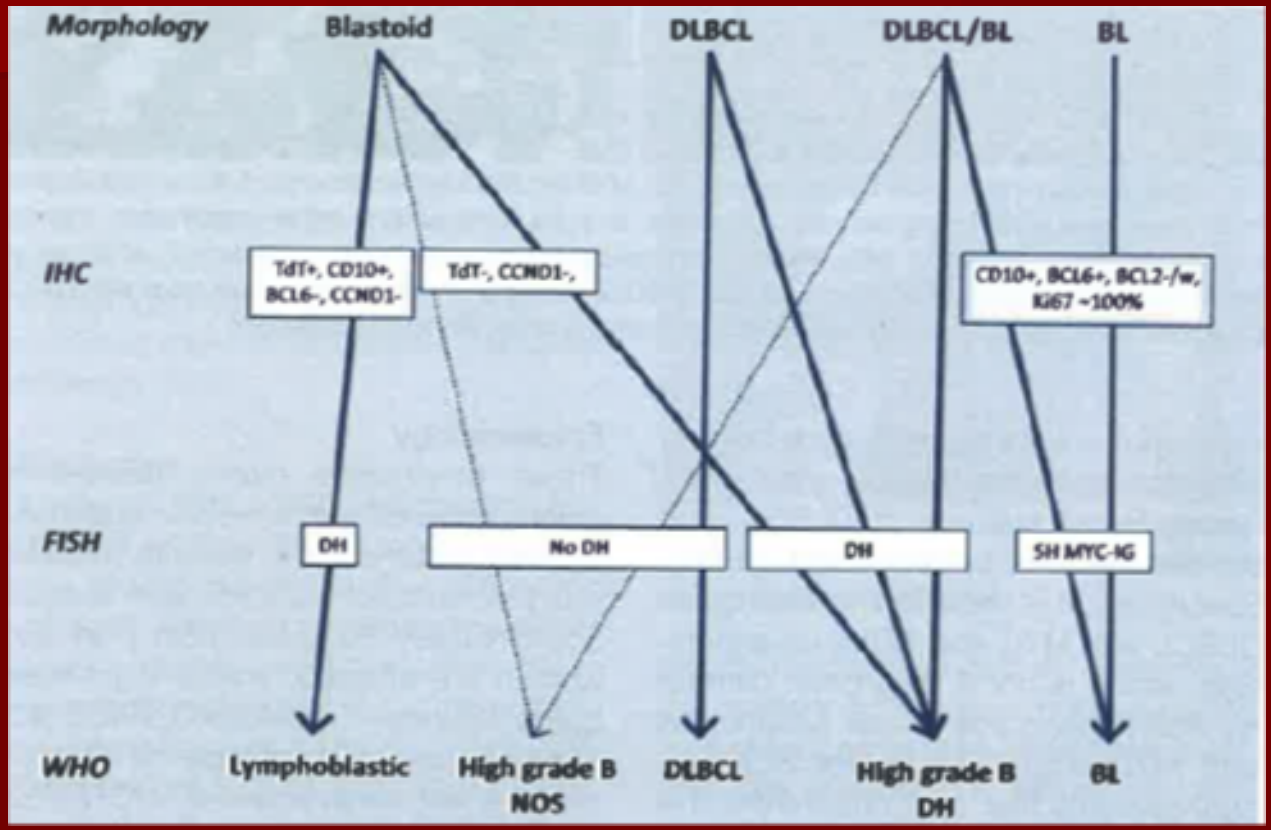
Mature B-cell neoplasms:

Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
  Splenic diffuse red pulp small B-cell lymphoma
  Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
  Waldenstr¨om macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
m heavy-chain disease
g heavy-chain disease
a heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
  Pediatric nodal marginal zone lymphoma
Follicular lymphoma
  In situ follicular neoplasia*
  Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*

Large B-cell lymphoma with IRF4 rearrangement*
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
  In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
  Germinal center B-cell type*
  Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV1 DLBCL, NOS*
EBV1 mucocutaneous ulcer*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK1 large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV81 DLBCL, NOS*
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration*
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

BLOOD, 19 MAY 2016 x VOLUME 127, NUMBER 20

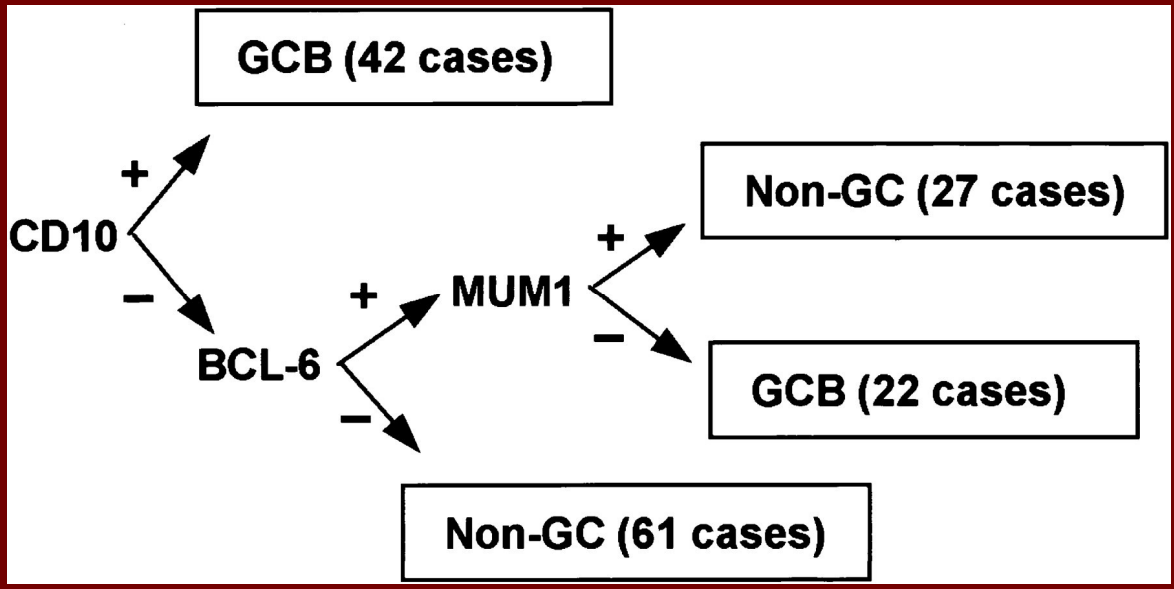
Large B Cell lymphomas



Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2017.

"Traditional Classification of DLBCL Cell of Origin

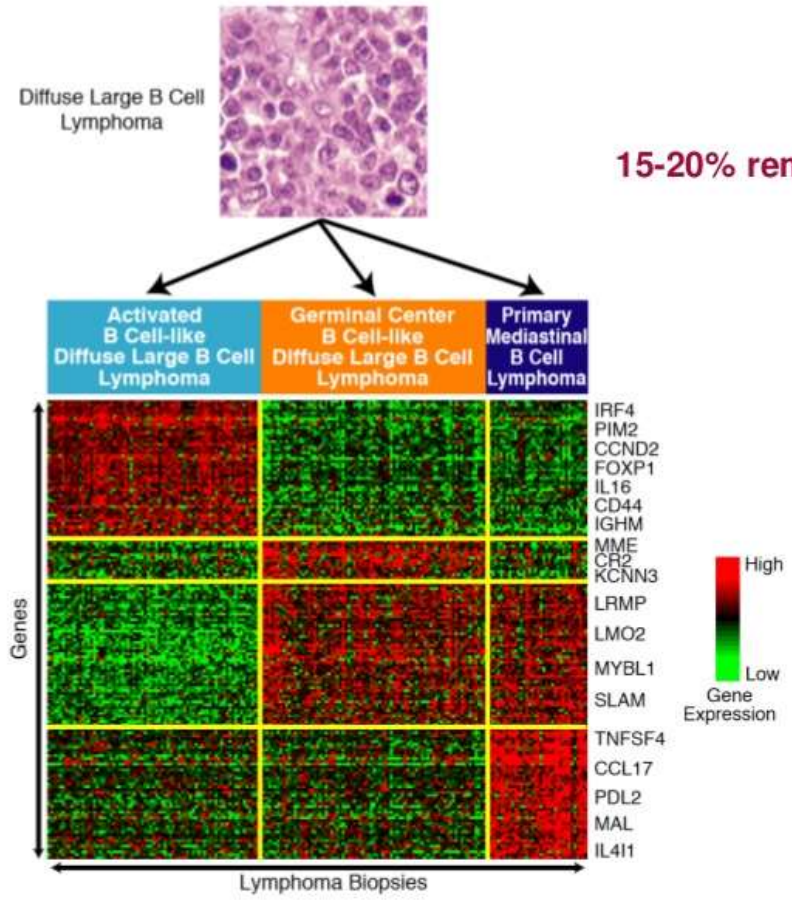
- **Hans algorithm** –sensitivity (85 to 90 percent), specificity (52 to 82 percent), positive predictive value (55 to 82 percent), and negative predictive value (83 to 90 percent) when compared with GEP
- **Tally method** – CD10 and GCET1 MUM1 and FOXP1, LMO2. Subsequent reports have estimated the sensitivity (80 to 99 percent), specificity (54 to 86 percent), positive predictive value (55 to 87 percent), and negative predictive value (79 to 99 percent) when compared with GEP
- Lymph2Cx platform — An alternative approach that is being explored is the use of new technologies that precisely quantify RNA transcript levels in formalin-fixed paraffin-embedded tissue sections.



Hans CP, et al. Blood. 2004.

DLBCL is molecularly different diseases

Gene expression profiling — GEP by means of complementary DNA microarrays ("Lymphochip" microarrays) is an evolving approach to classification and diagnosis of non-Hodgkin lymphoma



Roschewski, Staudt, Wilson *Nat Rev Clin Oncol* 2014 Jan;11(1):12-23

NGS studies in DLBCL

- Somatic mutations common in both DLBCL subtypes are
- Mutations of *TP53*
- genes involved in immunosurveillance (*B2M*, *CD58*),
- alterations in epigenetic regulators (*CREBBP/EP300*, *KMT2D/C* [*MLL2/3*], *MEF2B*)
- oncogenic activation of *BCL6*.

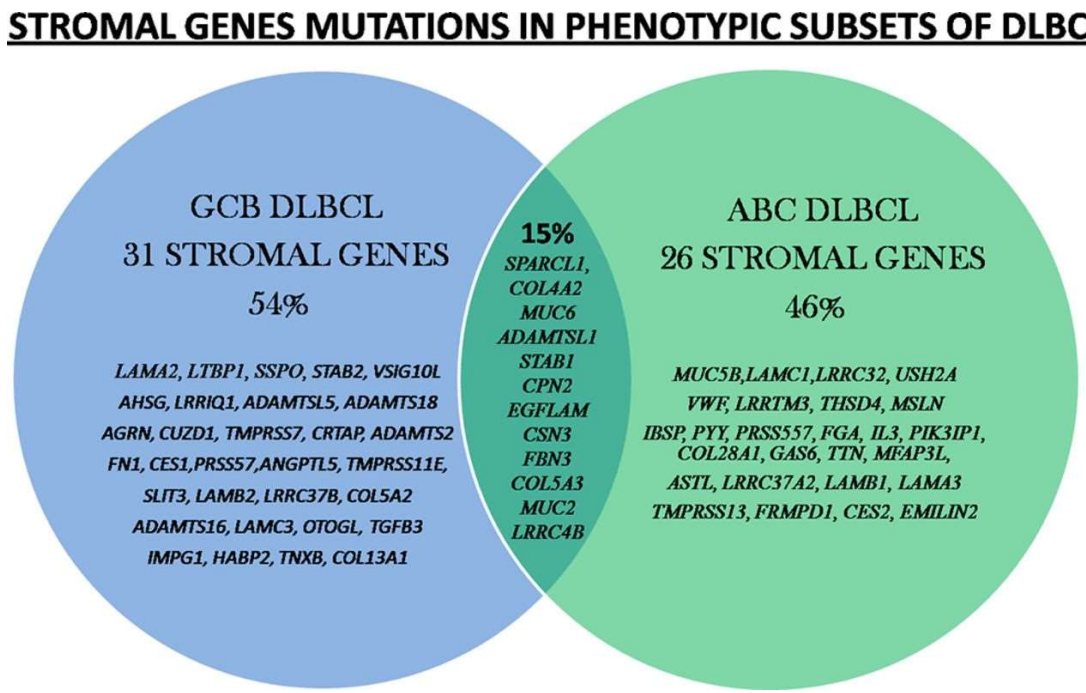
GCB-DLBCL

- alteration in the histone methyl transferase *EZH2*, *BCL2* translocations, and mutations in the cell motility regulator *GNA13*,

ABC-DLBCL have

- mutations in genes (*MYD88*, *CD79A*, *CARD11*, *TNFAIP3*) activating the B-cell receptor/Toll-like receptor and NF-κB pathways.

Mutational Spectrum of Stromal Genes By Whole Exome Sequencing and Stromal-Cellular Interaction in Diffuse Large B-Cell Lymphoma



Vaishali Aggarwal,Radhika Srinivasan, MD PhD,Amanjit Bal, MD,Pankaj Malhotra, MD MBBS,Gaurav Prakash, MD DM,Subhash Varma, MBBS, MD,Ashim Das, MD, Mutational Spectrum of Stromal Genes By Whole Exome Sequencing and Stromal-Cellular Interaction in Diffuse Large B-Cell Lymphoma, Blood, 2015, Figure 1.

Deep sequencing — Deep sequencing of DLBCL genomic DNA has confirmed that heterogeneity in DLBCL extends to the tumor cell genome. Studies that included nearly 2000 cases of DLBCL identified driver mutations that may identify genetically distinct subtypes of GCB and non-GCB DLBCL, with different clinical outcomes following standard therapy.

Cell-free plasma DNA — Circulating cell-free DNA can be quantified in plasma by next-generation sequencing of IgH gene segments derived from DLBCL. In initial studies, tumor DNA load was reported to correlate with imaging-based tumor stage and to be a sensitive predictor of disease relapse or response to therapy

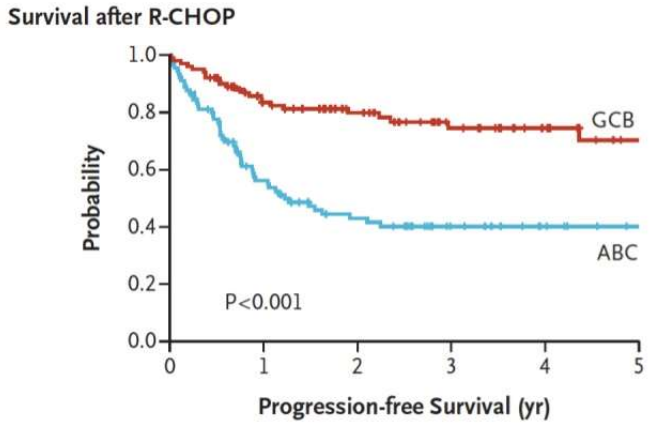
Germinal center B cell type (GCB) –

- GEP that resembles a normal germinal center B cell.
- demonstrate t(14;18) translocations in approximately 30 to 40 percent of cases
- have a superior rate of five-year survival with standard R-CHOP therapy.

Activated B cell type (ABC) –

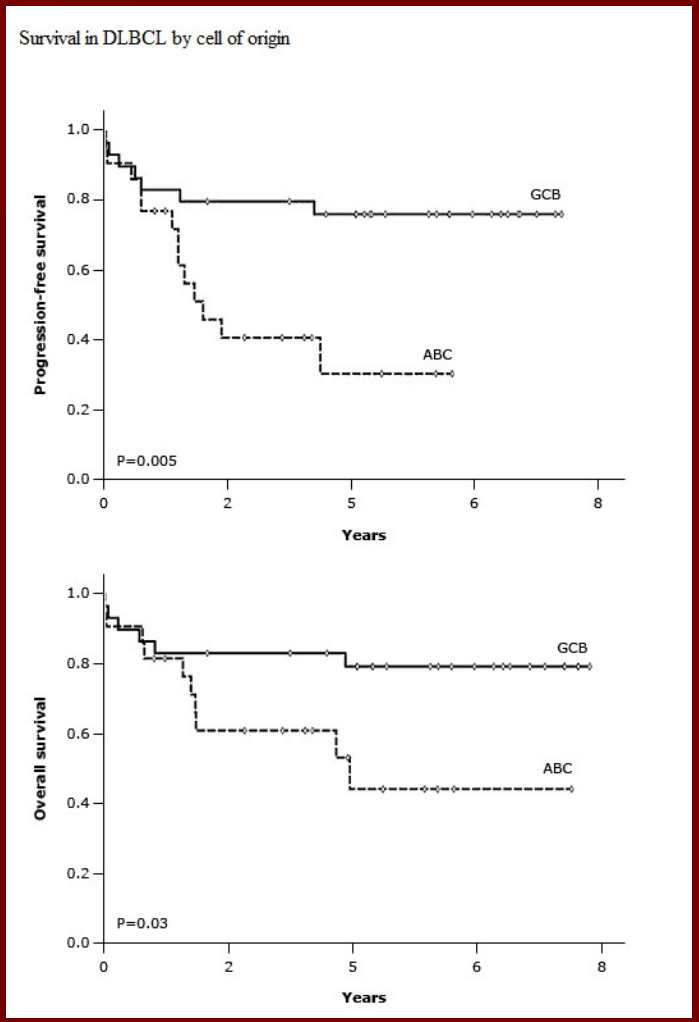
- GEP that resembles an activated B cell.
- frequently demonstrate trisomy 3, deletion of CDKN2A, which encodes INK4A/ARF, and constitutive activation of the anti-apoptotic nuclear factor kappa B (NF-kB) pathway,
- rarely have t(14;18) translocations.
- ABC tumors are associated with inferior rates of five-year survival following standard R-CHOP.
- They may respond to len, ibrutinib, venetoclax and velcade better than GCB subtype

Outcomes by molecular subtype with R-CHOP



DLBCL Subtype	3-Yr Progression-free Survival (%)
GCB	74
ABC	40

Rosenwald and Staudt. N Eng J Medi 2010. 362: 1417



Blood 2011

Table 2. Characteristics of Newly Defined Diffuse Large B-Cell Lymphoma Groups Based on Shared Genetic Aberrancies

Genetic Subtype/Cluster	Genetic Abnormalities	Cell of Origin	5-yr Overall Survival
MCD	*MYD88* L265P mutations *CD79B* mutations	ABC	26%
BN2	*BCL6* fusions *NOTCH2* mutations	ABC, GCB, and unclassified	36%
N1	*NOTCH1* mutations	ABC	65%
EZB	*EZH2* mutations *BCL2* translocations	GCB	68%
Cluster 1	*BCL6* structural variants NOTCH2 signaling	ABC	79%
Cluster 2	Biallelic inactivation of *TP53, 17p* loss	ABC and GCB	62%
Cluster 3	*BCL2, KMT2D, CREBBP, EZH2* mutations	GCB	57%
Cluster 4	BCR/PI3K signaling, NF-kB and RAS/JAK/STAT pathways	GCB	72%
Cluster 5	*18q* gain, *BCL2* and *MALT1* expression	ABC	54%
Cluster 0	No cohesive alterations	NA	100%

ABC = activated B-cell–like; BCR = B-cell receptor; GCB = germinal center B-cell–like; NA = not available; NF-kB = nuclear factor kappa B; PI3K = phosphoinositide 3-kinase.

Rutherford et al, Oncology (Williston Park). 32(9):445-9. 2018

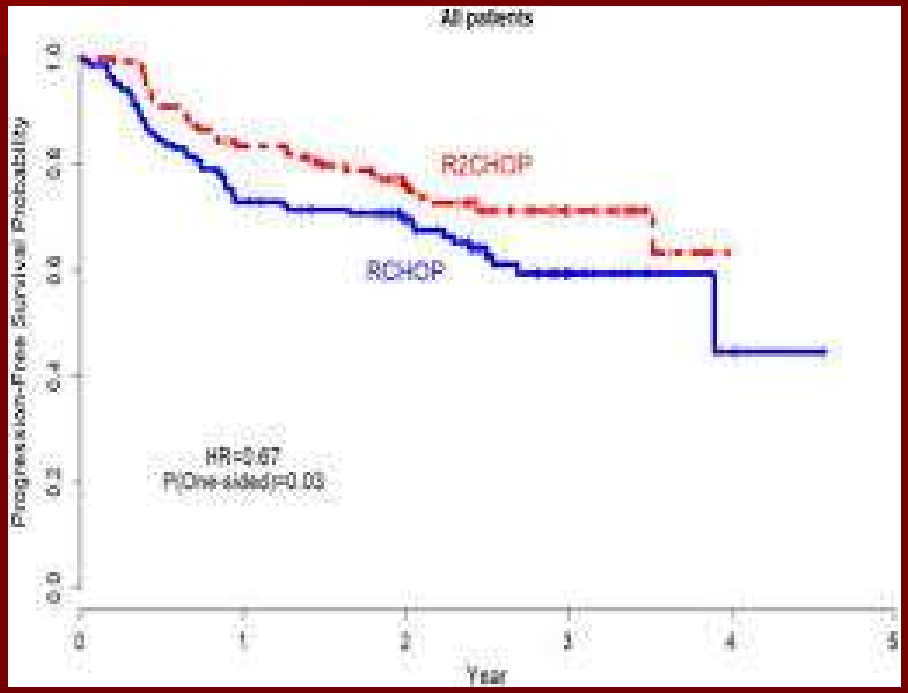
Table 1. Randomized Clinical Trials Incorporating Targeted Treatments in Newly Diagnosed Diffuse Large B-Cell Lymphoma

Study	COO Enrolled	Treatment	N	Results
ECOG 1412 (NCT01856192)	GCB and non-GCB	R-CHOP vs R-CHOP-lenalidomide	NA	Positive trial
LYM2034[25]	Non-GCB	R-CHOP vs R-CAP-bortezomib	164	CR rate: 66.2% vs 64.4% 2-yr PFS rate: 77.1% vs 76.2%
PHOENIX (NCT01855750)	Non-GCB	R-CHOP vs R-CHOP-ibrutinib	NA	Positive trial?
PYRAMID[24]	Non-GCB	R-CHOP vs R-CHOP-bortezomib	206	CR rate: 49% vs 58% 2-yr PFS rate: 78% vs 82%
REMoDL-B[26]	GCB and non-GCB	R-CHOP vs R-CHOP-bortezomib	1,076	30-mo PFS rate: 70.1% vs 74.3%
ROBUST (NCT02285062)	ABC	R-CHOP vs R-CHOP-lenalidomide	NA	Negative trial

ABC = activated B-cell–like; COO = cell of origin; CR = complete response; ECOG = Eastern Cooperative Oncology Group; GCB = germinal center B-cell–like; NA = not available; PFS = progression-free survival; R-CAP = rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Rutherford et al,Oncology (Williston Park). 32(9):445-9. 2018

ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP



Nowakowski GS, et al Hematol Oncol, 37: 37-38. doi:10.1002/hon.6_2629.

Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non–Germinal Center B-Cell Diffuse Large B-Cell Lymphoma

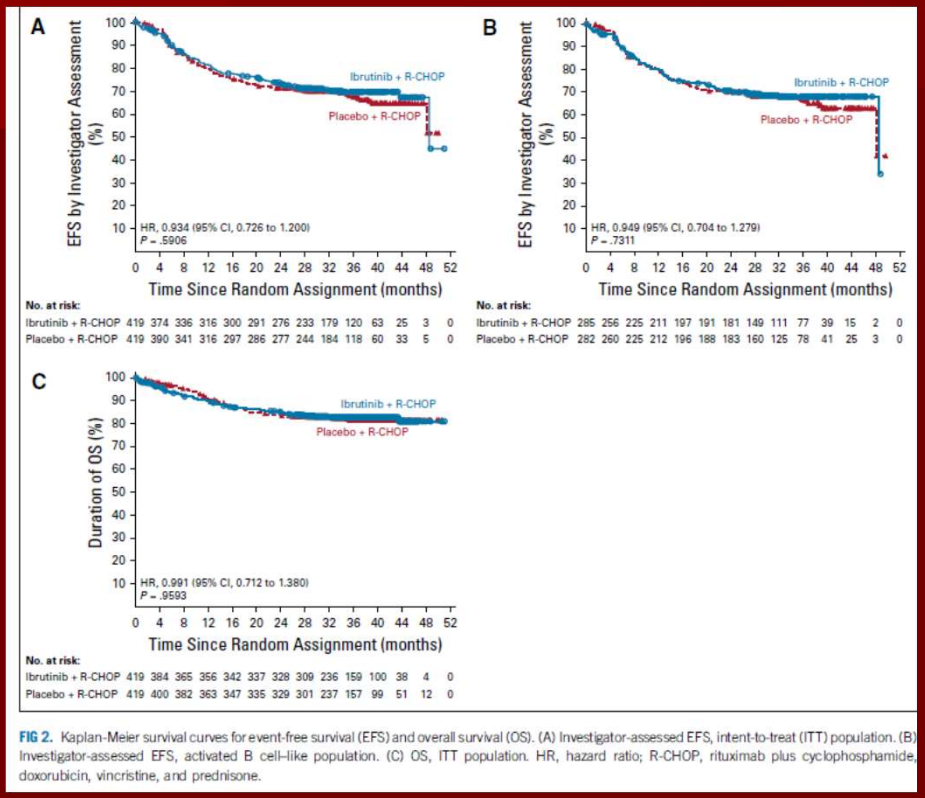
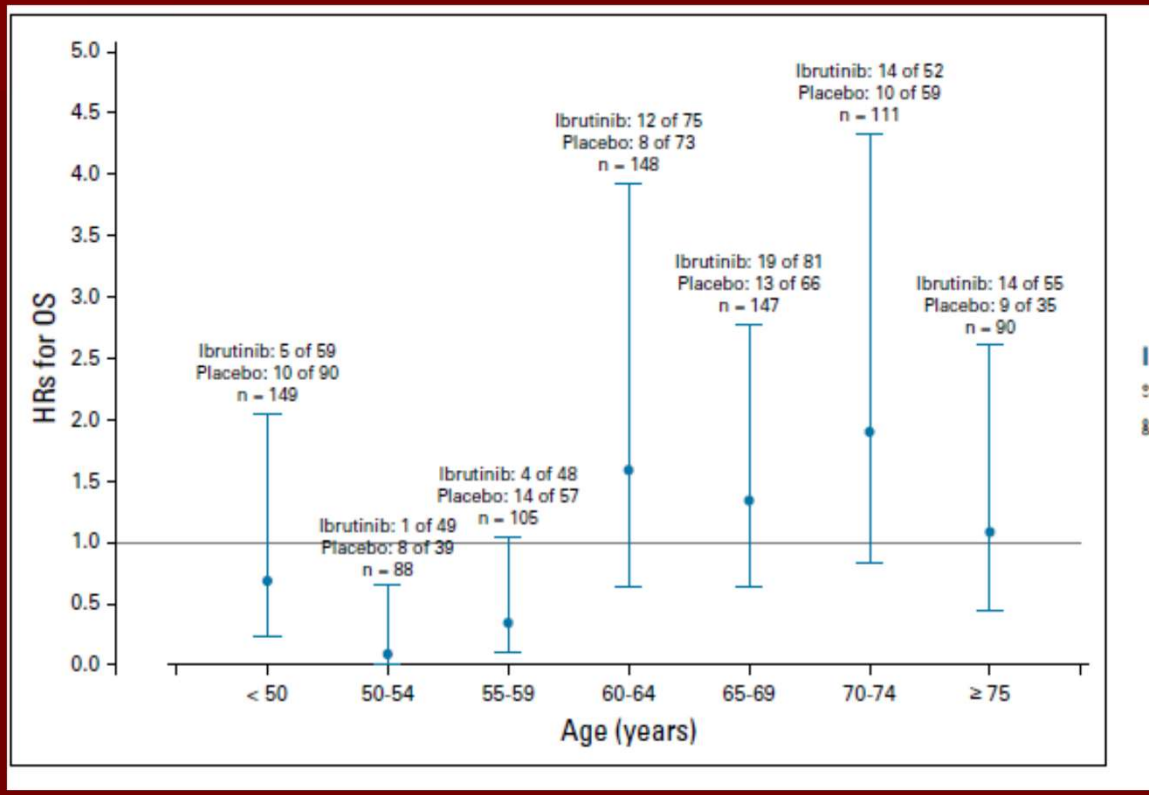


FIG 2. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS). (A) Investigator-assessed EFS, intent-to-treat (ITT) population. (B) Investigator-assessed EFS, activated B cell–like population. (C) OS, ITT population. HR, hazard ratio; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.



Younes et al J Clin Oncol. 2019 May 20; 37(15): 1285–1295.

c-MYC and *BCL2*

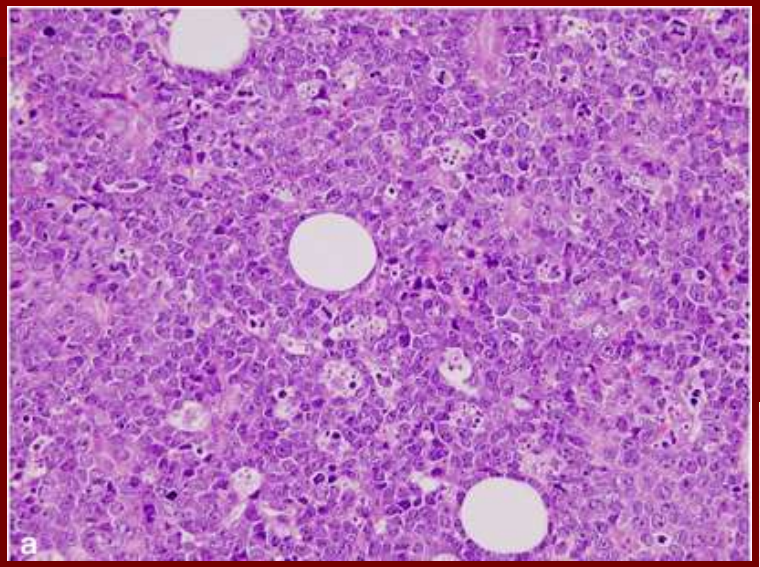
- ***BCL2* gene**
  - Located on chromosome18q21
  - An apoptosis inhibitor
  - Most common- t(14;18)(q32;q21). t(2;18) or t(18;22)
  - t(14;18) is observed in 70-95% of FL and 20-30% of DLBCL

- ***c-MYC* gene**
  - Located on chromosome 8q24
  - An accelerator of cell proliferation
  - Commonly- t(8;14)(q24;q32). t(2;8) or t(8;22)
  - 8q24/*MYC* translocation is detected in 90-95% of BL, 41-80% of BLL, and up to 10% of DLCBL.

High Grade B cell lymphomas: HGBCL

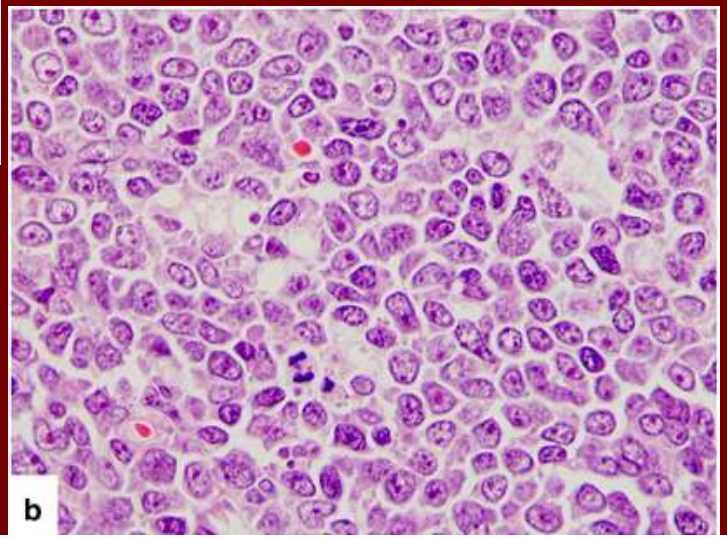
- All LBCL with MYC and BCL2 and/or BCL6 rearrangements will be included in a single category to be designated HGBL, with MYC and BCL2 and/or BCL6 rearrangements
- High Grade B cell lymphoma, NOS: blastoid or cases intermediate between DLBCL and BL, but which lack a MYC and BCL2 and/or BCL6 rearrangement, will be placed in the category of HGBL, NOS

Morphology



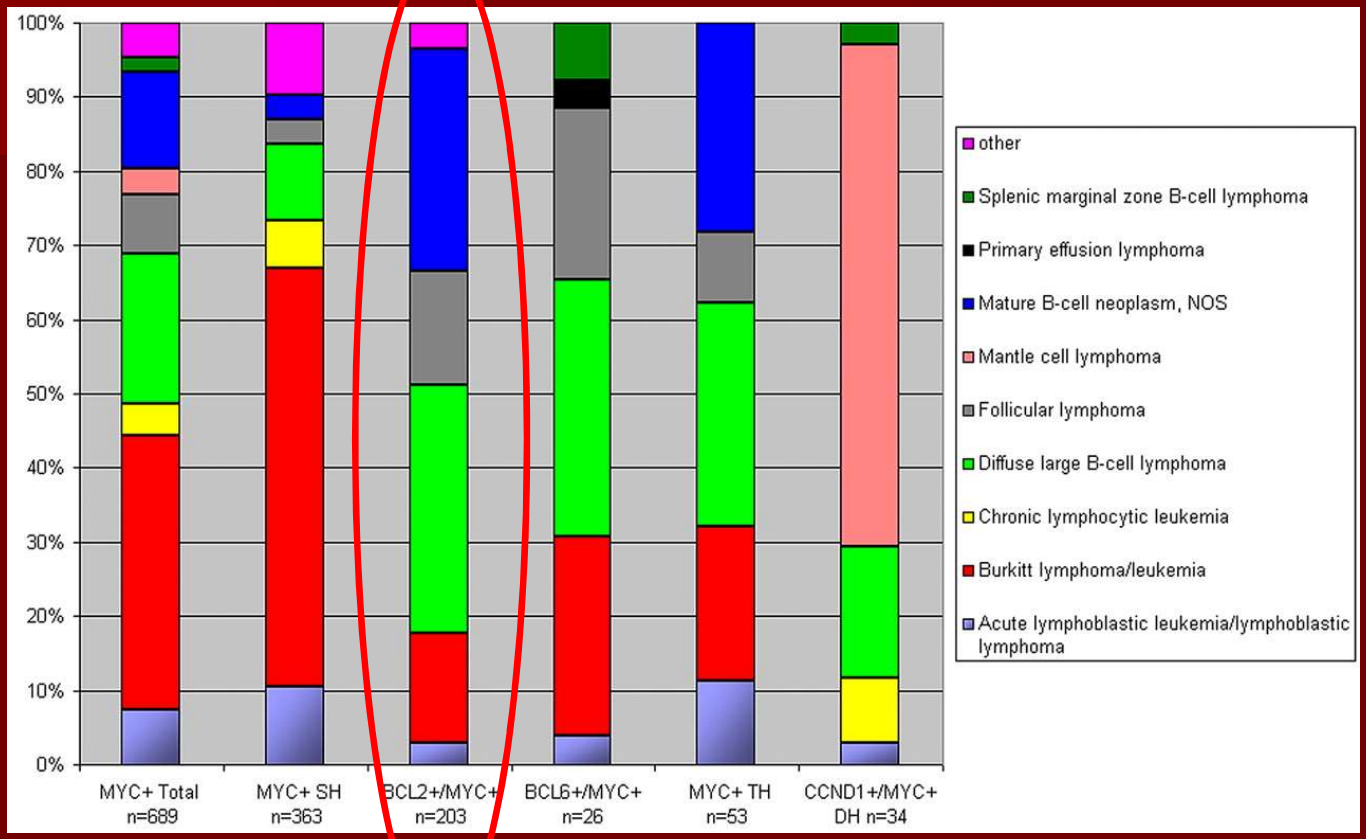
B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma

Diffuse large B cell lymphoma



Li S et al. Modern Pathology 2012;25:145-156.

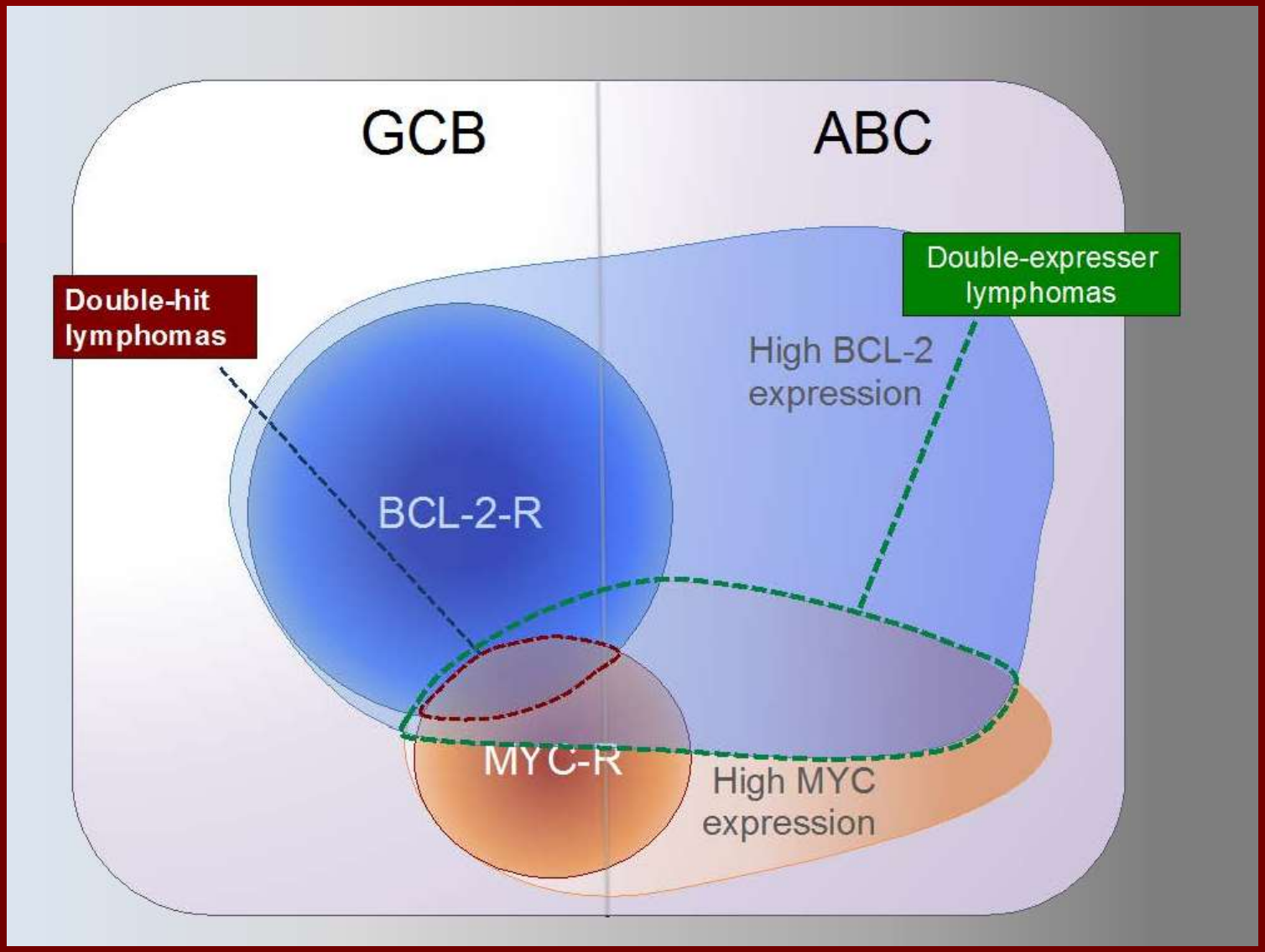
Distribution of morphologies according to breakpoints



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Aukema S M et al. Blood 2011;117:2319-2331

Data from the Mitelman Database of Chromosome Aberrations in Cancer


GCB
ABC
Double-hit lymphomas
Double-expresser lymphomas
High BCL-2 expression
BCL-2-R
MYC-R
High MYC expression

"Double-Expressor" DLBCL

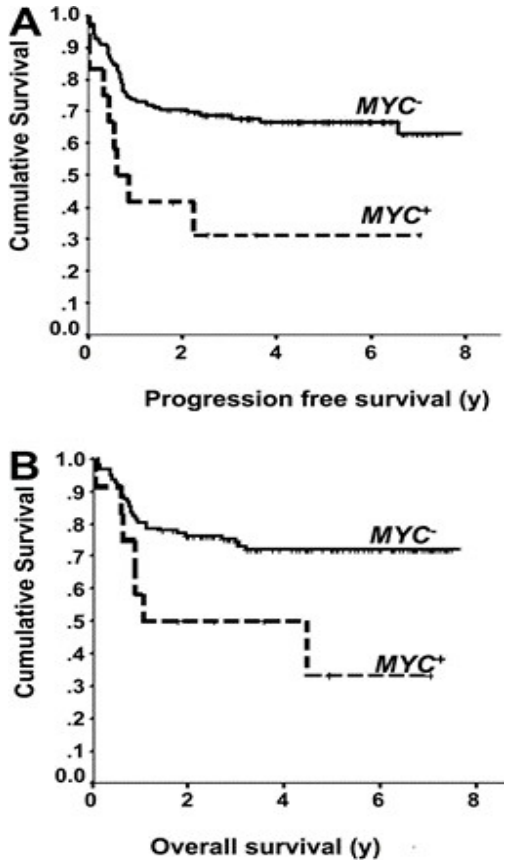
- 30% to 50% of DLBCL demonstrates MYC protein expression.
  - Generally defined as 40% MYC-expressing cells
- Concomitant expression of BCL2 is present within 20% to 35% of DLBCL cases.
  - Generally defined as >50% BCL2-expressing cells
- The WHO now considers the MYC/BCL2 "double expression" as a prognostic indicator in DLBCL, NOS but not as a separate entity.
- Double-expressor lymphomas have a worse outcome than other DLBCL, NOS but do not behave as poorly as High-grade B-cell lymphomas.
  - 5-year OS: 30% in double expressors and 70% in DLBCL, NOS
  - 5-year PFS: 21% in double expressors and 63% in DLBCL, NOS

Swerdlow SH, et al. Blood. 2016. Johnson NA, et al. Journal of Clinical Oncology. 2012.

Dobule Hit Lymphomas

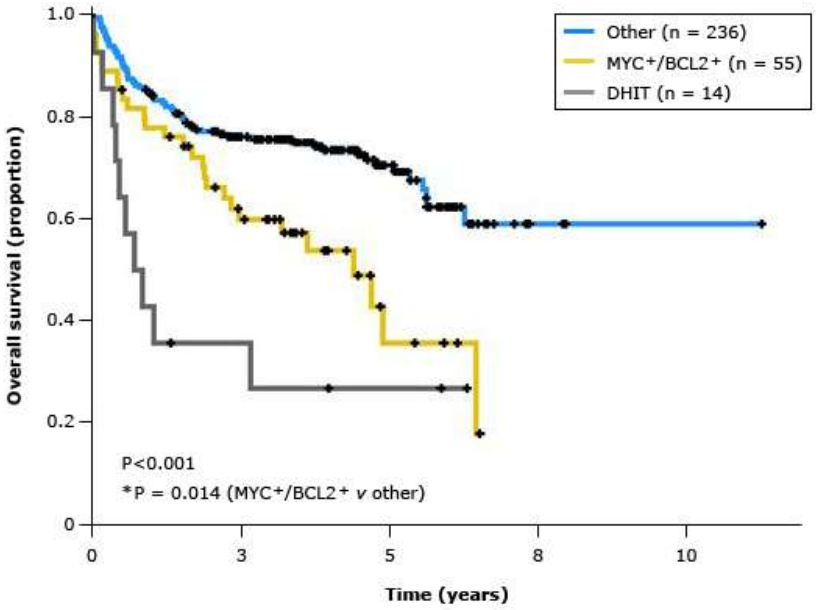
- 95% with DLBCL or high grade histology
  - Formerly classified as unclassifiable
  - Reclassified as HGBL-NOS
  - Can follow transformation from indolent
  - Rarely lymphoblastic leukemia/lymphoma
- 90% HGBL-DH present with high risk features
  - Leukocytosis
  - CNS disease
  - LDH 3x ULN

MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy



Kerry J. et al, MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy, Blood, 2009,

Survival in double hit and double expressor diffuse large B cell lymphoma



Overall survival in 307 patients with diffuse large B cell lymphoma according to molecular subtype. Double hit lymphoma (DHIT) were those that had translocations of MYC and BCL2. The MYC+/BCL2+ lymphoma subgroup included those that expressed both MYC and BCL2 on immunohistochemistry and excluded those meeting the requirements for DHIT. Four DHIT patient cases had no MYC protein expression; one had a missing value for BCL2 protein expression.

From: Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012; 30(28):3452-9. Reprinted with permission.

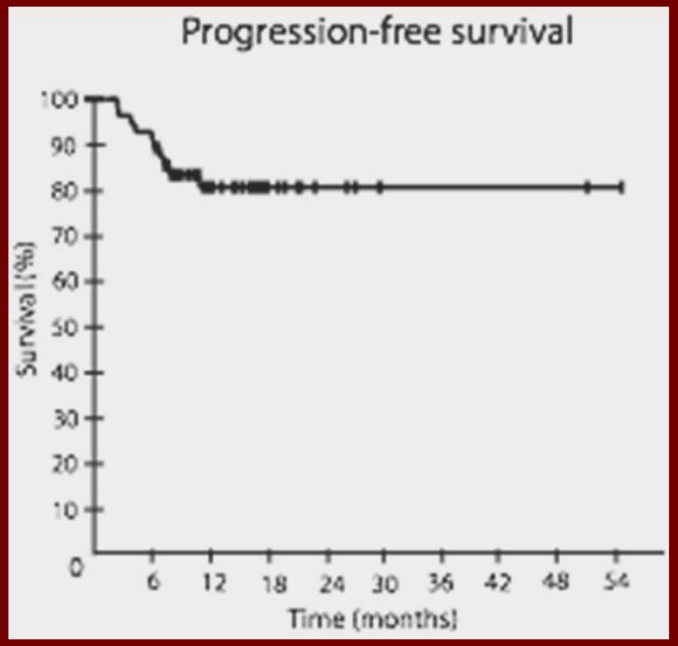
What is the best therapy

Rational therapy for DE DLBCL

- Outcomes after R-CHOP are generally poor
- Median age a bit older making escalation hard
- Da- R-EPOCH?
  - In a small NCI study DE-DLBCL not inferior
  - NCTN 50303 (R-CHOP v R-EPOCH) will be analyzed
  - CNS ppx is reccommended
- Novel potential targets:
  - NFkB given enriched for ABC type. (R^2 CHOP)
  - BCL-2 antagonists (venetoclax + chemo backbone)

DA-EPOCH-R in MYC-Rearranged Aggressive B-Cell Lymphoma

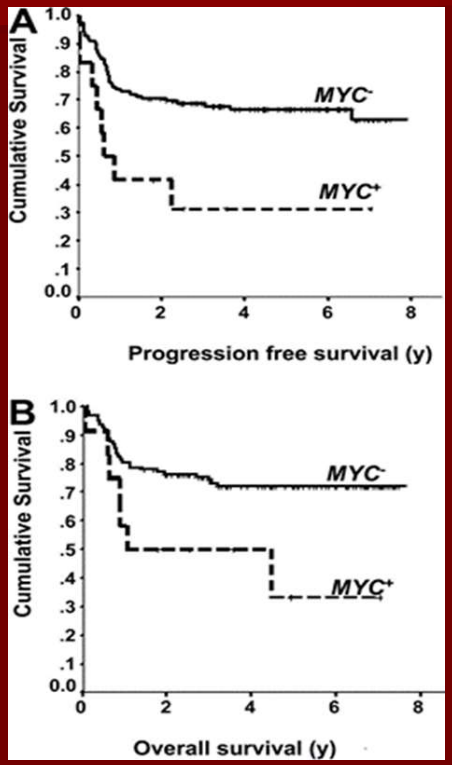
- Prospective multicenter study DA-EPOCH-R x
  N= 52
- DLBCL (86%), BCL-U (14%)
- MYC-R (100%), BCL2 (45%)



- Median f/u 14 months,
  PFS = 79%
- MYC/BLC2 + (double hit)
  PFS = 87%

Dunleavy et al Ab # 395, ASH 2014

Dose-adjusted EPOCH-R in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: A prospective, multicentre, single-arm phase 2 study



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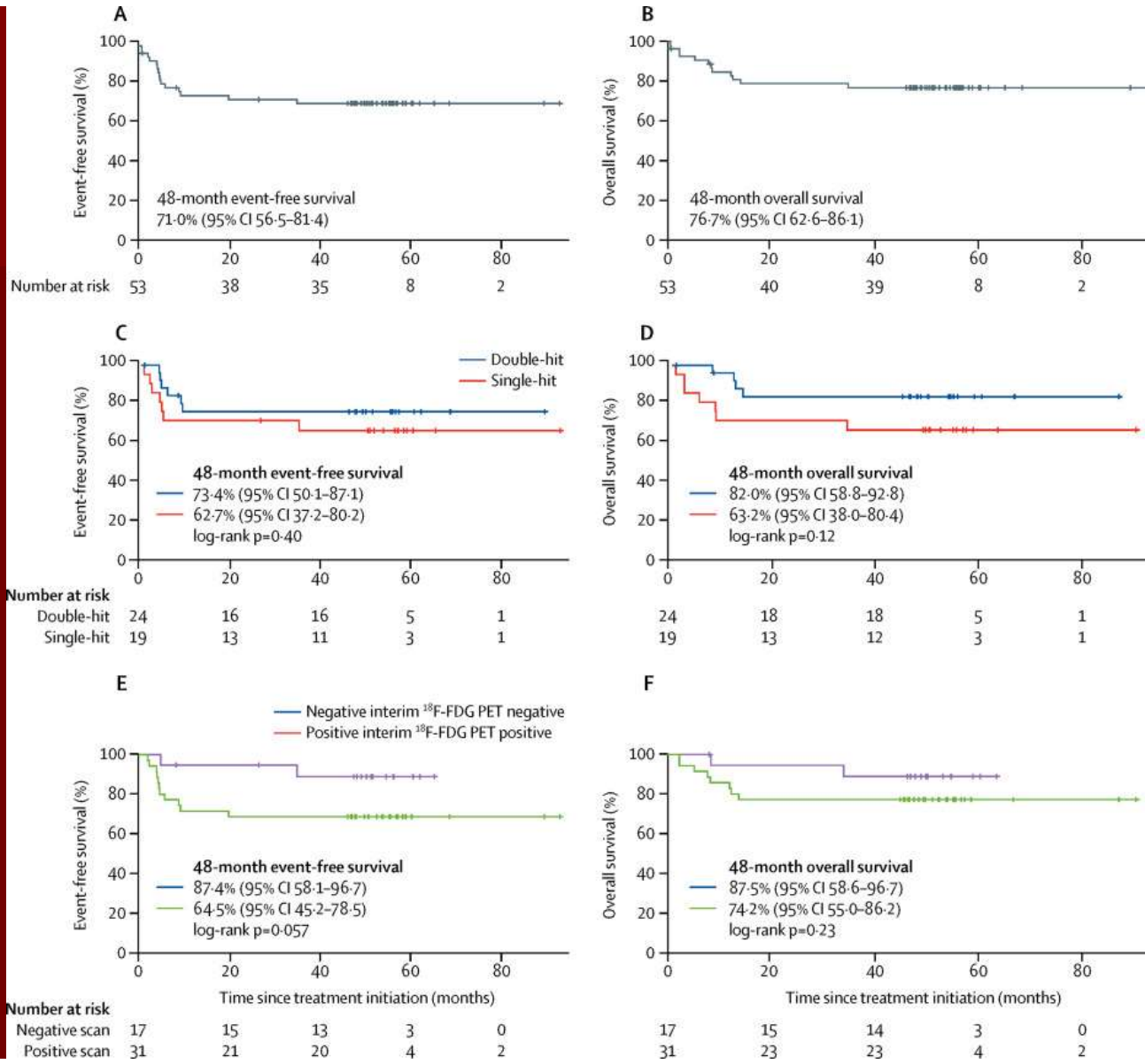
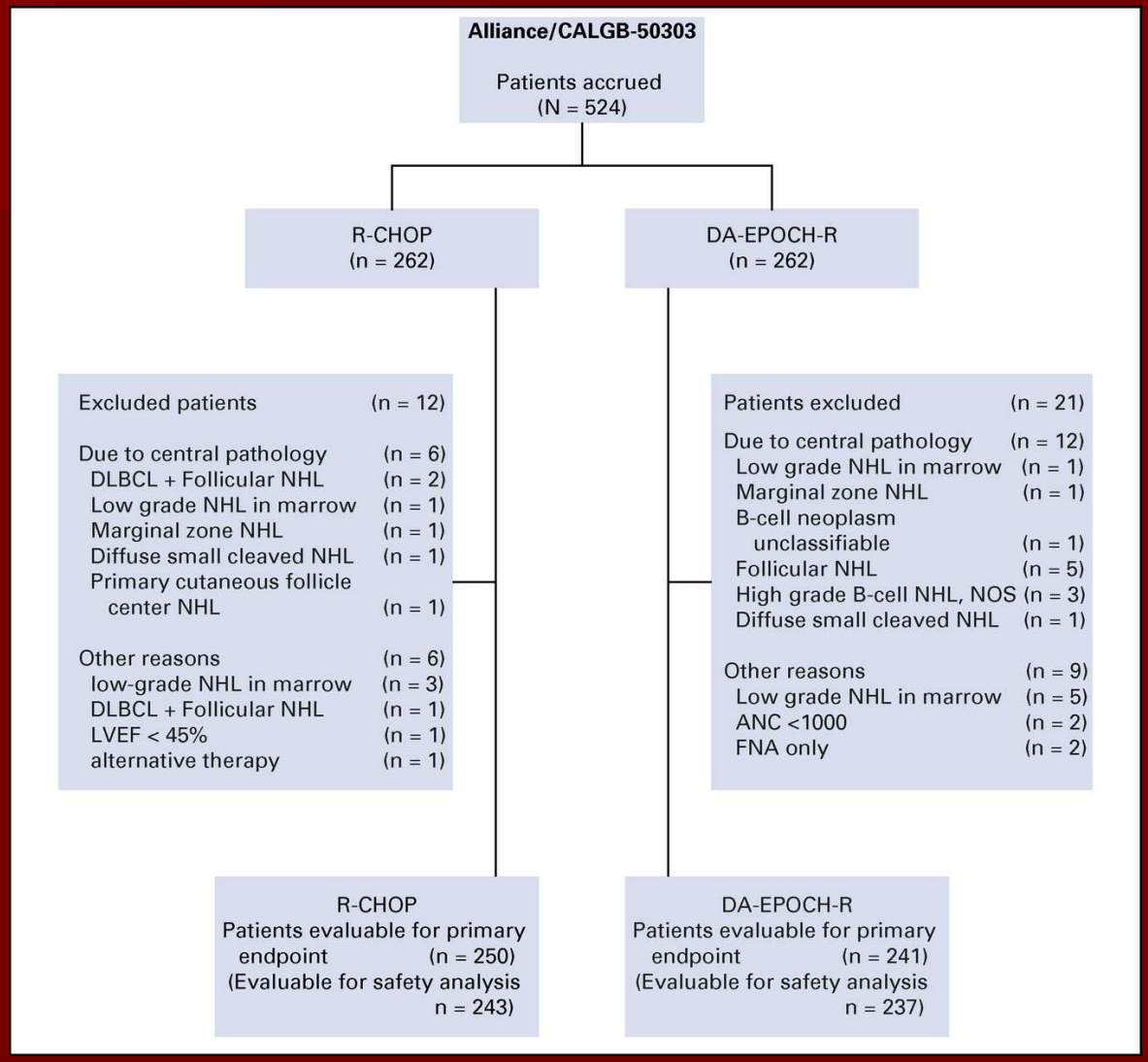
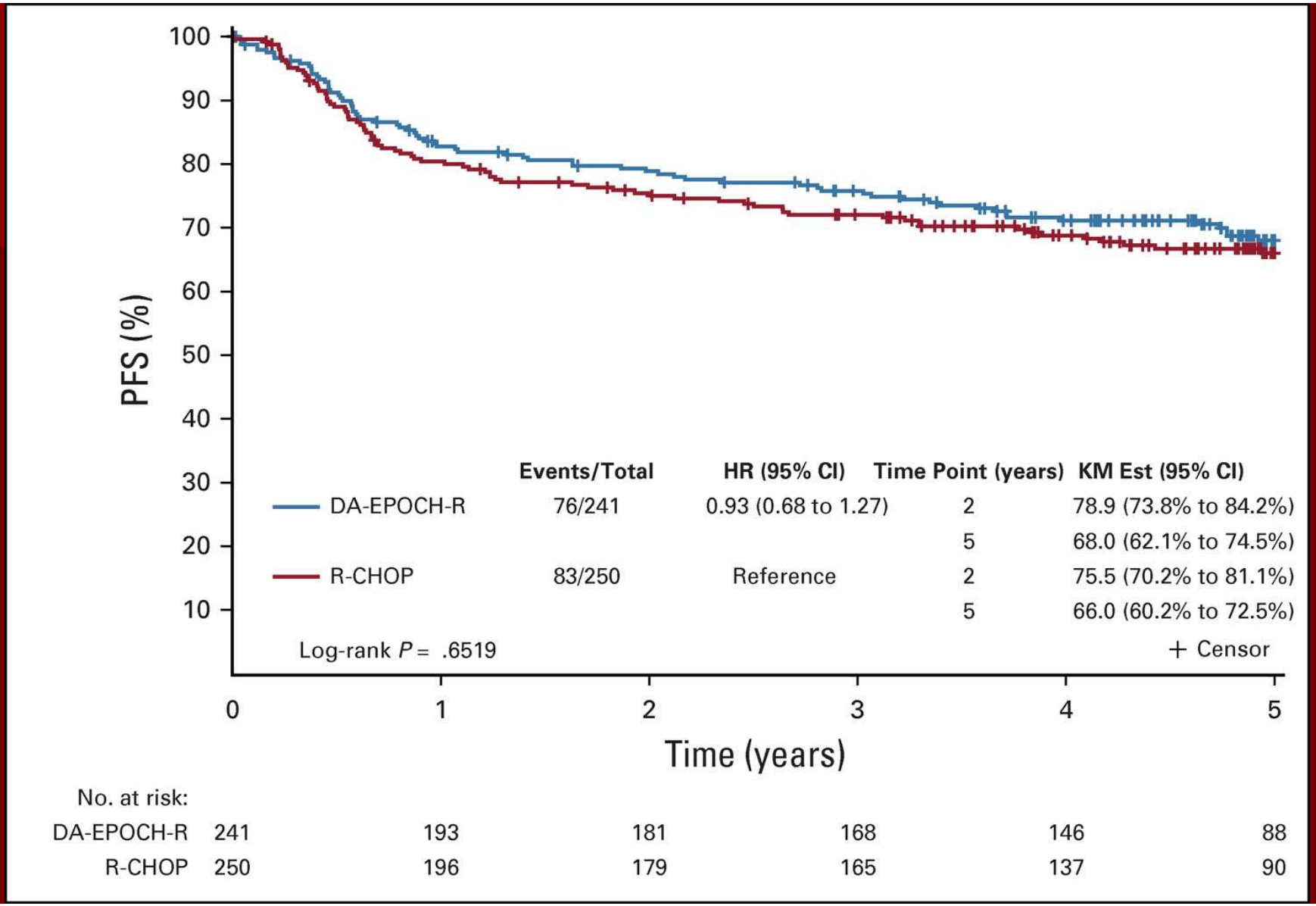
Haematology
Volume 5, Issue 12, December 2018, Pages e609-e617



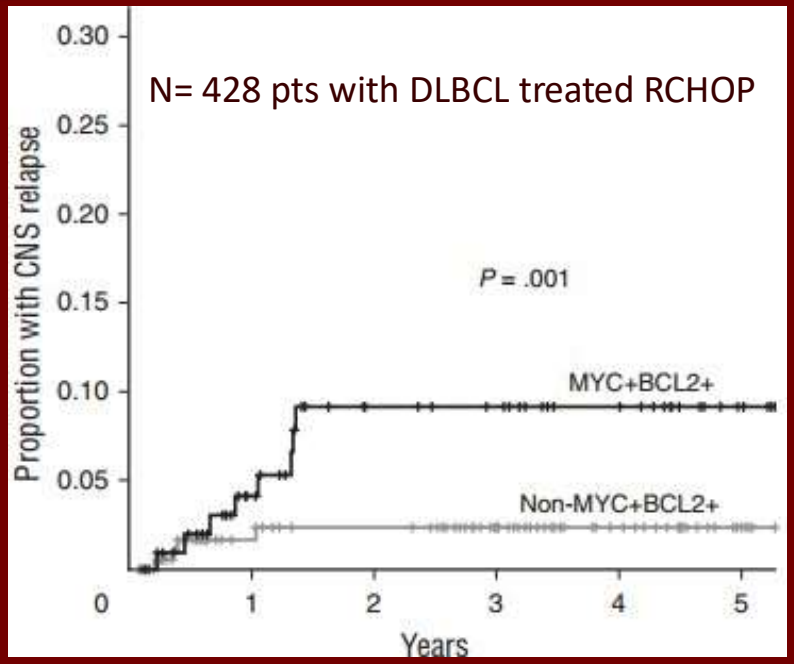
CALGB, Cancer and Leukemia Group B; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma;.

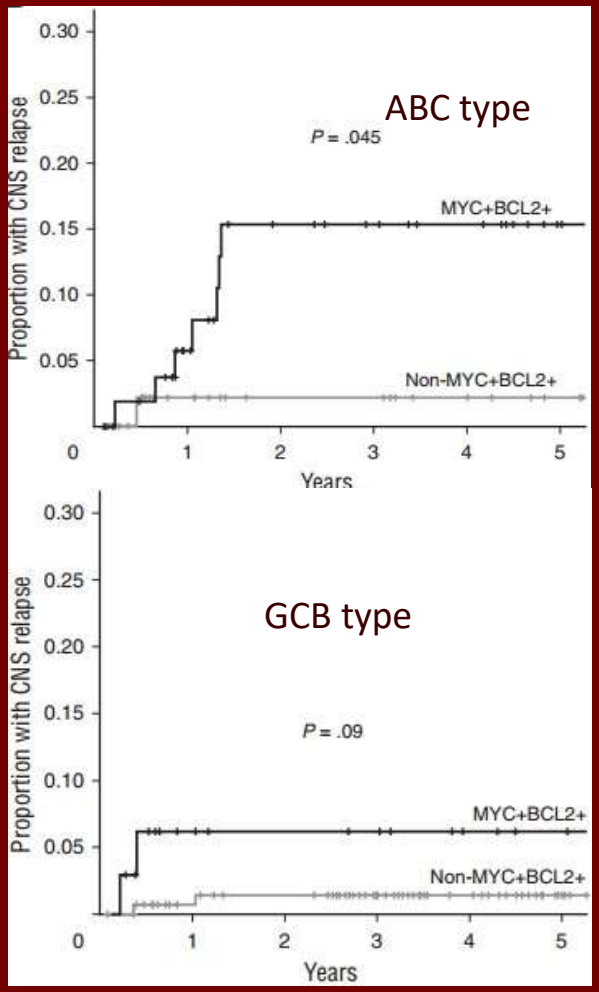


Bartlett et al; *Journal of Clinical Oncology* 2019 371790-1799.


100
90
80
70
60
50
40
30
20
10
PFS (%)
Events/Total
HR (95% CI)
Time Point (years)
KM Est (95% CI)
DA-EPOCH-R
76/241
0.93 (0.68 to 1.27)
2
78.9 (73.8% to 84.2%)
5
68.0 (62.1% to 74.5%)
R-CHOP
83/250
Reference
2
75.5 (70.2% to 81.1%)
5
66.0 (60.2% to 72.5%)
Log-rank P = .6519
+ Censor
0
1
2
3
4
5
Time (years)
No. at risk:
DA-EPOCH-R 241 193 181 168 146 88
R-CHOP 250 196 179 165 137 90

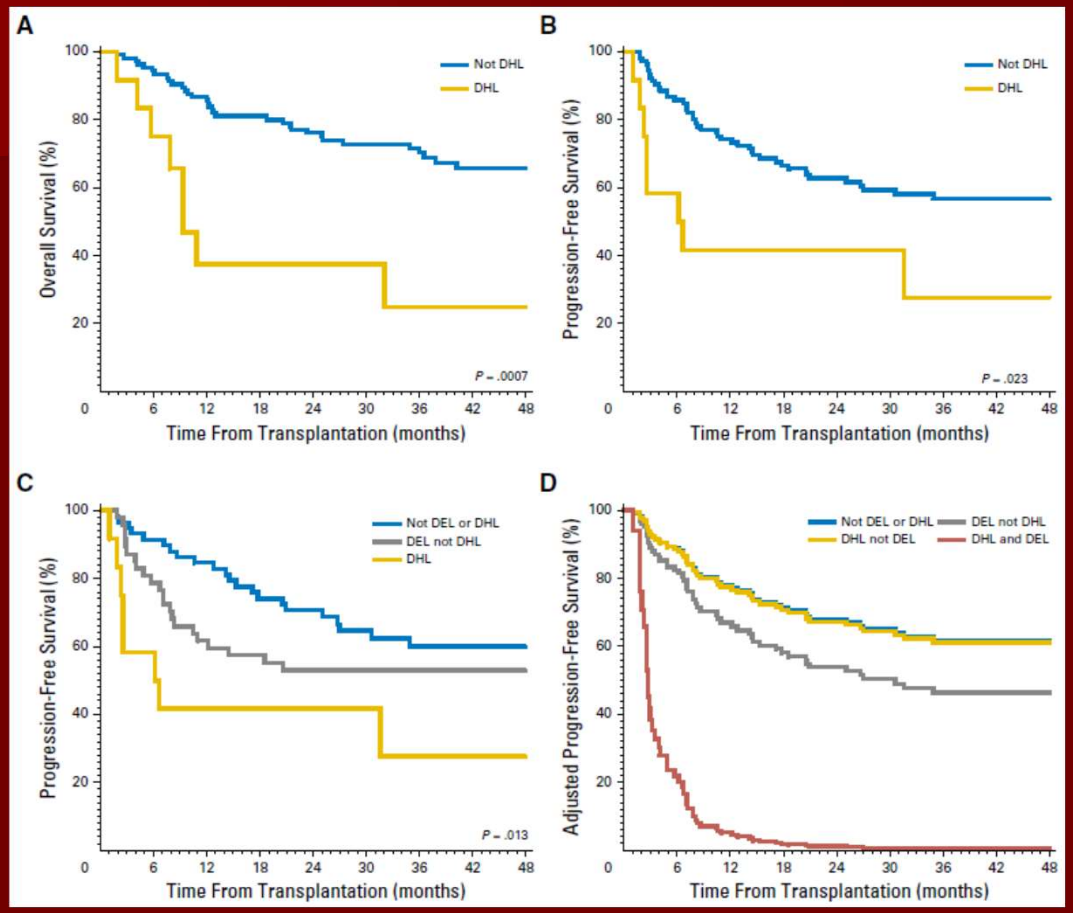
CNS Relapse Risk in DE-DLBCL





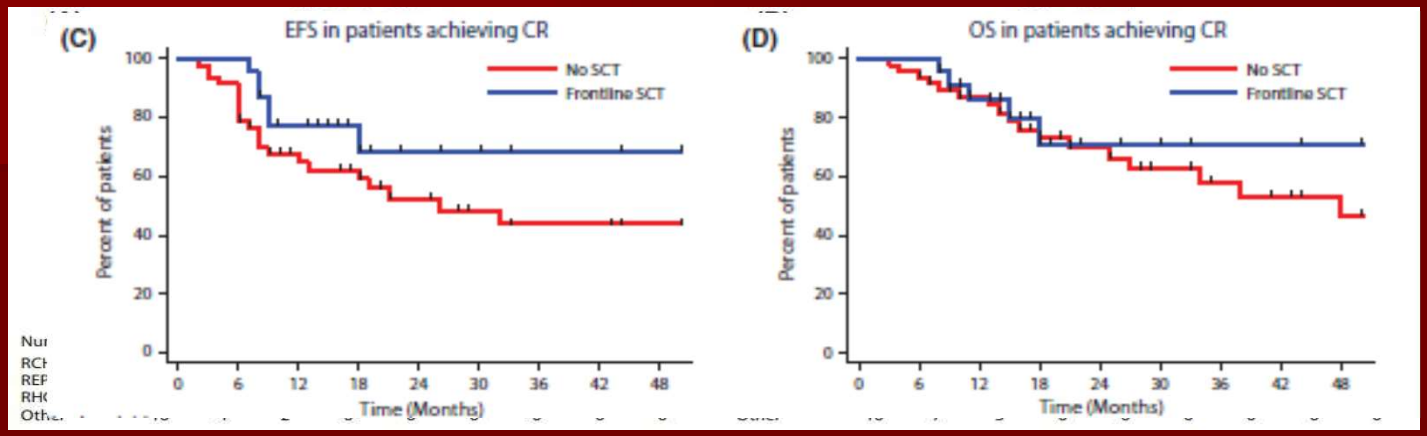
Savage et al. BLOOD 2016; 127

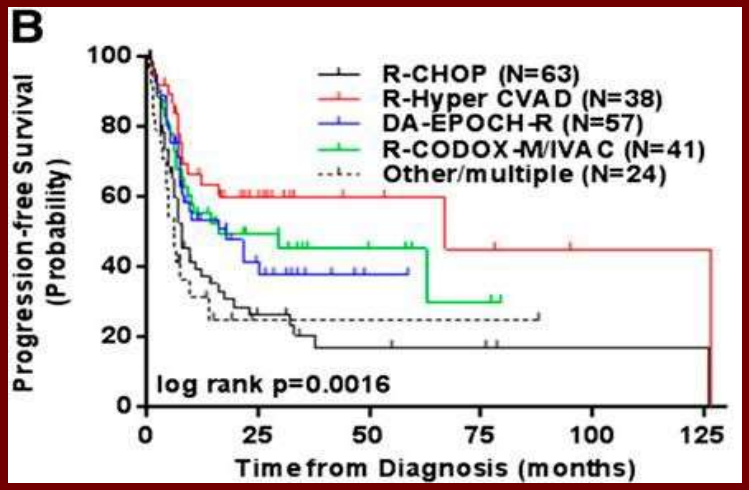
Relapsed DEL/DHL and AutoPSCT

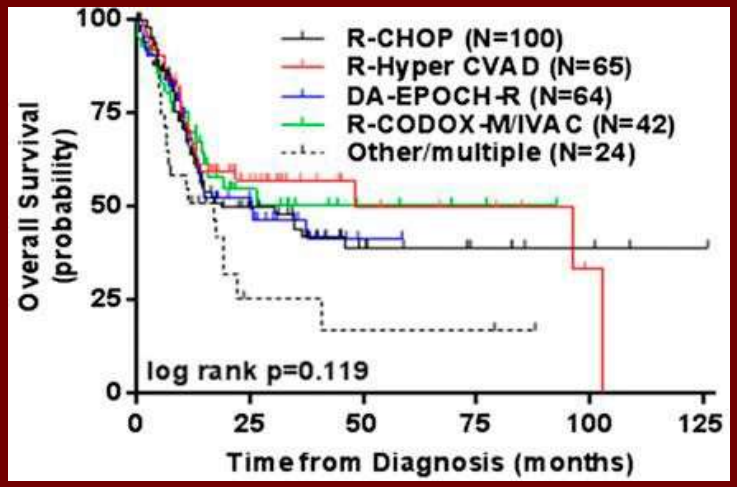


Herrera et al J Clin Oncol 2016

Rational Therapy for DH DLBCL

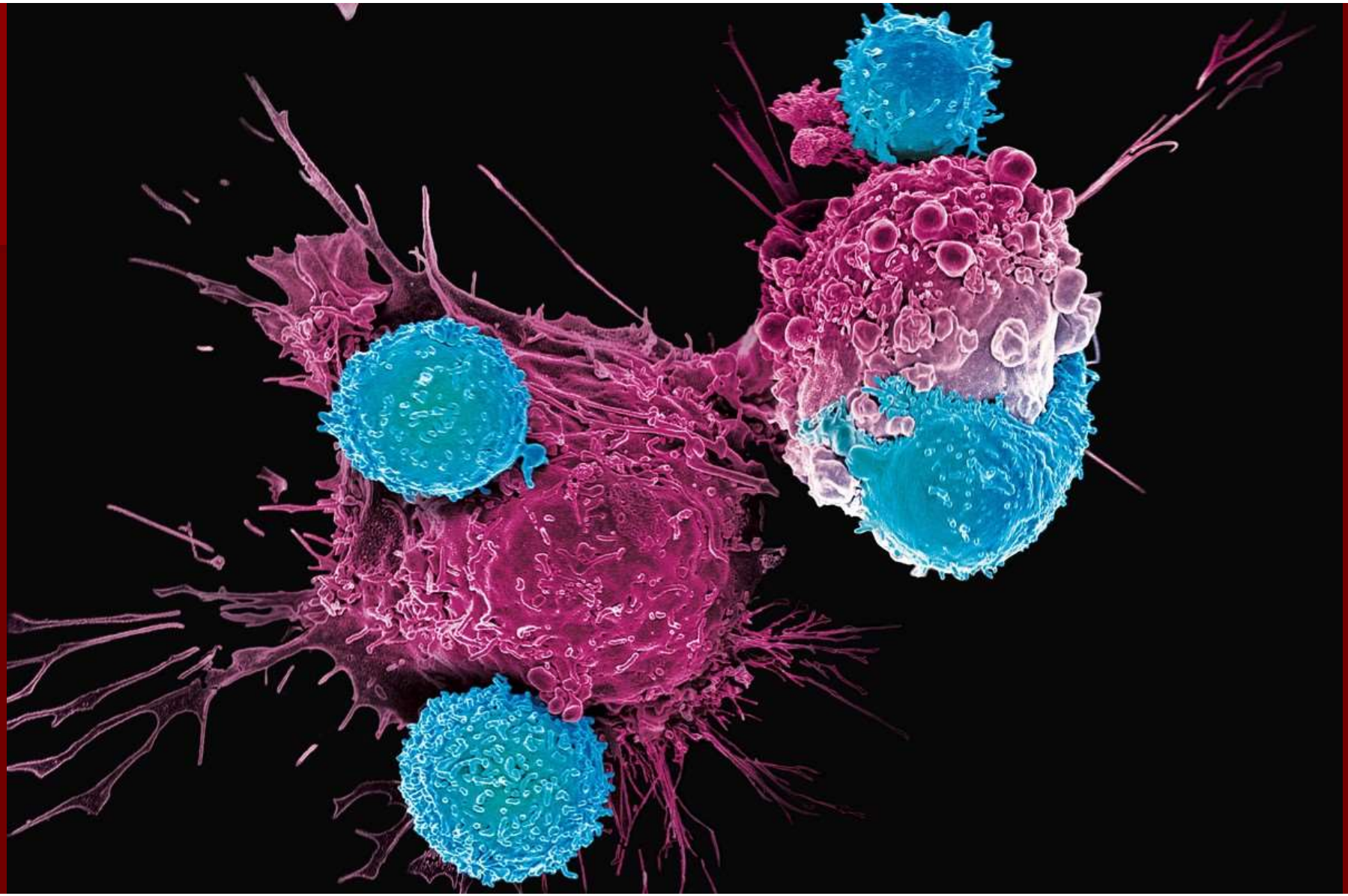






Oki et al Br J. Haem 2014

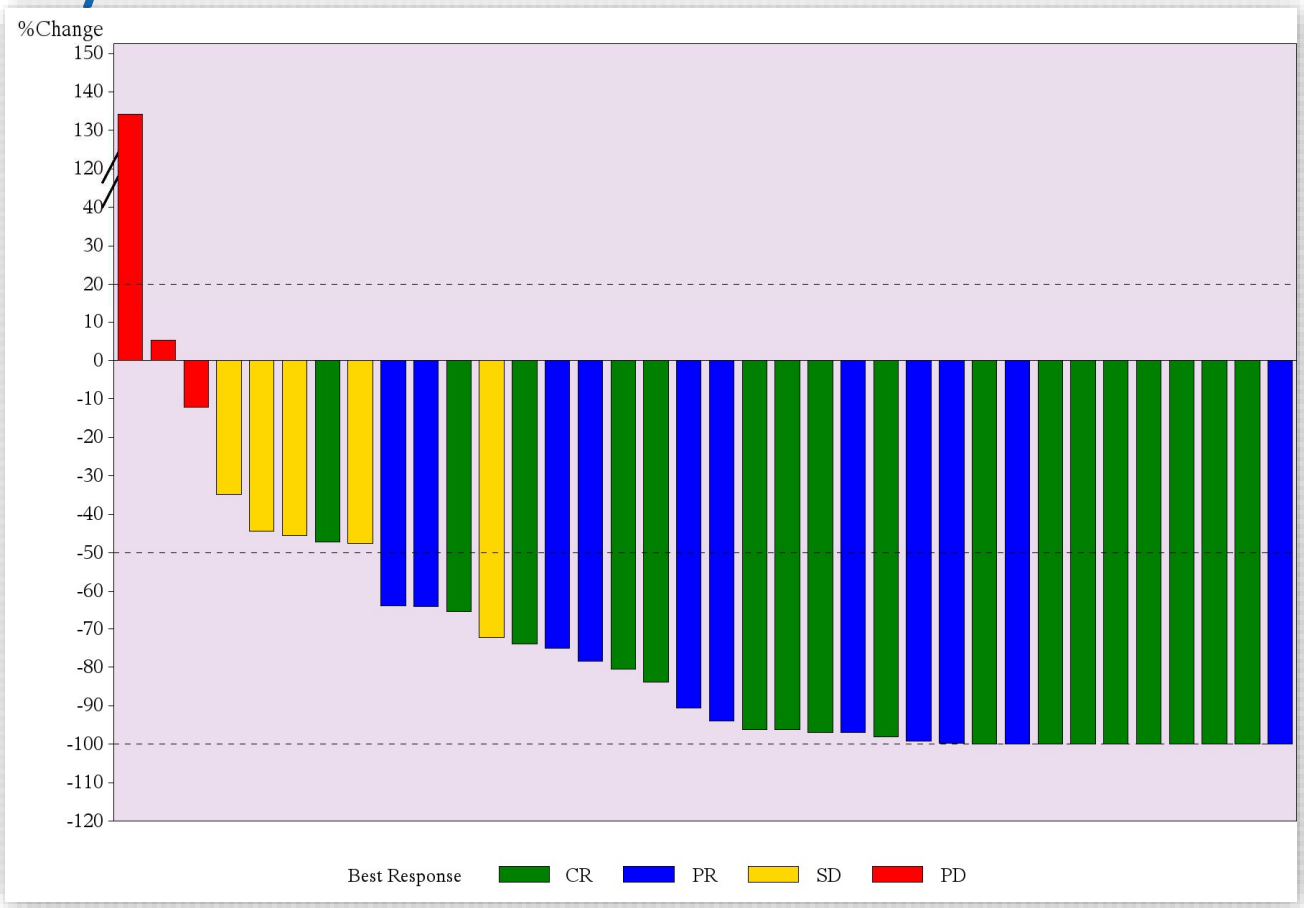
Petrich et al BLOOD 2014



Commonly used CAR T cells for lymphomas

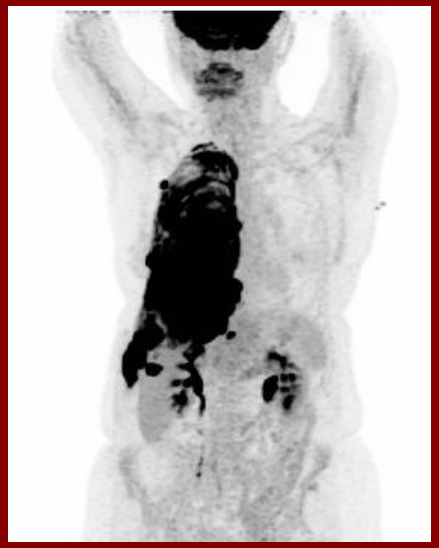
Company		Juno		Novartis		Gilead	
Product		JCAR017		KYMRIAH Tisagenlecleucel		YESCARTA Axicabtagene ciloleucel	
US Status		P1-2		BLA Filed		Approved	
Trial		Transcend		Juliet		ZUMA-1	
Efficacy	Follow-Up	3 Mon	6 Mon	3 Mon	6 Mon	3 Mon	6 Mon
	Patients	N=19	N=14	N=81		N=101	
	Objective Response Rate (ORR)	74%	50%	38%	37%	54%	41%
	Complete Response (CR)	68%	50%	32%	30%	36%	36%
Safety	Patients	N=67		N=81		N=101	
	Cytokine Release Syndrome (CRS)	1% Severe 40% Any		23% Severe 58% Any		13% Severe 94% Any	
	Neurotoxicity	15% Severe 21% Any		12% Severe 58% Any		31% Severe 84% Any	

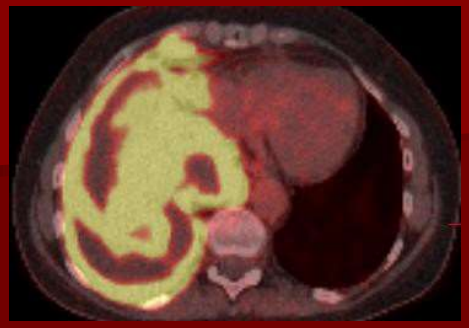
Depth of Best Response in NCI B Cell Lymphoma Study



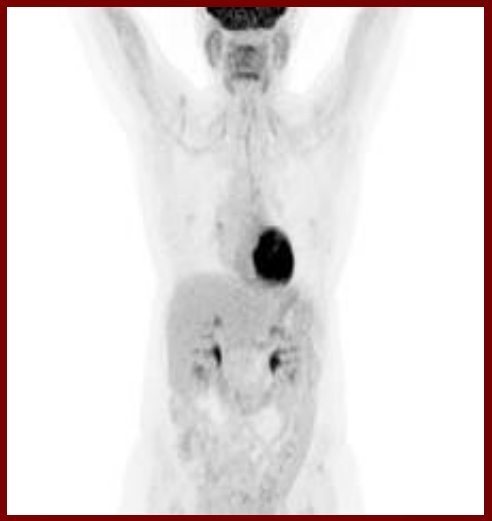
Response in Patient with Refractory DLBCL

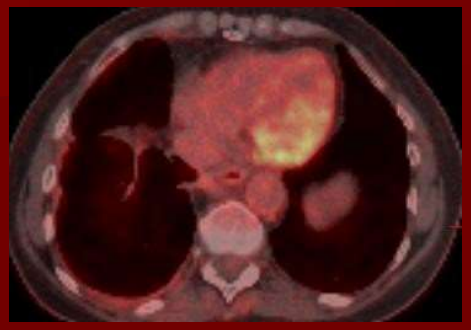
Before treatment





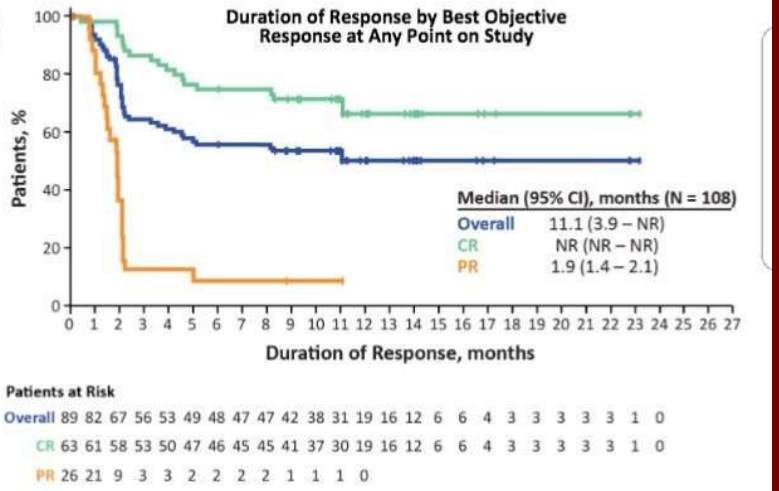
6 months after treatment





ZUMA-1 Long-Term Follow-Up

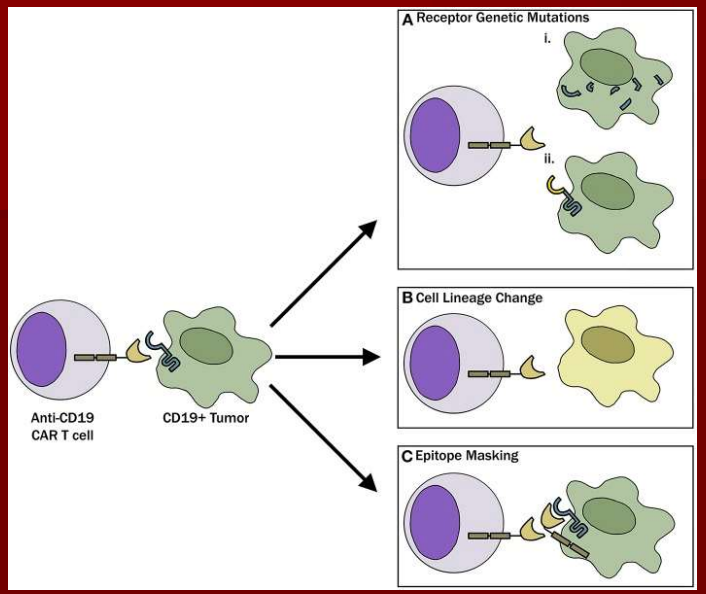
- Long-term follow-up (median 15.4 mo) of both Phase 1 and 2 (N = 108) demonstrated[1]:
  - ORR = 82%; CR rate = 58%
    - Ongoing responses in 42% (40% CRs)
  - Median OS = not reached
- 12% Grade ≥ 3 CRS; 31% Grade ≥ 3 neurologic events

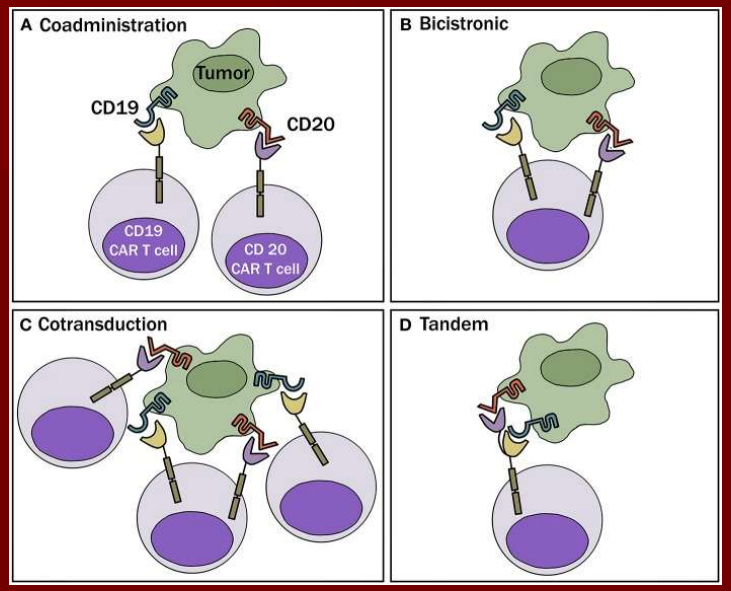


CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response.

1. From Neelapu SS and Locke FL, et al. *N Engl J Med*. 2017;277:2531-2544.

Avoiding Antigen Escape





Early results of phase I CD19/CD20 CAR T cells in DLBCL from Medical College of Wisconcin:

- Fourteen of 17 patients had a response,(11 CR, 3 PR).
- Eleven patients were treated at the target dose of 2.5 x 10^6 cells/kg, 9 had a CR and 1 PR

Shah NN et al. ASCO 2019.

Summary

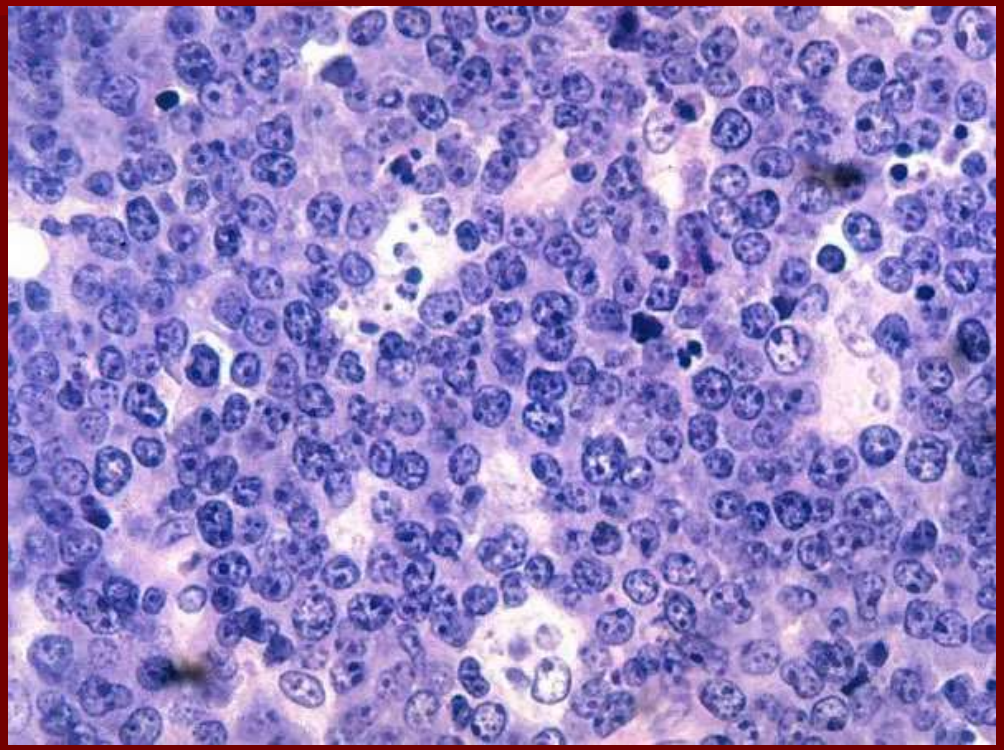
- Double Hit and Double Expressing BCL represent another step toward individualized management strategies.
- DHL is clearest threat but uncommon (~6%)
- DEL probably a threat and more common (25%)
- Diagnostic testing strategies are in transition
- R-CHOP seems unappealing for DEL, but……
- DA-R-EPOCH likely standard for DHL-for now….
  - CNS attention is a high priority.

Histologic Transformation of FL

- Incidence-varies widely
  - 24-70% overall
  - 11-17% at 5yrs, ~30% at 10yrs
  - Generally accepted 2-3%/yr
- Risk factors- unknown
  - Chemotherapy ? No consensus but not thought to increase risk
  - t(14:18) > 90%
  - Myc translocations 8-12%
  - Increased Myc expression **70% of transformed FL**

Casulo C et al Blood, 2015 Yano T, Jaffe E, Blood 1992, Davies A et al BJH 2006

Burkitt Lymphoma



Burkitt Lymphoma Defined

Endemic/Sporadic/Immunodeficiency

- Histologically-monotonous small cleaved cell, with "starry sky" appearance
- Immunephenotypically-CD20/CD10+, CD34/tdt-
- Molecularly- t(8:14)-nearly 70-80%, T(2:8) and t(8:22) 10-15% 10% false - FISH
- -Not Dx t(8:14) also found in BLU (30-50%) and DLCL (5-15%)
- Gene expression profiling Dx of the future "BL signature"

- Mutations in the transcription factor TCF3 or its negative regulator ID3 occur in about 70% of sporadic and immunodeficiency-related BL and 40% of endemic cases.
- TCF3 promotes survival and proliferation in lymphoid cells by activating the B-cell receptor/PI3K signaling pathways and modulating the expression of cyclin D3,which is also mutated in 30% of BL

Burkitt-like lymphoma with 11q aberration

- these lymphomas have more complex karyotypes, lower levels of MYC expression, a certain degree of cytological pleomorphism, occasionally a follicular pattern, and frequently a nodal presentation. The clinical course seems to be similar to BL

Burkitt Lymphoma Defined

- Clinically
  - Median age 45, Bimodal 0-15 and > 60yrs (35%)
  - Children > adults (2X): 1-2% adult 30-40 childhood NHL
  - Rapidly progressive nodal & Extranodal Dz
    - CNS/leptomeningeal/Intestinal/BM
    - Abdomen most common site, H/N 2nd, BM (20%)
    - Endemic: jaw/orbits
  - EBV + in endemic, rare in sporadic, ~40% HIV

Burkitt Lymphoma Treatment

Table II. Results of selected regimens in adult BL series with at least 50 patients.

Study	Group	N	Median age	CR	EFS	OS
Soussain *et al* (1995)	French LMB	65	26	89%	64%	74% (3 years)
Lee *et al* (2001)	CALGB regimen	54	44	80%	42% est.	–
Mead *et al* (2002)	UK/Multinational CODOX-M/IVAC	52	35	77%	65% (2 years)	73% (2 years)
Rizzieri *et al* (2004)	CALGB 9251					
	Cohort I	52	44	79%		54% (3 years)
	Cohort II	40	50	68%		50% (3 years)
Diviné *et al* (2005)	GELA/GOELAMS LMB 89	72	33	72%	65% (2 years)	70% (2 years)
Thomas *et al* (2006)	MDACC					
	Hyper-CVAD					
	Cohort I	48	48	85%	52% (3 years)	53% (3 years)
	Cohort II (+R)	31	46	86%	80% (3 years)	89% (3 years)
Hoelzer *et al* (2007)	GMALL (+R)	115	36	90%		91% (3 years)
Mead *et al* (2008)	UK/Multinational CODOX-M/IVAC	53	37		64% (2 years)	67% (2 years)

CR, complete response; EFS, event-free survival; OS, overall survival; LMB, Lymphome Malins de Burkitt; CALGB, Cancer and Leukemia Group B; GELA, Groupe d' Etude des Lymphomes de l' Adulte; GOELAMS, Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang; MDACC, MD Anderson Cancer Center; GMALL, German Multicentre Study Group for Adult ALL; CODOX-M/IVAC, cyclophosphamide, cytarabine, doxorubicin, leucovorin, methotrexate, vincristine/cytarabine, etoposide, ifosfamide, methotrexate; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, R, rituximab.

Burkitt Lymphoma Treatment-cont

- CODOX-M/IVAC-R*
  - 87% CR, OS 87% at 5 yrs-
- DA-EPOCH-R**
  - 97%CR, OS 100% at 2 yr

* Maruyama et al 2010, ** Dunleavy et al 2011-no pt had BM or CNS involvement

Prognostic Factors

- Age > 40 yr
- High LDH
- CNS
- Advanced stage
- Failure to achieve a CR after 4-6 weeks

Prognostic Factors

- Do they help with treatment decisions ?
  - Data is very weak-small numbers
  - Low risk-CODOX-M
  - High risk CODOX-M/IVAC or Hyper-CVAD/HD MTX/Ara-c
  - Elderly & HIV + consider DA-EPOCH-R (Dunleavy et al 2011, Little et al 2003). Caution using R w/ low CD4 count (<50-100)

Burkitt Lymphoma Relapsed/Refractory

- RICE, RGDP, RIVAC, DA-EPOCH, HIDAC+R
- Chemosensitive relapse
  - AutoPSCT- OS 37% at 3ys*
- Chemoresistent
  - OS 7% at 3yrs*
- CNS + at presentation consider allo PSCT
  - 7/9pts DF at 18mo (med age 21yr)

* Sweetenham et al 2007,

Bottom Line

- Most patients-R-DA-EPOCH
- Infirm/Elderly/HIV-DA-EPOCH-R
- Early stage CODOX-M-R or abbreviated DA-R-EPOCH
- Everyone gets CNS prophylaxis
- High risk consider HyperCVAD
- Relapsed-Consider Auto (or ? Allo)PSCT or a clinical trial
- CAR T cells are working in relapsed/refractory Burkitt L