Diagnosis and Management of High Grade B-cell Lymphomas

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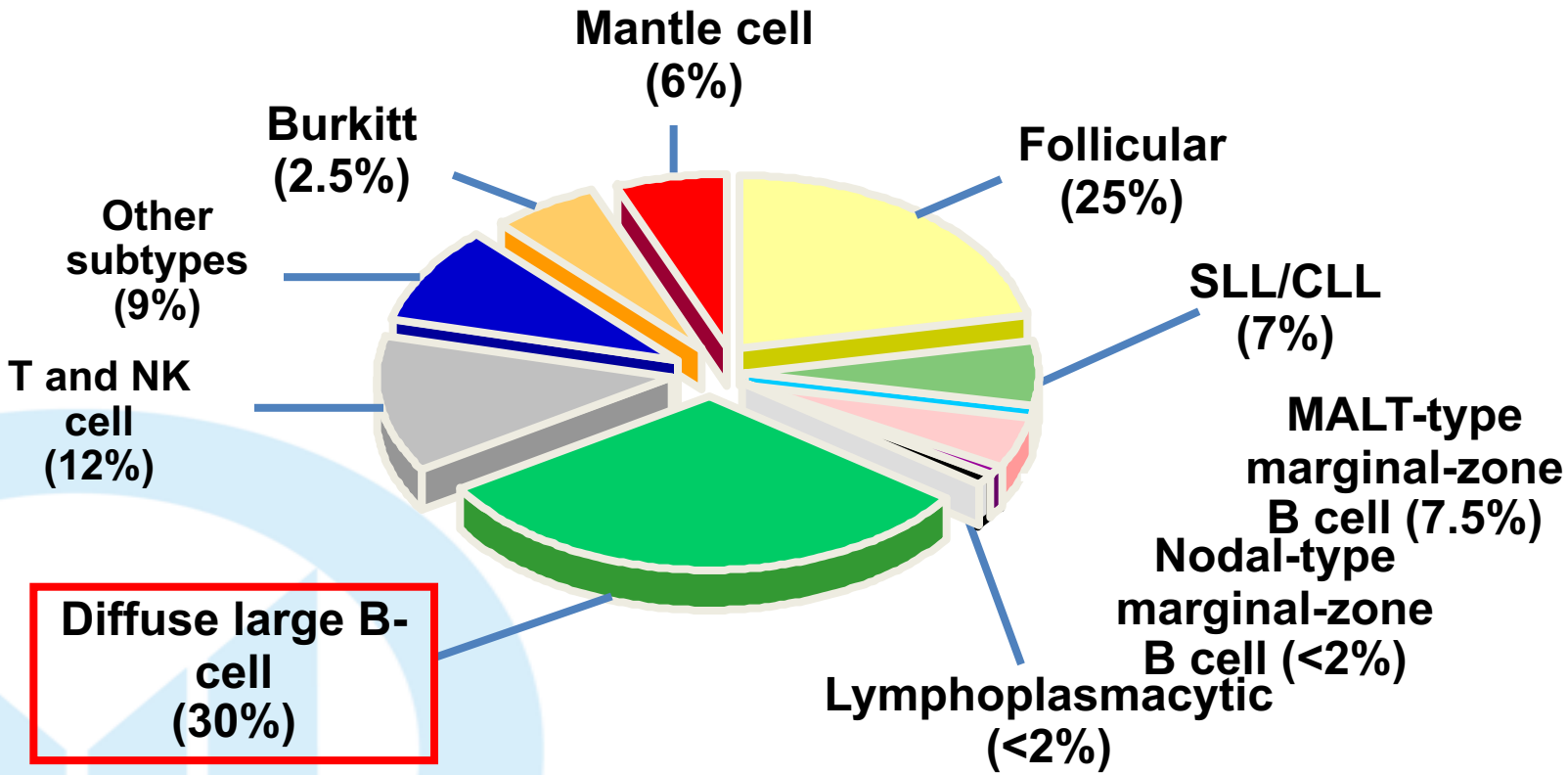
Outline

- Prevalence and Definition
- Prognostic Relevance of MYC and BCL2 aberrartions
- Current management

Most Common Subtypes of NHL



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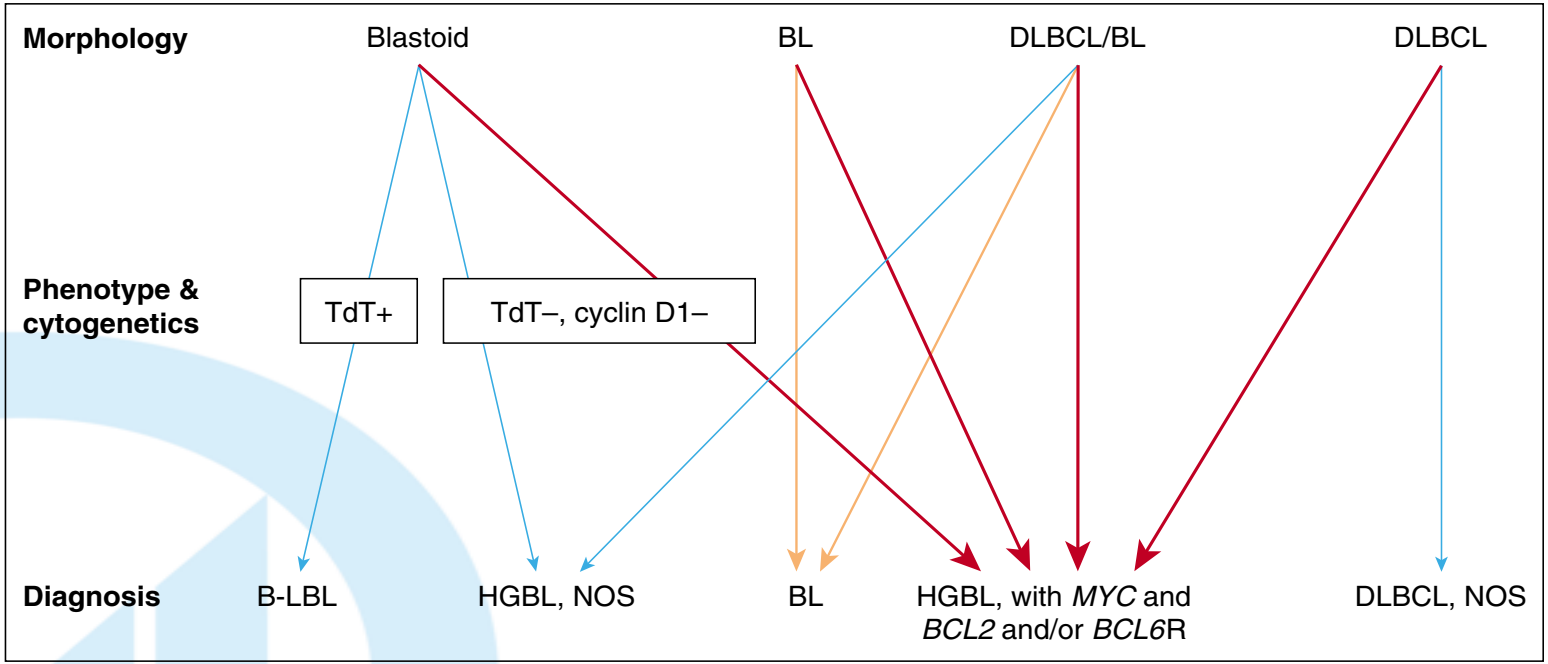
Lichtman MA. Williams Hematology. 7th ed. New York, NY: McGraw Hill. 2006;1408.

WHO 2016: Refinements of aggressive B-cell lymphomas classification



Swerdlow et al. Blood 2017 (127): 20

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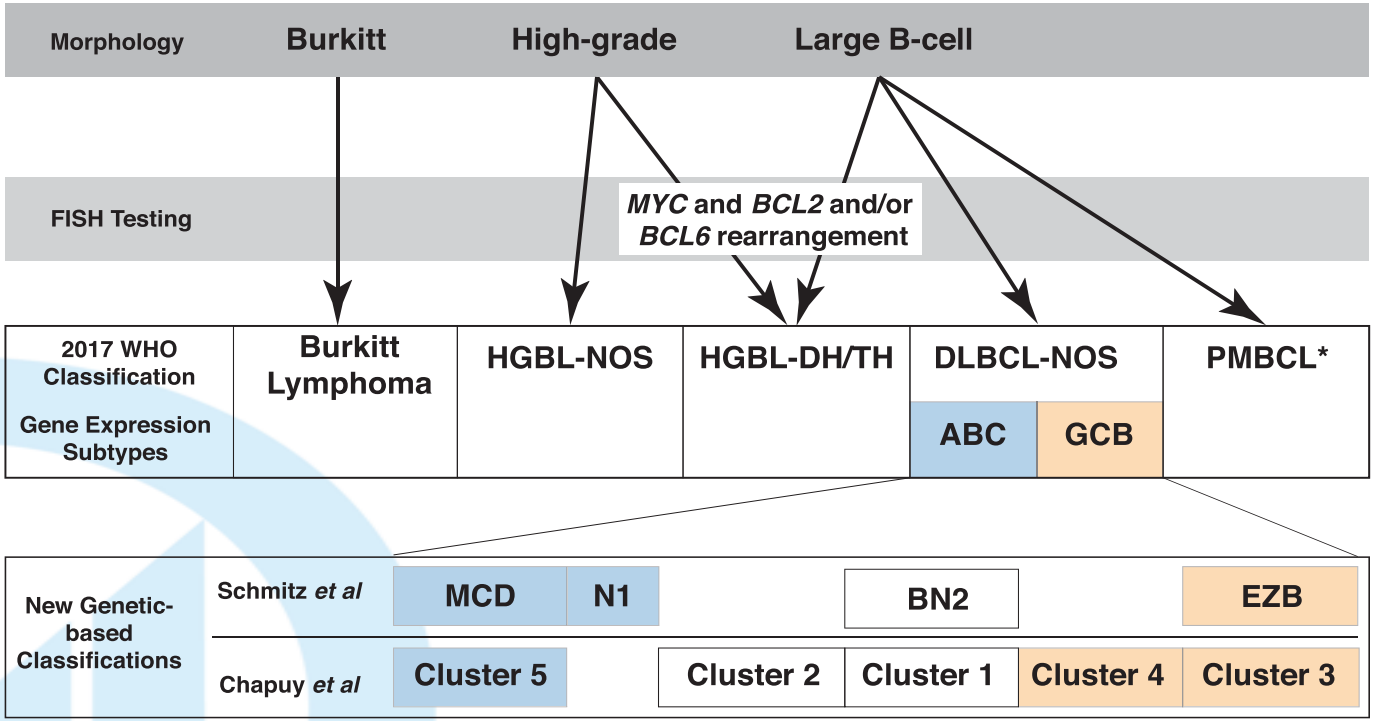
Evolving role of NGS in aggressive B-cell lymphomas classification



Pasqualucci. Blood 2018

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High grade B cell lymphomas

WHO Revised 4th Ed.	WHO 5th Ed.	ICC
High grade B cell lymphoma, NOS	High grade B cell lymphoma, NOS [3]	High grade B cell lymphoma, NOS [3]
High grade B cell lymphoma with *MYC* and *BCL2* or *BCL6* rearrangements	**Diffuse large B cell lymphoma / high grade B cell lymphoma with *MYC* and *BCL2* rearrangements** [1]	**High grade B cell lymphoma with *MYC* and *BCL2* rearrangements**
		High grade B cell lymphoma with *MYC* and *BCL6* rearrangements (provisional) [1]
Burkitt lymphoma	Burkitt lymphoma	Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration (provisional)	**High grade B cell lymphoma with 11q aberration** [2]	**Large B cell lymphoma with 11q aberration (provisional)** [2]

[1] WHO 5th: HGBCL with *MYC* and *BCL6* now under **DLBCL, NOS**, or **HGBL, NOS** (rare). However, BCL6-R should be reported (for clinical trial etc).

Downgraded to provisional in ICC. To allow continued studies. Morphology (DLBCL vs HGBL) should be reported.

[2] **WHO 5th LBCL with 11q acceptable**. Although morphologically resembles BL, genetically (GEP and mutational spectrum) closer to DLBCL than to BL. Cases with a BL-like appearance that lack MYC rearrangement should be tested for the 11q gain/loss by FISH.

[3] **HGBL, NOS with expression of TdT**, not to diagnose as B-ALL, based on mutational studies, CD34 negativity and presence of isolated or double-hit MYC rearrangement.

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Chromosomal breakpoints in DLBCL

Study	N	*MYC*+ total %	*MYC*+ SH %	*BCL2*/ *MYC*+ DH %	*BCL6*/ *MYC*+ DH %	*BCL2*/ *BCL6*/ *MYC*+ TH %	All DH and TH %
Barrans 2010	245	14%	2%	8%	1%	3%	12%
Obermann 2009	220	4%	3%	0	0	0	1%
Yoon 2008	137	7%	7%	1%	1%	1%	3%
Tibiletti 2009	74	16%	4%	7%	7%	1%	12%
Copie-Bergman 2009	68	3%	3%	0	0	0	0
Van Imhoff 2006	58	15%	8%	5%	2%	0	7%
Savage 2009	135	9%	7%	2%	NA	NA	NA
Klapper 2008	117	8%	NA	NA	NA	NA	NA

Aukema et al, Blood 2011

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Clinical features of “double hit” lymphoma

Study	N DH/ total N (%)	DH w prior iNHL %	Med age	St III/IV %	LDH > NI %	BM + %	CNS + %	> 1 ENS %	IPI Hi/HiI %
Bertrand 2007	10/17 (59%)	10%	58	70%	NA	NA	NA	NA	56%
Johnson 2009	54/54 (100%)	46%	62	76%	50%	71%	NA	35%	70%
Kanungo 2006	14/14 (100%)	None	55	NA	93%	79%	21%	57%	NA
Le Gouill 2007	16/16 (100%)	25%	61	100%	100%	94%	50%	88%	81%
Macpherson 1999	15/39 (38%)	46%	65	92%	80%	69%	NA	62%	90%
Niitsu 2009	19/19 (100%)	None	61	100%	100%	84%	21%	63%	89%
Snuderl 2010	20/20 (100%)	15%	64	95%	100%	59%	45%	30%	85%
Tomita 2009	27/27 (100%)	17%	51	96%	93%	65%	9%	65%	87%

Aukema et al, Blood 2011

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Clinical differences between MYC-R and non MYC-R DLBCL patients: Lunenburg Biomarker Consortium

N= 2383	Without MYC-R	With MYC-R
Age ≥ 60	65.7%	72.7%
IPI score 0-2 3-5	 57.7% 43.3%	 47.0% 53.0%
Ann Arbor stage I-II III-IV	 40.6% 59.3%	 32.1% 67.9%
Extranodal sites ≥1	23.5%	32.2%
Elevated LDH	53.1%	65.9%

N= 2383	N(%)
MYC negative	2119 (92.2%)
MYC positive SH (IG) DHT/TH (IG) SH (non IG) DH/TH (non IG)	 40 (1.7%) 54 (2.4%) 17 (0.7%) 53 (2.3%)
Missing	100

Rosenwald et al, J Clin Oncol 2019

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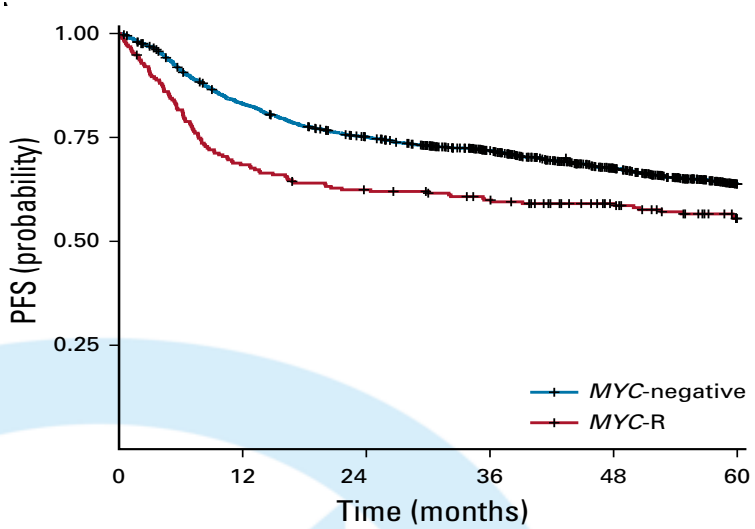
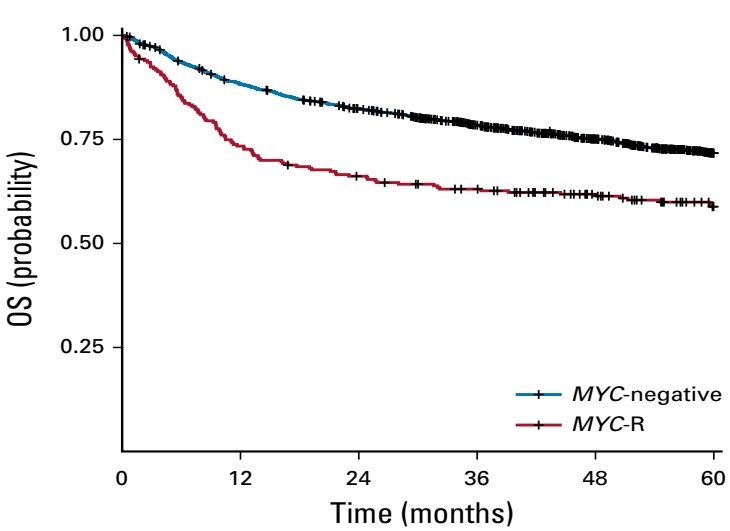
MYC rearrangement as prognostic marker: Lunenburg Biomarker Consortium





Rosenwald et al, J Clin Oncol 2019

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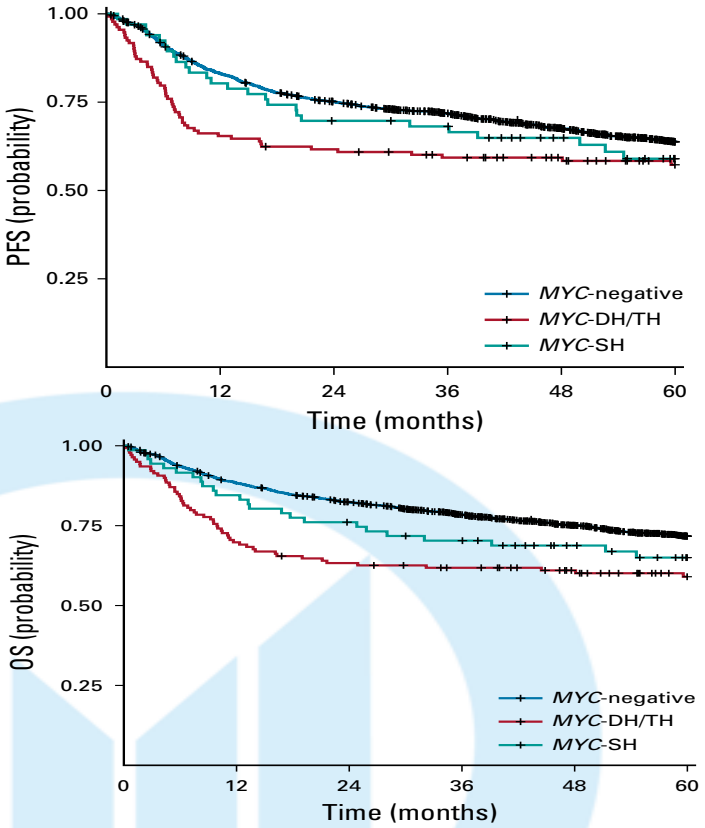

N= 2383	PFS	OS
	HR (95% CI), p	HR (95% CI), p
MYC-negative	1	1
MYC-DH/TH before 24 mo	1.67 (1.25-2.23), <.001	2.20 (1.64-2.96), <.001
MYC-DH/TH after 24 mo	0.42 (0.17-1.02), 0.055	0.44 (0.18-1.08), .073
MYC-SH	1.22 (0.82-1.80), 0.25	1.45 (0.96-2.18), .077
IPI low	1	1
IPI high	2.51 (2.18-2.90), <.001	2.82 (2.40-3.32), <.001

Rosenwald et al, J Clin Oncol 2019

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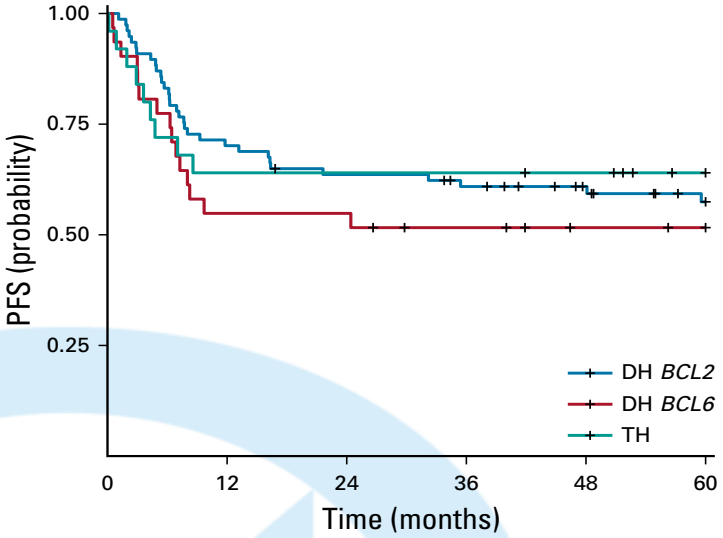
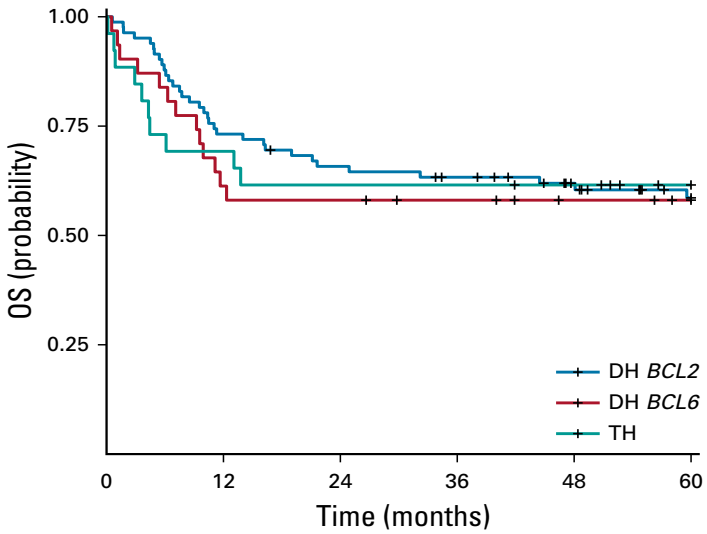
Different outcomes in double or triple hit lymphomas? Lunenburg Biomarker Consortium





Rosenwald et al, J Clin Oncol 2019

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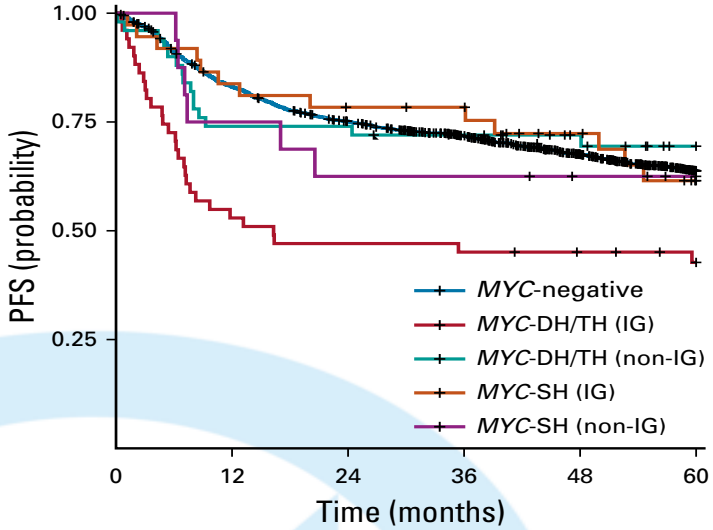
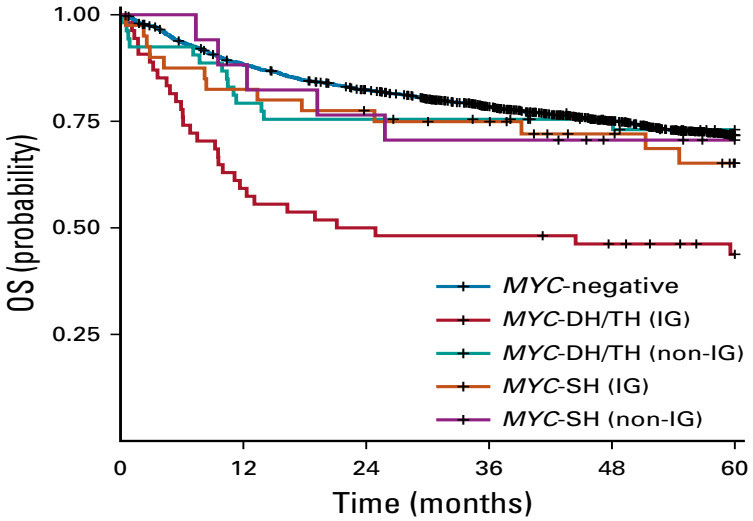
Is the translocation partner important?: The Lunenburg Lymphoma Biomarker Consortium





Johnson al. *J Clin Oncol* 2012; 30:3452--9

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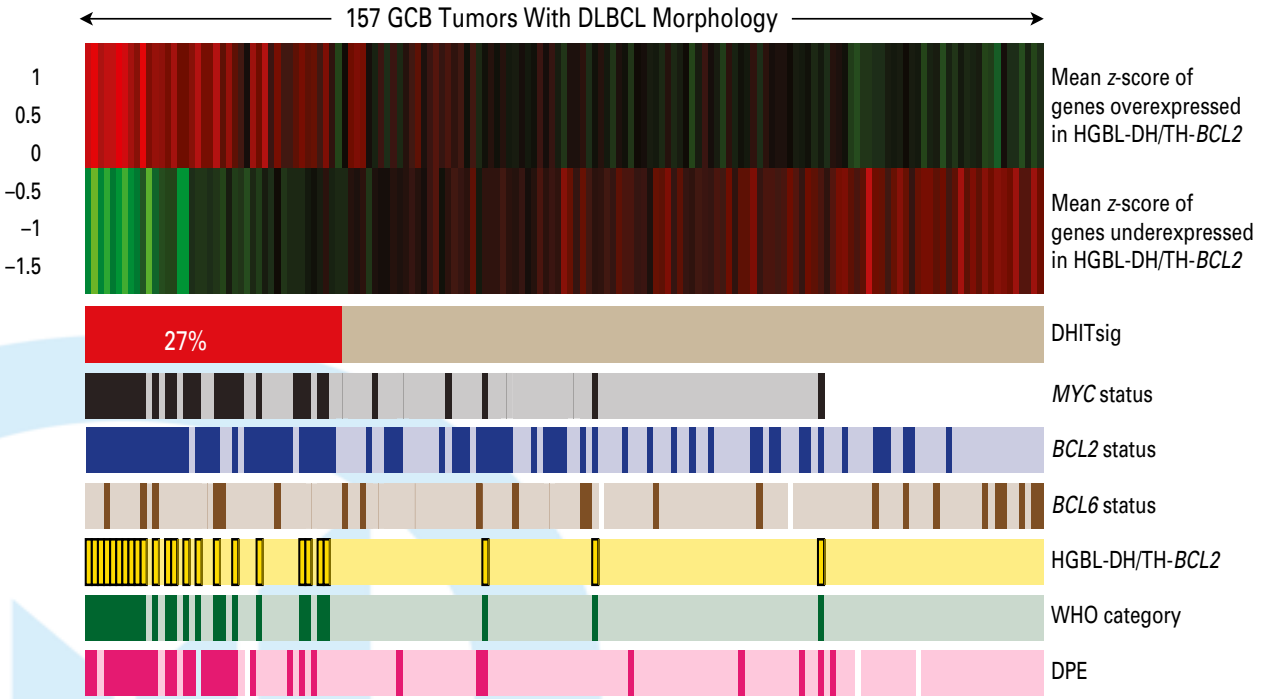
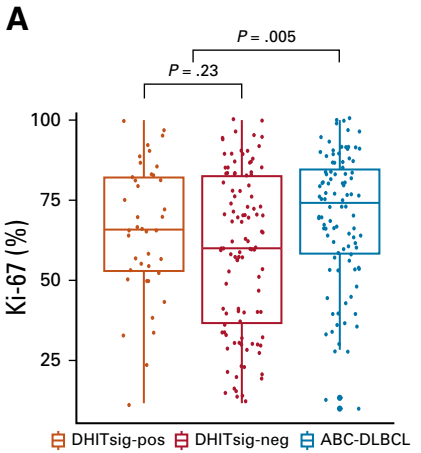
Double hit gene signature in GCB DLBCL: Distinct prognostic group





Ennishi D et al. *J Clin Oncol* 2019; 30:3452--9

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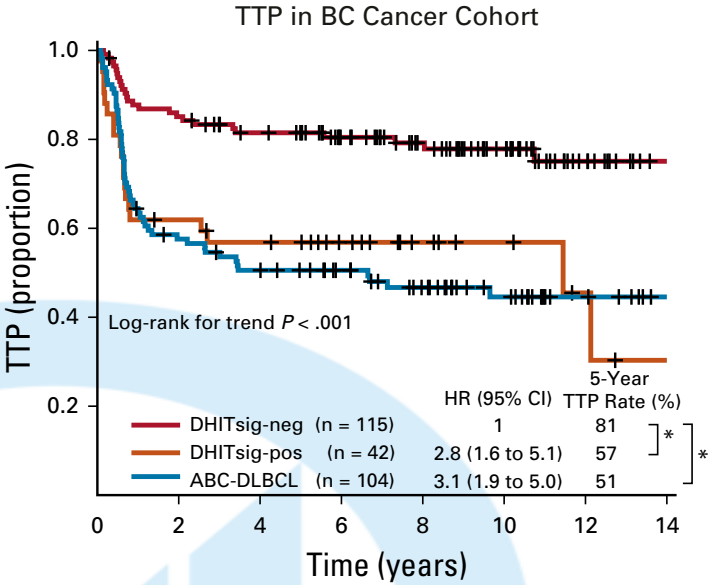
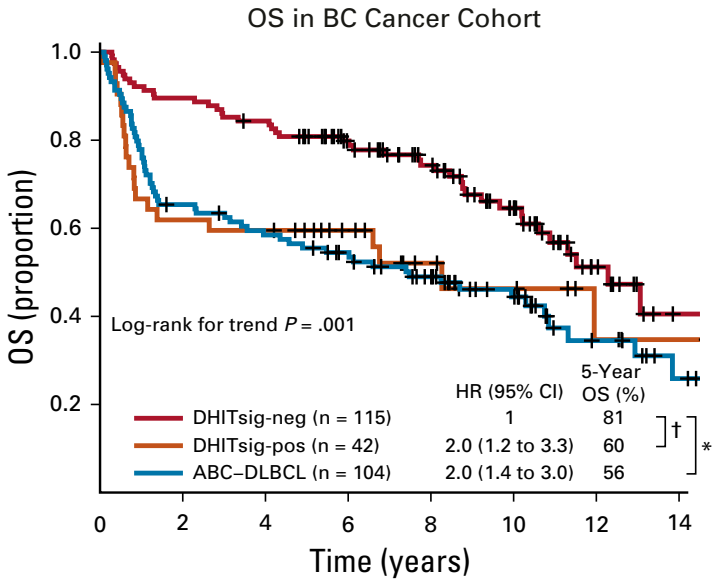
Double hit gene signature in GCB DLBCL: Correlation with Outcomes





Ennishi D et AL. *J Clin Oncol* 2019; 30:3452--9

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Double-Hit Status With TP53 Abnormalities Predicts Poor Survival in Patients With Germinal Center B-Cell Like (GCB) DLBCL Treated With R-CHOP

Background

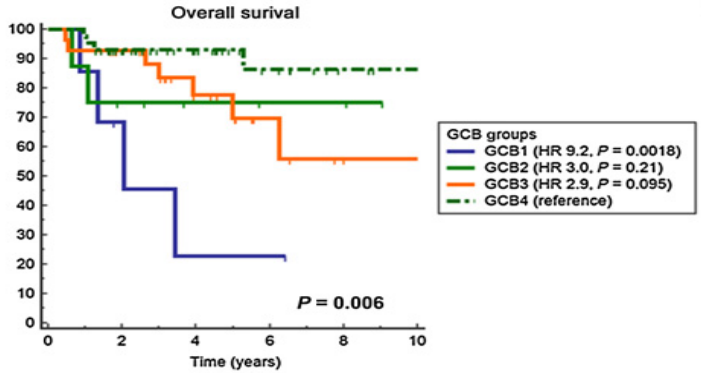
Genomic analysis of cases of de novo GCB DLBCL, including those patients with DH lymphoma (presence of *MYC* and *BCL2* and/or *BCL6* translocations)

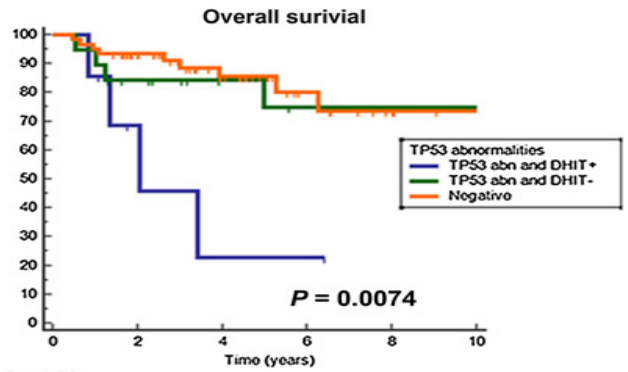
The objective was to develop a molecular subtyping schema to risk-stratify patients with GCB DLBCL treated with R-CHOP

Results

87 non GCB DLBCL cases divided into 4 groups:

- GCB1 (DH positive, *TP53* inactivation): poor survival
- GCB2 (DH positive, *TP53* wildtype): good survival
- GCB3 (DH negative, *EZH2* mutation and/or *BCL2* translocation): intermediate survival
- GCB4 (DH negative, without *EZH2* mutation or *BCL2* translocation): excellent survival





Song et A. ASH Meeting Abstracts 2020: 533

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Chemotherapy studies in MYC+ DLBCL and "double hit" lymphoma

Study	Population	Treatment	PFS/RFS/EFS	OS
Savage KJ et al, Blood 2019	MYC+:12 (8 DE) MYC-: 123	R-CHOP MYC+ vs MYC-	5-year PFS: 66% *MYC*- vs 31% *MYC*+ (P = 0.006)	5-year OS: 72% MYC- vs 33% MYC+ (P=0.016)
Johnson et al, JCO 2012	14 DHL 55 DEL 236 other DLBCL	R-CHOP in de novo DLBCL	5-year PFS: DHL: 18% DEL: 32% Non-DHL/DEL DLBCL: 65%	5-year OS: DHL: 27% (P < 0.001) DEL: 36% (p=0.014) Non-DHL/DEL DLBCL: 71%
Horn H et al. Blood 2013	29 DHL/THL 321 other DLBCL	CHOP-14 +/-R novo DLBCL on RICOVER study	3-year EFS R-CHOP DHL group: 38.1% for MYC+/BCL2+ 50.0% for MYC+/BCL6+	3-year OS R-CHOP DHL group: 35.7% for MYC+/BCL2+ 75.0% for MYC+/BCL6+
Petrich AM et al. Blood 2014	311 total patients 286 DHL 25 THL	R-Hyper-CVAD: 65 DA-EPOCH-R: 64 R-CODOX-M/IVAC: 42 R-CHOP: 10 R-ICE: 9 Other regimens: 31 patients	Median PFS: Intensive Regimen: 21.6 months R-CHOP: 7.8 months (P=0.001) All patients: 10.9 months 2-year PFS all patients: 40%	Median OS all patients: 21.9 months Median OS NR if CR to frontline therapy; no difference with consolidation auto/allo SCT 2-year OS all patients: 49%
Oki Y et al. BJH 2014	129 DHL	R-CHOP: 57 pts R-EPOCH: 28 pts R-HyperCVAD/MA: 34 pts Other regimen: 10 patients	2-year & 3-year EFS: R-CHOP: 25% & 20% R-EPOCH: 67% & 67% R-HyperCVAD/MA: 32% & 32% Other: < 10% & < 10% All: 33% & 29%	2-year & 3-year OS: R-CHOP: 41% & 35% R-EPOCH: 76% & 76% R-HyperCVAD/MA: 44% & 40% Other: < 12% & < 12% All: 44% & 38%

Aukema et al, Blood 2011

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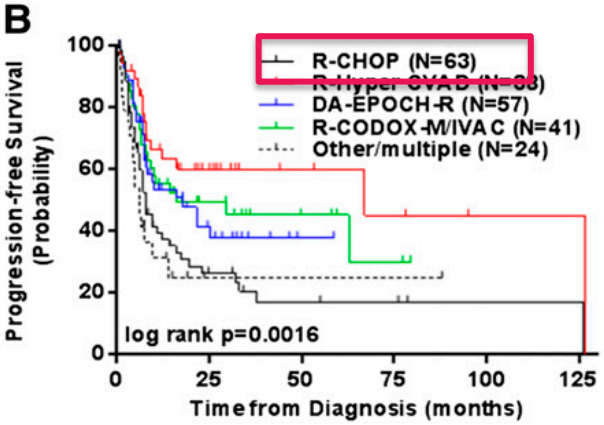
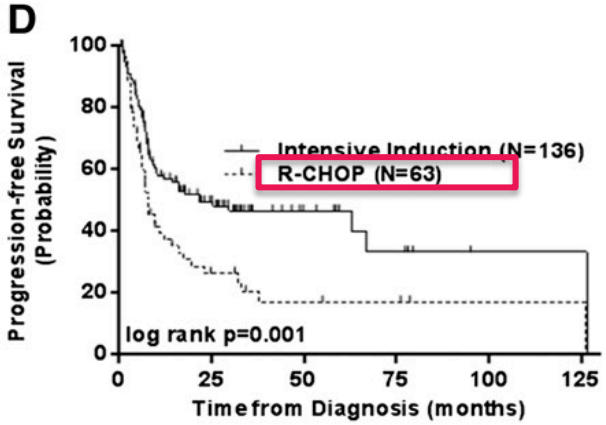
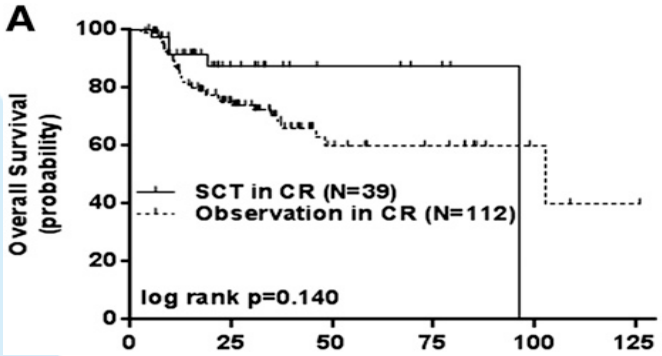
Outcomes in double hit lymphoma: Intensification of treatment- Multicenter retrospective analysis







Petrich et al. *Blood 2014*

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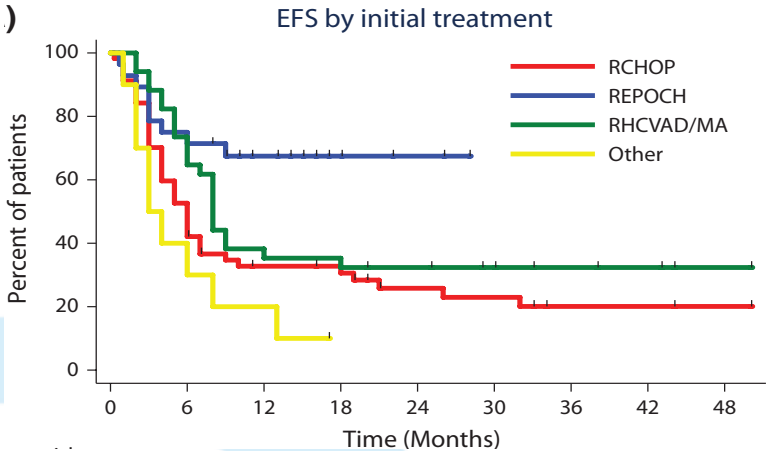
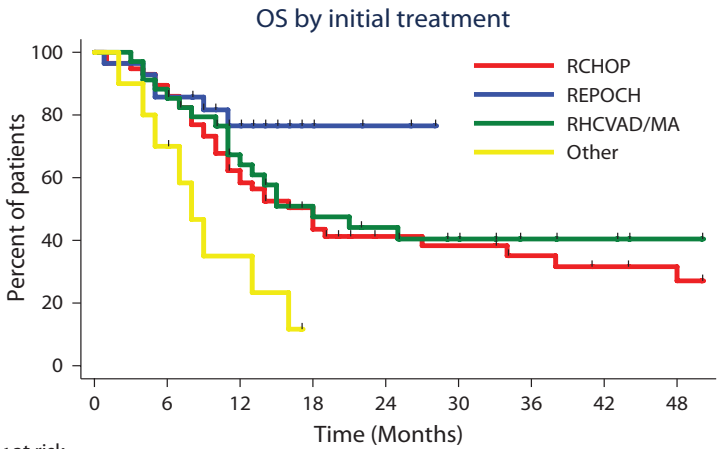
Outcomes in double hit lymphoma: Intensification of treatment-





Oki et al, *Br J Haematol* 2014

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CALGB/Alliance 50303: Study Design

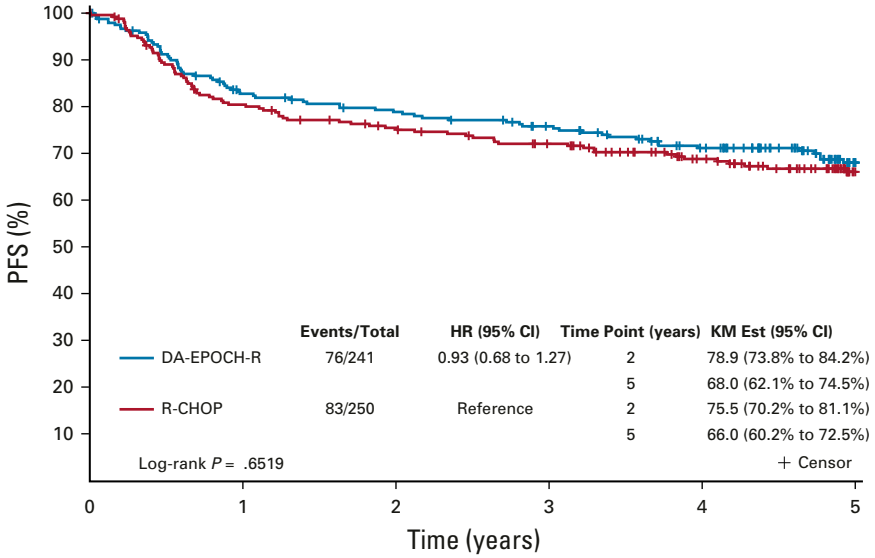
Untreated, newly diagnosed stage II-IV DLBCL (stage I PMBCL), ECOG PS 0-2, LVEF > 45%, tumor biopsies available, no CNS disease (N = 465)

DA-EPOCH-R*
(n = 232)

6 cycles

R-CHOP*
(n = 233)

- **Primary endpoint: EFS**
- Secondary endpoints:
  - RR
  - OS
  - Safety



42 DEL, 13 with MYC-R, 3 confirmed DHL

Wilson WH, et al. ASH 2016. Abstract 469.
Wilson WH, et al. Blood. 2002;99:2685-2693.

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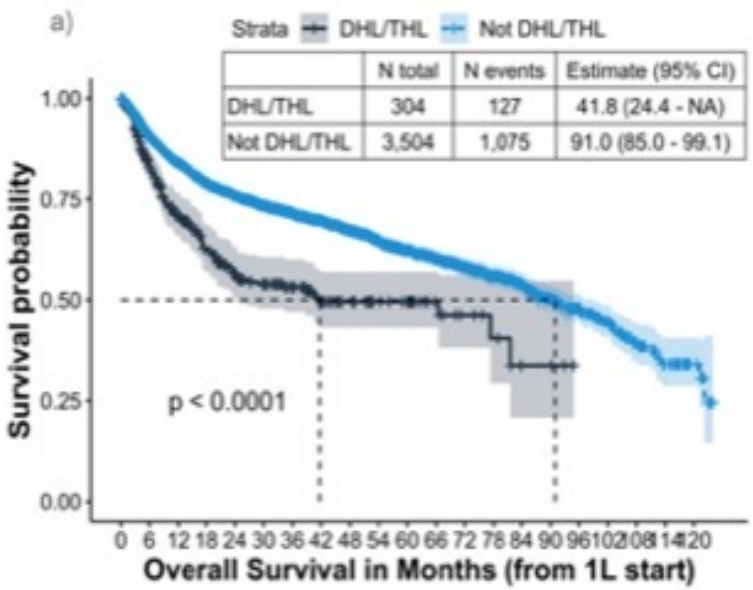
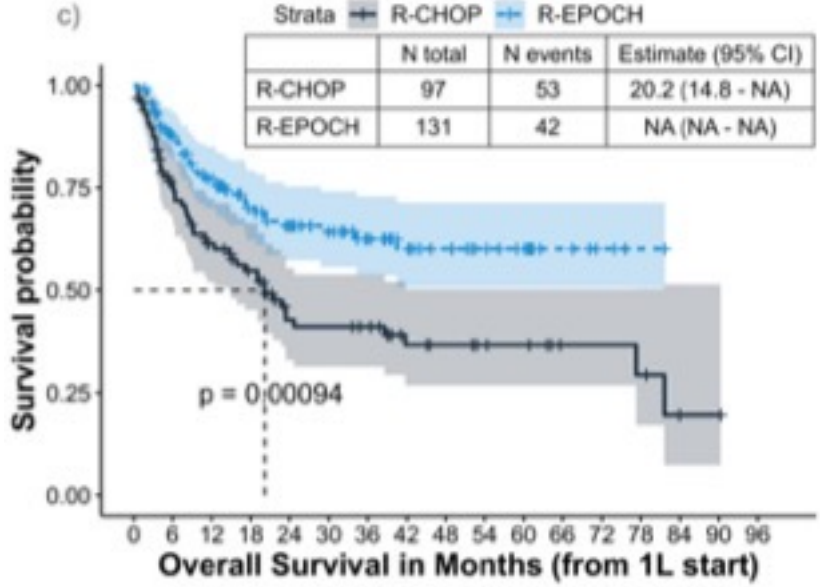
Overall survival between R-CHOP or R-EPOCH for MYC-R, double hit or triple hit DLBCL

- Retrospective study using Flatiron electronic health record (EHR). About 280 sites





Magnuson et Al. EHA 2021, Goyal et al, Haematologica 2022

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Evaluation of Dose-Adjusted EPOCH-R Compared with R-CHOP for the Treatment of High-Risk, Aggressive B-cell Lymphomas: A Single Center Experience

DA-EPOCH-R

N = 36

Median age, years [range]	**64 [38;79]**
IPI Score ≥ 3, n (%)	**27 (75)**
Stage III/IV, n (%)	**29 (80.6)**
Extranodal Sites ≥ 2, n (%)	**19 (52.8)**
DEL, n (%)	**13 (36.1)**
DHL/THL, n (%)	**13 (36)**

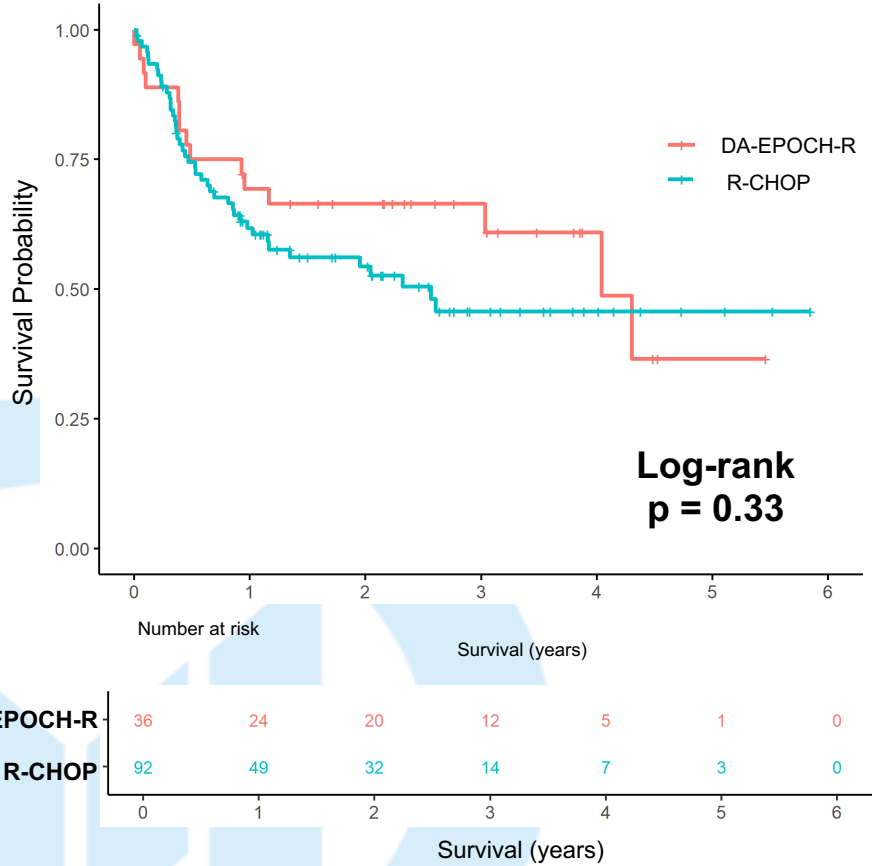
R-CHOP

N = 92

Median age, years [range]	**66 [33;85]**
IPI Score ≥ 3, n (%)	**85 (92.4)**
Stage III/IV, n (%)	**84 (92.3)**
Extranodal Sites ≥ 2, n (%)	**55 (59.8)**
DEL, n (%)	**21 (22.8)**
DHL/THL, n (%)	**10 (11)**

Rockwell et Al. *ASH Meeting Abstracts* 2020

No difference in PFS between DA-EPOCH-R and R-CHOP



PFS at 1 year

DA-EPOCH-R	R-CHOP
69%	62%
PFS	PFS
(95% CI: 56.0, 86.0)	(95% CI: 52.0, 73.0)

PFS at 5 years

DA-EPOCH-R	R-CHOP
37%	46%
PFS	PFS
(95% CI: 17.0, 79.0)	(95% CI: 35.0, 59.0)

PFS was higher in the DA-EPOCH-R arm for patients with *MYC*-R (p=0.0224) and DHL/THL (p=0.045)

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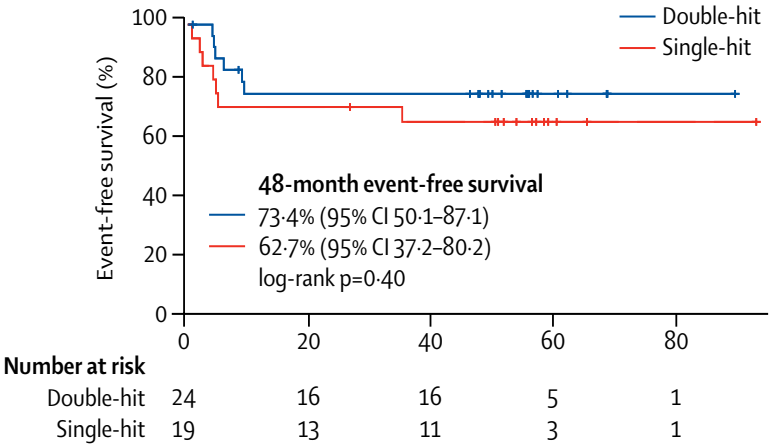
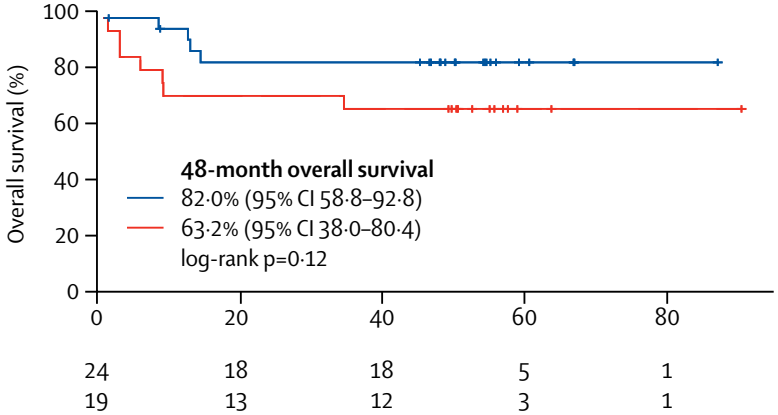
DA-EPOCH for DLBCL with MYC rearrangements: Multicenter Prospective Study





Dunleavy el al. *Lancet Haematol* 2018

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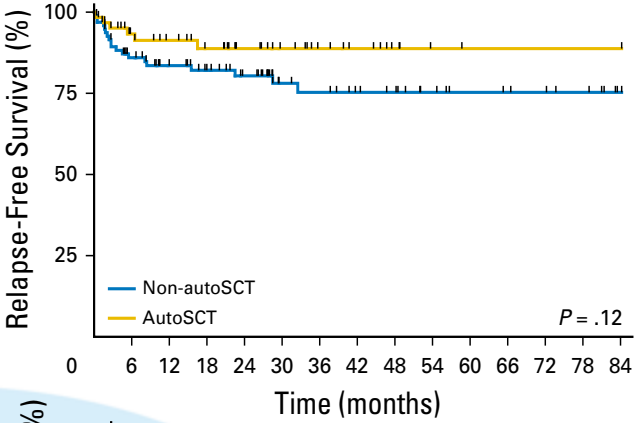
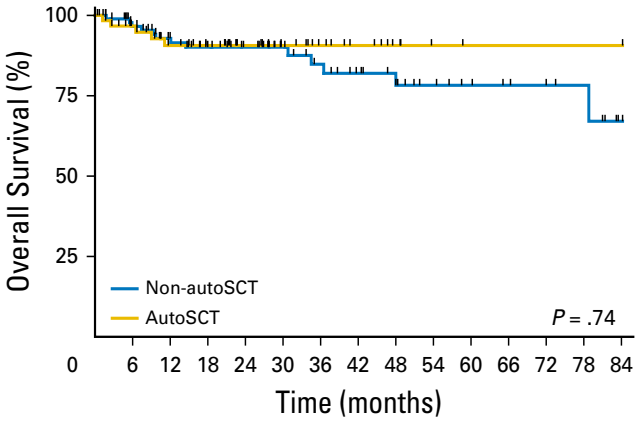
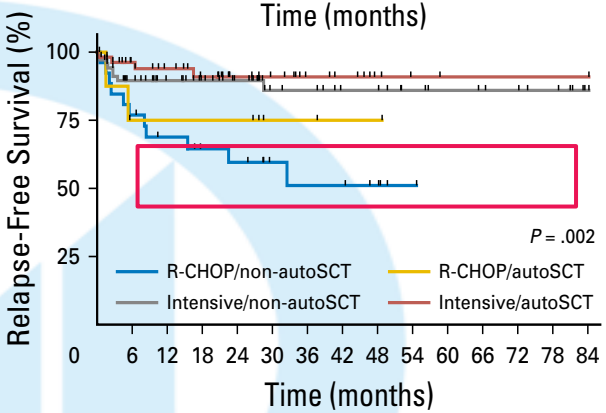
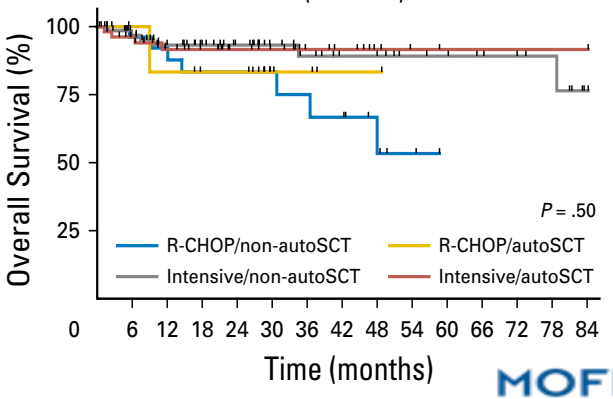
Outcomes in double hit lymphoma in CR1: Role of Autologous HCT









Landsburg et al. *J Cin Oncol 2017*

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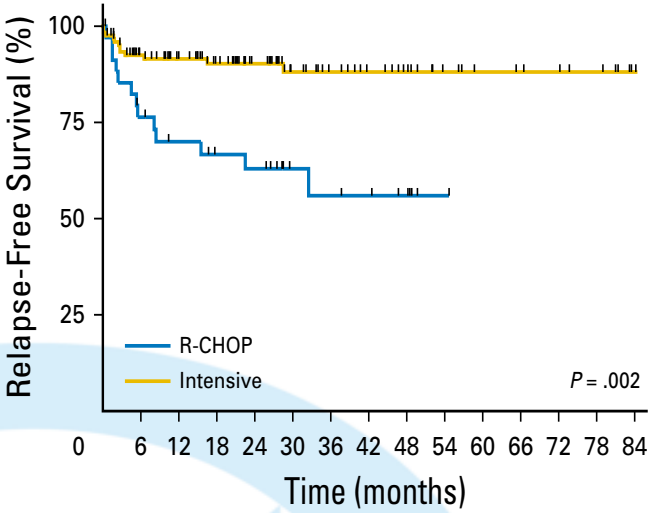
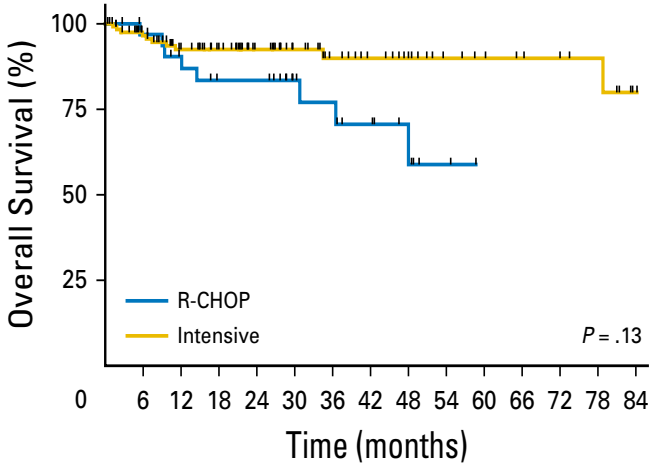
Outcomes in double hit lymphoma in CR1: Role of Autologous HCT





R-CHOP remains inferior whether patients receive auto HCT or not.

Landsburg et al. *J Clin Oncol 2014*

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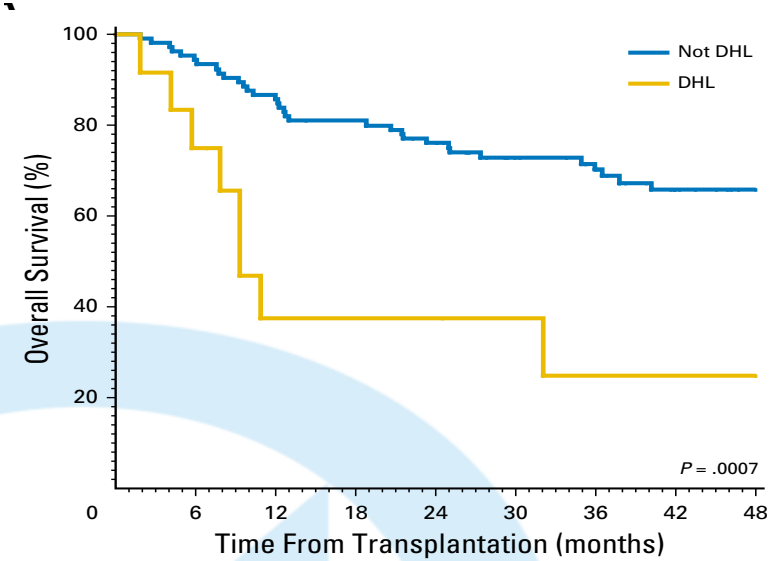
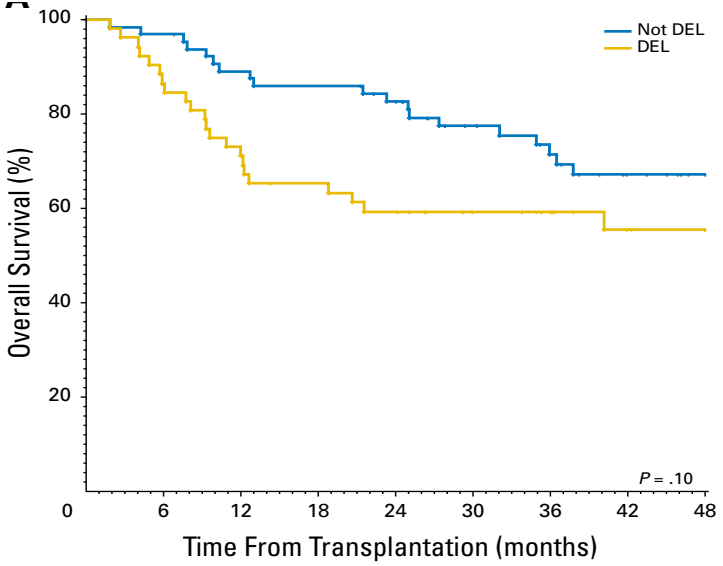
Outcomes of Double Expressor and Double Hit Lymphoma after autologous HCT: Inferior Outcomes





Herrera A et al, JCO 2016

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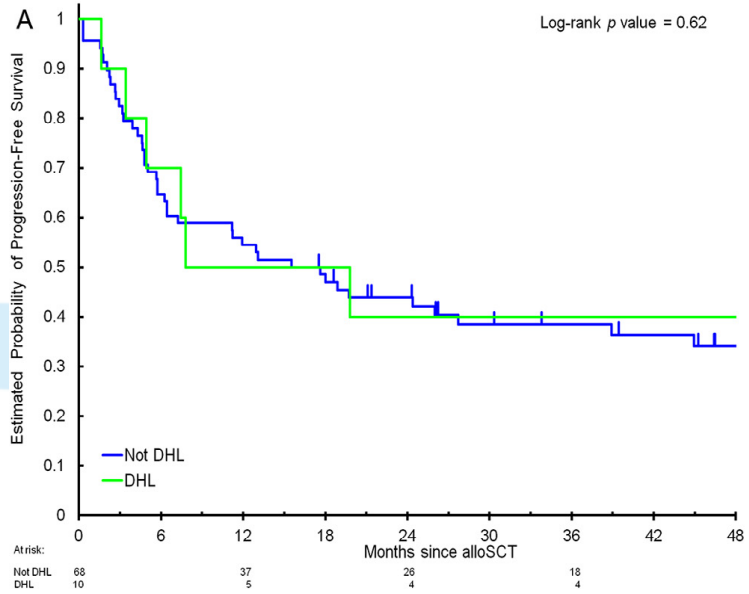
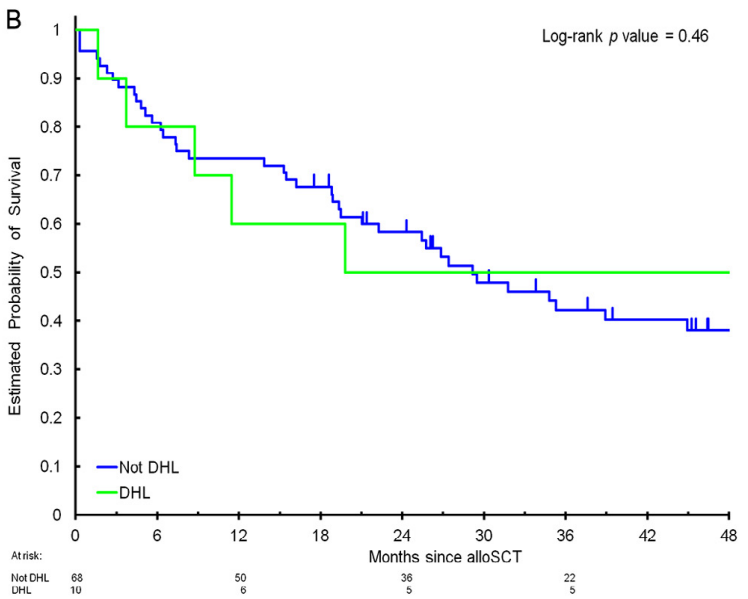
Allogeneic HCT seems to offer similar outcomes to non DHL/THL





Herrera A et al, BBMT 2018

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Alliance 051701: DHL Cohort Study Design

- Randomized, open-label phase II/III trial in cohort of patients with DHL (data cutoff: July 8, 2021)
  - **DA-EPOCH-R + venetoclax safety signal led to early closure, data release on December 2, 2020**

Stratified by IPI, prior cycle of DA-EPOCH-R, and DHL subtype

Six 21-day cycles

Adults with DHL,*
ECOG PS ≤2;
adequate organ function;
no known CNS involvement;
no uncontrolled HIV, HBV, HCV;
receipt of steroids, radiation, or single cycle of CT prior to enrolment allowed
(N = 73†)

→ DA-EPOCH-R + Venetoclax 600 mg/day on Days 4-8 of cycle 1; Days 1-5 of cycles 2-6 (n = 37)

→ DA-EPOCH-R (n = 36)

Continue until PD, unacceptable toxicity or completion of 6 cycles

Follow-up for 10 yr or until death

*High grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6; MYC/BCL6*-positive DHL requires BCL2 expression.
†Planned N = 106.

- Primary endpoint: PFS (phase II)
- Secondary endpoints: OS, safety, response rate

Abramson. ASH 2021. Abstr 523. NCT03984448.

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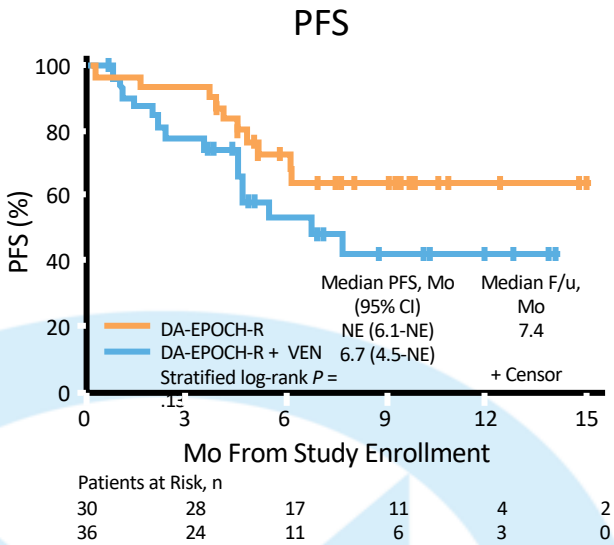
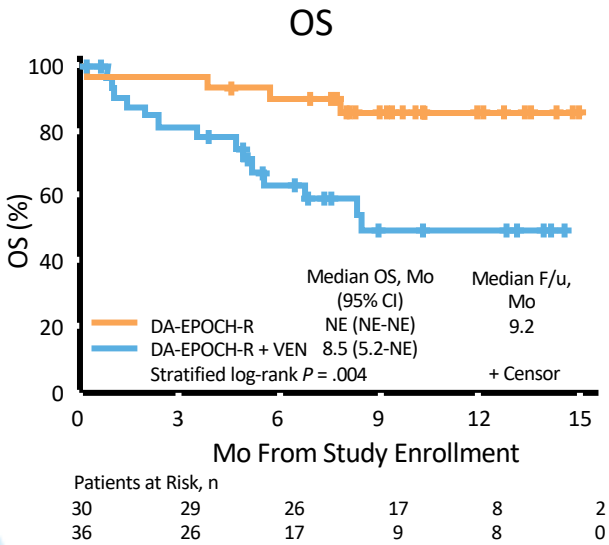
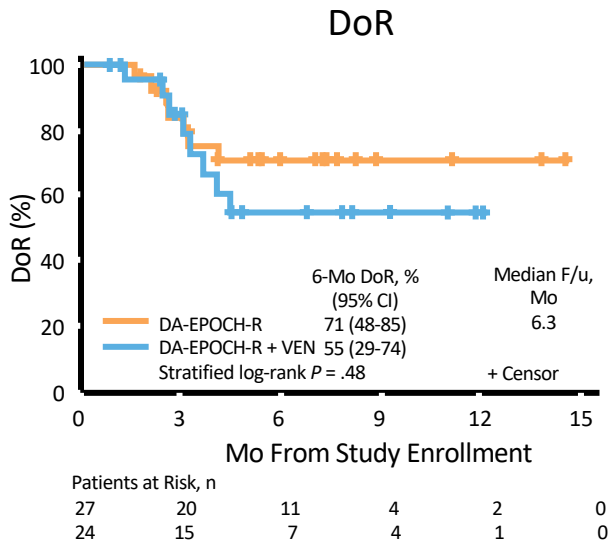
Alliance 051701: Efficacy Outcomes Ven-DA-EPOCH-R associated with poor outcomes







Grade 5 AEs on or ≤30 days after treatment: 3.3% (1/30) with DA-EPOCH-R* vs 17.1% (6/35) with DA-EPOCH-R plus venetoclax†
49% completed Ven-DA-EPOCH-R vs 70% that completed DA-EPOCH-R

Abramson. ASH 2021. Abstr 523. .

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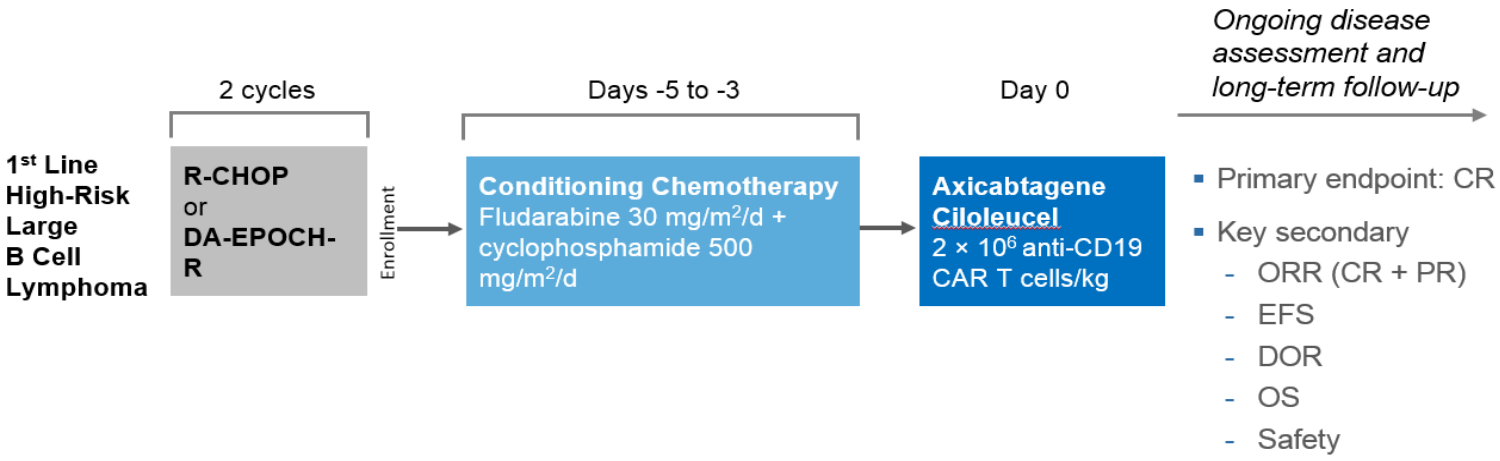
ZUMA-12 Study Design: Frontline CART therapy for high risk DLBCL (IPI > 3 or MYCBCL2/BCL6 rearrangements)



High-risk is defined as PET+ disease after 2 cycles of chemotherapy

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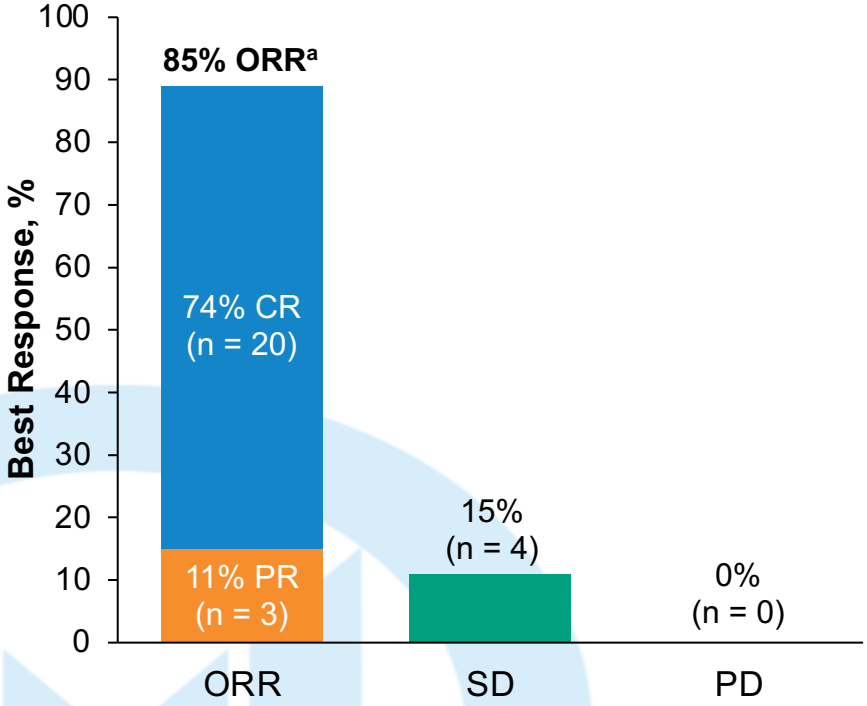
ZUMA-12: ORR Was 85% and CR Rate Was 74%



- Enrolled/Leukapheresis= 37 pts. Evaluable for **safety**= 32 pts and for **efficacy**= 27 pts
- Median age 61 (23 – 86). Older than 65 yo 41%
- Stage III/IV 87%
- **Double/Triple Hit Lymphoma 45%**
- Deauville 4/5: 50/50%

- Median follow up 9.3 months (0.9 – 18 months)
- 70% pts had more than 6 mo follow up
- **ORR 88%, CR 74%**
- 5 pts with initial PR/SD converted into CR
- **Median DOR, PFS and OS were not reached**

Neelapu et AL. *ASH Meeting Abstracts* 2021

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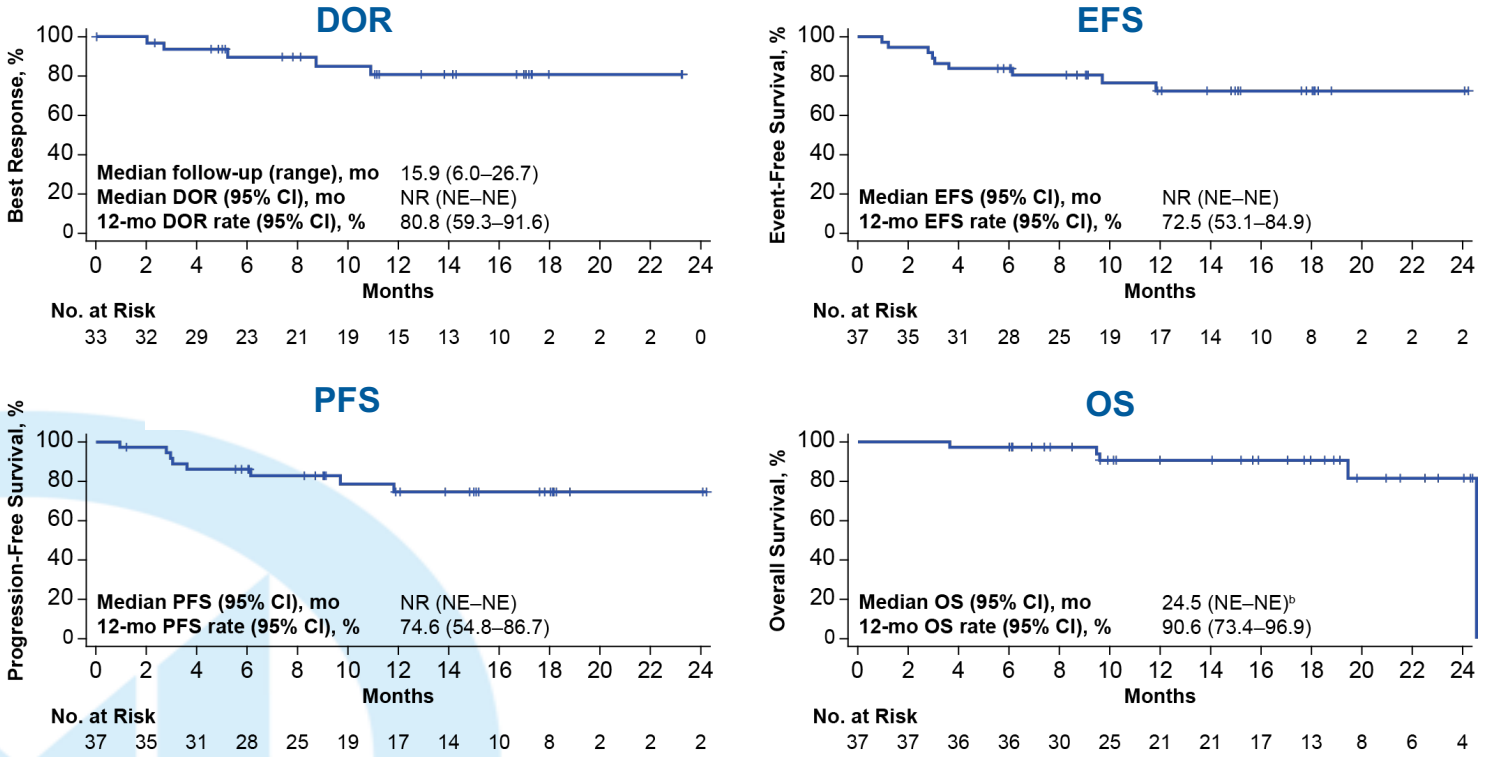
Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]



[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg. [b] One patient died after progression (cause of death was progression).

Herrera A et al. JCO 2016

DOR, duration of response; EFS, event-free survival; mo, month; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

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Summary

- DHL/THL represent a heterogeneous disease with poor outcomes
- Intense regimens are preferred in majority of cases. Exceptions: Elderly? Limited stage DHL?
- Relapse/Refractory DHL/THL have poor outcomes. Allogeneic HCT is recommended in those achieving response after salvage therapy
- CART therapy is currently approved for DLBCL after failure post 2 lines of therapy and includes DHL/THL
- Consider clinical trials