

THE DOUBLE HIT /HGBL* AND THE DOUBLE EXPRESSOR LYMPHOMAS : treatment

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Disclosure: Monica Balzarotti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X	X	
Eli Lilly					X	X	
BMS						X	
BeOne					X		
J&J					X	X	
Abbvie						X	
Astrazeneca						X	

GCB?

ABC?

Double-hit?
lymphomas?

BCL-2-R?

High BCL-2
expression?

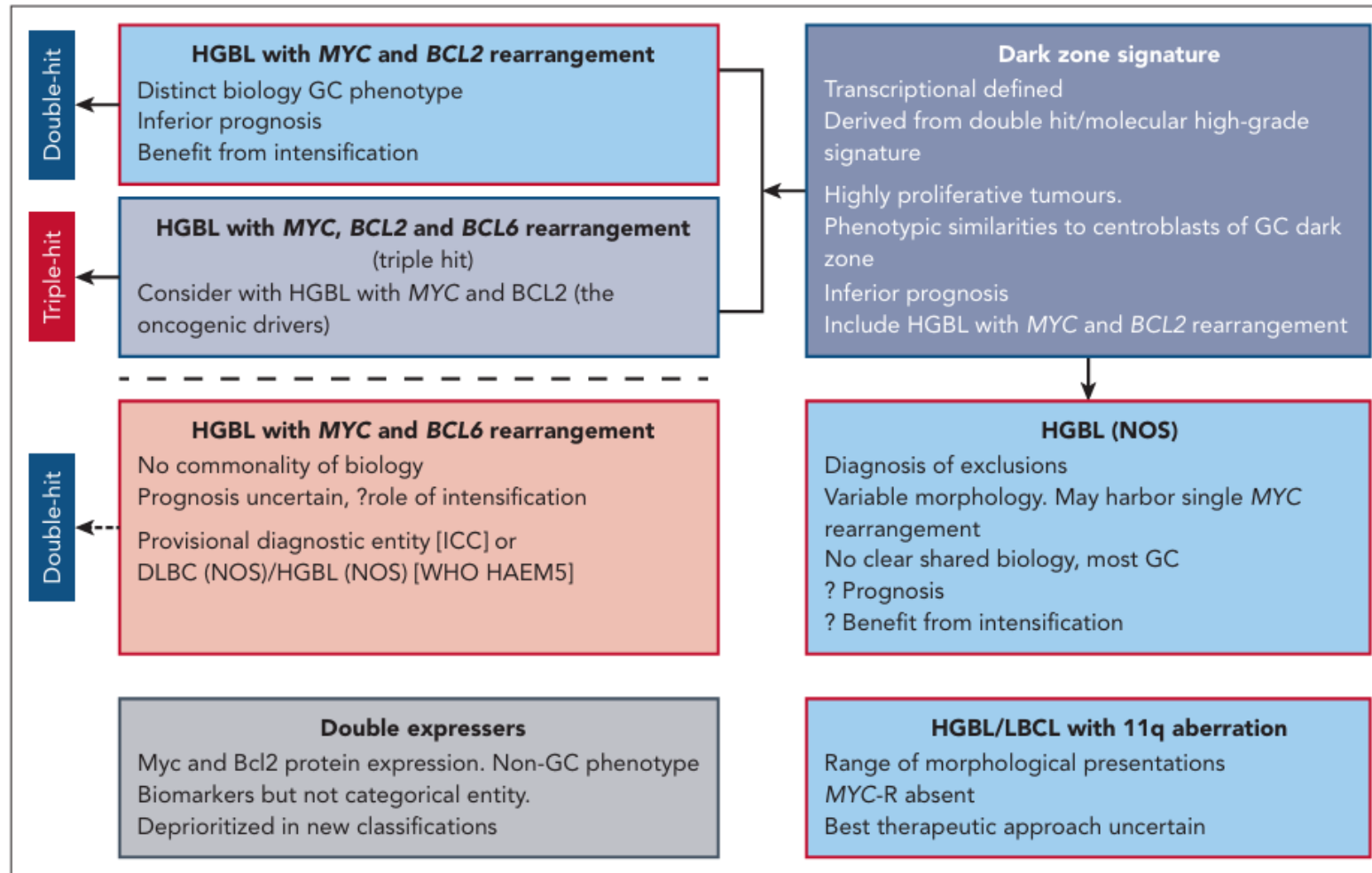
MYC-R?

High MYC
expression?

The high-grade B-cell lymphomas: double hit and more

Blood 2025

Andrew J. Davies



DOUBLE HIT LYMPHOMAS (DHL)

first line treatment

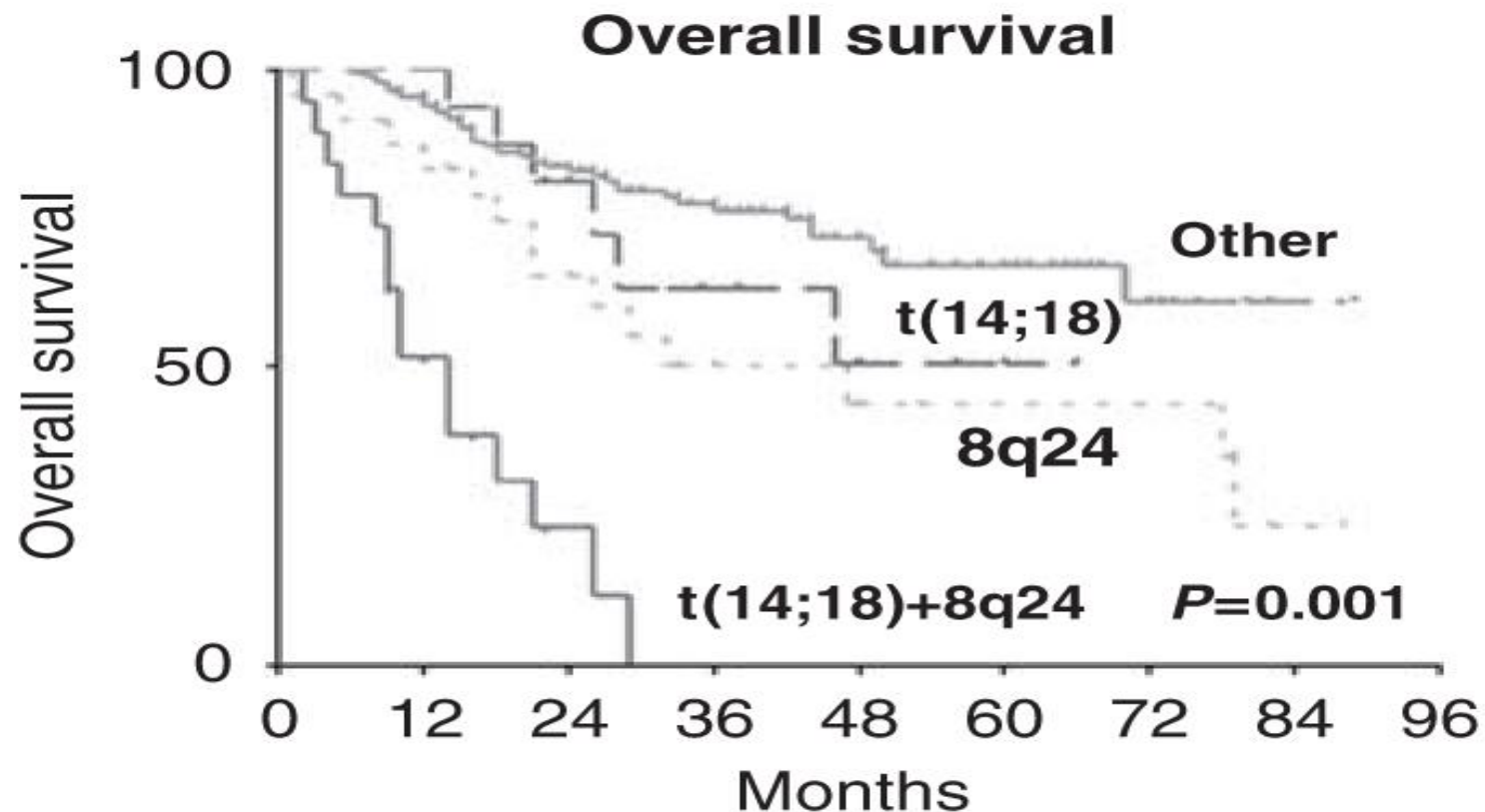


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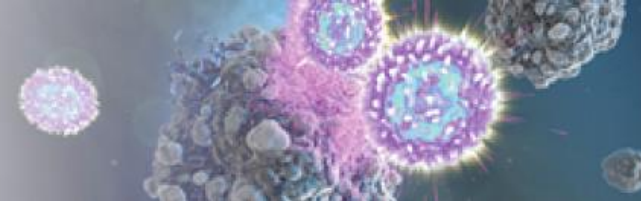
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DLBCLs with *MYC* and *BCL2* **translocations** are characterized by inferior survival

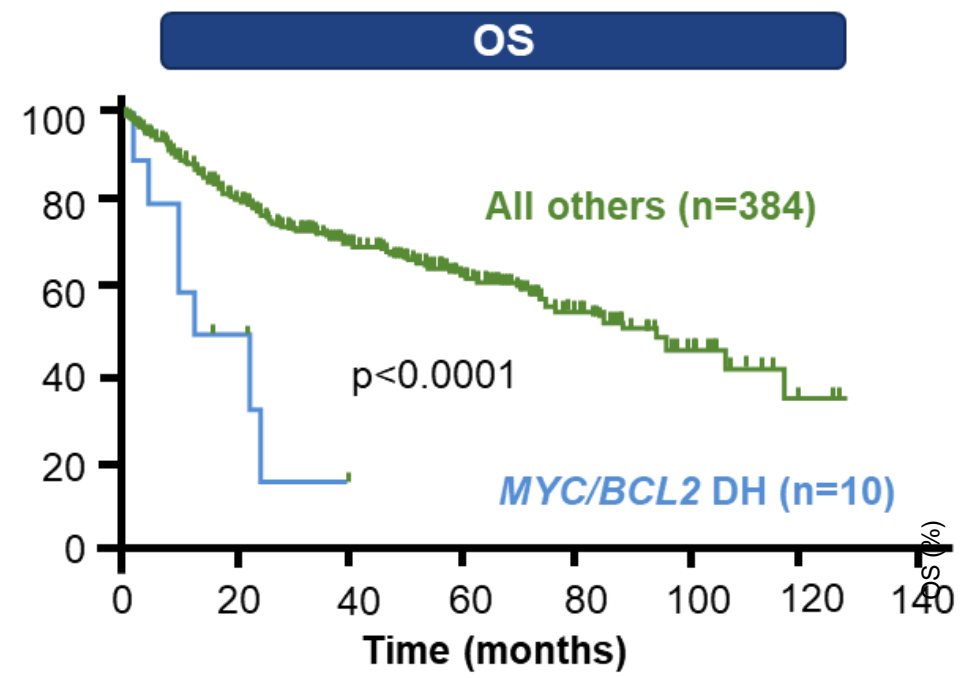


Niitsu et al., Leukemia 2009



Patients with **DHL** respond poorly to chemotherapy and have very poor survival outcomes

- Since the 2016 WHO revised classification of lymphoid neoplasms, genomic translocations in *MYC*, *BCL* and/or *BCL6* oncogenes were added to HGBL¹
 - HGBL occurs in <10% cases of DLBCL²



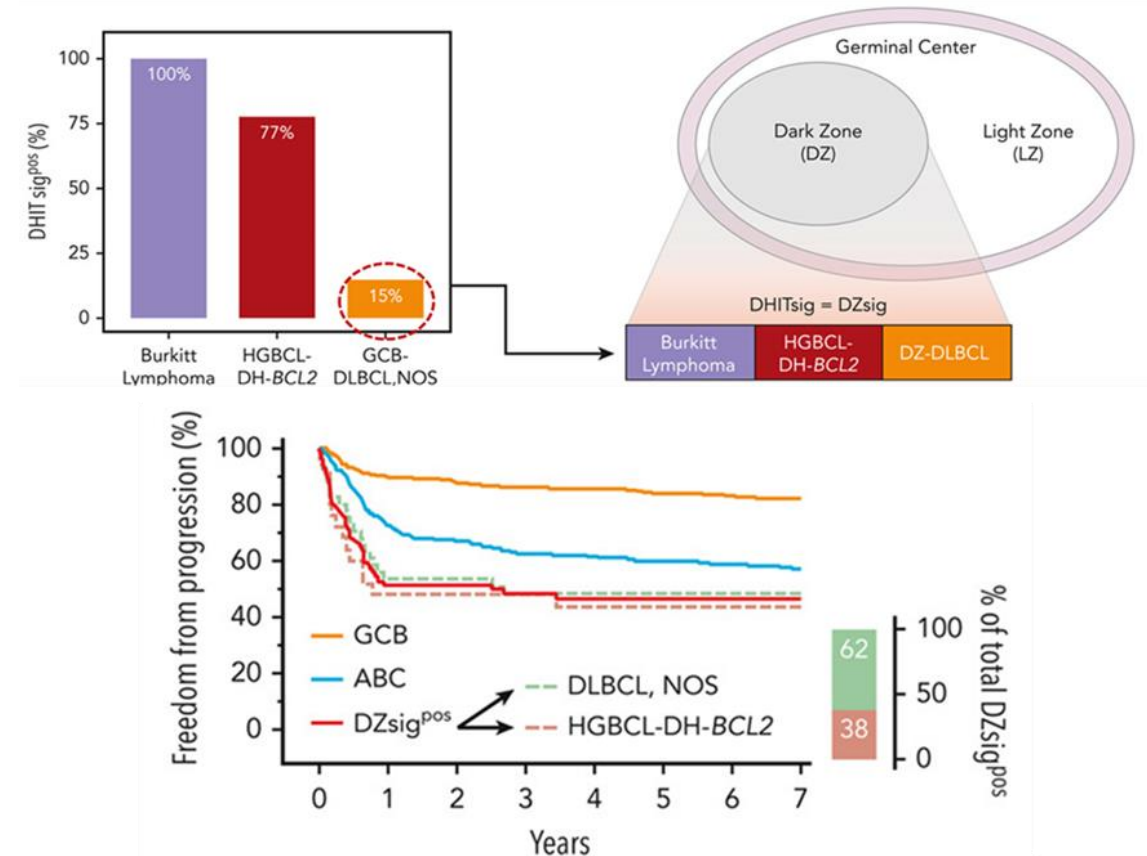
Patients with double-hit lymphomas respond poorly to chemotherapy and have very poor survival outcomes

Swerdlow SH, et al. Blood 2016; 127:2375–2390.
Friedberg JW. Blood 2017; 130: 590–596

Dark zone signature beyond HGBCL-DH-BCL2

- DHITsig expression extends beyond HGBCL-DH-BCL2 to identify dark zone lymphomas and was thus renamed the “Dzsig”
- Dzsig defines a “Dark Zone–like” molecular phenotype. ***Tumors expressing Dzsig share transcriptional programs of the germinal center dark zone, including high proliferation and immune-silent features.→ These cases represent a distinct molecular subgroup within GCB-DLBCL.***
- Patients with Dzsig+ DLBCL have markedly inferior progression-free survival, similar to HGBCL-DH-BCL2, and clearly worse than conventional GCB-DLBCL.
- Most Dzsig-positive cases are NOT double-hit lymphomas. **Among all Dzsig+ tumors: 62% are GCB-DLBCL NOS, 38% are HGBCL-DH-BCL2**

1. DHITsig expression extends beyond HGBCL-DH-BCL2 to identify dark zone lymphomas, and was thus renamed the “dark zone signature” (Dzsig)



The DHIT signature (renamed DarkZone signature – Dzsig) is present not only in Burkitt lymphoma (100%) and HGBCL-DH-BCL2 (77%), but also in ~15% of GCB-DLBCL, NOS.→ Dzsig identifies a broader high-risk biological group than classical double-hit disease.

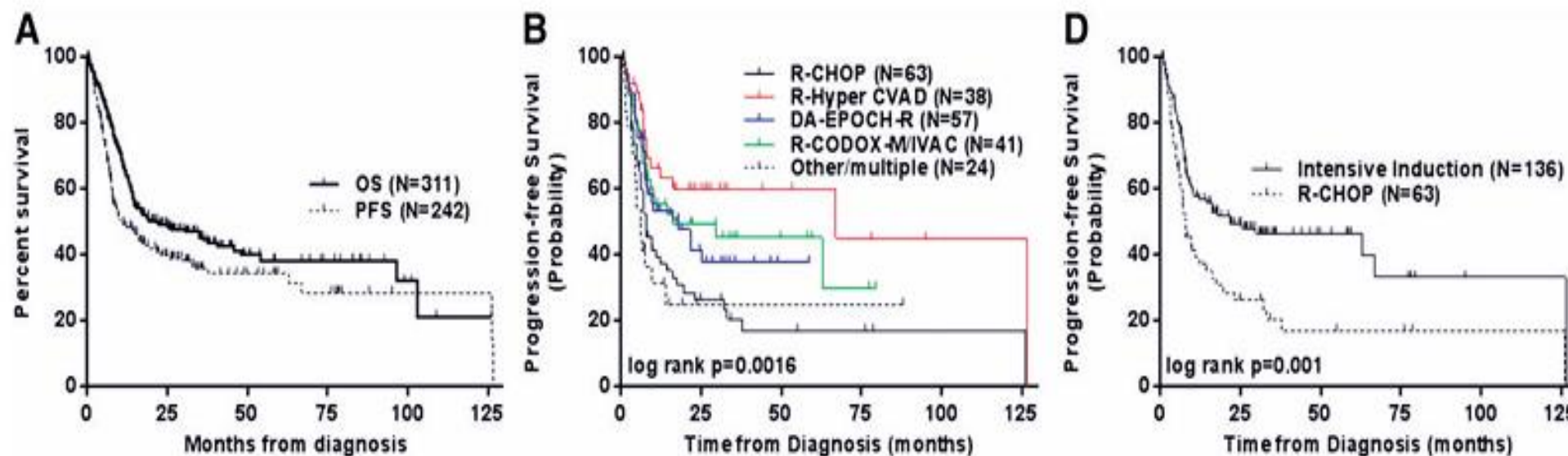
Pabst GW, 1929
Young RM, et al. Immunol Rev. 2019
Alduaij W, et al. BLOOD 2023

DHL: role of intensive regimens

311 pts DHL- median age 60 (19-87);

- DLBCL= 154 (50%) BCLU= 150(48%)
- BCL2 += 87%; BCL6+ =6% triple Hit= 6%
- GCB= 58 %

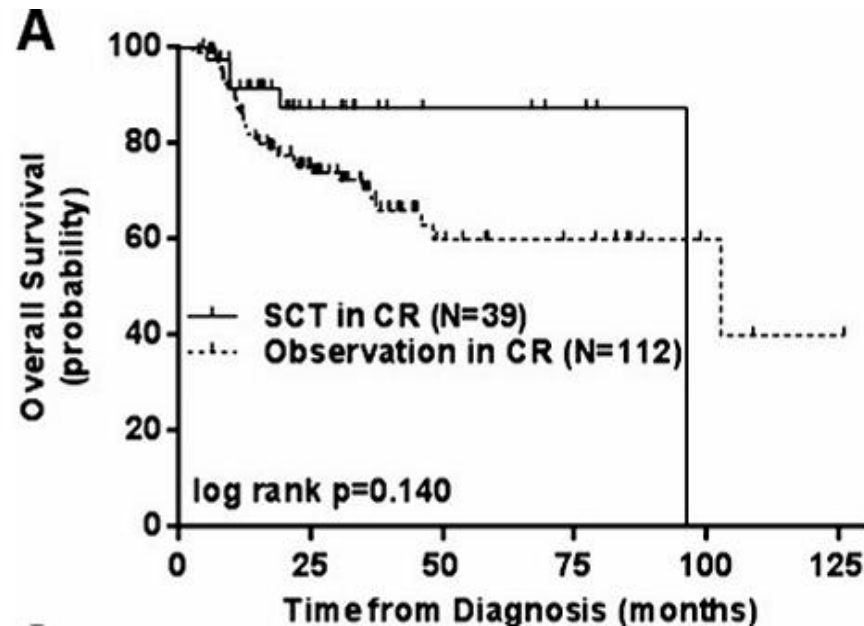
R-CHOP	100 (32)
R-Hyper-CVAD	66 (21)
DA-EPOCH-R	64 (21)
R-CODOX-M/IVAC	42 (14)
R-ICE	9 (3)
Others	31 (10)



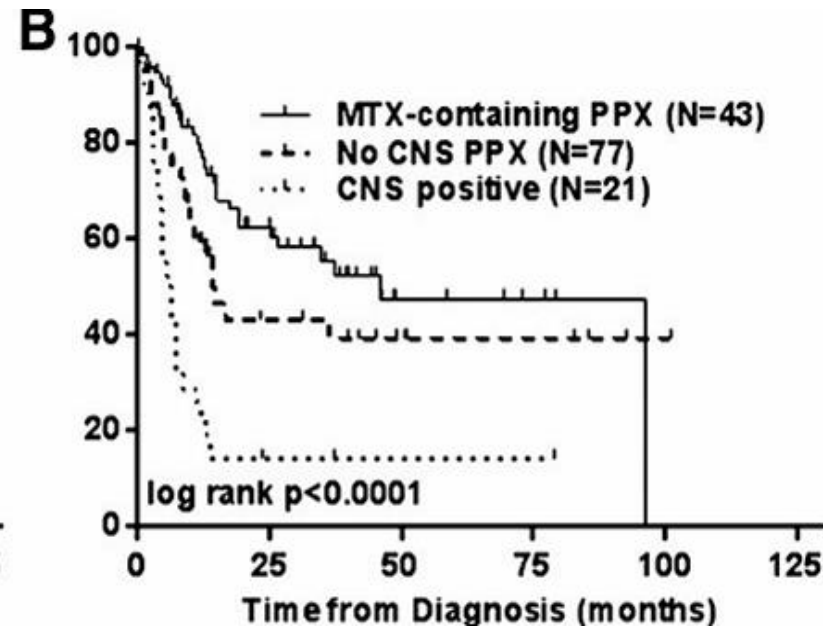
Educational ASH 2014

Petrich M, Gandhi M et al Blood 2014

DHL: role of frontline ASCT and CNS prophylaxis



For patients in CR, median OS was similar for those observed (103 months) and those undergoing consolidation SCT of any type .



CNS prophylaxis mandatory

Petrich M, Gandhi M et al 2014

Population-wide introduction of dose-adjusted EPOCH-R in high-grade B-cell lymphoma with *MYC/BCL2* rearrangements, DLBCL morphology

Waleed Alduaij,^{1,2} Laurie H. Sehn,^{1,2} Jean-Nicolas Champagne,^{1,3} Brett Collinge,^{1,4} Susana Ben-Neriah,¹ Aixiang Jiang,^{1,4} Laura K. Hilton,¹ Merrill Boyle,¹ Barbara Meissner,¹ Graham W. Slack,^{1,4} Pedro Farinha,^{1,4} Jeffrey W. Craig,^{1,5} Kerry J. Savage,^{1,2} Diego Villa,^{1,2} Alina S. Gerrie,^{1,2} Ciara L. Freeman,^{1,6} Andrew J. Mungall,^{1,7} Christian Steidl,^{1,4} and David W. Scott^{1,2}

Characteristic	DA-EPOCH-R Era (2015-2020)	Historic Era (2005-2010)
Patients	66	38
Age >60 y	59%	63%
Stage III-IV	86%	71%
High IPI	39%	31%
DA-EPOCH-R	71%	0%
R-CHOP	23%	84%

Key findings

- 104 HGBCL-DH-BCL2 patients
- Population-based comparison
- Balanced baseline characteristics
- DA-EPOCH-R adopted in 2015-2020

Population-wide introduction of DA-EPOCH-R is associated with improved outcomes in HGBCL-DH-BCL2 with DLBCL morphology

Alduaij A, et al Blood Adv 2026

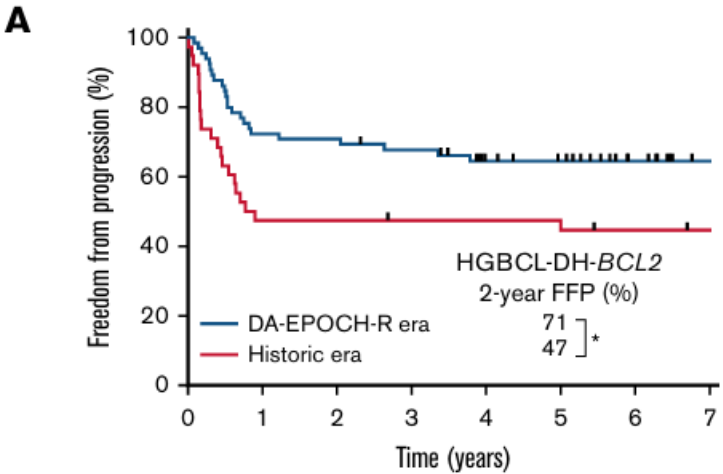


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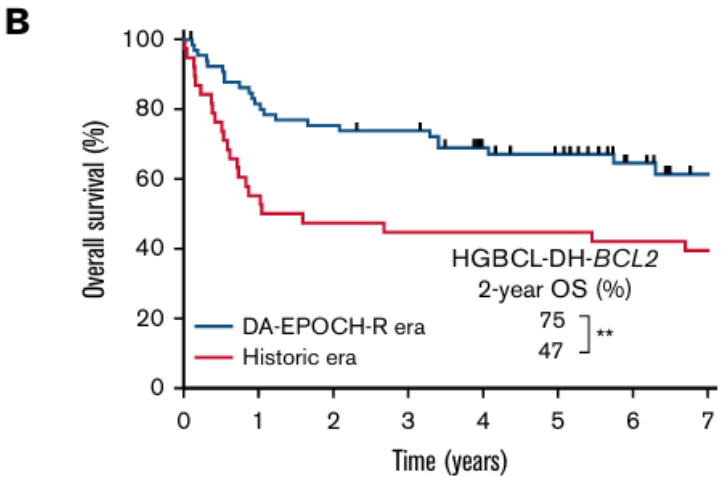
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DHL: survival benefit with R-DA-EPOCH



No. at risk:

DAEPOCHR	66	47	46	43	34	31	20	12
Historic	38	18	18	17	17	17	15	14



No. at risk:

DAEPOCHR	66	53	49	47	37	33	22	14
Historic	38	21	18	17	17	17	16	15

Outcome	DA-EPOCH-R	Historic	P
2y FFP	71%	47%	0.02
2y OS	75%	47%	0.008

Greatest benefit observed in:

- IG::MYC subgroup
- DZsig-positive tumors

Multivariable analysis

- FFP HR 0.38 (p=0.003)
- OS HR 0.38 (p=0.002)

Conclusion: after DA-EPOCH-R introduction, outcomes improved most in the IG::MYC and dark-zone signature– positive subgroups of HGBCL-DH-BCL2.

Alduaij A, et al Blood Adv 2026





Final response assessment by subtype

COHORT 2 POLARCHP first line

- N = 162, IPI 3-5
- HGBL 15, evaluable 14

Response	De novo (N=118)	Transform (N=11)	High-grade (N=14)	TCHR (N=3)	PMBCL (N=6)	Other (N=10)	Total (N=162)
Not assessed	1 (0.85)	1 (9.09)	1 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)	3 (1.85)
CR	86 (72.88)	9 (81.82)	11 (78.57)	1 (33.33)	6 (100.00)	6 (60.00)	119 (73.46)
PR	15 (12.71)	1 (9.09)	0 (0.00)	2 (66.67)	0 (0.00)	0 (0.00)	18 (11.11)
PD	5 (4.24)	0 (0.00)	1 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)	6 (3.70)
EW: AE	1 (0.85)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.62)
EW: PD/rel	3 (2.54)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (20.00)	5 (3.09)
EW: Death	5 (4.24)	0 (0.00)	1 (7.14)	0 (0.00)	0 (0.00)	2 (20.00)	8 (4.94)
EW: Other	2 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.23)

Tavarozzi R, et al, SIE 2026

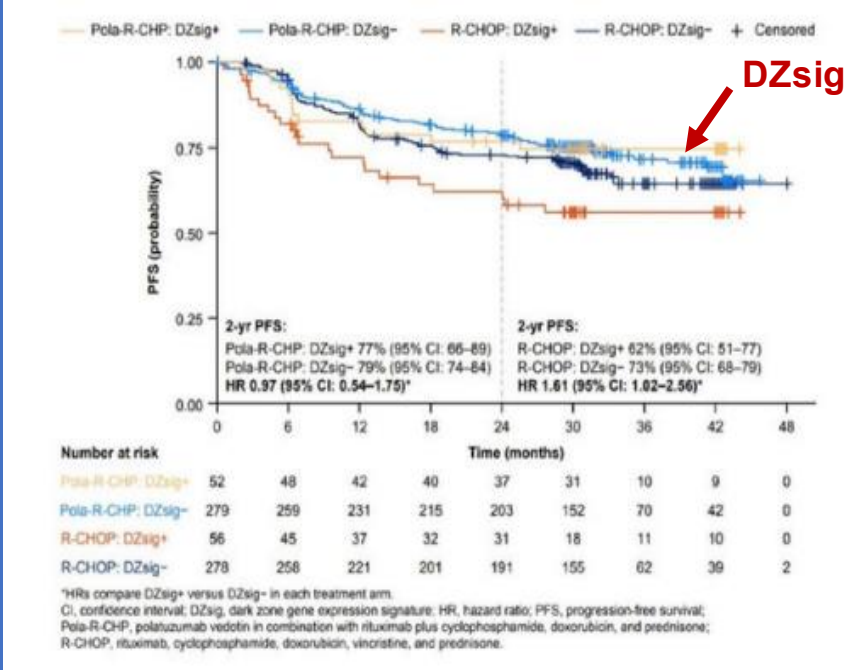
Deciphering the Clinical Benefit of Pola-R-CHP versus R-CHOP in Different Genetic Subtypes Beyond Cell of Origin in the POLARIX



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Subtypes	Prevalence, n (%)		2-yr PFS, % (95% CI)	
	Pola-R-CHP n = 292	R-CHOP n = 302	Pola-R-CHP	R-CHOP
EZB	81 (28)	73 (24)	83 (76–92)	75 (65–86)
MCD	33 (11)	40 (13)	85 (73–98)	75 (63–90)
BN2	27 (9)	26 (9)	78 (63–95)	88 (77–100)
N1	1 (>1)	1 (>1)	NA	NA
ST2	17 (6)	15 (5)	76 (57–100)	86 (69–100)
Genetically composite	10 (3)	13 (4)	50 (27–93)	77 (57–100)
Other	123 (42)	134 (44)	74 (67–82)	62 (54–71)

BN2, BCL6 fusions and NOTCH2 mutations; CI, confidence intervals; EZB, EZH2 mutations and BCL2 translocations; MCD, MYD88^{L265P} and CD79B mutations; NA, not applicable; N1, NOTCH1 mutations; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ST2, SGK1 and TET2 mutated.



Morschhauser, ASH 2023



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DOUBLE EXPRESSOR LYMPHOMAS (DEL)

first line treatment



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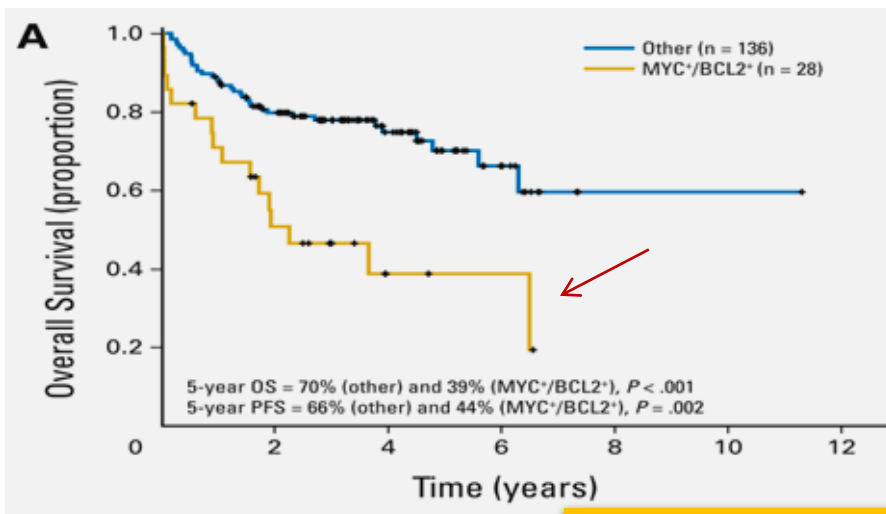
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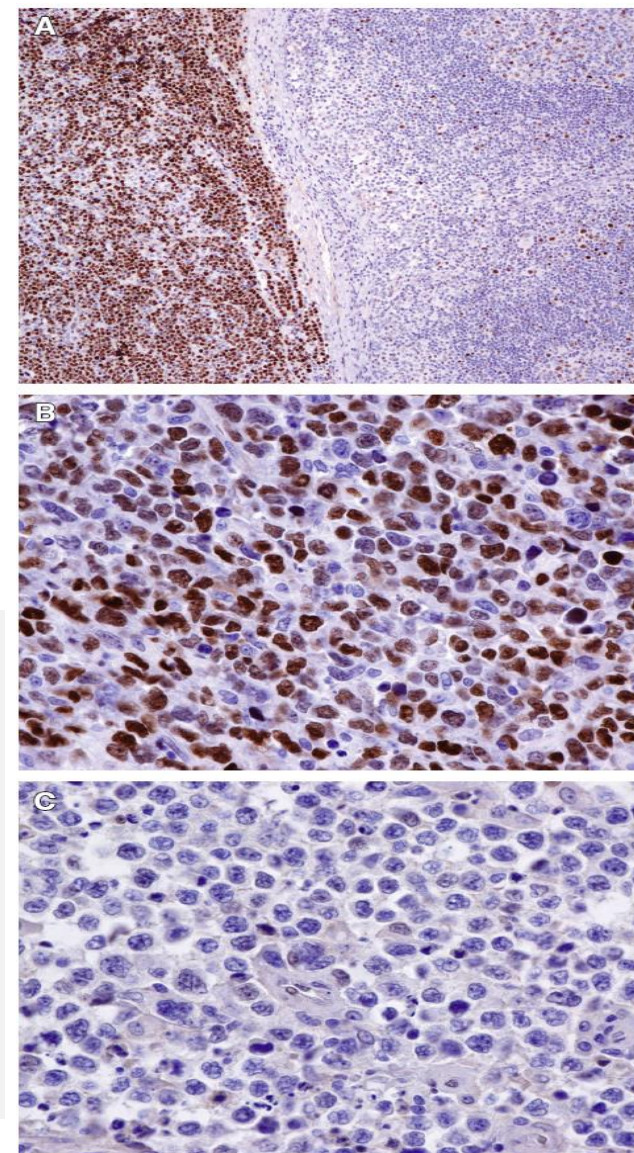
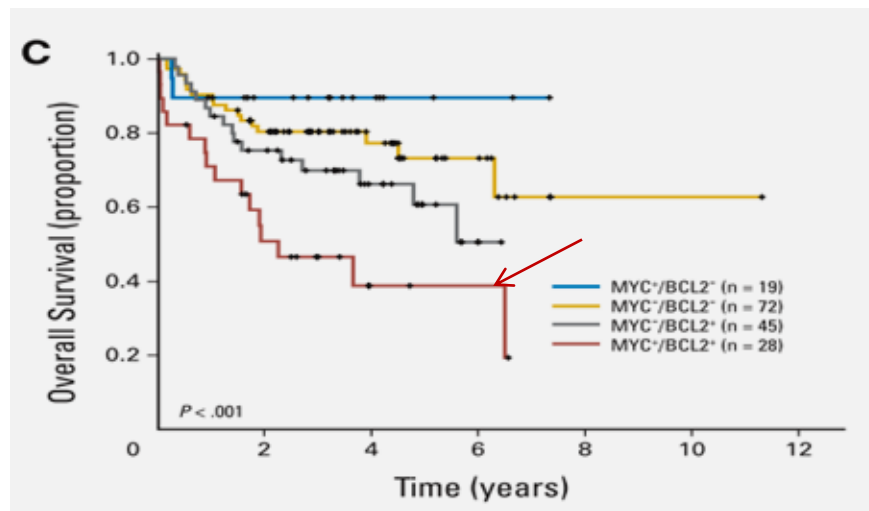
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone



Nathalie A. Johnson, Graham W. Slack, Kerry J. Savage, Joseph M. Connors, Susana Ben-Neriah, Sanja Rogic, David W. Scott, King L. Tan, Christian Steidl, Laurie H. Sehn, Wing C. Chan, Javeed Iqbal, Paul N. Meyer, Georg Lenz, George Wright, Lisa M. Rimsza, Carlo Valentino, Patrick Brunhoeber, Thomas M. Grogan, Rita M. Braziel, James R. Cook, Raymond R. Tubbs, Dennis D. Weisenburger, Elias Campo, Andreas Rosenwald, German Ott, Jan Delabie, Christina Holcroft, Elaine S. Jaffe, Louis M. Staudt, and Randy D. Gascoyne



Myc+: $\geq 40\%$ pos.
Bcl2+: $\geq 50\%$ pos.



Johnson et al J.Clin. Oncol 2012



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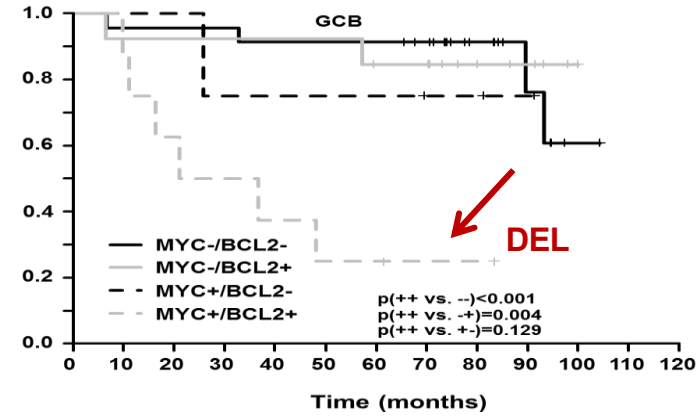
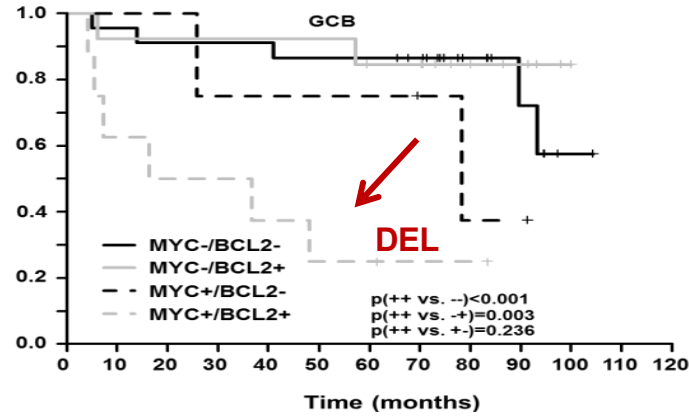
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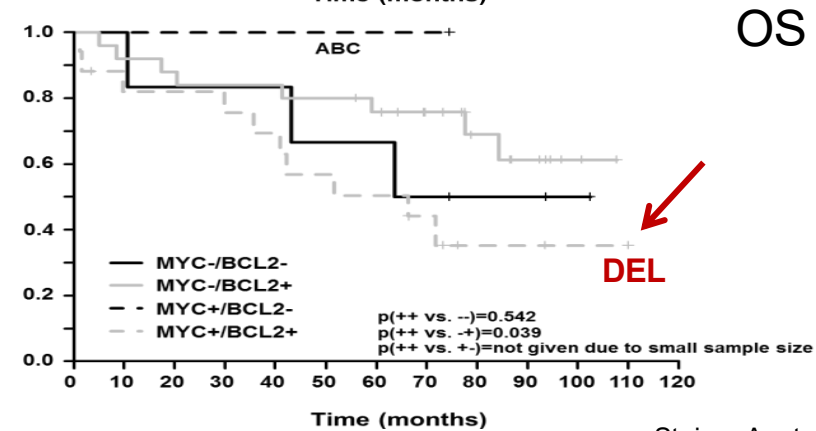
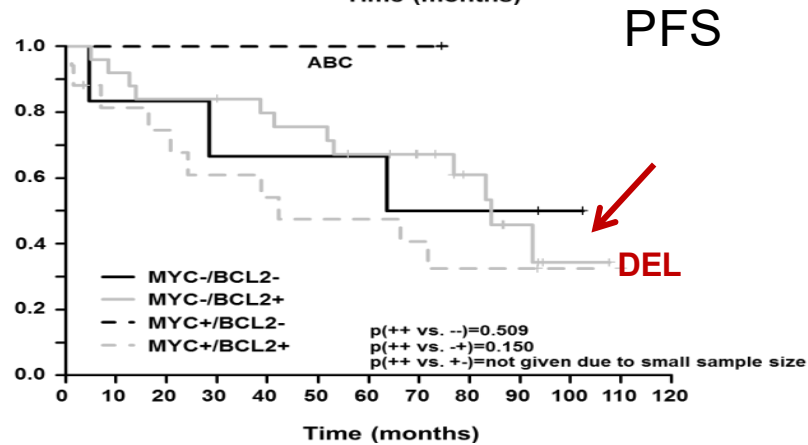
Clinical Impact of the Cell-of-Origin Classification and the MYC/BCL2 Dual Expresser Status in Diffuse Large B-Cell Lymphoma Treated Within Prospective Clinical Trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group

Survival Analysis of COO-Classified MYC/BCL2 Dual Expressers

GCB



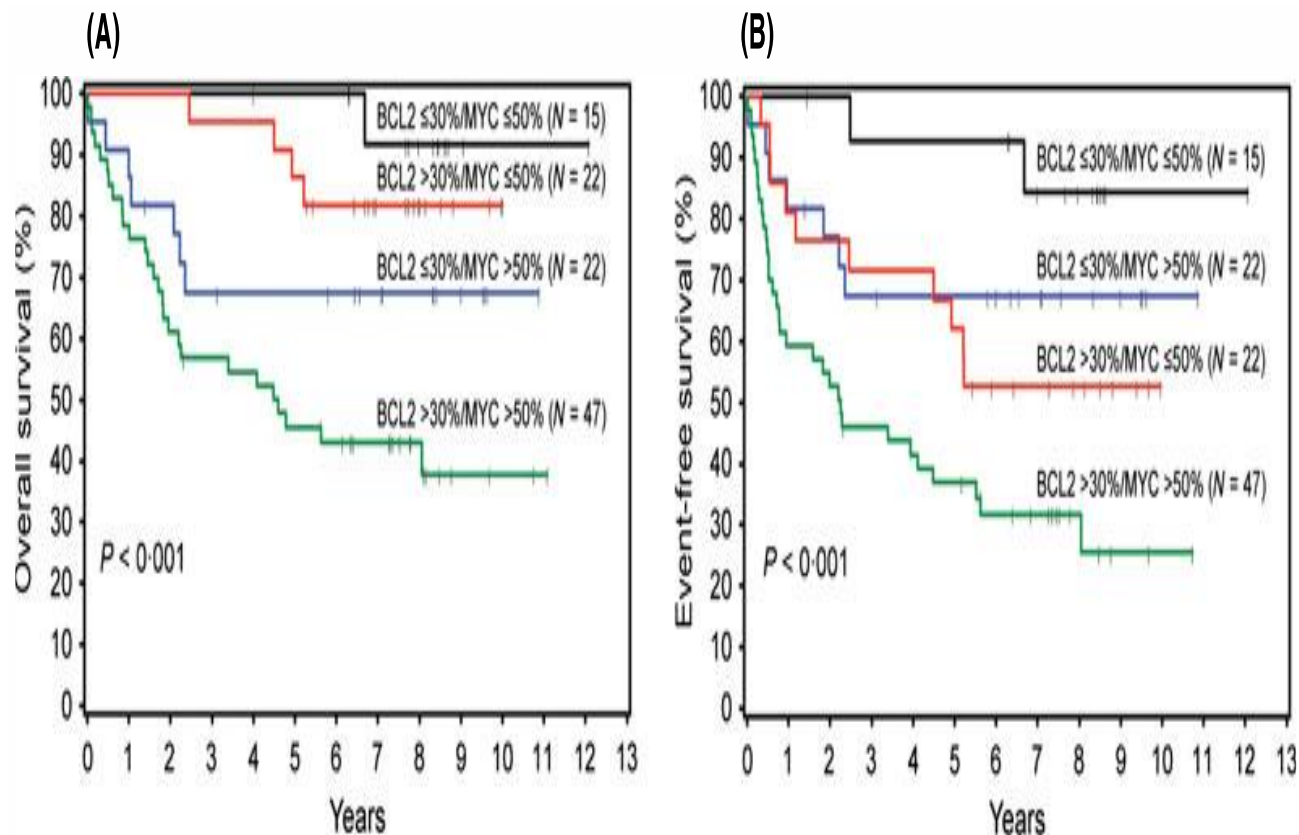
ABC



Staiger A. et al . J.Clin Oncol 2017

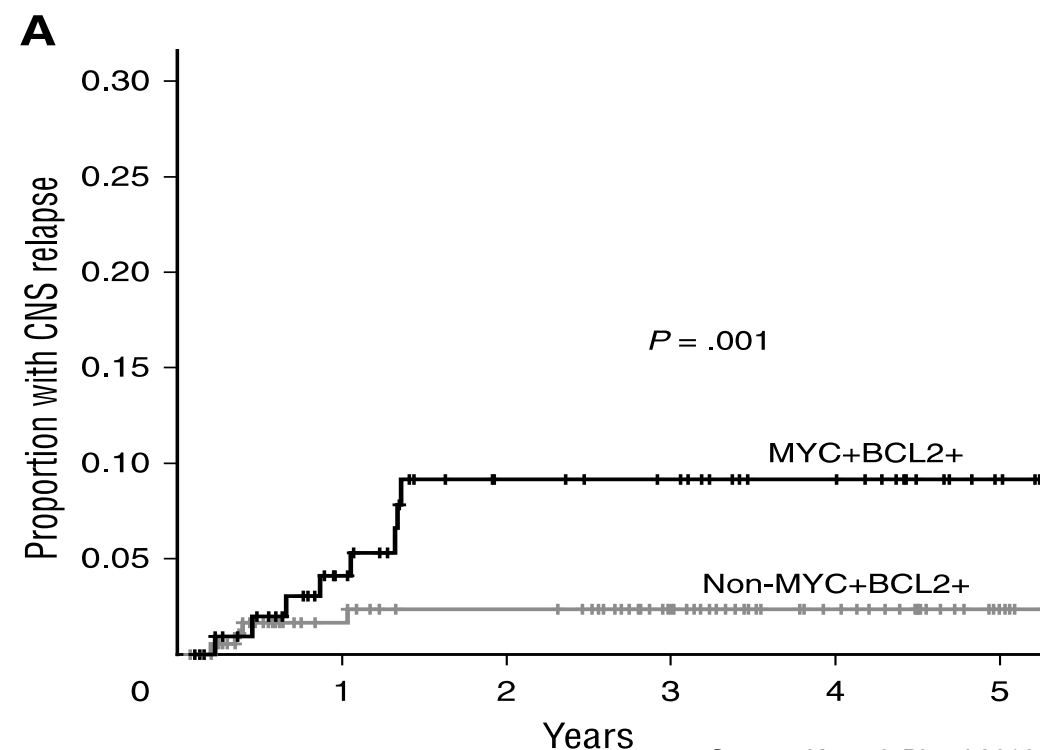
DEL- prognostic impact and risk of CNS relapse

MYC and BCL2 protein expression predicts survival in patients with diffuse large B-cell lymphoma treated with rituximab



Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL

Kerry J. Savage,¹ Graham W. Slack,² Anja Mottok,² Laurie H. Sehn,¹ Diego Villa,¹ Roopesh Kansara,³ Robert Kridel,² Christian Steidl,² Daisuke Ennishi,² King L. Tan,² Susana Ben-Neriah,² Nathalie A. Johnson,⁴ Joseph M. Connors,¹ Pedro Farinha,² David W. Scott,¹ and Randy D. Gascoyne²



Savage K, et al, Blood 2016

Do DEL need more intensive approach than R-CHOP?

The case of R-DA-EPOCH

Leukemia (2019) 33:1047–1051
<https://doi.org/10.1038/s41375-018-0320-9>

Lymphoma

Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma

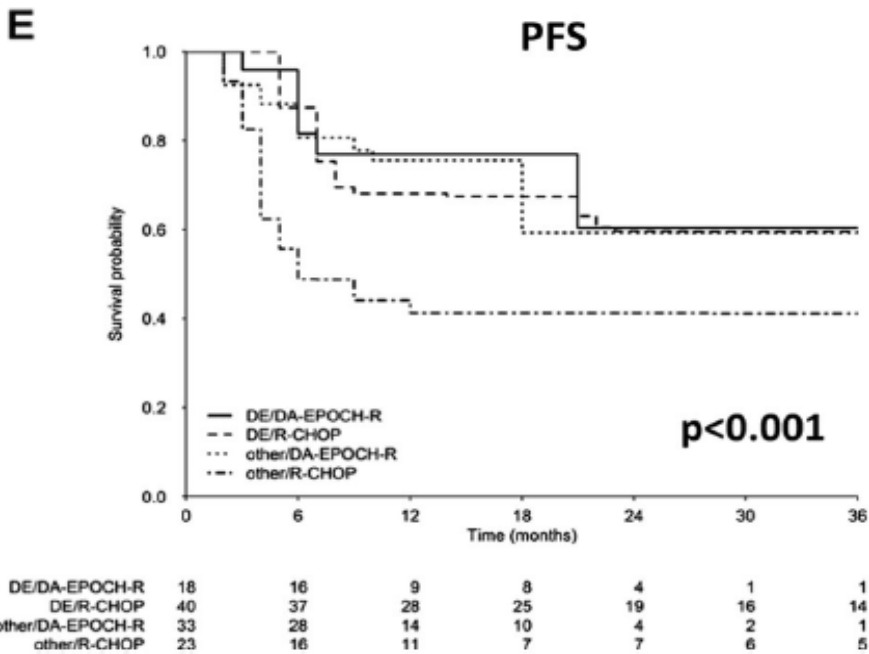


Table 1 Clinical and biological characteristics

Variable	ALL N = 114	DA-EPOCH-R N = 51	R-CHOP N = 63	SMD before/after
Age				
Median	62 years	58 years	65 years	0.296/<0.001
Range	29–81	29–79	36–81	
Age > 65 years	43 (38%)	14 (27%)	29 (46%)	
Sex				
Male	70 (62%)	32 (63%)	38 (60%)	0.049/0.018
Female	44 (38%)	19 (37%)	25 (40%)	
Histology				
DLBCL	106 (93%)	47 (92%)	59 (94%)	
Transformed	8 (7%)	4 (8%)	4 (6%)	—
Stage				
I–II	28 (25%)	8 (16%)	20 (32%)	0.850/0.079
III–IV	86 (75%)	43 (84%)	43 (68%)	
IPI				
1–2	62 (54%)	24 (47%)	38 (60%)	0.332/0.101
3–5	52 (46%)	27 (53%)	25 (40%)	
BM involvement				
Yes	22 (19%)	16 (32%)	6 (10%)	0.552/0.421
No	92 (81%)	35 (68%)	57 (90%)	
Extranodal involvement ^a				
Yes	69 (60%)	46 (90%)	23 (36%)	—
No	45 (40%)	5 (10%)	40 (64%)	
CNS involvement				
Leptomeningeal	3 (3%)	2 (4%)	1 (1%)	—
Cytogenetic abnormalities				
DE-only	58 (51%)	18 (35%)	40 (63%)	0.749/0.119
DE with SH	29 (25%)	16 (31%)	13 (21%)	
DE with DH/TH	10 (9%)	8 (16%)	2 (3%)	
DE with atypical DH	15 (13%)	9 (18%)	6 (10%)	
Missing	2 (2%)	0 (0%)	2 (3%)	
FISH rearrangements				
MYC R	7 (6%)	5 (10%)	—	—
BCL2 R	8 (7%)	5 (10%)	2 (3%)	
BCL6 R	14 (12%)	6 (12%)	3 (5%)	
MYC R/BCL2 R	5 (4%)	4 (7%)	8 (13%)	
MYC R/BCL6 R	2 (2%)	2 (4%)	1 (2%)	
MYC R/BCL2 R/BCL6 R	3 (3%)	2 (4%)	0 (0%)	
Cell of origin (Hans)				
GCB	42 (37%)	22 (43%)	20 (31%)	0.334/0.049
Non GCB	57 (50%)	25 (49%)	32 (51%)	
Not evaluable	15 (13%)	4 (8%)	11 (18%)	

Dodero A. et al, Leukemia 2019

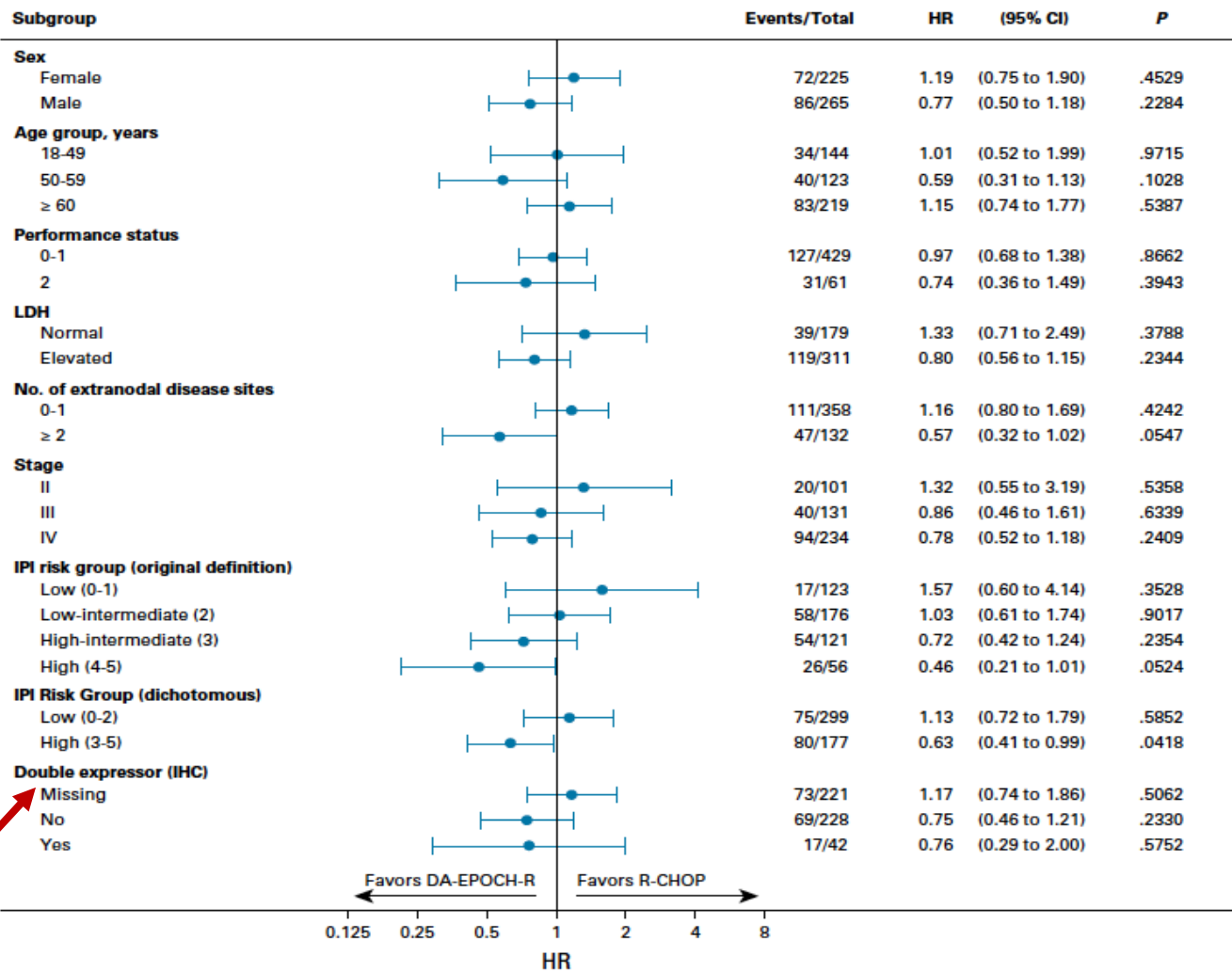


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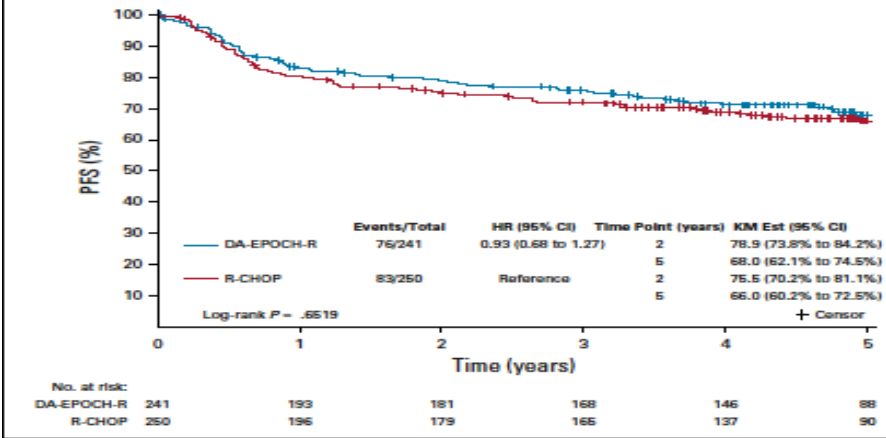
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Is DA-EPOCH-R superior to R-CHOP in DEL?



Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303



524 DLBCL patients; DEL: 15.6%
No differences by treatment arm in the MYC rearranged or patients with DEL phenotype: this subset was of insufficient size for statistical comparison

Bartlett NL, et al. J Clin Oncol 2019

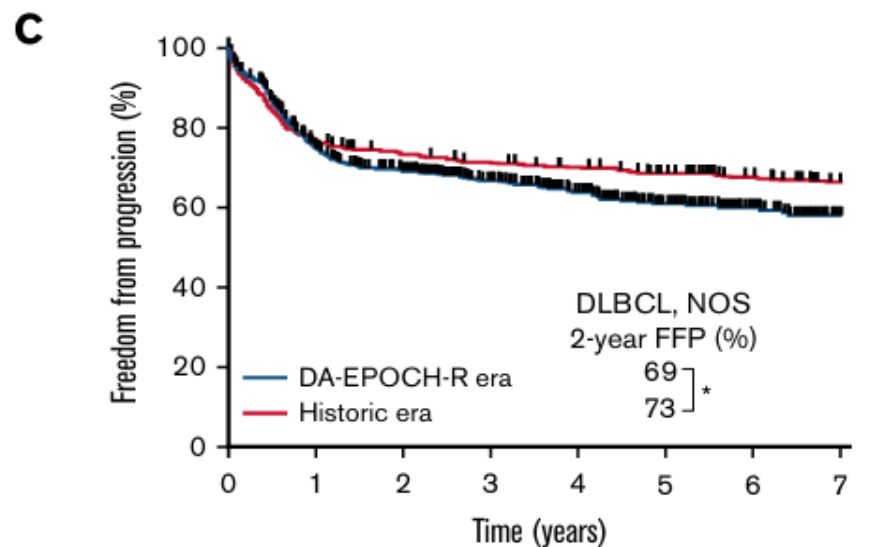


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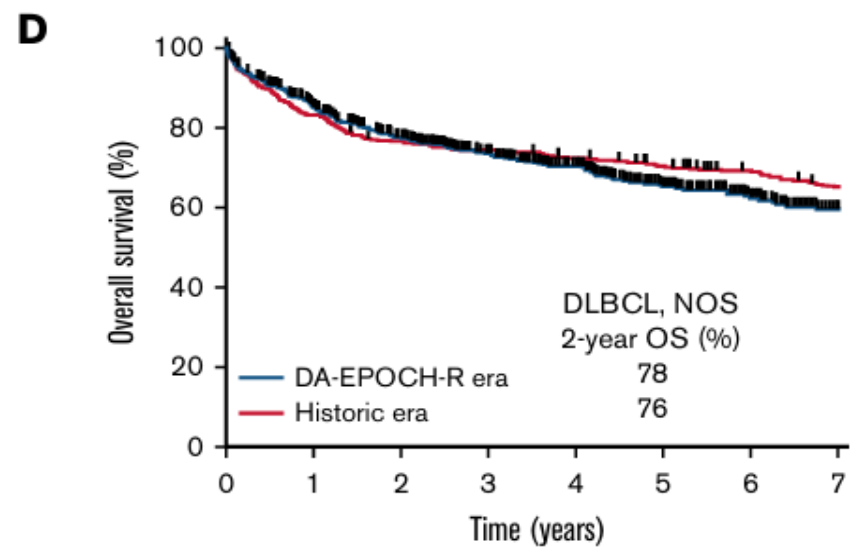
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R-CHOP vs R-DA -EPOCH in non DHL (mostly DEL)



No. at risk:

DAEPOCHR	626	434	365	279	208	144	102	57
Historic	534	406	383	370	357	339	320	303



No. at risk:

DAEPOCHR	627	499	420	328	250	173	122	71
Historic	534	443	405	394	382	367	349	327

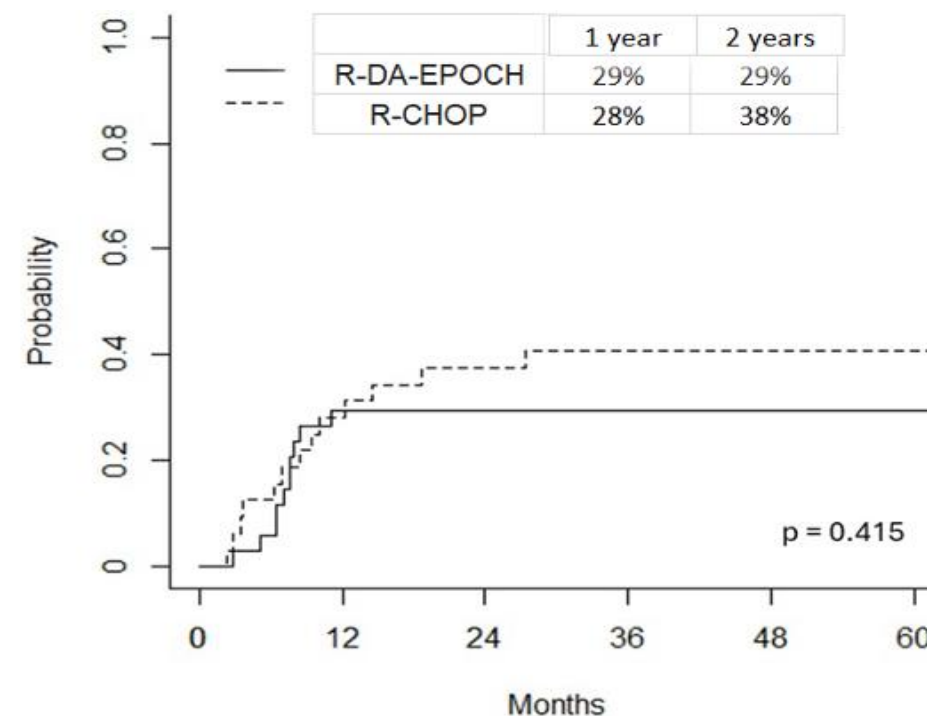
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RCHOP vs R-DA -EPOCH in non DHL : Humanitas experience

Characteristic	Total N=66	R-CHOP (n=32)	R-DA-EPOCH (n=34)	P value
Median age (range)	64 (22–80)	68 (22–80)	63 (25–76)	0.2920
Sex (M/F)	34 / 32	15 / 17	19 / 15	0.6270
(%)	(51.5 / 48.5)	(46.9 / 53.1)	(55.9 / 44.1)	NA
Comorbidity (No/Yes)	18 / 48	lug.25	nov.23	0.4970
(%)	(27.3 / 72.7)	(21.9 / 78.1)	(32.4 / 67.6)	NA
Stage (II/III/IV)	2 / 13 / 51	0 / 7 / 25	02.06.2026	0.2450
(%)	(3.0 / 19.7 / 77.3)	(0 / 21.9 / 78.1)	(5.9 / 17.6 / 76.5)	NA
IPI (0–1 / 2–3 / 4–5)	9 / 37 / 20	4 / 16 / 12	5 / 21 / 8	0.4640
(%)	(13.6 / 56.1 / 30.3)	(12.5 / 50.0 / 37.5)	(14.7 / 61.8 / 23.5)	NA
CNS-IPI (0–3 / 4–5)	41 / 25	18 / 14	23.nov	0.4830
(%)	(62.1 / 37.9)	(56.3 / 43.8)	(67.6 / 32.4)	NA
Bulky disease (No/Yes)	43 / 23	24.ago	19 / 15	0.1700
(%)	(65.2 / 34.8)	(75.0 / 25.0)	(55.9 / 44.1)	NA
ECOG PS (0–1 / ≥2)	44 / 22	21.nov	23.nov	1.0000
(%)	(66.7 / 33.3)	(65.6 / 34.4)	(67.6 / 32.4)	NA
LDH > ULN (No/Yes/Missing)	19 / 46 / 1	11 / 20 / 1	8 / 26 / 0	0.4320
(%)	(28.8 / 69.7 / 1.5)	(35.5 / 64.5 / 3.1)	(23.5 / 76.5 / 0.0)	NA
Extranodal sites (0–1 / ≥2)	59 / 7	25.lug	34 / 0	0.0043
(%)	(89.4 / 10.6)	(78.1 / 21.9)	(100 / 0)	NA
Bone marrow involvement (No/Yes)	56 / 10	28.apr	28.giu	0.8100
(%)	(84.8 / 15.2)	(87.5 / 12.5)	(82.4 / 17.6)	NA
COO (GCB / non-GCB / Missing)	19 / 41 / 6	7 / 21 / 4	12 / 20 / 2	0.4470
(%)	(28.8 / 62.1 / 9.1)	(21.9 / 65.6 / 12.5)	(35.3 / 58.8 / 5.9)	NA
IHC (MYC+BCL2 / MYC+BCL6 / MYC+BCL2+BCL6)	03.08.1960	0 / 5 / 27	03.03.1933	0.1790
(%)	(4.5 / 12.1 / 90.9)	(0 / 15.6 / 84.4)	(8.8 / 8.8 / 97.1)	NA
Ki-67 (<90% / ≥90% / Missing)	36 / 27 / 3	15 / 15 / 2	21.12.2001	0.4020
(%)	(54.5 / 40.9 / 4.5)	(50.0 / 50.0 / 6.3)	(63.6 / 36.4 / 2.9)	NA

DEL lymphomas, advanced stage

- ✓ RCHOP 2010-2015 vs R-DA-EPOCH 2016-2023
- ✓ Matched comparison by Chi-square or Fisher's exact test



Pistolese F,.... Balzarotti M..., SIE 2025

Do DEL need more drugs than R-CHOP?

The case of BTK inhibitors

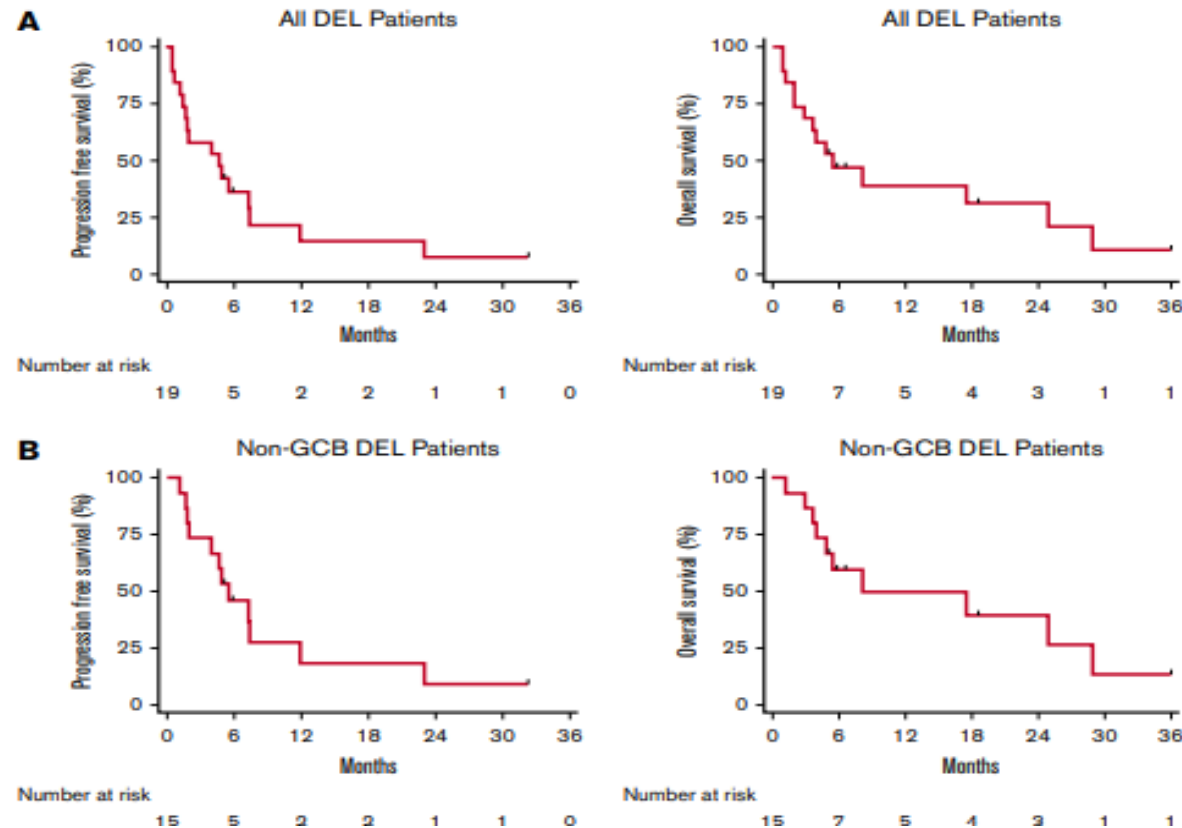
Outcomes of patients with relapsed/refractory double-expressor B-cell lymphoma treated with ibrutinib monotherapy

Daniel J. Landsburg,¹ Mitchell E. Hughes,² Alexa Koike,³ David Bond,⁴ Kami J. Maddocks,⁴ Ling Guo,⁵ Allison M. Winter,⁶ Brian T. Hill,⁶ Sarah L. Ondrejka,⁷ Eric D. Hsi,⁷ Sunita D. Nasta,¹ Jakub Svoboda,¹ Stephen J. Schuster,¹ and Agata M. Bogusz³

¹Department of Medicine, ²Department of Pharmacy, and ³Department of Pathology, University of Pennsylvania, Philadelphia, PA; ⁴Department of Internal Medicine and ⁵Department of Pathology, The Ohio State University, Columbus, OH; and ⁶Department of Hematology/Oncology and ⁷Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, OH

19 DELs, 15 non CGB COO

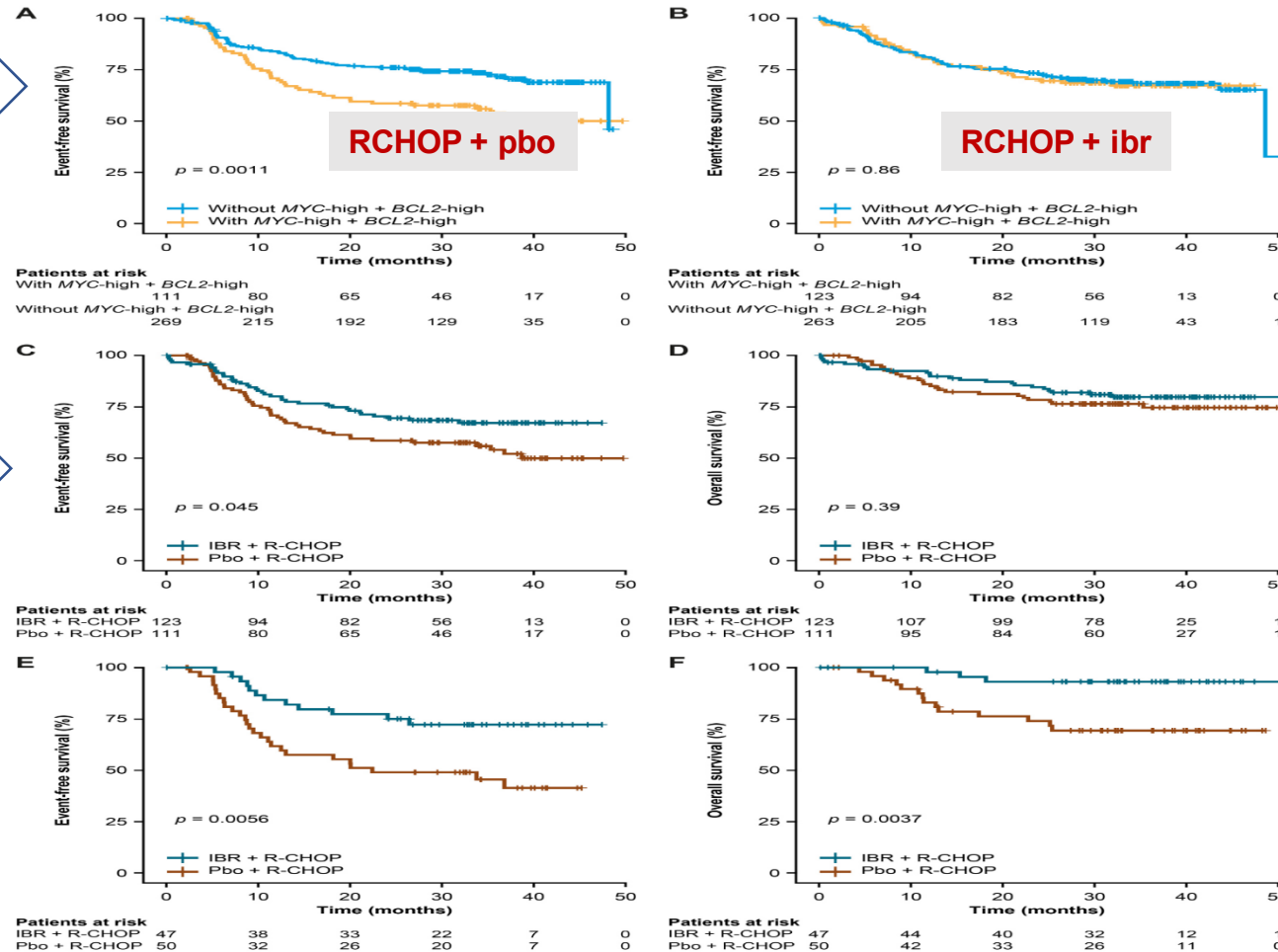
- ORR 60%
- CR rate 47%



Immunohistochemical stratification of treatment? ibrutinib-R-CHOP in double expressor DLBCL



Figure. Kaplan-Meier curves for EFS in patients with *MYC*-high + *BCL2*-high versus without (A) in the pbo + R-CHOP arm and (B) in the IBR + R-CHOP arm in the ITT population, (C) EFS and (D) OS in the IBR + R-CHOP versus pbo + R-CHOP arm in patients with *MYC*-high + *BCL2*-high in the ITT population, (E) EFS and (F) OS in the IBR + R-CHOP versus pbo + R-CHOP arm in patients < 60 years with *MYC*-high + *BCL2*-high



Clinical
Impact of Ibrutinib with R-CHOP in
Untreated Non-GCB DLBCL Co-
Expressing BCL2 and MYC Genes in
the Phase 3 Phoenix Trial

Johnson P, et al: Blood 2019



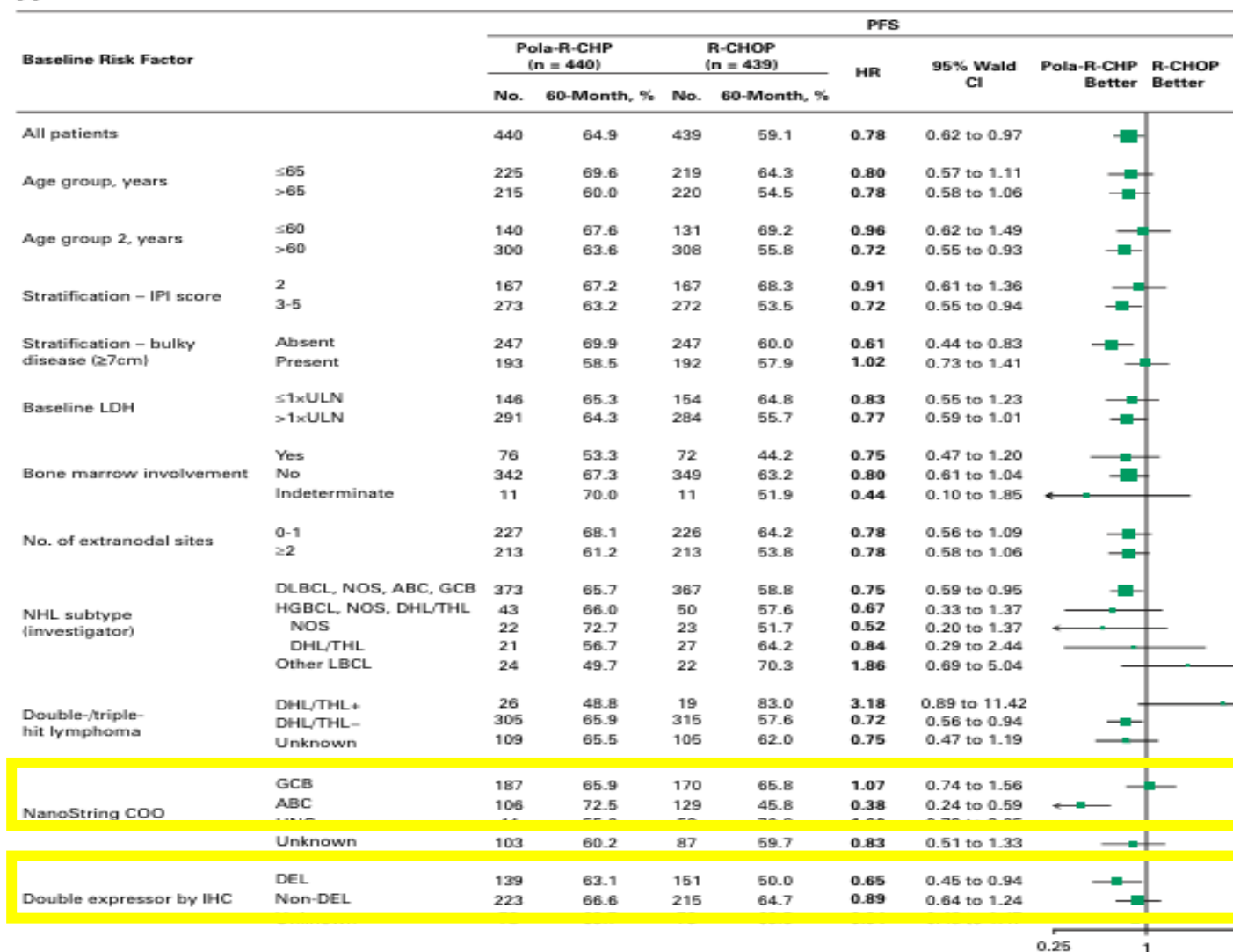
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POLA-R-CHP investigator-assessed PFS by subgroup

A

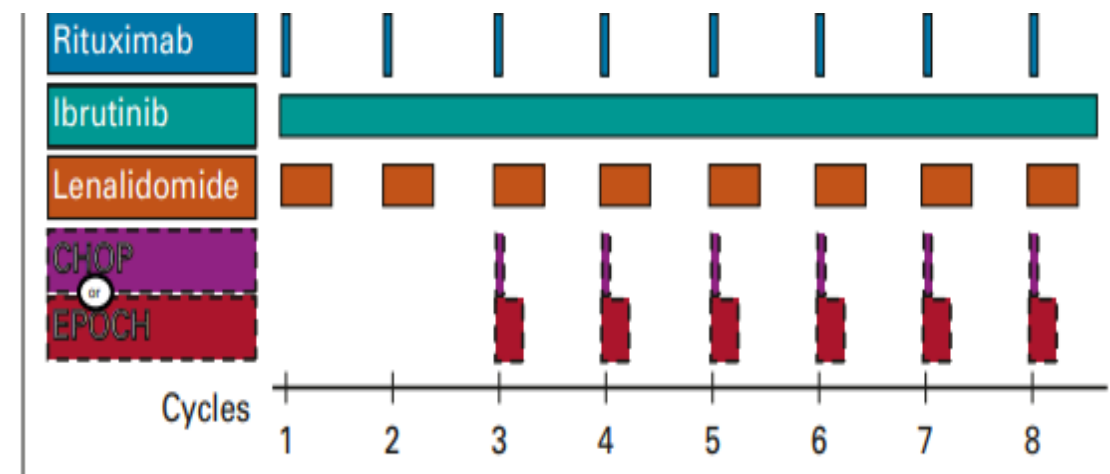


**PFS advantage in
POLAR-CHP DEL group**

Morschhauser et al , JCO 2025 .

first line DLBCL: a chemofree approach

Smart Start: R+Len+Ibrutinib (RLI) Lead-in Prior to Addition of Chemotherapy for Newly Diagnosed DLBCL



- Primary Objectives
 - 1A: To determine the ORR at the end of 2 cycles of RLI alone
 - 1B: To determine the CR rate at the end of RLI x 2 + RLI combined

original reports Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma

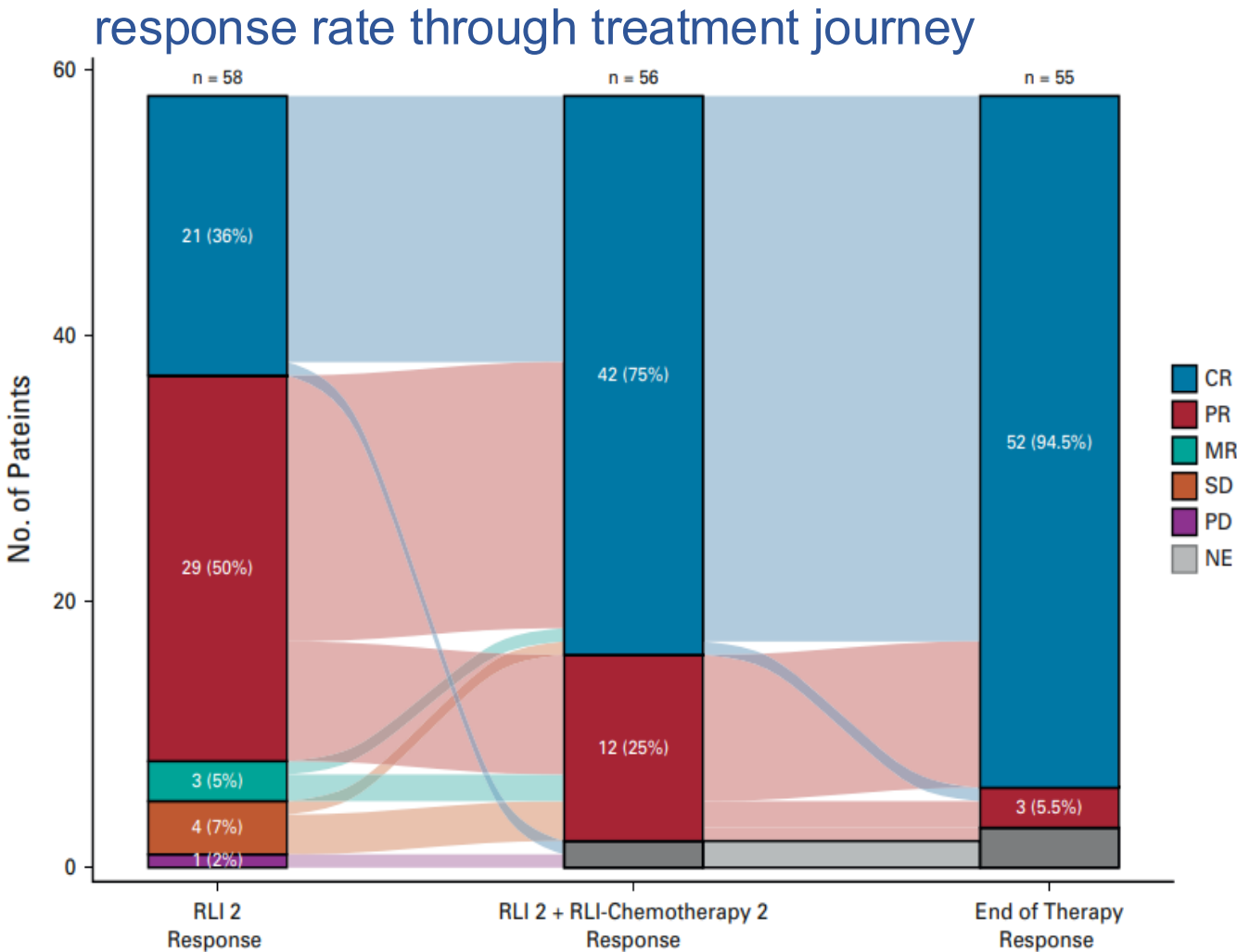
Jason Westin, MD, MS¹; R. Eric Davis, MD¹; Lei Feng, MS²; Fredrick Hagemeister, MD¹; Raphael Steiner, MD¹; Hun Ju Lee, MD¹; Luis Fayad, MD¹; Loretta Nastoupil, MD¹; Sairah Ahmed, MD¹; Alma Rodriguez, MD¹; Michelle Fanale, MD^{1,3}; Felipe Samaniego, MD¹; Swaminathan P. Iyer, MD¹; Ranjit Nair, MD¹; Yasuhiro Oki, MD¹; Nathan Fowler, MD¹; Michael Wang, MD¹; Man Chun John Ma, PhD¹; Francisco Vega, MD⁴; Timothy McDonnell, MD⁴; Chelsea Pinnix, MD, PhD⁵; Donna Griffith, RN¹; Yang Lu, MD⁶; Sanjit Tewari, MD⁶; Ryan Sun, PhD²; David W. Scott, MBChB, PhD⁷; Christopher R. Flowers, MD¹; Sattva Neelapu, MD¹; and Michael R. Green, PhD^{1,8}

N	60	non GCB (IHC)
Median age	63,5	range 29-83
Age > 70	17	28%
Stage III-IV	38	63%
IPI 3-5	25	42%
Elevated LDH	33	55%
Ki67> 90%	23	45%
DEL (39 tested)	24	62%

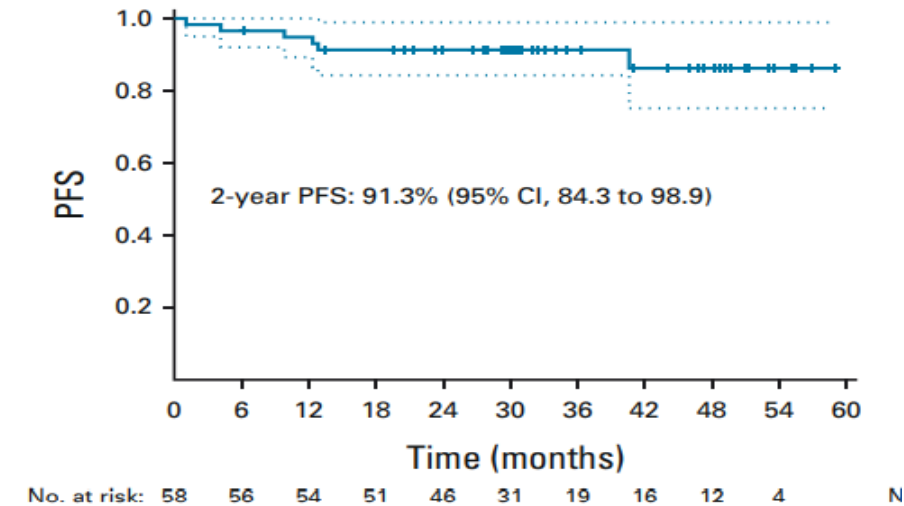
Westin J et al, JCO 2023



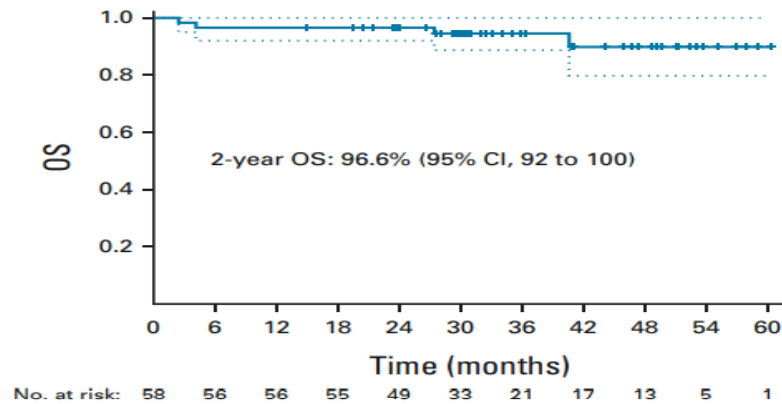
Smart Start results



B



C



no difference between CHOP and EPOCH (no dose adjustment)

Westin J et al, JCO 2023



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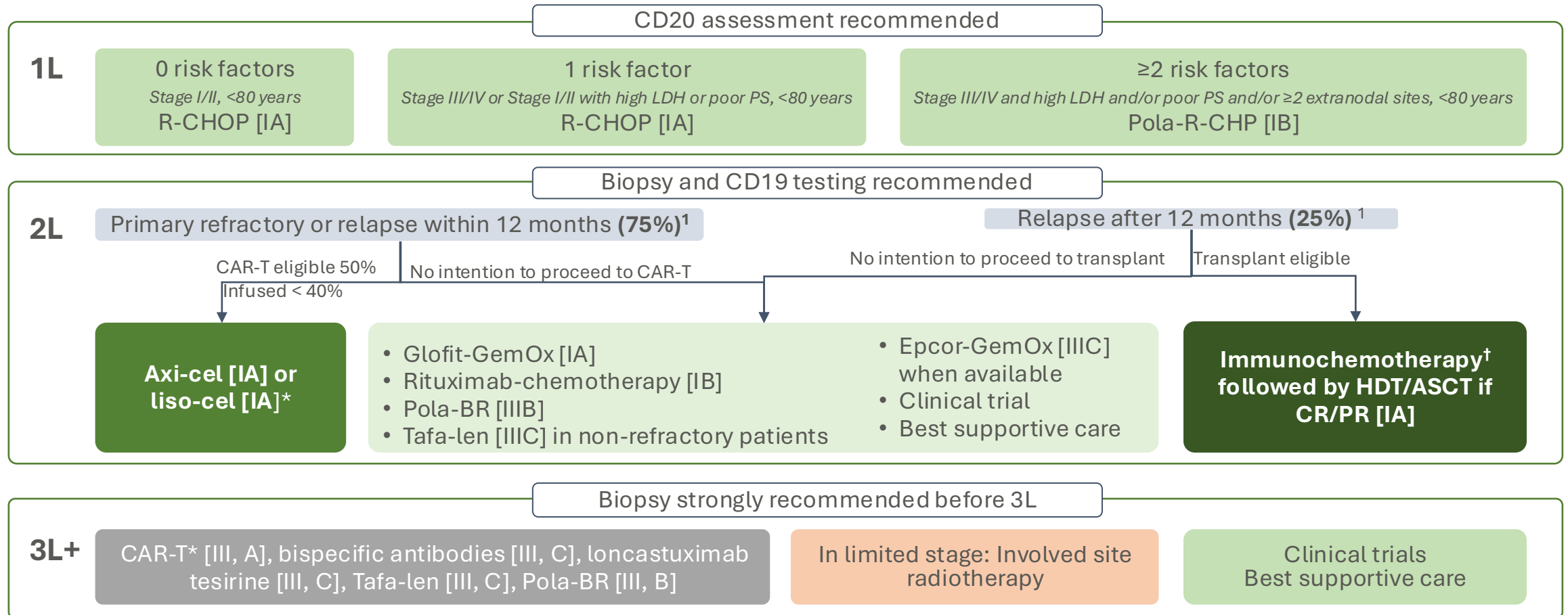
Treatment of refractory/relapsed disease DEL, DHL,HGBL, etc



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Thieblemont et al. *Hemasphere* 2025.

CART-SIE experience in HGBL

Objective and Study Population

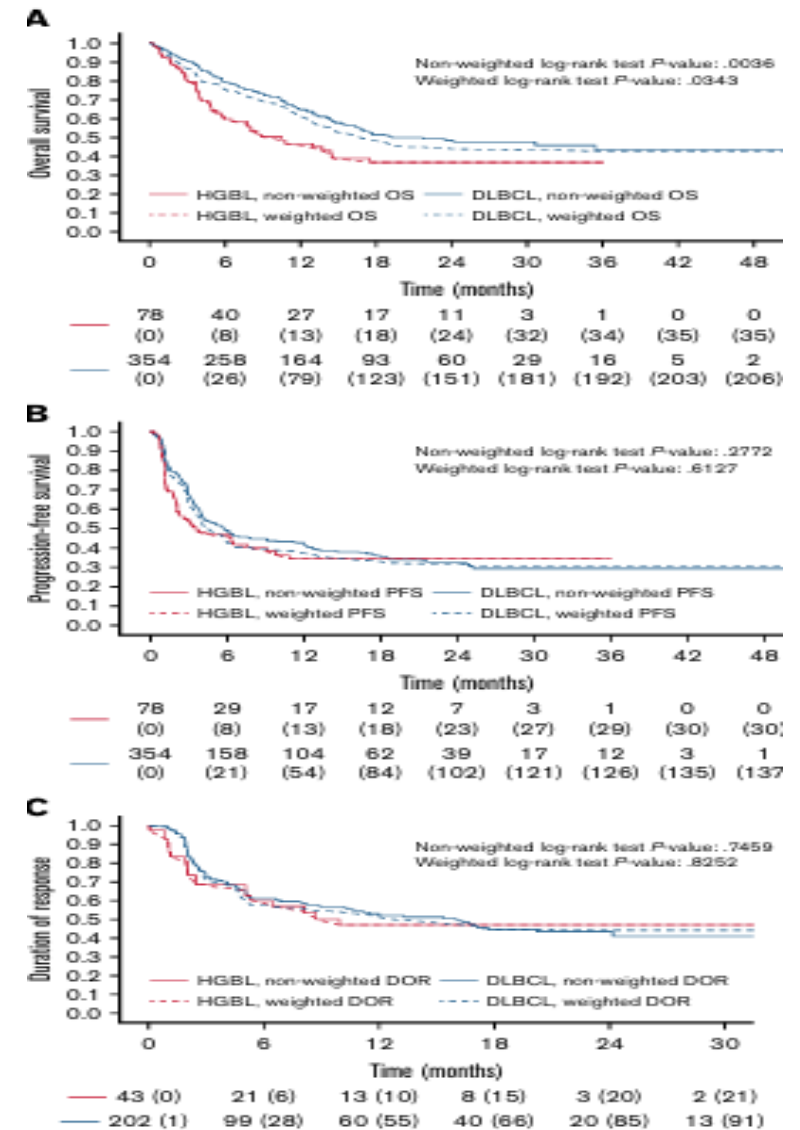
Predictive value of subtype (HGBL versus DLBCL) using a weighted log-rank test and a weighted Cox model in pts treated with CD19 CAR T cells in third line or beyond

N = 432 pts CD19 CAR T cells infused Axicel (n = 210) Tisacel (n = 222)	N = 78 HGBL
	N = 354 DLBCL

Median FU 22.86 months (9.14-24.84)

- 2 yr estimated PFS 34% (vs 33% in DLBCL)
- 2 yr estimated DOR 47% (vs 43 in DLBCL)
- 2 yr estimated OS 34% (vs 49% in DLBCL)

The 2 yr OS difference between HBGBL and DLBCL remained significant following weighted log-rank tests; this difference was related to inferior survival after CART failure in HGBL



A Dodero, et al Blood Adv, 2025,

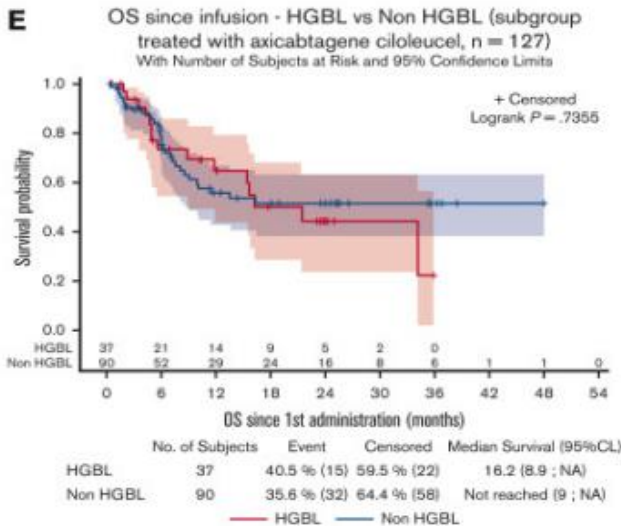
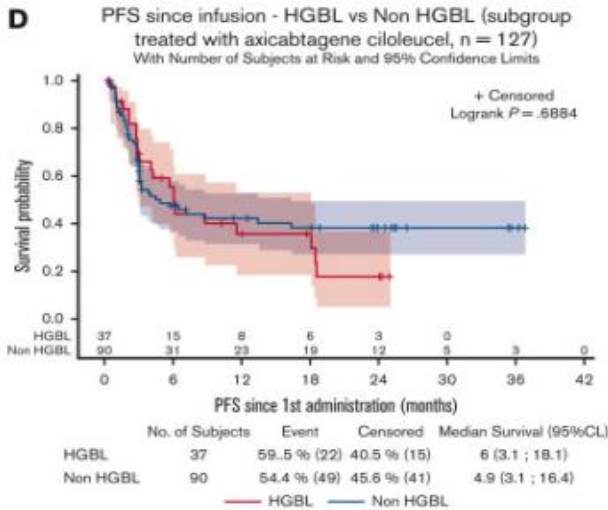
DESCART experience in HGBL



Table 1.. Characteristics of patients with HGBL vs non-HGBL at the date of eligibility

Eligibility, N = 228			P value
Characteristic	HGBL, n = 73	Non-HGBL, n = 155	
Age, median (range), y	62 (26-78)	62 (17-79)	.743
Male sex, n (%)	47 (64.4)	100 (64.5)	1.000
ECOG ≥2, n (%)	9 (12.3)	23 (14.8)	.836
Ann Arbor stage III or later, n (%)	63 (86.3)	125 (80.6)	.259
LDH elevated (>1N), n (%)	52 (71.2)	119 (76.8)	.509
aalPI ≥2, n (%)	45 (61.6)	94 (60.6)	.417
Previous lines, median (IQR)	2 (2-7)	2 (2-9)	.650

Infused 60 Infused 135



Phina-Zebin et al Blood Adv, 2025,

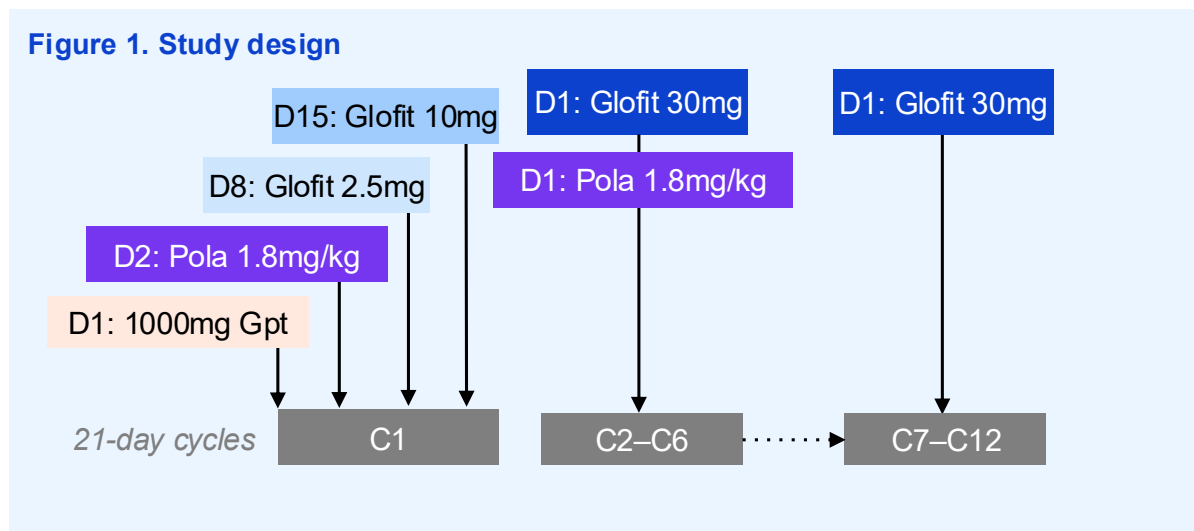


Glofi Pola in HGBL

③ Efficacy and Safety of Glofitamab Plus Polatuzumab Vedotin in Relapsed/Refractory Large B-Cell Lymphoma Including High-Grade B-Cell Lymphoma: Results From a Phase Ib/II Trial

Martin Hutchings, MD, PhD¹ ; Anna Sureda, MD, PhD² ; Francesc Bosch, MD, PhD³ ; Thomas Stauffer Larsen, MD, PhD⁴ ; Paolo Corradini, MD⁵ ; Abraham Avigdor, MD⁶; María José Terol, MD, PhD⁷ ; Antonio Rueda Dominguez, MD, PhD⁸ ; Antonio Pinto, MD⁹; Alan Skarbnik, MD¹⁰; Raul Cordoba, MD, PhD¹¹ ; Judit Meszaros Jørgensen, MD, PhD¹²; Pier Luigi Zinzani, MD, PhD^{13,14} ; Wilfred Leung, PhD¹⁵; Alessia Bottos, PhD¹⁶ ; Donghang Li, PhD¹⁷; James Relf, MD¹⁸; Maneesh Tandon, MBChB¹⁸; Gila Sellam, PhD¹⁶; and Giuseppe Gritti, MD, PhD¹⁹ 

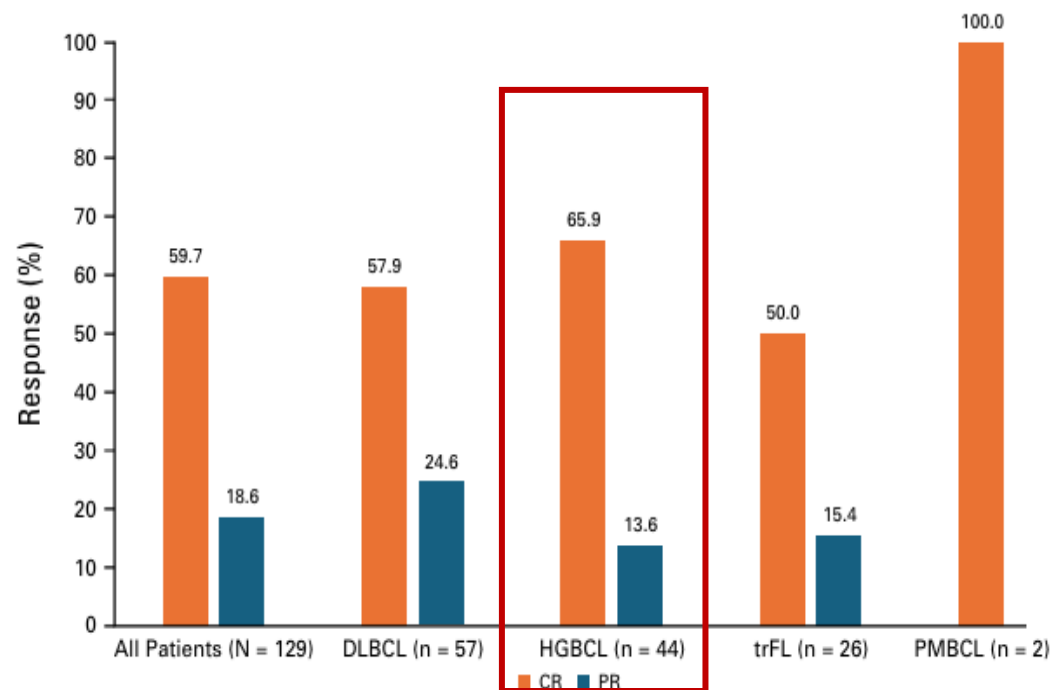
Figure 1. Study design



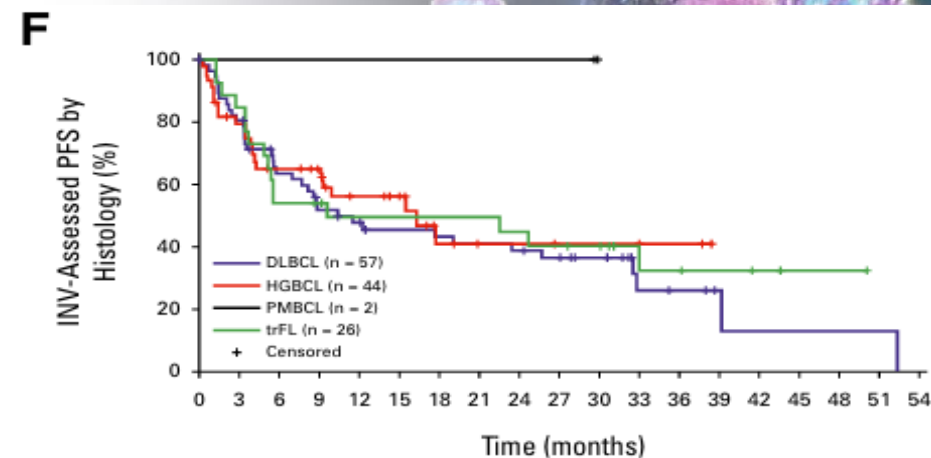
Characteristic	All Patients (N = 129)	Patients With HGBCL (n = 44)
Age, years, median (range)	67.0 (23-84)	66.5 (24-84)
DHL/THL status, No. (%) ^b		
DHL/THL positive	23 (17.8)	19 (43.2)
DHL/THL negative	59 (45.7)	12 (27.3)
DHL/THL missing	47 (36.4)	13 (29.5)
Cell-of-origin, No. (%) ^a		
GCB	62 (48.1)	22 (50.0)
Non-GCB	39 (30.2)	11 (25.0)
Unknown	28 (21.7)	11 (25.0)
Previous lines of therapy, No., median (range)	2 (1-7)	1 (1-5)
No. of previous lines of therapy, No. (%)		
1	53 (41.1)	24 (54.5)
≥2	76 (58.9)	20 (45.5)
Previous CAR T-cell therapy, No. (%)	28 (21.7)	3 (6.8)
Refractory to previous CAR T-cell therapy, No. (%)	22 (17.1)	2 (4.5)
Refractory to the first line of previous therapy, No. (%)	80 (62.0)	31 (70.5)
Refractory to any previous therapy, No. (%)	102 (79.1)	36 (81.8)
Refractory to any previous anti-CD20 therapy	97 (75.2)	35 (79.5)
Refractory to most recent previous therapy, No. (%)	92 (71.3)	34 (77.3)

Hutchings et al, JCO 2025

Glofi Pola in HGBL

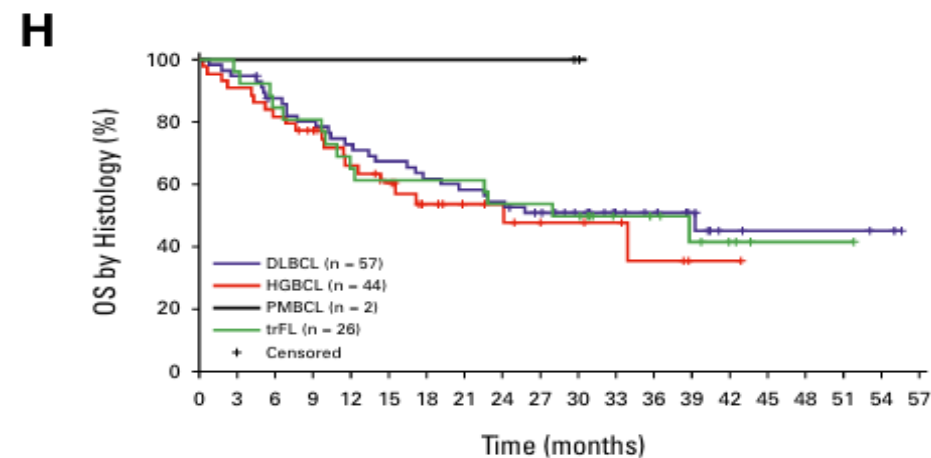


Median FU 19.2 months
Median DOR NR
Median PFS 16.3 months



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
DLBCL	57	45	33	26	23	20	19	18	17	15	12	5	4	2	1	1	1	1	NE
HGBCL	44	33	26	23	17	14	7	4	4	3	3	2	2	NE	NE	NE	NE	NE	NE
PMBCL	2	2	2	2	2	2	2	2	2	2	NE	NE	NE	NE	NE	NE	NE	NE	NE
trFL	26	22	14	13	11	11	11	11	10	9	8	5	4	3	2	1	1	NE	NE



Hutchings et al, JCO 2025



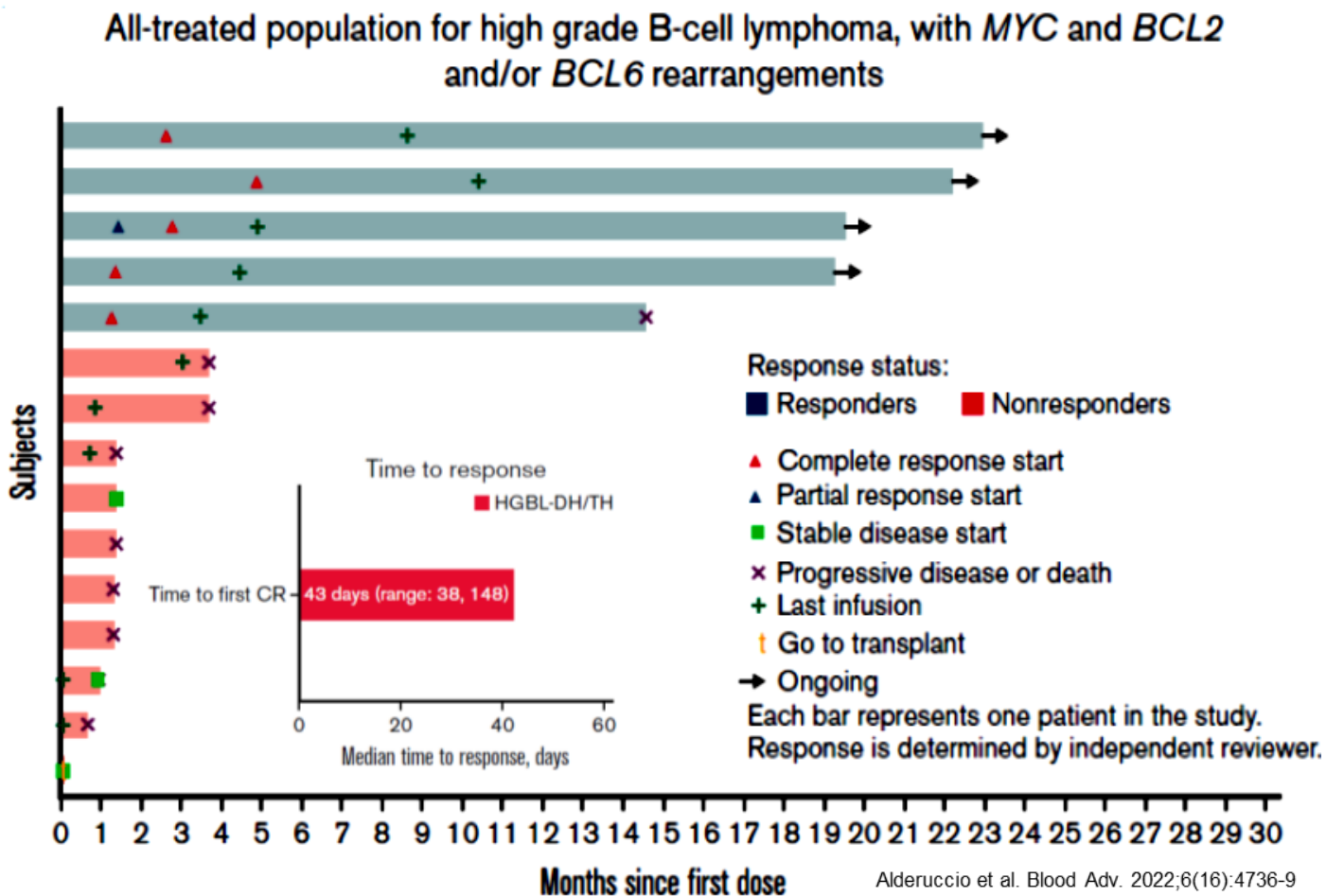
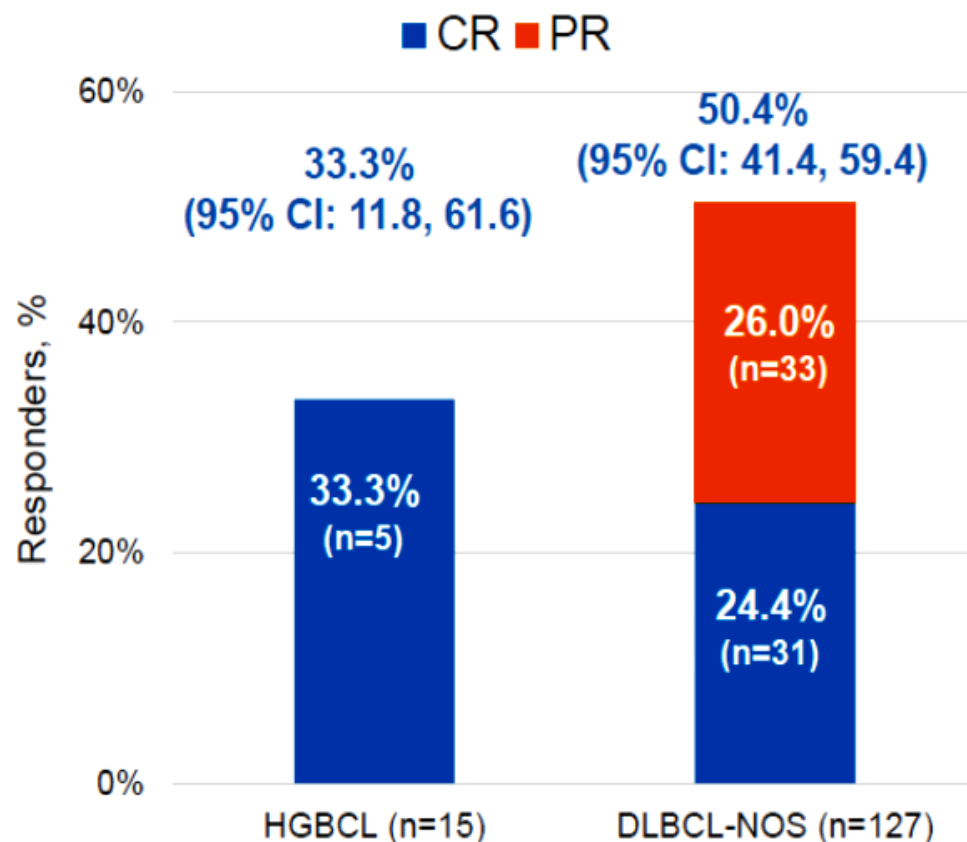
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Loncastuximab tesirine activity in HGBCL (LOTIS-2 subset analysis)

HGBCL/DLBCL NOS Response Rates



Conclusions

- Double Hit/High grade lymphoma
 - despite worse than DLBCL, the outcome has improved since the systematic use of intensive regimen
 - CNS prophylaxis mandatory
- Double Expressor Lymphoma
 - R-DA- EPOCH has demonstrated limited advantage over R-CHOP
 - addition of biological molecules , such as BTKi, to CIT backbone seems to be a right way forward
- At relapse
 - CART show activity similar to DLBCL-
 - bispecific/pola as well as lonca- based approaches have demonstrated encouraging results