Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Double-hit Lymphoma: Do We Still Need Intensified Chemotherapy?

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Disclosures

- Consultant for Kita Pharma & Novartis

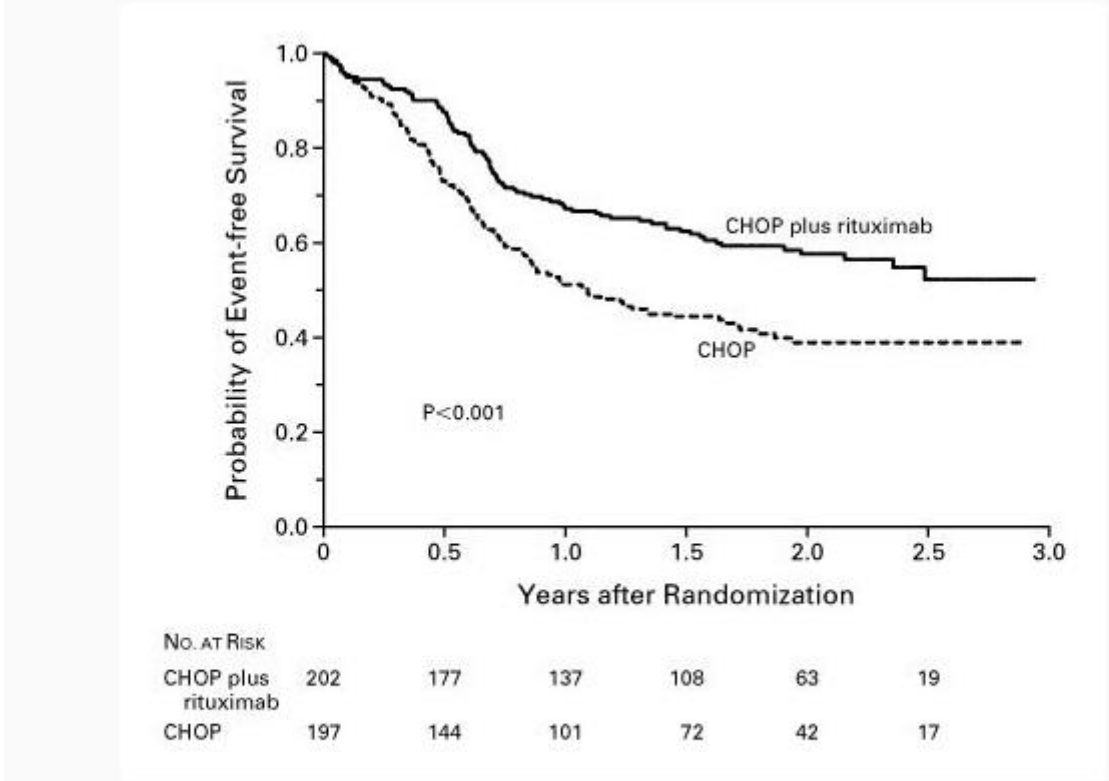
This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

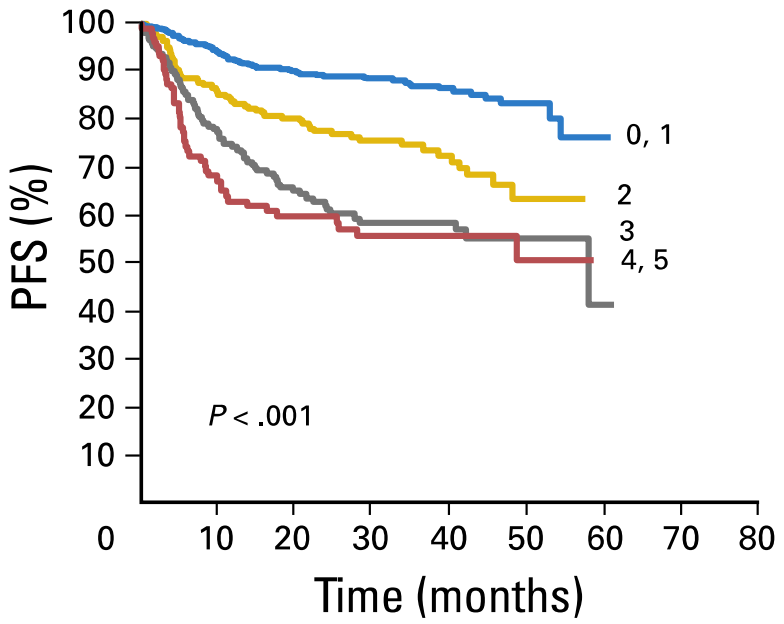
Diffuse Large B-cell Lymphoma

2002 --RCHOP became the standard of care for front-line



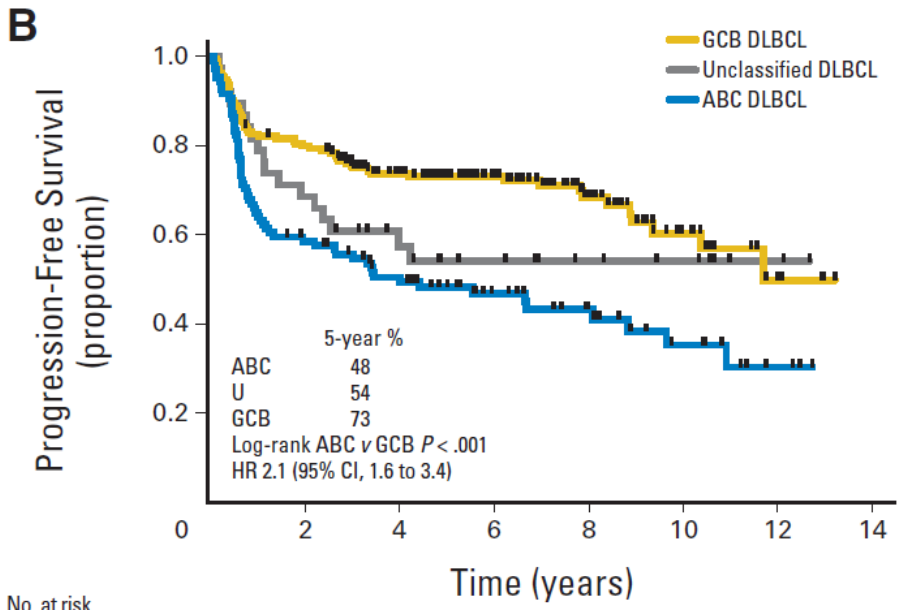
DLBCL - Who Relapses?

International Prognostic Index



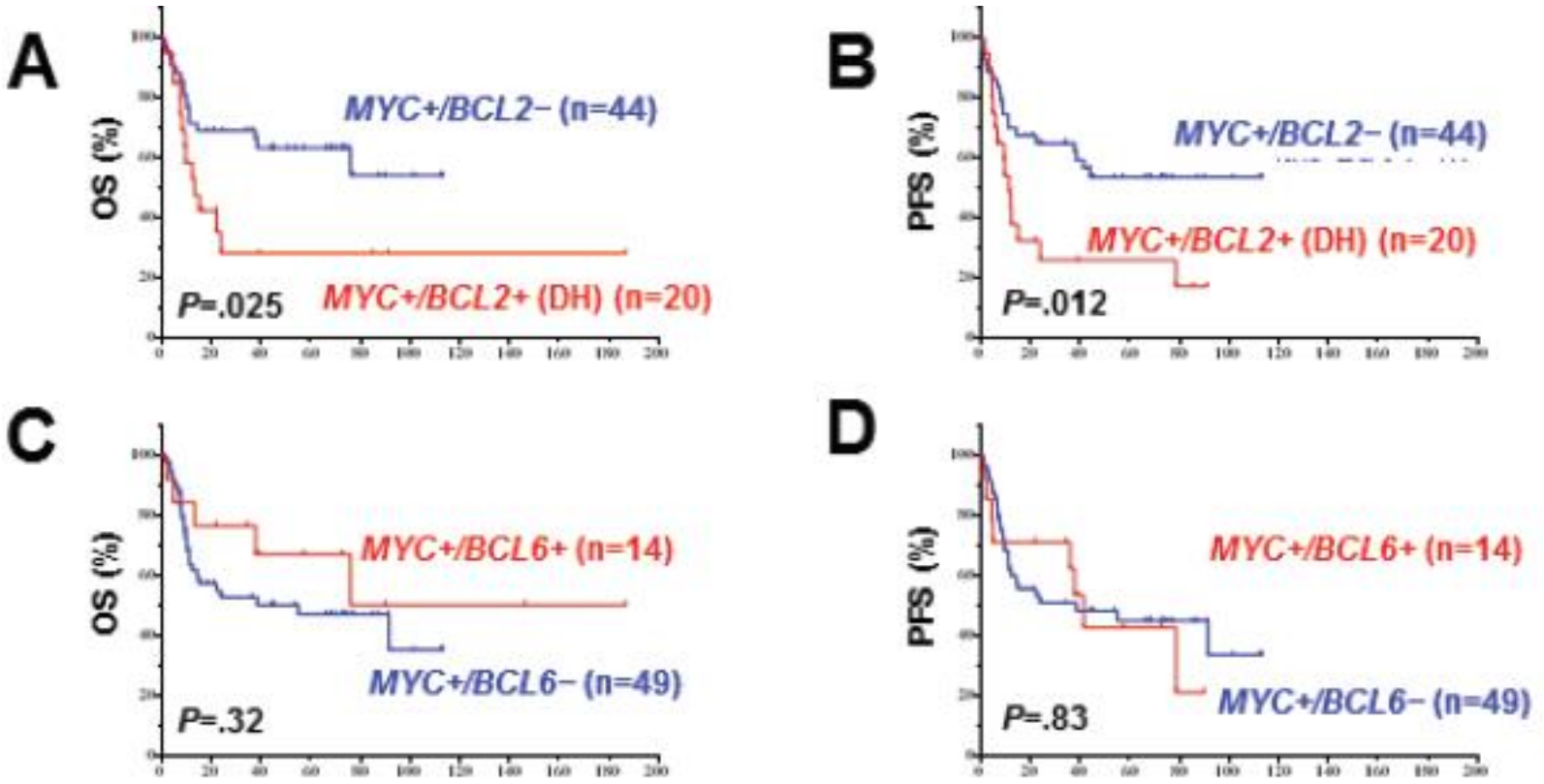
Ziepert et al. *J Clin Oncol* 28:2373-2380

Cell of Origin



Scott et al. *J Clin Oncol* 33:2848-2856

MYC/BCL2-DH vs MYC/BCL6-DH



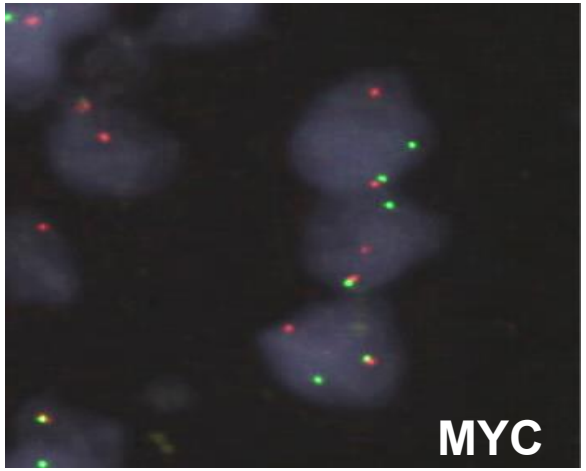
Ye et al. Oncotarget 2016

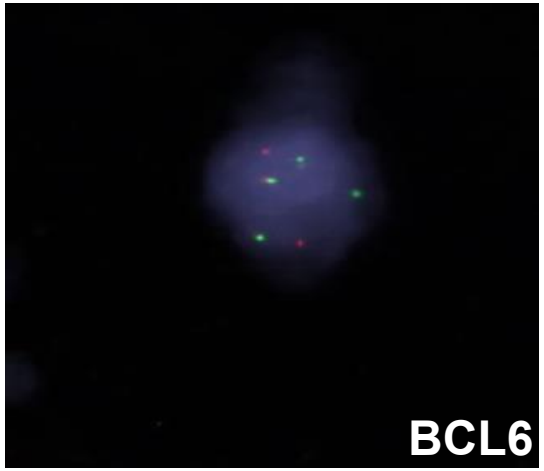
Definitions: Double-Hit Lymphoma (DHL)

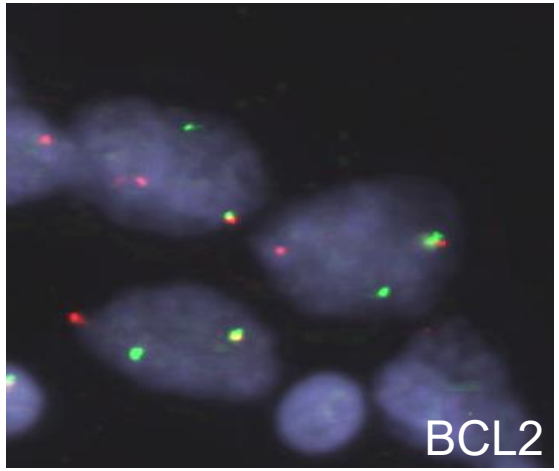
How many?: 5-12% of LBCL

WHO: LBCL containing MYC and BCL2 rearrangements as confirmed by FISH testing.

ICC: MYC rearrangement paired with rearrangement in either BCL2 or BCL6



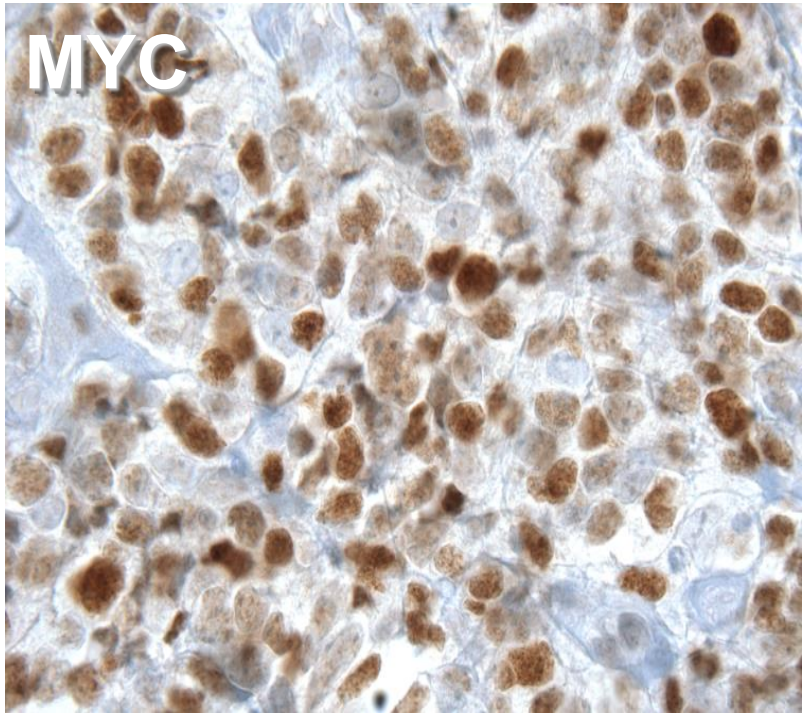


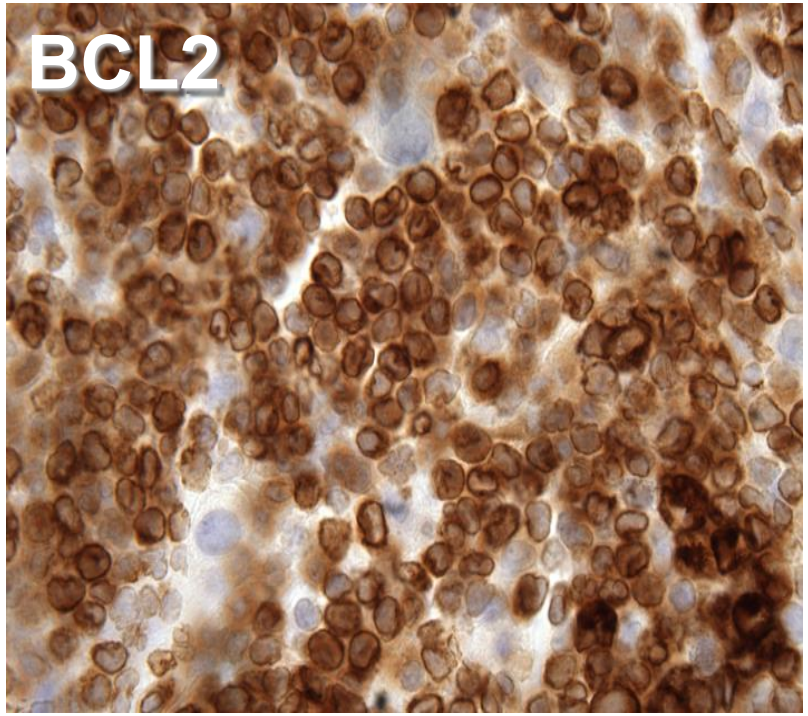


Definitions: Double Expressor Lymphoma (DEL)

Protein overexpression of MYC (>40%) and BCL2 (>50%) by IHC.

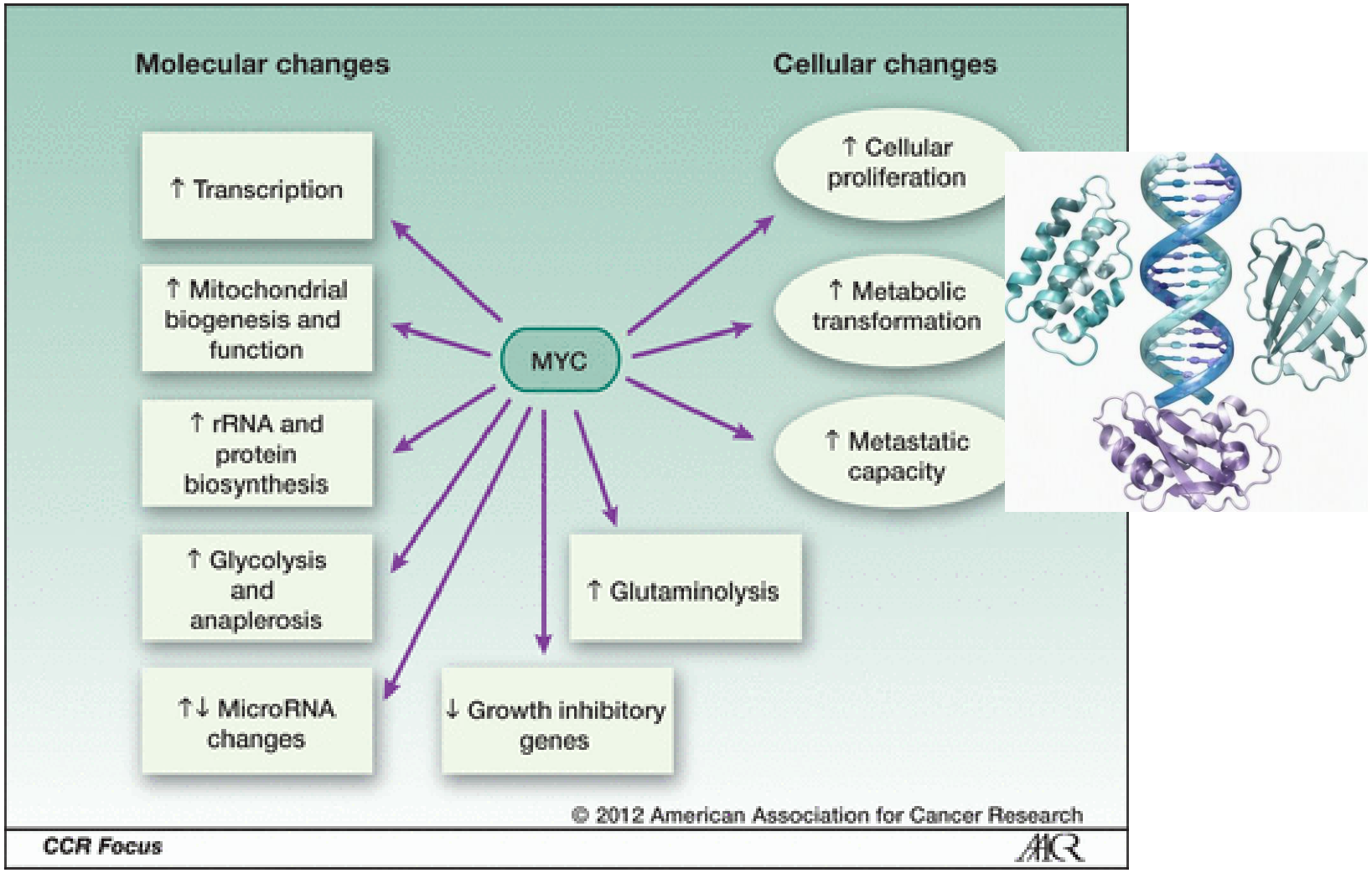
- **21-34% of newly diagnosed DLBCL**
- **likely results from gene amplification and post-translational processing**





Photos courtesy of S. Rodig, 1000x

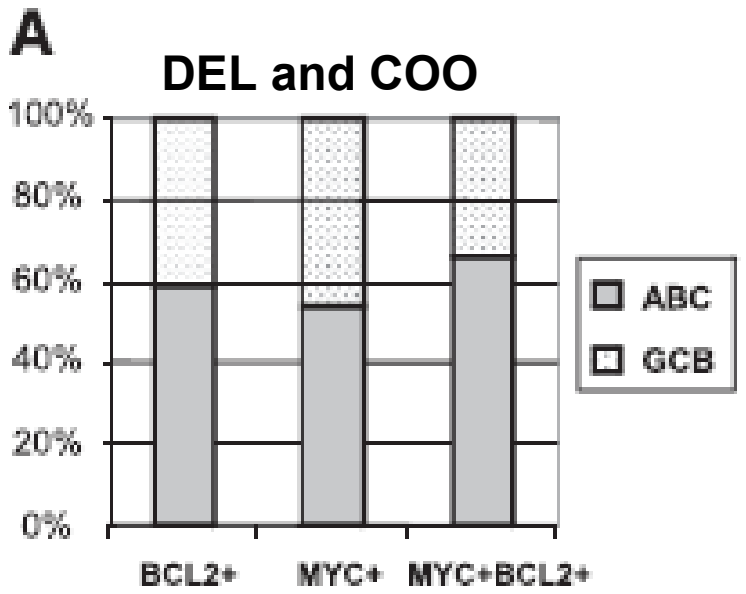
MYC, BCL2, and BCL6



Miller et al. Clin Cancer Res. 2012 Oct 15;18(20):5546-53.

Clinical features: Cell-of-Origin, DHL, and DEL

DHL cases occur with GCB LBC (80% to 90%)
DEL usually non-GCB subtype: 58-76%



Hu et al Blood 2013 121: 4021-4031

DEL and DHL – High-risk clinical features

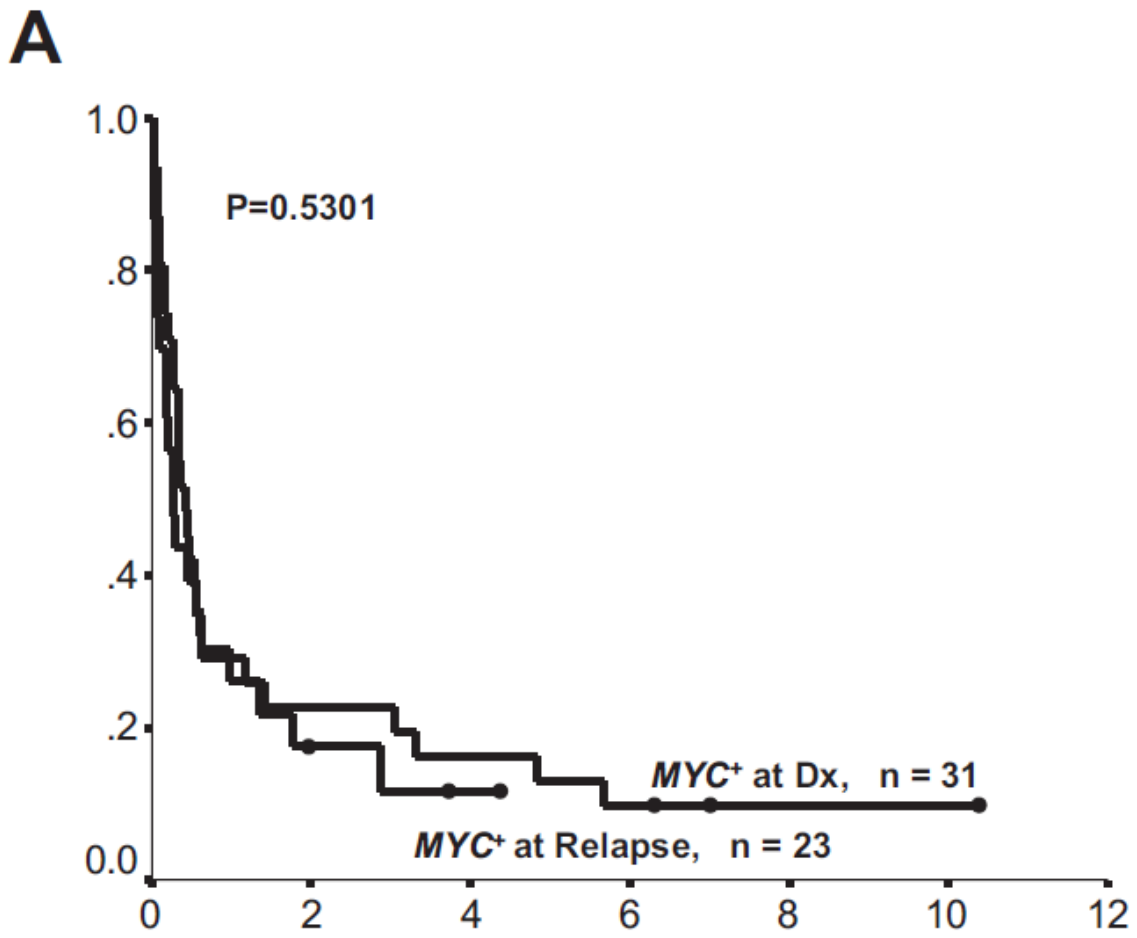
DHL tend to be

Table I. Baseline characteristics of patients with cytogenetic double hit lymphomas in selected studies.

Study	*n* DHL/total (%)	Male (%)	Median age, years	Prior indolent lymphoma	Stage III/IV (%)	LDH >ULN (%)	B symptoms (%)	>1 EN site (%)	CNS+ (%)	BM+ (%)	IPI ≥4 (%)	GCB type (%)	Median ki67, %
Johnson *et al* (2009)	54/54	32 (59)	NR	20 (37)	41 (76)	27 (50)	NR	19 (35)	NR	32 (59)	14 (26)	34 (63)	NR
Niitsu *et al* (2009)	19/394 (4·8)	10 (53)	61	NR	19 (100)*	19 (100)*	11 (58)	17 (89)	4 (21)	16 (84)*	17 (89)	15 (79)	80
Tomita *et al* (2009)	27/27† (100)	15/27 (56)	51	5/23 (22)	22/23 (96)	25/27 (92)	10/22 (45)	15/23 (65)	2/23 (9)	15/23 (65)	20/23 (87)	18/19 (95)	70
Barrans *et al* (2010)	27/303‡ (8·6)	15 (43)	68·5	NR	21 (69)*	NR	NR	NR	NR	NR	10 (30)*	24 (77)*	76
Snuderl *et al* (2010)	20/60 (33)	11 (55)	63*	6 (30)	18 (90)	Med 3·5 × ULN*	NR	NR	4/11 (44)	10/17 (59)*	8 (40)	18 (90)	80
Pedersen *et al* (2012, 2014)	23/228 (10)	11 (48)	64	10 (42)	19 (83)	14/17 (82)	NR	8/17 (47)	NR	4/17 (24)	5 (29)	17/17 (100)*	70
Oki *et al* (2014)	129/129	84 (65)	62	14 (11)	109 (84)	68/99 (69)	NR	63 (49)	5 (4)	54 (42)	28 (26)	107/115 (93)	85
Petrich *et al* (2014)	311/311	181 (67)	60	67 (22)	255 (81)	236 (76)	139 (45)	87 (28)	23 (7)	129 (41)	85 (27)	181/209 (87)	NR

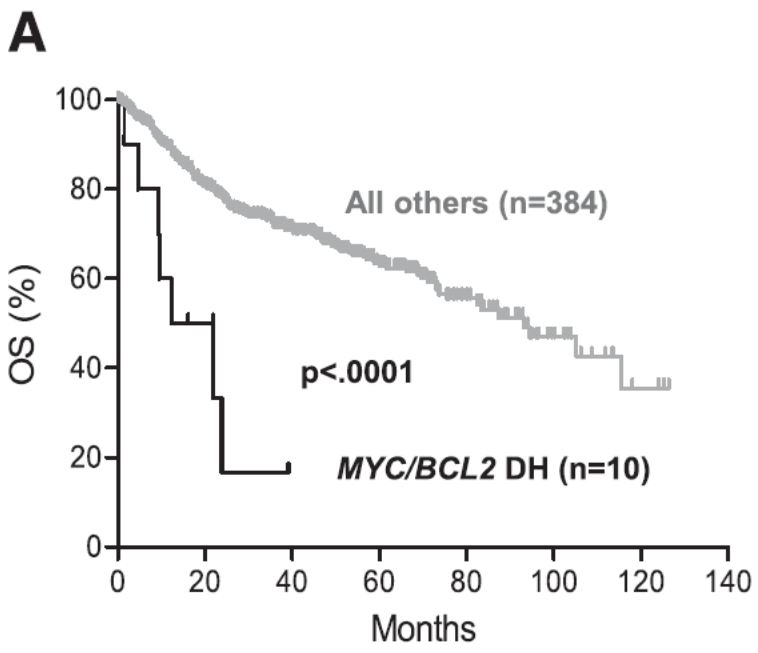
Cheah et al. BJH 2015

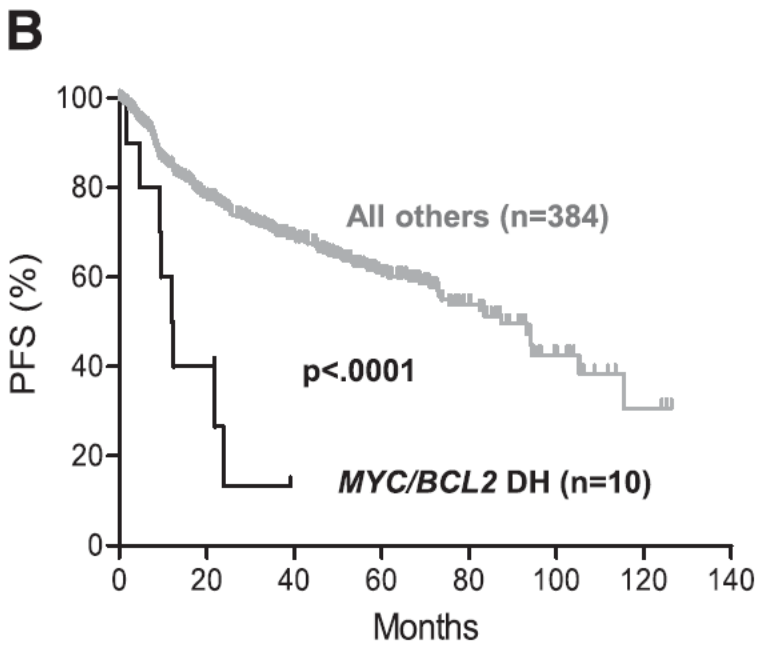
DHL: Outcomes with R-CHOP



Johnson et al. Blood 2009

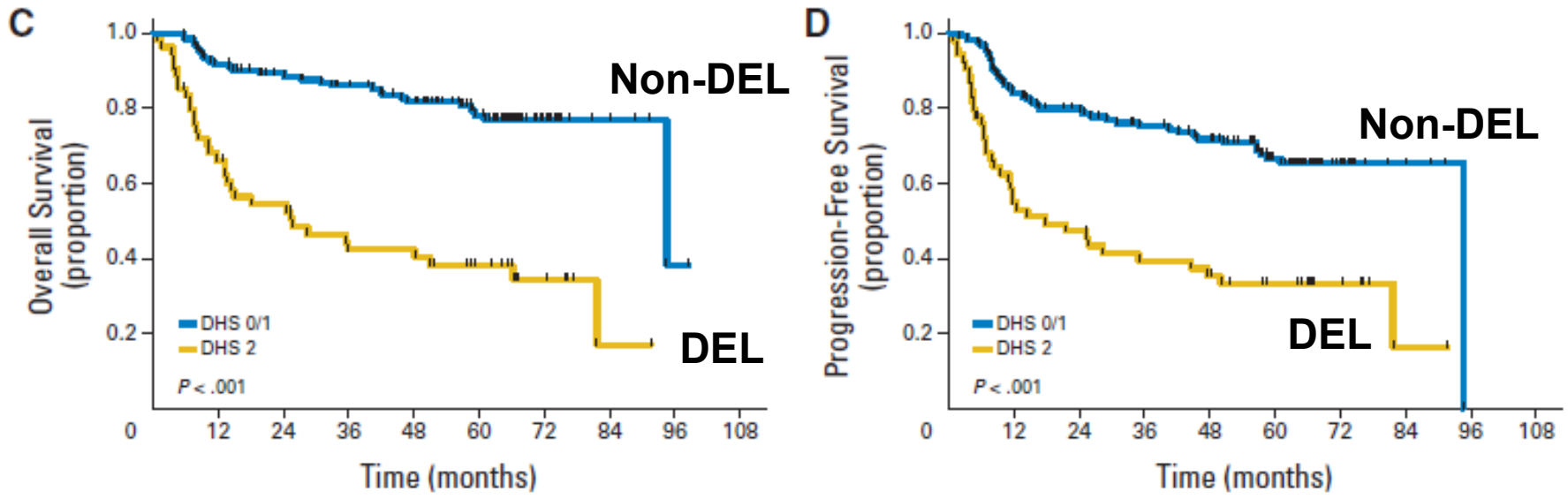
DHL: Outcomes with R-CHOP





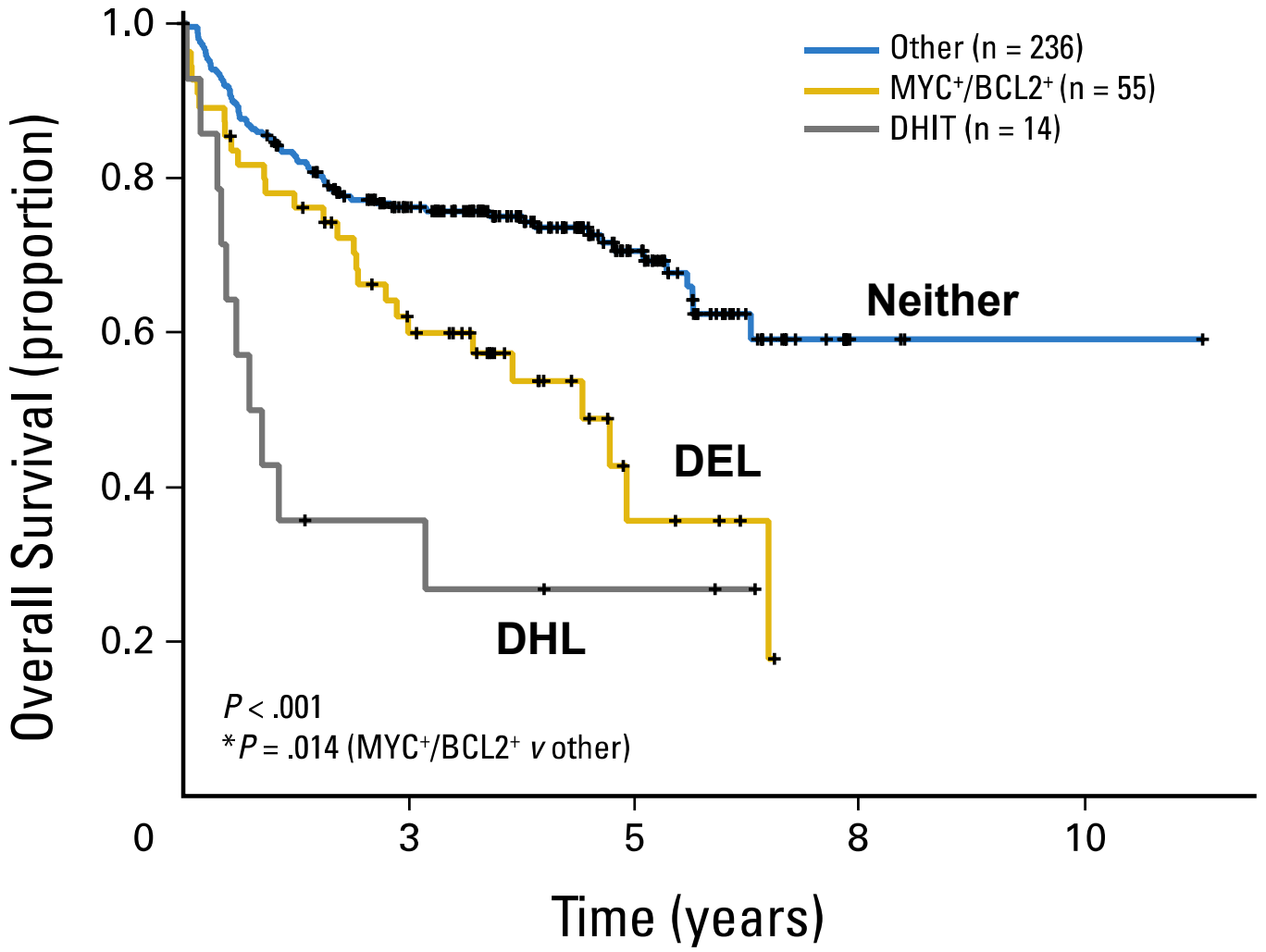
Hu et al.
Blood 2013

DEL: Outcomes with R-CHOP



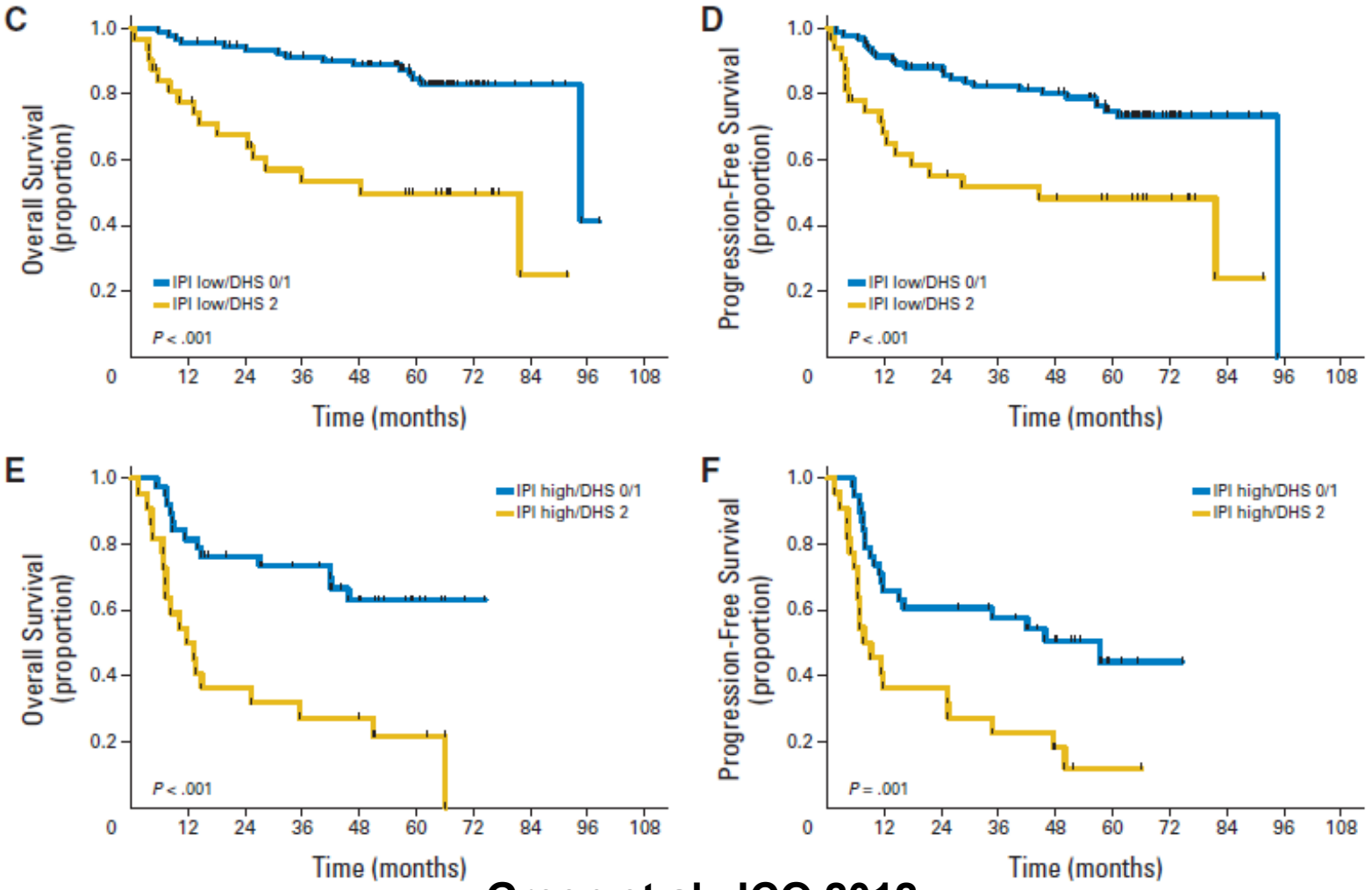
Green et al. JCO 2012

Outcomes in DEL and DHL after R-CHOP



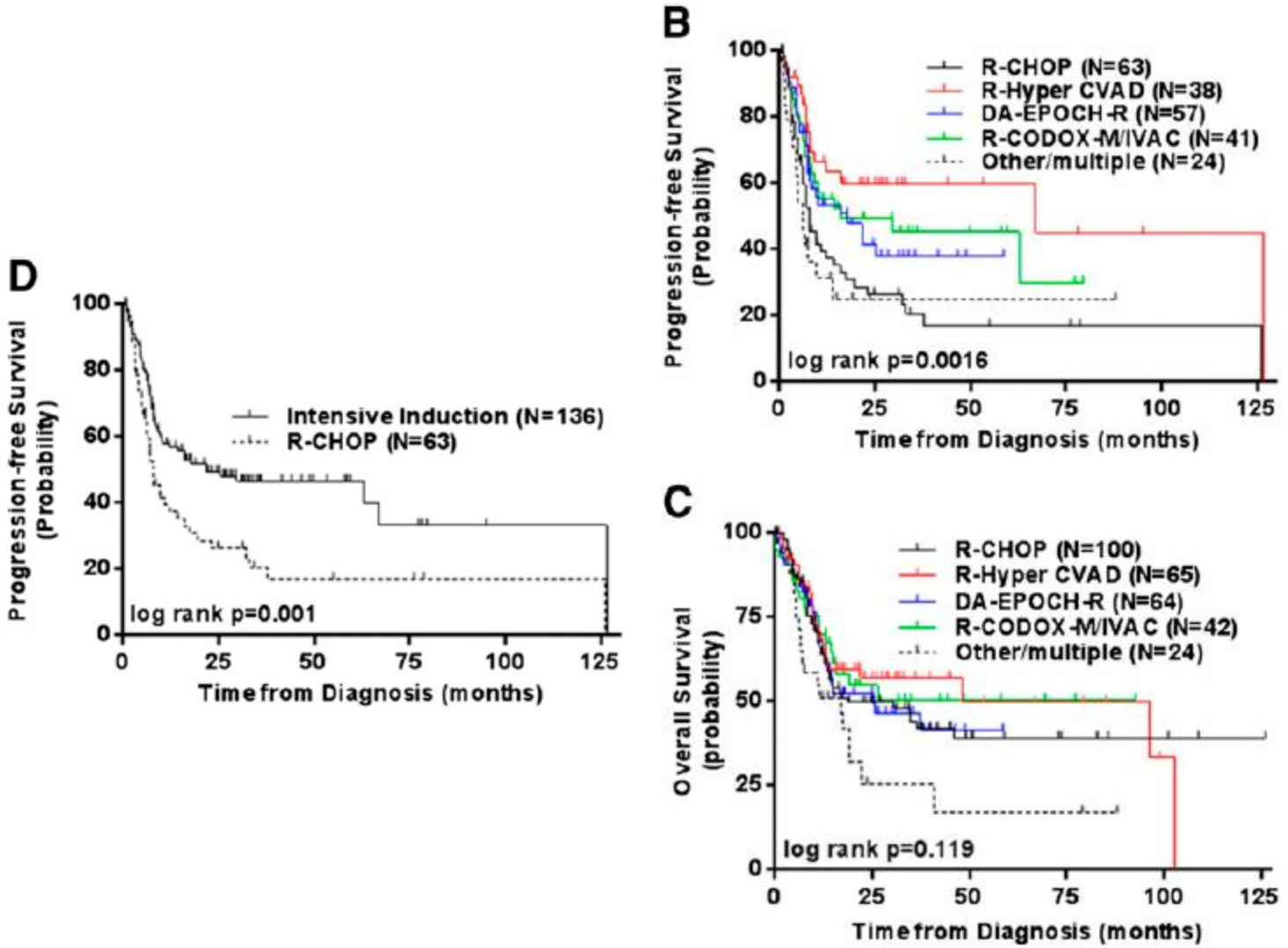
Johnson et al. *JCO* 2012

DEL is prognostic independent of IPI



Green et al. JCO 2012

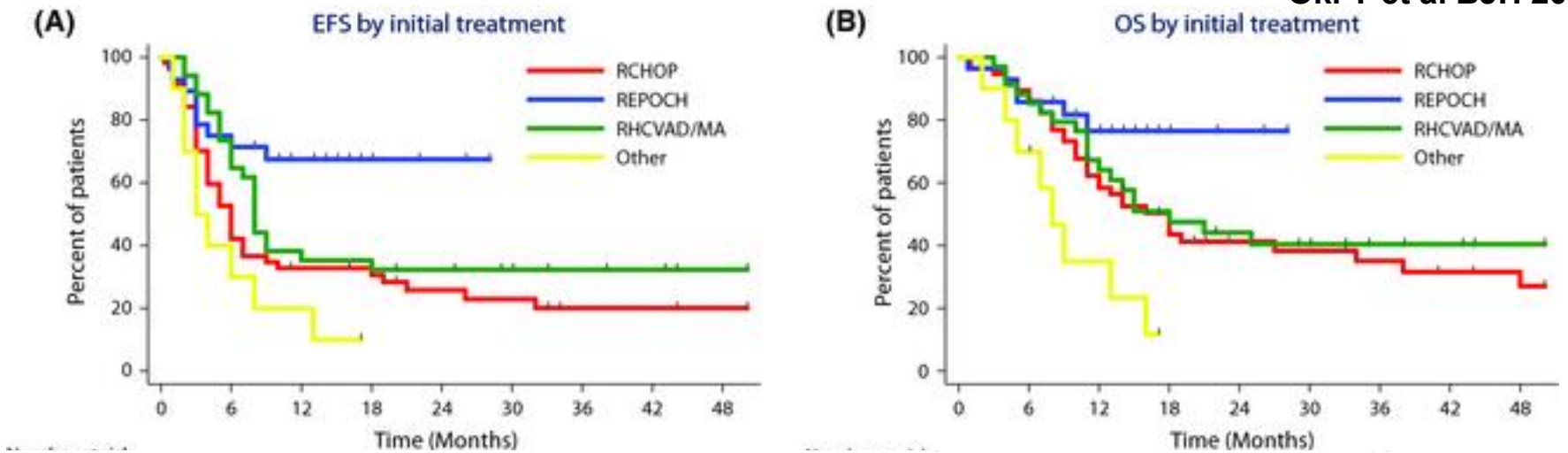
Intensive Regimens vs R-CHOP for DHL

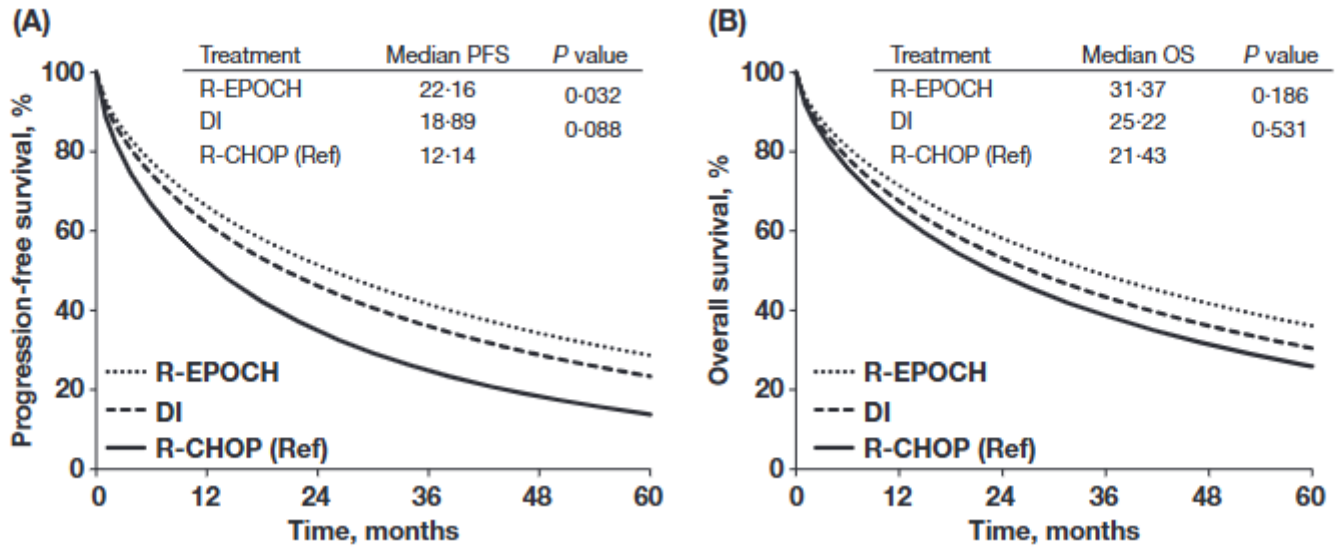


Petrich AM et al Blood 2014

Intensive Induction Regimens for DHL

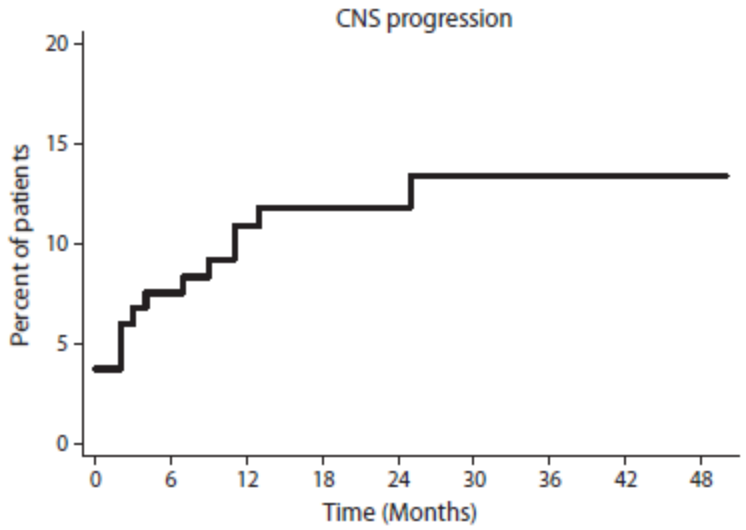
Oki Y et al BJH 2014



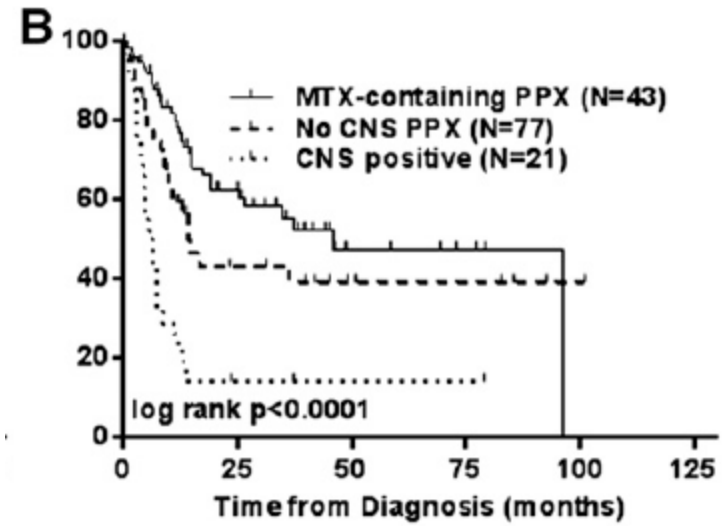


Meta-analysis, Howlett et al, BJH 2015

CNS prophylaxis for DHL

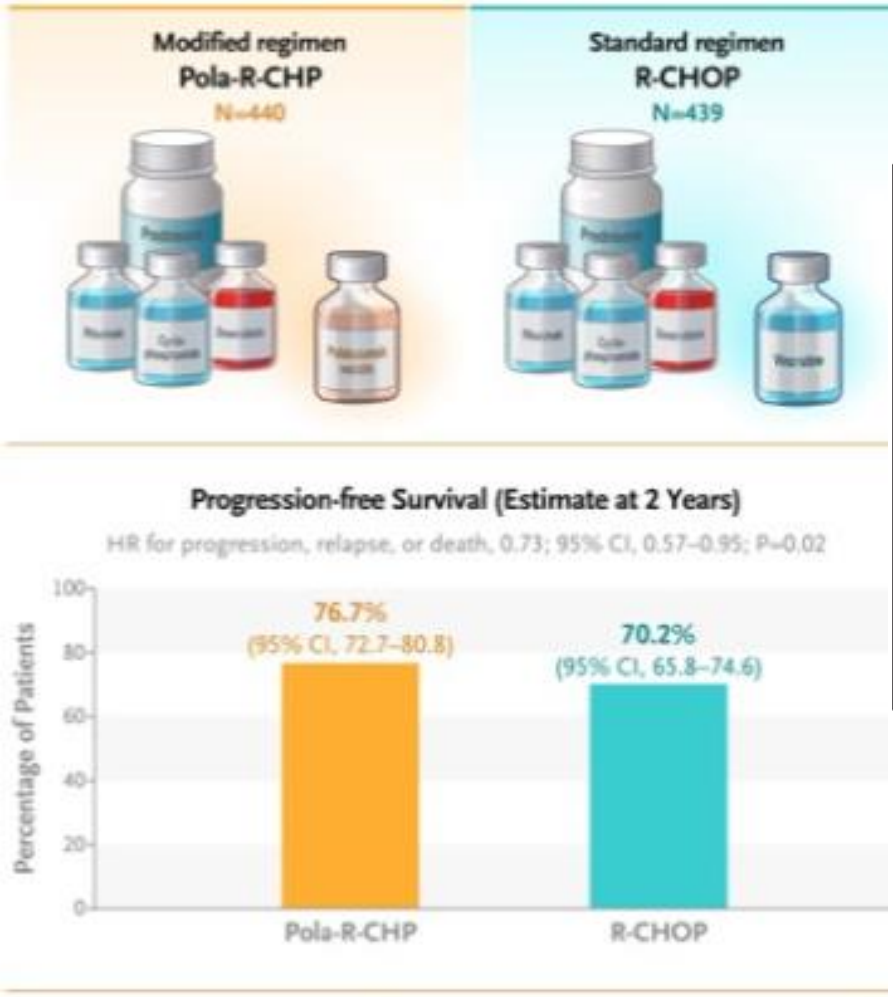


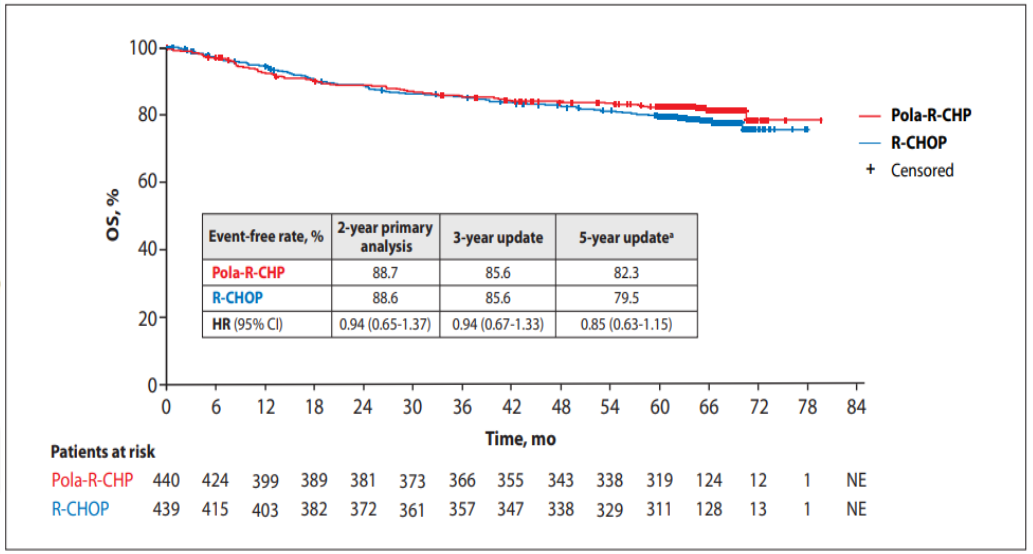
Oki Y et al BJH 2014



Petrich AM et al Blood 2014

5-year follow-up POLARIX





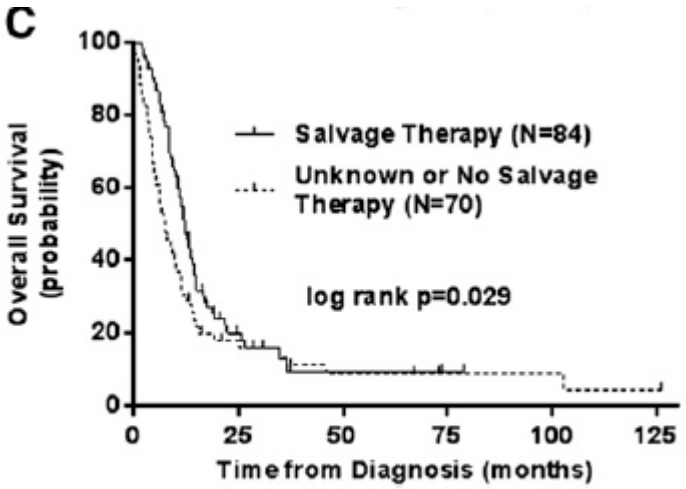
Event-free rate, %	2-year primary analysis	3-year update	5-year update[a]
Pola-R-CHP	88.7	85.6	82.3
R-CHOP	88.6	85.6	79.5
HR (95% CI)	0.94 (0.65-1.37)	0.94 (0.67-1.33)	0.85 (0.63-1.15)

Patients at risk															
Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

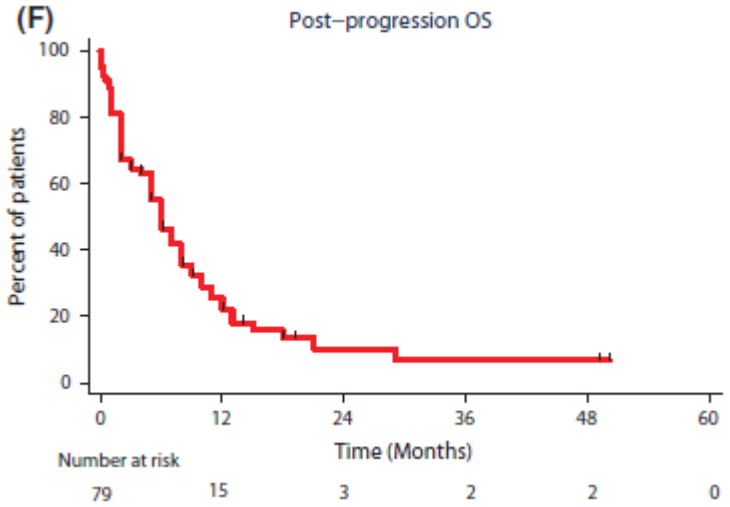
Improvement in PFS over RCHOP persisted at 5 years with PFS of 64.9% vs 59.1%

OS at 5 years 82.3% vs 79.5%

Why we consider consolidation…



Petrich AM et al Blood 2014



Oki Y et al BJH 2014

No significant advantage to autoHSCT in CR1

- Petrich et al BLOOD 2014
- Chen et al – Leuk Lymphoma 2018, no improvement in 2y PFS or OS with ASCT after REPOCH
- Landsburg—JCO 2017, multi-institutional

Double Expressing (MYC/BCL2) and Double Hit Diffuse Large B-cell Lymphoma Have Inferior Survival After Autologous Stem Cell Transplantation

Alex F. Herrera, Matthew Mei, Lawrence Low, Reid W. Merryman, Joo Y. Song, Victoria Bedell, Heather Sun, Tanya Paris, Tracey Stiller, Jennifer R. Brown, Elizabeth Budde, Robert Chen, Matthew S. Davids, Arnold Freedman, David C. Fisher, Eric D. Jacobsen, Caron A. Jacobson, Haesook T. Kim, Ann S. LaCasce, Joyce Murata-Collins, Auayporn P. Nademanee, Joycelynne Palmer, German A. Pihan, Tanya Siddiqi, Aliyah R. Sohani, Leslie Popplewell, Jasmine Zain, Larry W. Kwak, David M. Weinstock, Stephen J. Forman, Dennis D. Weisenburger, Young Kim, Scott J. Rodig, Amrita Krishnan, and Philippe Armand

City of Hope (COH) and Dana-Farber Cancer Institute (DFCI)

American Society of Hematology Annual Meeting 2015

Double-Hit and Double-Expressor Lymphomas Are Not Associated With An Adverse Outcome After Allogeneic Stem Cell Transplantation

Alex F. Herrera, Joo Y. Song, Gabriel K. Griffin, Liana Nikolaenko, Matthew Mei, Victoria Bedell, Paola Dal Cin, Christine Pak, Tracey Stiller, Heather Sun, Edwin P. Alyea, Lihua E. Budde, Robert Chen, Yi-Bin Chen, Wing C. Chan, Corey S. Cutler, Vincent T. Ho, John Koreth, Amrita Krishnan, Joyce L. Murata-Collins, Sarah Nikiforow, Joycelynne Palmer, German A. Pihan, Raju Pillai, Leslie Popplewell, Steven T. Rosen, Tanya Siddiqi, Aliyah R. Sohani, Jasmine Zain, Larry W. Kwak, Dennis D. Weisenburger, Auayporn P. Nademanee, David M. Weinstock, Robert J. Soiffer, Joseph H. Antin, Young Kim, Scott J. Rodig, Stephen J. Forman, and Philippe Armand

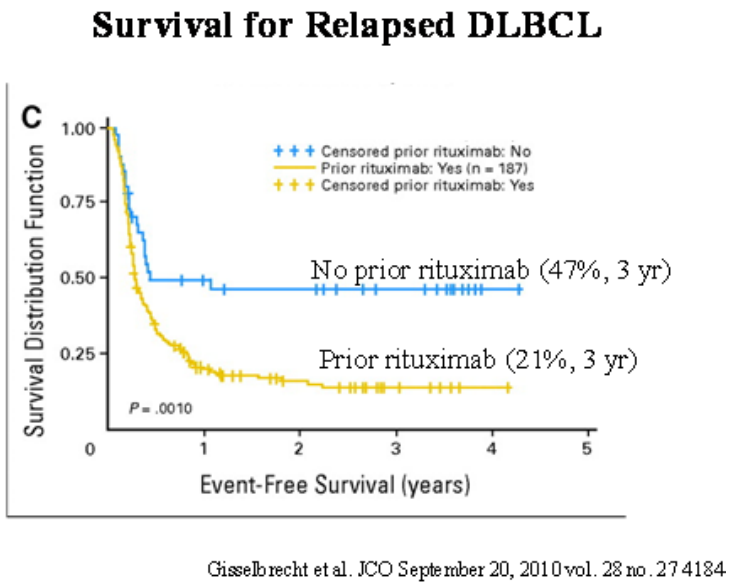
City of Hope (COH) and Dana-Farber Cancer Institute (DFCI)

American Society of Hematology Annual Meeting 2016

First Relapse DLBCL approach–

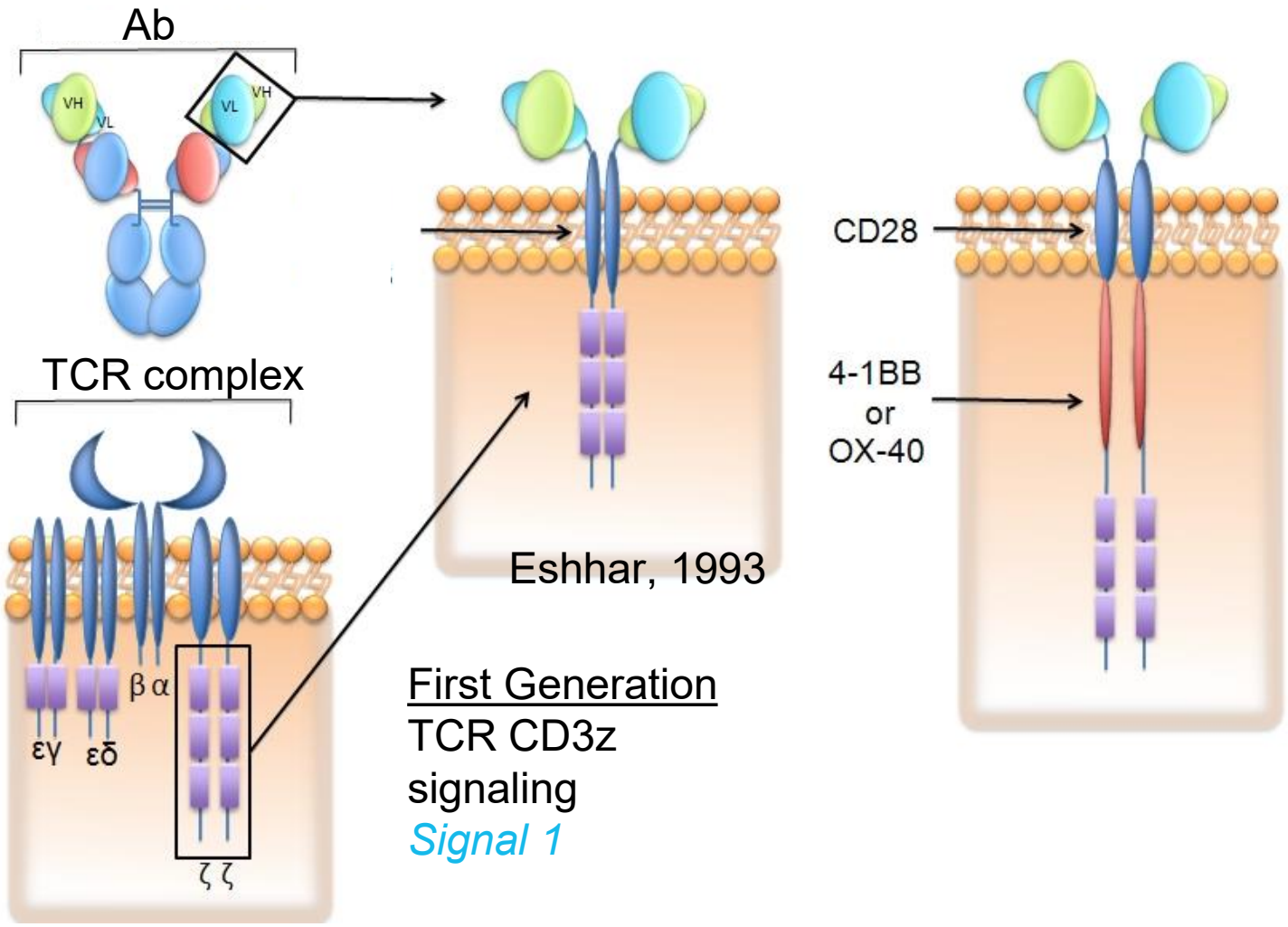
Patients with relapsed/refractory DLBCL responding to second-line chemotherapy receiving autologous hematopoietic stem cell transplantation (aHSCT), have a 20 to 50% probability of disease-free survival at 3 to 5 years.

Relapse of lymphoma continues to be the most common cause of mortality after aHSCT. Most relapses occur during the first two years post-aHSCT



Gisselbrecht et al, JCO 28: 4184, 2010

Chimeric Antigen Receptor (CAR)



Chekmasova & Brentjens; Discovery To

the MIRACLE of SCIENCE with SOUL

Phase 3 trials of CAR19 vs. SOC in 2L transplant-eligible DLBCL with primary refractory disease or relapse within 12 months of 1L

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell Product	Axicabtagene ciloleucel (Axi-cel)	Lisocabtagene maraleucel (Liso-cel)	Tisagenlecleucel (Tisa-cel)
CAR Construct	CD19.**CD28**.CD3z	CD19.**41BB**.CD3z	CD19.**41BB**.CD3z
# Enrolled	359	184	322
Median Follow Up	24.9 months	6.2 months	10 months
% Infused in CAR-T Arm	94%	98%	96%
% Received Bridging in CAR-T Arm	36%	63%	83%
% to HDT-ASCT in SOC Arm	36%	47%	33%
% SOC Crossover to CAR-T	56%	55%	51%
Median EFS	8.3 vs. 2 months	10.1 vs. 2.3 months	3 vs. 3 months
Hazard Ratio	0.398 (P < 0.0001)	0.349 (P < 0.0001)	1.07 (P = 0.69)
CR Rate	65% vs. 32%	66% vs. 39%	28% vs. 28%
Grade ≥3 CRS / ICANS	6% / 21%	1% / 4%	5% / 3%

1. Locke F et al. ASH 2021, Abstract # 2. 2. Kamdar M et al. ASH 2021, Abstract # 91. 3. Bishop M et al. ASH 2021, Abstract # LBA-6.

Zuma-7 results in DHL and DEL LBCL

Locke et al NEJM 2022

No. at Risk

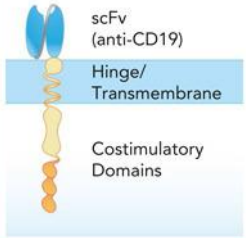
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6		
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			

Three-Year Follow-Up in ZUMA-12: Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in High-Risk Large B-Cell Lymphoma (LBCL)

Axi-Cel: Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for R/R LBCL



- ZUMA-12 is a study of axi-cel as first-line treatment in patients with high-risk LBCL
- In this analysis, we report efficacy and safety outcomes from ZUMA-12 after a median follow-up of ≥40 months

ZUMA-12: Phase 2 study of axi-cel in high-risk LBCL

High-Risk LBCL (N = 40)

- High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* translocations (double- or triple-hit), and/or LBCL with IPI ≥3 any time before enrollment
- Positive interim PET after 2 cycles of anti-CD20 mAb + anthracycline-containing regimen

Axi-Cel Treatment

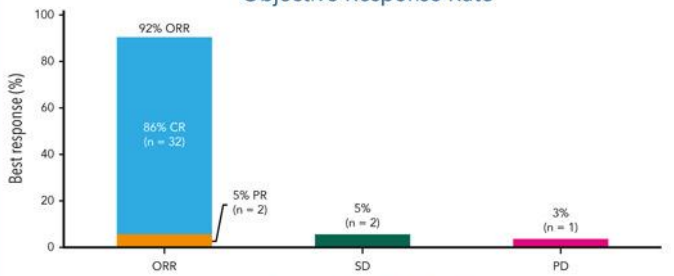
Leukapheresis → Lymphodepletion → Axi-cel infusion

Key Long-Term Endpoints

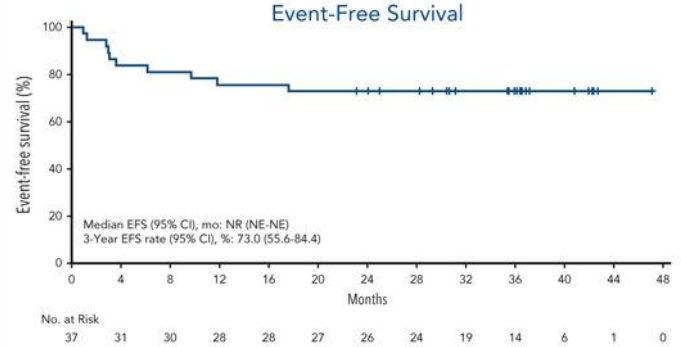
- CR, ORR, DOR, EFS, PFS, OS
- CAR T cells in blood and cytokine levels in serum
- Safety

Long-Term Outcomes

Objective Response Rate



Event-Free Survival



- Safety outcomes were similar to the primary analysis, with no new safety signals observed

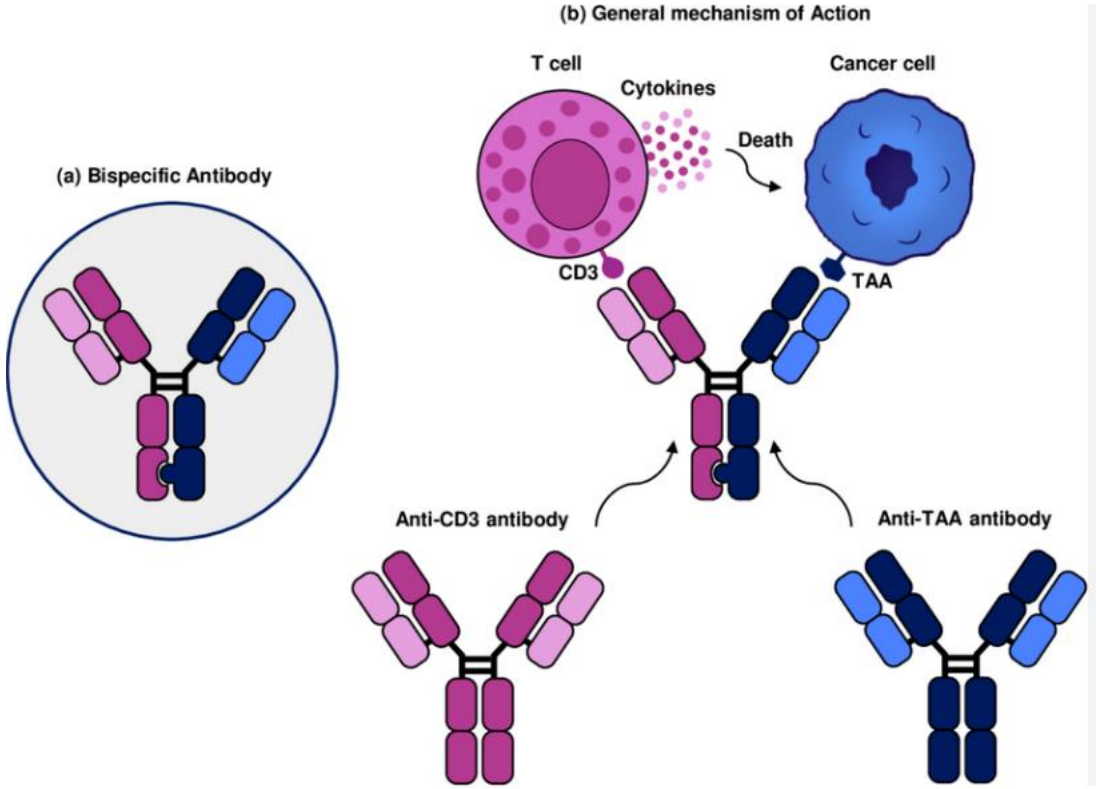
Conclusions: In this updated analysis of ZUMA-12 after 3 years of follow-up, axi-cel demonstrated continued durability and favorable survival, with no new safety signals observed (NCT03761056).

*Chavez et al. DOI: 10.1182/**blood**.2024027347*

blood Visual Abstract

Feature	ZUMA-12	ZUMA-23
Study Phase	Phase 2	Phase 3
Trial Design	Single-arm (Everyone gets the treatment)	Randomized (Patients split 1:1 into two groups)
Comparison Group	None	Standard chemoimmunotherapy
Patient Group Size	Smaller (~40 patients treated)	Larger global trial
High-Risk Lymphoma Criteria	Double- or triple-hit lymphomas, or an IPI score of 3+ **and** a positive interim PET scan	IPI score of 4–5 (Interim PET scan requirement removed; double/triple hit excluded)
Progression-Free Survival (PFS)	**75.1%** at 3 years (Median PFS has not been reached)	*Data pending* (Evaluating if axi-cel improves PFS over standard chemo)
Overall Survival (OS)	**81.1%** at 3 years (Median OS has not been reached)	*Data pending* (Evaluating if axi-cel improves OS over standard chemo)

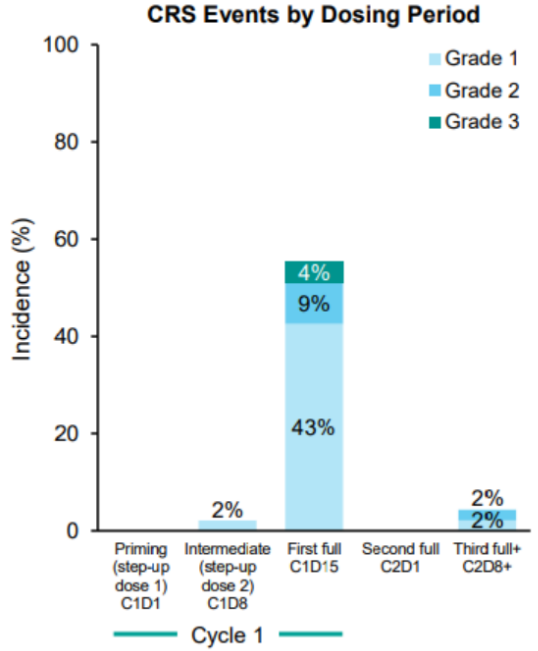
Bispecific antibody



EPCORE NHL-2 Arm 1

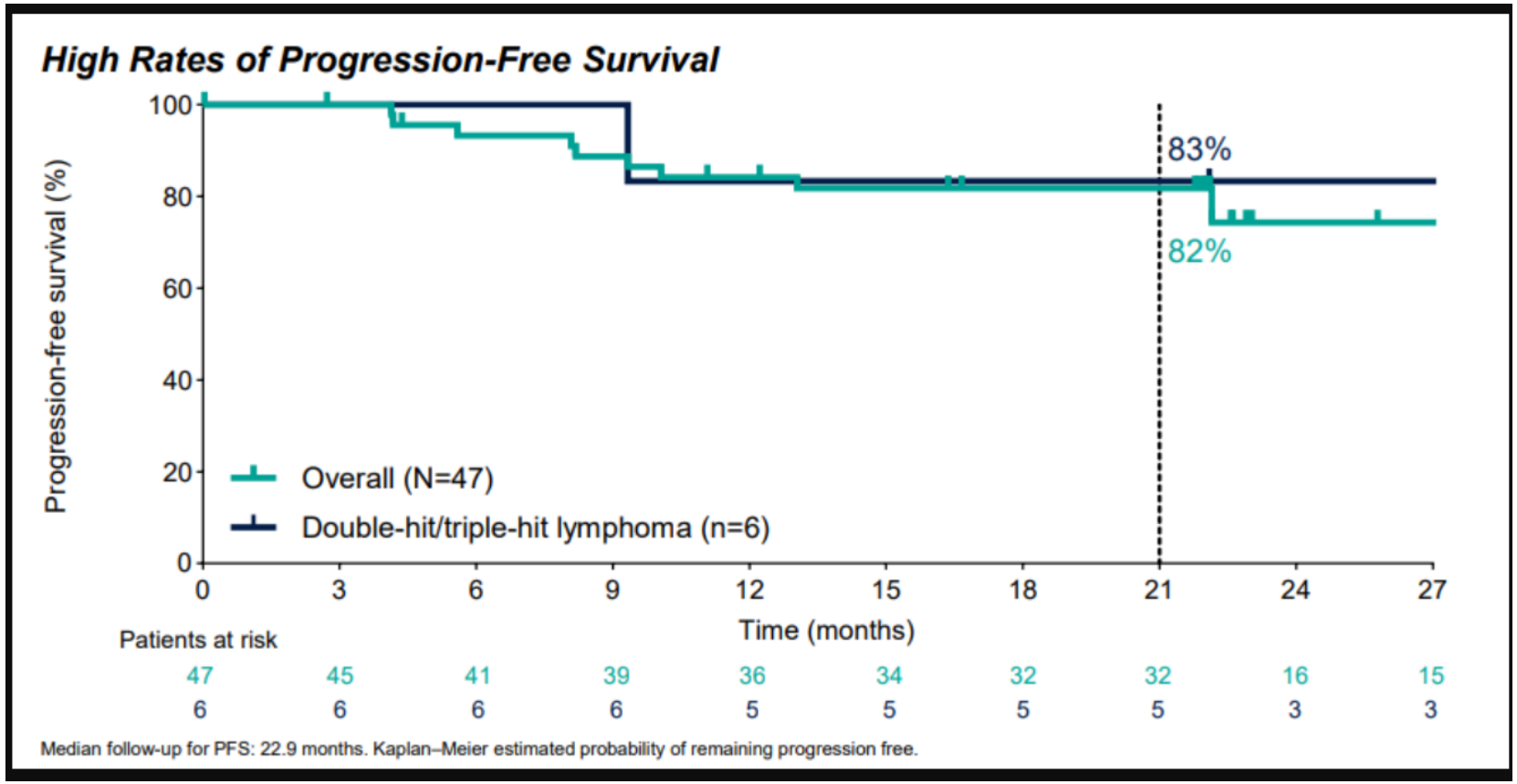
CRS and ICANS Mostly Low Grade

CRS	N=47
CRS, n (%)[a]	28 (60)
Grade 1	21 (45)
Grade 2	5 (11)
Grade 3	2 (4)
CRS resolution, n/n (%)	28/28 (100)
Median time to CRS onset from first full dose, d (range)	2 (1–7)
Median time to CRS resolution, d (range)[b]	2 (1–11)
Treated with tocilizumab for CRS, n (%)	5 (11)
CRS leading to treatment discontinuation, n (%)	0
ICANS	**N=47**
ICANS, n (%)[a,c]	2 (4)
Grade 1	1 (2)
Grade 2	1 (2)
ICANS resolution, n/n (%)	2/2 (100)
Median time to ICANS resolution, d (range)[b]	2.5 (1–4)
ICANS leading to treatment discontinuation, n (%)	0



[a]Graded by Lee et al 2019 criteria. [b]Median is based on longest event duration in patients with >1 event. [c]Signs and symptoms included confusional state, disorientation, and dysmetria.

EPCORE NHL-2 Arm 1



24M OS rate was 87% overall and 83% in patients with DHL or THL.

Falchi et al, ASH 2024

After 21M, PFS was 82%

Double-Hit and Double-Expressor Lymphomas Are Not Associated With An Adverse Outcome After Allogeneic Stem Cell Transplantation

Alex F. Herrera, Joo Y. Song, Gabriel K. Griffin, Liana Nikolaenko, Matthew Mei, Victoria Bedell, Paola Dal Cin, Christine Pak, Tracey Stiller, Heather Sun, Edwin P. Alyea, Lihua E. Budde, Robert Chen, Yi-Bin Chen, Wing C. Chan, Corey S. Cutler, Vincent T. Ho, John Koreth, Amrita Krishnan, Joyce L. Murata-Collins, Sarah Nikiforow, Joycelynne Palmer, German A. Pihan, Raju Pillai, Leslie Popplewell, Steven T. Rosen, Tanya Siddiqi, Aliyah R. Sohani, Jasmine Zain, Larry W. Kwak, Dennis D. Weisenburger, Auayporn P. Nademanee, David M. Weinstock, Robert J. Soiffer, Joseph H. Antin, Young Kim, Scott J. Rodig, Stephen J. Forman, and Philippe Armand

City of Hope (COH) and Dana-Farber Cancer Institute (DFCI)

American Society of Hematology Annual Meeting 2016

Rationale

Poorer ASCT outcome in R/R DEL and DHL patients (Herrera et al. *JCO* 2016)

50% of R/R DLBCL pts never make it to ASCT(Gisselbrecht et al. *JCO* 2010)

Allogeneic SCT (alloSCT) produces durable remission in a proportion of R/R DLBCL pts who fail or are not candidates for ASCT (Fenske et al. *BJH* 2016, Bacher et al. *Blood* 2012)

Can alloSCT overcome the chemoresistance of DEL/DHL in pts with R/R DLBCL?

Thank You

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Questions?

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