Disclosures

Prof. Wojciech Jurczak, M.D., Ph.D.

Advisory Boards :

Sandoz Novartis, Roche, Janssen, Acerta, Abbvie, TG Therapeutics, Teva, Takeda, Spectrum, NovoNordisk, Mundipharma,

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Polish Lymphoma Research Group

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Polish Lymphoma Research Group

Chłoniak rozlany z dużych komórek B

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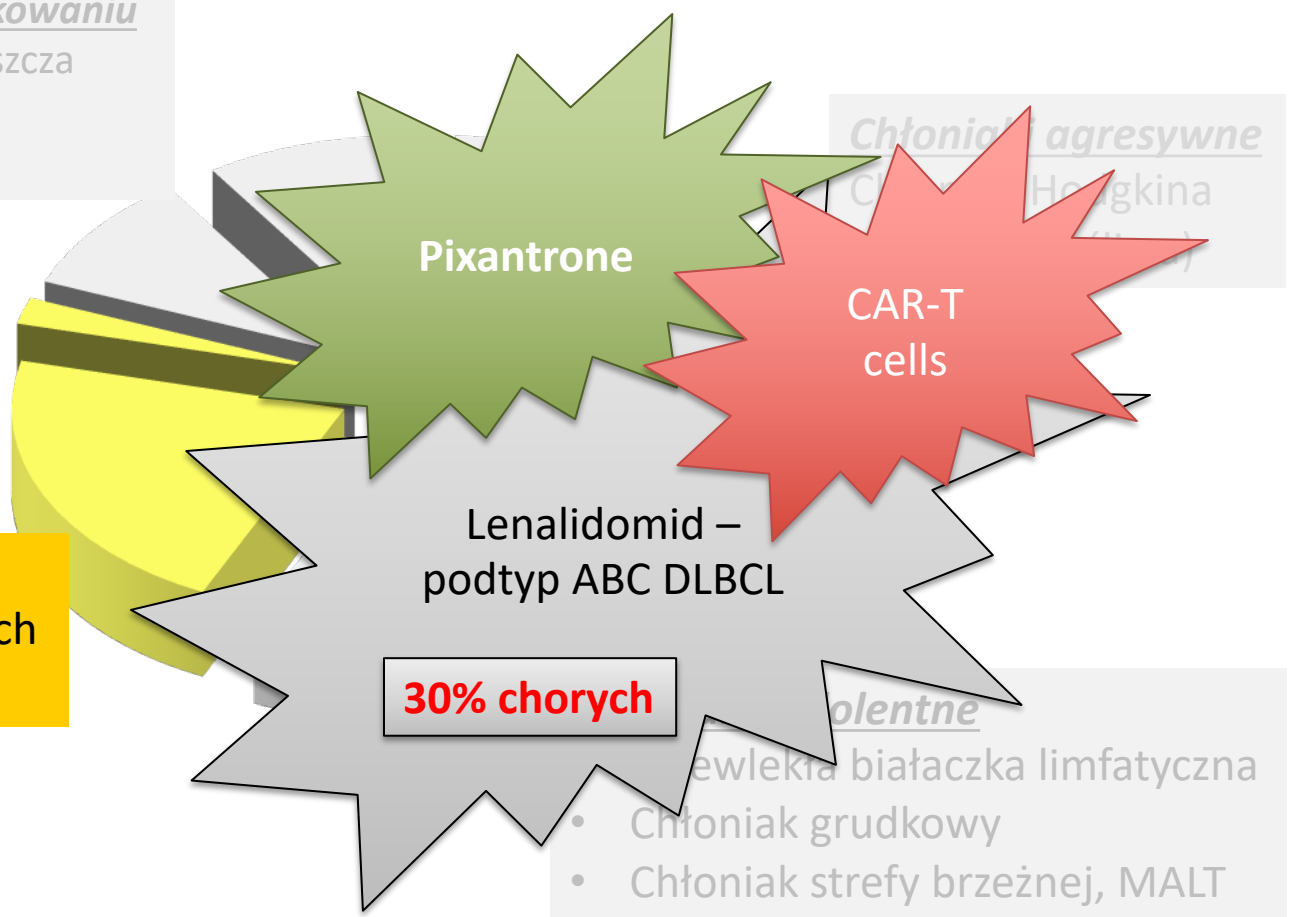
Chłoniaki o dużej dynamice – duża szansa na całkowite wyleczenie choroby

Chłoniaki o niepewnym rokowaniu
- Chłoniak z komórek płaszcza
- Szpiczak mnogi
- Chłoniaki z komórek T

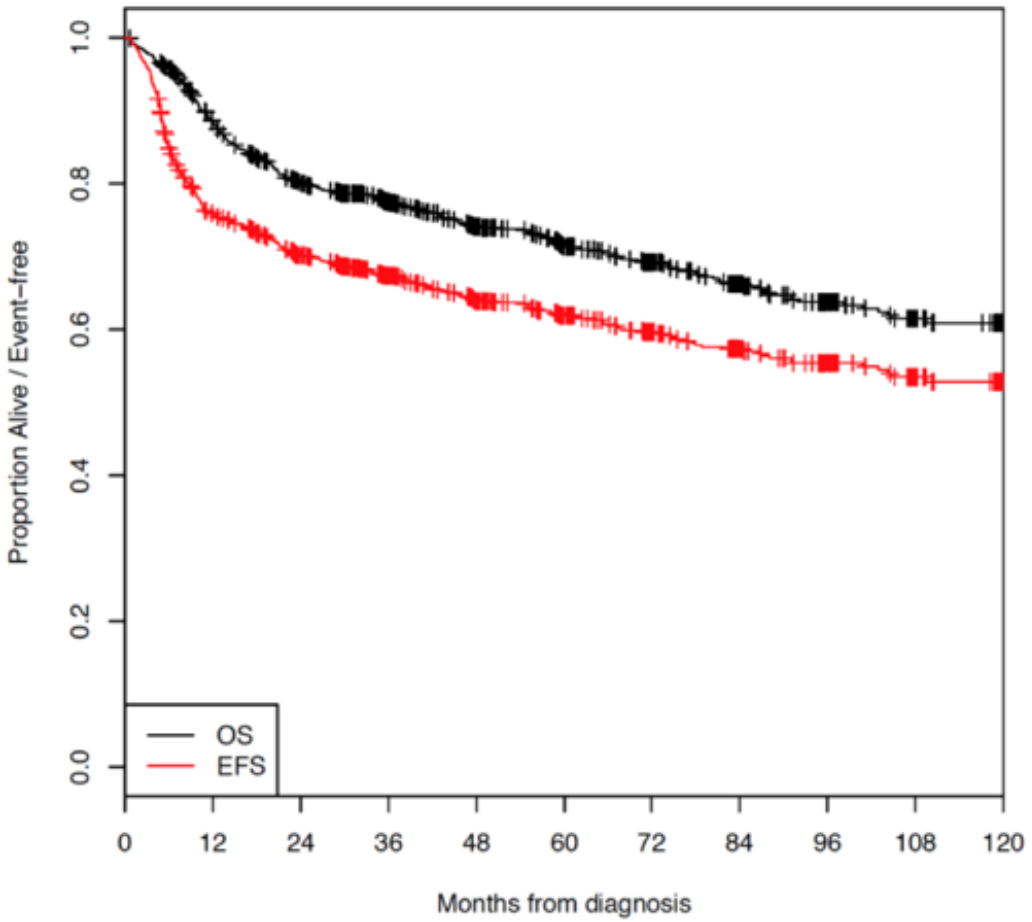


Chłoniaki agresywne
- Chłoniak rozlany z dużych komórek B

Chłoniaki agresywne
- Chłoniak z komórek Hodgkina

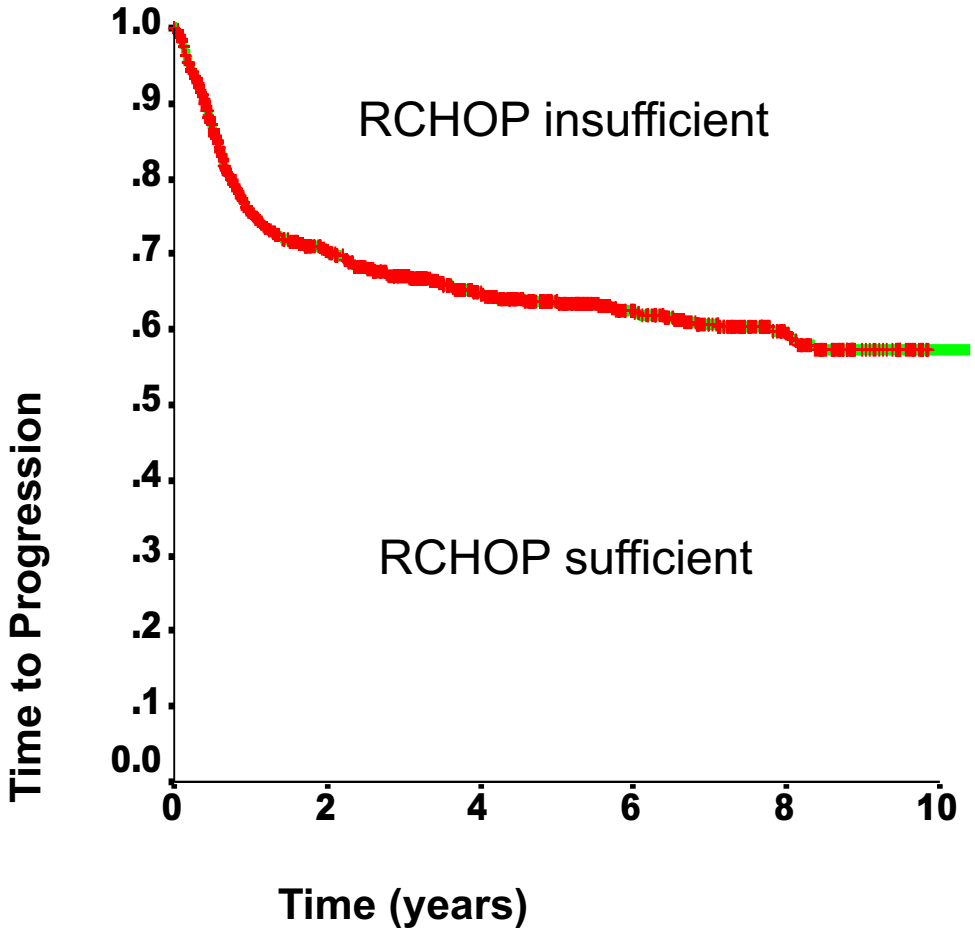
olentne
- ewlekła białaczka limfatyczna
- Chłoniak grudkowy
- Chłoniak strefy brzeżnej, MALT

DLBCL – wyniki z Mayo Clinic (6-8 x R-CHOP i podobne, 2002 – 2012, N = 1030)



- **Wysoko postawiona poprzeczka** – trudno będzie poprawić te wyniki.
- Chorzy **uczestniczący w badaniach klinicznych mają lepsze wyniki** od obserwowanych w “real life” (również w grupach kontrolnych)
- **Wczesna wznowa / oporność na R-CHOP, oznacza niekorzystne rokowanie**

DLBCL – heterogenna grupa chorych



- **Clinical factors**
  - IPI (R-IPI)
- **GEP**
  - ACB vs GCB
- **Protein expression**
  - MYC and BCL2
- **Chromosomal alterations**
  - MYC, BCL2, BCL6
- **Somatic mutations**
  - MYD88, EZH2…

ARDI od R-CHOP is an IPI independent RF in DLBCL

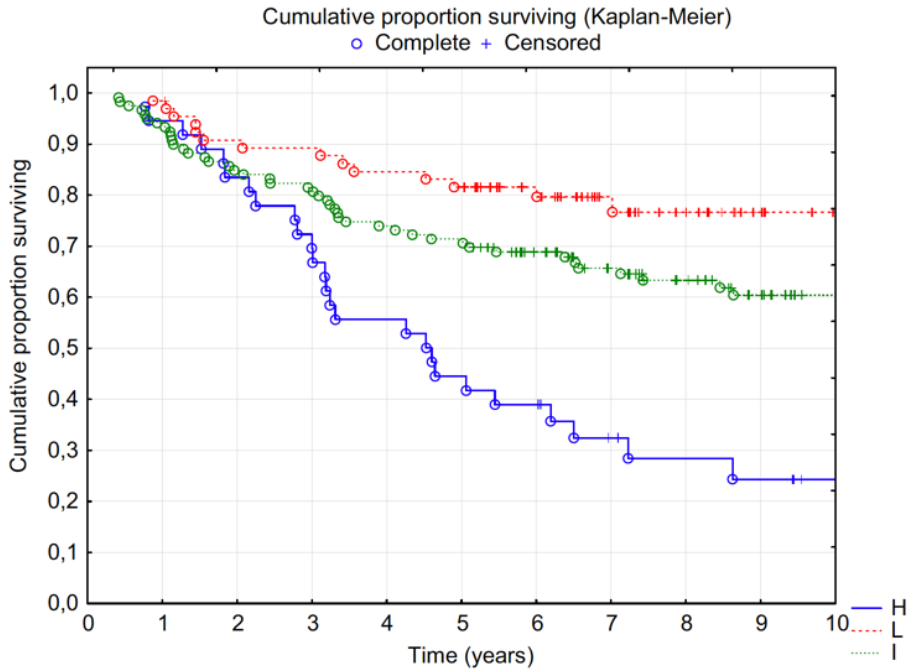


FIGURE 2 OS according to IPI (Kaplan-Meier analysis, $P < 0.00001$)

IPI	High	Intermediate	Low
Median OS	4.5 years	Not reached	Not reached

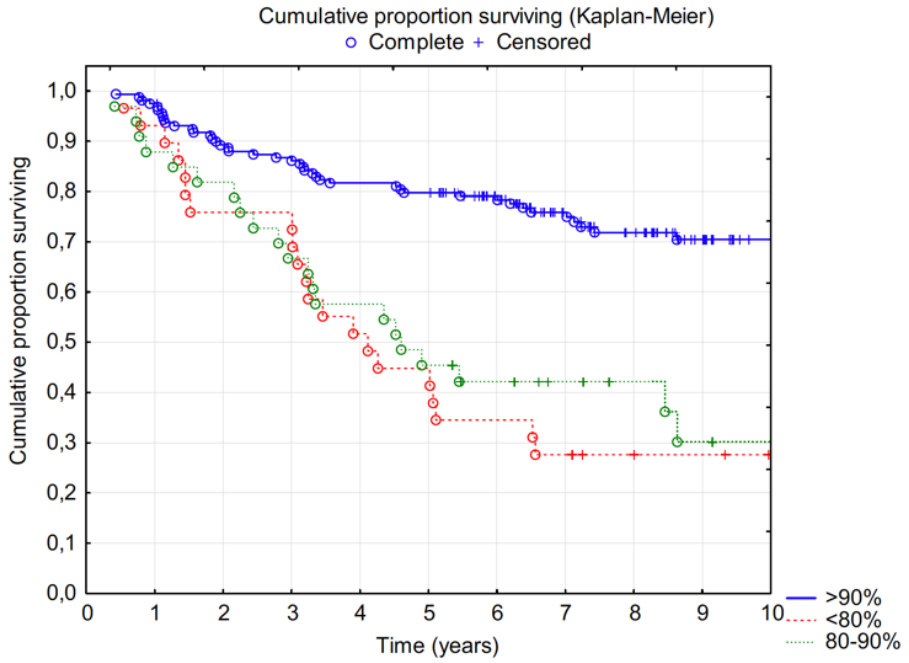


FIGURE 4 OS according to the ARDI (Kaplan-Meier analysis, $P < 0.00001$)

ARDI	<80%	80%-90%	>90%
Median OS	4.0 years	4.6 years	Not reached

Danecka et al., Cancer Medicine 2018

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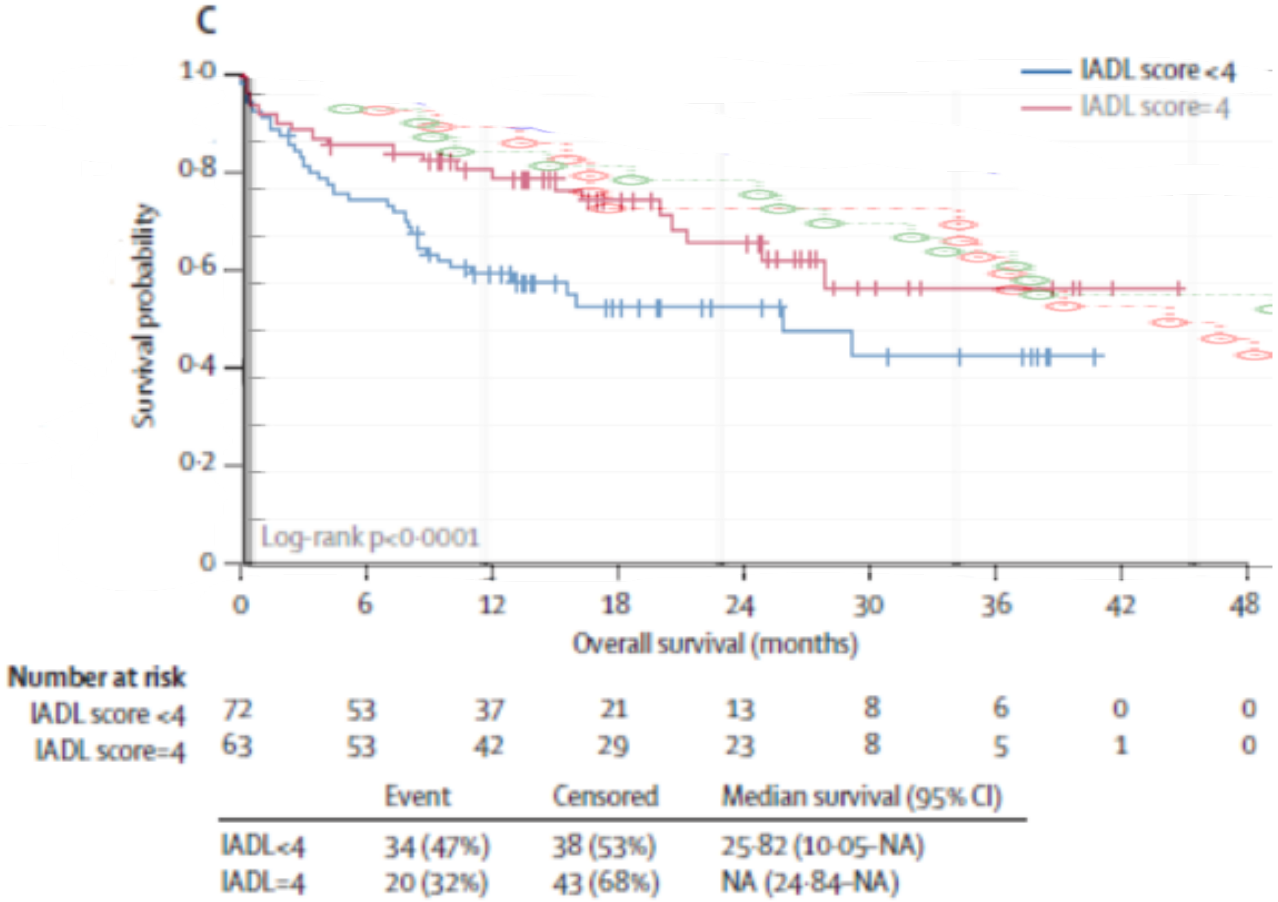
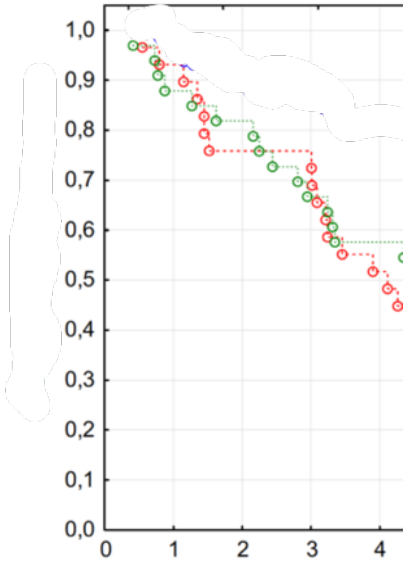
R-mini CHOP for elderly DLBCL (> 80 years)



	Event	Censored	Median survival (95% CI)
IADL<4	34 (47%)	38 (53%)	25·82 (10·05–NA)
IADL=4	20 (32%)	43 (68%)	NA (24·84–NA)

Peyrade et al: Lancet Oncol 2011



R-CHOP - reduced ARDI
80-90%
<80%

Danecka et al., Cancer Medicine 2018

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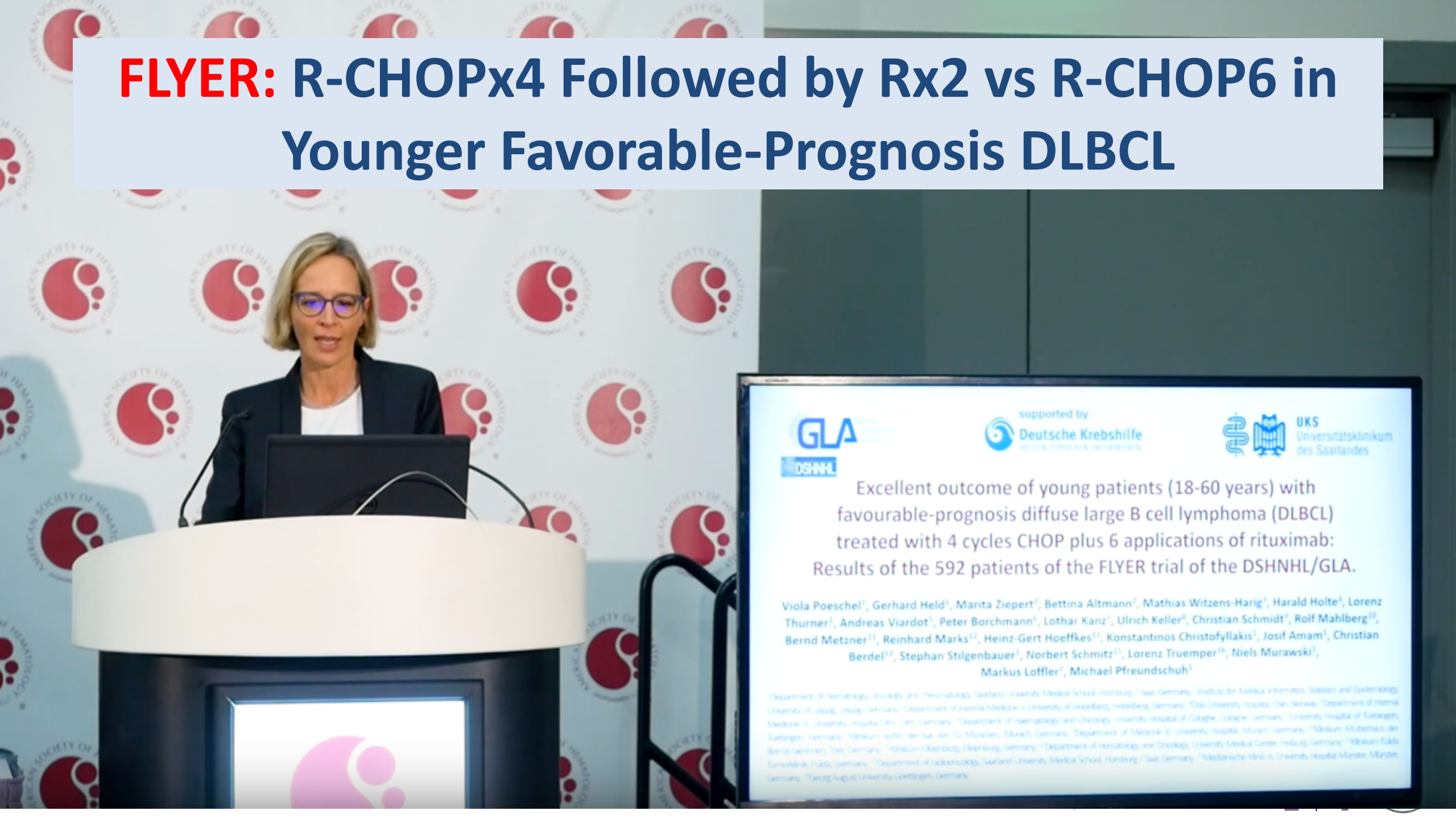
FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL



FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL – study design

untreated aggressive
B-cell lymphoma, 18-60 yrs,
stage I/II disease, IPI = 0, no bulky disease (< 7.5 cm)
(N = 588)

R-CHOP x 4 cycles followed by **Rituximab** x 2 cycles
(n = 293)

R-CHOP x 6 cycles
(n = 295)

- Primary endpoint: PFS, 3-yr PFS rate (non-inferiority study)
  - Assumed 3-yr PFS rate of 93% with R-CHOP x 6
  - Difference up to -5.5% allowed with R-CHOP x 4 → R x 2 while still proving noninferiority with 80% power and 1-sided α = 0.05 (planned sample size: N = 592, assuming 10% loss yields final N = 532)
- Other endpoints: response, EFS, OS, safety

Pfreundschuh. Lancet Oncol. 2006;7:379.
Poeschel. ASH 2018. Abstr 781.

FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL - Baseline Characteristics

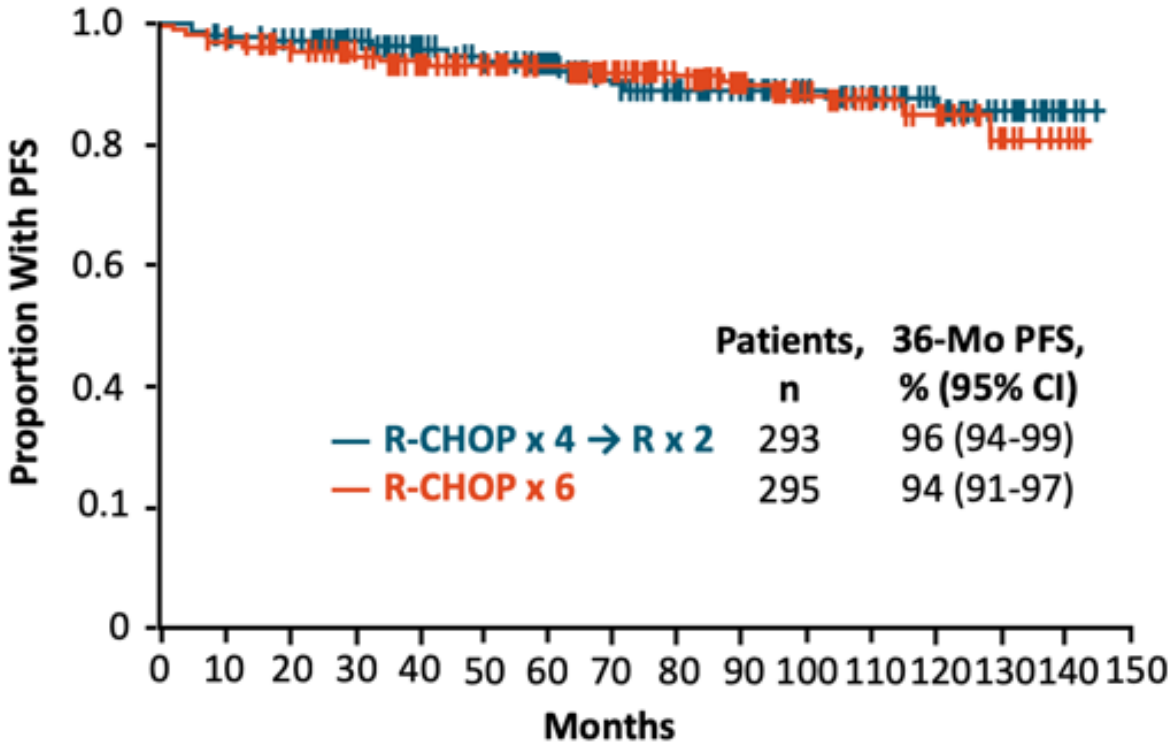
Characteristic	R-CHOP x 4 → R x 2 (n = 293)	R-CHOP x 6 (n = 295)
Female, n (%)	118 (40)	116 (39)
Median age, yrs (range)	49 (18-60)	47 (19-60)
Stage, n (%)		
▪ I	174 (59)	172 (58)
▪ II	117 (40)	119 (40)
▪ III/IV	2 (1)	4 (1)
Age-adjusted IPI, n (%)		
▪ **0**	**291 (99)**	**291 (99)**
▪ **1**	**2 (1)**	**4 (1)**
Extralymph. involvement, n (%)	95 (32)	96 (32)
Bulky disease, n (%)	1 (0.3)	1 (0.3)
B symptoms, n (%)	27 (9)	9 (3)

Pathology	R-CHOP x 4 → R x 2 (n = 257)	R-CHOP x 6 (n = 251)
DLBCL, %	78	80
▪ Centroblastic	40	44
▪ Immunoblastic	2	2
▪ Plasmoplastic	0.4	0
▪ Anaplastic large cell	2	0.4
▪ T-cell–rich B-cell lymphoma	1	0.4
▪ NOS	32	34
▪ Prim. mediast. B-cell lymphoma	2	0.4
Follicular lymphoma IIIB/III + DLBCL, %	5/9	3/10
Burkitt lymphoma, %	1	1
MCL (blastoid), %	0	0.4
Aggressive MZL, %	0.4	1
NOS, %	2	1
Unclassified (insufficient material), %	1	1

- **No patients had LDH > UNV or ECOG PS > 1**
- Significantly higher frequency of B symptoms at baseline in R-CHOP x 4 → R x 2 arm (*P* = .002)

Poeschel. ASH 2018. Abstr 781.

FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL - PFS (primary endpoint)



After median f/u of 66 mos, PFS noninferior with R-CHOP x 4 → R x 2 vs R-CHOP x 6

Poeschel. ASH 2018. Abstr 781.

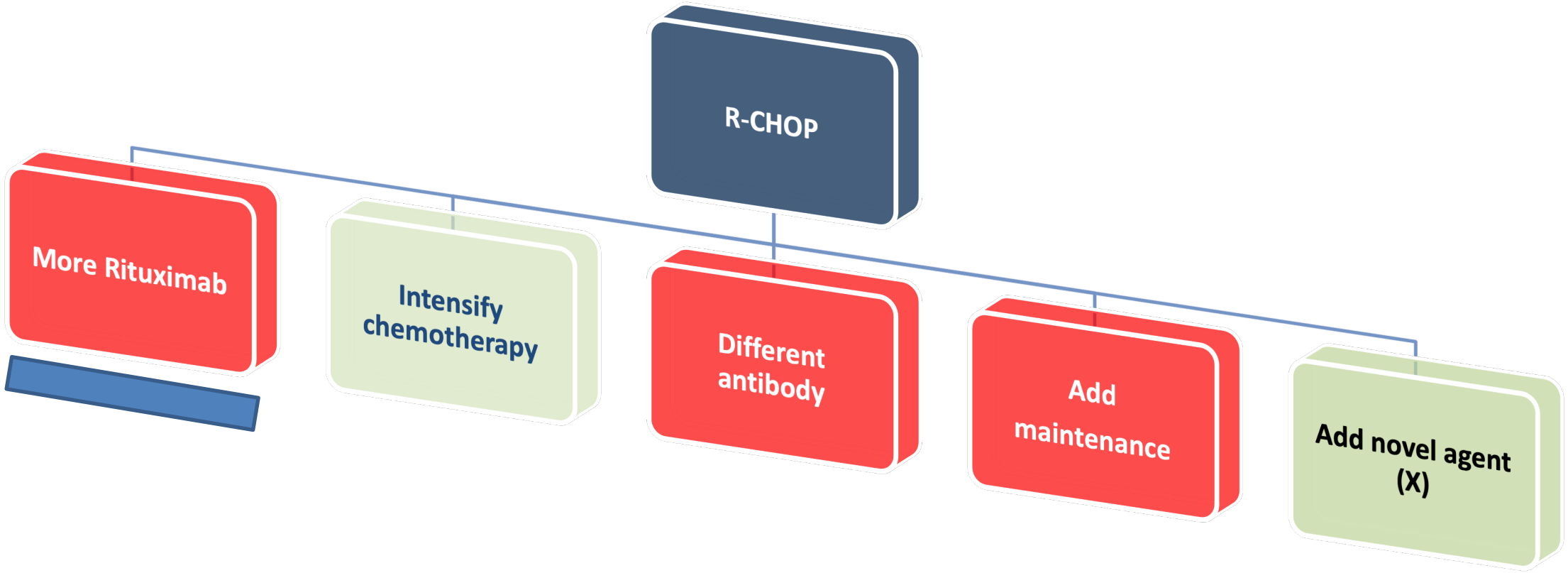
FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL – Safety

AE, n	R-CHOP x 4 → R x 2 (n = 293)		R-CHOP x 6 (n = 295)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AEs				
▪ Leukocytopenia*	171	80	237	110
▪ Anemia*	107	2	172	8
▪ Thrombocytopenia*	16	5	17	7
Nonhematologic AEs	835	46	1295	70
▪ Paresthesia	227	12	370	14
▪ Nausea	195	6	319	12
▪ Infection	98	20	156	23
▪ Vomiting	56	1	117	7
▪ Mucositis	68	1	105	3

- **Nonhematologic AEs with reduced by approximately one third**
- **Therapy-associated mortality rate was 0% with R-CHOP x 4 → R x 2 vs 1% with R-CHOP x 6**

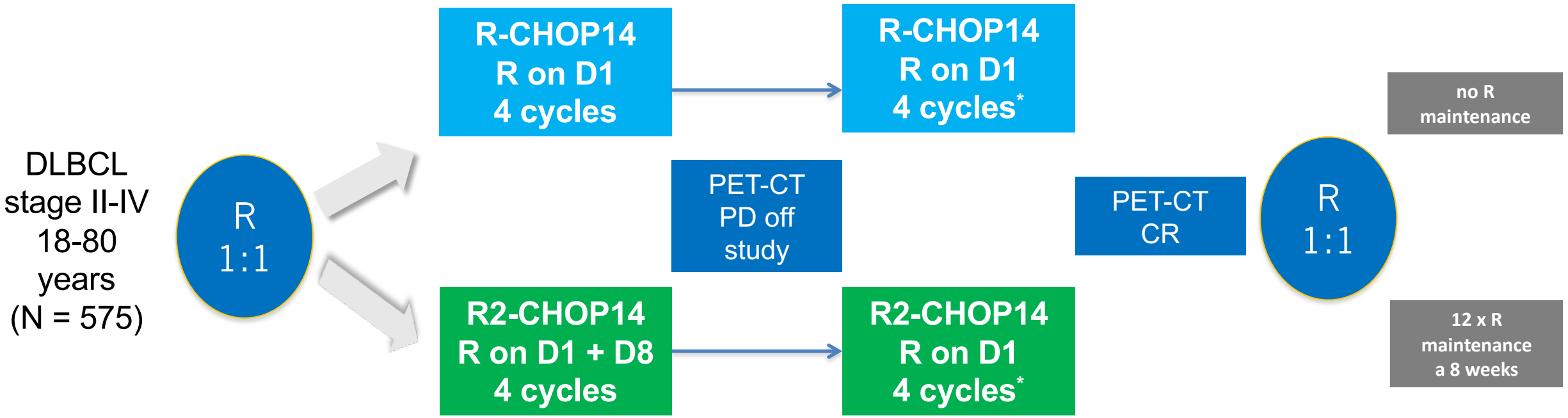
Poeschel. ASH 2018. Abstr 781.

How to improve R-CHOP ?



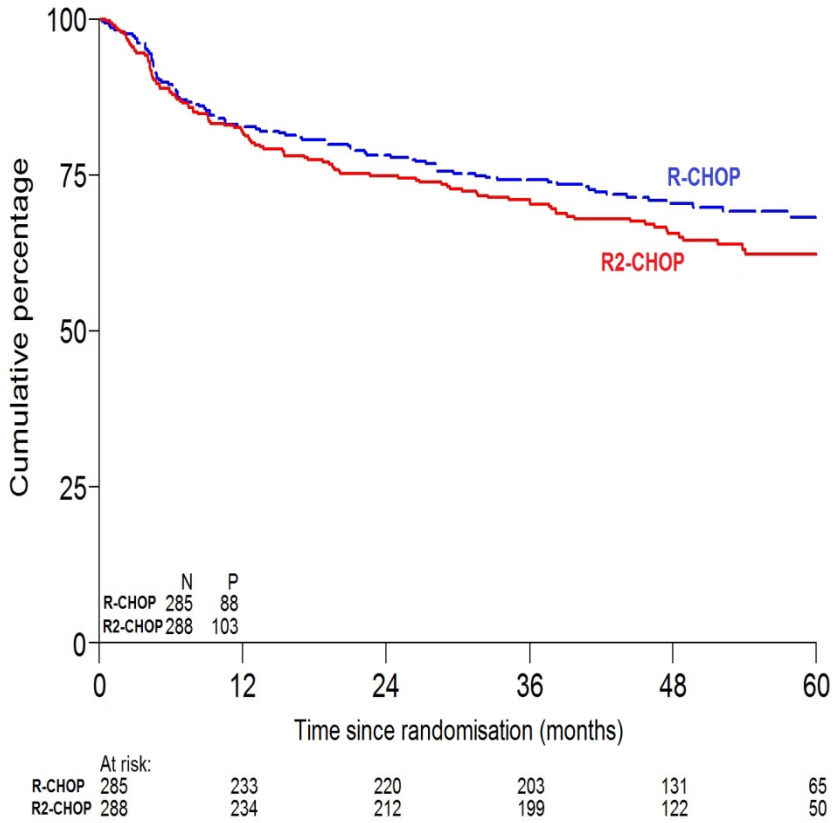
Courtesy of G. Nowakowski

“More Rituximab”



Presented by: PJ Lugtenburg ASCO 2016

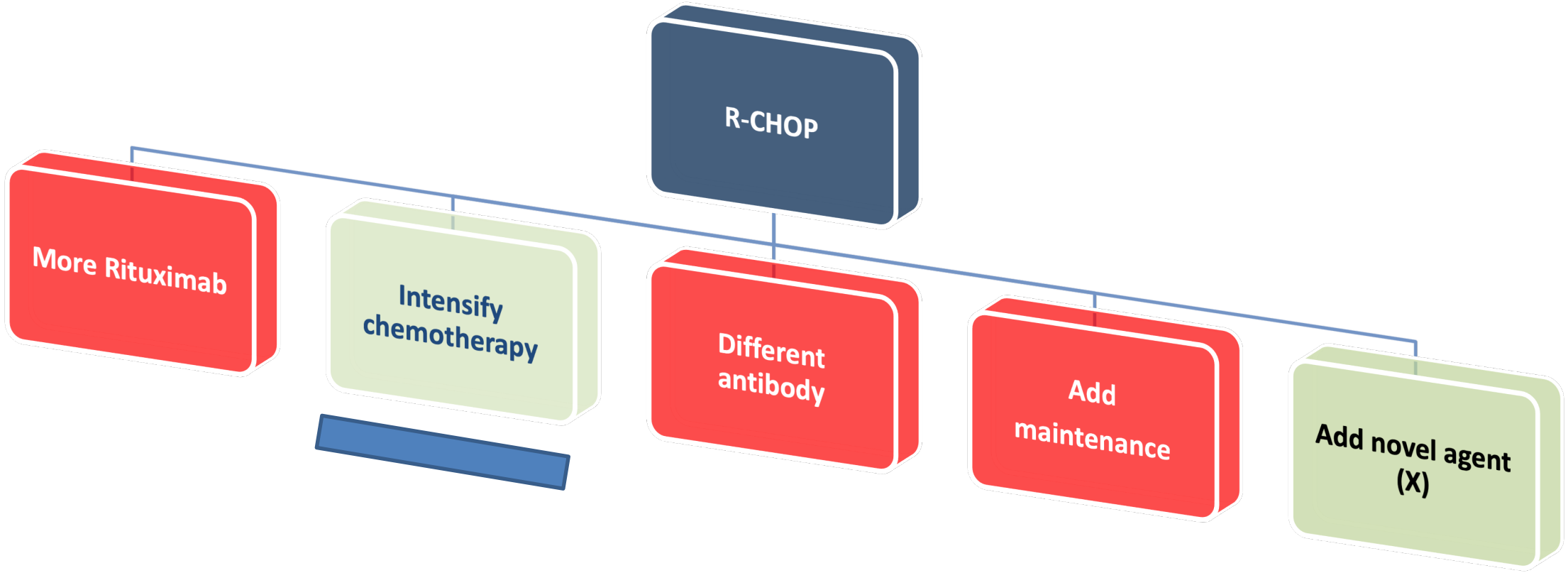
“More Rituximab”



PFS	R-CHOP	R2-CHOP
3-year	74%	71%
	HR 1.20 (95% CI 0.90-1.60) *P* = .17	
5-year	68%	62%

Presented by: PJ Lugtenburg ASCO 2016

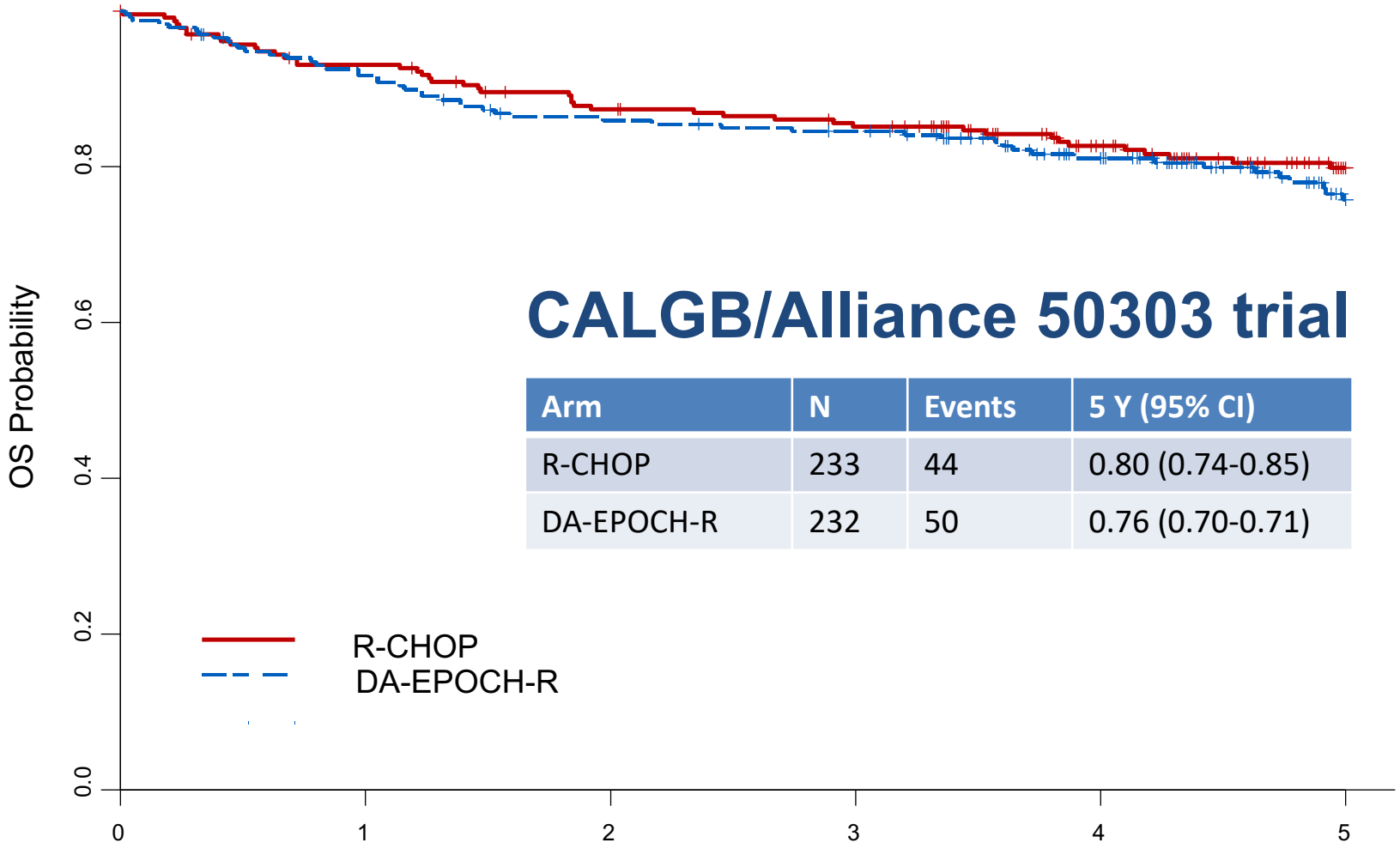
How to improve R-CHOP ?



Courtesy of G. Nowakowski

Rituximab Is "A Great Equaliser" of Chemotherapy Regimens

CHOP
CHOP-14
CHOEP
DA-EPOCH



CALGB/Alliance 50303 trial

Arm	N	Events	5 Y (95% CI)
R-CHOP	233	44	0.80 (0.74-0.85)
DA-EPOCH-R	232	50	0.76 (0.70-0.71)

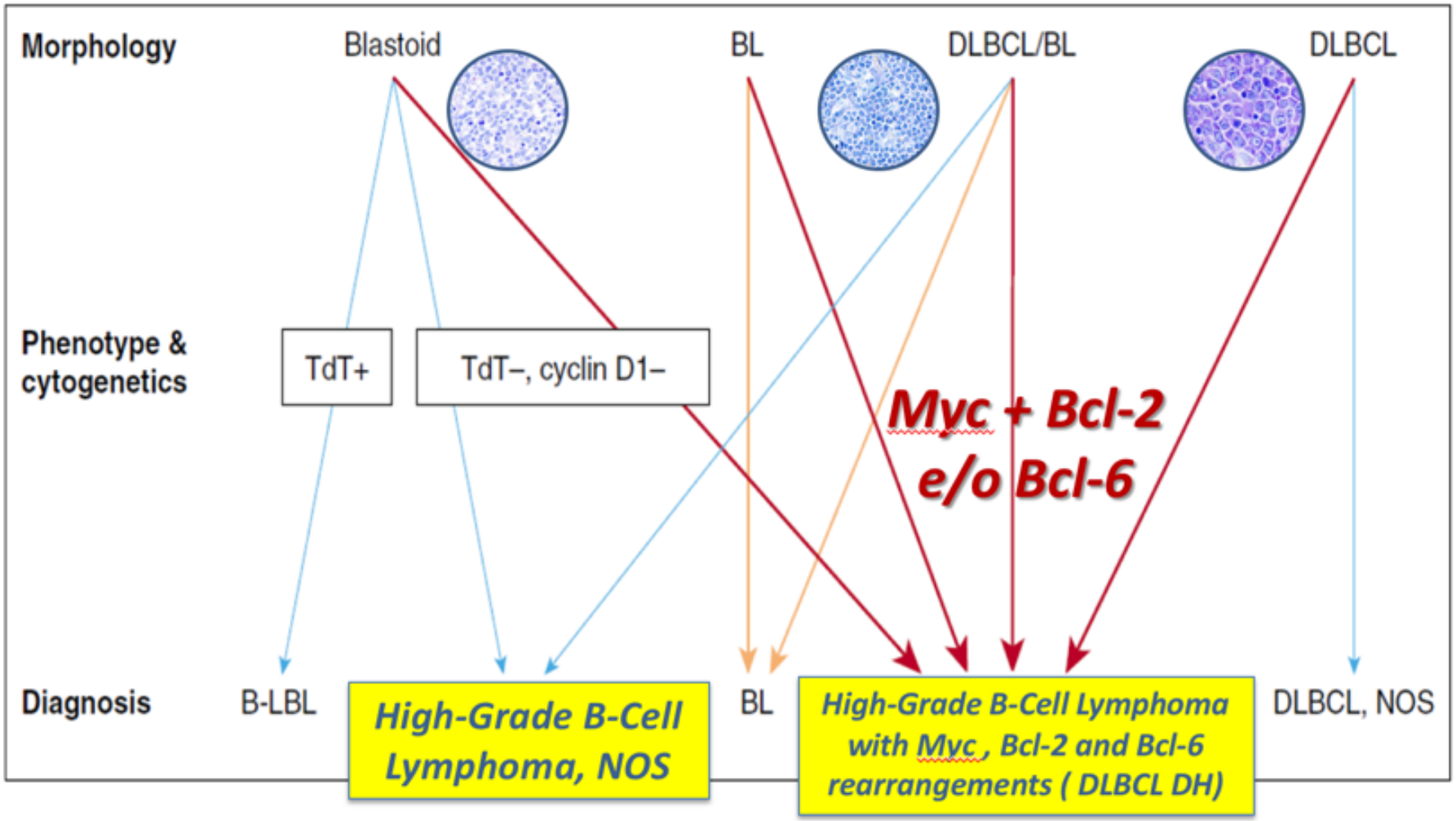
Wilson WH, et al.: ASH 2016

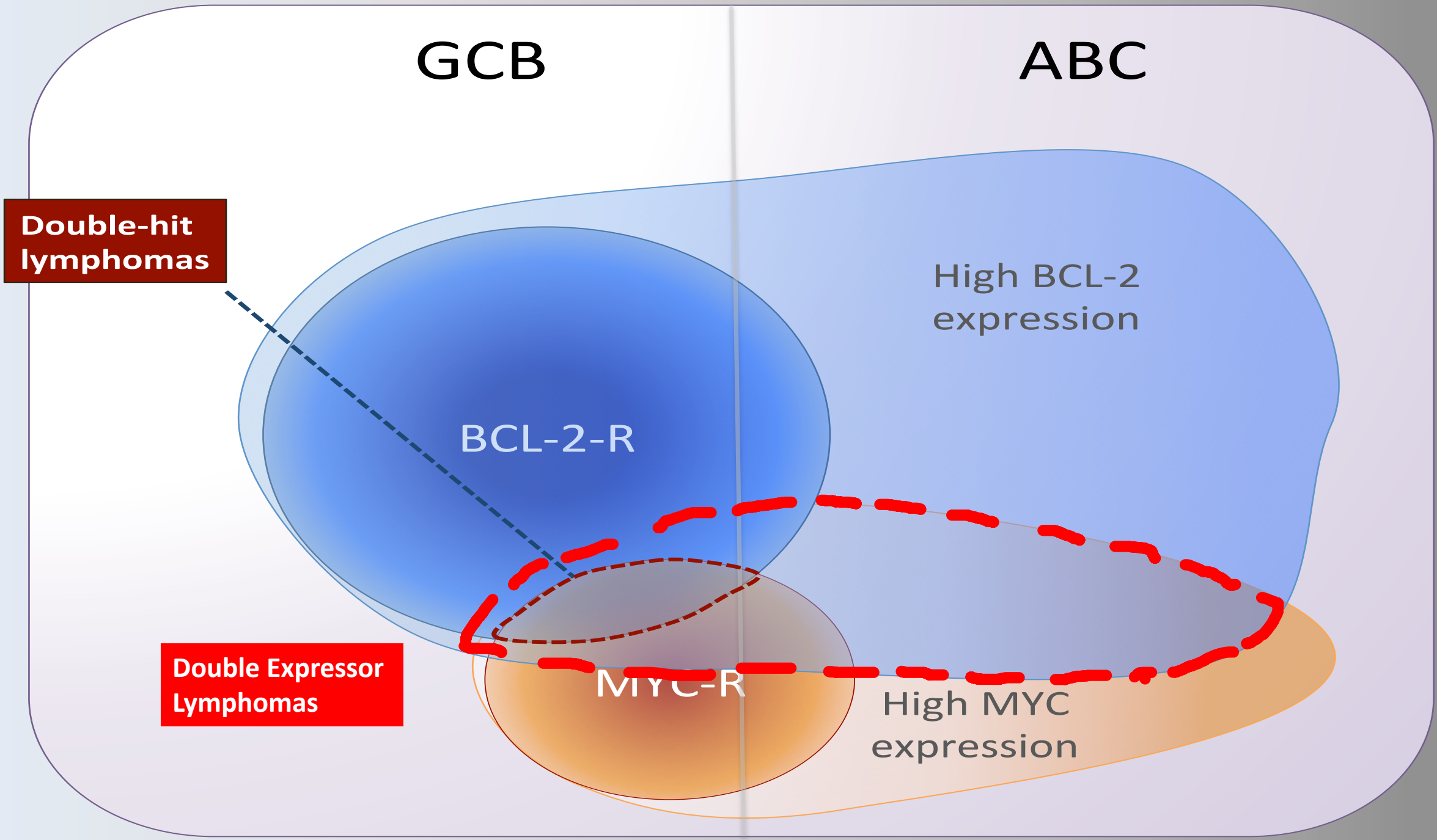
Phase 3 Study of R-CHOP vs DA-EPOCH-R in Patients With Untreated DLBCL (CALGB/Alliance 50303): Grade 3-5 Toxicities

Event	R-CHOP	DA-EPOCH-R	P value
Treatment related deaths*	2%	2%	.975
ALL Gr 3-4	76.3%	96.5%	<.001
Hematologic	73.1%	97.7%	<.001
Non-Hematologic	41.3%	70.9%	<.001
ANC	68%	96%	<.001
Platelets	**11%**	**65%**	**<.001**
Febrile neutropenia	**17%**	**35%**	**<.001**
Infection	11%	14%	.169
Mucositis	2%	6%	.011
Neuropathy - sensory	**2%**	**14%**	**<.001**
Neuropathy - motor	**1%**	**8%**	**<.001**

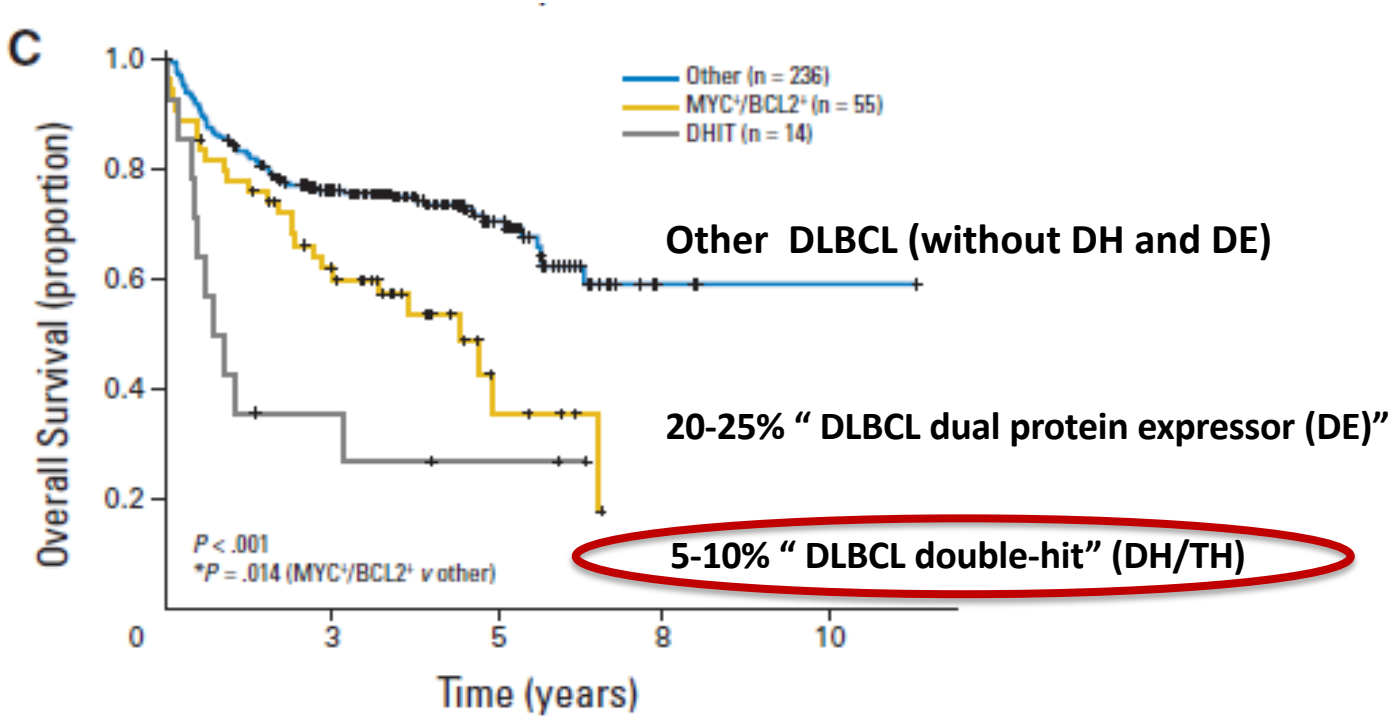
Wilson WH, et al.: ASH 2016

2016: Revision of the WHO classification of lymphoid neoplasms (HGBCL)




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

DLBCL cases that express both MYC and BCL2 are characterized by adverse prognosis



Other DLBCL (without DH and DE)

20-25% " DLBCL dual protein expressor (DE)"

5-10% " DLBCL double-hit" (DH/TH)

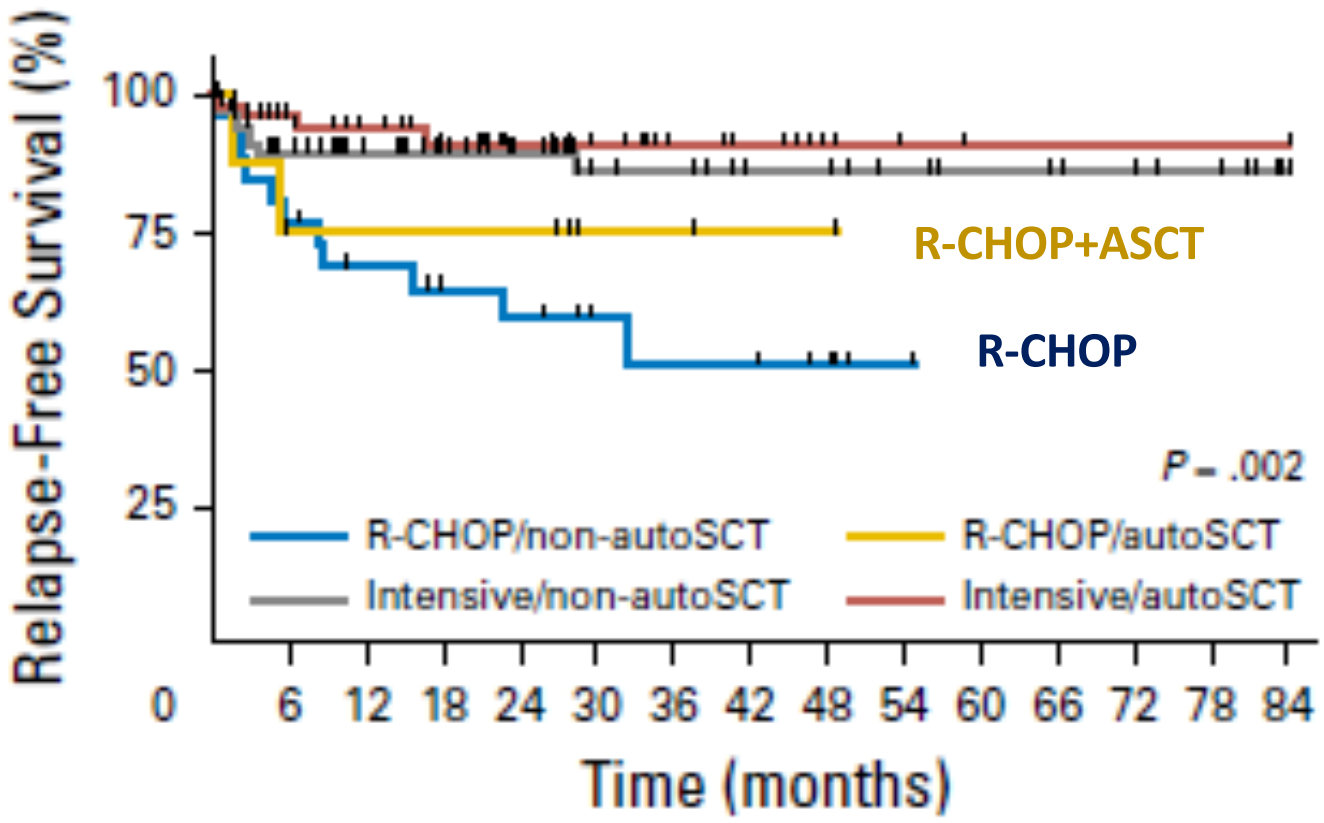
R-CHOP 21

DA-EPOCH-R, R-CHOP + X

NO R-CHOP 21 !!!!
Intensive regimens +/- ASCT or DA-EPOCH-R
CNS prophylaxis (HD-MTX /ARAC or IT MTX)

Johnson et al., JCO, 2012

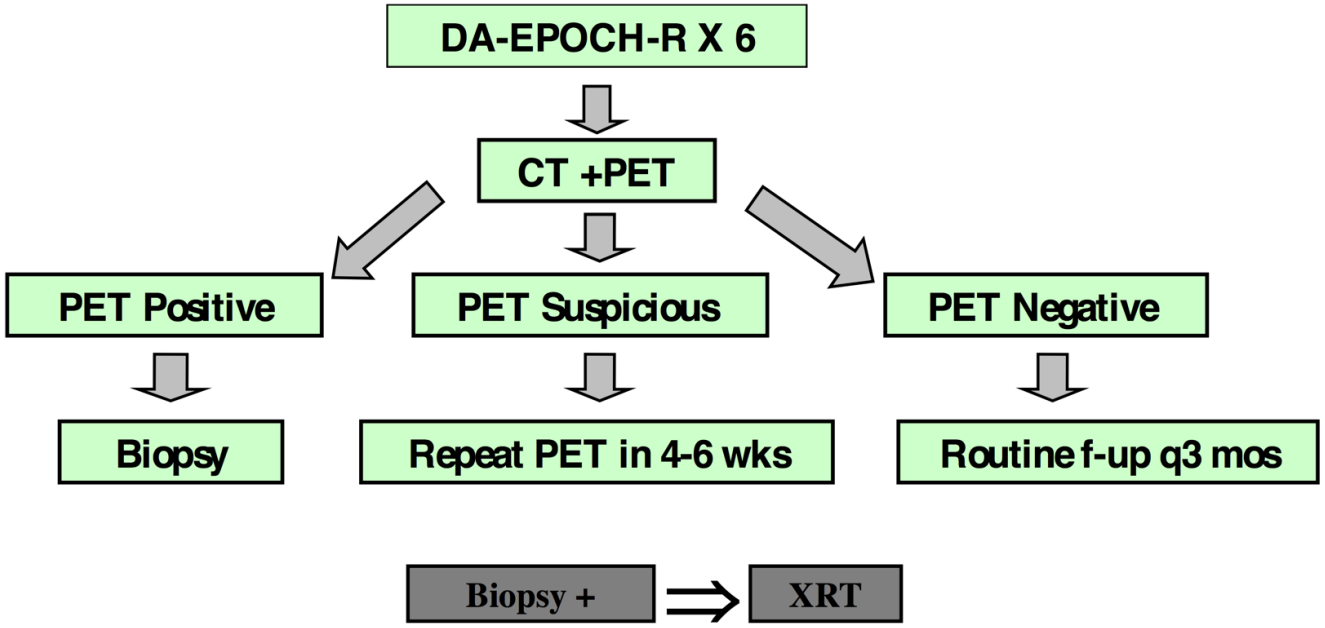
R-CHOP-21 is not adequate for double hit DLBCL

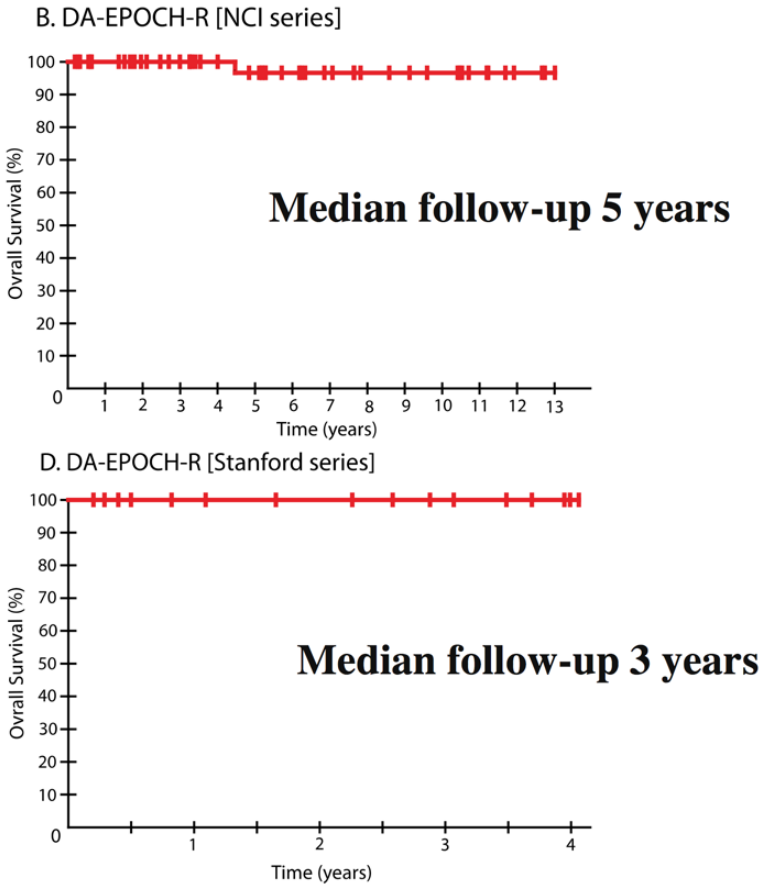


R-hyperCVAD/MA,
R-DA-EPOCH,
R-CODOX-M/IVAC

Landsburg D et al . J.Clin. Oncol 2017

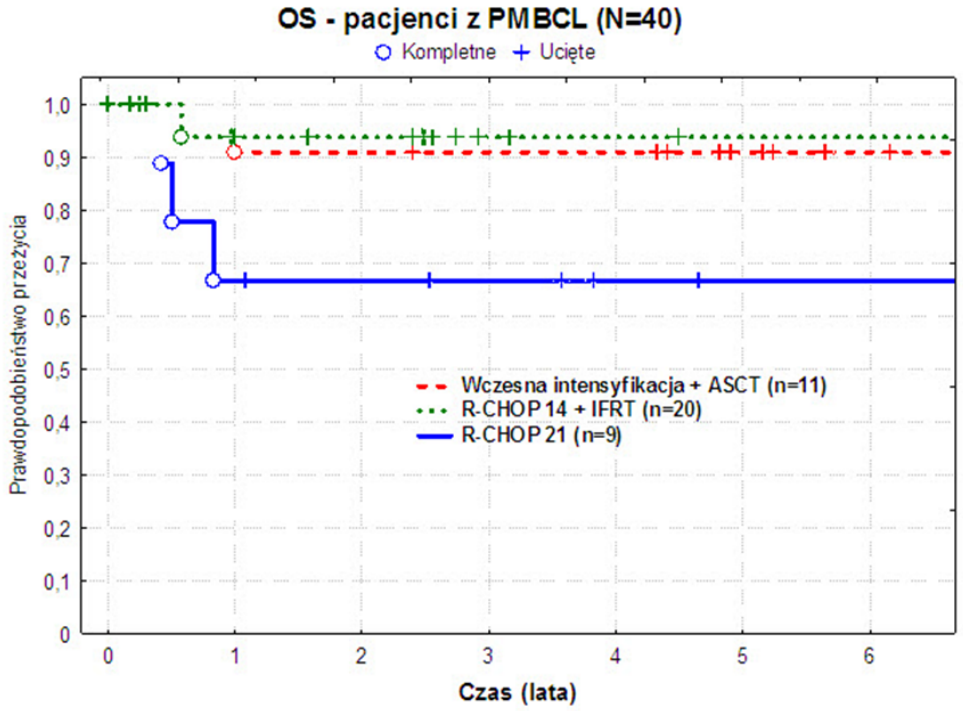
R-CHOP 21 is not adequate for PMBCL





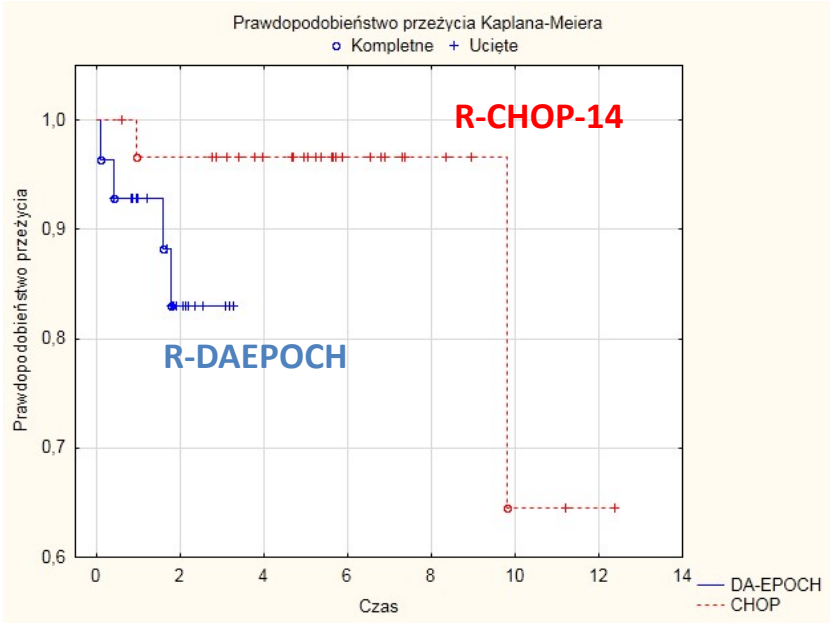
Dunleavy et al, NEJM 2013

R-CHOP 21 is not adequate for PMBCL



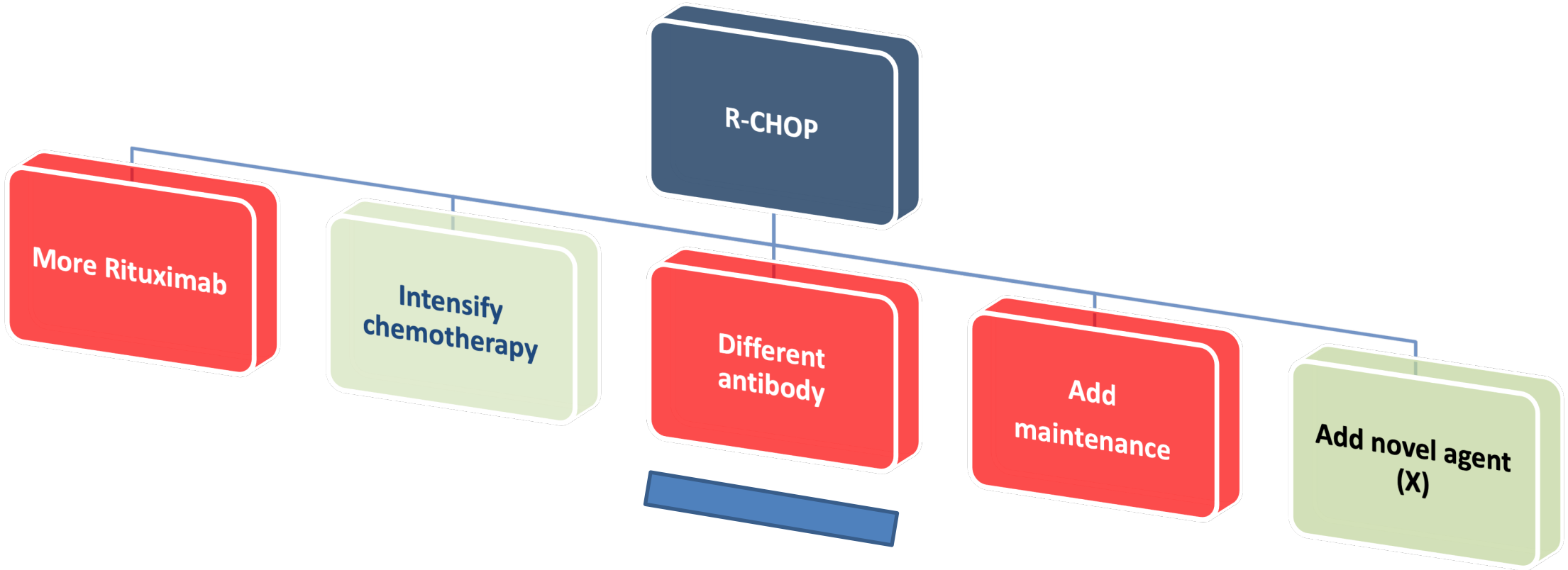
Jurczak et al., ASH 2010

OS



Giza et al., w przygotowaniu

How to improve R-CHOP ?



Courtesy of G. Nowakowski

Second generation CD20 antibodies in DLBCL

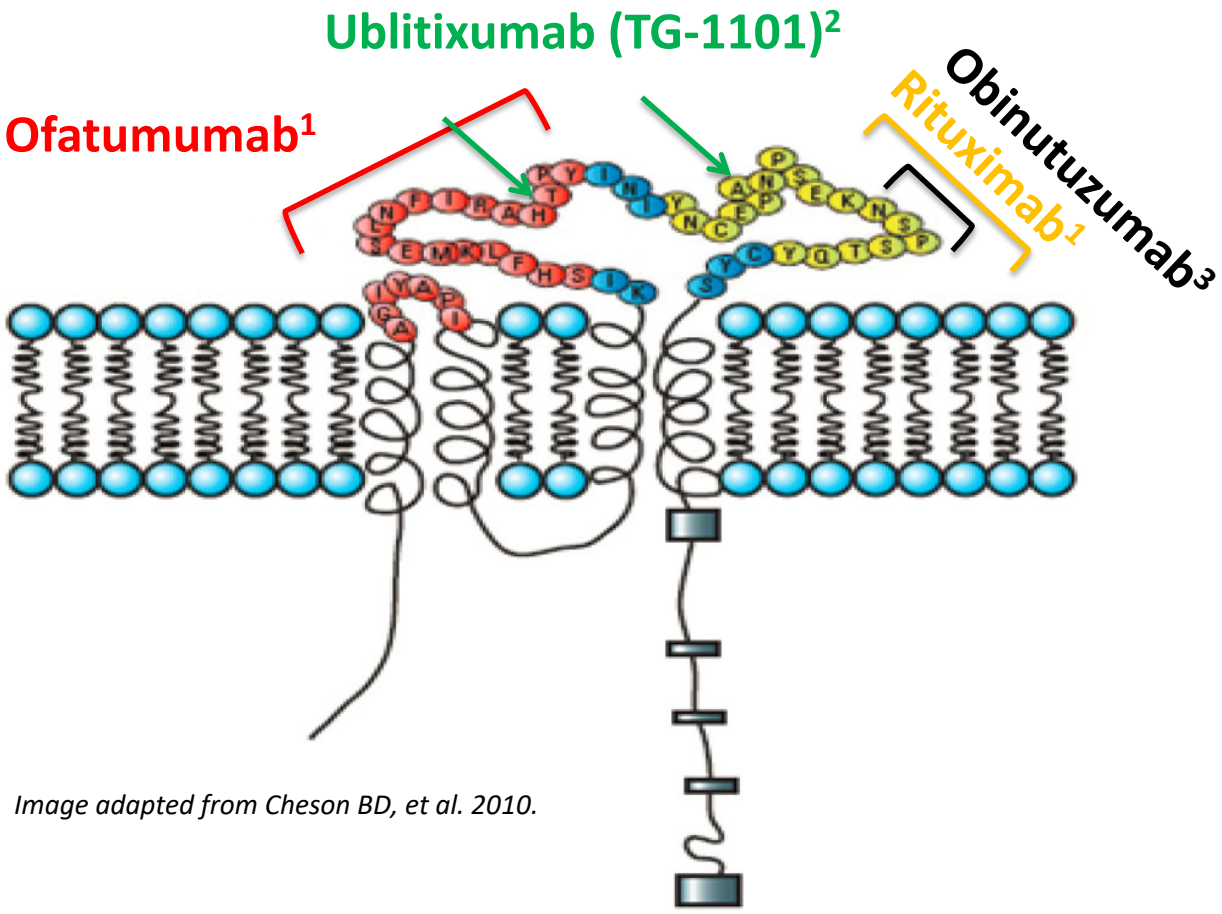


Image adapted from Cheson BD, et al. 2010.

Antibody	Key characteristics/results
Ofatumumab[1,4]	• Type 1 human IgG1κ mAb[1] • Improved CDC and ADCC vs rituximab (preclinical)[1] • No difference in efficacy between O-DHAP and R-DHAP as salvage treatment of R/R DLBCL[4]
Ublitixumab[2]	• Type 1 chimeric IgG1 mAb • Glycoengineered for enhanced ADCC • Activity in 'low' CD20 expressing cell lines • Single agent responses observed in rituximab refractory patients • Significant activity in combination with bendamustine in advanced DLBCL[5]
Obinutuzumab[3,6-8]	• Type II glycoengineered, humanized IgG1κ mAb[3,6] • Unlike Type I, does not induce rafting of CD20 and shows low CDC activity[3] • G-CHOP did not significantly improve investigator-assessed PFS vs R-CHOP (GOYA Phase III)[7] • Shown effective combined with lenalidomide in R/R DLBCL[8]

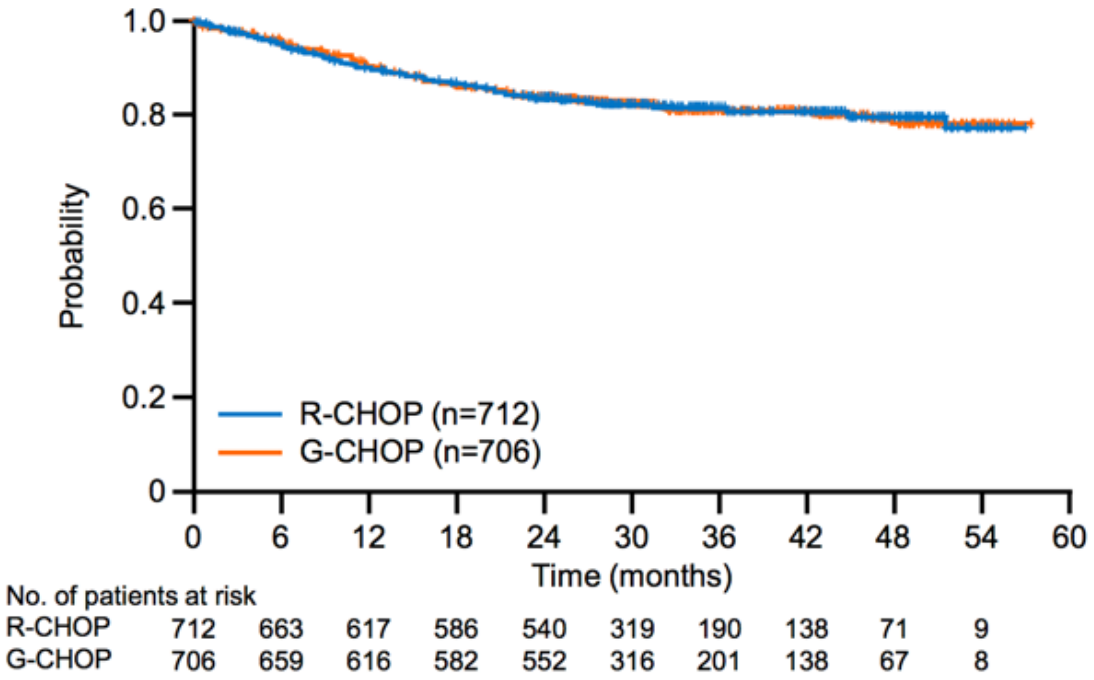
1. Cheson B.D. J Clin. Oncol 2010;28:3525-3530; **2.** O'Connor O.A. et al. ASCO 2014; **3.** Klein C. et al. mAbs 2012;5:22-33; **4.** Van Imhoff GW, et al. Journal of Clinical Oncology 2017;35:544–551; **5.** Lunning M, et al. Blood 2016;128:4197; **6.** Morschhauser FA, et al. Journal of Clinical Oncology 2013;31:2912–2919; **7.**Vitolo U, et al. ASH 2016; **8.** Morschhauser F., et al. ASH 2016.

Chemotherapy May Be "A Great Equaliser" of Monoclonal Antibodies

Rituximab
Obinutuzumab
MOR 208 ?

OS in previously untreated DLBCL patients (GOYA trial)

Kaplan-Meier plot of OS by treatment arm



	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	126 (17.7)	126 (17.8)
1-yr OS, %	89.9	90.7
2-yr OS, %	83.7	83.9
3-yr OS, %	81.4	81.2
HR (95% CI), p-value*	1.00 (0.78, 1.28), p=0.9982	

Median follow-up: 29 months

Vitolo et al.: 2016

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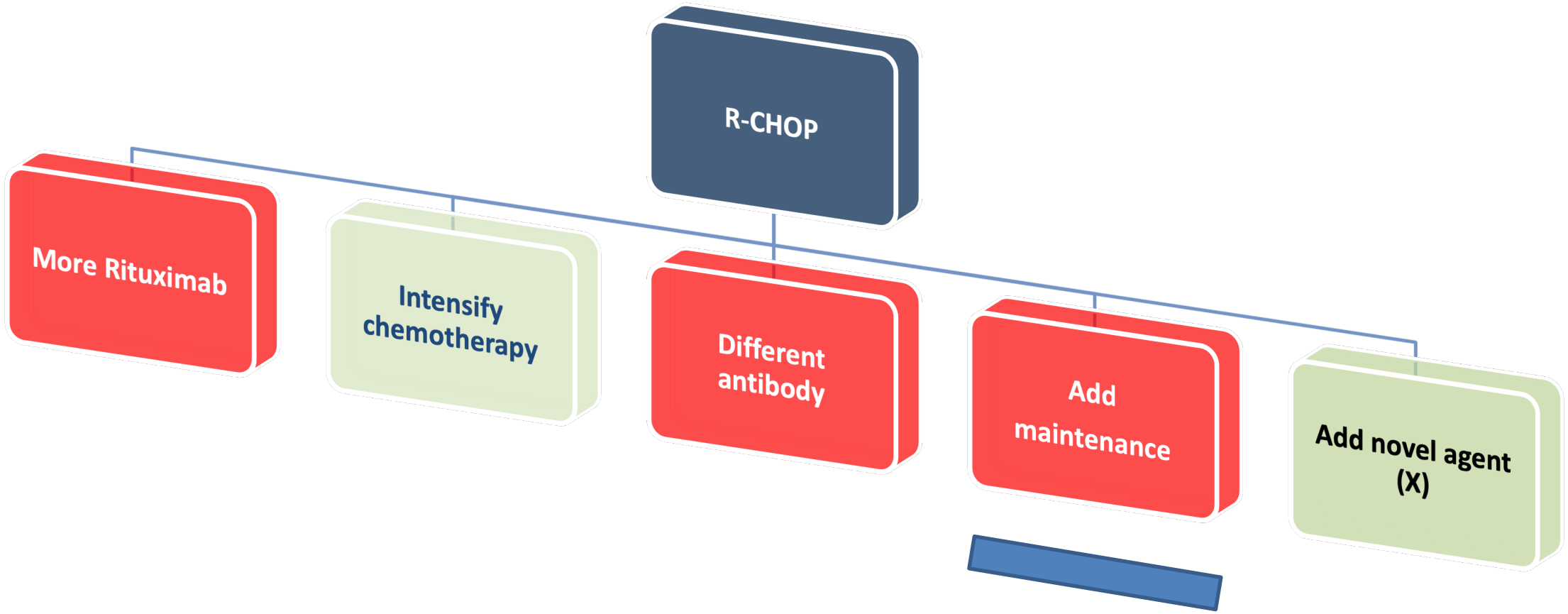
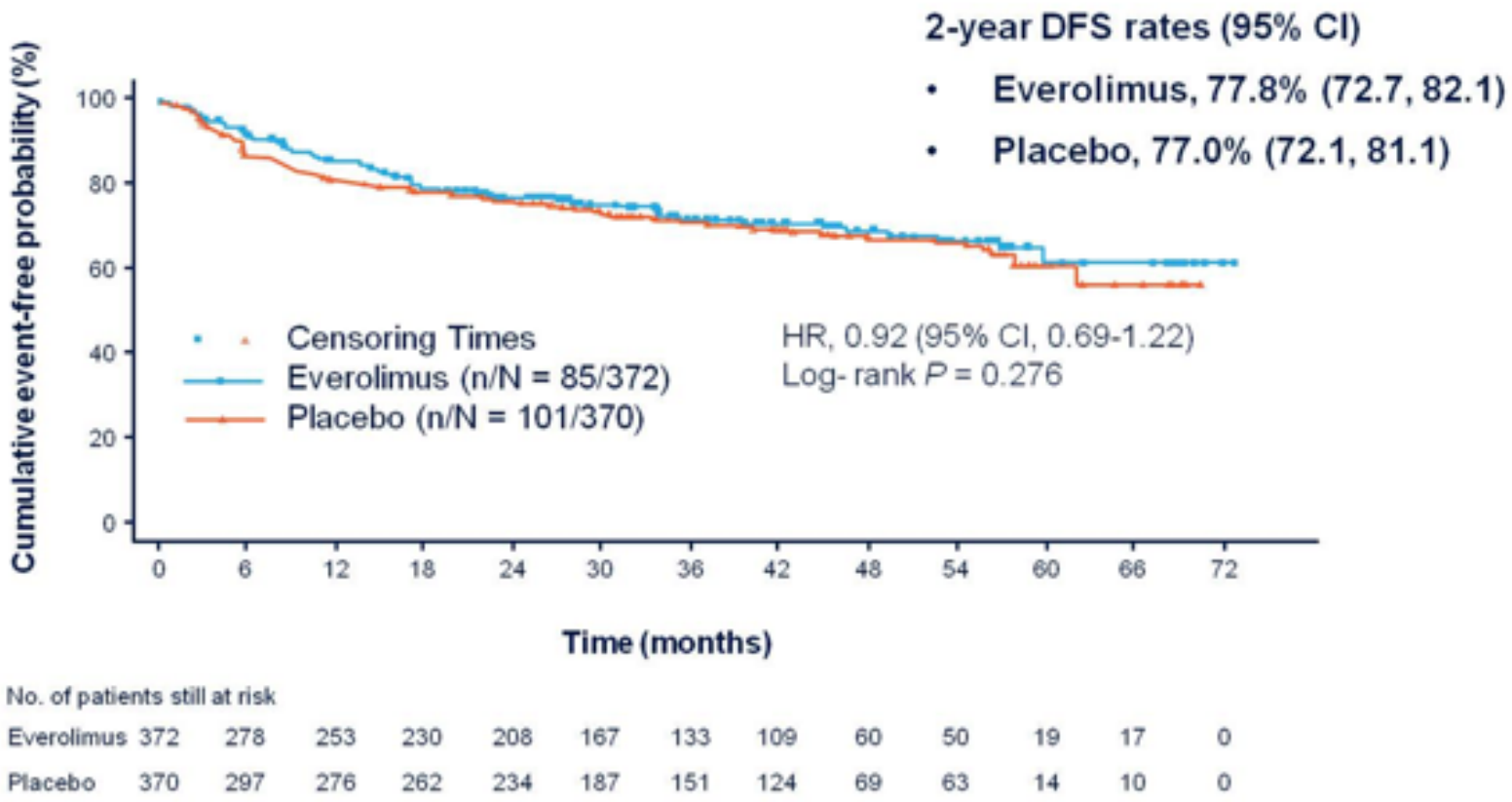
How to improve R-CHOP ?



Courtesy of G. Nowakowski

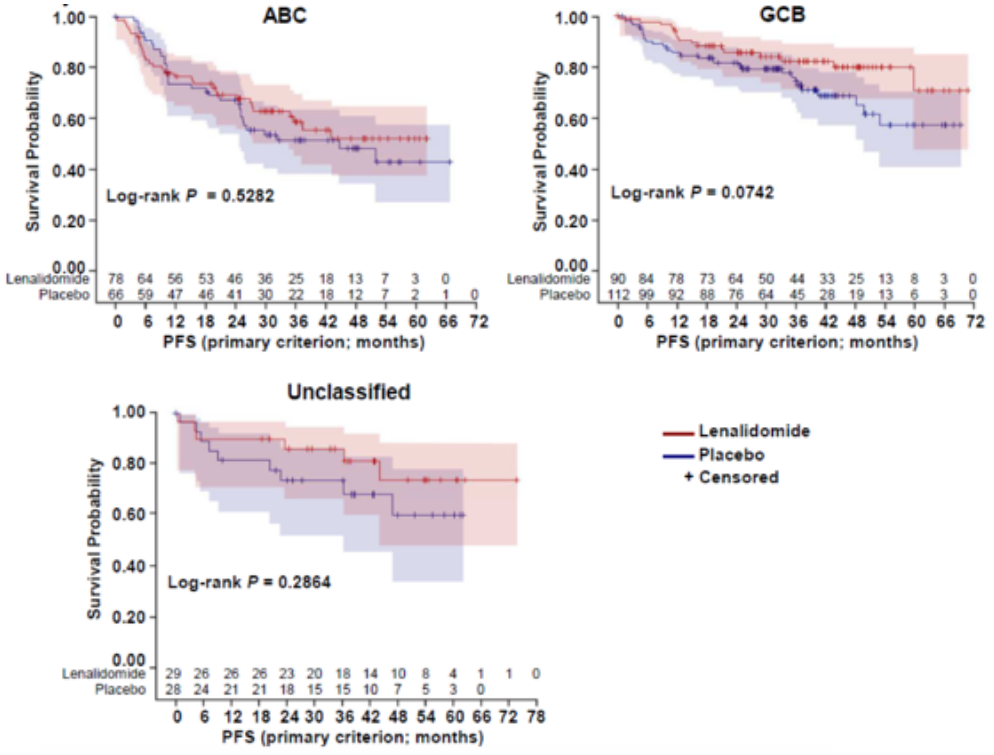
Everolimus maintenance



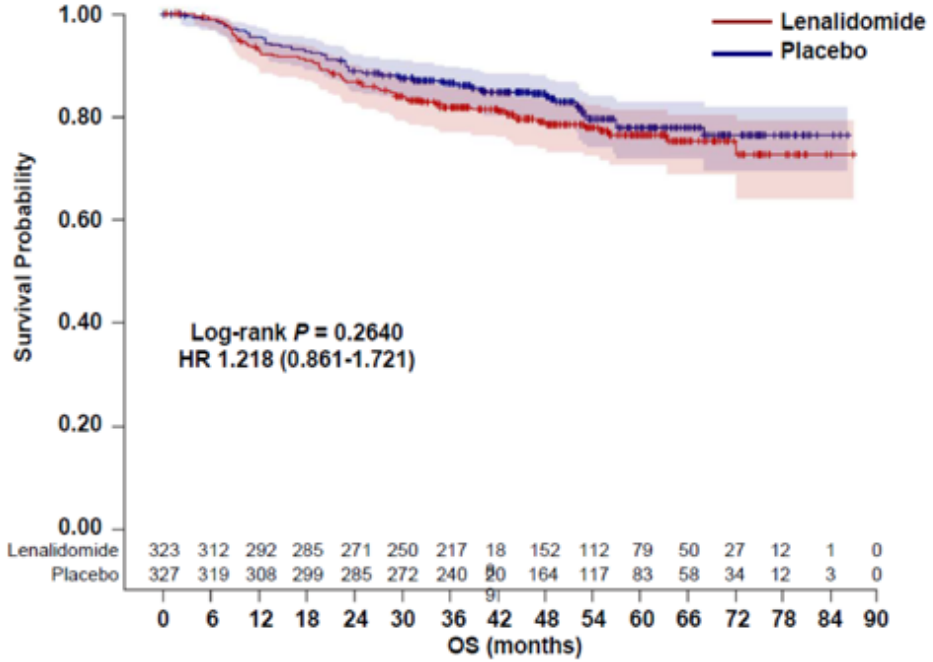
Witzig at 2016 ASCO Annual Meeting

Lenalidomide maintenance (REMARC trial)

PFS



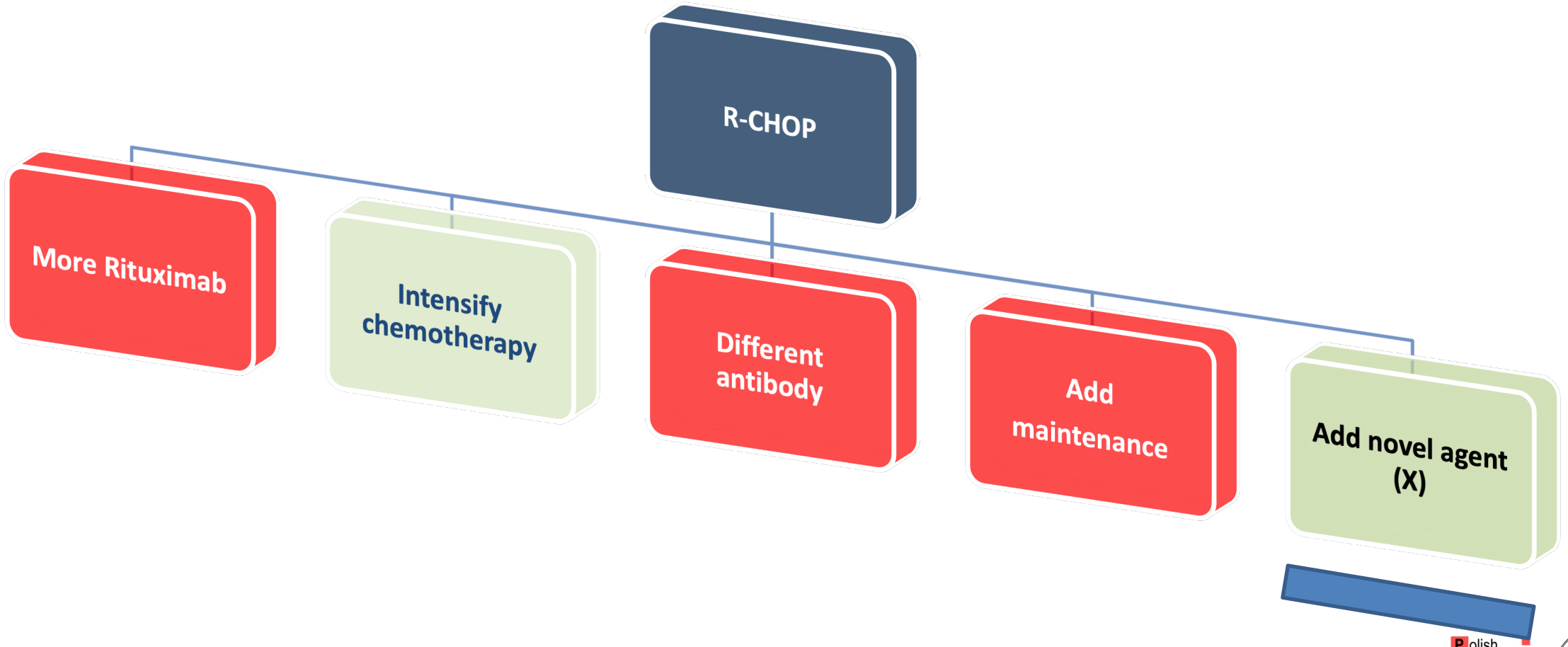
OS



- At a median follow-up of 52 months, there was no statistical difference between arms
- Multivariate analysis showed that treatment arm was not a statistically significant factor

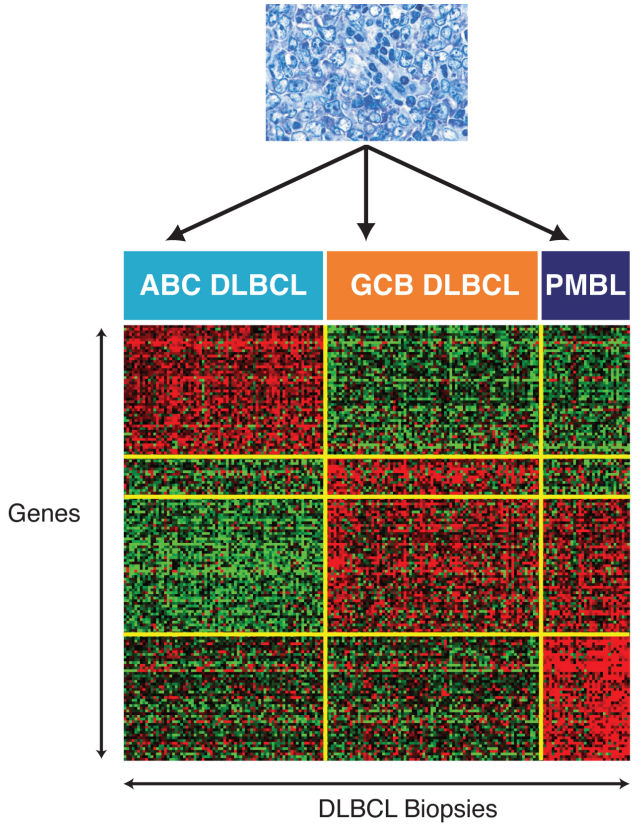
Thieblemont, ASH 2016

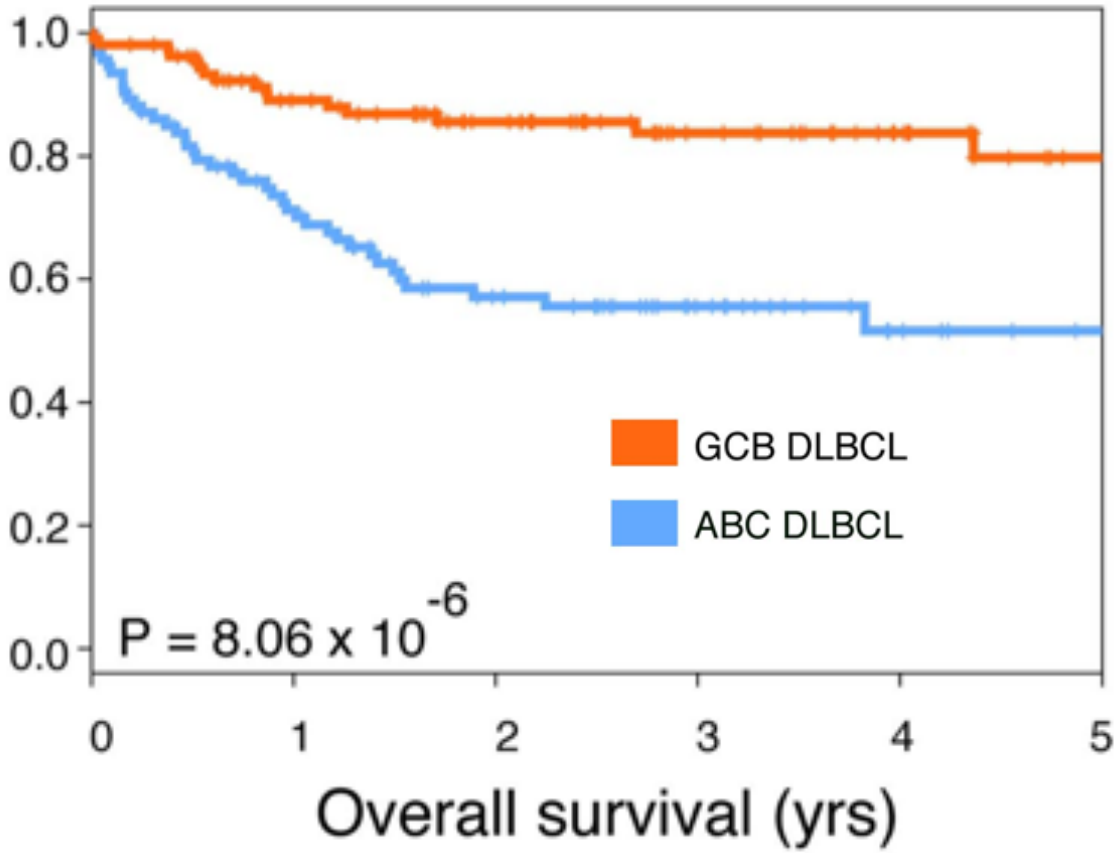
How to improve R-CHOP ?



Courtesy of G. Nowakowski

ABC and GCB DLBCL determined by GEP have significantly different survival rates following R-CHOP





Lenz et al, JCO, 2011
Lenz et al., NEJM, 2008

ABC and GCB DLBCL determined by Nanostring test

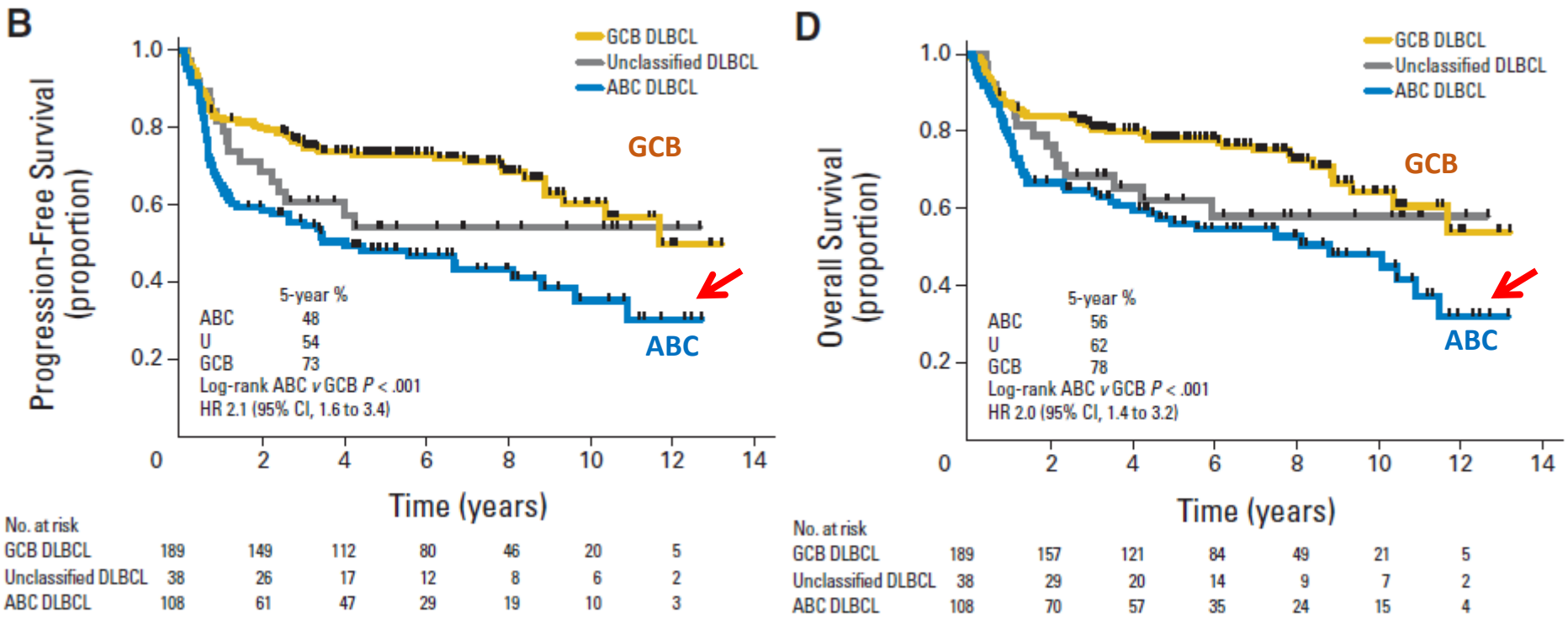
(in formalin fixed paraffin embedded tissue biopsies, N = 344)

ABC=108 (31%)

GCB=189 (55%)

Unclassicable=38 (11%)

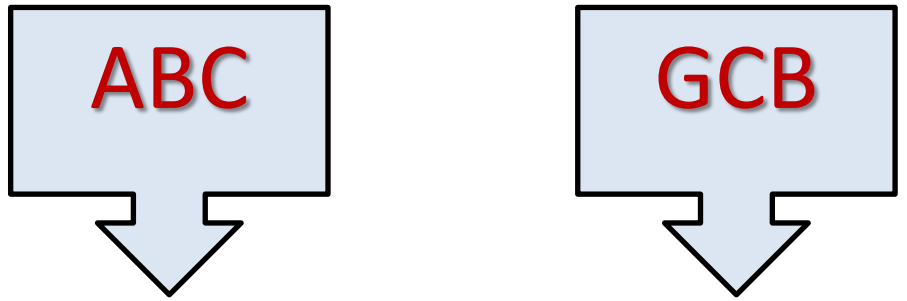
The Nanostring technology could predict survival of DLBCL in our daily clinical practice



Scott et al., JCO 2015

Molecular driven therapy: R-CHOP + Novel drugs

New Agent	Mechanism
Lenalidomide	Immunomodulator
Bortezomib	Proteasome inhibitor
Everolimus	mTOR inhibitor
Panobinostat	HDACs inihibitor
Ibrutinib	BTK inhibitor
Tamatinib	Inhibitors of Syk in B-cell signaling pathway
Enzastaurin	PKCβ-selective inhibitors
ABT 199	Pro-apoptotic ABT-263 Bcl-2 family
SELINEXOR	Selective inhibitor of nuclear export (SINE)



Proteasome inhibitors

BTK inhibitors

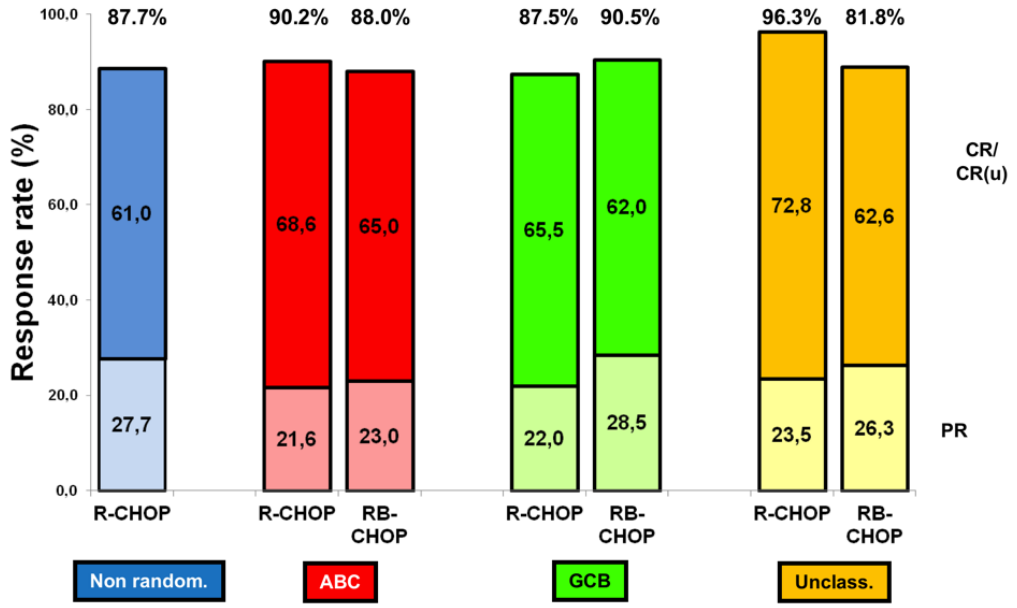
Immunomodulators

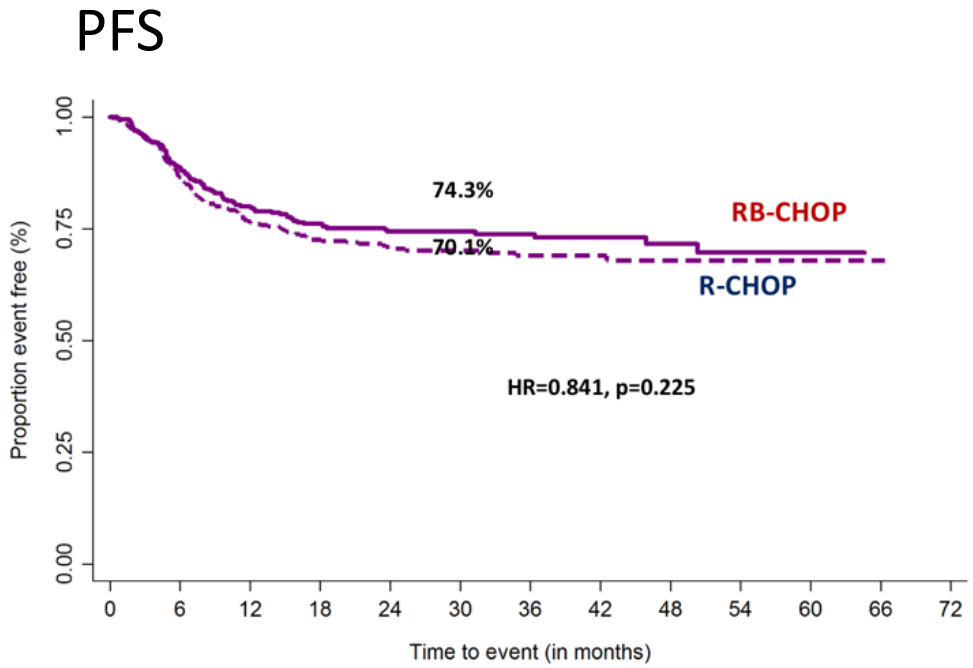
Histone modifiers

BCL2 inhibitors

PTEN/PI3K

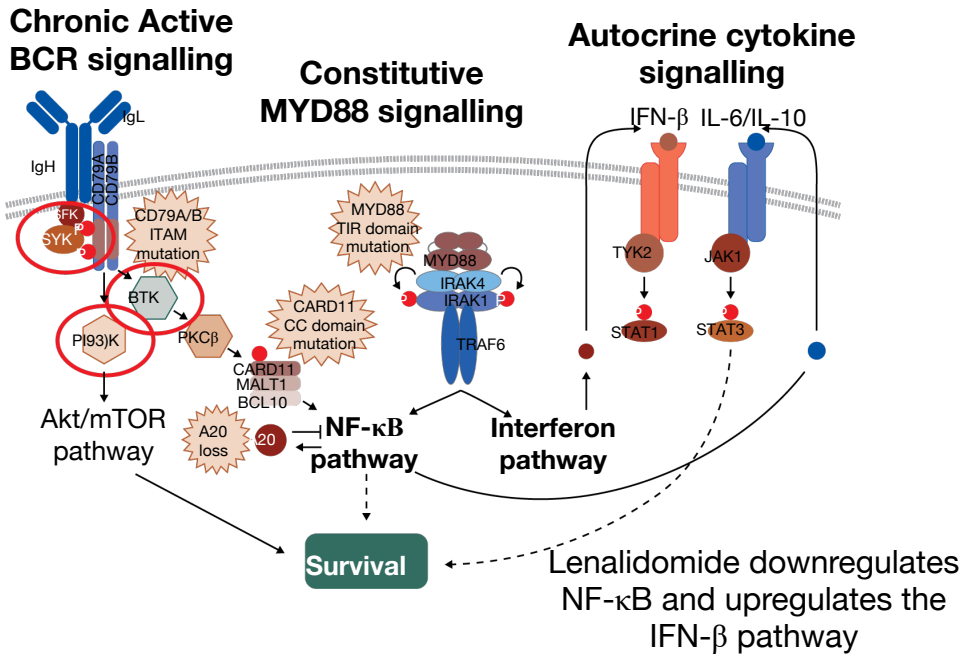
R-CHOP + Bortezomib (REMoDL-B Study)

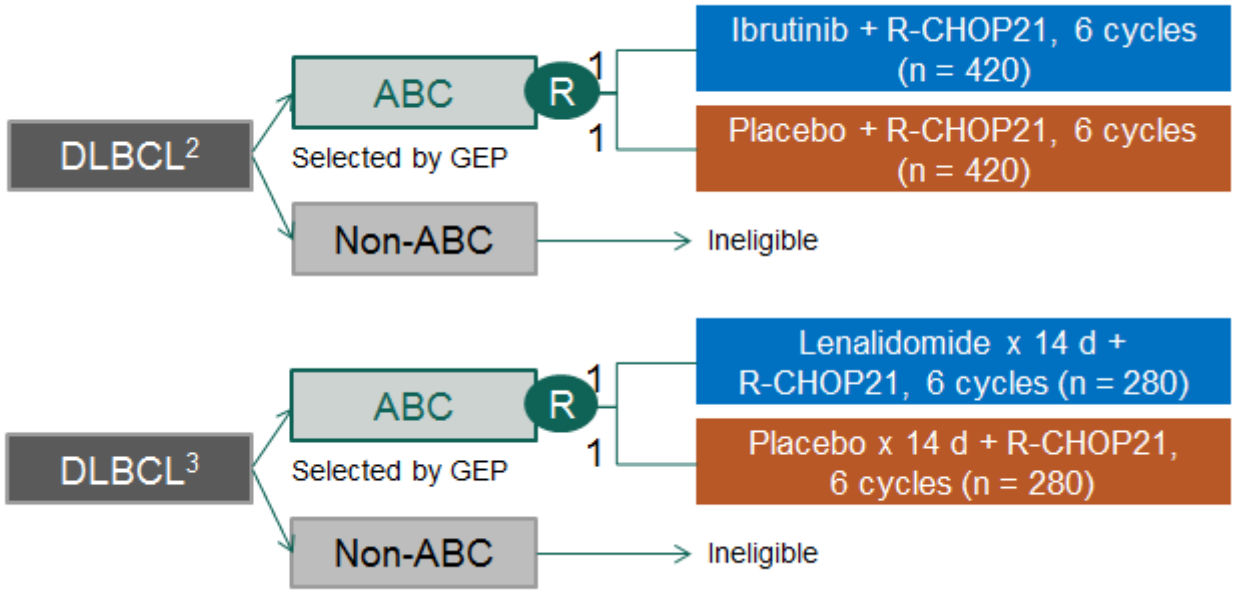




Davis et al, 2017

Lenalidomide and Ibrutinib in ABC-DLBCL: Phase 3 Trials Are Underway(≠)





Shaffer AL 3rd et al. *Ann Rev Immunol*. 2012;30:565-610.

2. ClinicalTrials.gov Identifier: NCT01855750;
3. ClinicalTrials.gov Identifier: NCT02285062.

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - study design

International, randomized, double-blind phase III trial[1]

Patients with untreated non-GCB DLBCL determined centrally by Hans-based IHC; stage II-IV measurable disease; R-IPI ≥ 1; ECOG PS 0-2
(N = 838)

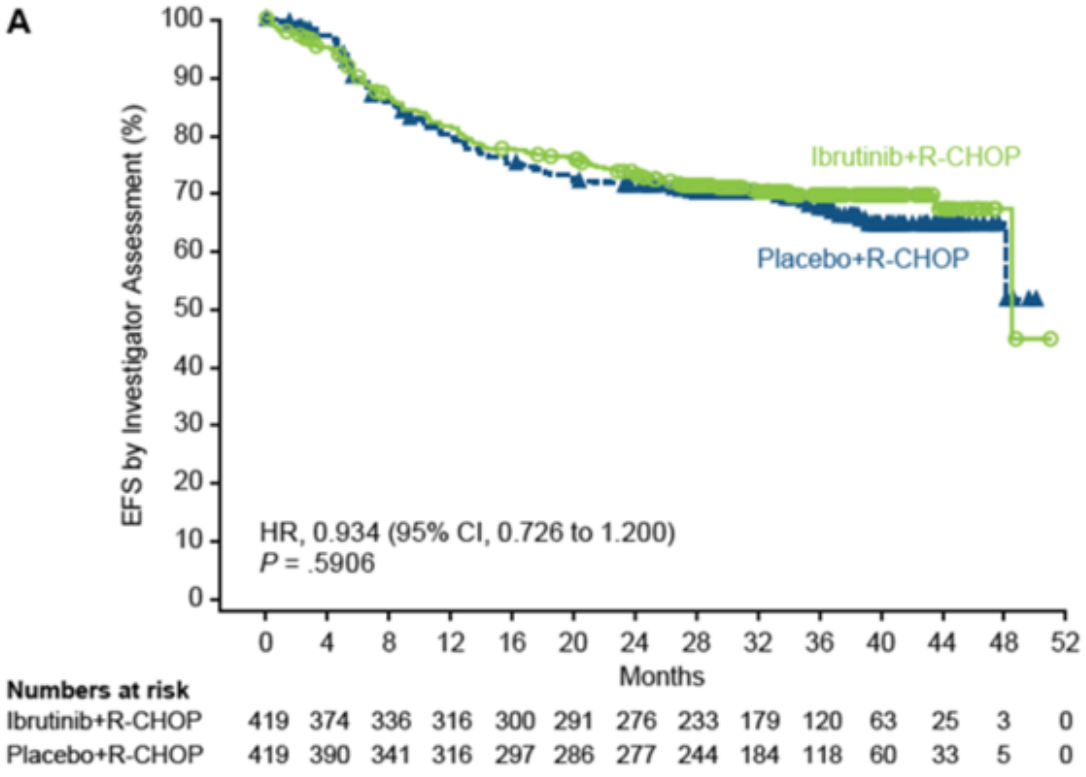
→ **Ibrutinib** 560 mg PO QD + **R-CHOP***
(n = 419)

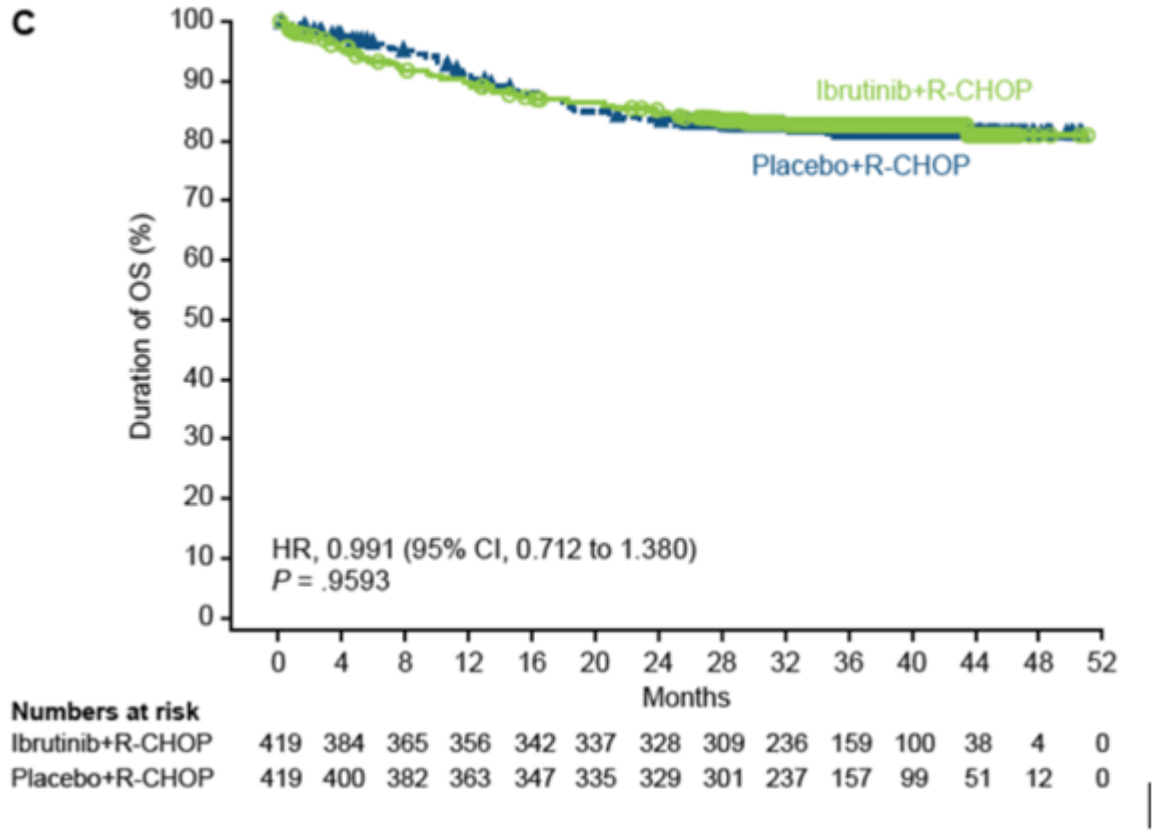
→ **Placebo** + **R-CHOP***
(n = 419)

- **Primary endpoint:** EFS in ITT population and ABC subgroup (determined retrospectively by gene expression profiling)
- **Secondary endpoints:** CR rate, OS, PFS, safety

Younes et al ASH 2018
Younes et al JCO 2019

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - EFS (Primary Endpoint)



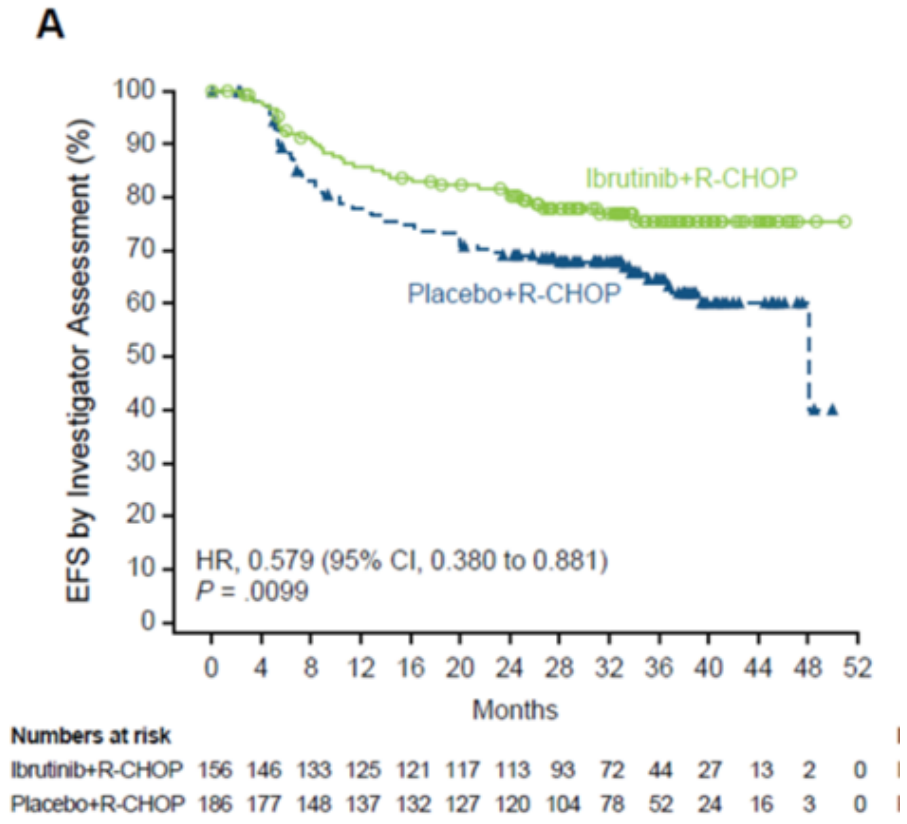


- **Addition of ibrutinib to R-CHOP did not significantly improve EFS**

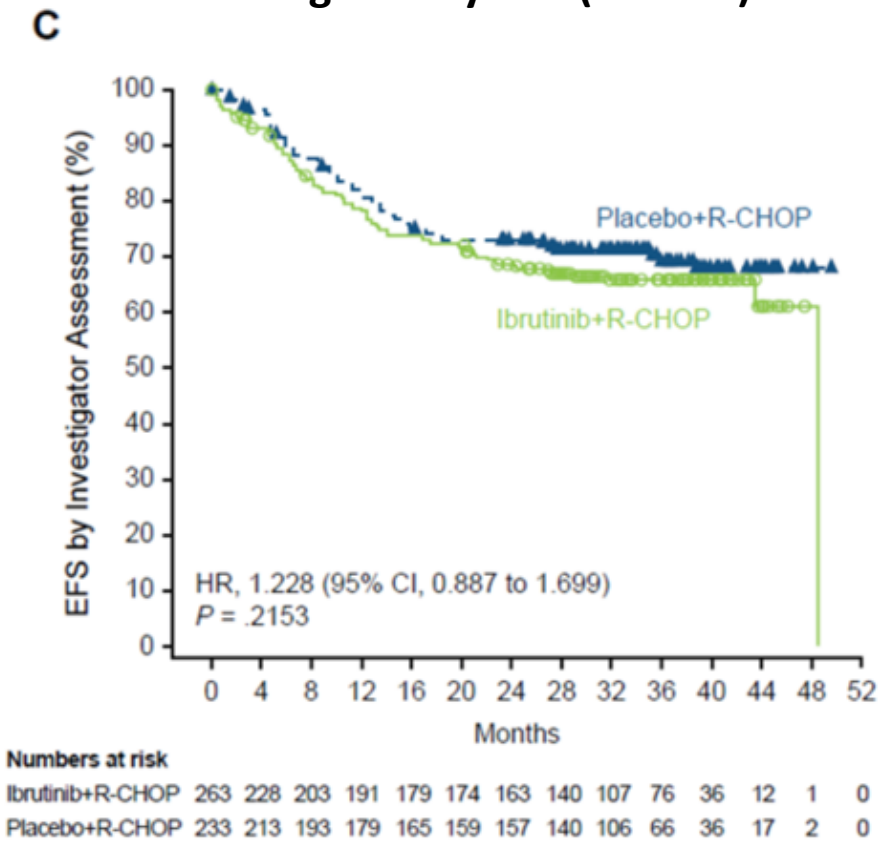
Younes et al ASH 2018
Younes et al JCO 2019

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - EFS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)

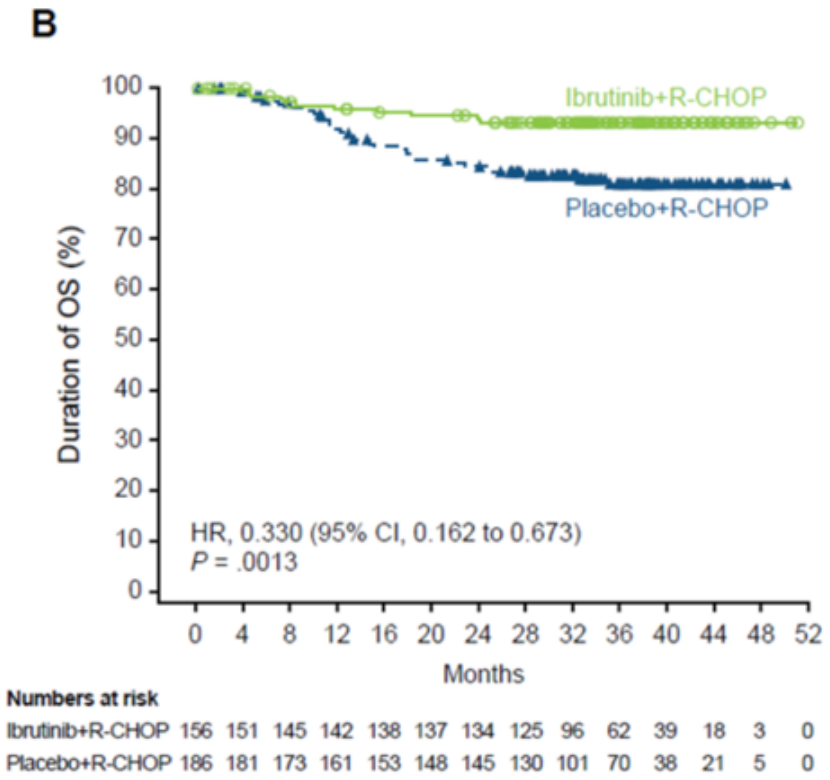


Younes et al ASH 2018
Younes et al JCO 2019

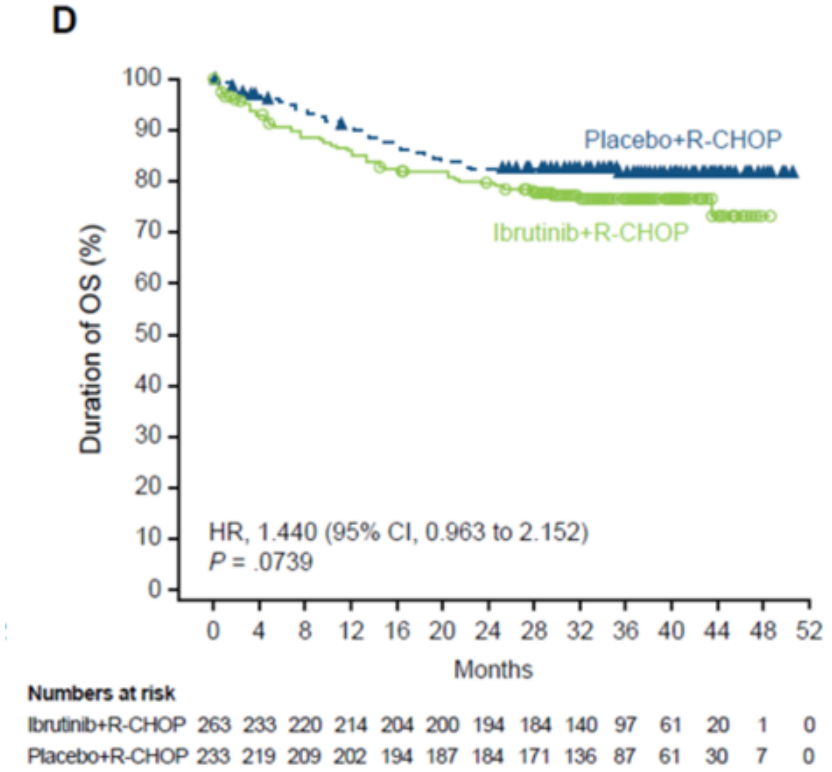
Polish Lymphoma Research Group

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - OS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)



Younes et al ASH 2018
Younes et al JCO 2019

Polish Lymphoma Research Group

PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - AEs and Treatment Exposure by Age

- Among patients aged < 60 yrs and ≥ 60 yrs, AEs were similar between treatment arms
- **Higher rates of both serious AEs and AEs leading to treatment discontinuation were observed in older patients receiving ibrutinib + R-CHOP vs placebo + R-CHOP**
  - Primary TEAEs leading to dose reduction/discontinuation were febrile neutropenia and peripheral neuropathy
- In the safety population, **drug exposure was lower** with ibrutinib + R-CHOP vs placebo + R-CHOP, **particularly among older patients**

Patients Receiving ≥ 6 Cycles of Treatment, n (%)	Age < 60 Yrs		Age ≥ 60 Yrs	
	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
R-CHOP exposure	143 (92.9)	172 (93.0)	193 (**73.7**)	207 (**88.8**)
Ibrutinib or placebo exposure	138 (89.6)	170 (91.9)	178 (**67.9**)	202 (**86.7**)

Younes et al ASH 2018
Younes et al JCO 2019

DLBCL leczenie I rzutu – refundacja w ramach NFZ

Program lekowy z Rituximabem ogranicza prawo chorych do leczenia zgodnie ze standardem

Przypadki	Schematy chemioterapii
Większość przypadków (*)	**R-CHOP**
Chorzy, u których musimy zredukować intensywność chemioterapii	**R-mini CHOP, BR**
Przypadki szczególne, wymagające intensyfikacji leczenia: • PMBCL, • Double Hit, Double Expressor	• **R-DAEPOCH, R-CHOP-14** • **R-DAEPOCH, R-HyperCVAD/MA, rozważenie konsolidacji z ASCT**

The standard of care in R/R DLBCL

ESMO recommendations for DLBCL

- First relapse/progression[1]

Eligible for transplant	Not eligible for transplant
• Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) as salvage treatment • For chemosensitive patients: R-HDCT with **ASCT as remission** consolidation • Consider **allogeneic transplantation** in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse	• Platinum and/or gemcitabine-based regimens • **Clinical trials with novel drugs**

- >2 relapse/progression[1]

Eligible for transplant	Not eligible for transplant
• **Allogeneic transplantation** • **Clinical trials with novel drugs**	• **Clinical trials with novel drugs** • Palliative care

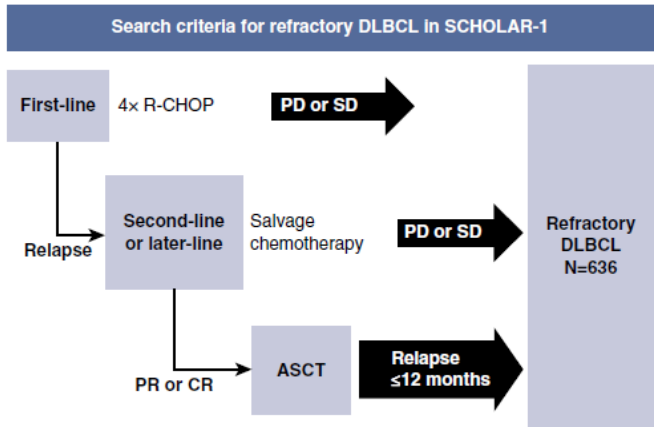
1. Tilly H et al. Annals of Oncology 2015;26(Suppl 5): v116–v125.

Jaki jest najlepszy schemat chemioterapii ratującej ?

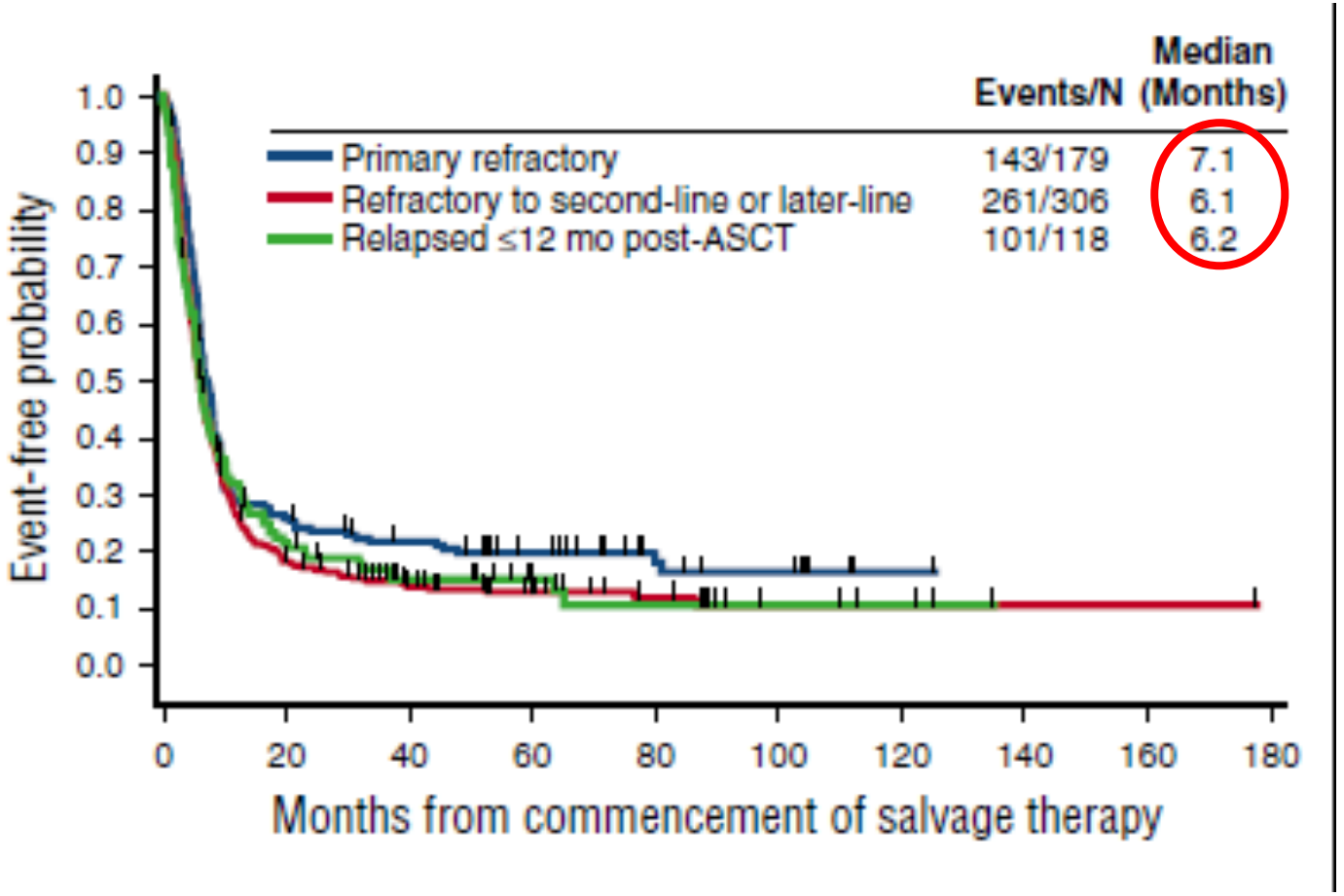
CHEMIOTERAPIA

- R-ESHAP/ R-DHAP
- R-IGEV
- PREBEN
- R-ICE
- .....

R/R DLBCL – SCHOLAR-1 study



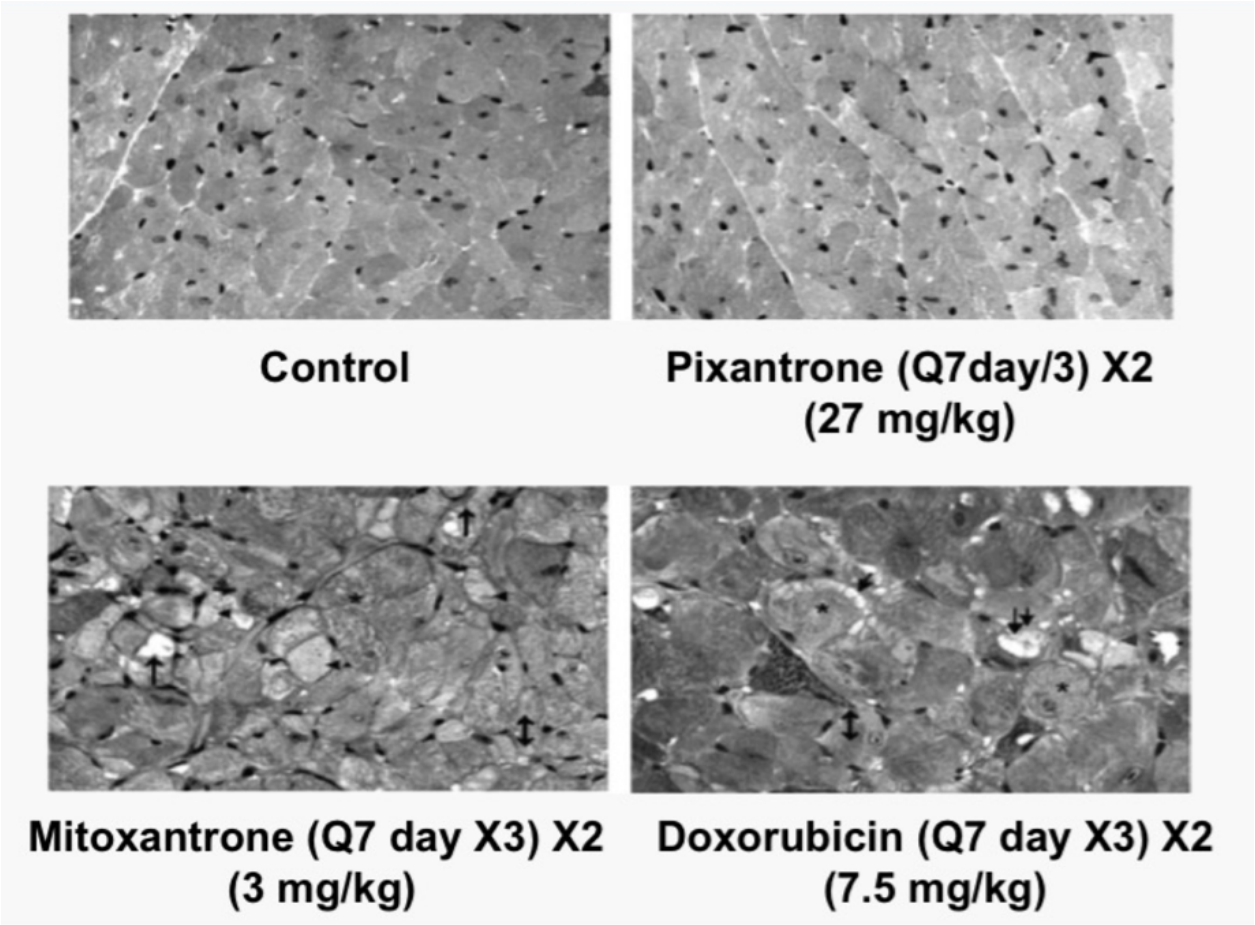
Need to identify at diagnosis these unfavourable group of patients and improve or change their first line treatment (R-CHOP)

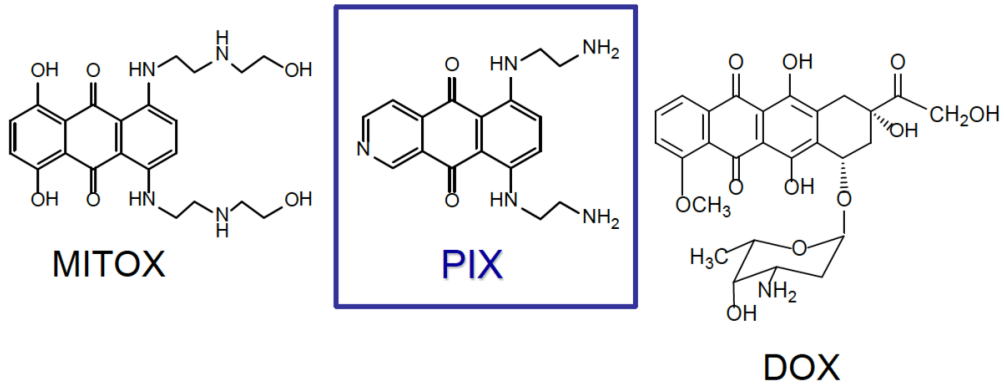


Crump et al. Blood 2017

Polish Lymphoma Research Group

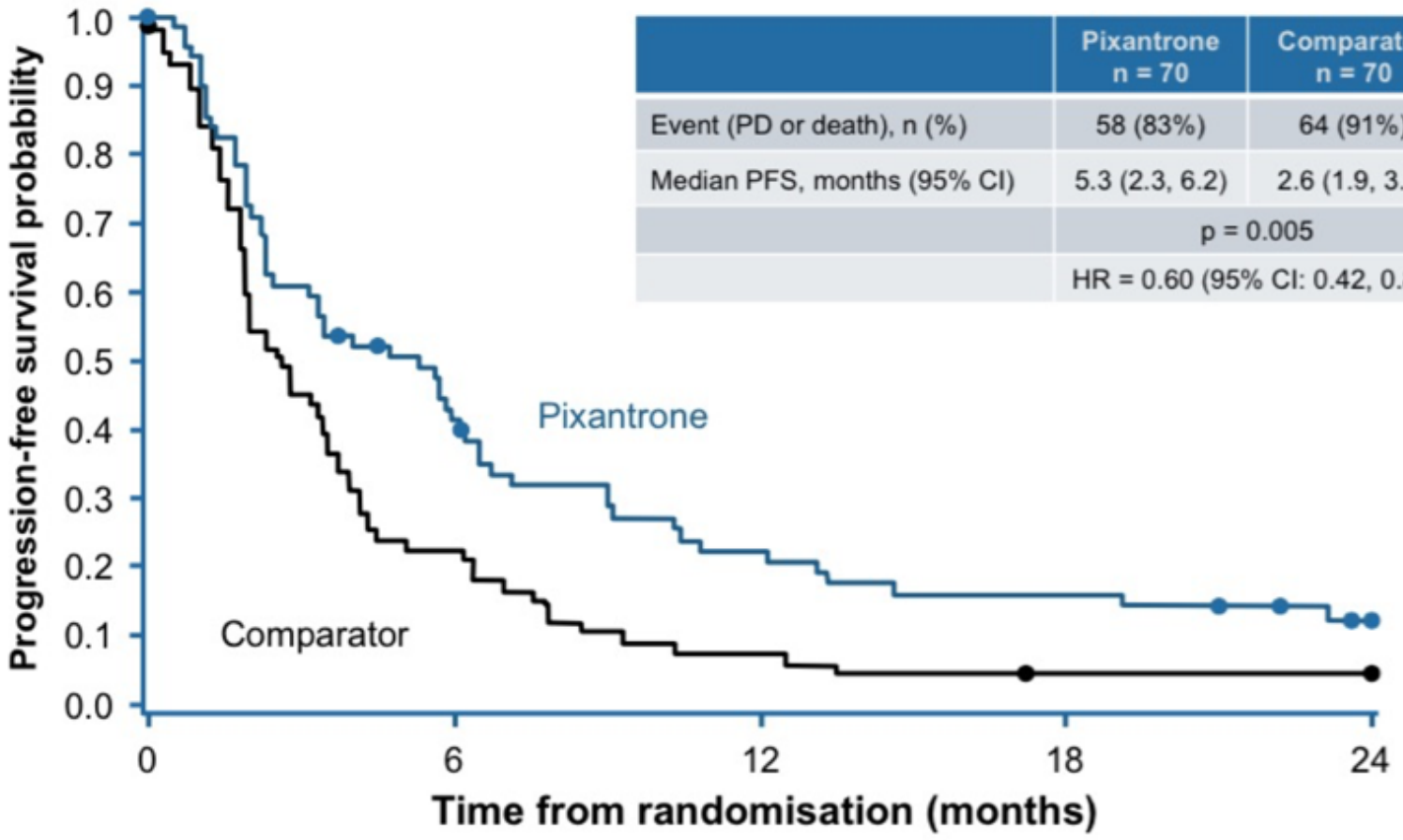
Pixantrone resembles anthracyclins, but is less cardiotoxic





By courtesy of SERVIER

Pixantrone – registered for R/R DLBCL, 3rd line



	Pixantrone n = 70	Comparator n = 70
Event (PD or death), n (%)	58 (83%)	64 (91%)
Median PFS, months (95% CI)	5.3 (2.3, 6.2)	2.6 (1.9, 3.5)
	p = 0.005	
	HR = 0.60 (95% CI: 0.42, 0.86)	

Pettengell R, et al., Lancet Oncol. 2012;13:696-706.

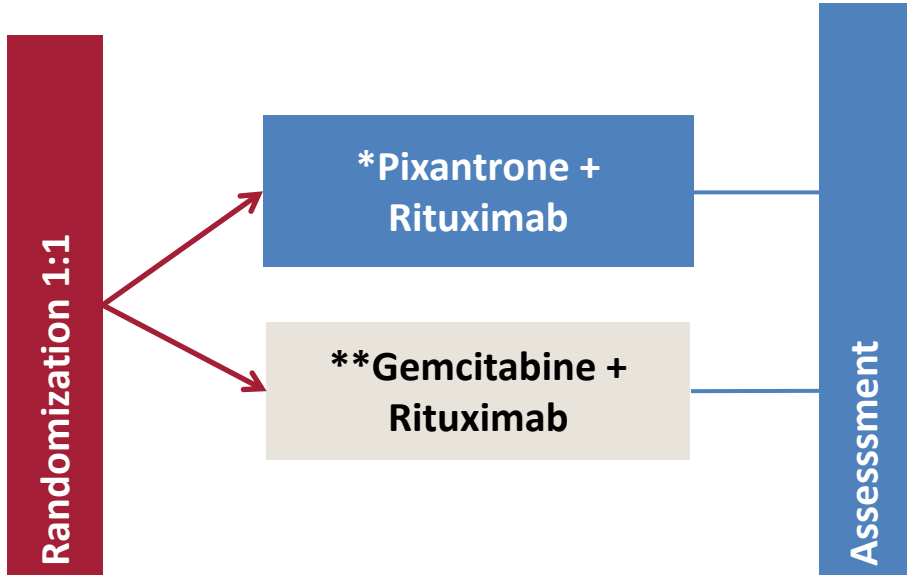
Pixantrone – ongoing phase III in R/R DLBCL, 2nd line

Objectives of the study

- Should confirm current MA
- If positive, could extend label to 2nd line use

Study design

Relapse after CHOP-R therapy or equivalent regime and are ineligible for stem cell transplant
n≈260



* Pixantrone + R: rituximab 375 mg/m^2 i.v. on Day 1 and pixantrone 50 mg/m2 IV on Days 1, 8, and 15. Regimen is given in 28-day cycles. Up to 6 cycles may be administered.

**Gemcitabine + R: rituximab 375 mg/m^2 i.v on Day 1 and gemcitabine 1000 mg/m2 IV on Days 1, 8, and 15. Regimen is given in 28-day cycles. Up to 6 cycles may be administered.

Friedberg J 2011 American Society of Hematology
Belada et al. 2016. Future Oncology

P4189 Results of a phase 3 randomized multicenter study comparing pixantrone + rituximab with gemcitabine + rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation

Gilles Andre Salles,[1] Wojciech Jurczak,[2] David J. Andorsky,[3] Donald P. Quick,[4] Jack W. Singer,[5] Simran Bedi Singh,[5] Lixia Wang,[5] Anton Egorov,[6] Christine Gabarroca,[6] Ruth Pettengell[7]

[1]Hematology Department Centre Hospitalier Lyon-Sud, Pierre-Benite, France; [2]Jagiellonian University, Krakow, Poland; [3]Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO, USA; [4]Joe Arrington Cancer Research and Treatment Center, Lubbock, TX, USA; [5]CTI Biopharma, Seattle, WA, USA; [6]Institut de Recherches Internationales Servier, Suresnes, France; [7]St. George's Hospital, London, United Kingdom.

CONCLUSIONS

- This was the first study to investigate the efficacy of pixantrone + rituximab (PIX+R) versus gemcitabine + rituximab (GEM+R) as second-line or later therapy in patients with relapsed aggressive B-cell NHL non-eligible for SCT.
- PIX+R was associated with a numerically higher ORR and CR rate compared with GEM+R, but this did not translate into prolonged PFS or OS in the PIX+R group.
- Although the study did not meet its primary endpoint, the PFS observed in the two treatment groups was longer than previously reported values in similar patient populations.

BACKGROUND

- There are limited treatment options for patients with relapsed aggressive B-cell non-Hodgkin lymphoma (NHL),[1] especially for those who are not candidates for high-dose therapy and stem cell transplantation (SCT).
- Reasons for ineligibility for intensive treatment include advanced age and overall condition, comorbidities, failure to respond to standard salvage treatment regimens, progressive disease following previous SCT, and presence of other adverse risk factors.[2]
- Pixantrone is an aza-anthracenedione agent derived from anthracyclines with proven reduced potential of cardiotoxicity and maintained antitumor activity.
- A previous phase 3 trial compared pixantrone with comparator chemotherapy (vinorelbine, oxaliplatin, ifosfamide, etoposide, gemcitabine, or mitoxantrone) in patients with aggressive NHL who had relapsed or were refractory to ≥2 previous lines of chemotherapy, and showed a significantly higher complete response (CR) rate and longer progression-free survival (PFS) in the pixantrone group.[3,4]
- This phase 3 study (PIX306) evaluated the efficacy of a combination of PIX+R versus GEM+R in the treatment of patients with relapsed aggressive B-cell NHL who progressed after ≥1 rituximab-containing multi-agent regimen and were not eligible for SCT.
- The primary results of the core analysis of the PIX306 trial are presented here.

RESULTS

Patients

- A total of 312 patients were randomized to treatment; the baseline characteristics of patients were well-balanced between the two treatment groups **(Table 1)**.

Table 1. Baseline characteristics of patients included in the study.

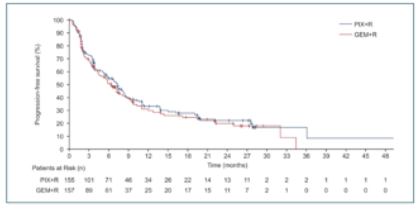
	PIX-R N=155	GEM-R N=157	Total N=312
Median age, years (range)	73.0 (30–91)	73.0 (26–90)	73.0 (30–91)
≥65 years	119 (76.8)	119 (75.8)	246 (78.8)
Male	69 (44.5)	67 (42.7)	136 (43.6)
Investigator-assessed histology			
DLBCL	122 (78.7)	120 (76.4)	242 (77.6)
DLBCL transformed from indolent lymphoma	22 (14.2)	21 (13.4)	43 (13.8)
FL Grade 3	11 (7.1)	16 (10.2)	27 (8.7)
Time since initial diagnosis (DLBCL/FL Grade 3), months	22.0	23.5	22.5
Ann Arbor stage of NHL			
I	11 (7.1)	9 (5.7)	20 (6.4)
II	32 (20.6)	30 (19.1)	62 (19.9)
III	38 (24.5)	37 (23.6)	75 (24.4)
IV	74 (47.7)	81 (51.6)	155 (49.7)
No. of extranodal sites			
0	57 (36.8)	60 (38.2)	117 (37.5)
1	49 (31.6)	38 (24.2)	87 (27.9)
>1	49 (31.6)	59 (37.6)	108 (34.6)
No. of prior lines of therapy for DLBCL or FL Grade 3			
0	9 (5.8)	5 (3.2)	14 (4.5)
1	93 (60.0)	100 (63.7)	193 (61.9)
2	25 (22.6)	33 (21.0)	68 (21.8)
3	18 (11.6)	19 (11.5)	36 (11.5)
International Prognostic Index (IPI) score			
0	2 (1.3)	0	2 (0.6)
1	24 (15.5)	17 (10.8)	41 (13.1)
2	47 (29.9)	53 (33.8)	103 (33.0)
≥3	82 (52.9)	86 (54.8)	168 (53.8)
Time between initiation of first-line therapy to first relapse			
<1 year	56 (36.1)	58 (36.9)	114 (36.5)
≥1 year	97 (62.6)	99 (63.1)	196 (62.8)
Prior stem cell transplantation			
Yes	17 (11.0)	16 (10.2)	33 (10.6)
No	138 (89.0)	141 (89.8)	279 (89.4)

Values presented as n (%) unless otherwise stated.
DLBCL, de novo diffuse large B-cell lymphoma; FL, follicular lymphoma.

Efficacy

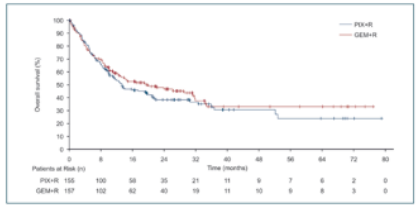
- The primary efficacy endpoint of the study was not met (P=0.28; HR=0.85; 95% CI: 0.64, 1.14; **Figure 1**). A total of 197 PFS events were reported (102 with PIX+R vs 95 with GEM+R).
- The median PFS (95% CI) was 7.3 months (5.2, 8.4) in the PIX+R group and 6.3 months (4.4, 8.1) in the GEM+R group.

Figure 1. Progression-free survival (PFS) in the intention-to-treat population during the study (N=312).



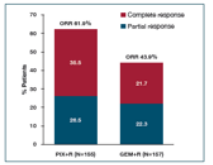
- According to the hierarchical testing procedure and given that the primary endpoint was not met, the secondary efficacy endpoints were not tested.
- The median OS (95% CI) in the PIX+R and the GEM+R groups was 13.3 (10.1, 19.8) versus 19.6 (12.4, 31.9) months, respectively (HR=1.13; 95% CI: 0.83, 1.53; **Figure 2**).

Figure 2. Overall survival (OS) in the intention-to-treat population during the study (N=312).



- ORR was 61.9% versus 43.9% in the PIX+R and GEM+R groups, respectively **(Figure 3)**, and CR was observed in 35.5% of patients in the PIX+R group compared with 21.7% in the GEM+R group.

Figure 3. Objective response rate (ORR) in the intention-to-treat population (N=312).



Safety

- Both treatment regimens were reasonably tolerated, and no new safety signals were reported **(Table 2)**.

Table 2. Summary of safety.

	PIX+R N=153	GEM+R N=157
Commonly reported AEs		
Neutropenia	106 (69.3)	88 (59.1)
Fatigue	45 (29.4)	35 (23.5)
Anemia	42 (27.5)	75 (50.3)
Nausea	38 (24.8)	24 (16.1)
Constipation	36 (23.5)	20 (13.4)
Alopecia	29 (19.0)	2 (1.3)
Anorexia	28 (18.3)	16 (10.7)
Thrombocytopenia	25 (16.3)	98 (65.8)
Diarrhea	24 (15.7)	21 (14.1)
Pyrexia	24 (15.7)	38 (25.5)
Grade 3/4 TEAEs		
Neutropenia	97 (63.4)	83 (55.7)
Anemia	26 (17.0)	56 (37.6)
Thrombocytopenia	17 (11.1)	55 (36.9)
Leukopenia	12 (7.8)	15 (10.1)
Lymphopenia	9 (5.9)	3 (2.0)
Infections and infestations	24 (15.7)	30 (20.1)
Gastrointestinal disorders	17 (11.1)	9 (6.0)
Cardiac safety		
Patients with ≥1 Grade 3/4 cardiac TEAE	28 (18.3)	13 (8.1)
Atrial fibrillation	4 (2.6)	3 (2.0)
Cardiac failure	3 (2.0)	0
Cardiac failure congestive	1 (0.7)	2 (1.3)
Ejection fraction decreased	4 (2.6)	1 (0.7)
Deaths		
Deaths during the treatment period	12 (7.8)	16 (10.7)
Deaths due to AE	3 (2.0)	7 (4.7)
Deaths due to disease progression	7 (4.6)	7 (4.7)
Deaths due to other reasons	2 (1.3)**	2 (1.3)**

Safety is reported in all randomized patients who received at least one administration of the study drug. All values are presented as n (%). *Viral pneumonia and asthenia. **Acute renal failure and sepsis. AE, adverse event; GEM, gemcitabine; PIX, pixantrone; R, rituximab; TEAE, treatment-emergent adverse event.

METHODS

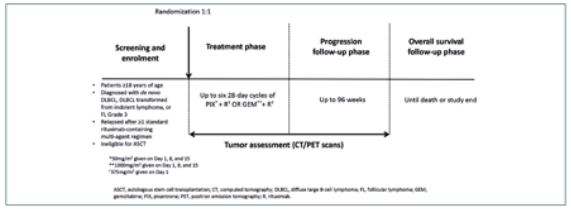
Patients

- This multicenter, randomized, open-label phase 3 study enrolled patients who were:
  - ≥18 years of age;
  - Diagnosed with de novo diffuse large B-cell lymphoma (DLBCL), DLBCL transformed from indolent lymphoma, or follicular lymphoma (FL) Grade 3 and received:
    - de novo DLBCL: 1–3 prior regimens for DLBCL
    - DLBCL transformed from indolent lymphoma: 1–4 prior regimens for NHL of any type
    - FL Grade 3: 1–3 prior regimens for FL of any grade;
  - Relapsed after ≥1 standard rituximab-containing multi-agent regimen;
  - Ineligible for autologous SCT for the following reasons: relapse after previous SCT, no response to a standard salvage regimen, unable to mobilize an adequate number of stem cells for SCT, unsuitable/unwilling to undergo SCT for any other reason.
- Patients with primary refractory de novo DLBCL and FL Grade 3 (defined as progression within 12 weeks of the last cycle of the first-line treatment regimen) were excluded; patients with DLBCL transformed from indolent lymphoma were required to have a complete or partial response to NHL therapy lasting ≥12 weeks.
- All patients were required to be free of any major cardiac pathology for <6 months before enrolment including New York Heart Association class III or IV heart disease and myocardial infarction.
  - Patients were required to have a left ventricular ejection fraction (LVEF) of ≥45% and serum troponin T in the normal range.
  - Patients previously treated with doxorubicin or equivalent were required to have a cumulative dose of <450 mg/m² at enrolment.
- Patients were selected by the investigator and their histological diagnosis was reviewed and confirmed by an independent Central Pathology Review Committee after randomization.

Randomization and treatment

- Patients were randomized 1:1 using an interactive web response system to receive PIX 50 mg/m² or GEM 1000 mg/m² on Days 1, 8, and 15 of a 28-day cycle, each in combination with R 375 mg/m² on Day 1, for up to six cycles **(Figure 4)**.
- Patients were followed for up to 96 weeks for disease progression.

Figure 4. Study design.



- Randomization was balanced and non-adaptive, and was stratified by the number of prior lines of therapy (0–2 vs ≥3) for DLBCL or FL Grade 3, the International Prognostic Index (IPI) score (0–2 vs ≥3), and the time until first relapse after initiation of first-line therapy for DLBCL or FL Grade 3 (<1 year vs ≥1 year).

Endpoints

- The primary endpoint was Independent Radiology Committee-assessed PFS, based on the modified International Working Group 2007 revised response criteria.[5]
- Secondary endpoints included:
  - Overall survival (OS)
  - Overall response rate (ORR)
  - CR rate
  - Safety.

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1. Volpetti S, Zaja F, Fanin R. Onco Targets Ther. 2014;7:865-72. 2. Kuruvilla J, Keating A, Crump M. Blood. 2011;117(7):4206-17. 3. Pettengell R, Coiffier B, Narayanan G, et al. Lancet Oncol. 2012;13(7):696-706. 4. Pettengell R, Sebban C, Zinzani PL, et al. Br J Haematol. 2016;174(5):692-9. 5. Cheson BD, Pfistner B, Juweid ME, et al. J Clin Oncol. 2007;25(5):579-86.

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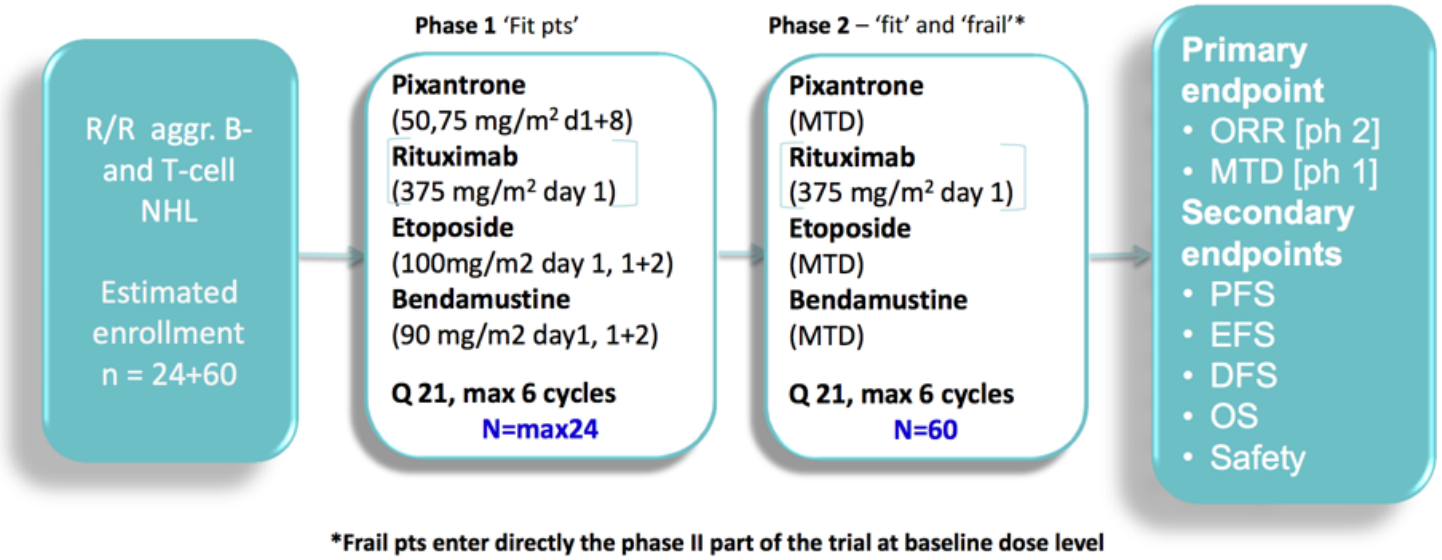
For any queries related to information found on this poster please contact Gilles Andre Salles (gilles.salles@chu-lyon.fr).

Salles et al, ASH 2018

PREBEN - Pixantrone, Etoposide, Bendamustine (& Rituximab)

NORDIC LYMPHOMA GROUP

DEDICATED TO PROMOTING RESEARCH IN TREATMENT, BIOLOGY AND EPIDEMIOLOGY OF MALIGNANT LYMPHOMAS IN THE NORDIC COUNTRIES



*Frail pts enter directly the phase II part of the trial at baseline dose level

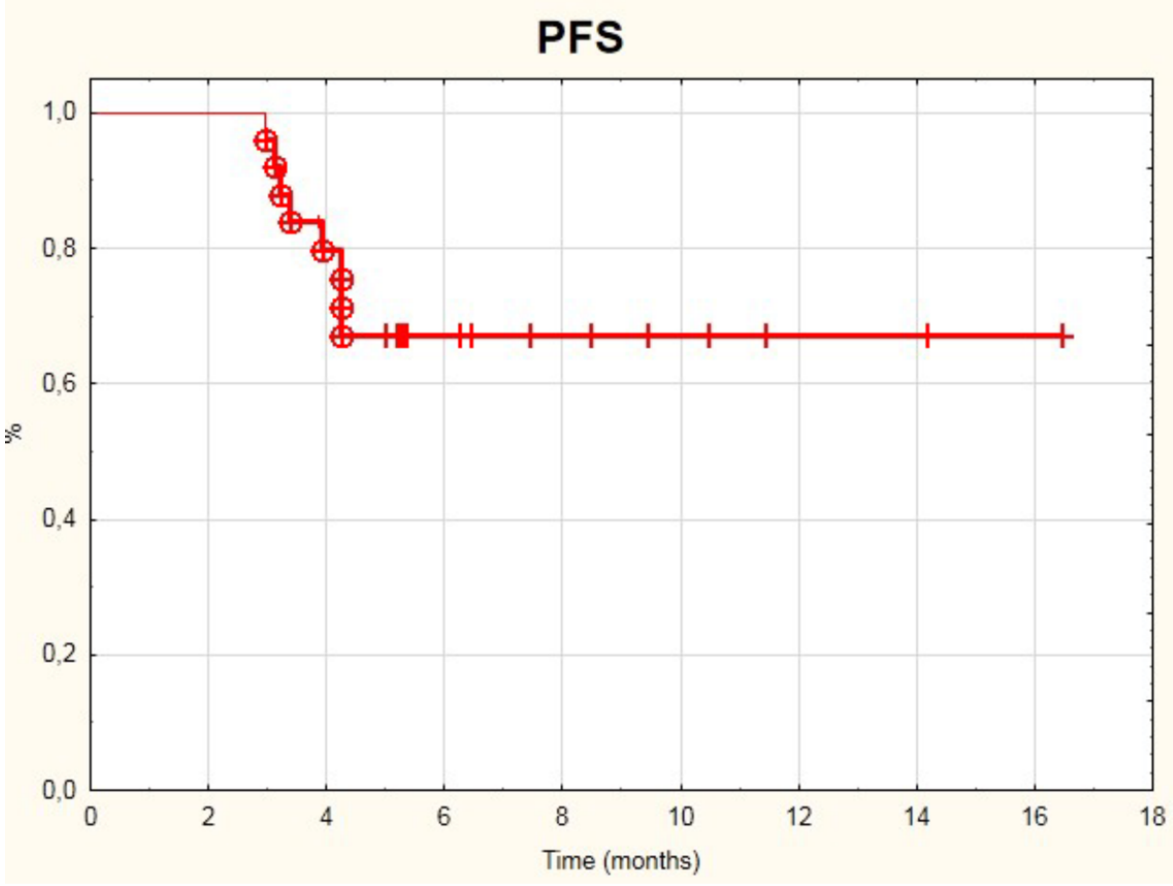
- CR in DLBCL (CR 40%, PR 20%) and PTCL (CR 25%, PR 50%)
- Response durations are in the range 4–17+ months
- Out-patient regimen
- Grade 3-4 infections in 40% of patients

Michael Roost Clausen et al., ASH 2016

Polish Lymphoma Research Group

PREBEN – real life experience (PLRG)

Parameter	Number of patients	Complete response n (%)	Partial response n (%)	Stable or progressive disease n (%)
All group	25	10 (40)	7 (28)	8 (32)
Age ≥ 60 years	8	2 (25)	2 (25)	4 (50)
Lymphoma subtype				
DLBCL	15	5 (33.3)	4 (26.7)	6 (40)
TIN	7	3 (42.9)	3 (42.9)	1 (14.2)
PTCL	3	2 (66.7)	0 (0)	1 (33.3)
DOR of the last treatment				
≥ 12 months	6	2 (33.3)	2 (33.3)	2 (33.3)
< 12 months	19	8 (42.1)	5 (26.3)	6 (31.6)
Disease status				
Primary refractory	**17**	6 (35.2)	4 (23.5)	7 (41.1)
Refractory to salvage platinum-based regimens	**15**	4 (26.7)	4 (26.7)	7 (46.6)
Relapsed	**8**	4 (50)	3 (37.5)	1 (12.5)
Relapsed after ASCT	4	1 (25)	2 (50)	1 (25)



Danecka et al., Pharmacol. Reports 2019

Polish Lymphoma Research Group

KEYNOTE-170/KEYNOTE-013:
Pembrolizumab in R/R PMBCL

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL – study design

Phase Ib KEYNOTE-013

R/R PMBCL patients
≥ 18 yrs of age without ASCT*
(N = 21)

Pembrolizumab
10 mg/kg Q2W (patients 1-10)
or 200 mg Q3W (patients 11-21)

Treatment up to 2 yrs or until unacceptable toxicity, PD, or study withdrawal

Phase II KEYNOTE-170

R/R PMBCL patients
≥ 18 yrs of age without ASCT,* failed ≥ 2 prior regimens
(N = 53)

Pembrolizumab
200 mg Q3W

Treatment up to 2 yrs or until unacceptable toxicity, PD, or study withdrawal

Primary endpoints: ORR, safety (KEYNOTE-013 only)

Secondary endpoints: DoR, PFS, OS, safety (KEYNOTE-170)

*Failed, ineligible, or refused.

Armand. ASH 2018. Abstr 228. NCT02576990.

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL - Baseline Characteristics

Characteristic	KEYNOTE-013 (N = 21)	KEYNOTE-170 (N = 53)
Median age, yrs (range)	31 (22-62)	33 (20-61)
Female, n %	14 (67)	30 (57)
Prior transplant, n (%)	8 (38)	14 (26)
Median prior therapies, n (range)	3 (2-9)	3 (2-8)
Prior radiation, n (%)	15 (71)	17 (32)
Prior rituximab, n (%)	21 (100)	53 (100)

Armand. ASH 2018. Abstr 228.

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL - efficacy

Characteristic, n (%)	KEYNOTE-013 (N = 21)	KEYNOTE-170† (N = 53)
OR	**10 (48)**	**24 (45)**
▪ CR	7 (33)	7 (13)
▪ PR	3 (14)	17 (32)
SD	5 (24)	5 (9)
PD	4 (19)	12 (23)
Nonevaluable/ no assessment*	2 (10)	12 (23)

Characteristic	KEYNOTE-013 (N = 21)	KEYNOTE-170 (N = 53)
Median duration of follow-up, mos	29.1	12.5
Median time to response, mos	2.7§	2.8‖
PFS		
▪ **12-mo, %**	**47**	**38**
▪ **Median, (range)**	**10.4 months (3.4-NR)**	**5.5 months (2.8-12.1)**
OS		
▪ **12-mo, %**	**65**	**58**
▪ **Median, (range)**	**31.4 months (4.9-NR)**	**NR months (7.3-NR)**

Armand. ASH 2018. Abstr 228.

Phase II KEYNOTE-170/KEYNOTE-013: Pembrolizumab in R/R PMBCL - safety

TRAEs, n (%)	KEYNOTE-013 (N = 21)	KEYNOTE-170 (N = 53)
Any TRAEs	***15 (71)***	***30 (57)***
Grade 3/4 TRAEs	5 (24)	12 (23)
▪ Neutropenia	3 (14)	7 (13)
▪ Febrile neutropenia	1 (5)*	1 (2)
▪ Fatigue	1 (5)	0
▪ Increased ALT	1 (5)	1 (2)
▪ Increased AST	0	1 (2)*
▪ Hyponatremia	1 (5)	0
▪ C difficile infection	0	1 (2)
▪ Pneumonia	0	1 (2)
▪ Tumor flare	0	1 (2)
▪ VTE	0	1 (2)

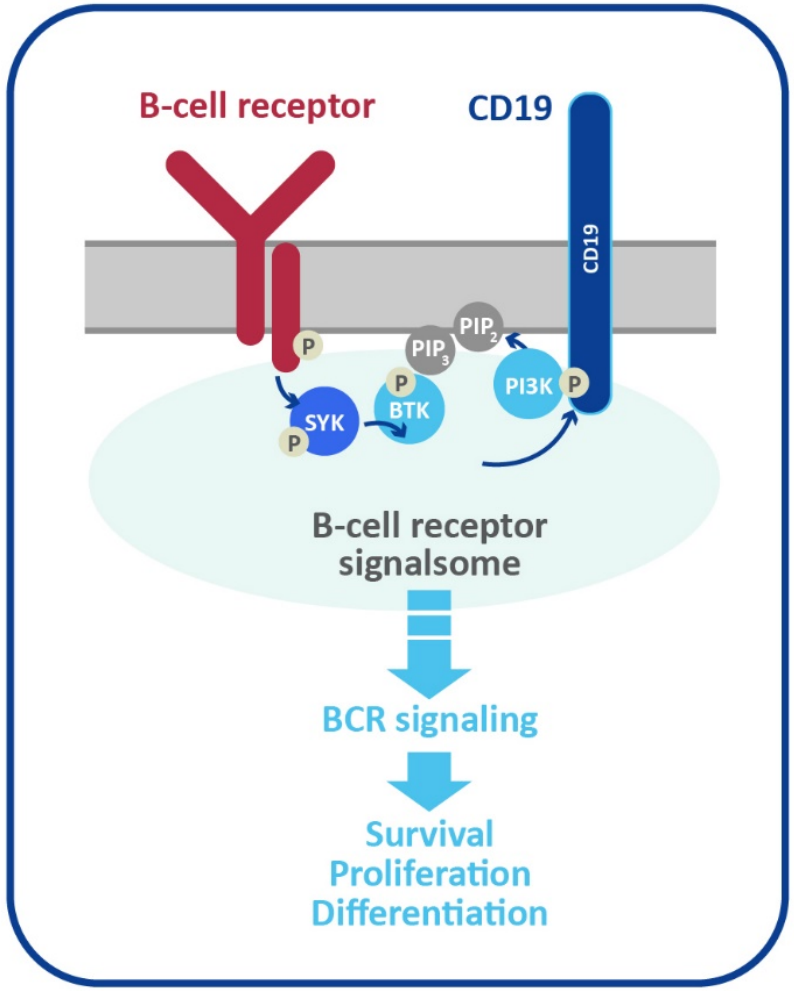
AEs, n (%)	KEYNOTE-013 (N = 21)	KEYNOTE-170 (N = 53)
Immune-mediated AEs§	4 (19)	6 (11)
▪ Grade 3/4	1 (5)†	1 (2)‡

Armand. ASH 2018. Abstr 228.

CD19: Role and therapeutic target

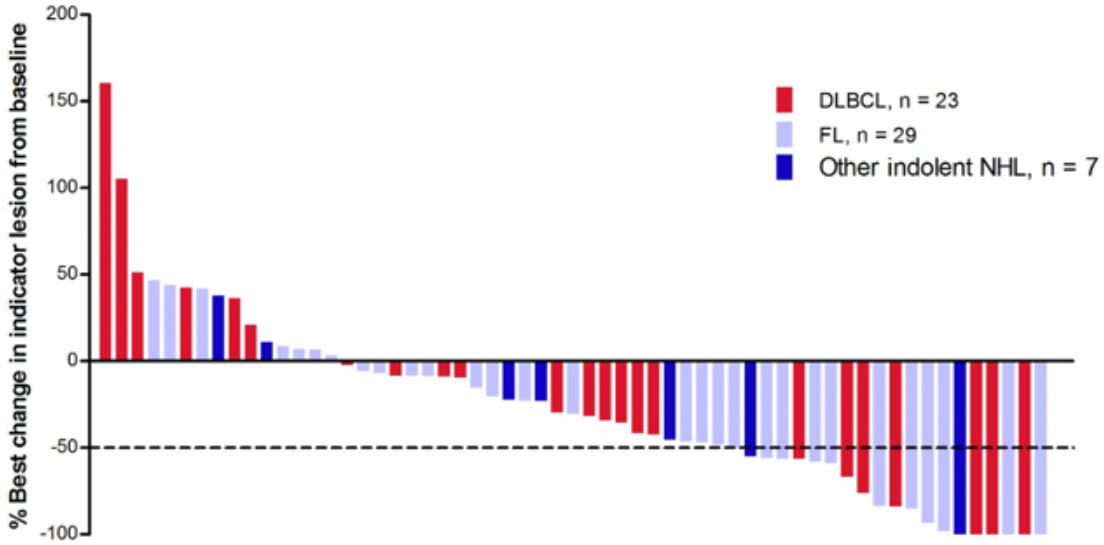
- CD19 plays a key role in B-cell:
  - **Development**[1]
  - **Proliferation**[1]
  - **Signalling**[1]
- CD19 enhances B-cell antigen receptor (BCR) signalling[2-4]
  - CD19 amplifies **PI3K** and **BTK** activity[2-4]
- CD19 expression is **maintained despite loss of CD20 expression** following treatment with CD20 antibodies[2]

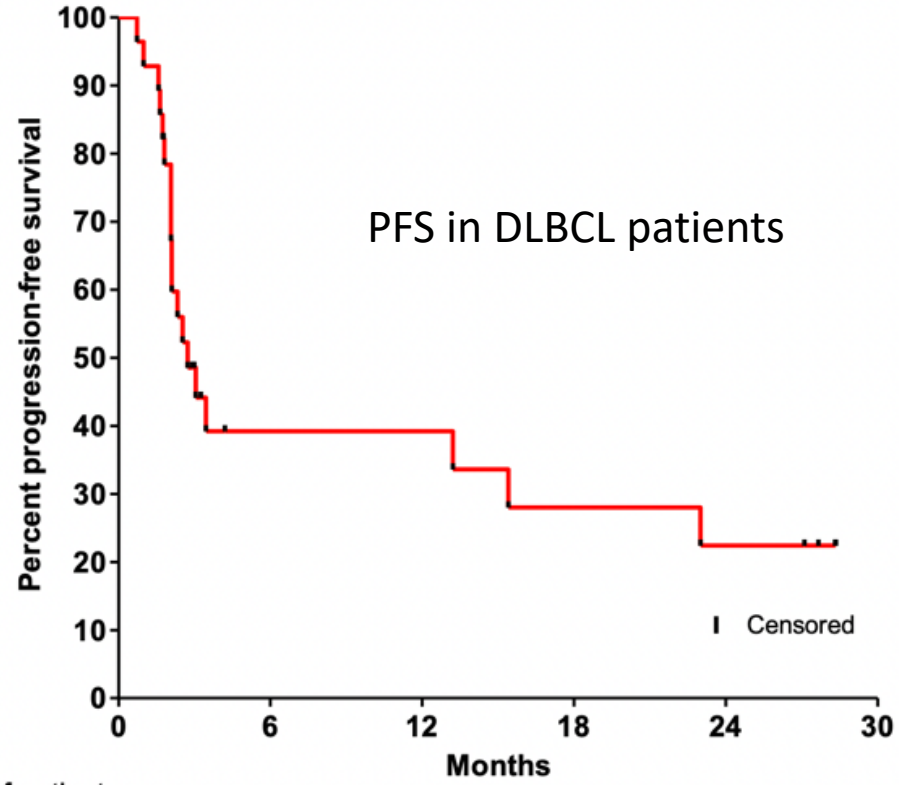
Therefore, **CD19** appears an **attractive target** for **new therapeutic approaches** to B-cell malignancies



1. Katz B-Z and Herishanu Y. Leukemia & Lymphoma 2014; 55:999–1006; 2. Fujimoto M, et al. Semin Immunol 1998;10:267-77;
3.Fujimoto M, et al. Immunity 2000;13:47-57; 4. Poe JC, et al. J Immunol;2012:2318-25.

Anty CD19 w leczeniu DLBCL

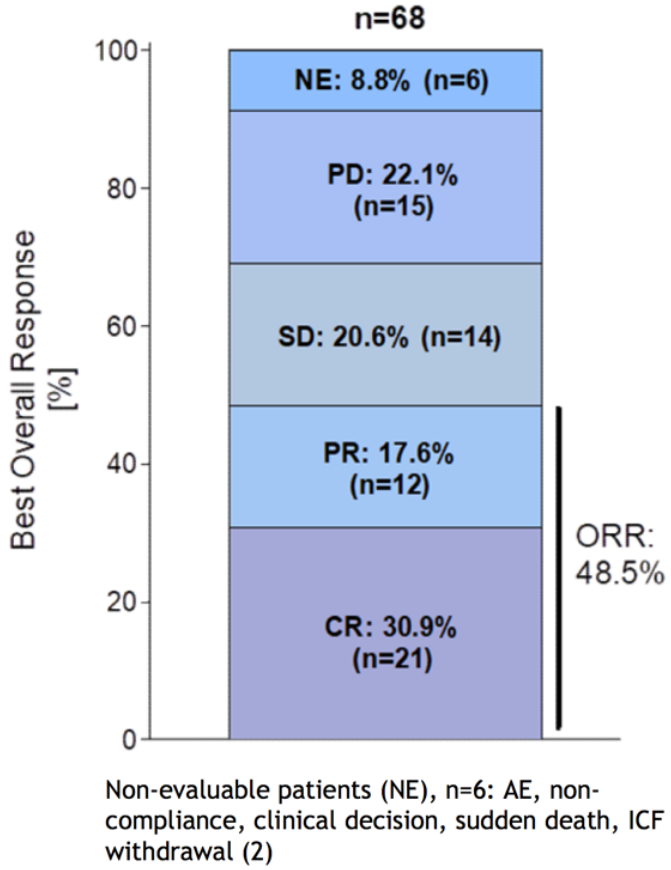




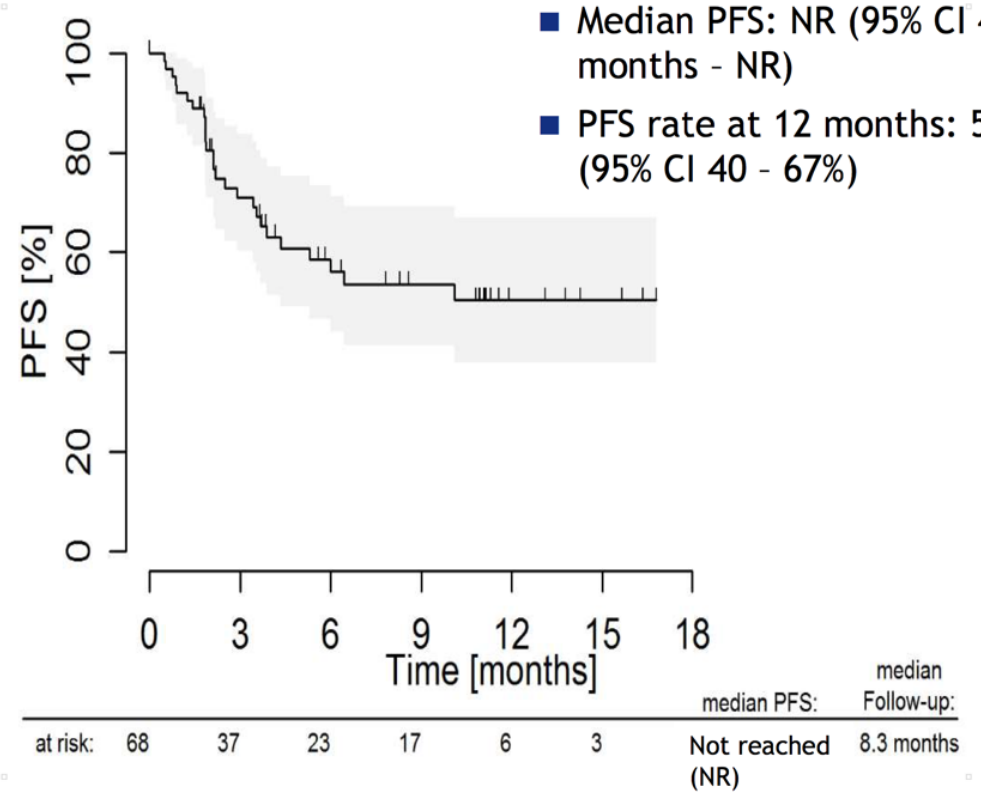
PFS in DLBCL patients

Jurczak et al. – Ann Oncol 2018

L-MIND trial (Lenalidomide + MOR 208)



Non-evaluable patients (NE), n=6: AE, non-compliance, clinical decision, sudden death, ICF withdrawal (2)



- MOR208 in combination with lenalidomide showed highly encouraging efficacy

Data cut-off: December 12, 2017

Salles et al, ASH 2018

Second generation immunomodulator
Lenalidomide -/+ CD20 in R/R DLBCL

Single-agent lenalidomide (Phase II/III)[1]

No. of patients	N=51
ORR	28%
CR	10%
Median PFS, weeks	13.6

Lenalidomide **+ rituximab** (Phase II)[2]

No. of patients	N=32
ORR	28%
CR	22%
Median PFS, months	3.7

Lenalidomide **+ obinutuzumab** (Phase II)[3]

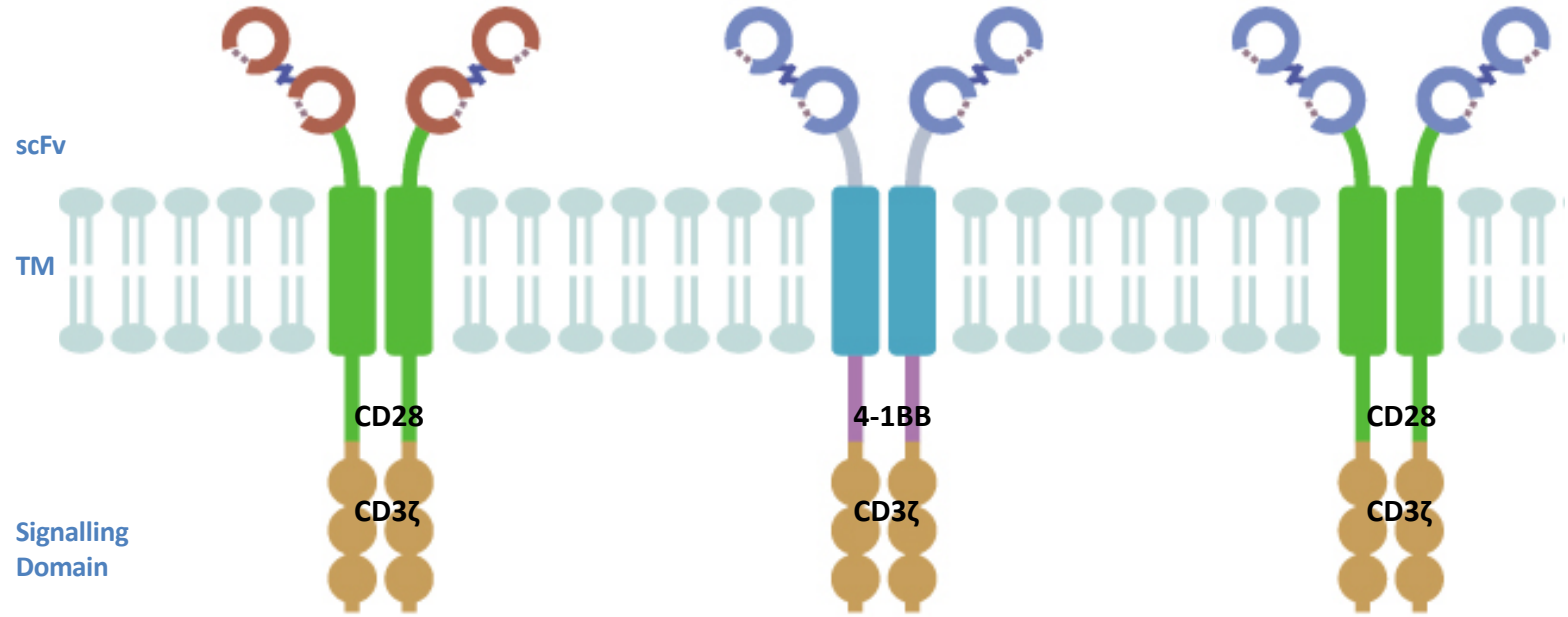
No. of patients	N=71
ORR	45%
CR	16%
Median PFS, months	4.1

Lenalidomide **+ MOR208** (Phase II; preliminary data)[4]

No. of patients	N=34
ORR	56%
CR	32%
Median PFS, months	N/A

1. Czuczman MS, et al. Clin Cancer Res 2017; doi: 10.1158/1078-0432.CCR-16-2818; **2.** Wang M, et al. Leukemia 2013;27:1902–1909;
3. Morschhauser F, et al. ASH 2016; **4.** Maddocks KJ, et al. ASCO 2017.

CD19 Chimeric Antigen Receptor (CAR)-T-cell therapies in R/R DLBCL

	Axi-cel	CTL19	JCAR017
CD19 Ab			
CD28/4-1BB CD3ζ			
	NCI FMC63-28z	UPenn CD19-BB-z	MSKCC 19-28z
Gene transfer	Retrovirus	Lentivirus	Retrovirus

CD19 CAR-T-cell therapies in R/R DLBCL patients – Baseline characteristics

	Axi-cel[1] ZUMA-1	CTL19[2] JULIET	JCAR017[3] TRANSCEND NHL001
Number of patients	101	51	55
Age median (range)	58 (23–76)	56 (24-75)	61(29-82)
ECOG 0-1	64%	100%	87%
Stage III-IV	85%	NA	NA
Prior therapies			
Median (range)	64% with ≥3 lines	Median 3 (2-7)	Median 3 (1-11)
Refractoriness	77% refractory* to ≥2nd line		76% chemorefractory+
Prior ASCT	21%	51%	44%

* No response to last chemotherapy or SD ≤ 6 months
+ Stable disease (SD) or progressive disease (PD) to last chemo-containing regimen or relapse < 12 months after autologous SCT.

1. Neelapu et al. ICML 2017; 2. Schuster et al. ICML 2017; 3. Abramson et al. ASCO 2017

CD19 CAR-T-cell therapies in R/R DLBCL patients – Summary of preliminary efficacy and safety

	Axi-cel[1] ZUMA-1 n=101	Tisagenlecleucel[2] JULIET n=51	JCAR017[3] TRANSCEND n=54
Best ORR	82%	59%	76%
Best CR	**54%**	**43%**	**52%**
Median DoR	8.2 mo	na	~9 mo
Median Follow-up	8.7 mo	na	na
Ongoing Responses	39% (31% CR)	37% (CRs)	na

CAR-T-cells:

- Impressive preliminary response rates in patients eligible for treatment[1,2]
- Reserved for relatively young, fit, chemorefractory and heavily-pretreated patients
- CRS and neurotoxicity to be managed
- Use restricted to specifically prepared centers

1. Neelapu et al. ICML 2017; 2. Schuster et al. ICML 2017; 3. Abramson et al. ASCO 2017

ZUMA-1: Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL

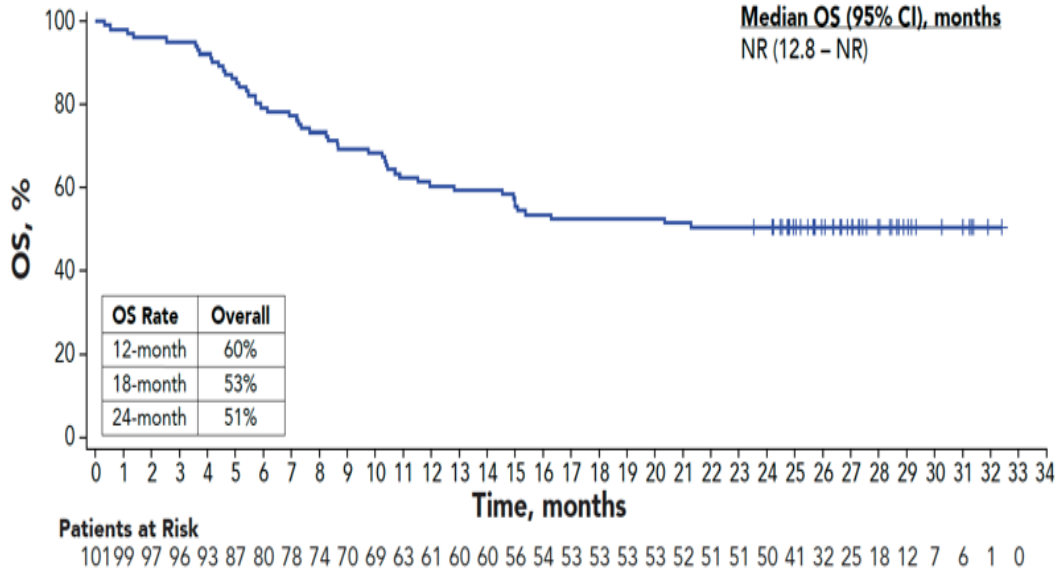
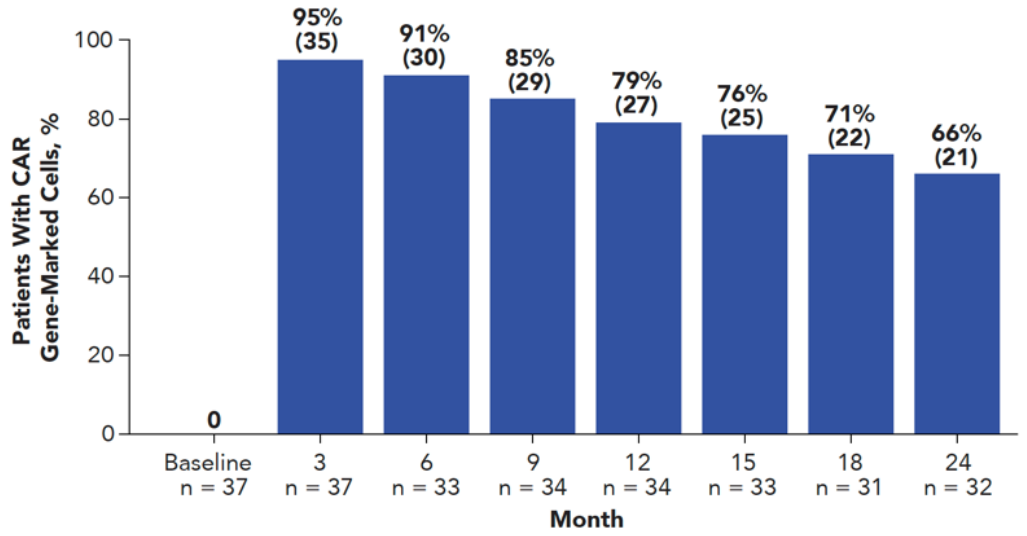


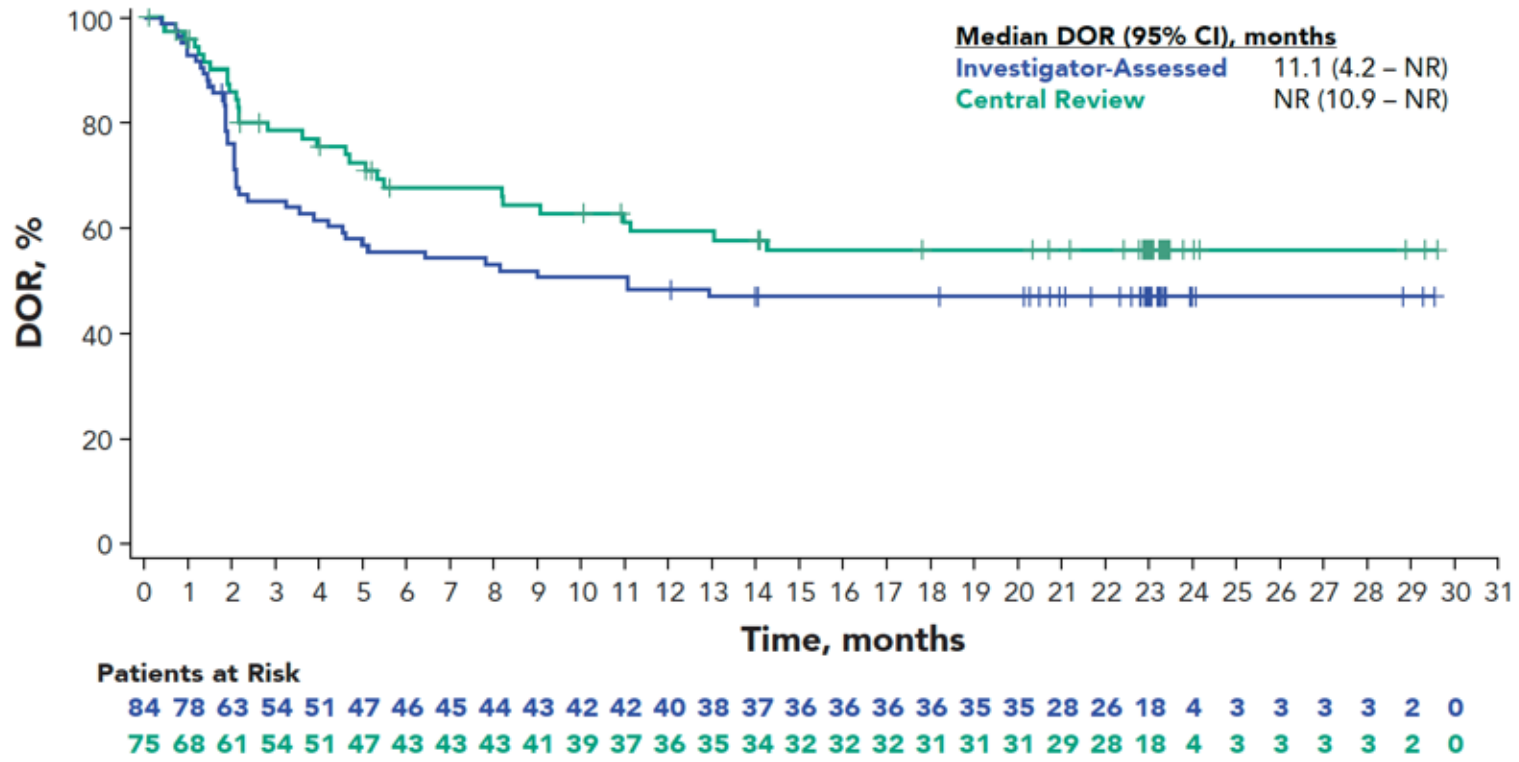
Figure 7. Proportion of Patients With Detectable CAR Gene-Marked T Cells in Blood Among Patients With Ongoing Response Over Time



Gene-marked CAR T cells were enumerated by quantitative PCR. The lower limit of quantification of the assay was 2 gene-marked CAR T cells per 100,000 PBMCs (0.002%). Values shown indicate the proportion (top) and number (in parenthesis) of patients with gene-marked CAR T cells in blood at a given time point. Number of patients evaluated at each time point are shown on x-axis. This analysis excludes 2 patients who received subsequent anticancer therapy while in response to axi-cel.
CAR, chimeric antigen receptor; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction.

Sattva S. Neelapu et al. - Poset 2967 ASH 2018

2-Year Follow-Up and High-Risk Subset Analysis of ZUMA-1, Axicabtagene Ciloleucel (Axi-Cel) in Patients R/R DLBCL



Median duration of response was NR (95% CI, 10.9 months – NR) by central review because of several patients with early progressive disease who were assessed as in response by central review and had to be censored for receiving next anticancer therapy.
DOR, duration of response; NR, not reached.

Sattva S. Neelapu et al. - Poset 2967 ASH 2018

R/R DLBCL - podsumowanie

- **Im lepsze są wyniki leczenia I rzutu, tym gorzej rokują chorzy ze wznową/ opornością procesu**
- Małe prawdopodobieństwo wieloletnich remisji chorych leczonych „chemioterapią ratującą”, **spadek znaczenia ASCT**
- **Male prawdopodobieństwo wieloletnich remisji chorych leczonych lekami o alternatywnym do cytosatatyków mechanizmach działania w monoterapii -** w większości przypadków można się spodziewać jedynie PR czy SD, optymalne schematy w których kojarzy się 2-3 leki nie są jeszcze znane (za to na pewną są niezwykle kosztowne)
- Kwestie **jakości życia** i efektów działań niepożądanych
- Nadzieje jakie wiąże się z nowoczesną immunoterapią, **CAR-T cells, Allo (MUD) SCT**

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VIII Myeloma and Lymphoma International Conference

(former „Complex treatment of plasma cell dyscrasia")

6-8 th September 2019, KRAKOW

VENUE: Jagiellonian University Medical College, Św. Anny 12 Str.