Disclosures

PROF. DR HAB. WOJCIECH JURCZAK

RADY DORADCZE:

SANDOZ NOVARTIS, ROCHE, JANSSEN, ACERTA, ABBVIE, TG THERAPEUTICS, TEVA, TAKEDA, SPECTRUM, NOVONORDISK, MUNDIPHARMA, CELLTRION

FINANSOWANIE BADAŃ:

CELGENE, ABBVIE, GILEAD, TGTHERAPEUTICS, JANSSEN, ACERTA,, MERCK, BEGENE, PHARMACYCLICS, PFIZER, ROCHE, SANDOZ – NOVARTIS, TAKEDA, TEVA, SERVUIER, EISAI, CELLTRIONE, CELGENE

Nowotwory układu chłonnego
Standardy postępowania w praktyce klinicznej

Prof. Wojciech Jurczak, M.D., Ph.D.
Dpt of Hematology, Jagiellonian University
wojciech.jurczak@uj.edu.pl, (+48 602 338290)

Polish Lymphoma Research Group

Zachorowania na chłoniaki w Polsce

Zachorowania 64 000		Zgony 52 000
24%	Płuco	32%
12%	Jelito grube	10%
11%	Prostata	7%
6%	Pęcherz moczowy	4%
5%	Żołądek	7%
po 4%	Skóra, krtań, nerka	

Zachorowania 62 000		Zgony 40 000
22%	Pierś	13%
10%	Jelito grube	11%
8%	Płuco	13%
7%	Trzon macicy	2%
5%	Jajnik	6%
5%	Szyjka macicy	5%
po 4%	Skóra, żołądek	

5-6% **chłoniaki** 4%

5-6% **chłoniaki.** 4%

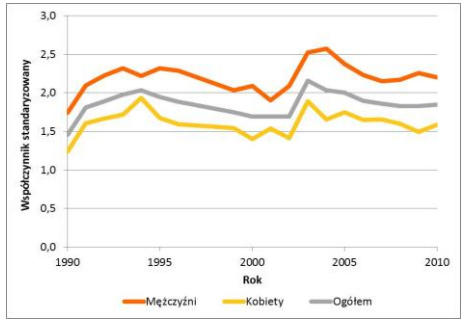
… blisko 7500 nowych przypadków rocznie

Jurczak et al. , Pol J Pathol 2006

Zachorowania na chłoniaki w Polsce

Mieloproliferacje

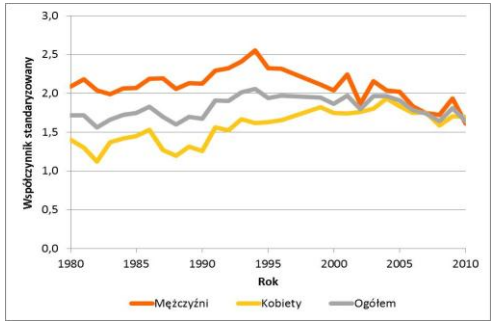
Współczynnik zapadalności 1.8 → 11.8%



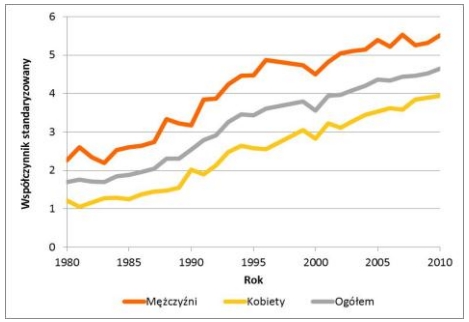
CML i AML – 1,8 → **11.8%**

Chłoniaki

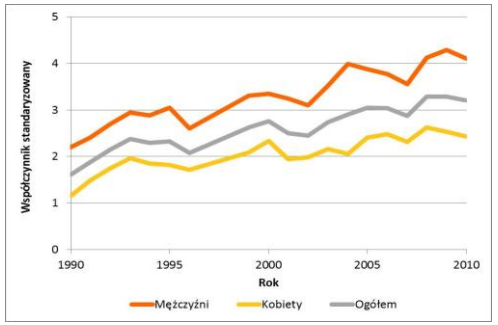
Współczynnik zapadalności 13.5 → 88.3%



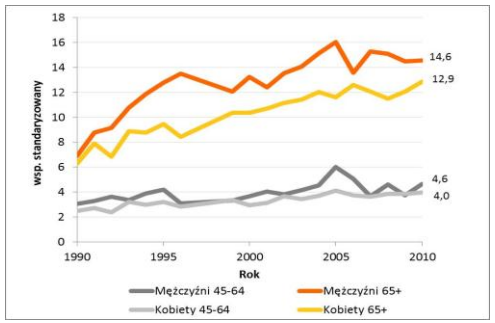
HD – 1,6 → **10.4%**



NHL – 4,7 → **30.7**



CLL i ALL – 3,2 → **20.9%**



Szpiczak – 4,0 → **26.1%**

KRN: http://onkologia.org.pl/k/epidemiologia/

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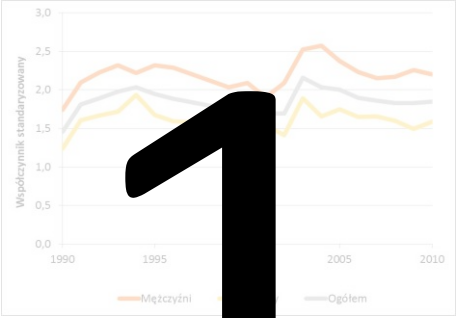
Zachorowania na chłoniaki w Polsce

Mieloproliferacje

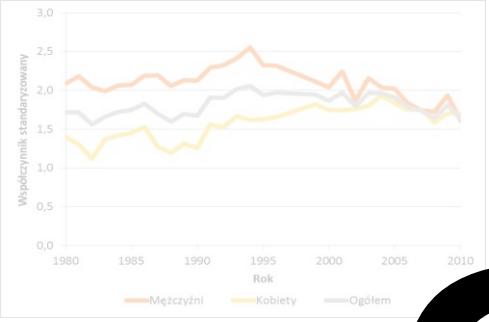
Współczynnik zapadalności 1.8 → 11.8%



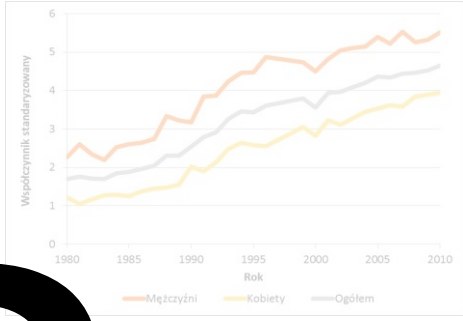
CML i AML – 1,8 → 11.8%

Chłoniaki

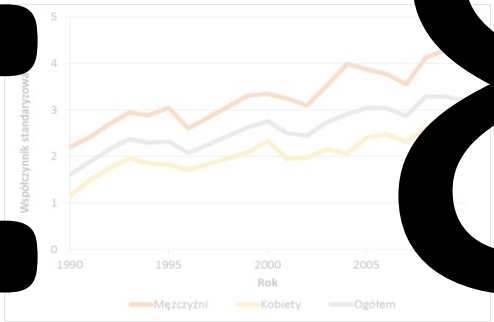
Współczynnik zapadalności 13.5 → 88.3%



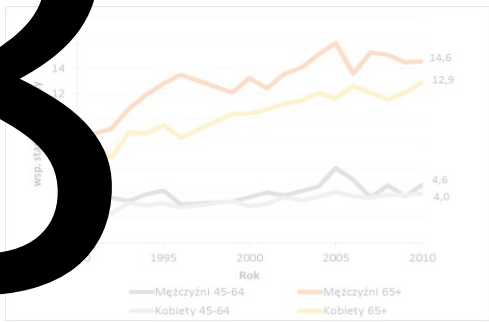
HD – 1,6 → 10.4%



NHL – 4,7 → 30.7



CLL i ALL – 3,2 → 20.9%



Szpiczak – 4,0 → 26.1%

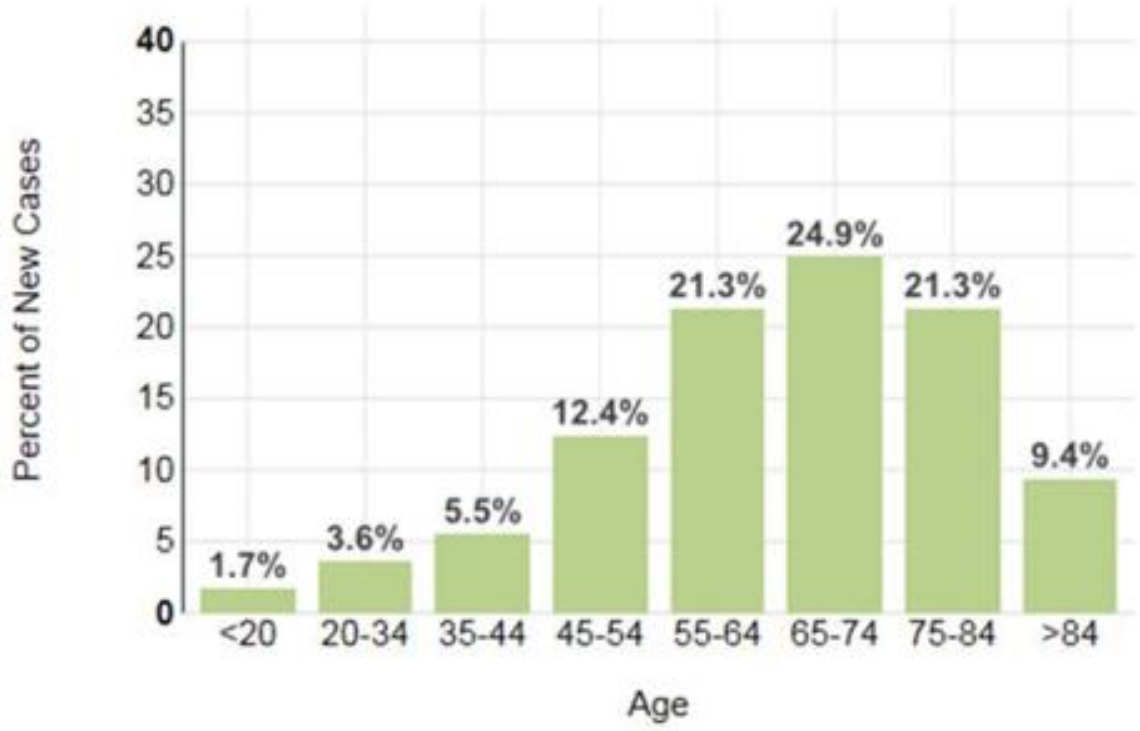
1 : 8

KRN: http://onkologia.org.pl/k/epidemiologia/

Prof. Wojciech Jurczak MD,PhD

Polish Lymphoma Research Group

Chłoniaki – choroby osób starszych



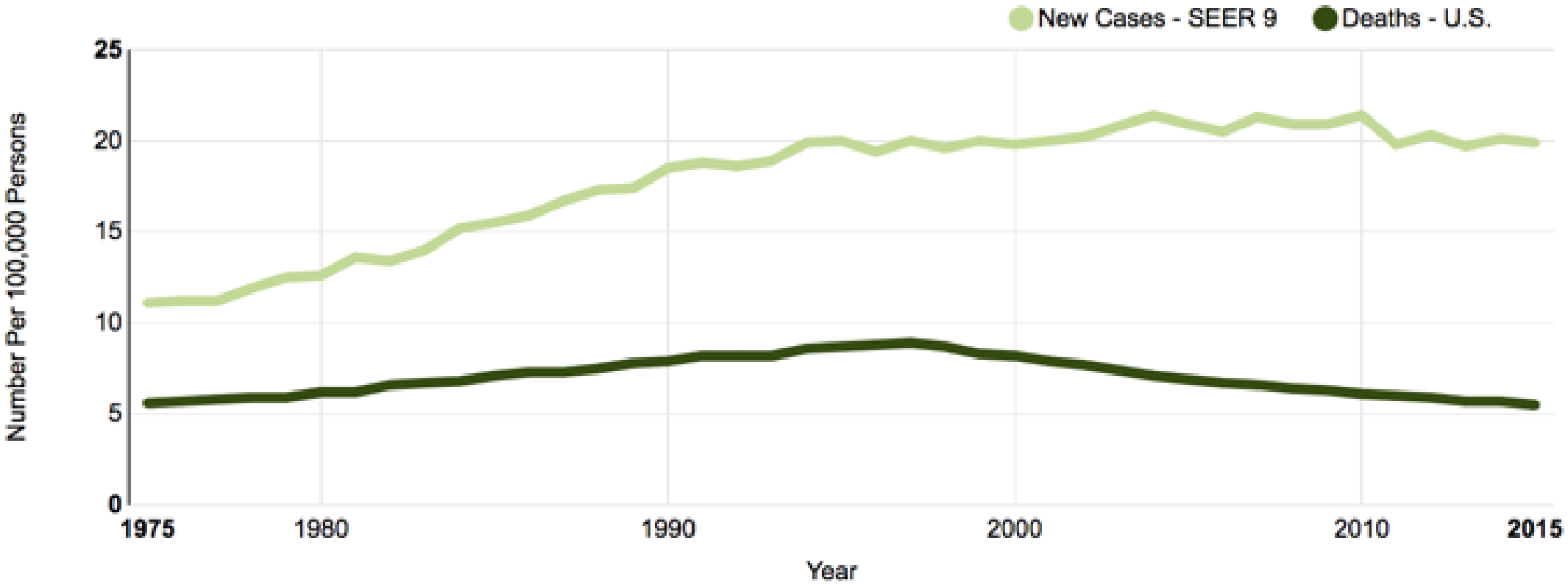
Non-Hodgkin lymphoma is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis
67

https://seer.cancer.gov/statfacts/html/nhl.html

Polish Lymphoma Research Group

Chłoniaki – istotna poprawa rokowania po wprowadzeniu do praktyki klinicznej nowych leków



https://seer.cancer.gov/statfacts/html/nhl.html

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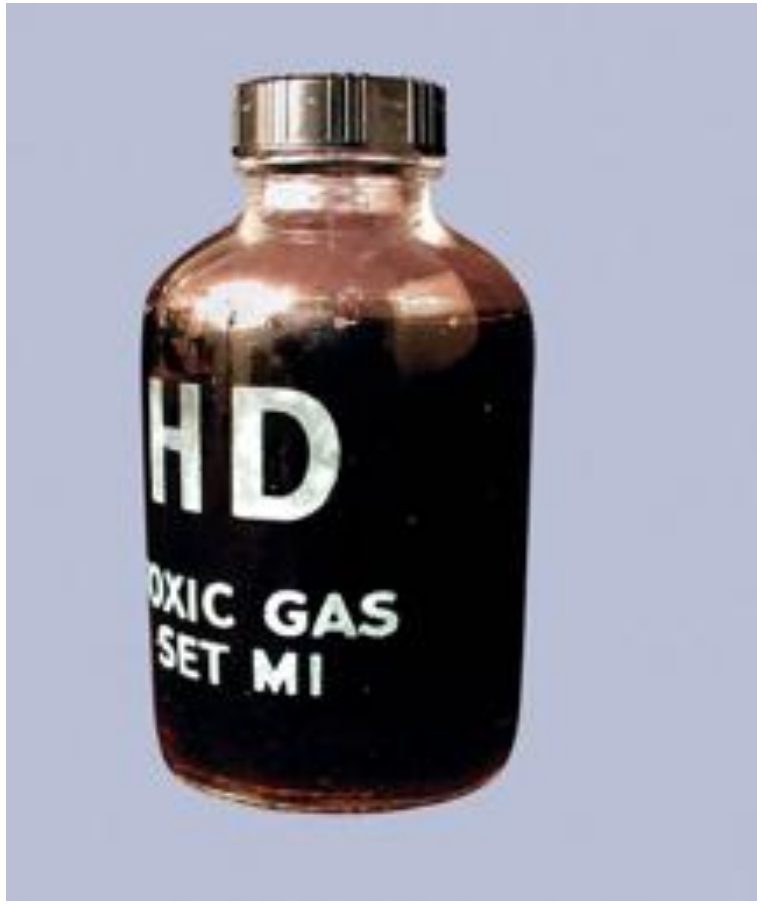
Leki alkilujące – wszystko rozpoczęło się w Ieper

Gaz musztardowy powodował u żołnierzy :

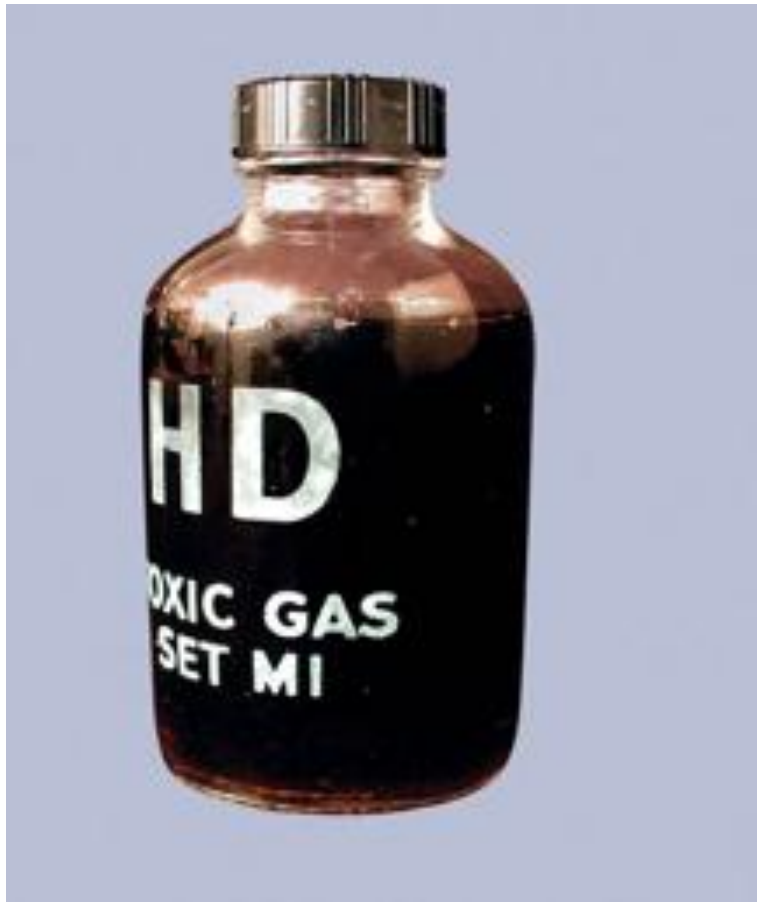
- owrzodzenia skóry
- Ślepotę
- uszkodzenia płuc
- nudności i wymioty
- procesy nowotworowe
- **spadek liczby limfocytów**



W 1940, opisano efekty podania nitrogranulogenu i .v. u chorych z chłoniakami - spektakularne, krótkotrwałe, remisje

Leki alkilujące – wszystko rozpoczęło się w Iepr

NHL	Hodgkin	CLL
R-CHOP	MOPP	FCR
R-CVP	ABVD	BR
B-R	BEACOPP	Clb-O
ICE		
BEAM		
B-O		



W 1940, opisano efekty podania nitrogranulogenu i .v. u chorych z chłoniakami - spektakularne, krótkotrwałe, remisje

Krótka historia leczenia chłoniaków

Louis Goodman,
Alfred Gilman
Nitrogranulogen in HD

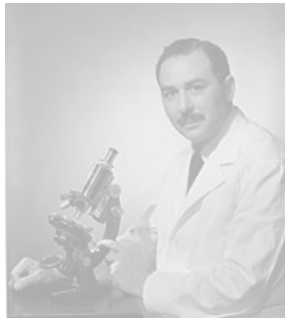
FDA registers CTX

FDA registers Cisplatin

Gianni Bonadonna ABVD

1942 1948 1959 1970 1975 1978 2003 2014

Sydney Farber
antymetabolites inALL

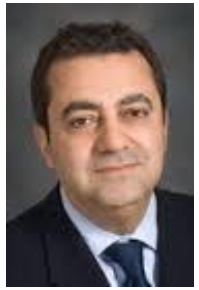


Polichemotherapy: 1970 MOPP, 1973 CHOP (Doxorubicin)

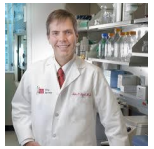
NCI 'gang of five': George Canellos, Bruce Chabner, Phillip Schein, Vincent DeVita i Robert Young

Volker Diehl – HD
Escalated BEACOPP

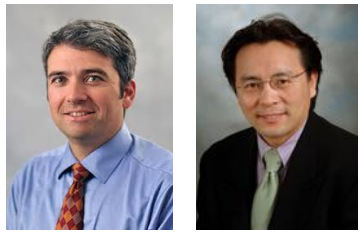
Bertrand Coiffier –
R-CHOP in DLBCL



Anas Younes
Brentuximab Vedotin



Michael Wang, Ajay Gopal &
J Byrd – Ibrutynib & Idelalisib



Andre Goy,
Marek Trneny
Lenalidomide

J.Seymour, S. Stilgenbauer
– Venetoclax

Immunoterapia:
- anty PD1
- CART cells

Nowe
przeciwciała
monoklonalne

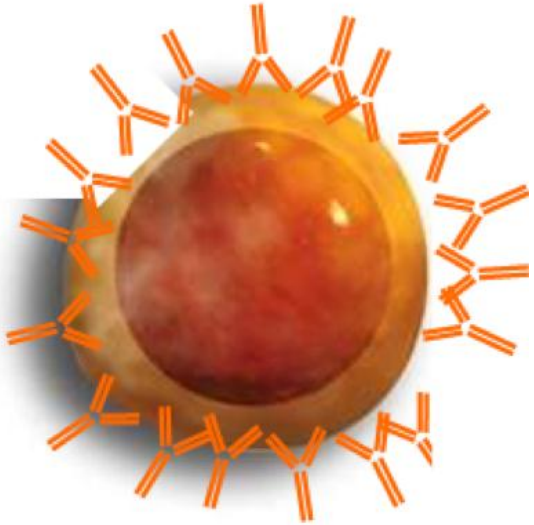
Prof. Wojciech Jurczak MD,PhD

Polish Lymphoma Research Group

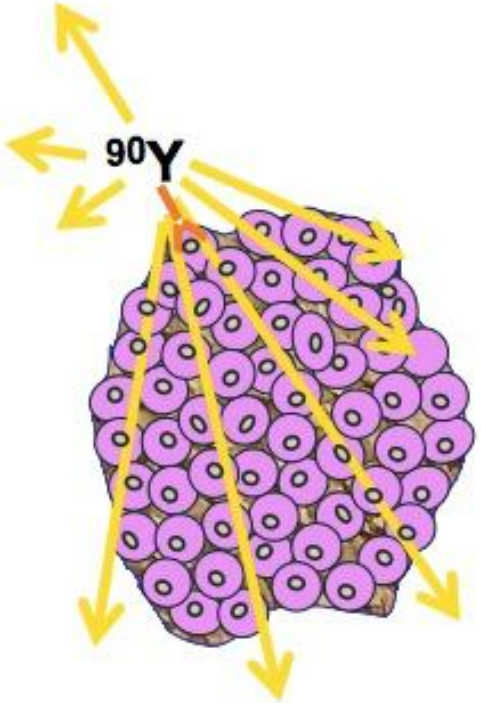
Terapia “celowana”

Polish Lymphoma Research Group

Przeciwciała monoklonalne

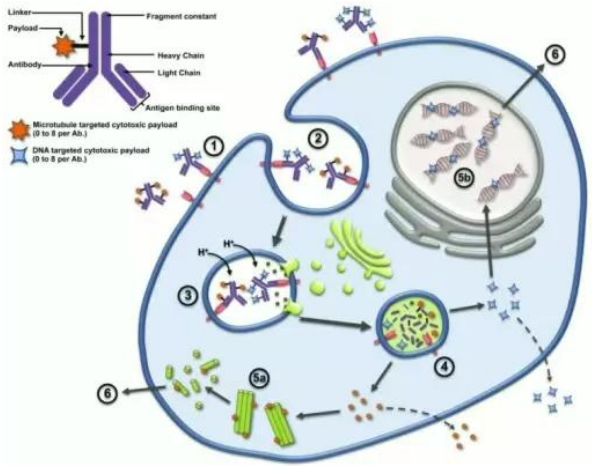


Rituximab,
Obinutuzumab,
MOR 208, ….

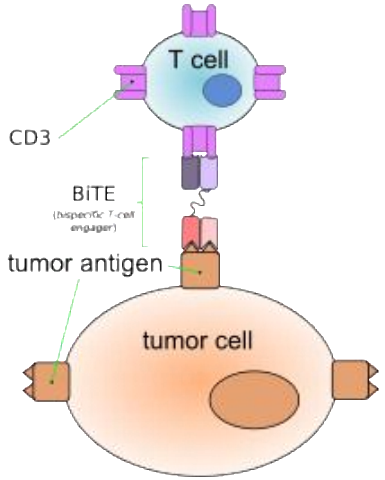


^{90}Y Ibritumomab

^{177}Lu Betalutin

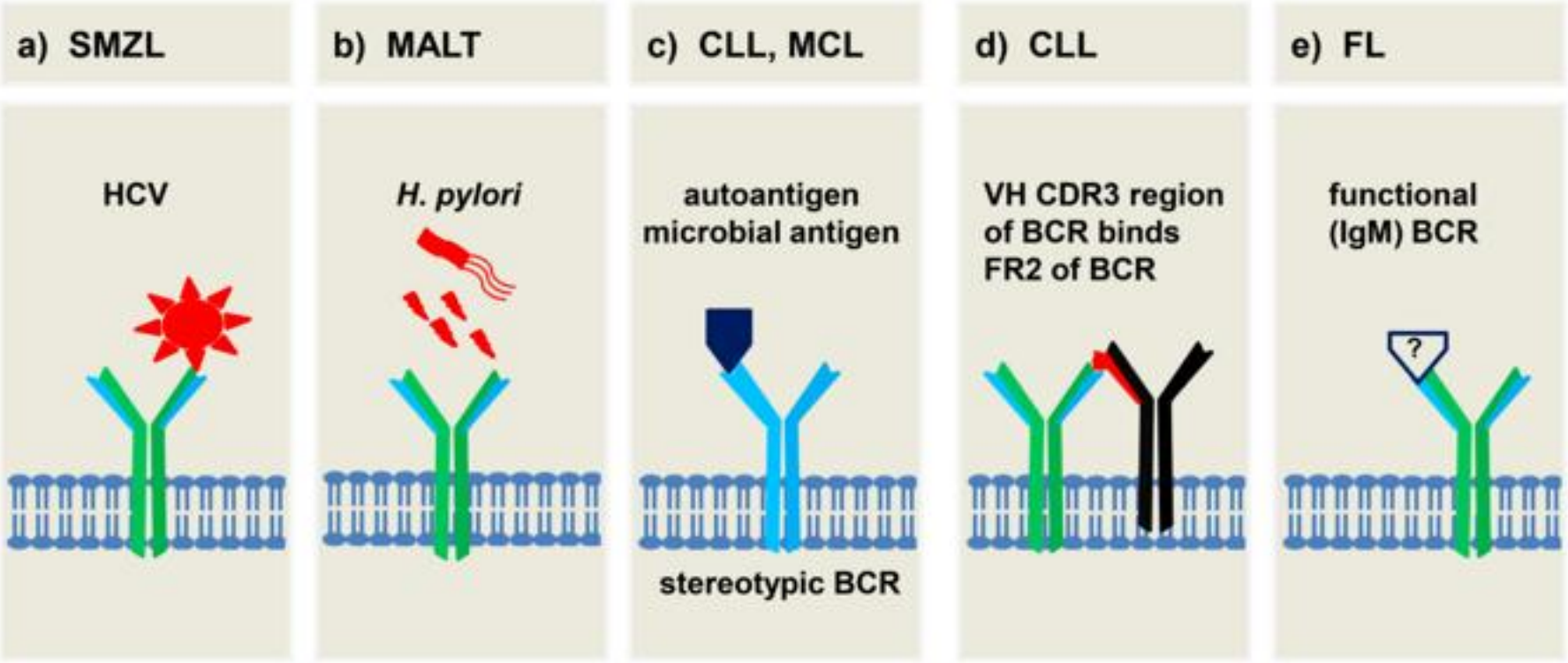


Brentuximab Vedotin
Polatuzumab Vedotin



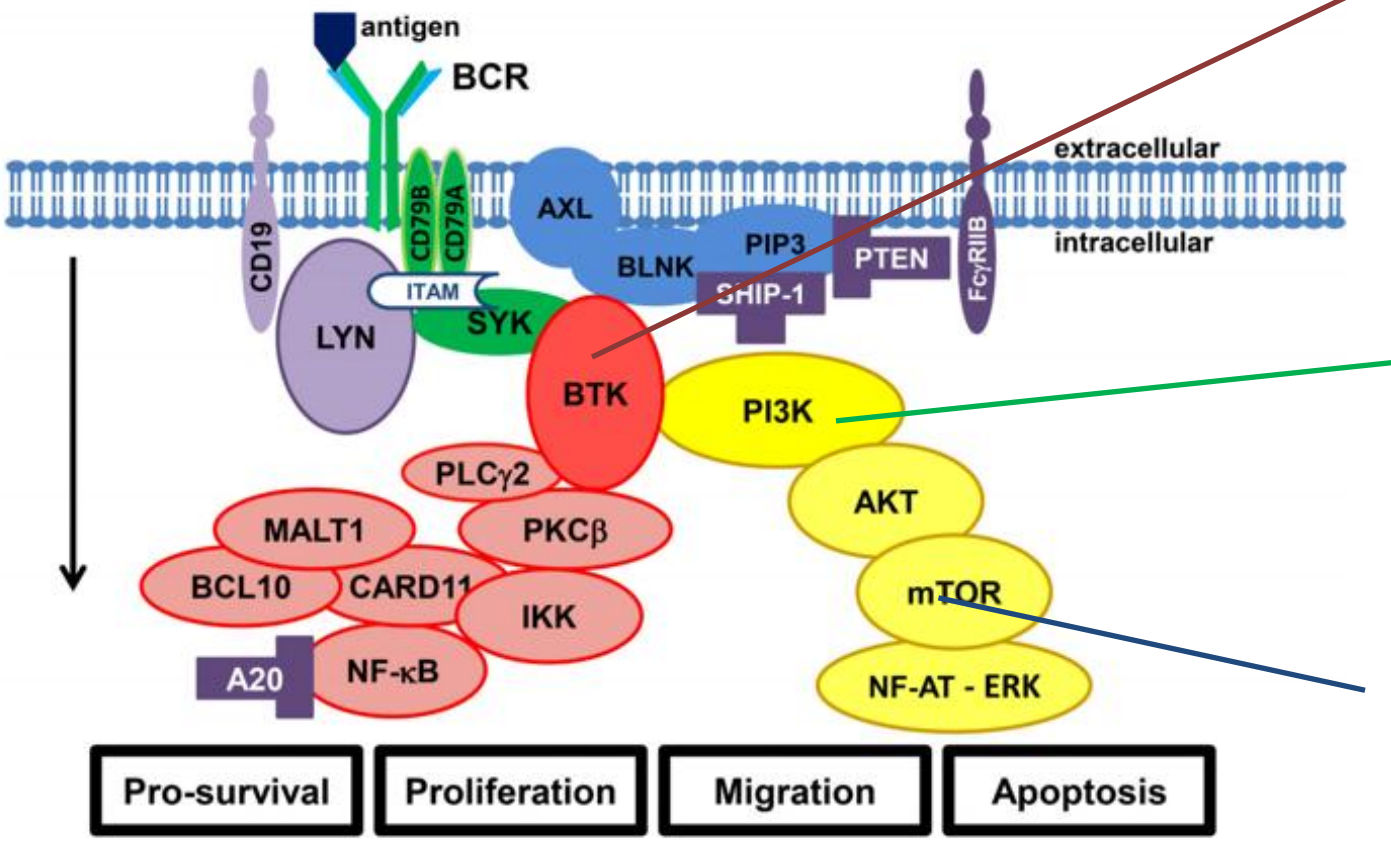
Blinatumomab
AFM-11
Mosunetuzumab

Pobudzenie receptora limfocytów B (BCR)



BCR is required for B-cell survival and differentiation at several stages of B-cell development from the pre-B cell stage and onwards

Drogi przekazywania syganłu wewnątrz-komórkowego po stymulacji BCR



Inhibitory kinazy Brutona:
- Ibrutynib
- Acalabrutynib
- BGB 3111
- M7583

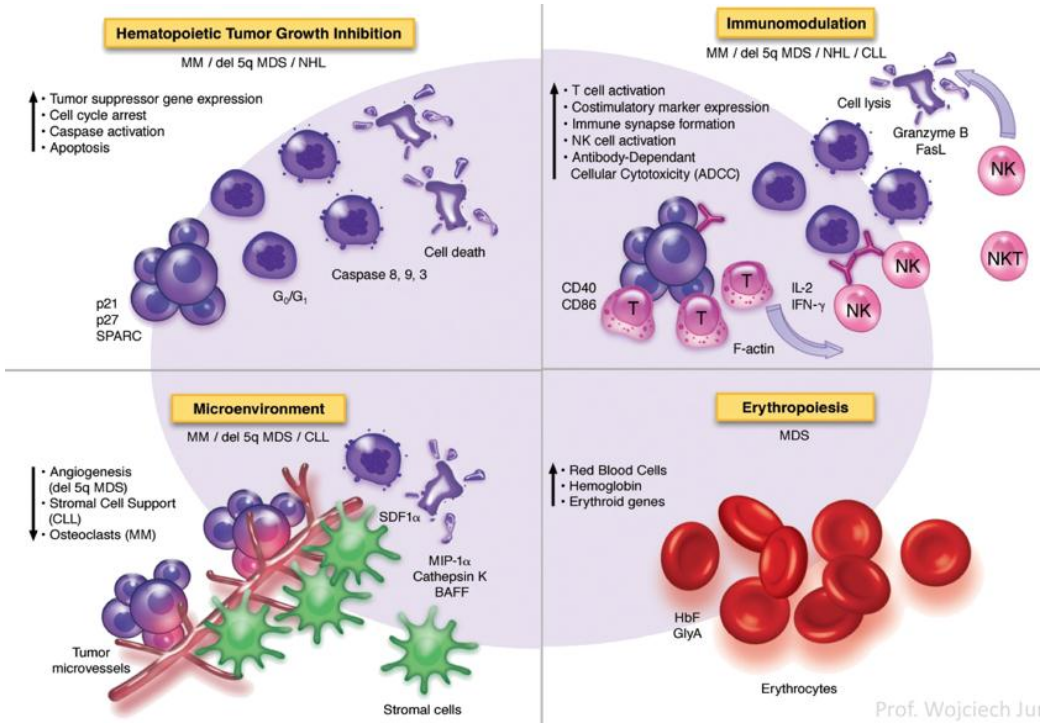
Inhibitory kinazy IP3:
- Idelalisib,
- Duvalisib,
- Copanlisib,
- Umbralisib

Inhibitory mTOR :
- Temsirolimus

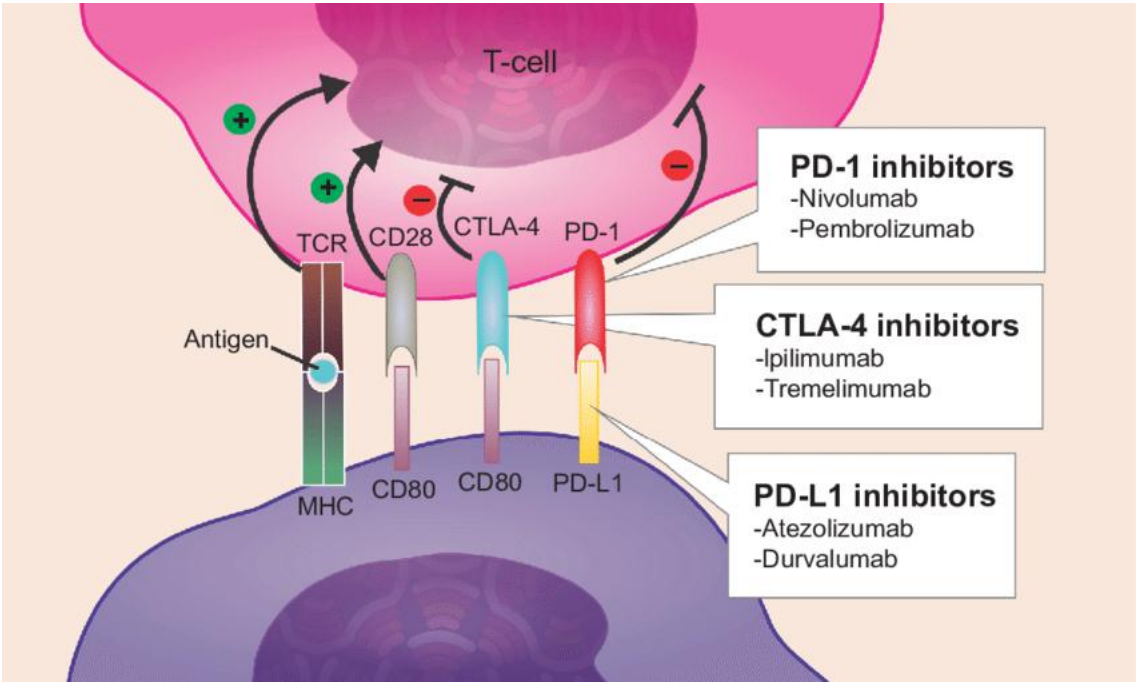
Inne leki o alternatywnym do cytostatyków mechanizmie działania

Lenalidomid - IMID

Lenalidomide

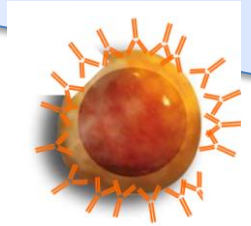


Checkpoint inhibitors

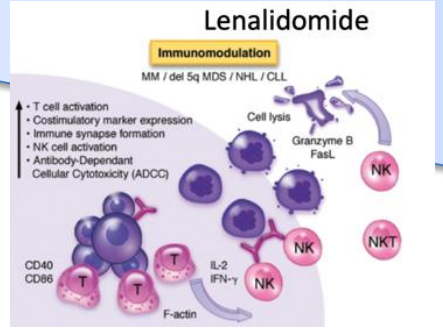


Immunoterapia

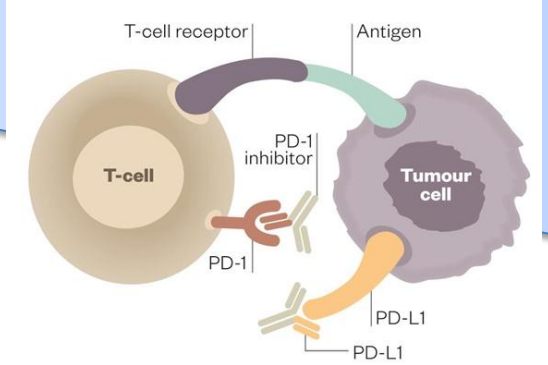
MoAb



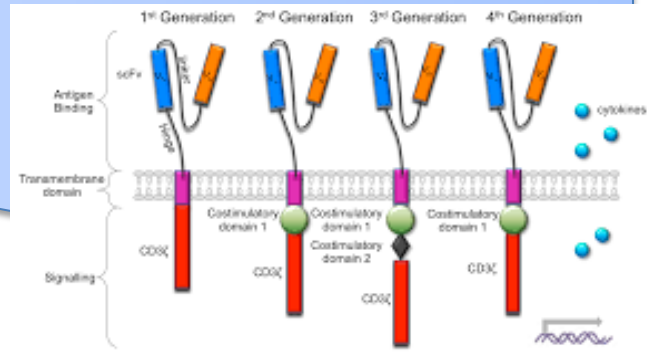
IMID



Checkpoint inhibitors



CAR-T cells



Polish Lymphoma Research Group

Dostępność w Polsce leków zarejestrowanych przez EMA I FDA

Leki dostępne

Leki częściowo dostępne

Leki Niedostępne

Inhibitory knazy Brutona (Ibrutynib)

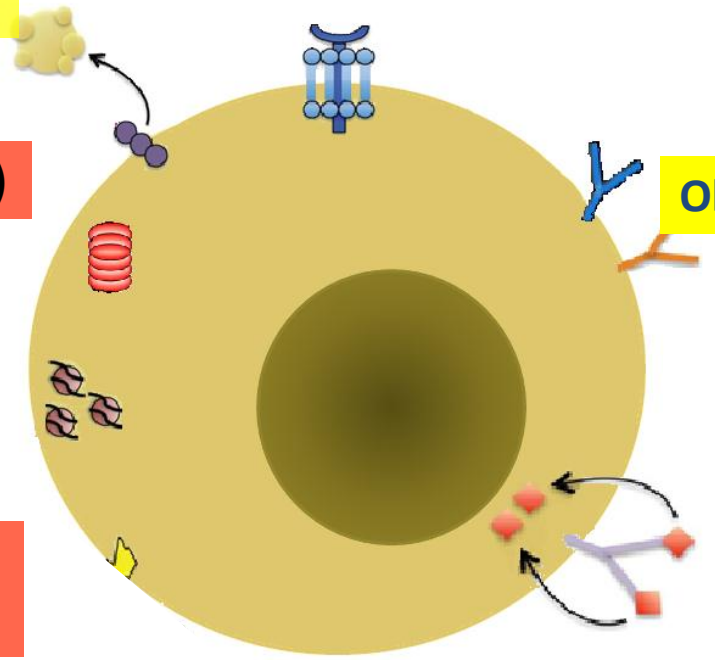
Inhibitory kinazy IP3 - Idelalisib

Inhibitory bcl-2 (Venetoclax)

Inhibitory HIDAC (Belinostat)

Inhibitory Proteasomu (Bortezomib)

Leki Immunomodulujące : Lenalidomid, Nivolumab



Obinutuzumab *(Gazyvaro)*

Biosymilary Rituximabu *(Truxima, Rixathon)*

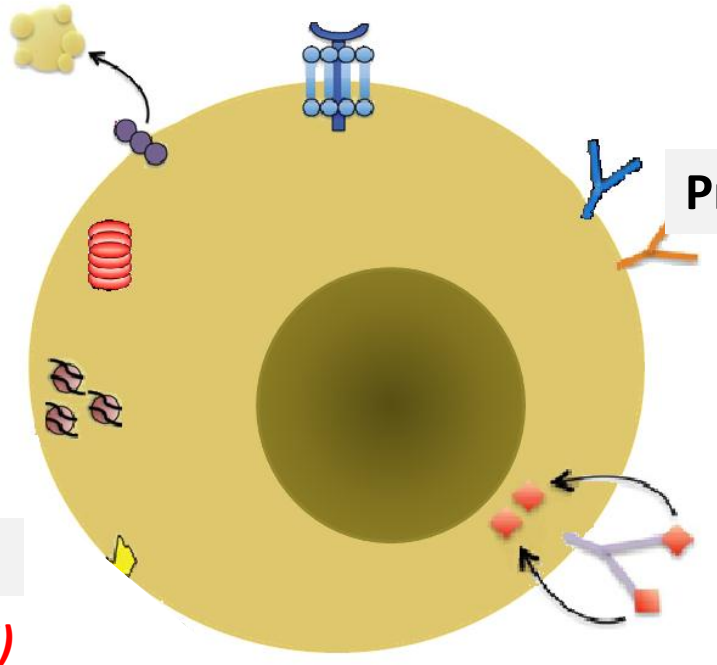
Brentuximab Vedotin *(Adcetris)*

Leki zarejestrowane przez EMA/ FDA - udział Kliniki Hematologii UJCM w Krakowie

Inhibitory knazy Brutona
(Ibrutinib, Acalabrutynib)

Inhibitory kinazy IP3
(Idelalisib)

Inhibitory bcl-2
(Venetoclax)



Przeciwciała monoklonalne

Inhibitory HIDAC
Belinostat

Biosymilary Rituximabu
(Truxima, Rixathon)

Obinutuzumab
(Gazyvaro)

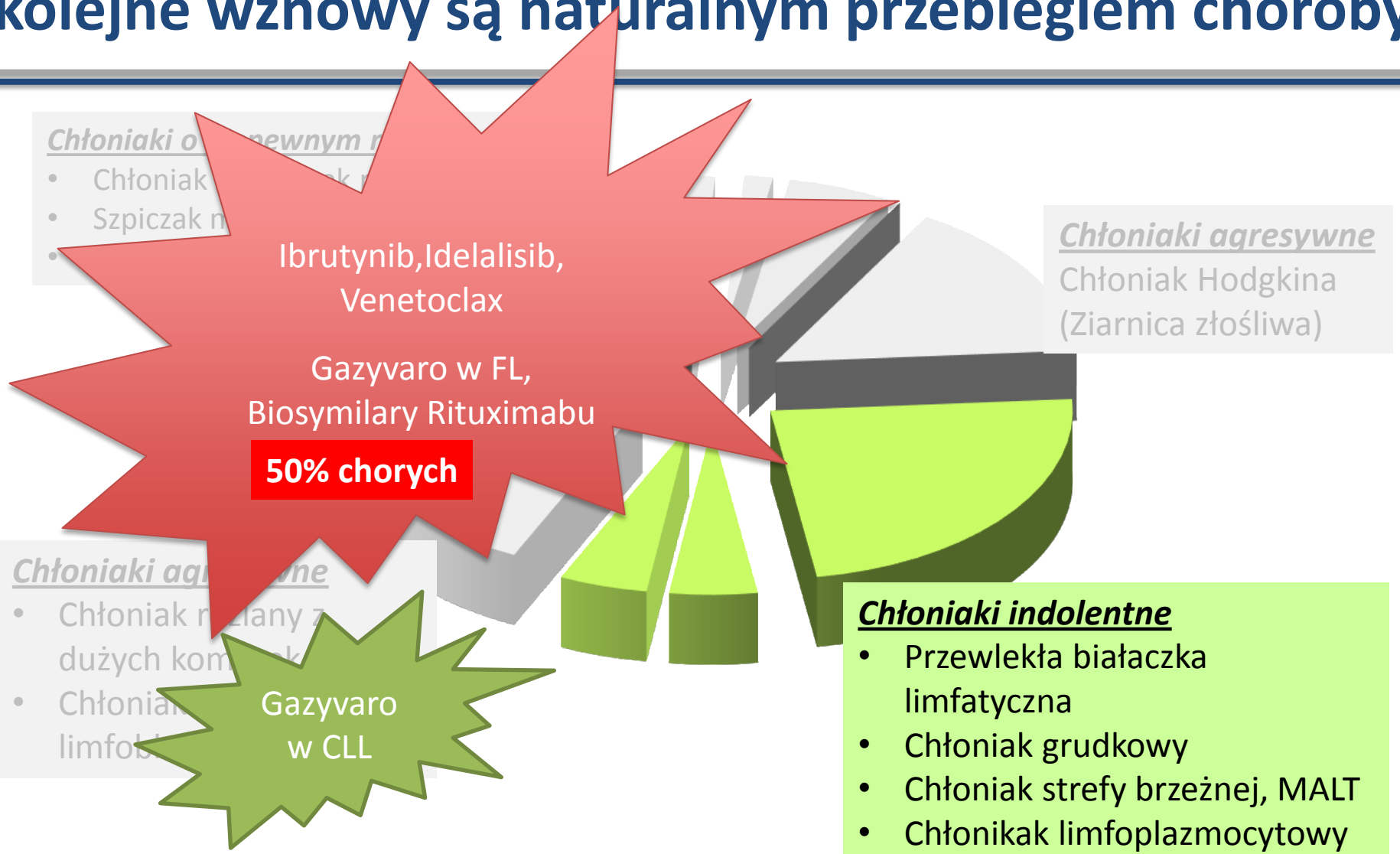
Leki Immunomodulujące
(Lenalidomid)

Brentuximab Vedotin *(Adcetris)*

Polish Lymphoma Research Group


B 591ZM

Chłoniaki indolentne (ok 4 000 / rok) – kolejne wznowy są naturalnym przebiegiem choroby



Wg. Rejestru Patologów PLRG

Polish Lymphoma Research Group

W ciągu swego życia chory może być poddany nie więcej niż 4-6 liniom leczenia ...

Wskazania do rozpoczęcia leczenia wg iwCLL 2008

Kategoria	Powód do rozpoczęcia leczenia
Objawy związane z CLL	▪ **Objawy B** (poty nocne, spadek wagi ciała, gorączki) ▪ Poważne zmęczenie
Masa guza	▪ Powiększenie się **węzłów** chłonnych (> 6-10 cm) ▪ Powiększenie się **śledziony** (ryzyko pęknięcia) ▪ Czas **podwojenia się leukocytozy <6 miesięcy** (gdy białe krwinki >30 x 10^9/L) ▪ Objawy związane z uciskiem narządów/ naczyń przez powiększone węzły
Niewydolność szpiku kostnego	▪ **Niedokrwistość** ▪ **Małopłytkowość**
Problemy psychologiczne	▪ Brak zrozumienia chorego, że nie jest leczony

Hallek M, et al. *Blood*. 2008;111:5446-5456.

Rokowanie chorych z CLL

Era chemiotrapii

1960s, 1970s

Leki alkilujące
- Chlorambucil
- Cyclophosfamid

5% CR

1980s

Analogi puryn
- Fludarabina
- Kladrybina

5% - 20% CR

1990s

Bendamustyna

30% CR

Wydłużenie PFS
Bez wpływu na OS

OS: 5-7 lat

Era Immuno-chemiotrapii

2000s

Chemio-immunoterapia

45% CR;

Wydłużenie PFS
Wydłużenie OS

OS: 10-12 lat

Aktualny standard

2010s

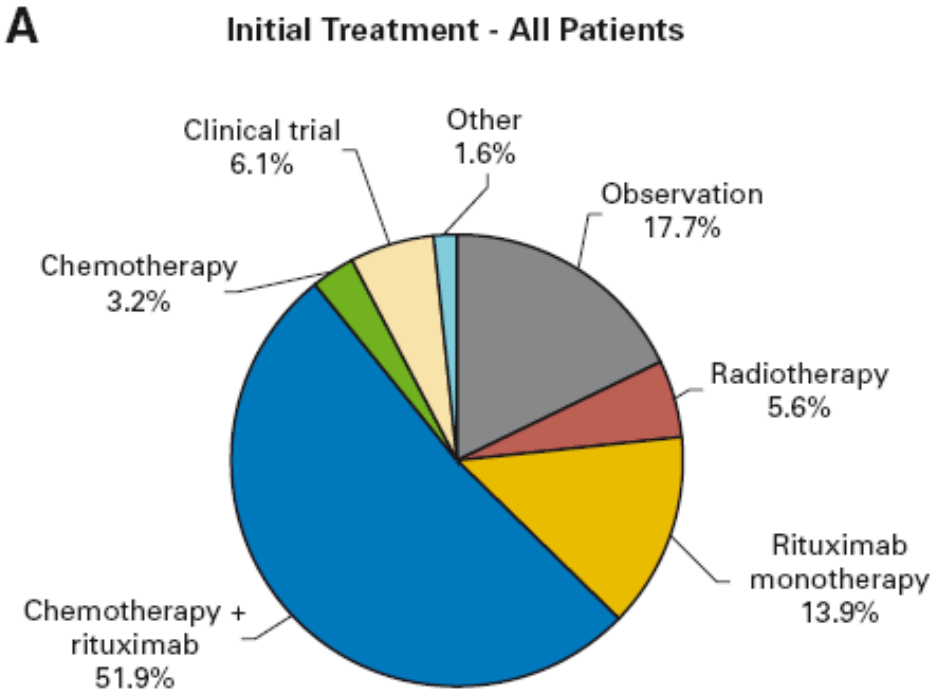
Nowe leki o alternatywnym do cytostatków mechanizmie działania (BCR, BCL2, IMiDs, ?)
+
Nowe przeciwciała

Dalsze Wydłużenie PFS
Dalsze wydłużenie OS

OS 15-20 lat

W leczeniu I rzutu iNHL, nie stosuje się chemioterapii, bez jej skojarzenia z przeciwciałami monoklonalnymi

Praktyka kliniczna w USA
FL, N= 2728, lata 2004-2007



Friedberg, et al., JCO 2009

MoAb - wszystko zaczęło się od Rituximabu…

Rejstracja i rozwój oryginalnej cząsteczki Rituximabu (Roche)

Podskórna postać Rituximabu (Roche)

ASH 2016 – pierwsze biosymilary Rituximabu:
- GP2013 (Sandoz Novartis)
- CT-P10 (Celtrion)

Rituximab s.c. – stary lek, nowa jakość

Podawanie rituksimabu IV może zająć cały dzień

Poczekalnia	Przygotowanie w aptece	linia IV	Rituksimab podawany IV + okres obserwacji

Wstrzyknięcie rituksimabu SC zajmuje ok. 5 minut[1]

Nie wymaga przygotowania w aptece, dostępu IV ani obowiązkowej obserwacji

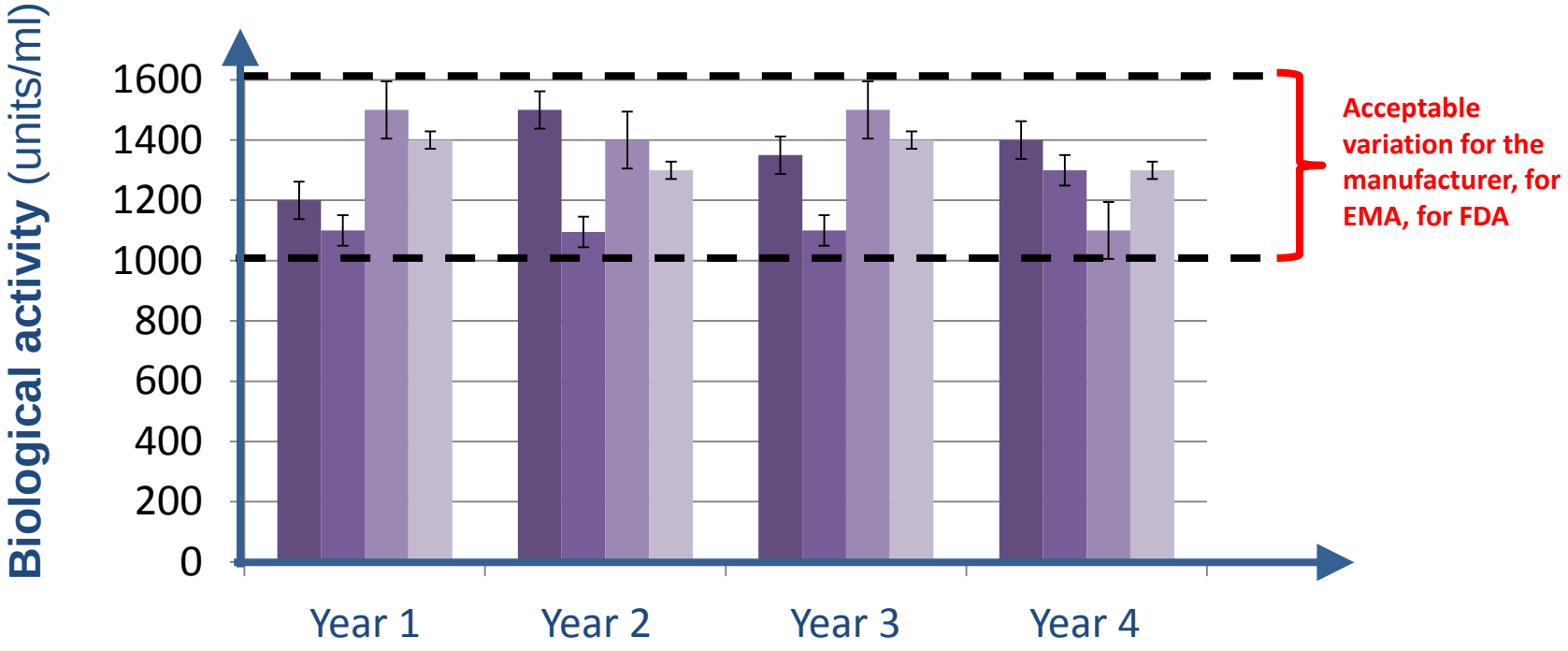
Poczekal-nia	Przy goto wani e

Oszczędność czasu po podaniu SC w porównaniu z podaniem IV

Podawanie rituksimabu SC

Biologicals Are SimilarBut Not Identical

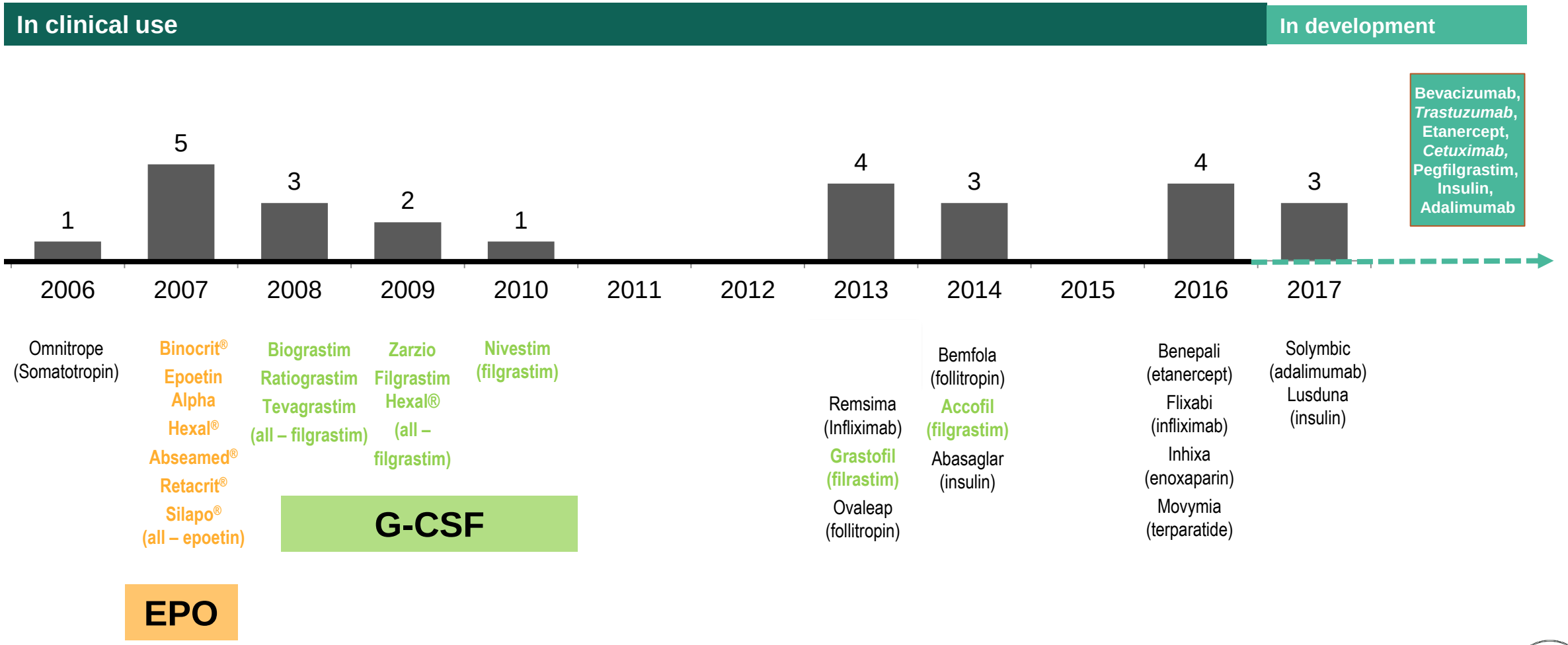
"Nonidenticality" is a normal principle in biotechnology.
No batch of any biologic is "identical" to the others.



Każda partia wytworzonego leku biologicznego różni się nieznacznie

“podobne, choć nie identyczne”, biosimilary

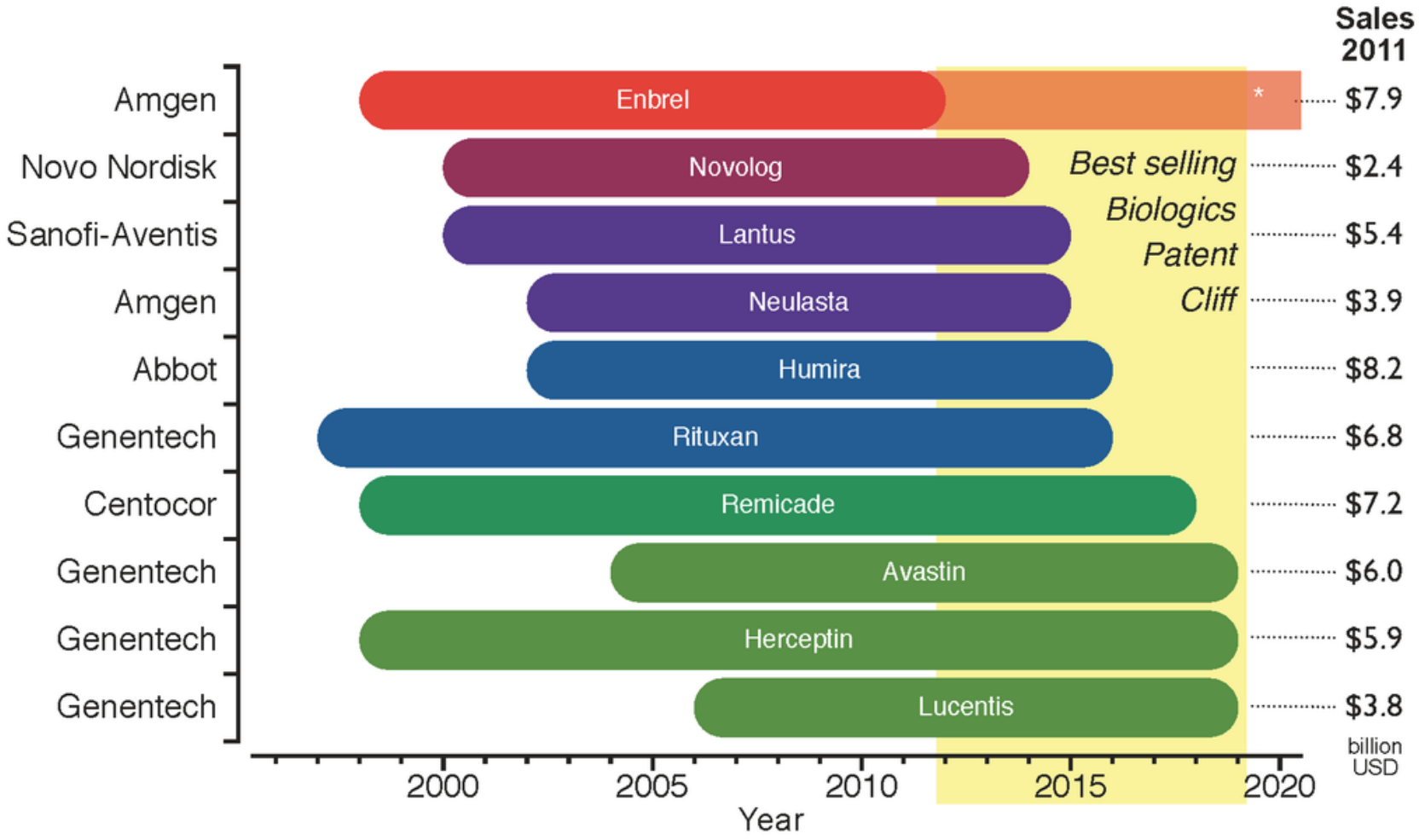
Biosimilars Approved by EMA



G-CSF: Granulocyte-colony stimulating factor; EMA: European Medicines Agency; EPO: epoetin.

EMA website. http://www.ema.europa.eu/ema/. Accessed 7 June 2017

Biosimilars which may be potentially developed in the next 10 years



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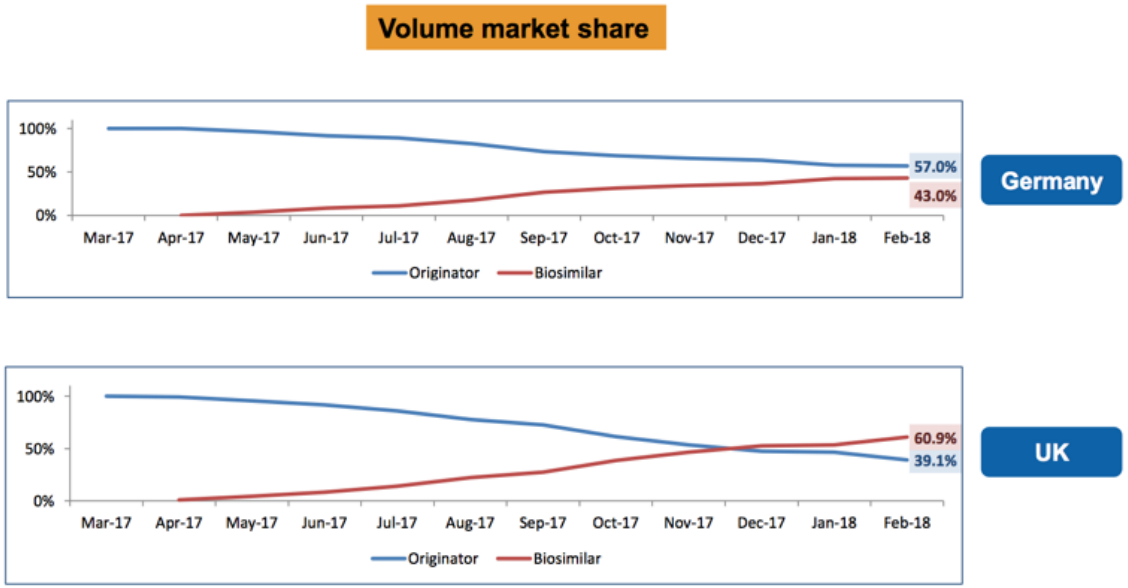
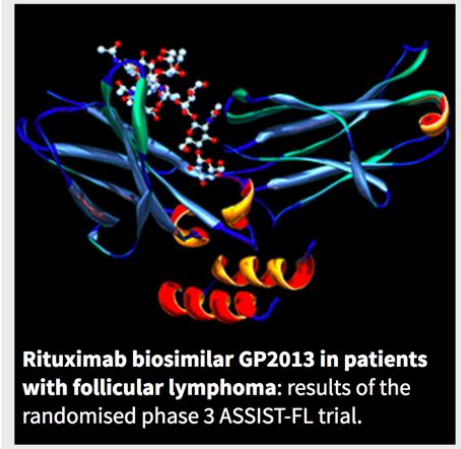
July 17 2017 was a milestone in Rituximab biosimilar development



Editor's Choice



Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study
Wojciech Jurczak, Ilídia Moreira, Govind Babu Kanakasetty, Eduardo Munhoz, Maria Asunción Echeveste, Pratyush Giri, and others
The Lancet Haematology, Vol. 4, No. 8, e350–e361Published: July 13, 2017

Rituximab biosimilars: introduction into clinical practice
Shinichi Makita, Kensei Tobinai
The Lancet Haematology, Vol. 4, No. 8, e342–e343 Published: July 13, 2017

Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial
Won Seog Kim, Christian Buske, Michinori Ogura, **Wojciech Jurczak**, Juan-Manuel Sancho, Edvard Zhavrid, and others
The Lancet Haematology, Vol. 4, No. 8, e362–e373 Published: July 13, 2017

Immunochemioterapia
Pozostaje standardem leczenia I rzutu

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CIRS wpływa na decyzje terapeutyczne

CIRS, ECOG

FCR
BR

Celem leczenia jest osiągnięcie długiego okresu remisji

BR, Ofatumomab-Chlorambucil

Celem leczenia jest kontrola choroby

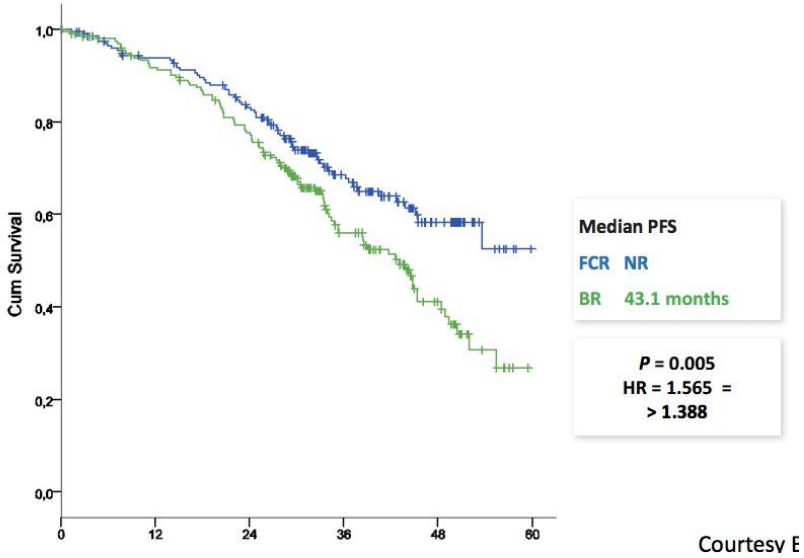
Nie

Celem leczenia jest łagodzenie objawów klinicznych

Goede V, Hallek M. *Drugs Aging 2011;*28,163-176.

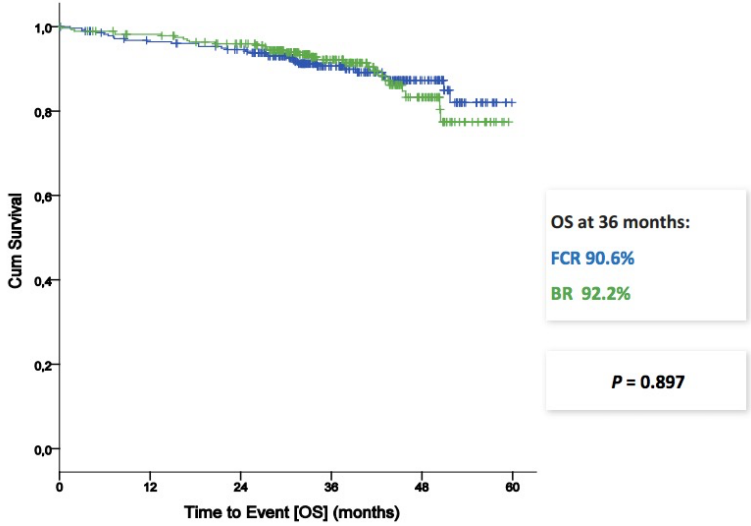
Badanie CLL-10 :
przeżycie wolne od zdarzeń (PFS) i całkowite (OS)

PFS



Courtesy E

OS



Eichhorst B et al., ASH 2014

Wybór schematu leczenia zależy od stanu chorego

	FCR	BR
Duration of follow up	✓	
ORR	✓	
CR	✓	
PFS	✓	
OS	✓	✓
Toxicity Profile		✓

Badanie CLL-10 : Zdarzenia niepożądane

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All Infections	**39.1**	**26.8**	**<0.001**
Infections during therapy only	22.6	17.3	0.1
Infections during first 5 months after therapy	11.8	3.6	<0.001
All infections in patients ≤ 65years	35.2	27.5	0.1
All infections in patients > 65years	**47.7**	20.6	<0.001

Hypoplazje szpiku po Fludarabinie > Bendamustynie

Eichhorst B et al., ASH 2014

Chłoniak grudkowy (FL) – leczenie I rzutu

INDUCTION

High tumor burden untreated follicular lymphoma

N=1217

→

Immunochemotherapy
8 x Rituximab
+
8 x CVP or
6 x CHOP or
6 x FCM

→

CR/CRu
PR

PD/SD
off study

MAINTENANCE

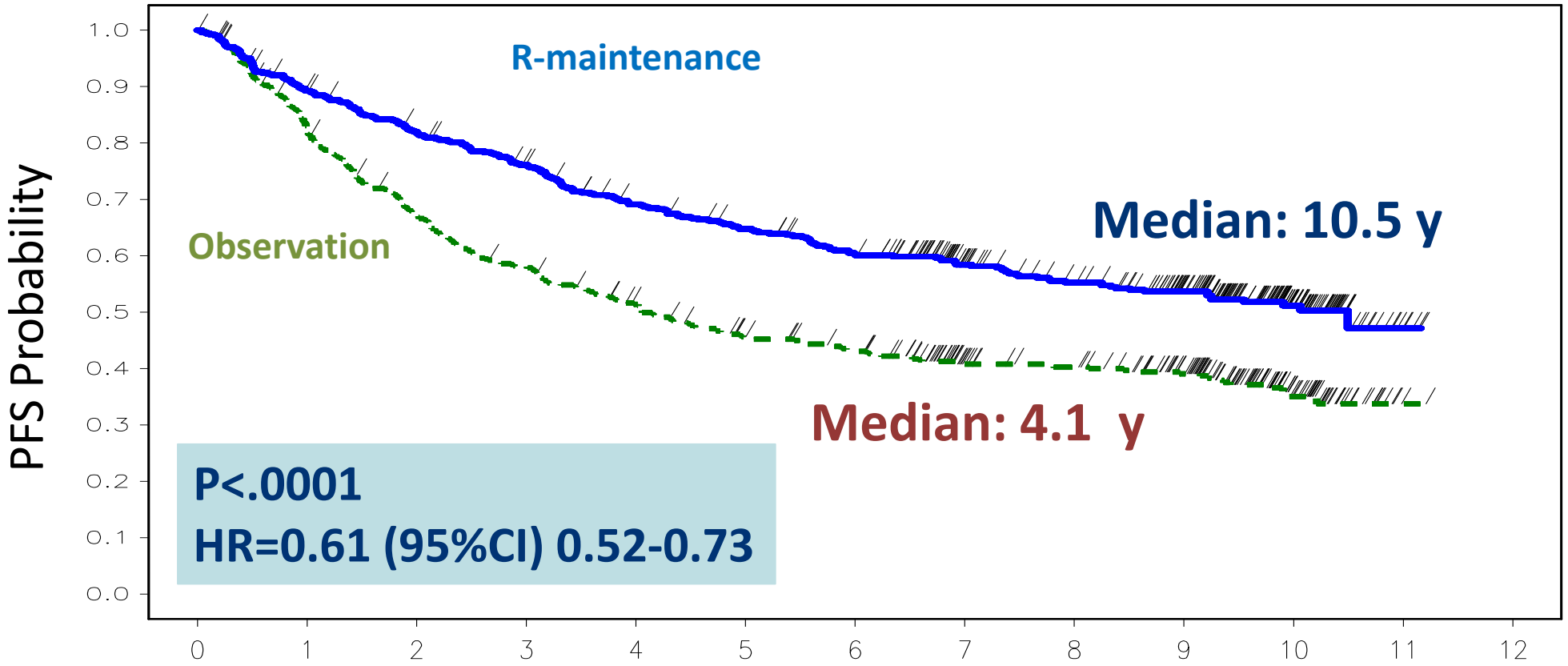
Rituximab maintenance
375 mg/m^2
every 8 weeks
for 2 years‡

Random 1:1*

Observation‡

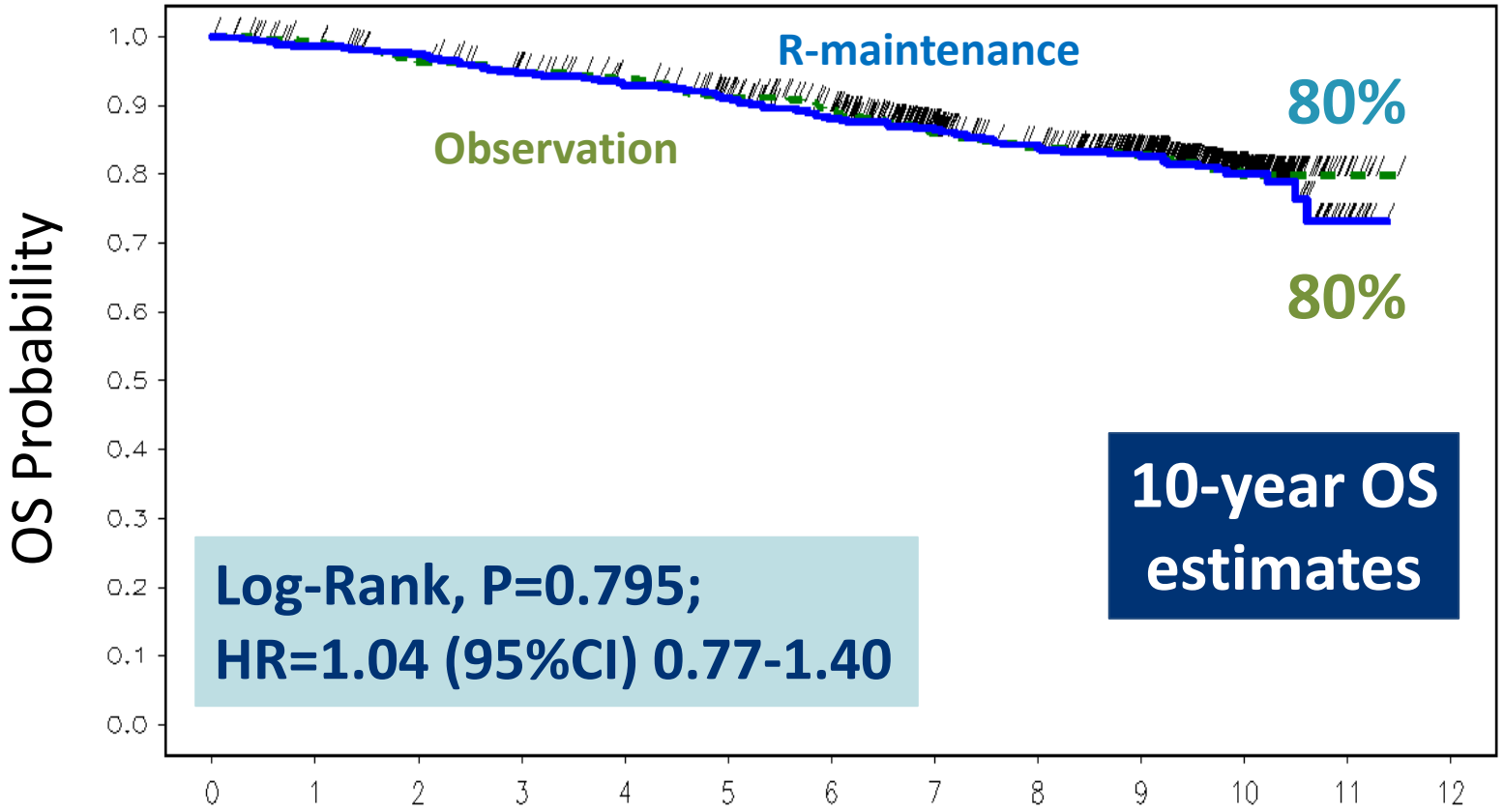
Salles et al., ASH 2017

PRIMA : Progression Free Survival at 10 years (from randomization)



No. left	0	1	2	3	4	5	6	7	8	9	10	11	12
Observation	513	415	336	290	251	217	200	155	147	122	41	1	0
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4	0

PRIMA : Overall Survival at 10 years (from randomization)



No. left													
Observation	513	501	485	472	460	440	412	319	297	256	91	8	0
Rituximab	505	492	480	464	449	432	407	341	313	261	107	8	0

Leczenie podtrzymujące Rytuksymabem

- Nie wydłuża OS
- Większa ilość AE (infekcje, wtórne procesy nowotworowe)
- Skuteczność Rituximabu w razie jego ponownego zastosowania
- Efektywność kosztowa

ASCO® Annual '16 Meeting

Leczenie podtrzymujące

Rytuksymab + chemioterapia jest postępowaniem z wyboru w FL

Mniejsza toksyczność (AE), Porównywalne OS

RR (zwłaszcza CR), PFS; potencjalnie rzadziej dochodzi do transformacji

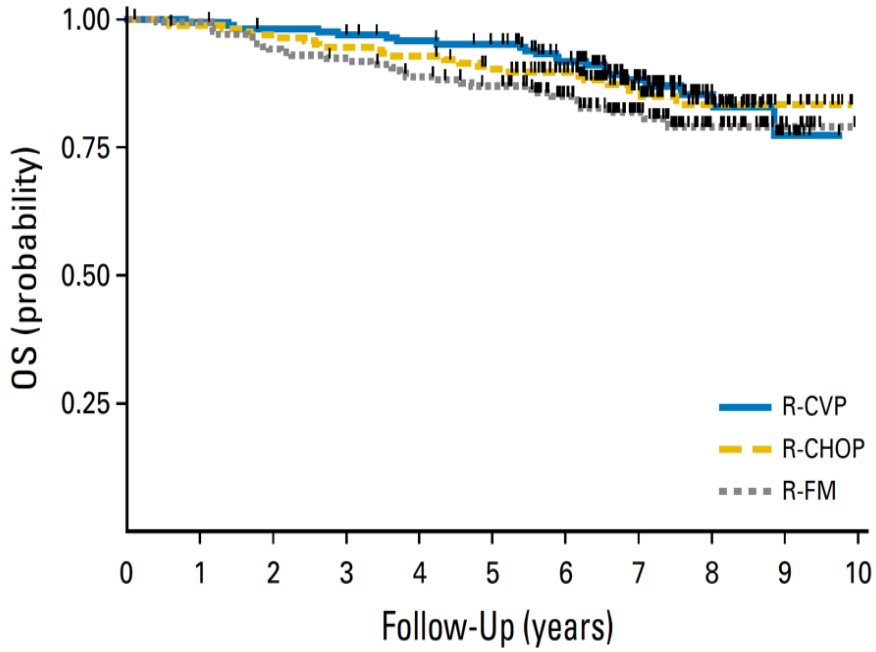
R-CVP

B-R

R-CHOP

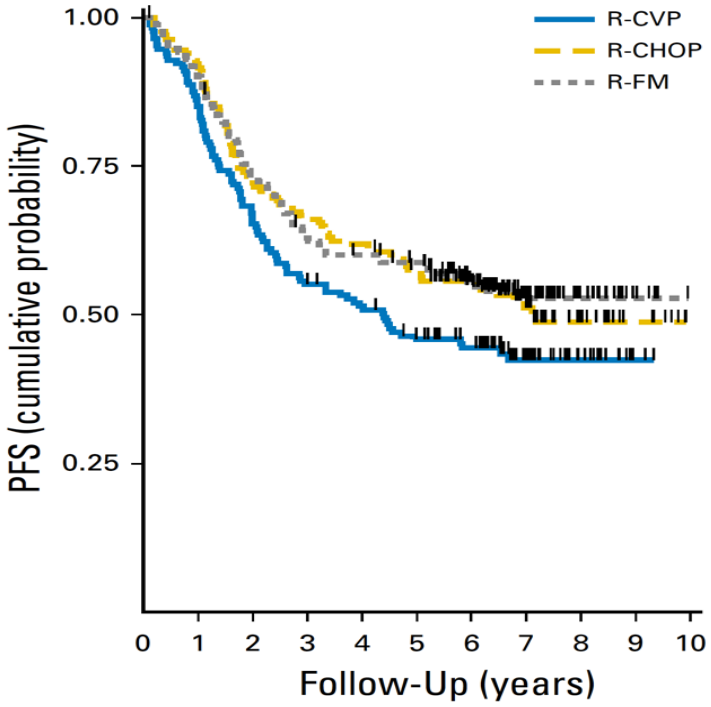
R-FC

Long-Term Results of the FOLL05 Trial (R-CVP vs R-CHOP vs R-FM)



No. at risk:

R-CVP	168	166	163	160	156	152	131	75	36	9	0
R-CHOP	165	162	159	155	152	144	126	76	42	13	0
R-FM	171	170	160	156	148	141	116	70	31	9	0



No. at risk:

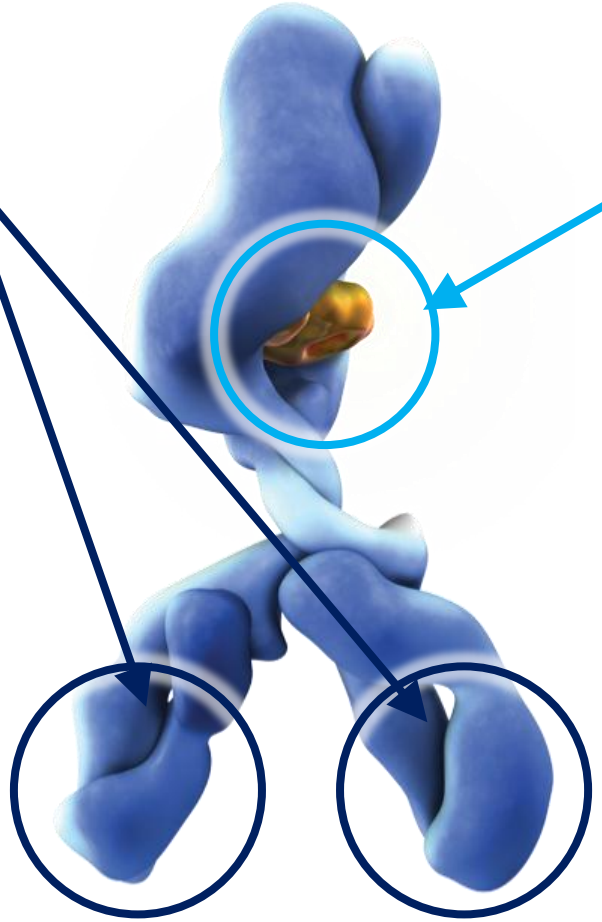
R-CVP	168	142	109	91	84	72	62	31	16	3	0
R-CHOP	165	152	119	109	102	92	76	46	20	8	0
R-FM	171	154	125	107	100	95	74	43	19	5	0

Luminari et al. JCO (2018)

Obinutuzumab

Przeciwciało typu II[5]

Śmierć komórki indukowana przez mAb aCD20 typu II zachodzi na **drodze nieapoptotycznej**, nie zależy od nadekspresji BCL-2 i aktywacji kaspaz



Region Fc wytworzony metodą glikoinżynierii[1]

Pozbawienie fukozy, co istotnie zwiększa powinowactwo MoAb do receptora FcγRIIIa na komórce efektorowej

1. Mössner E i wsp. Blood 2010; 4393-402;
5. Niederfellner G i wsp. Blood; 2011; 358-367

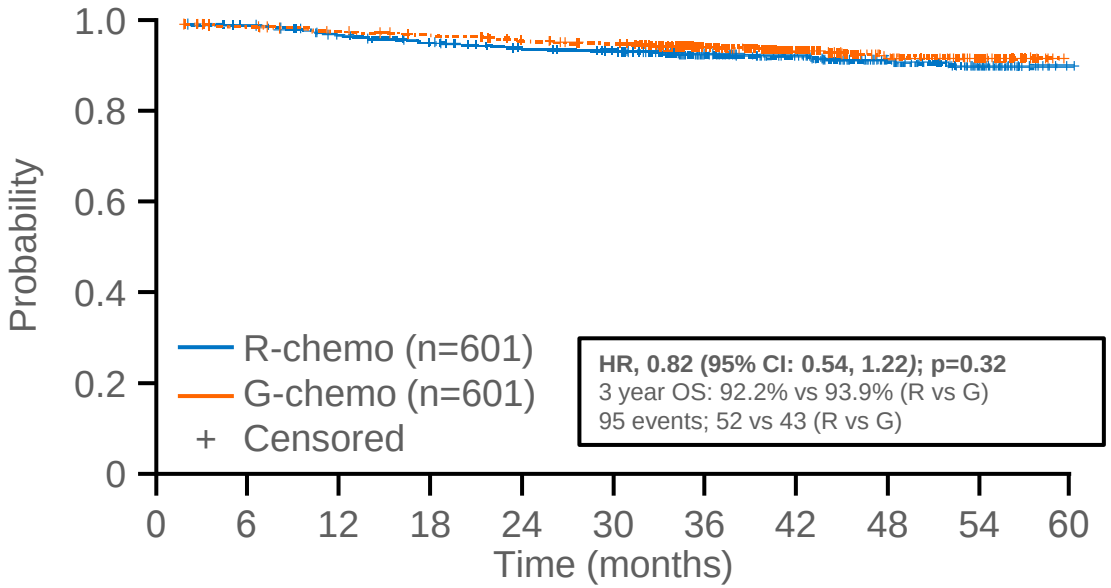
Chemotherapy May Be "A Great Equaliser" of Monoclonal Antibodies

Rituximab
Obinutuzumab
MOR 208 ?

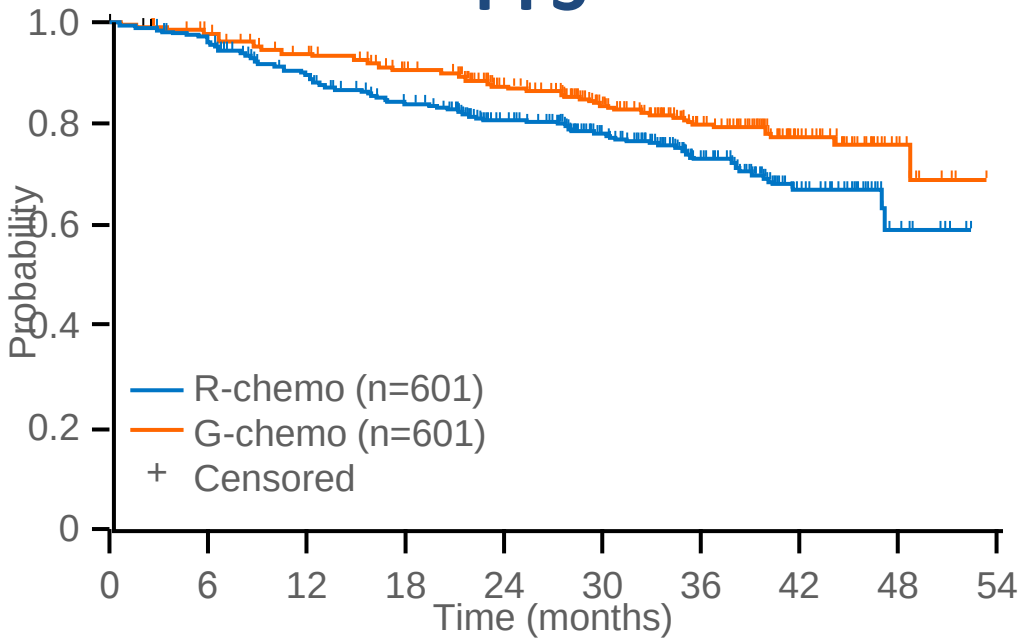
Unless it is CVP ?

OS in previously untreated elderly FL patients **(GALLIUM trial)**

OS



PFS



Marcus R, et al. N Engl J Med 2017;377:1331–44

The NEW ENGLAND JOURNAL of MEDICINE

- GALLIUM met its primary endpoint demonstrating a 34% reduction in the risk or PD/relapse or death for G-chemo vs R-chemo in FL patients

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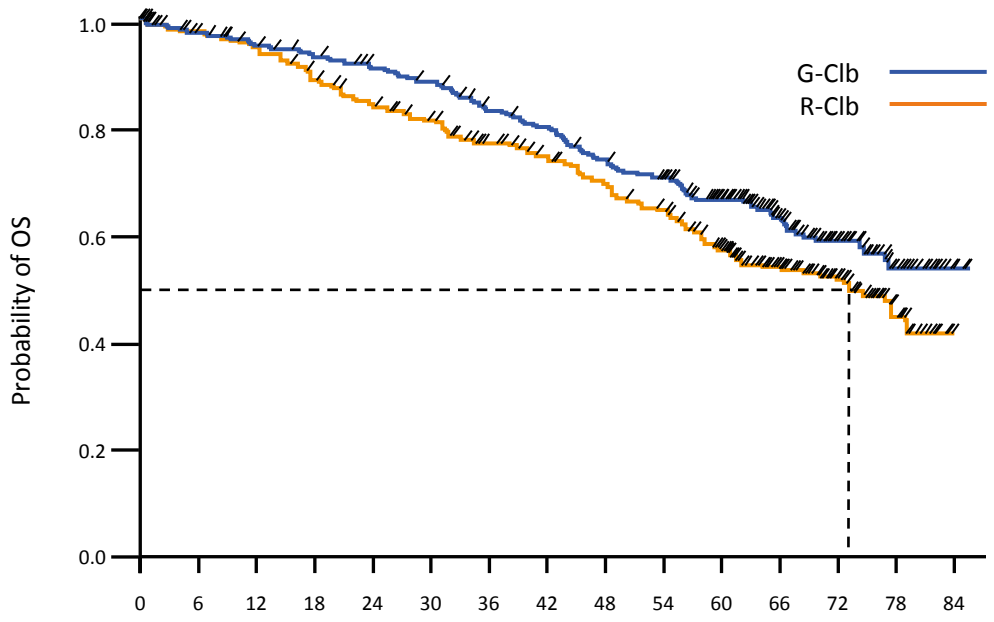
Chemotherapy May Be "A Great Equaliser" of Monoclonal Antibodies

Rituximab
Obinutuzumab
MOR 208 ?

Unless it is chlorambucil ?

OS in previously untreated elderly CLL patients **(CLL-11 trial)**



	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	121 (36.3)	147 (44.5)
5-year OS, % (95% CI)	66 (61–72)	57 (51–62)
Median OS, months	NR	73.1
HR (95% CI), p-value	0.76 (0.60–0.97), p=0.0245	

Median observation time: 59.4 months

Geode et al.: 2014

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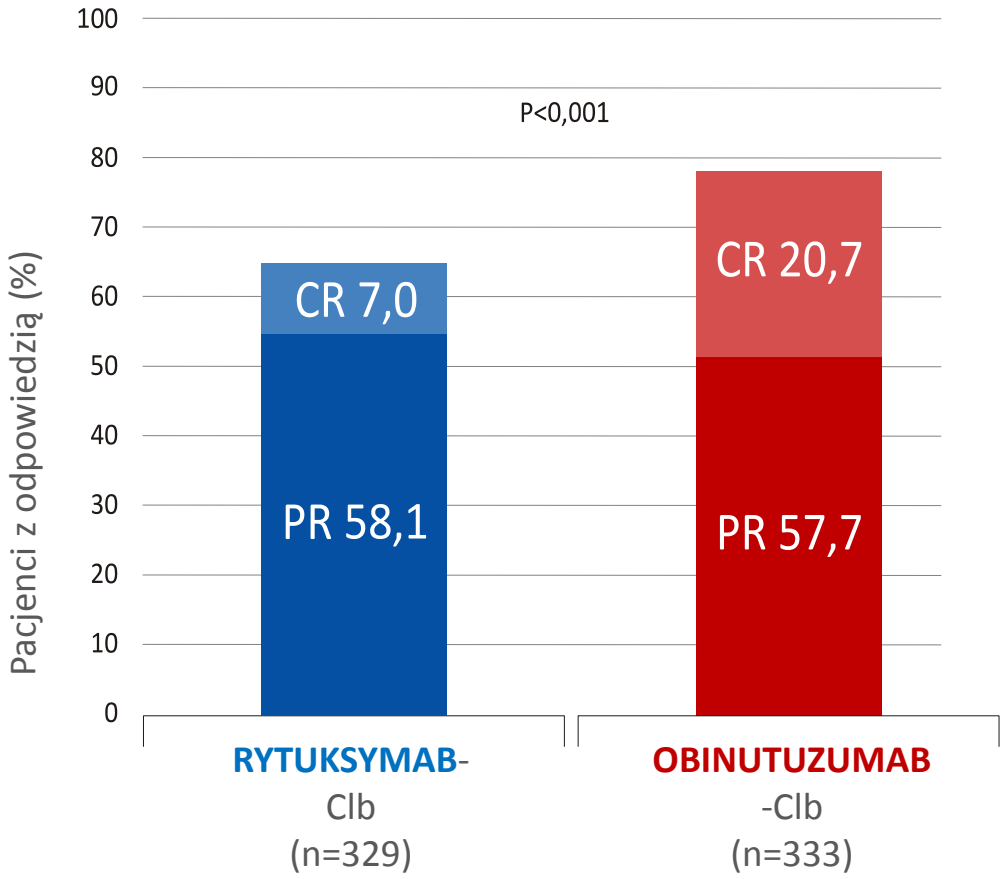
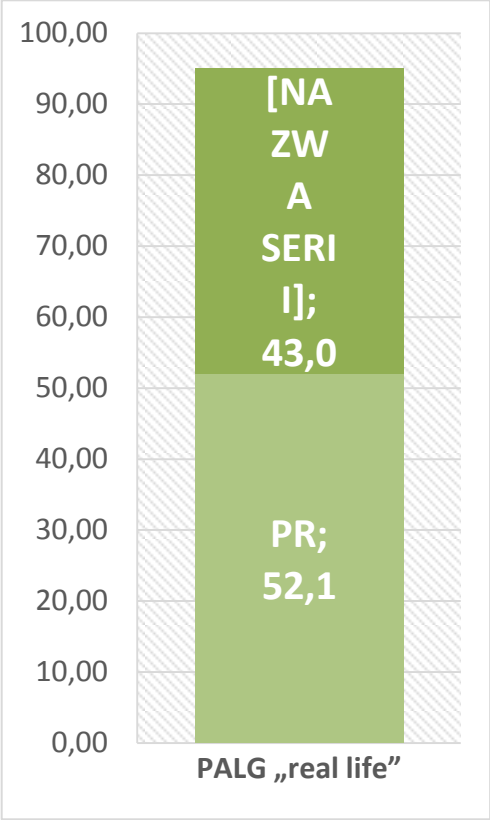
OBINUTUZUMAB W LECZENIU I LINII CLL – odpowiedź na leczenie





Długosz-Danecka et al., PAMW 2018

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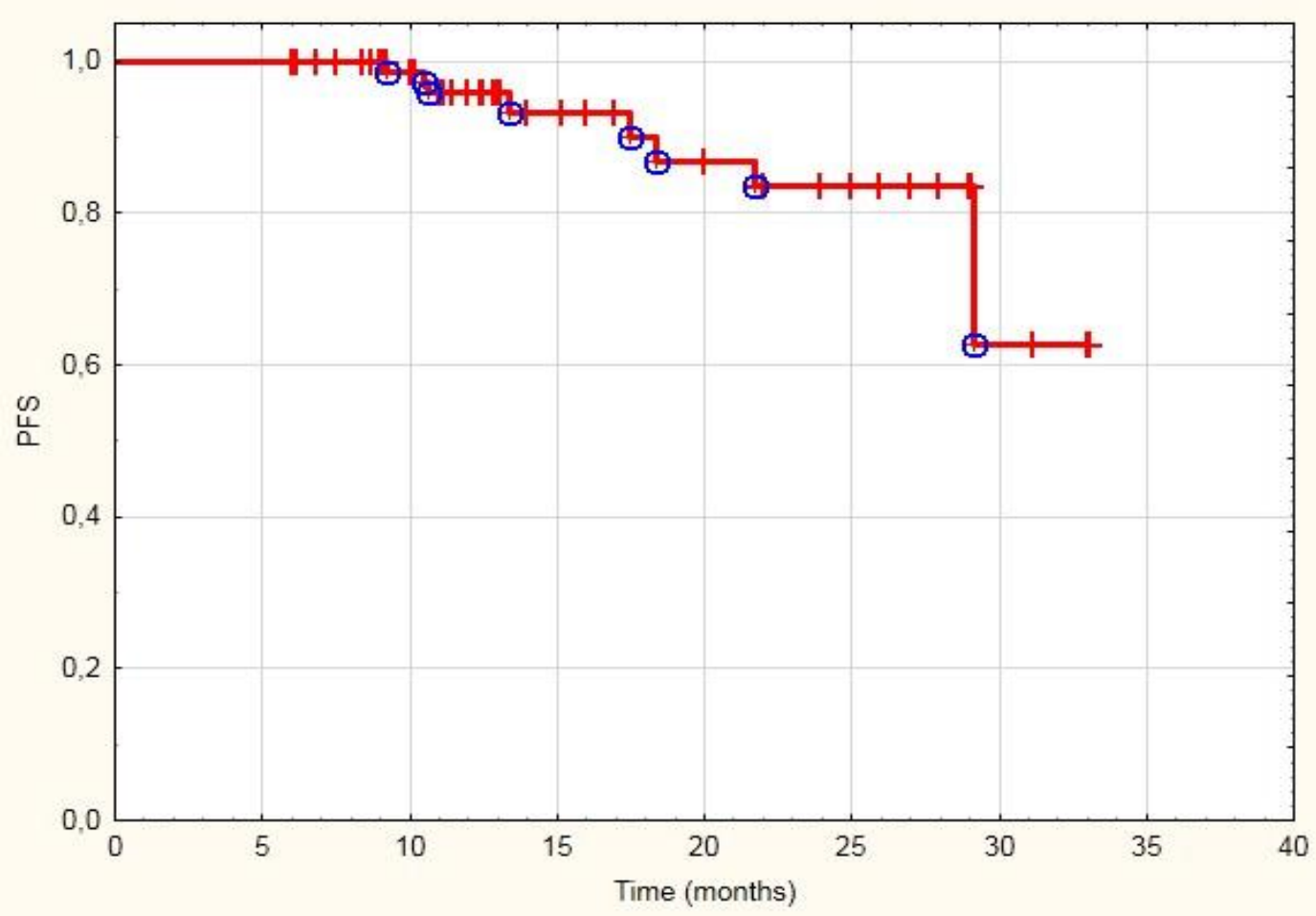
OBINUTUZUMAB W LECZENIU I LINII CLL – odpowiedź na leczenie

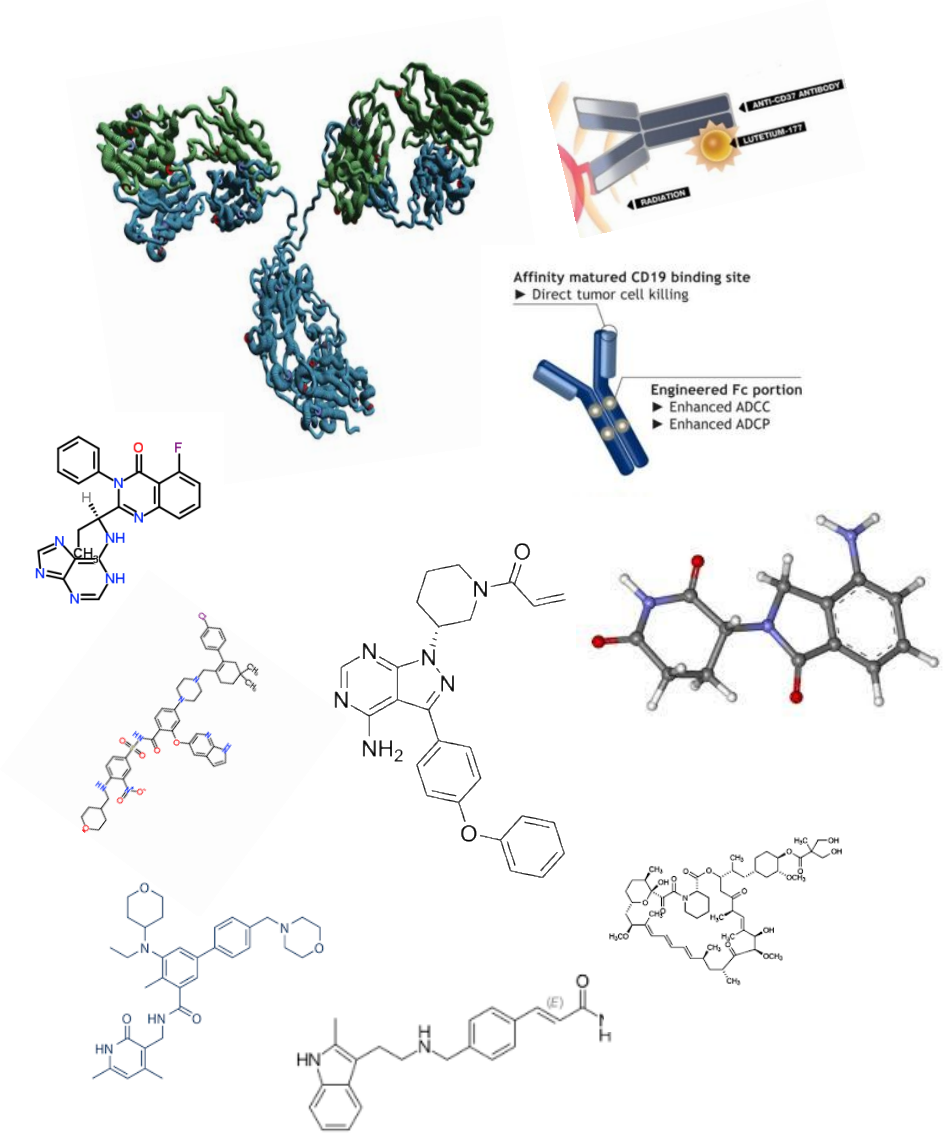


Mediana PFS – nie osiągnięto (mediana obserwacji 18 m-cy)

Szacowany PFS po 2 latach – 82%

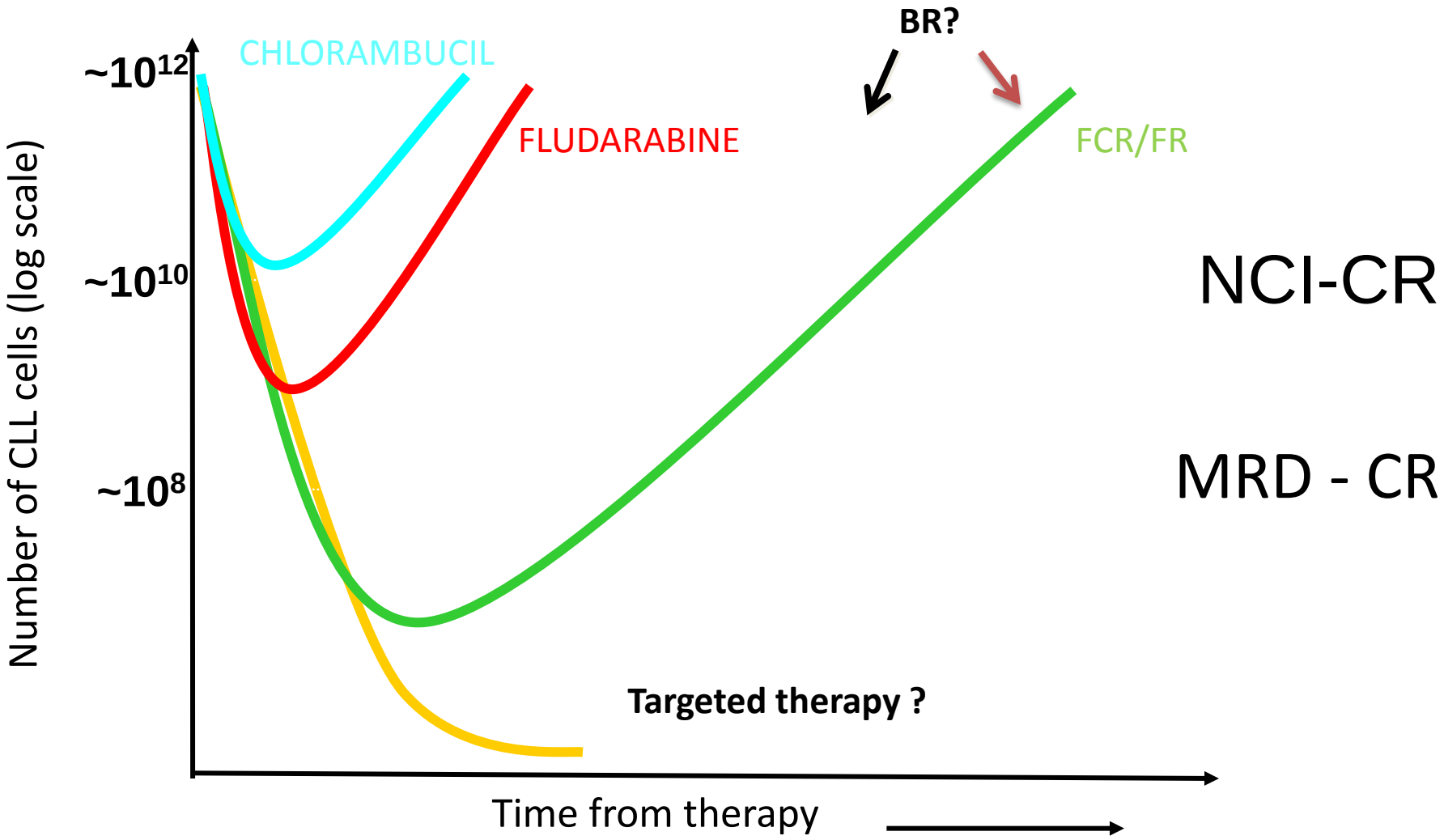
Długosz-Danecka et al., PAMW 2018

Potencjalna rola nowych leków w leczeniu iNHL



- **Alternatywny do cytostatyków mechanizm działania pozwala na przełamanie oporności R/R iNHL**
- **Inny profil toksyczności daje potencjalnie możliwość zastosowania w ciągu życia chorego większej liczby linii leczenia**
- **Szansa na większą ilość uzyskanych CR, dłuższy PFS i OS**
- **Wyleczenie iNHL ???**

Minimalna Choroba Resztkowa w CLL



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Częstość zaburzeń cytogenetycznych wzrasta w czasie trwania choroby

- Utrata lub mutacja genu kodującego p53
- Najgorzej rokująca grupa chorych z CLL
- Oporność na chemioterapię

Grupa chorych	Częstość del 17p /mutacji TP53
CLL przy rozpoznaniu	5% - 7% (17p-), 4 – 5% (TP53)
CLL po ≥1 linii leczenia	25% - 50% (17p-), 37% (TP53)
CLL we wznowie / oporności na Fludarabinę	40 - 50%

Hillmen P et al. *J Clin Oncol.* 2007;25:5616-5623; Hallek M, et al. *Lancet.* 2010;376:1164-1174; Grever MR, et al. *J Clin Oncol.* 2007;25:799-804; Oscier D, et al. *Haematologica.* 2010;95:1705-1712; Zenz T, et al. *Blood.* 2008;112:3322-3329; Zenz T, et al. *Blood.* 2009;114:2589-2597; Zenz T, et al. *J Clin Oncol.* 2010;28:4473-4479; Lozanski G, et al. *Blood.* 2004;103:3278-3281.

Idelalisib – wskazania rejestracyjne

R/R CLL: Idelalisib + Rituximab
CLL z del 17p, których nie można poddać immunochemioterapii : Idelalisib + Rituximab:
R/R FL: monoterapia

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Idelalisib – AE i SAE

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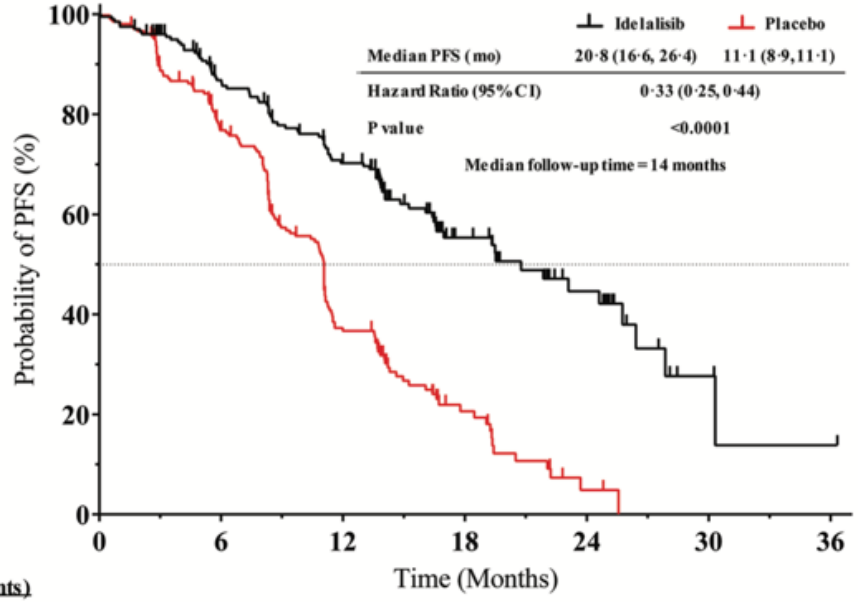
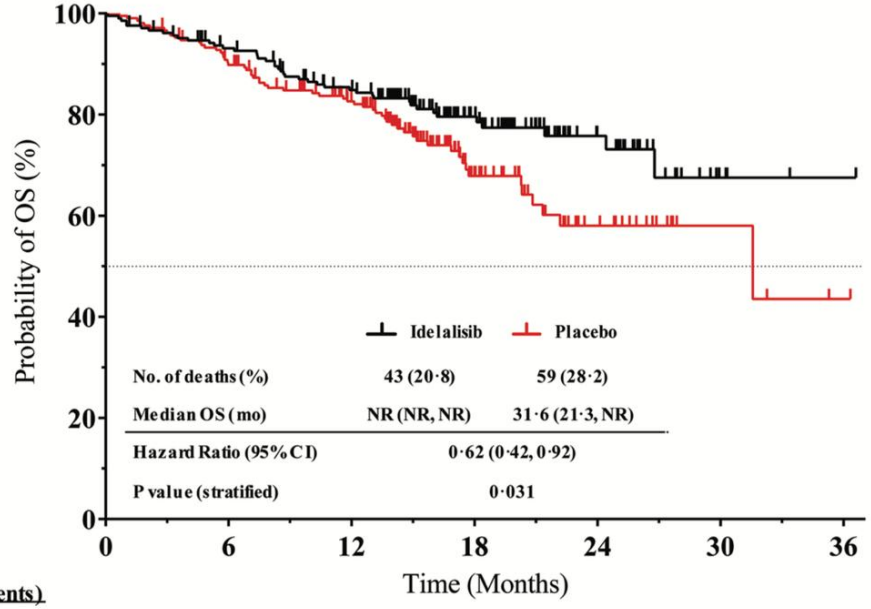
Idelalisib wydłuża PFS i OS u chorych z CLL we wznowie / oporności, leczonych BR



N at risk (events)							
Idelalisib + BR	207 (0)	156 (25)	118 (54)	40 (73)	18 (79)	3 (83)	1 (84)
Placebo + BR	209 (0)	146 (46)	63 (118)	16 (138)	2 (148)	0 (149)	0 (149)

N patients censored							
Idelalisib + BR	0	26	35	94	110	121	122
Placebo + BR	0	17	28	55	59	60	60



N at risk (events)							
Idelalisib + BR	207 (0)	184 (14)	158(30)	75(38)	29(41)	4(43)	1(43)
Placebo + BR	209 (0)	182 (21)	149(35)	51(53)	19(58)	4(58)	1(59)

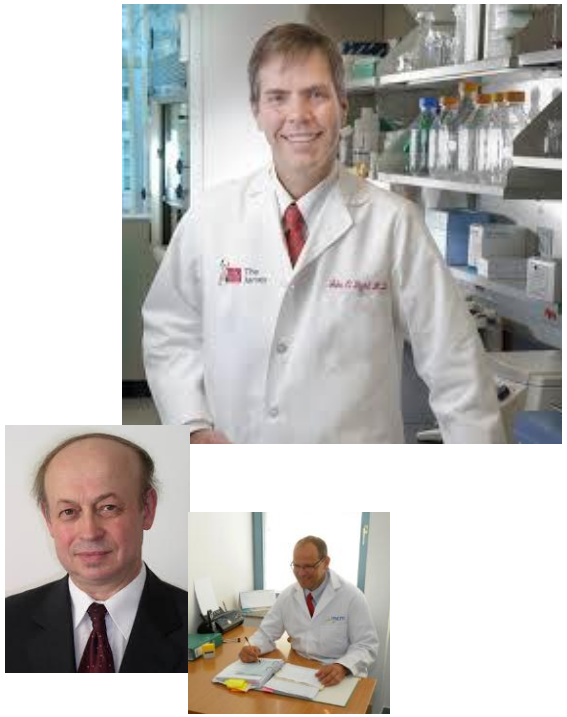
N patients censored							
Idelalisib + BR	0	9	19	94	137	160	163
Placebo + BR	0	6	25	105	132	147	149

2016 –Lancet Oncology, Zelenetz et al

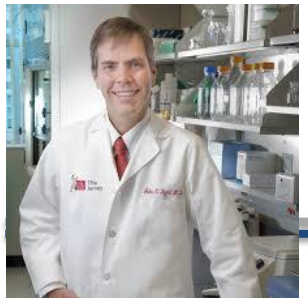
SAE – BR +/i Idelalisib

SAE	BR + Idelalisib, n (%)	BR - n (%)
Febrile neutropenia	**41 (20)**	**10 (5)**
Pneumonia	**29 (14)**	**15 (7)**
Pyrexia	**24 (12)**	**11 (5)**
Sepsis	**10 (5)**	**3 (1)**
Diarrhea	10 (5)	1 (1)
Neutropenia	9 (4)	3 (1)
Lower respiratory tract infection	**6 (3)**	**5 (2)**
Anemia	5 (2)	5 (2)
Neutropenic sepsis	**3 (1)**	**6 (3)**
Urinary tract infection	5 (2)	3 (1)
Pulmonary embolism	2 (1)	5 (2)
Respiratory tract infection	**2 (1)**	**5 (2)**
Abdominal pain	4 (2)	2 (1)
Bronchitis	1 (1)	5 (2)
Cough	**4 (2)**	**2 (1)**
Septic shock	**5 (2)**	**1 (1)**
Squamous cell carcinoma	1 (1)	5 (2)
Cellulitis	4 (2)	0
INFECTIONS	158(60%)	58 (27%)

Wskazania rejestracyjne Ibrutynibu



R/R MCL	Nov 2013
R/R CLL	Luty 2014
CLL z del 17 p	Lip 2014
Waldenstrom Makroglobulinemia	Sty 2015
CLL – starsi chorzy (leczenie I rzutu)	Mar 2016



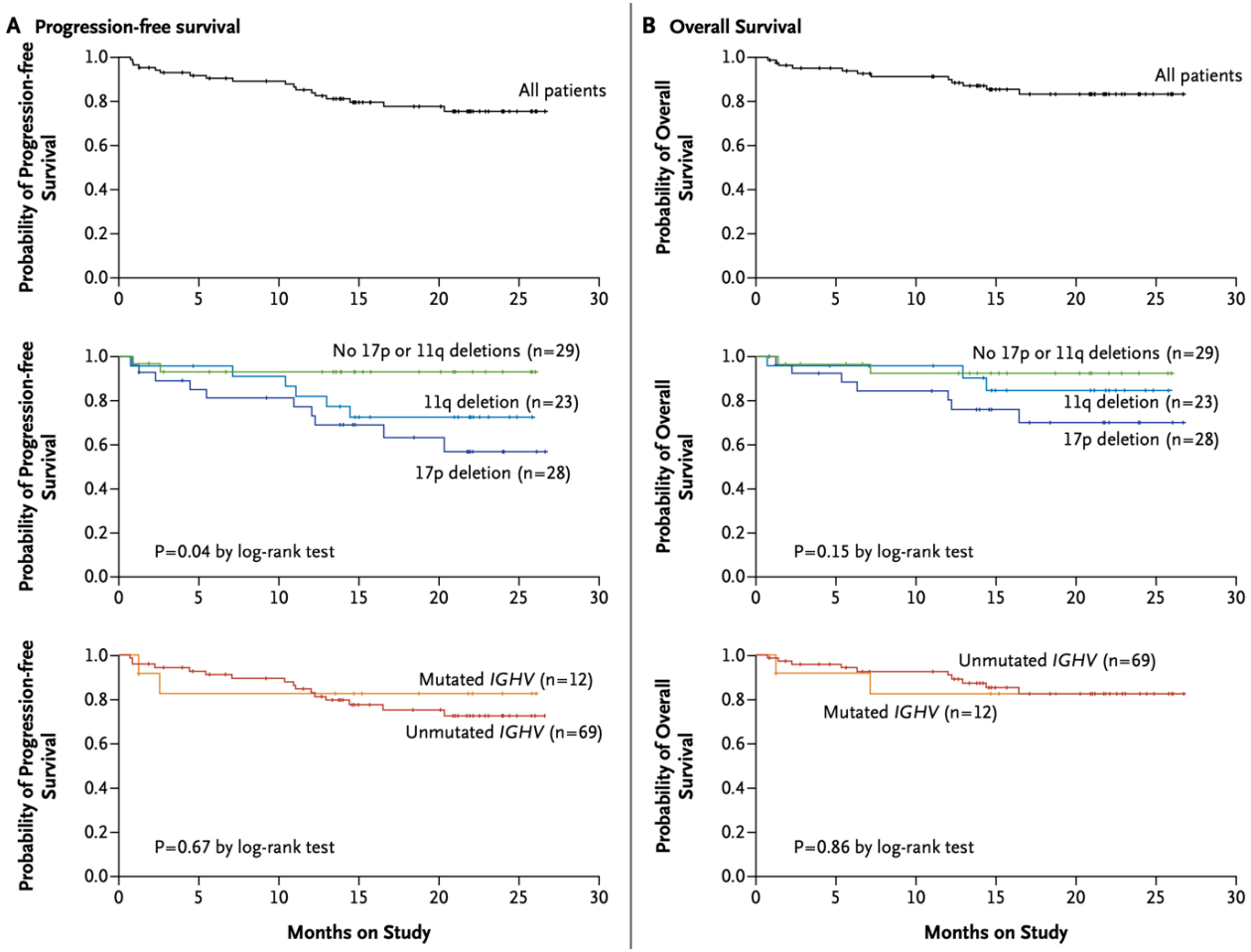
Ibrutynib w R/R CLL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.



Byrd et al., NEJM 2013

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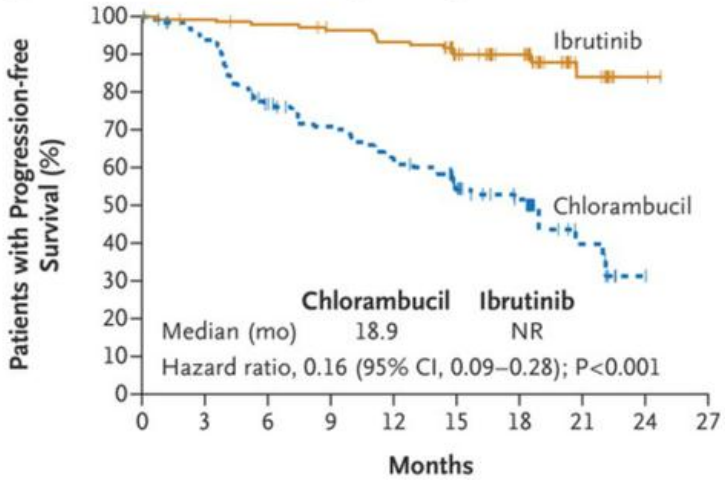
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

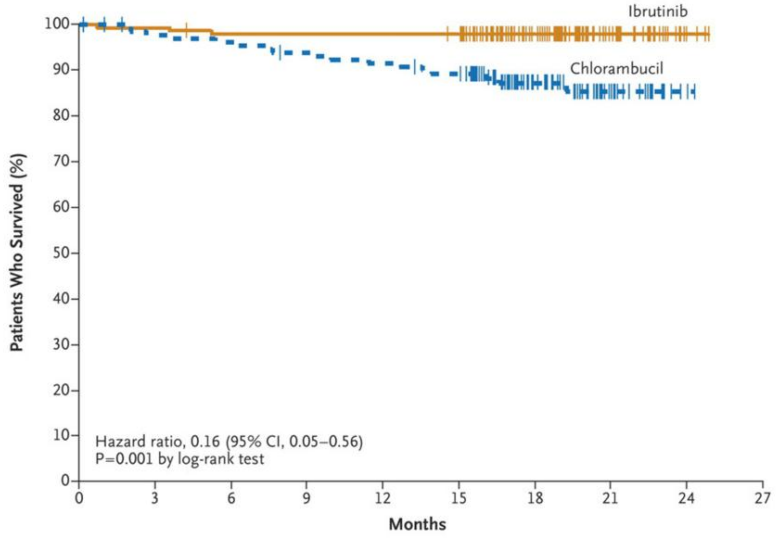
J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

A Progression-free Survival According to Independent Assessment



No. at Risk										
Ibrutinib	136	133	130	126	122	98	66	21	2	0
Chlorambucil	133	121	95	85	74	49	34	10	0	0

A Overall Survival



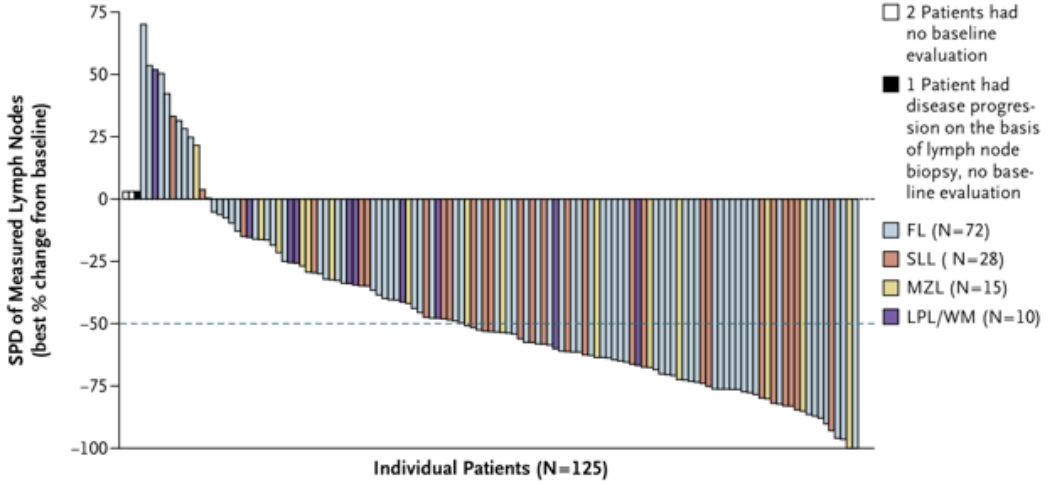
No. at Risk										
Ibrutinib	136	134	131	131	131	129	74	32	4	0
Chlorambucil	133	127	125	121	118	113	62	24	1	0

NEJM, Burger et al. 2016

Idelalisib vs Ibrutynib

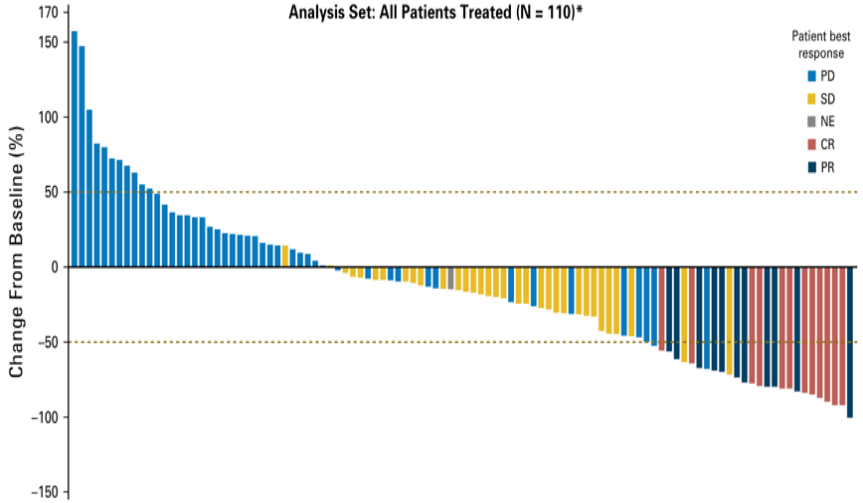
iNHL w Klinice Hematologii UJCM

Idelalisib in R/R iNHL



Gopal et al. NEJM 2014
Salles et al., Hematologica 2017

Ibrutynib in R/R iNHL



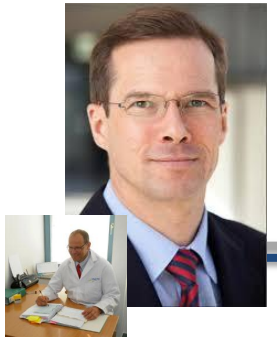
Gopal et al. JCO 2018

Polish Lymphoma Research Group

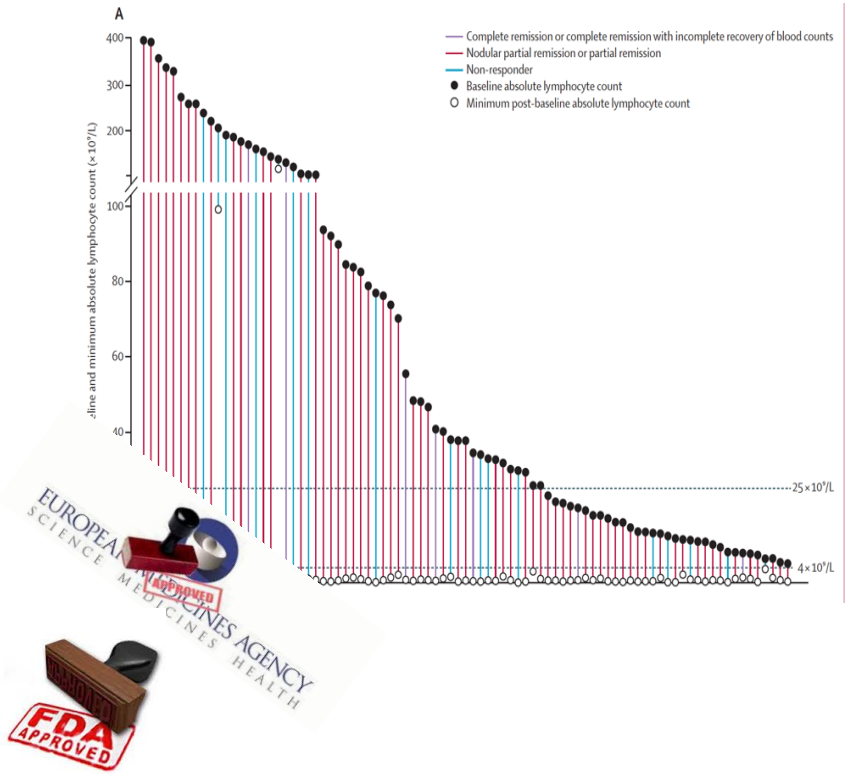
Idelalisib vs Ibrutynib

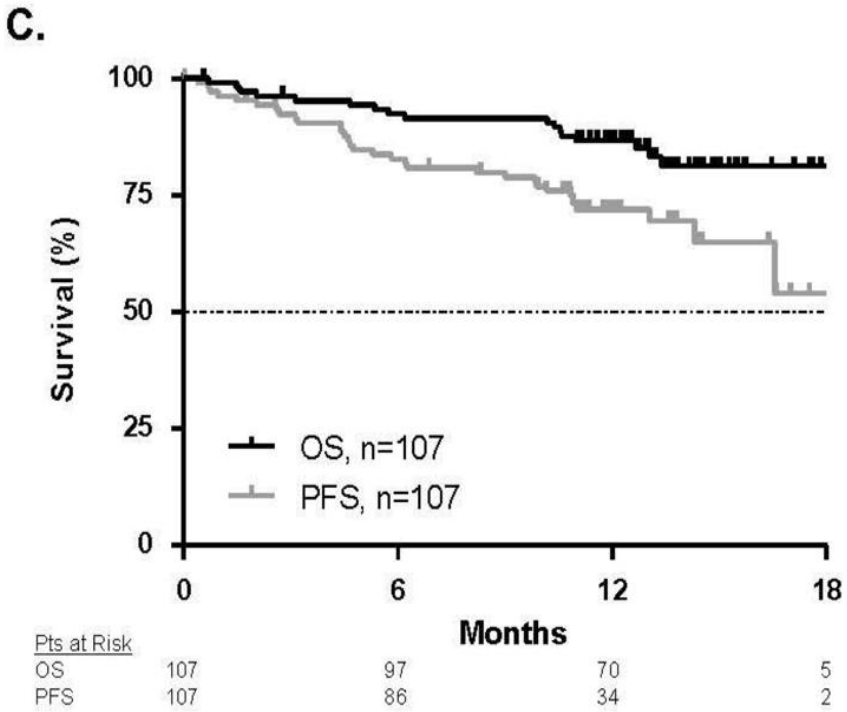
Idelalisib	Ibrutynib
Monoterapia w iNHL, W skojarzeniu z Rituximabem w CLL	Monoterapia
Infekcje	Trudność u chorych z lekami p-zakrzepowymi Kardiotoksyczność
iNHL, R/R CLL I rzut CLL (del1/MUTp53)	R/R CLL I rzut CLL (del 17p/MUTp53) I rzut CLL (chorzy starsi) R/R MCL WM

Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study



Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Steven Coutre, John F Seymour, Talha Munir, Soham D Puvvada, Clemens-Martin Wendtner, Andrew W Roberts, Wojciech Jurczak, Stephen P Mulligan, Sebastian Böttcher, Mehrdad Mobasher, Ming Zhu, Monali Desai, Brenda Chyla, Maria Verdugo, Sari Heitner Enschede, Elisa Cerri, Rod Humerickhouse, Gary Gordon, Michael Hallek, William G Wierda





2016 – Stilgenbauer et al., Lancet Oncology

Polish Lymphoma Research Group

iNHL w Klinice Hematologii UJCM

Radioimmunotherapy Confers Long-Term Survival to Lymphoma Patients with Acceptable Toxicity: Registry Analysis by the International Radioimmunotherapy Network

Karin Hohloch[1], Angelika Bischof Delaloye[2], Christiane Windemuth-Kieselbach[3], Jose Gómez-Codina[4], Werner Linkesch[5], Wojciech Jurczak[6], Roberto Cacchione[7], Cheolwon Suh[8], Pier Luigi Zinzani[9], and Lorenz Trümper[1]

[1]Göttingen Comprehensive Cancer Center, Georg August University, Göttingen, Germany; [2]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [3]Alcedis GmbH, Independent CRO, Giessen, Germany; [4]Hospital Univeristario La Fe, Valencia, Spain; [5]Klinische Abteilung für Hämatologie, Medical University Graz, Graz, Austria; [6]Department of Haematology, Jagiellonian University, Cracow, Poland; [7]CEMIC, Centro de Educación, Médica e Investigaciones Clínical, Norberto Quirno, Buenos Aires, Argentina; [8]Ulsan College of Medicine, Seoul, Korea; and [9]Istituto di Ematologia e Oncologia Medica, Università di Bologna, Bologna, Italy

The Radioimmunotherapy Network (RIT-N) is a Web-based, international registry collecting long-term observational data about radioimmunotherapy-treated patients with malignant lymphoma outside randomized clinical studies. The RIT-N collects unbiased data on treatment indications, disease stages, patients' conditions, lymphoma subtypes, and hematologic side effects of radioimmunotherapy treatment. **Methods:** RIT-N is located at the University of Göttingen, Germany, and collected data from 14 countries. Data were entered by investigators into a Web-based central database managed by an independent clinical research organization. **Results:** Patients (1,075) were enrolled from December 2006 until November 2009, and 467 patients with an observation time of at least 12 mo were included in the following analysis. Diagnoses were as follows: 58% follicular lymphoma and 42% other B-cell lymphomas. The mean overall survival was 28 mo for follicular lymphoma and 26 mo for other lymphoma subtypes. Hematotoxicity was mild for hemoglobin (World Health Organization grade II), with a median nadir of 10 g/dL, but severe (World Health Organization grade III) for platelets and leukocytes, with a median nadir of 7,000/μL and 2.2/μL, respectively. **Conclusion:** Clinical usage of radioimmunotherapy differs from the labeled indications and can be assessed by this registry, enabling analyses of outcome and toxicity data beyond clinical trials. This analysis proves that radioimmunotherapy in follicular lymphoma and other lymphoma subtypes is a safe and efficient treatment option.

Key Words: B-cell lymphoma; radioimmunotherapy; registry; treatment; RIT-Network

J Nucl Med 2011; 52:1354–1360
DOI: 10.2967/jnumed.111.089920

Radioimmunotherapy is a highly lymphoma-specific therapeutic approach with low side effects and a good tolerability established in the treatment of relapsed follicular lymphoma (FL) and in consolidation after first-line treatment (*1*). The current standard first-line therapy for FL patients in limited stage consists of involved-field radiation, with a local control rate of 95% and disease-free and overall survival (OS) rates of 37%–94% and 40%–93%, respectively (*2*). In advanced stages, however, FL is deemed incurable by conventional therapy. For asymptomatic patients with advanced-stage FL, watchful waiting is the recommended strategy, whereas for symptomatic patients a variety of single-agent or multiagent chemotherapy options with high response rates are available. The introduction of rituximab, a monoclonal anti-CD20 antibody, when combined with different chemotherapy regimens resulted in a significant superior treatment outcome, compared with chemotherapy alone (*3,4*). Relapses after conventional therapies are frequent, and subsequent treatment approaches are usually hampered by decreased response rates and shorter durations of remission with each successive treatment (*5,6*).

The introduction of radioimmunotherapy in 1993 provided a new and effective treatment option for FL patients. The active principle of radioimmunotherapy in lymphoma is the targeting of lymphoma cells by highly specific antibodies labeled with radioactive isotopes acting primarily by killing lymphoma cells via emission of β-particles

THE LANCET Haematology

Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study

Wojciech Jurczak, Akira Moreno, Govind Babu Kanakasetty, Eduardo Munhoz, Maria Asuncion Echeverte, Pattyosh Gil, Nelson Castro, Juliana Pereira, Luisa Akira, Sergey Alexeev, Eugeny Osmanov, Peijuan Zhu, Sypka Alexandrova, Angela Zubel, Olaf Hiehle, Jutta Amendorffer

Summary

Background GP2013 is a rituximab biosimilar developed to stringent development guidelines, including non-clinical and preclinical investigations and clinical trials in rheumatoid arthritis and follicular lymphoma. We aimed to compare the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of GP2013 plus cyclophosphamide, vincristine, and prednisone (GP2013-CVP) with rituximab-CVP (R-CVP) in patients with follicular lymphoma.

Methods In this phase 3, multinational, double-blind, randomised, controlled trial, adults (aged 18 years or older) with previously untreated, advanced stage (Ann Arbor stage III or IV) follicular lymphoma of WHO histological grades 1, 2, or 3a were randomly assigned (1:1) using interactive response technology to eight cycles of GP2013-CVP or R-CVP (combination phase), followed by monotherapy maintenance in responders for a 2-year period. Randomisation was stratified by Follicular Lymphoma International Prognostic Index risk group and geographic region. The primary endpoint was comparability in overall response, with equivalence concluded if the entire 95% CI was within a margin of –12% to 12%. The primary endpoint was analysed using the per-protocol set, which included all patients who received at least one (partial or complete) dose of investigational treatment and who did not have any major protocol deviations. The trial is registered with ClinicalTrials.gov, number NCT01419665, and is ongoing.

Findings Between Dec 1, 2011, and Jan 15, 2015, 858 patients were screened for eligibility. 314 patients were randomly assigned to GP2013, of whom 312 were given GP2013, and 315 were assigned to reference rituximab. Median follow-up was 11·6 months (IQR 5·8–18·2) for the primary analysis. The primary endpoint, equivalence of overall response, was met (271 [87%] of 311 patients with GP2013 and 274 [88%] of 313 patients with reference rituximab achieved an overall response; difference –0·40%; 95% CI –5·94 to 5·14). Occurrence of adverse events and serious adverse events was similar between the treatment groups (289 [93%] of 312 patients in the GP2013-CVP group had an adverse event and 71 [23%] of 312 patients had a serious adverse event; 288 [91%] of 315 patients in the R-CVP group had an adverse event and 63 [20%] had a serious adverse event). The most common adverse event was neutropenia (80 [26%] of 312 patients in the GP2013-CVP group and 93 [30%] of 315 patients in the R-CVP group in the combination phase and 23 [10%] of 231 patients in the GP2013-CVP group and 13 [6%] of 218 patients in the R-CVP group in the maintenance phase). The most common grade 3 or 4 adverse event during the combination and maintenance phase was neutropenia (55 [18%] of 312 patients in the GP2013-CVP group and 65 [21%] of 315 patients in the R-CVP group in the combination phase and 17 [7%] of 231 patients in the GP2013-CVP group and nine [4%] of 231 patients in the R-CVP group in the maintenance phase). The occurrence of anti-drug antibodies was similar in the treatment groups (five [2%] of 268 patients in the GP2013-CVP; three [1%] in the R-CVP group).

Interpretation Our results show that GP2013 represents a viable rituximab biosimilar candidate for patients with previously untreated advanced follicular lymphoma. The introduction of biosimilars provides additional therapeutic options with potential to increase access to effective and life-saving biological therapies such as rituximab.

THE LANCET Haematology

Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial

Won Seog Kim, Christian Buske, Michinori Ogura, Wojciech Jurczak, Juan-Manuel Sancho, Edvard Zhavrid, Jin Seok Kim, José-Ángel Hernández-Rivas, Aliaksandr Prokharau, Mariana Vasilica, Rajinish Nagarkar, Dzhelil Osmanov, Larry W Kwak, Sang Joon Lee, Sung Young Lee, Yun Ju Bae, Bertrand Coiffier

Summary

Background Studies in patients with rheumatoid arthritis have shown that the rituximab biosimilar CT-P10 (Celltrion, Incheon, South Korea) has equivalent efficacy and pharmacokinetics to rituximab. In this phase 3 study, we aimed to assess the non-inferior efficacy and pharmacokinetic equivalence of CT-P10 compared with rituximab, when used in combination with cyclophosphamide, vincristine, and prednisone (CVP) in patients with newly diagnosed advanced-stage follicular lymphoma.

Methods In this ongoing, randomised, double-blind, parallel-group, active-controlled study, patients aged 18 years or older with Ann Arbor stage III–IV follicular lymphoma were assigned 1:1 to CVP plus intravenous infusions of 375 mg/m² CT-P10 or rituximab on day 1 of eight 21-day cycles. Randomisation was done by the investigators using an interactive web or voice response system and a computer-generated randomisation schedule, prepared by a clinical research organisation. Randomisation was balanced using permuted blocks and was stratified by country, gender, and Follicular Lymphoma International Prognostic Index score (0–2 *vs* 3–5). Study teams from the sponsor and clinical research organisation, investigators, and patients were masked to treatment assignment. The study was divided into two parts: part 1 assessing equivalence of pharmacokinetics (in the pharmacokinetics subset), and part 2 assessing efficacy in all randomised patients (patients from the pharmacokinetics subset plus additional patients enrolled in part 2). Equivalence of pharmacokinetics was shown if the 90% CIs for the geometric mean ratio of CT-P10 to rituximab in AUCτ and $C_{max ss}$ were within the bounds of the equivalence margin of 80% and 125%. Non-inferiority of response was shown if the one-sided 97·5% CI lay on the positive side of the –7% margin, using a one-sided test done at the 2·5% significance level. The primary efficacy endpoint was the proportion of patients who had an overall response over eight cycles and was assessed in the efficacy population (all randomised patients). The primary pharmacokinetic endpoints were area under the serum concentration–time curve at steady state (AUCτ) and maximum serum concentration at steady state ($C_{max ss}$) at cycle 4, assessed in the pharmokinetic population. This trial is registered with ClinicalTrials.gov, number NCT02162771.

Findings Between July 28, 2014, and Dec 29, 2015, 140 patients were enrolled. Here we report data for the eight-cycle induction period, up to week 24. The proportion of patients with an overall response in the efficacy population was 64 (97·0%) of 66 patients in the CT-P10 treatment group and 63 (92·6%) of 68 patients in the rituximab treatment group (4·3%; one-sided 97·5% CI –4·25), which lay on the positive side of the predefined non-inferiority margin. The ratio of geometric least squares means (CT-P10/rituximab) was 102·25% (90% CI 94·05–111·17) for AUCτ and 100·67% (93·84–108·00) for $C_{max ss}$, with all CIs within the bioequivalence margin of 80–125%. Treatment-emergent adverse events were reported for 58 (83%) of 70 patients in the CT-P10 treatment group and 56 (80%) of 70 in the rituximab treatment group. The most common grade 3 or 4 treatment-emergent adverse event in each treatment group was neutropenia (grade 3, 15 [21%] of 70 patients in the CT-P10 group and seven [10%] of 70 patients in the rituximab group). The proportion of patients who experienced at least one treatment-emergent serious adverse event was 16 (23%) of 70 patients in the CT-P10 group and nine (13%) of 70 patients in the rituximab group.

Interpretation In this study, we show that CT-P10 exhibits non-inferior efficacy and pharmacokinetic equivalence to rituximab. The safety profile of CT-P10 was comparable to that of rituximab. CT-P10 might represent a new therapeutic option for advanced-stage follicular lymphoma.

Funding Celltrion, Inc.

NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D., Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S., Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D., Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

ABSTRACT

BACKGROUND

Phosphatidylinositol-3-kinase delta (PI3Kδ) mediates B-cell receptor signaling and microenvironmental support signals that promote the growth and survival of malignant B lymphocytes. In a phase 1 study, idelalisib, an orally active selective PI3Kδ inhibitor, showed antitumor activity in patients with previously treated indolent non-Hodgkin's lymphomas.

METHODS

In this single-group, open-label, phase 2 study, 125 patients with indolent non-Hodgkin's lymphomas who had not had a response to rituximab and an alkylating agent or had had a relapse within 6 months after receipt of those therapies were administered idelalisib, 150 mg twice daily, until the disease progressed or the patient withdrew from the study. The primary end point was the overall rate of response; secondary end points included the duration of response, progression-free survival, and safety.

RESULTS

The median age of the patients was 64 years (range, 33 to 87); patients had received a median of four prior therapies (range, 2 to 12). Subtypes of indolent non-Hodgkin's lymphoma included follicular lymphoma (72 patients), small lymphocytic lymphoma (28), marginal-zone lymphoma (15), and lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia (10). The response rate was 57% (71 of 125 patients), with 6% meeting the criteria for a complete response. The median time to a response was 1.9 months, the median duration of response was 12.5 months, and the median progression-free survival was 11 months. Similar response rates were observed across all subtypes of indolent non-Hodgkin's lymphoma, though the numbers were small for some categories. The most common adverse events of grade 3 or higher were neutropenia (in 27% of the patients), elevations in aminotransferase levels (in 13%), diarrhea (in 13%), and pneumonia (in 7%).

CONCLUSIONS

In this single-group study, idelalisib showed antitumor activity with an acceptable safety profile in patients with indolent non-Hodgkin's lymphoma who had received extensive prior treatment. (Funded by Gilead Sciences and others; ClinicalTrials.gov number, NCT01282424.)

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

Ibrutinib as Treatment for Patients With Relapsed/Refractory Follicular Lymphoma: Results From the Open-Label, Multicenter, Phase II DAWN Study

Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Rajendra N. Damle, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, and Gilles Salles

ABSTRACT

Purpose
The Bruton's tyrosine kinase inhibitor ibrutinib has demonstrated clinical activity in B-cell malignancies. The DAWN study assessed the efficacy and safety of single-agent ibrutinib in chemoimmunotherapy relapsed/refractory follicular lymphoma (FL) patients.

Methods
DAWN was an open-label, single-arm, phase II study of ibrutinib in patients with FL with two or more prior lines of therapy. Patients received ibrutinib 560 mg daily until progressive disease/unacceptable toxicity. The primary objective was independent review committee–assessed overall response rate (ORR; complete response plus partial response). Exploratory analyses of T-cell subsets in peripheral blood (baseline/cycle 3) and cytokines/chemokines (baseline/cycle 2) were performed for available samples.

Results
Between March 2013 and May 2016, 110 patients with a median of three prior lines of therapy were enrolled. At median follow-up of 27.7 months, ORR was 20.9% (95% CI, 13.7% to 29.7%, which did not meet the 18% lower-bound threshold for the primary end point). Twelve patients achieved a complete response (11%; 95% CI, 5.8% to 18.3%). Median duration of response was 19.4 months (range, 1 to ≥ 33 months), with a median progression-free survival of 4.6 months and a 30-month overall survival of 61% (95% CI, 0.51% to 0.70%). Lymphoma symptoms resolved in 67%. Seven of 32 patients who experienced initial radiologic progression responded upon continuing therapy (pseudoprogression). The most common adverse events were diarrhea, fatigue, cough, and muscle spasms; 48.2% of patients reported serious adverse events. In patients who experienced a response, regulatory T cells were downregulated at C3D1 ($P = .02$), and Th1-promoting (antitumor) cytokines interferon-γ and interleukin-12 increased ($P \leq .035$).

Conclusion
With an ORR of 20.9%, ibrutinib failed to meet its primary efficacy end point in chemoimmunotherapy in patients with relapsed/refractory FL, although responses were durable and associated with a reduction in regulatory T cells and increases in proinflammatory cytokines.

EHA EUROPEAN HEMATOLOGY ASSOCIATION

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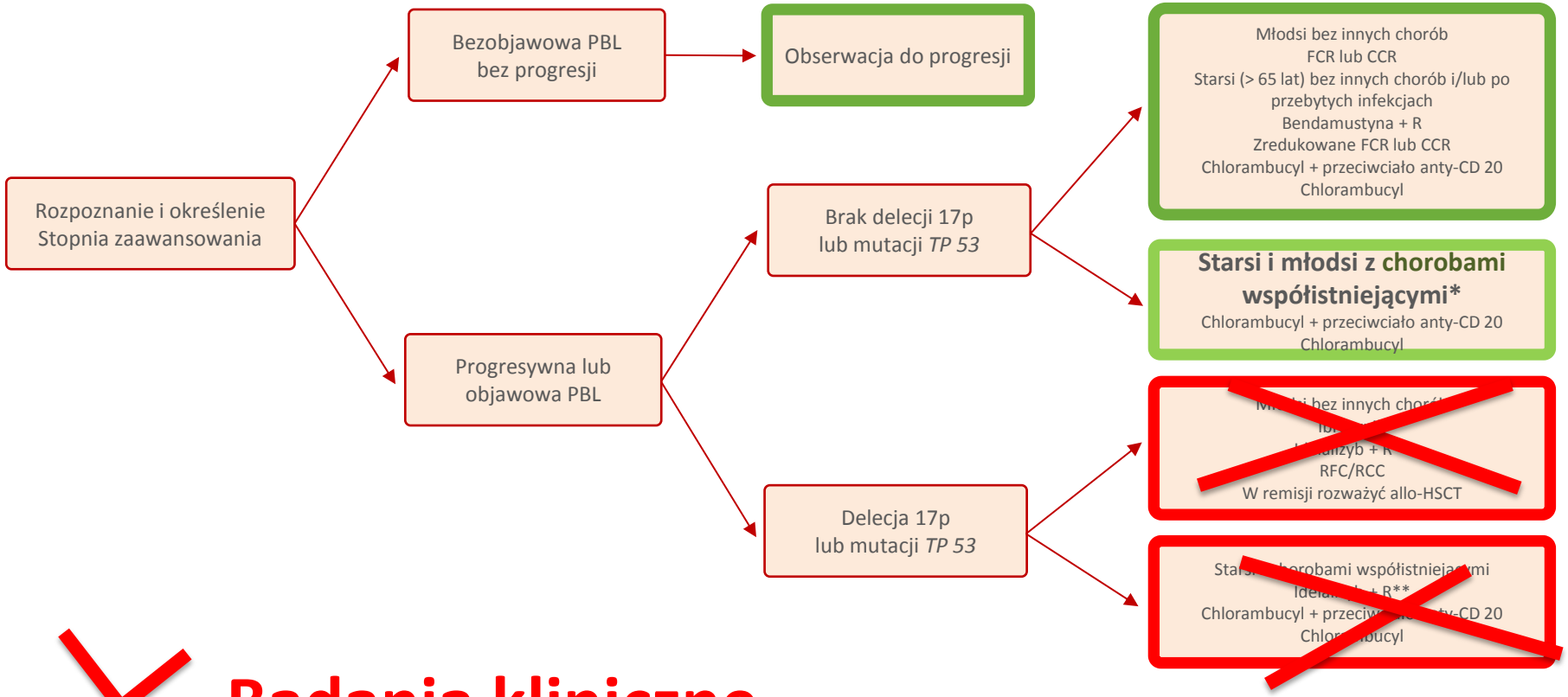
Efficacy And Safety Of Idelalisib In Patients With Relapsed, Rituximab-And Alkylating Agent-Refractory Follicular Lymphoma: A Subgroup Analysis Of A Phase 2 Study

Gilles Salles, Stephen J. Schuster, Sven de Vos, Nina D. Wagner-Johnston, Andreas Viardot, Kristie A. Blum, Christopher R. Flowers, Wojciech J. Jurczak, Ian W. Flinn, Brad S. Kahl, Peter Martin, Yeonhee Kim, Sanatan Shreay, Matthias Will, Bess Sorensen, Madlaina Breuleux, Pier Luigi Zinzani, Ajay K. Gopal

Haematologica April 2017 102: e156-e159; Doi:10.3324/haematol.2016.151738

Polish Lymphoma Research Group

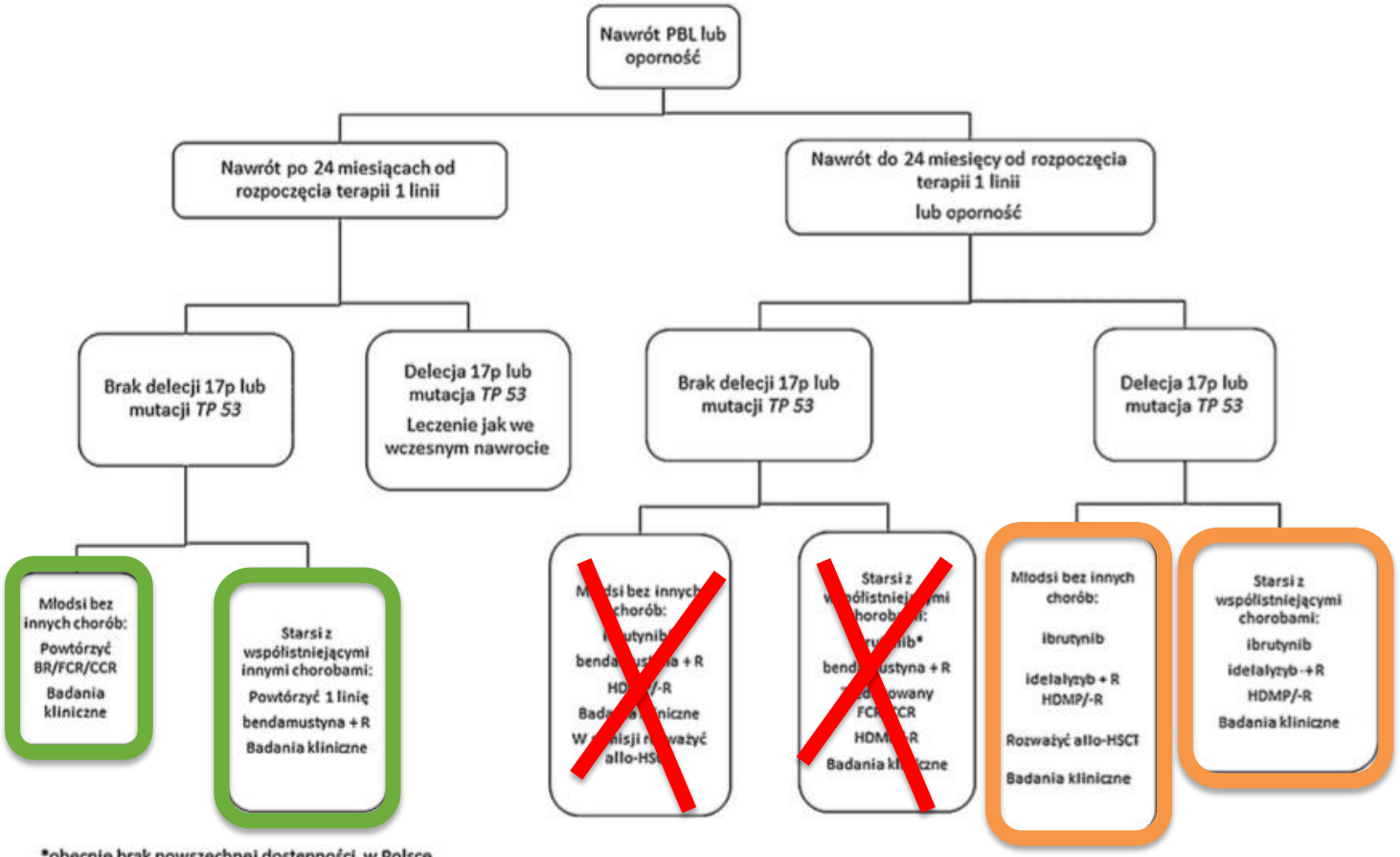
Rekomendacje CLL 2016 PALG/PLRG - Leczenie I linii



- Badania kliniczne

T.Robak i wsp. Acta Haematologica Polonica 47 (2016) 169-183

Rekomendacje CLL 2016 PALG/PLRG – nawrót/ oporność

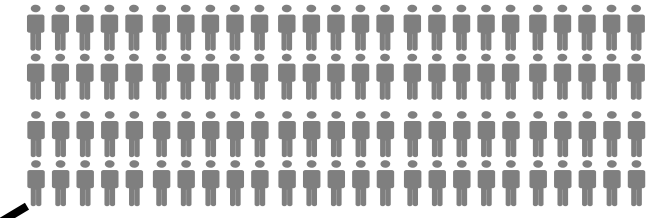


*obecnie brak powszechnej dostępności w Polsce

- Badania kliniczne

T.Robak i wsp. Acta Haematologica Polonica 47 (2016) 169-183

Na każdych 100 chorych z iNHL



U 10 występuje postać oporna na leczenie I rzutu

Opcje terapeutyczne dla tych chorych są ograniczone (1-3)

U 45 występuje progresja choroby w ciągu 5 lat

U 22 występuje postać oporna na leczenie II rzutu

U 23 występuje odpowiedź >2,5 roku na leczenie II rzutu

U 45 odpowiedź utrzymująca się > 5 lat

U większości tych chorych dojdzie ostatecznie do nawrotu

Mediana OS <3 lat

>1 nawrót oczekiwany w ciągu 5 lat

Mediana OS >5 lat[4]

1 nawrót oczekiwany w ciągu 5 lat

Mediana OS >10 lat

1. Kahl B i wsp. *Cancer* 2010; 116:106–114; 2. Horning SJ i wsp. J Clin Oncol 2005; 23:712–719. 3. Czuczman MS i wsp. *Blood* 2012; 119:3698–3704. 4. Dane szacunkowe na podstawie badania EORTC20981: Van Oers MH i wsp. *J Clin Oncol* 2010; 28:2853–2858.

Opcje terapeutyczne leczenia FL

Remisja >5 lat

Jeśli późniejszy nawrót → Powtórzenie R-chemioterapii I rzutu (+ leczenie podtrzymujące ?)

Nawrót w ciągu 2–5 lat

- Powtórzenie R-chemioterapii I rzutu (+ leczenie podtrzymujące ?)
- Inna R-chemioterapia (+ leczenie podtrzymujące ?)

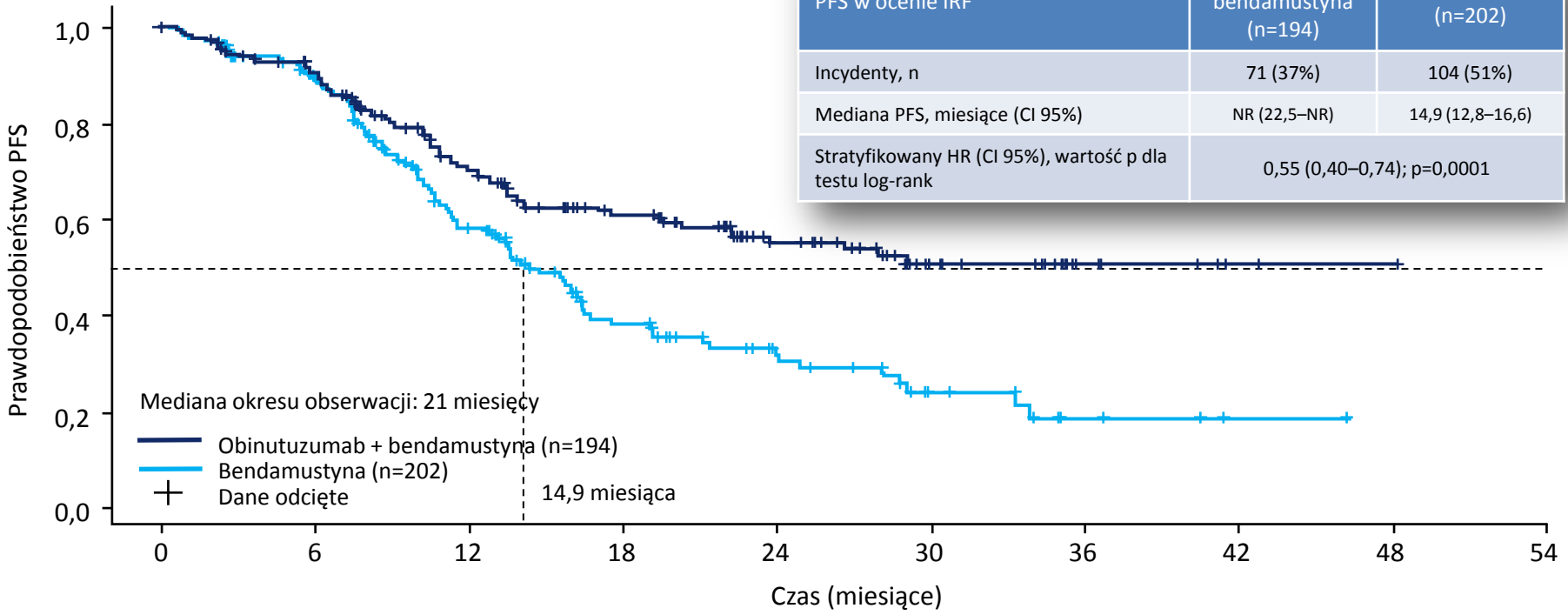
Nawrót w ciągu 2 lat

Oporność na leczenie I czy II linii

- Alternatywne schematy chemioterapii
- Inne MoAB, Inhibitory BTK, IP3, ……..
- ASCT, allo we wznowie po ASCT

GADOLIN - PFS

PFS w ocenie IRF	Obinutuzumab+ bendamustyna (n=194)	Bendamustyna (n=202)
Incydenty, n	71 (37%)	104 (51%)
Mediana PFS, miesiące (CI 95%)	NR (22,5–NR)	14,9 (12,8–16,6)
Stratyfikowany HR (CI 95%), wartość p dla testu log-rank	0,55 (0,40–0,74); p=0,0001	

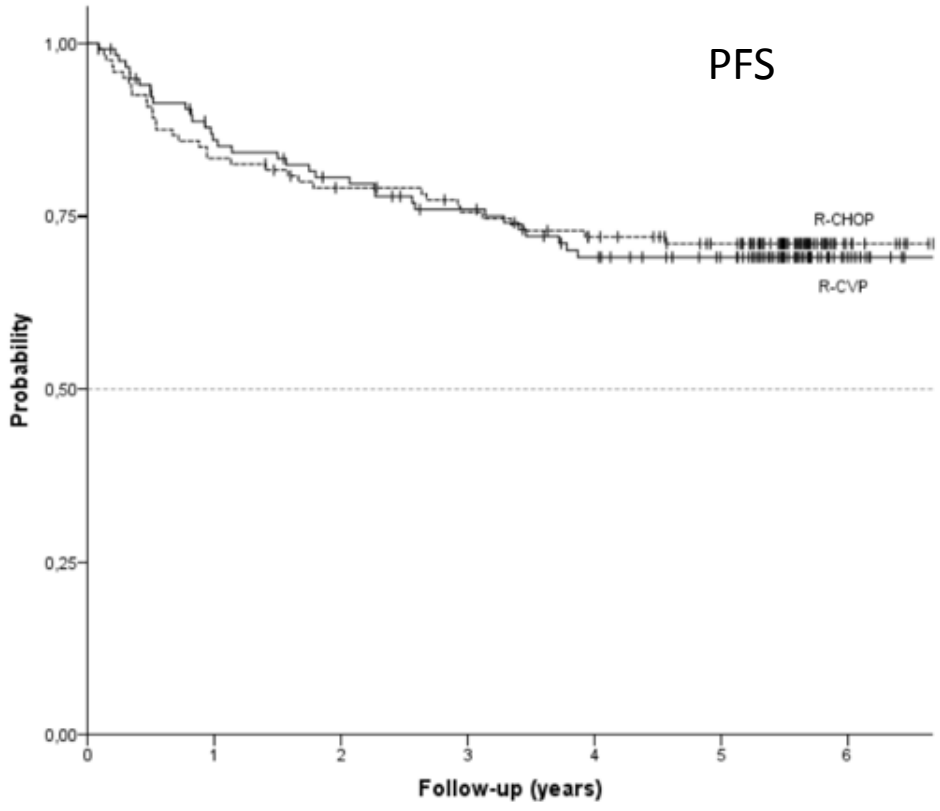


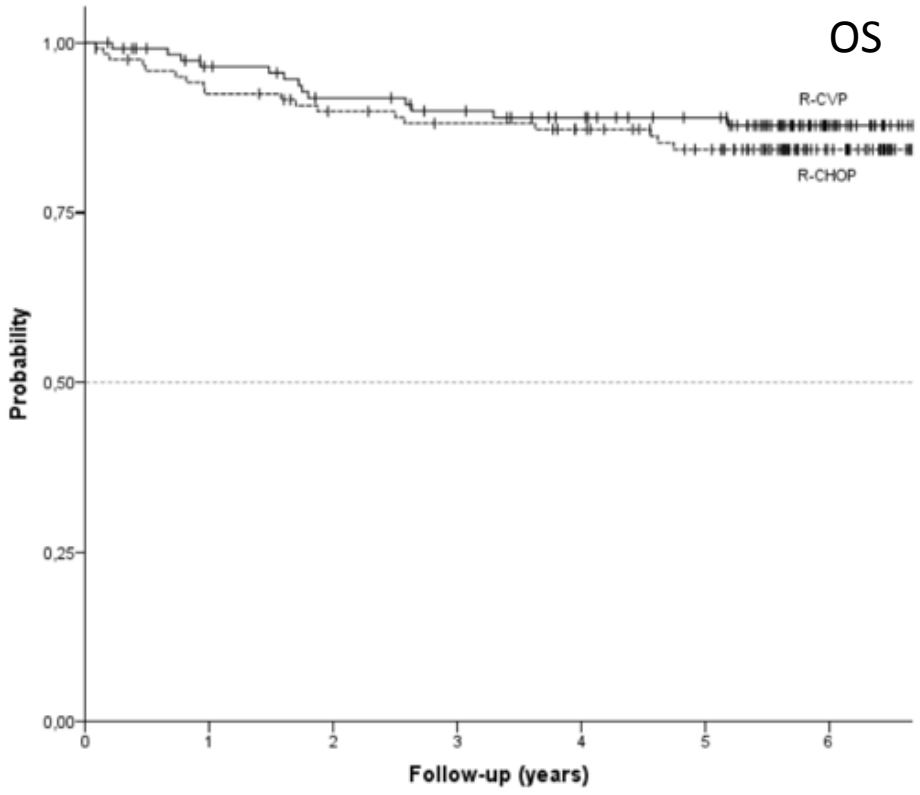
Liczba chorych w grupie ryzyka

194	157	108	77	51	27	7	2	1
202	150	89	46	28	15	5	2	

TTNT wynosił <2 lat w grupie otrzymującej bendamustynę, w grupie otrzymującej obinutuzumab w skojarzeniu z bendamustyną mediany nie osiągnięto

Badanie PLRG 4

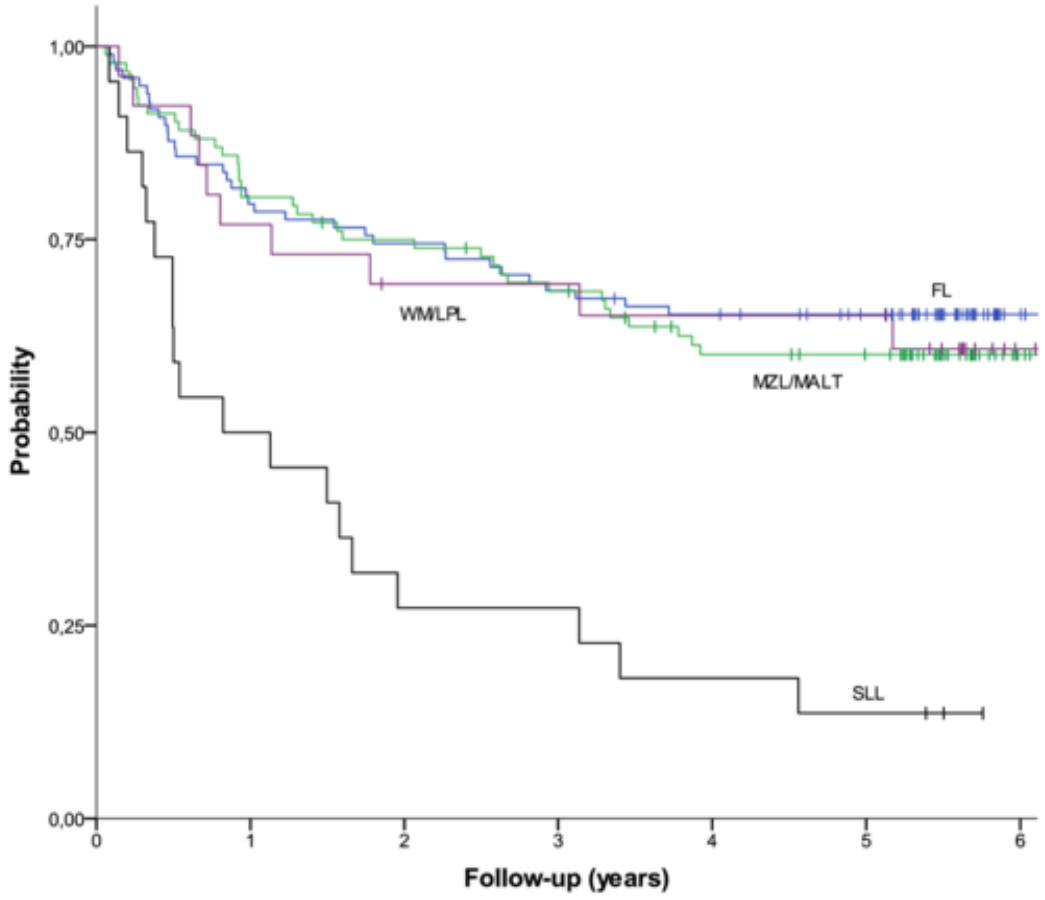




Walewski et al., ? 2019

Polish Lymphoma Research Group

Najczęściej stosowany schemat leczenie iNHL w Polsce, po badaniu PLRG 4



Linie leczenia

I — R-CVP → Rituximab mainteance

II — Obinutuzumab + Bendamustyna

III i dalsze — Badania kliniczne

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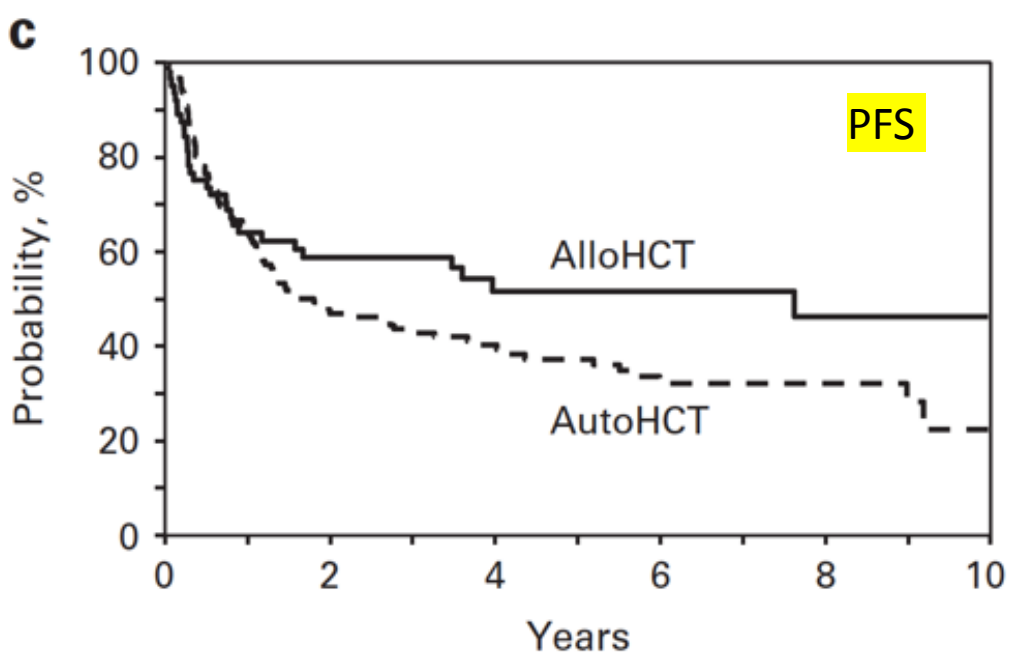
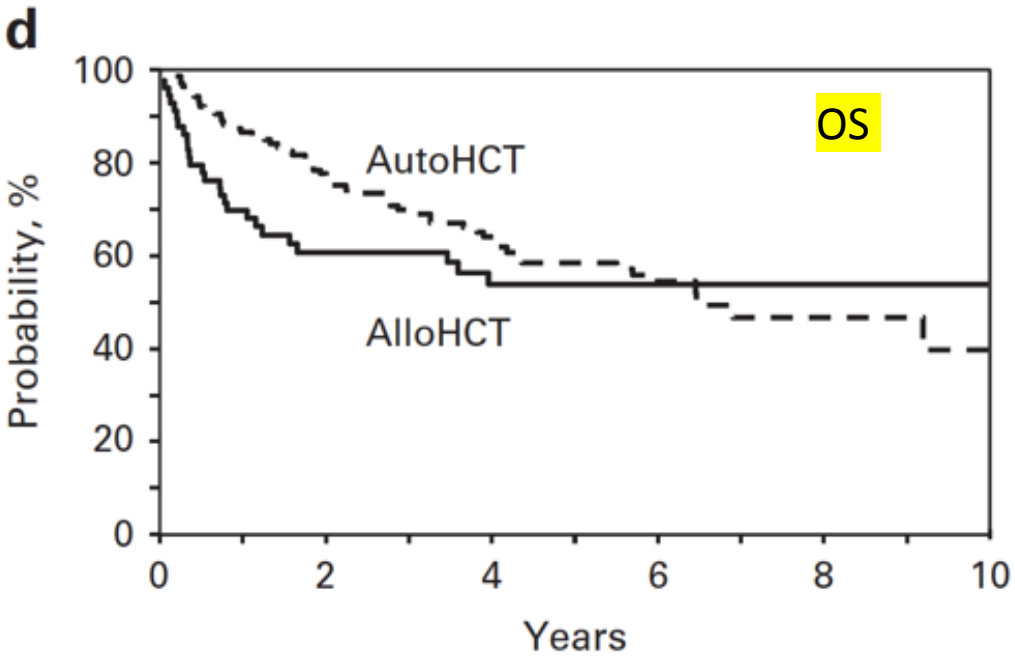
Rola transplantacji w FL GIII





- W pierwszych 24 miesiącach po przeszczepie autoSCT koreluje z OS (RR=0.42; p=0.005),
  U Pacjentów żyjących dłużej (ponad 24 miesiące) – autoSCT (w porównani z Allo SCT) koreluje z krótszym OS (RR=3.6; p= 0.04).

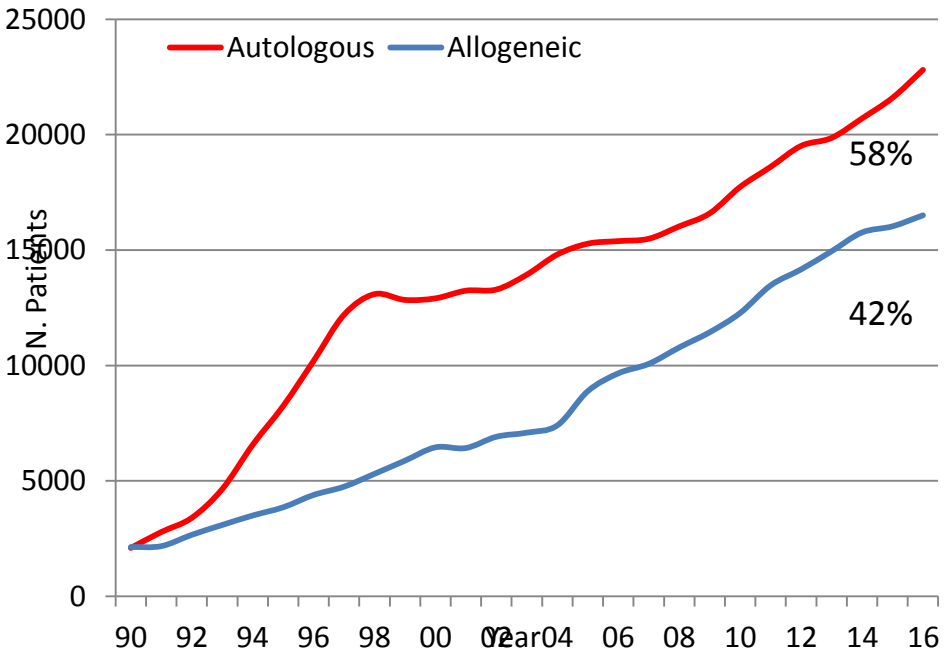
- Większa liczba zgonów nie związanych ze wznową chłoniaka po RIC allo SCT (4 *vs* 27%, p=0.001)
  kompensuje niższa liczba zgonów związanych z wznową / progresją chłoniaka (61 *vs* 20%, p=0.0001)

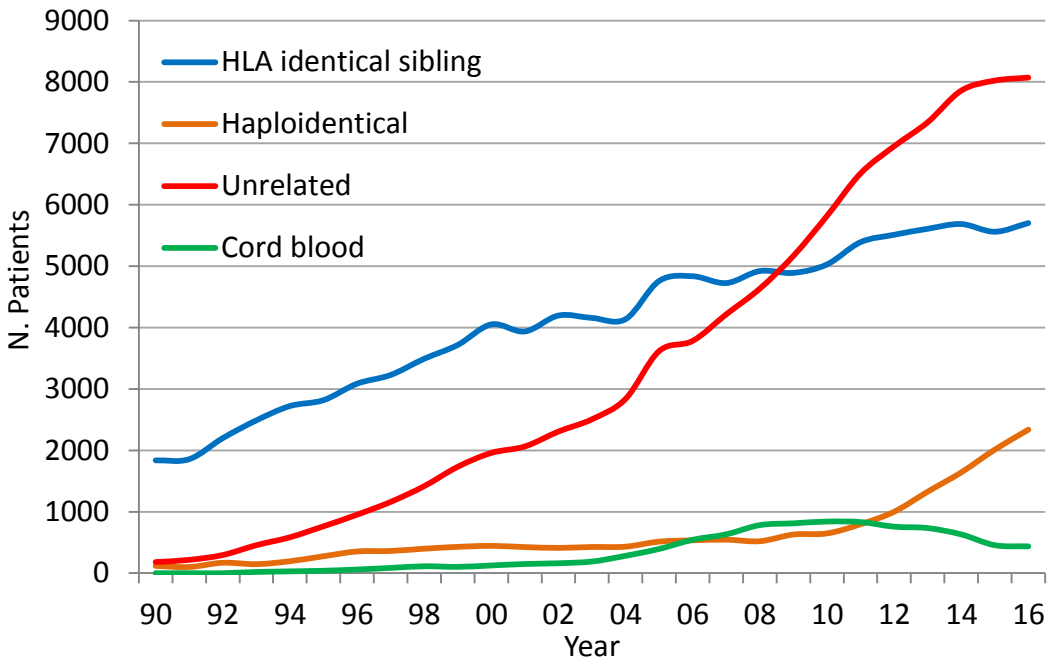
Klyuchnikov et al., Bone Marrow Transpl 2015

HSCT Activity in Europe 2016

Indication	Allogeneic 1st HSCT	Autologous 1st HSCT	Total
Leukemia	12,116	464	12,580
Lymphoma	**1,648**	**8,543**	10,191
Plasma cell disorder	463	11,931	12,394
Solid tumor	33	1,483	1,516
Non-malignant disorders	2,087	372	2,459
Bone marrow failure	*894*	*5*	*899*
Other	160	13	173
Total Patients	16,507	22,806	39,313

HSCT Activity in Europe 1990-2016





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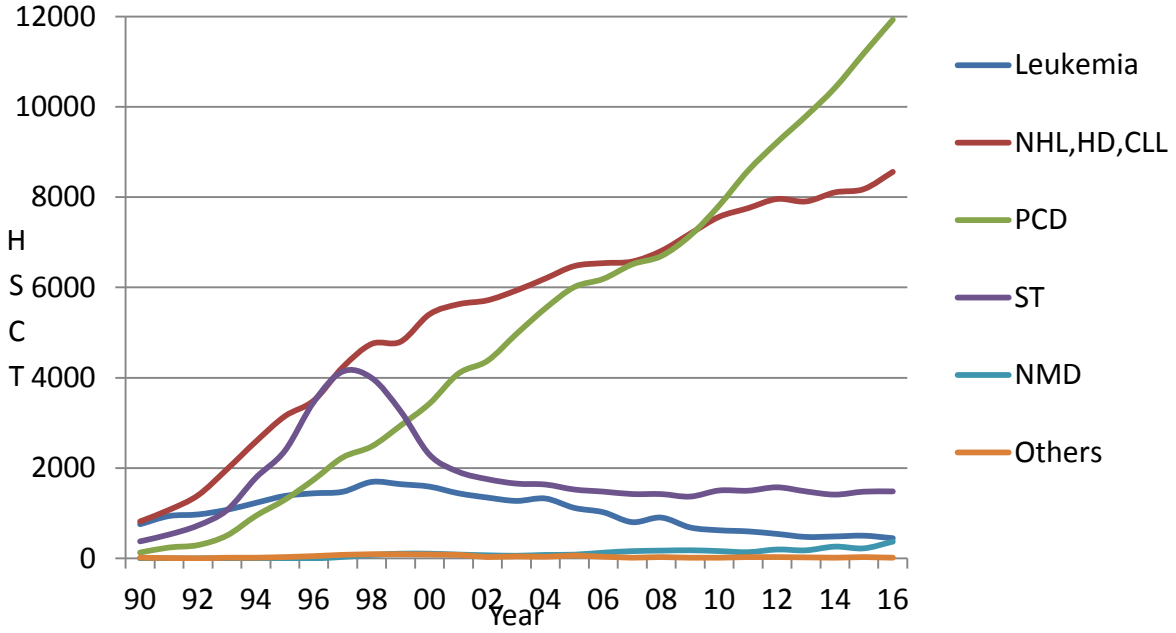
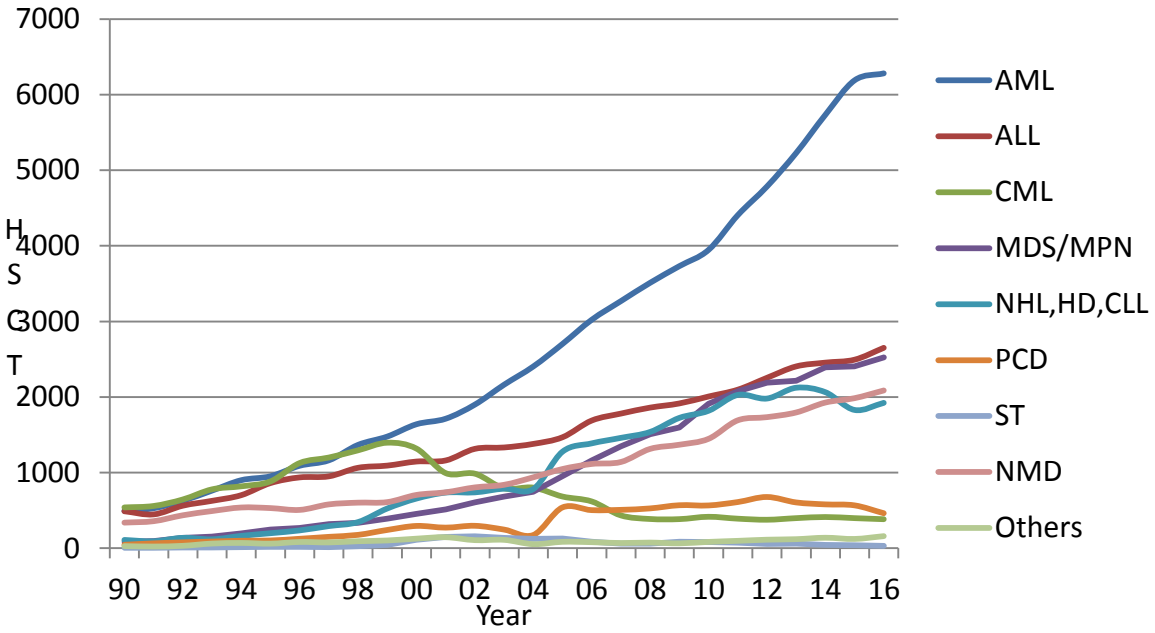
HSCT Activity in Europe 1990-2016

Autologous SCT



Allogeneic SCT



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B 591ZM

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 Hodgkina
(Ziarnica złośliwa)

Pixantrone

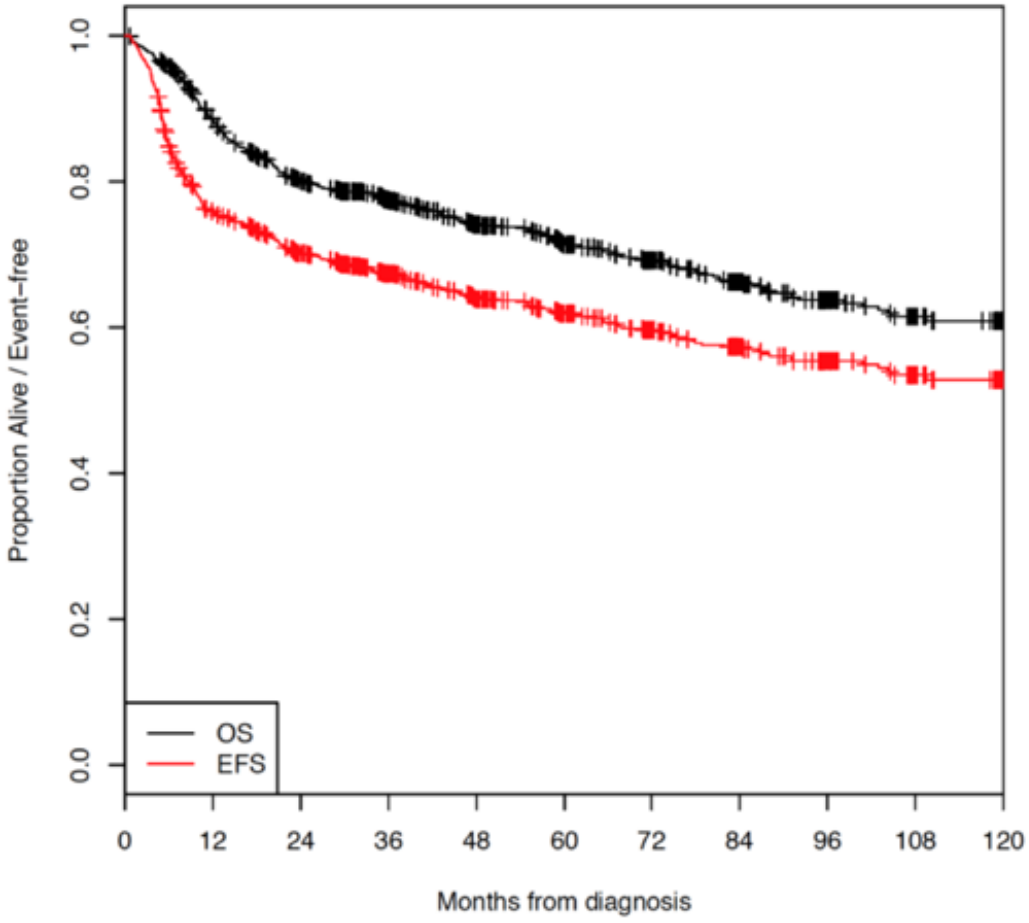
Ibrutynib,
Lenalidomid –
podtyp ABC DLBCL

30% chorych

Chłoniaki agresywne
- Chłoniak rozlany z dużych komórek B

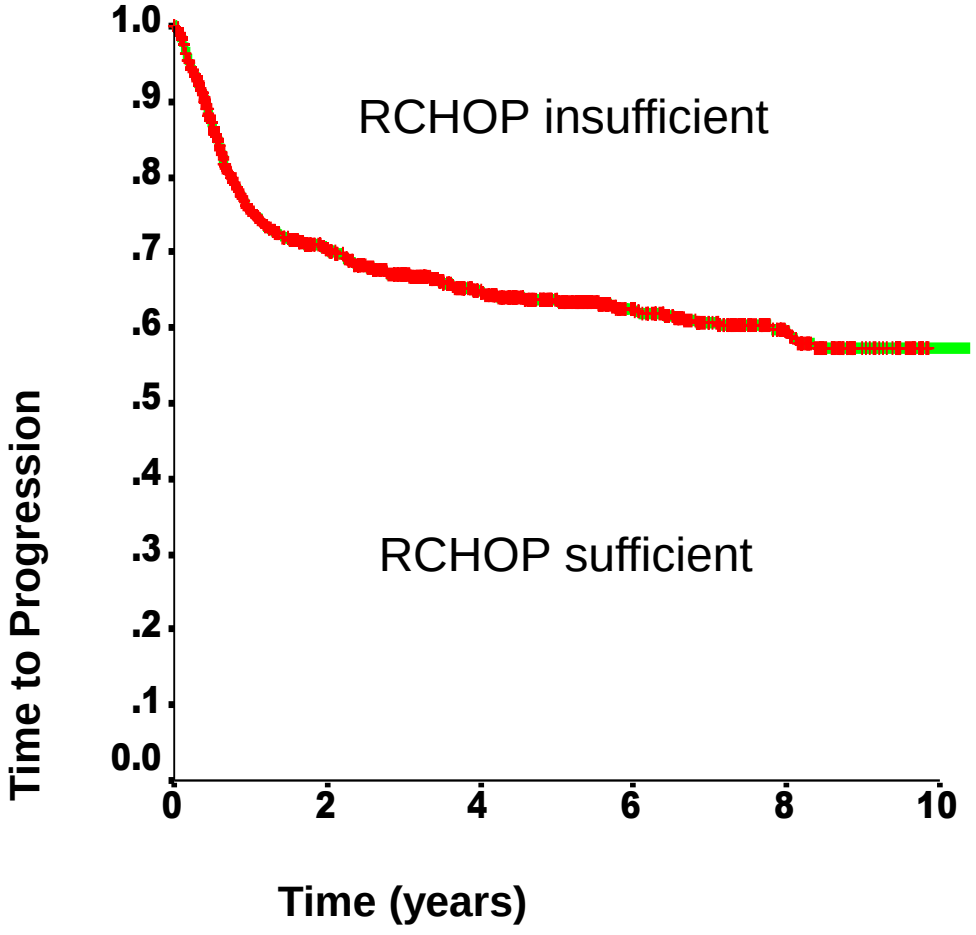
olentne
ewlekła białaczka limfatyczna
- Chłoniak grudkowy
- Chłoniak strefy brzeżnej, MALT

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

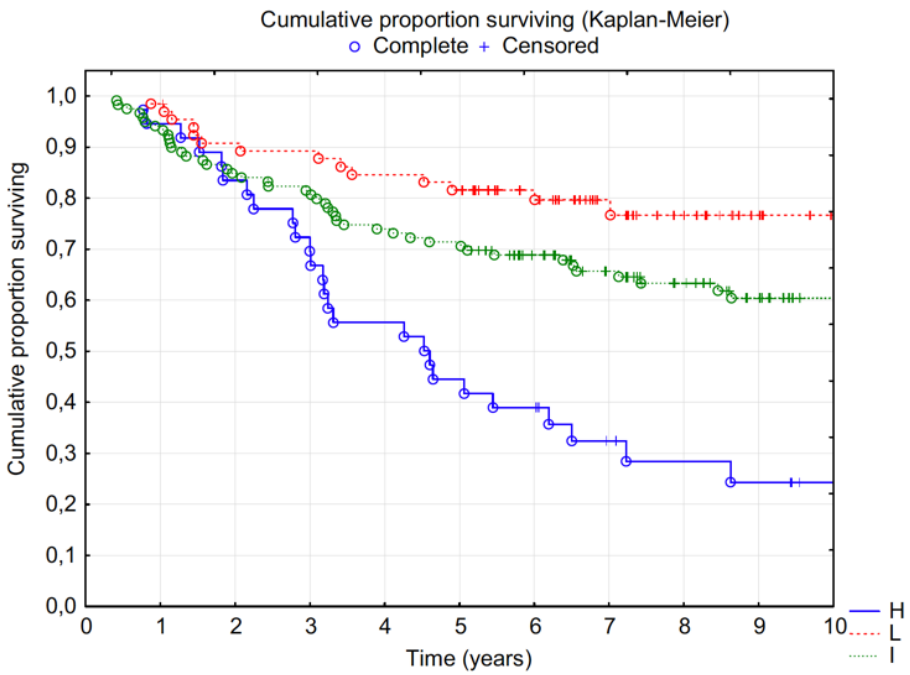


FIGURE 2 OS according to IPI (Kaplan-Meier analysis, $P < 0.00001$)

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

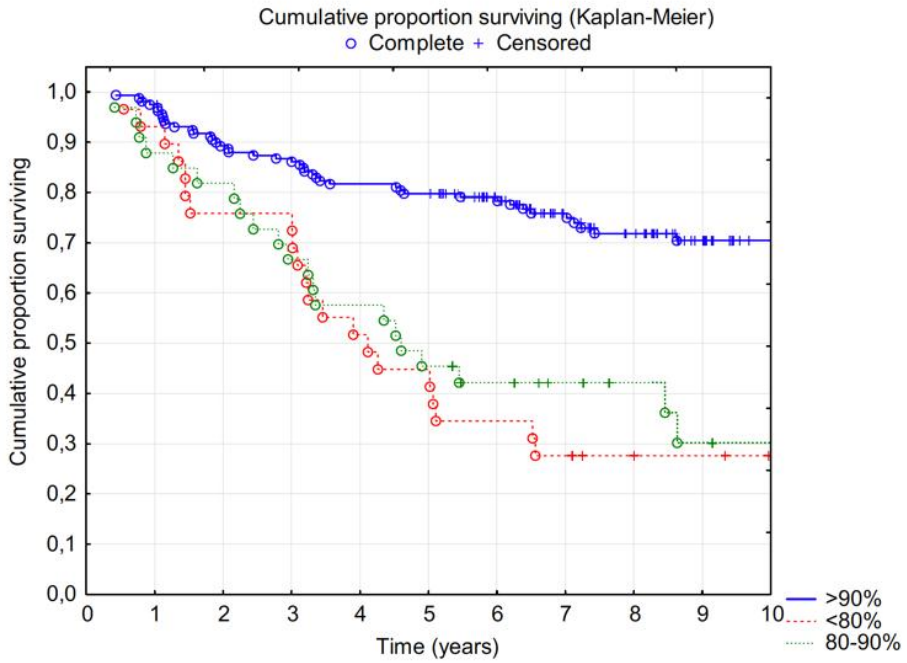


FIGURE 4 OS according to the ARDI (Kaplan-Meier analysis, $P < 0.00001$)

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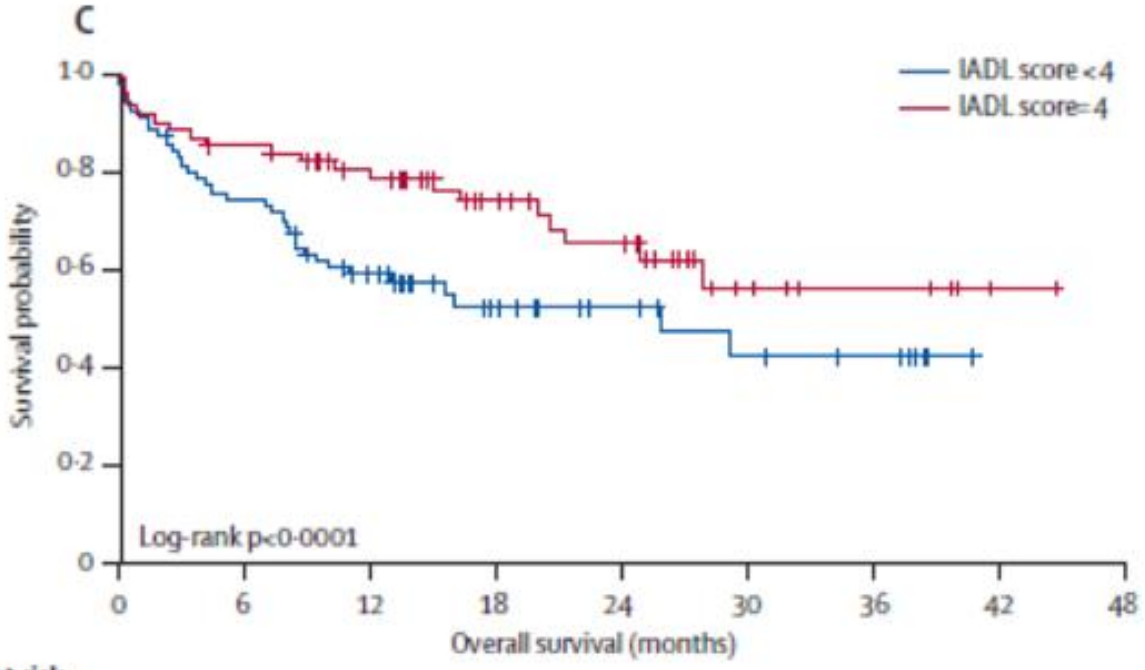
R-mini CHOP for elderly DLBCL (> 80 years)

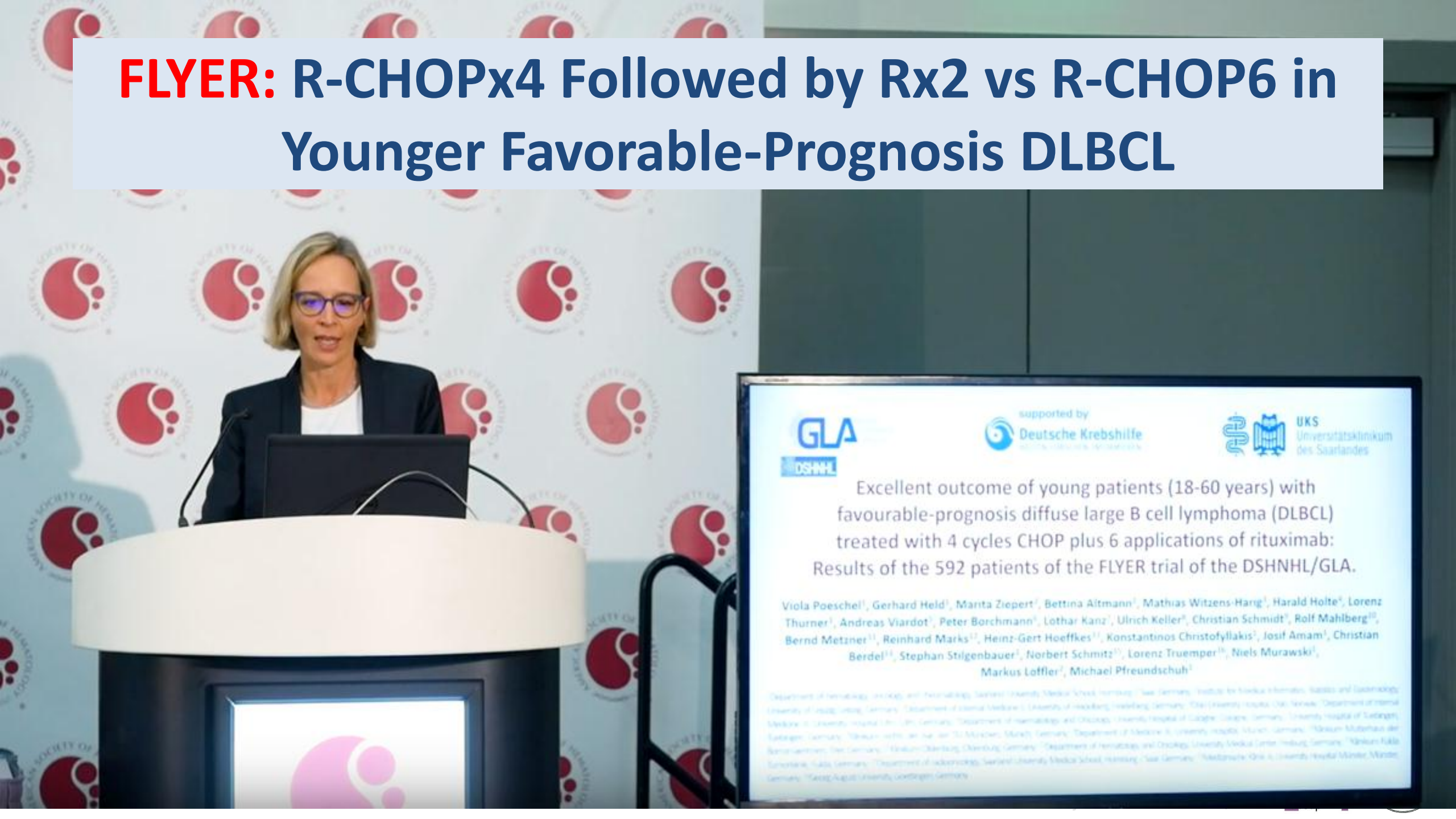


Number at risk									
IADL score <4	72	53	37	21	13	8	6	0	0
IADL score=4	63	53	42	29	23	8	5	1	0

	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

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)

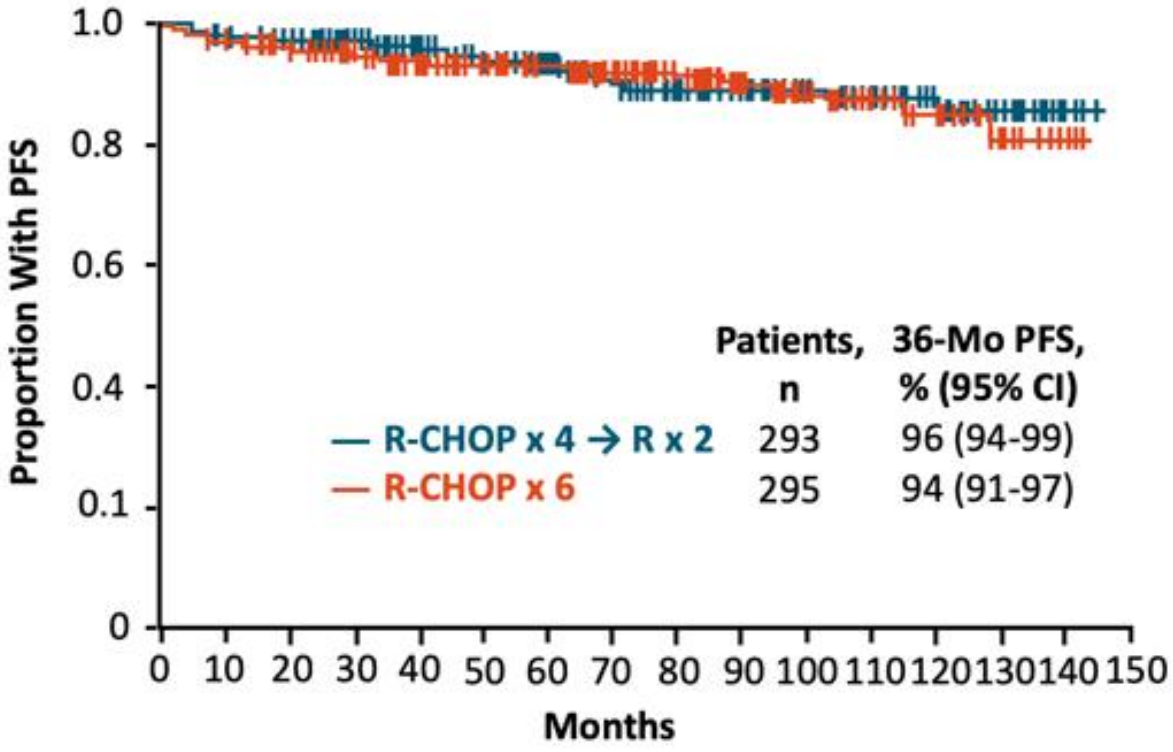
R-CHOP x 4 cycles followed by **Rituximab** x 2 cycles (n = 293)

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 $\alpha = 0.05$ (planned sample size: N = 592, assuming 10% loss yields final N = 532)
- Other endpoints: response, EFS, OS, safety

1. Pfreundschuh. Lancet Oncol. 2006;7:379. 2. Poeschel. ASH 2018. Abstr 781.

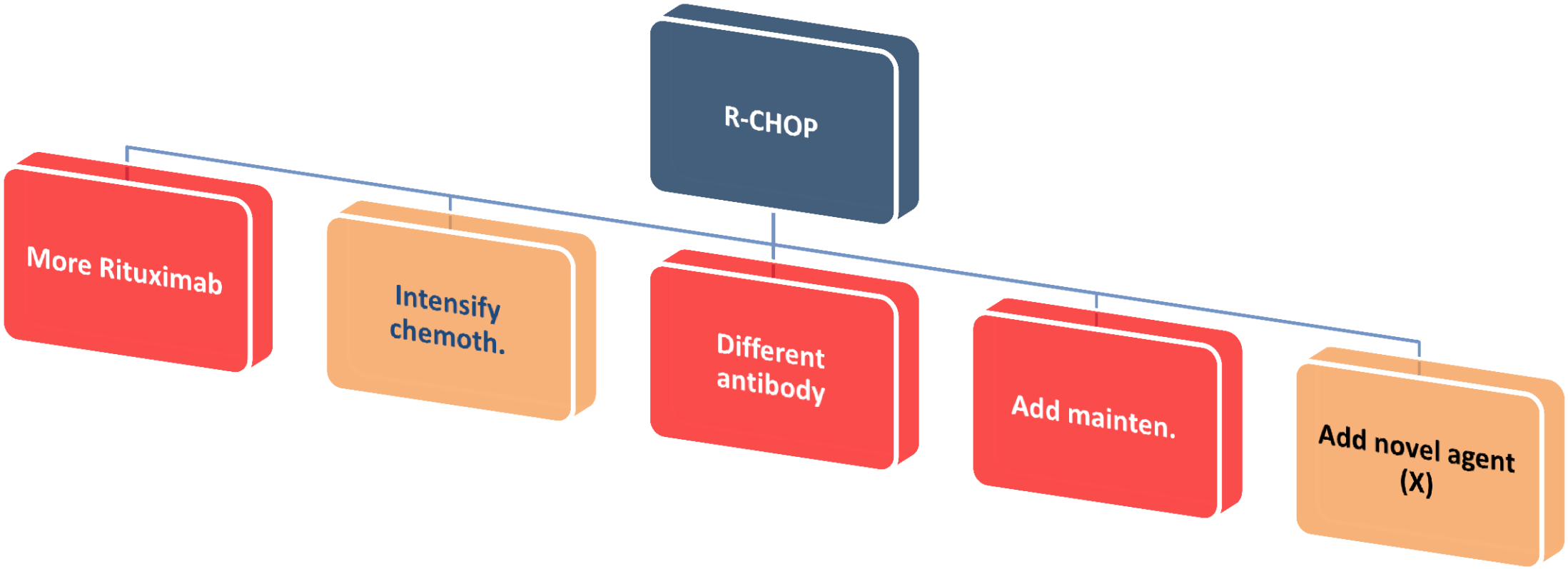
FLYER: R-CHOPx4 Followed by Rx2 vs R-CHOP6 in Younger Favorable-Prognosis DLBCL - PFS (primary endpoint)



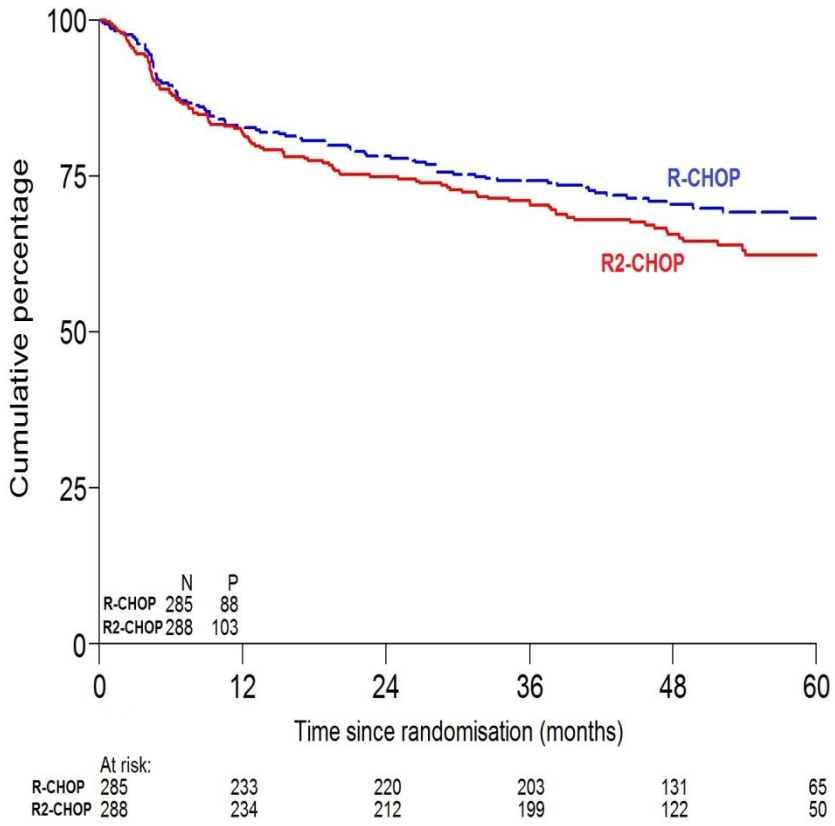
After median f/u of 66 mos, PFS noninferior with R-CHOP x 4 → R x 2 vs R-CHOP x 6

Poeschel. ASH 2018. Abstr 781.

How to improve R-CHOP ?



“More Rituximab”

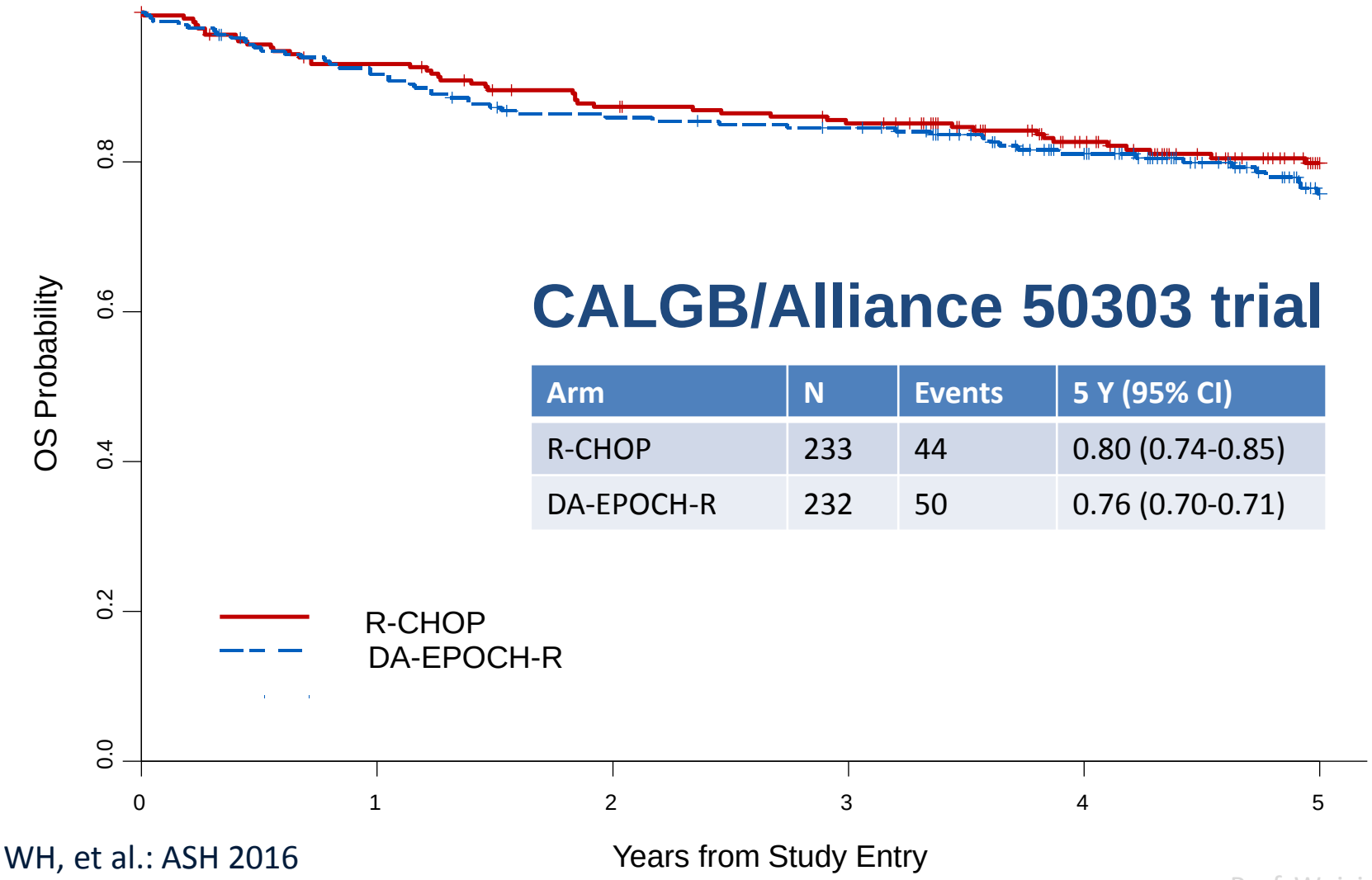


PFS	R-CHOP	R2-CHOP
3-year	74%	71%
	HR 1.20 (95% CI 0.90-1.60) *P* = .17	
5-year	68%	62%

Presented by: PJ Lugtenburg ASCO 2016

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

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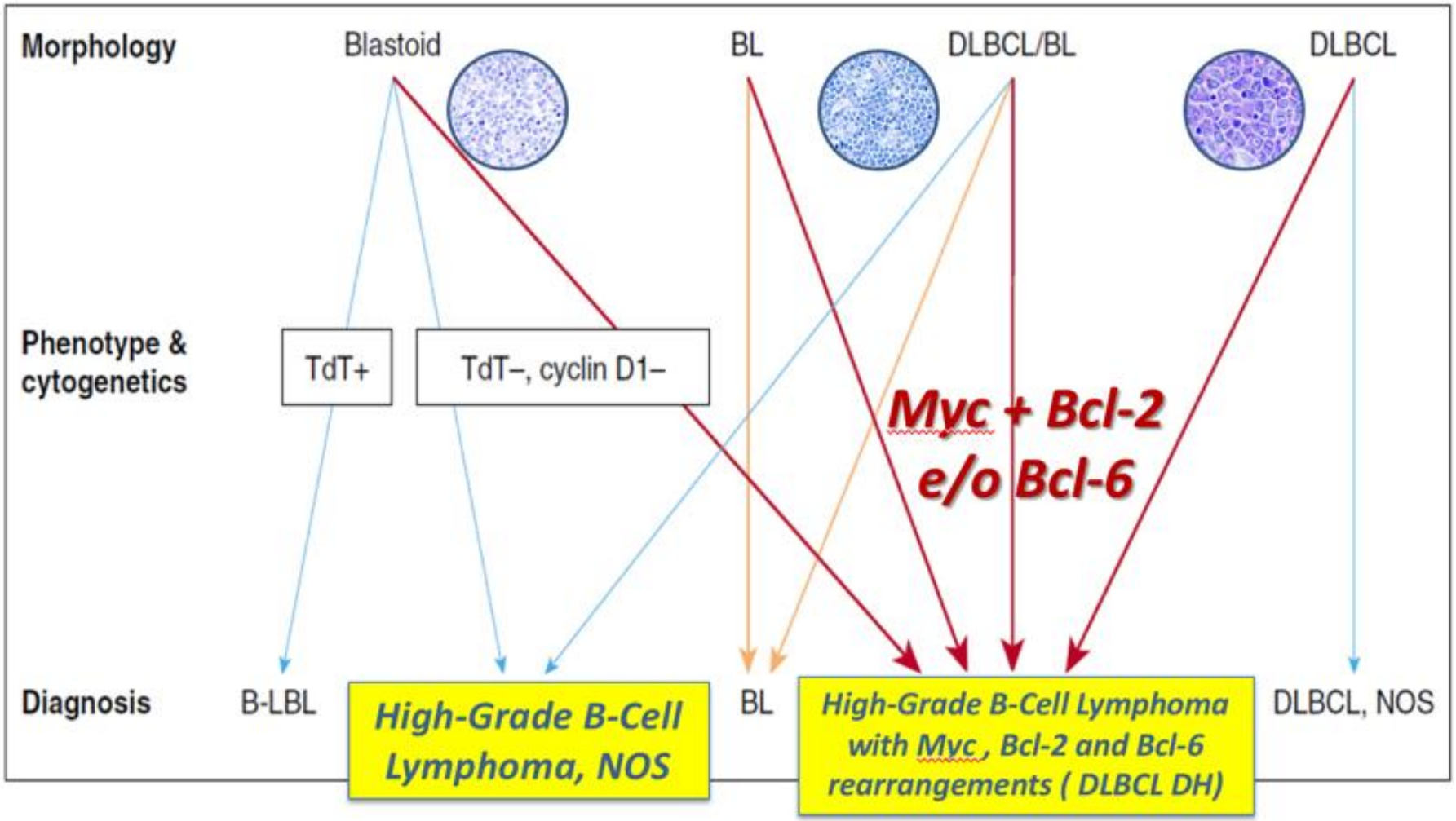
Phase 3 Study of R-CHOP vs DA-EPOCH-R in Patients With Untreated DLBCL (CALGB/Alliance 50303): Grade 3-5 Toxicities

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)



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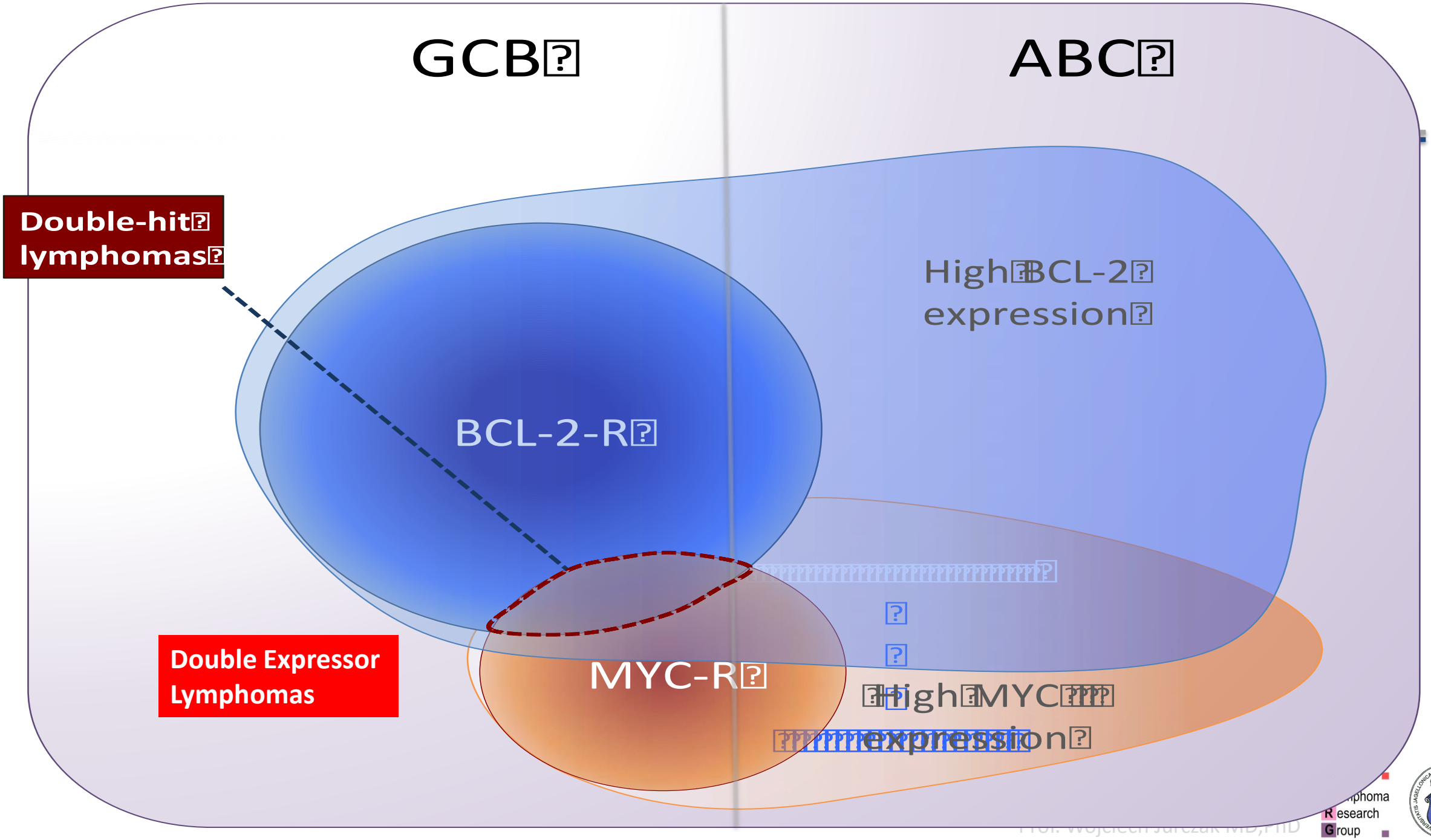
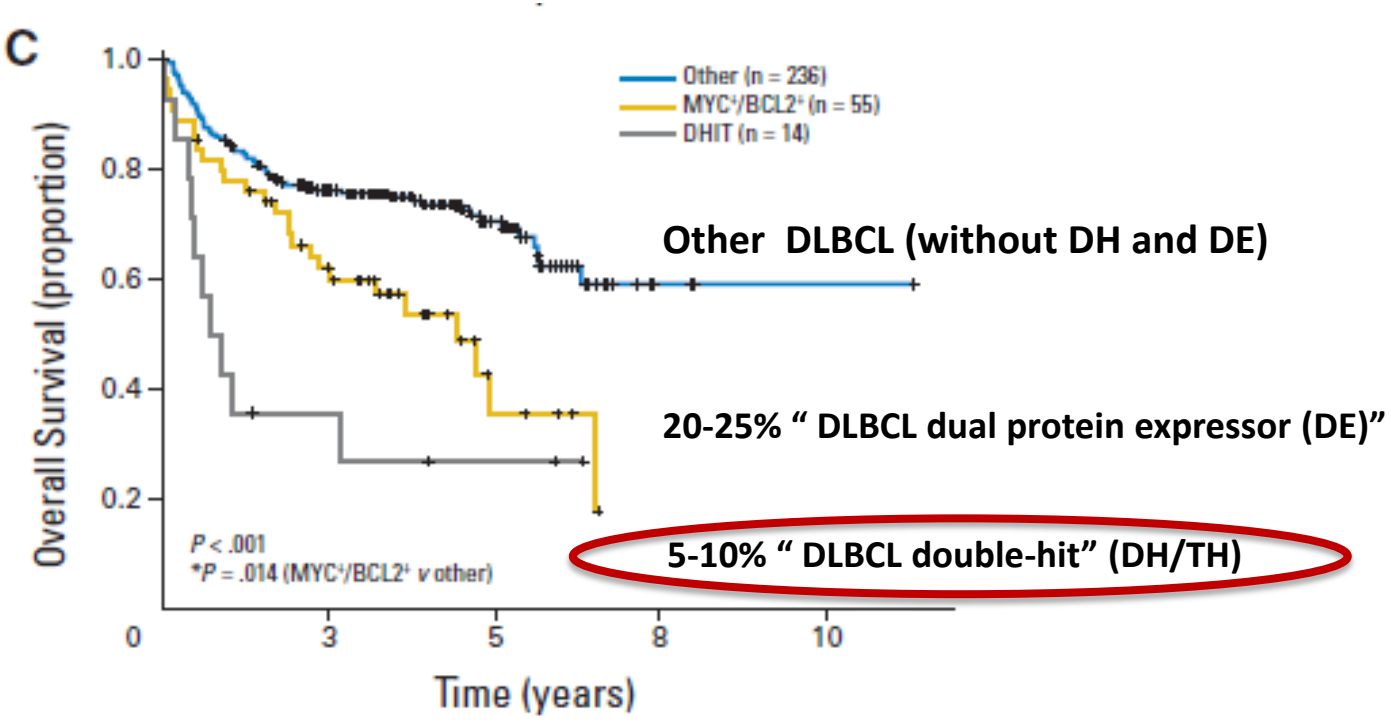

GCB
ABC
Double-hit lymphomas
High BCL-2 expression
BCL-2-R
MYC-R
High MYC expression
Double Expressor Lymphomas

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



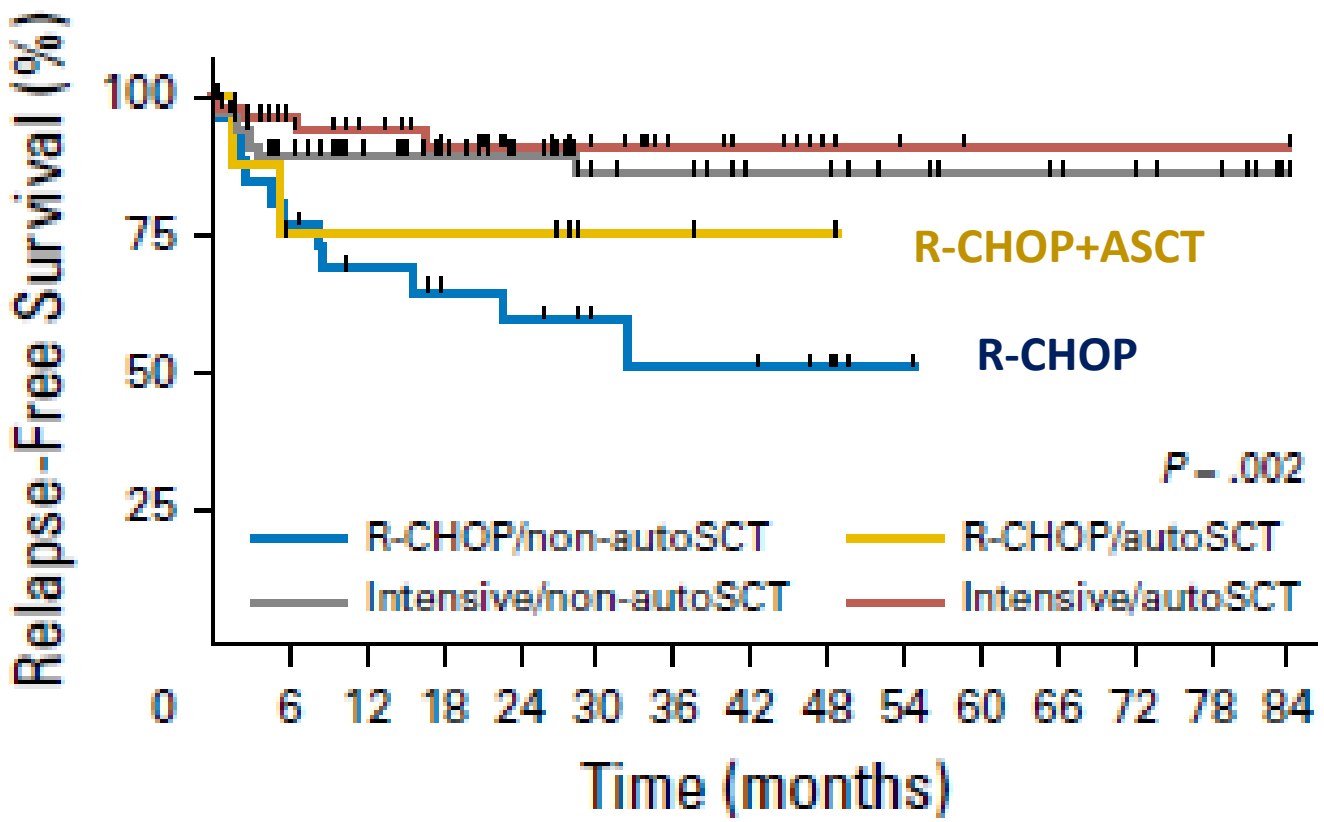
R-CHOP 21

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

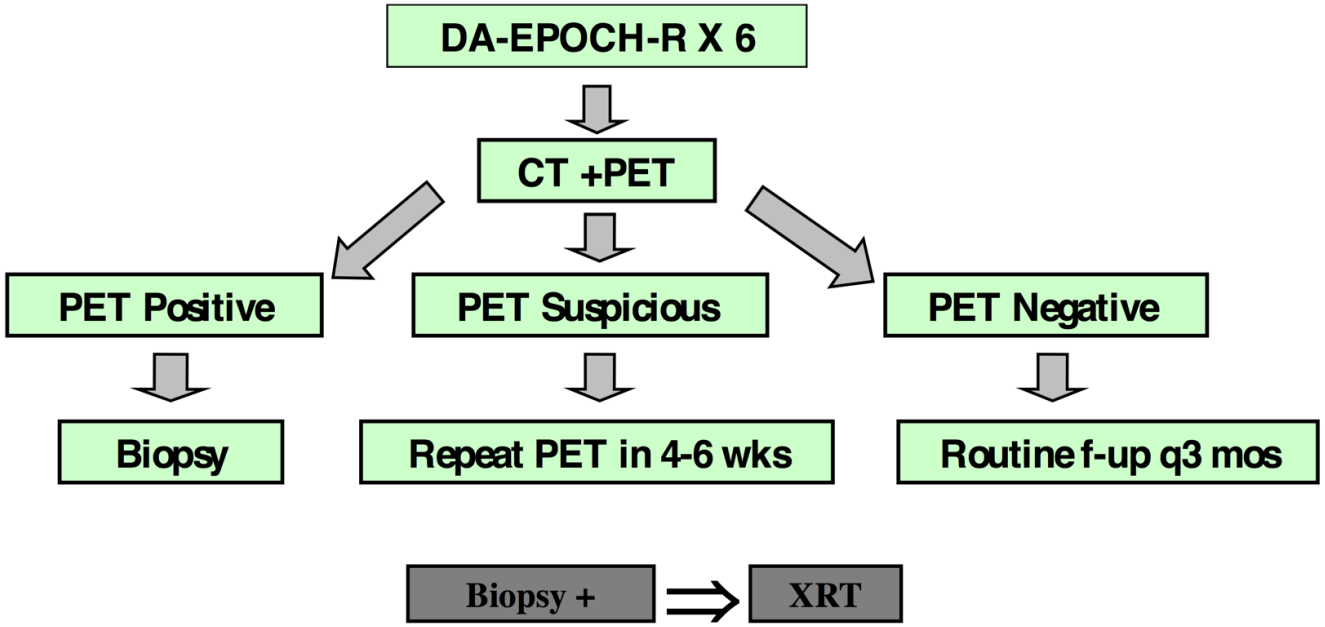
R-CHOP-21 is not adequate for double hit DLBCL

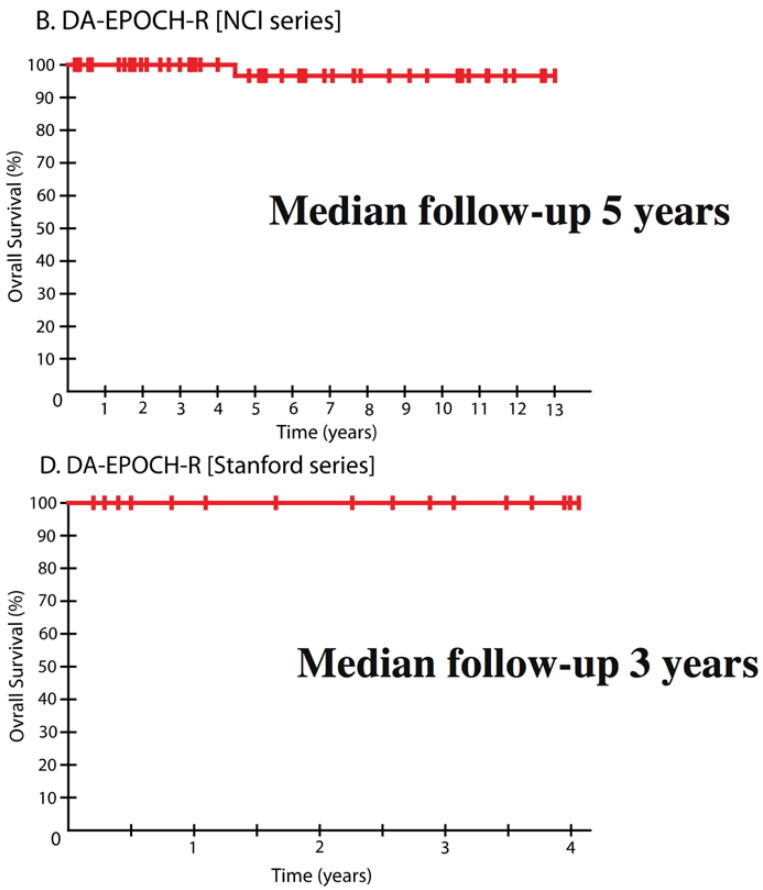


R-hyperCVAD/MA,
R-DA-EPOCH,
R-CODOX-M/IVAC

Landsburg D et al . J.Clin. Oncol 2017

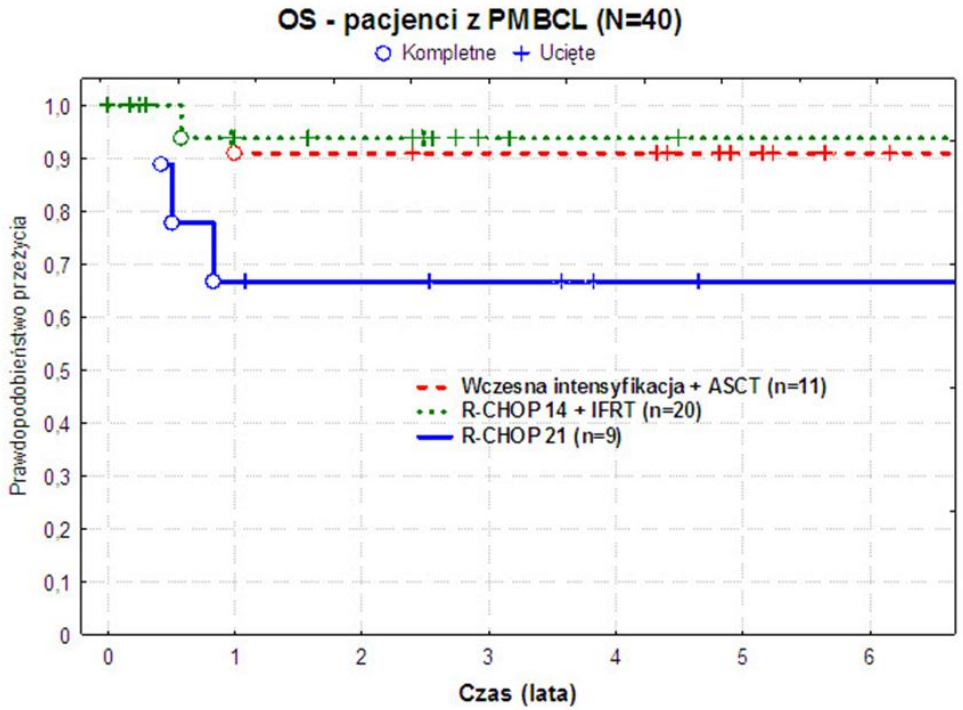
R-CHOP 21 is not adequate for PMBCL





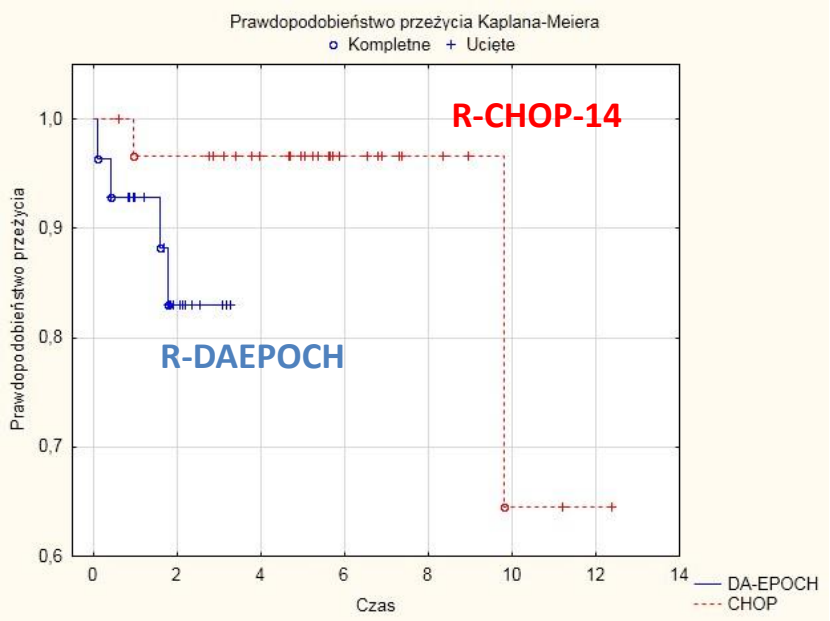
Dunleavy et al, NEJM 2013

R-CHOP 21 is not adequate for PMBCL



Jurczak et al., ASH 2010

OS



Giza et al., w przygotowaniu

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Second generation CD20 antibodies in DLBCL

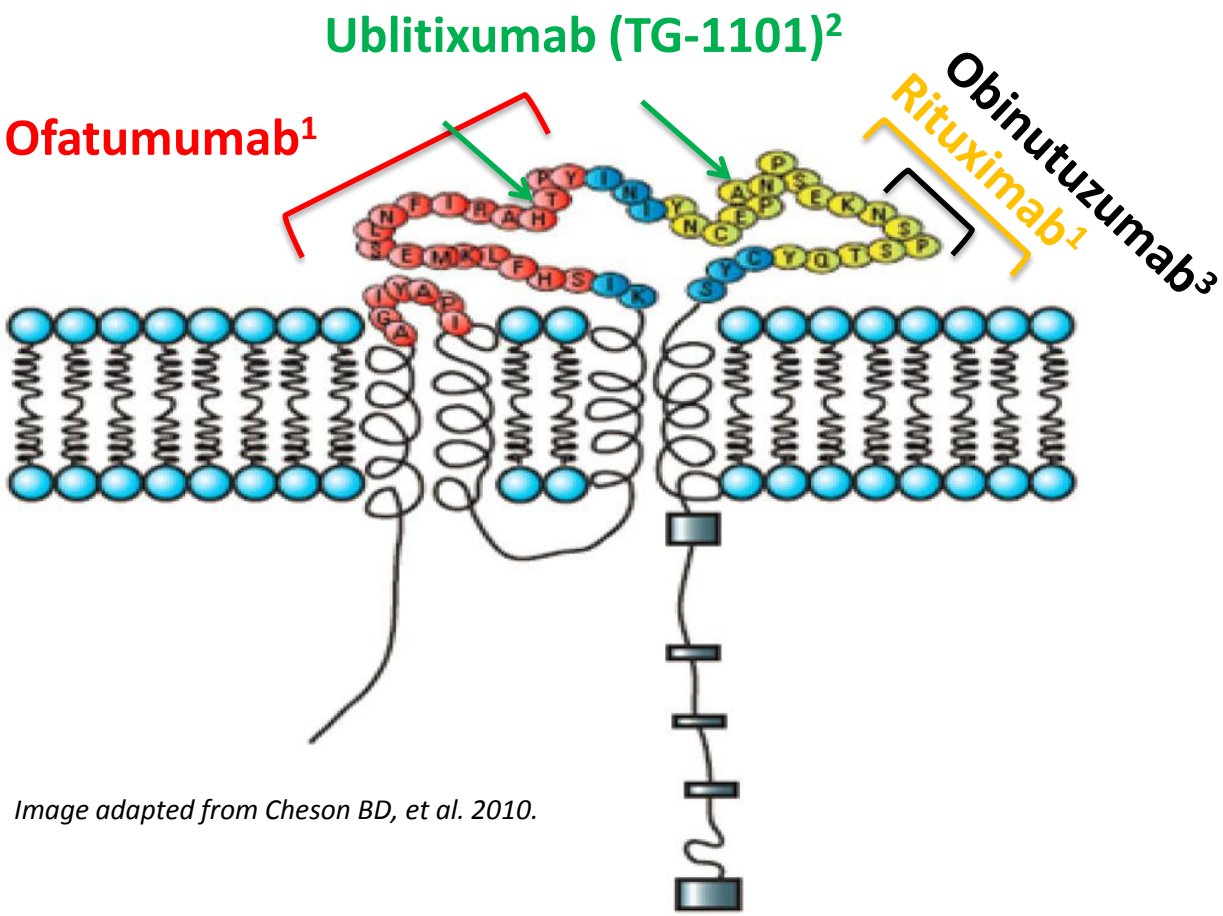


Image adapted from Cheson BD, et al. 2010.

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]

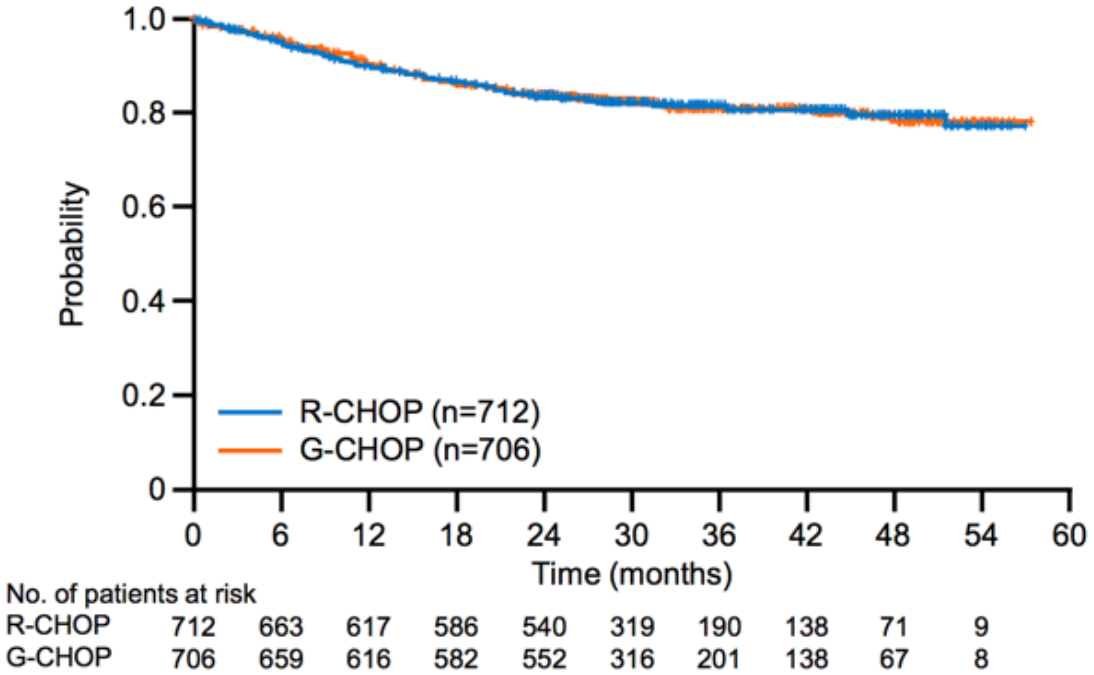
1. Cheson B.D. J Clin. Oncol 2010;28:3525-3530; **2.** O'Connor O.A. et al. ASCO 2014; **3.** Klein C. et al. mAbs 2012;5:22-33; **4.** Van Imhoff GW, et al. Journal of Clinical Oncology 2017;35:544–551; **5**. Lunning M, et al. Blood 2016;128:4197; **6**. Morschhauser FA, et al. Journal of Clinical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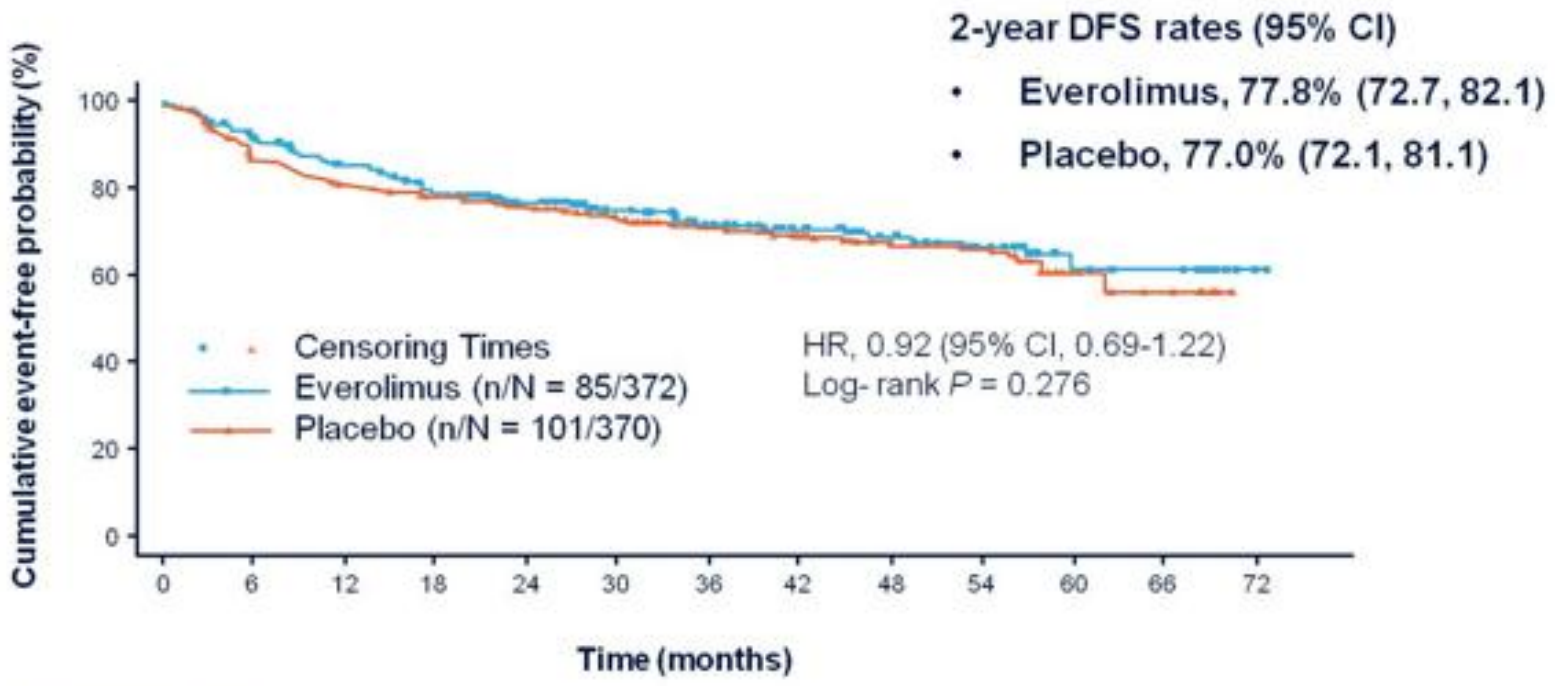
Everolimus maintenance



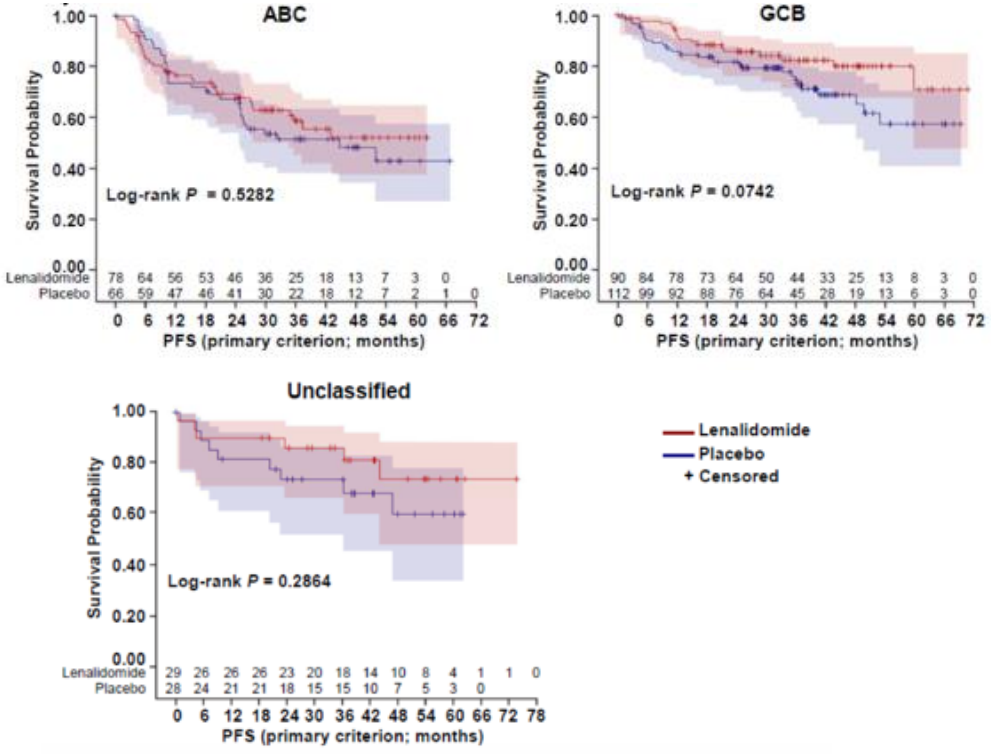
No. of patients still at risk

Everolimus	372	278	253	230	208	167	133	109	60	50	19	17	0
Placebo	370	297	276	262	234	187	151	124	69	63	14	10	0

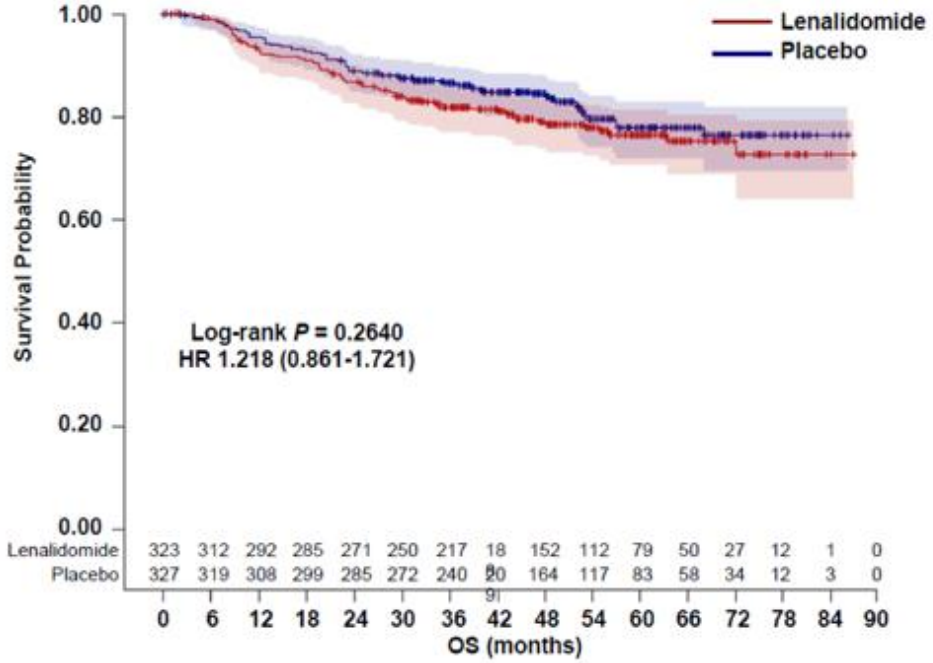
Witzig at 2016 ASCO Annual Meeting

Lenalidomide maintenance (REMARC trial)

PFS



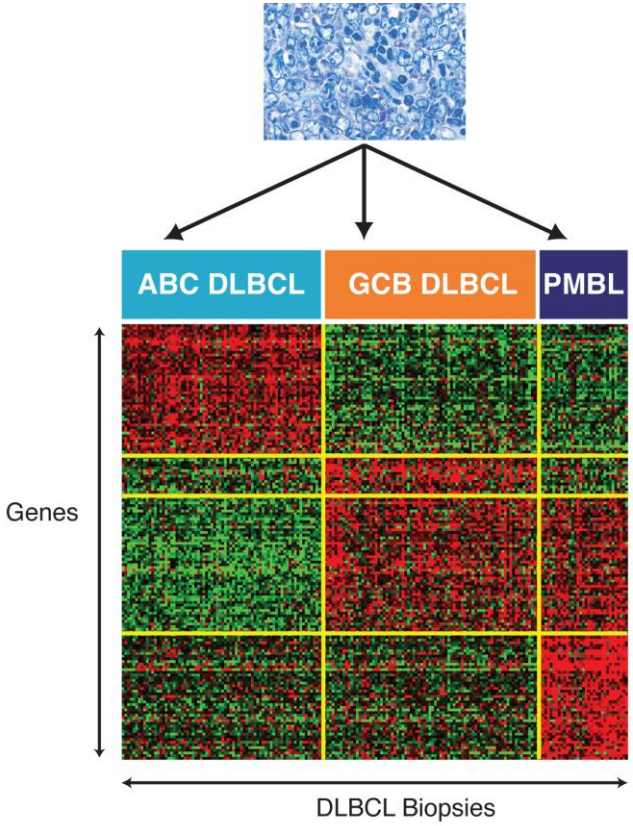
OS

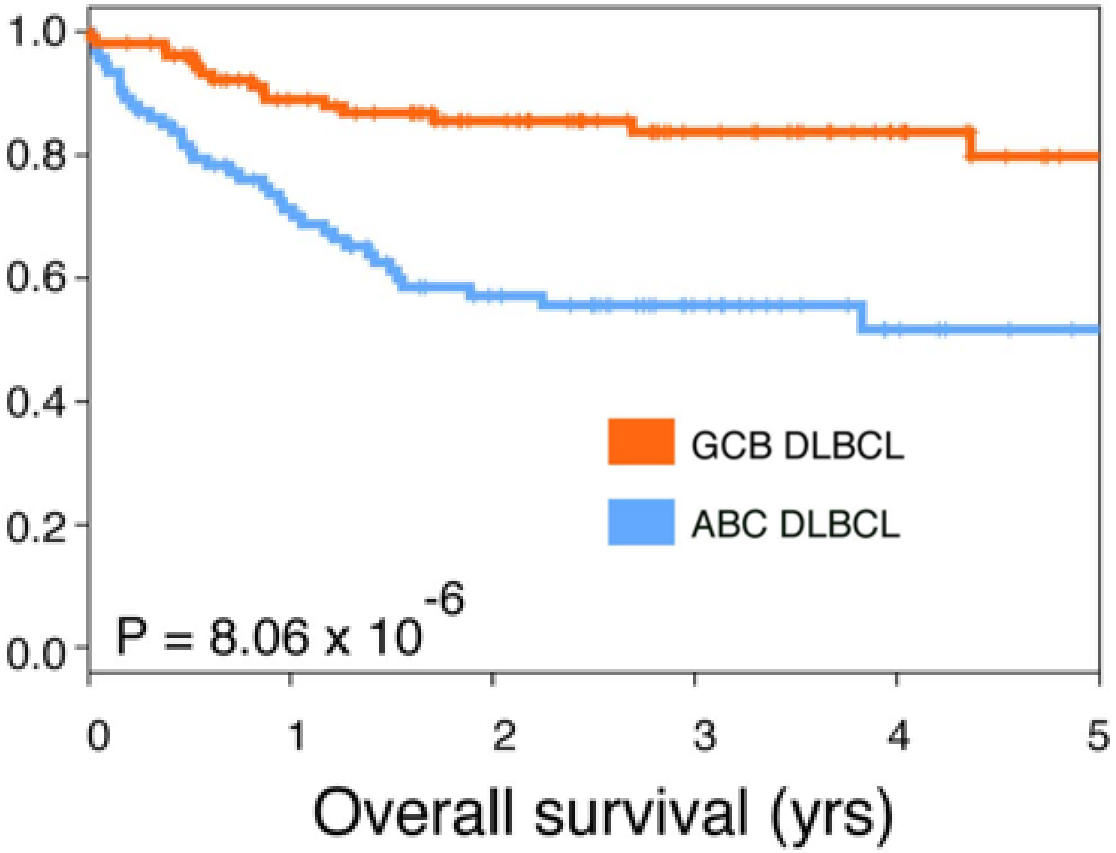


- At a median follow-up of 52 months, there was no statistical difference between arms
- Multivariate analysis showed that treatment arm was not a statistically significant factor

Thieblemont, ASH 2016

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





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

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ABC and GCB DLBCL determined by Nanostring test

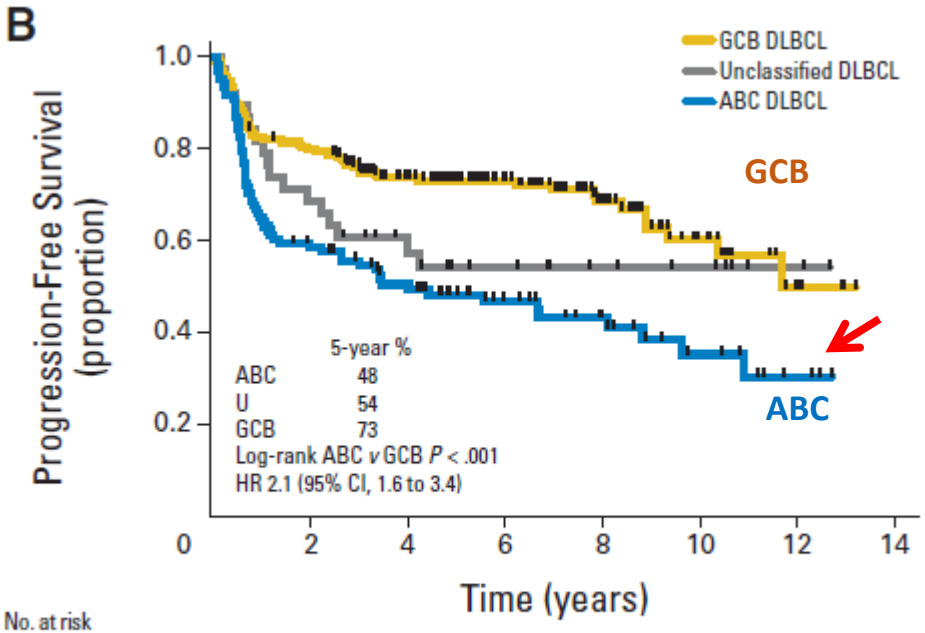
(in formalin fixed paraffin embedded tissue biopsies, N = 344)

ABC=108 (31%)

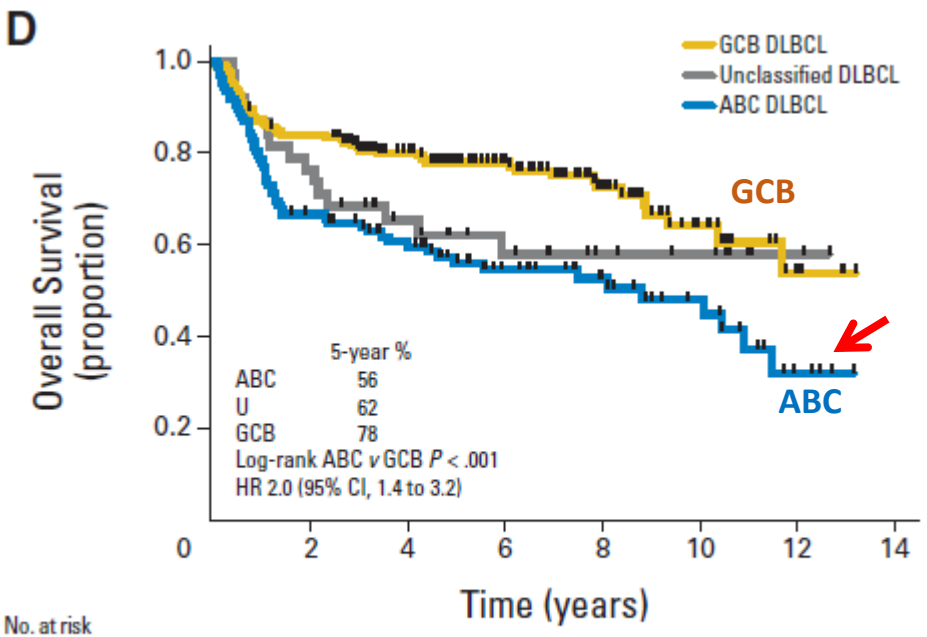
GCB=189 (55%)

Unclassicable=38 (11%)

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



No. at risk							
GCB DLBCL	189	149	112	80	46	20	5
Unclassified DLBCL	38	26	17	12	8	6	2
ABC DLBCL	108	61	47	29	19	10	3



No. at risk							
GCB DLBCL	189	157	121	84	49	21	5
Unclassified DLBCL	38	29	20	14	9	7	2
ABC DLBCL	108	70	57	35	24	15	4

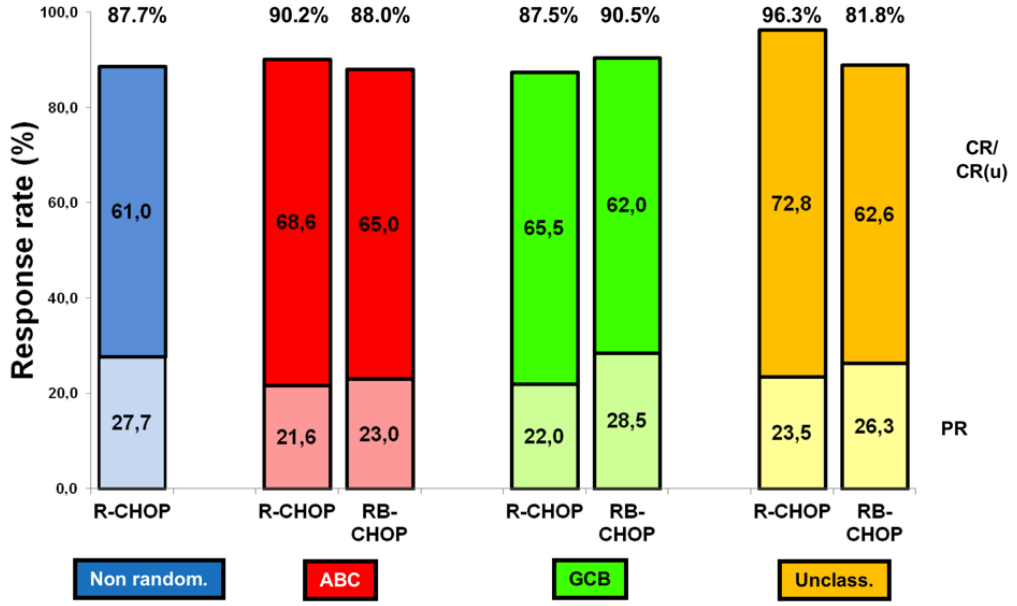
Scott et al., JCO 2015

Molecular driven therapy: R-CHOP + Novel drugs

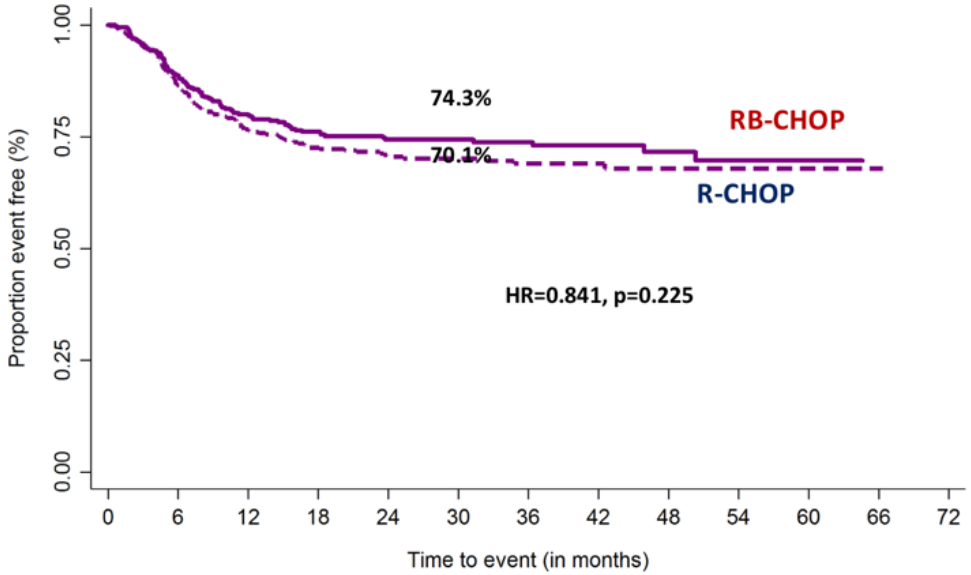
New Agent	Mechanism
Lenalidomide	Immunomodulator
Bortezomib	Proteasome inhibitor
Everolimus	mTOR inhibitor
Panobinostat	HDACs inihibitor
Ibrutinib	BTK inhibitor
Tamatinib	Inhibitors of Syk in B-cell signaling pathway
Enzastaurin	PKCβ-selective inhibitors
ABT 199	Pro-apoptotic ABT-263 Bcl-2 family
SELINEXOR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

ABC	GCB
Proteasome inhibitors	Histone modifiers
BTK inhibitors	BCL2 inhibitors
Immunomodulators	PTEN/PI3K

R-CHOP + Bortezomib (REMoDL-B Study)



PFS



Davis et al, 2017

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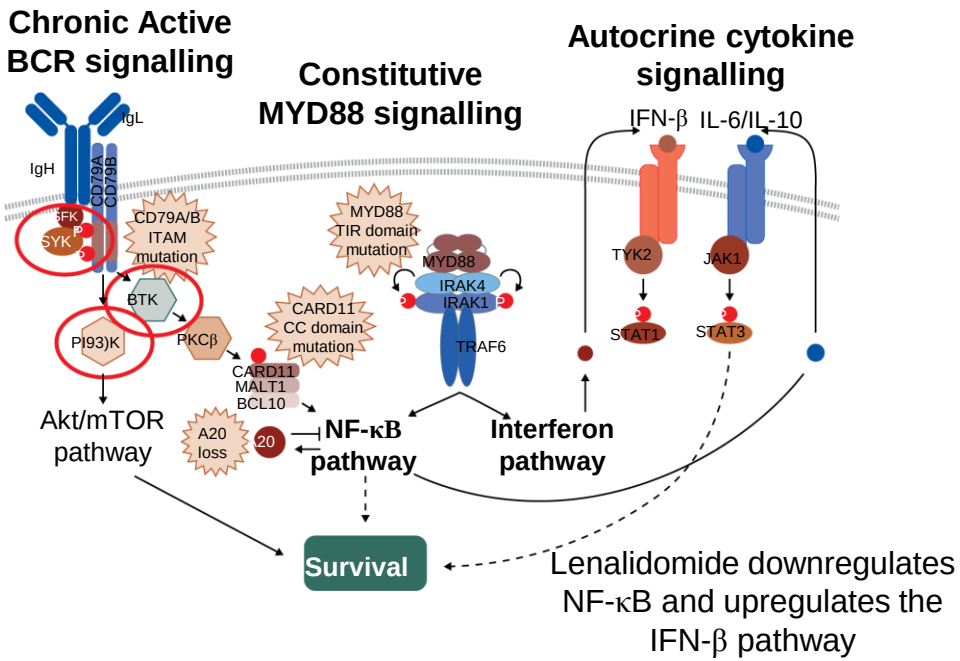
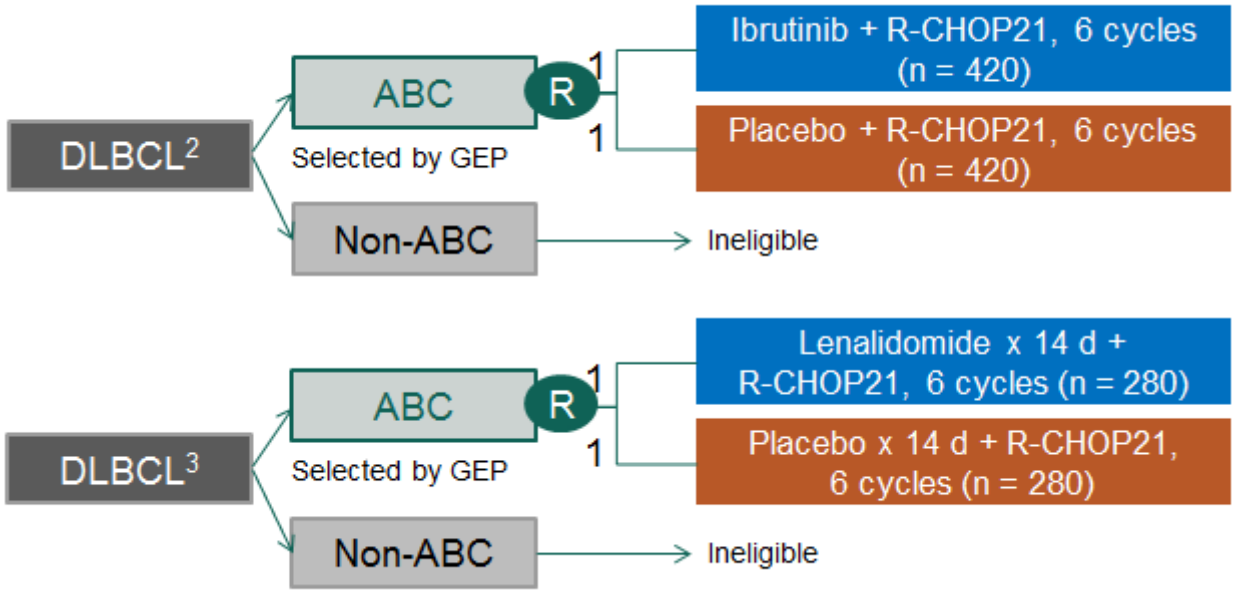
Lenalidomide and Ibrutinib in ABC-DLBCL: Phase 3 Trials Are Underway(‡)





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]

Stratified by R-IPI, region (US/Western Europe vs rest of world), no. prespecified R-CHOP cycles (6 vs 8)

6 or 8 x 21-d cycles

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)

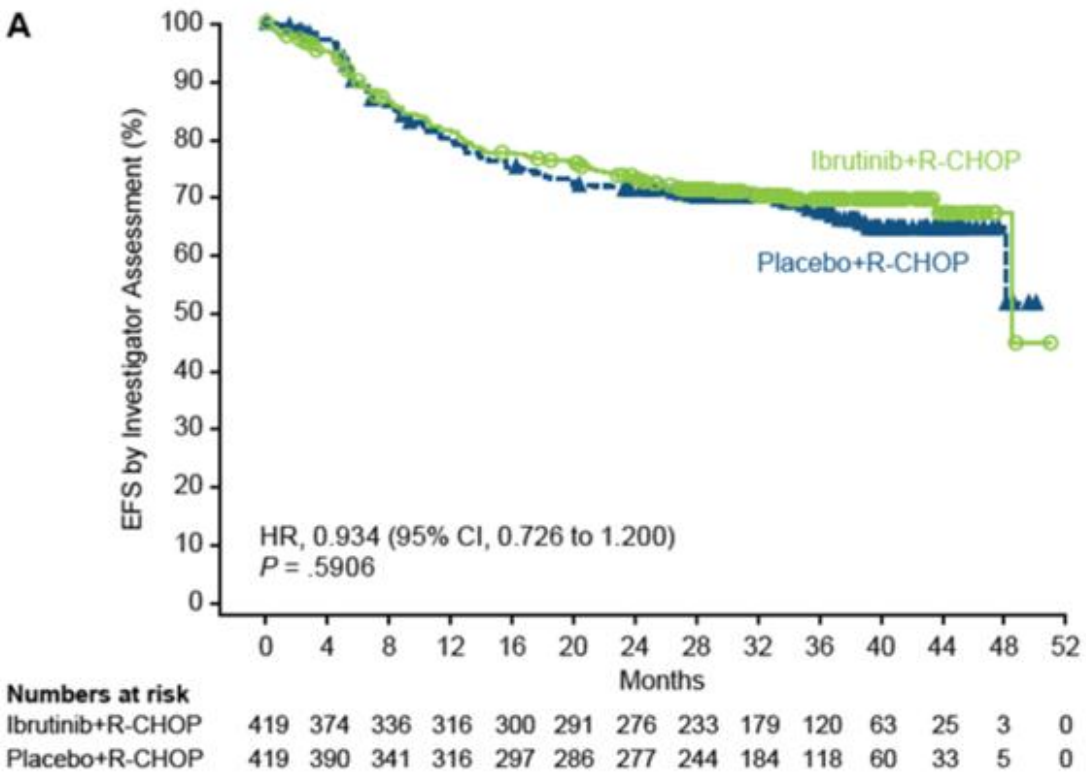
Placebo + **R-CHOP***
(n = 419)

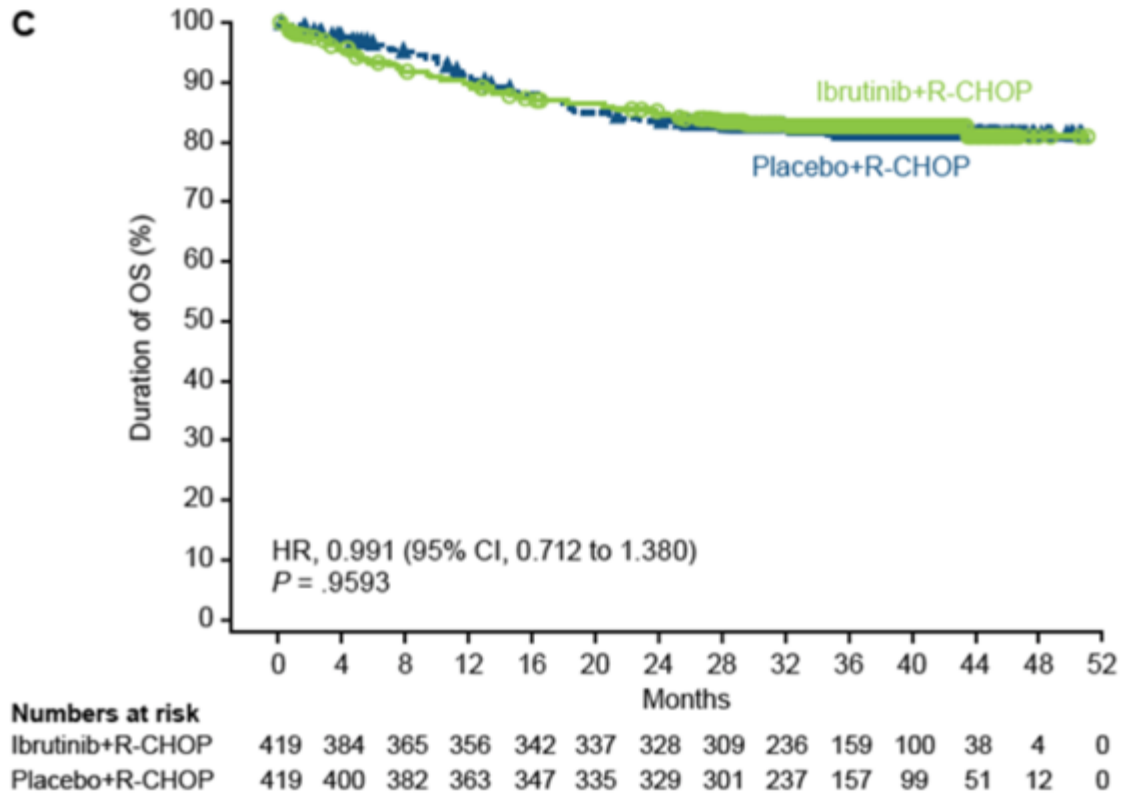
*Rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1, prednisone or equivalent 100 mg PO QD on Days 1-5. G-CSF and antibiotics permitted.[1,2]

- Primary endpoint: EFS in ITT population and ABC subgroup (determined retrospectively by gene expression profiling)
  - EFS events defined as PD, relapse from CR, starting subsequent disease-specific tx for PET-positive/biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death
- Secondary endpoints: CR rate, OS, PFS, safety
  - Response evaluated with Revised Response Criteria for Malignant Lymphoma[3]
- Exploratory stepwise analyses of potential interactions between treatment and prespecified BL characteristics for EFS and, if significant, PFS and OS

1. Younes. ASH 2018. Abstr 784. 2. NCT01855750. 3. Cheson. J Clin Oncol. 2007;25:579.

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





- **Addition of ibrutinib to R-CHOP did not significantly improve EFS in the ITT population or in those with ABC subtype**

Younes. ASH 2018. Abstr 784.

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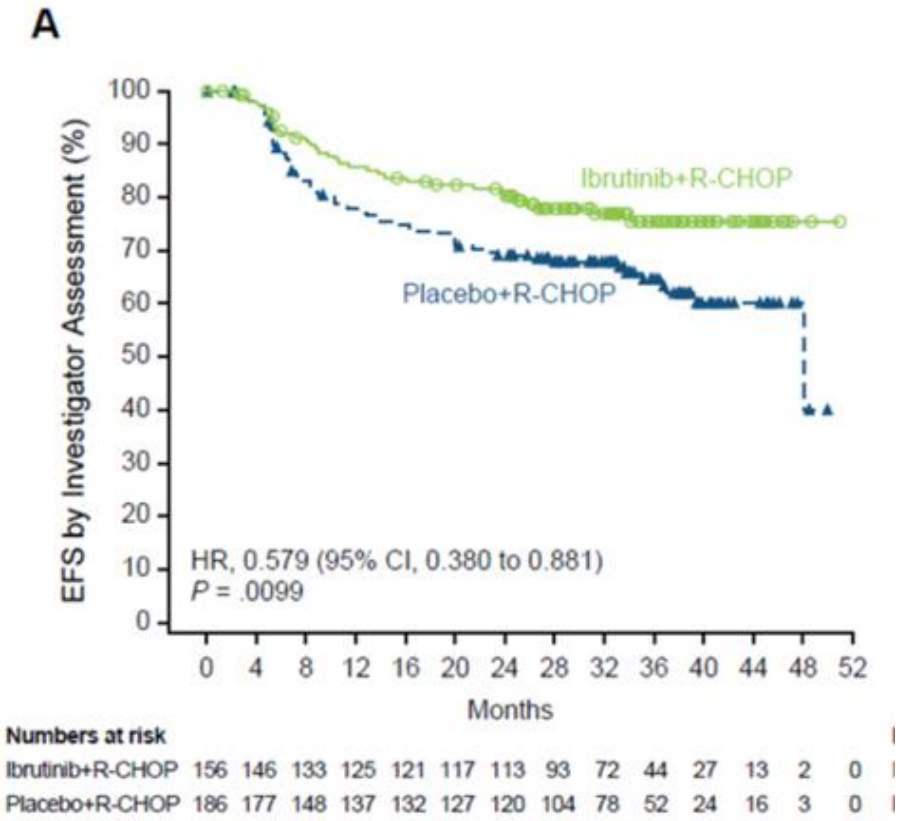
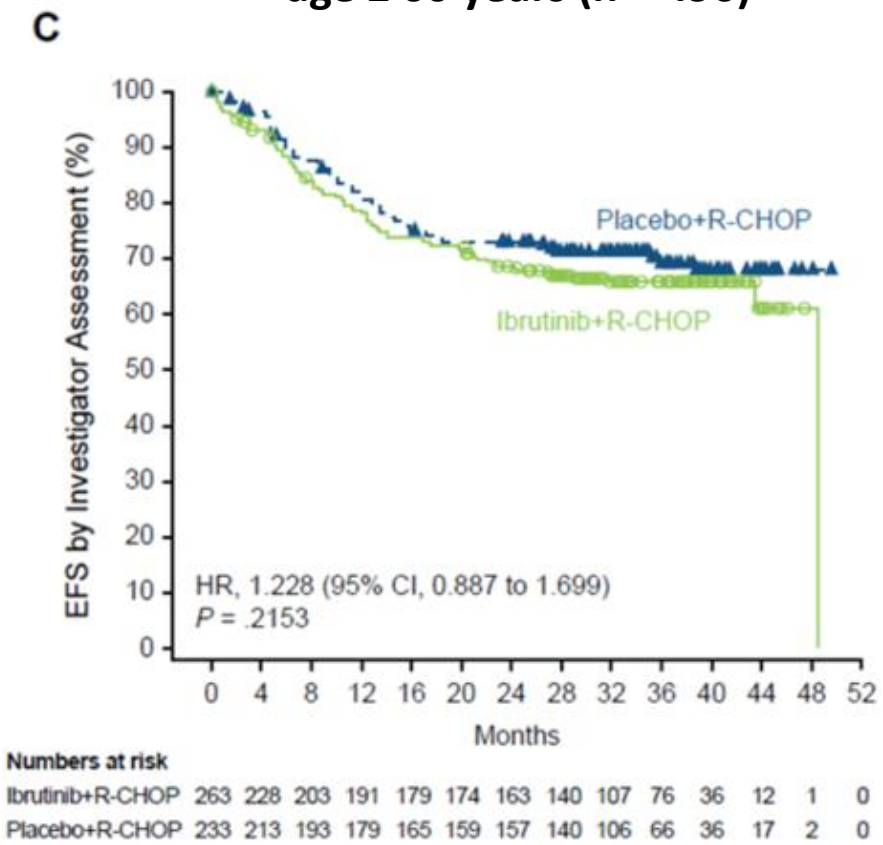
PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - EFS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)



Younes. ASH 2018. Abstr 784.

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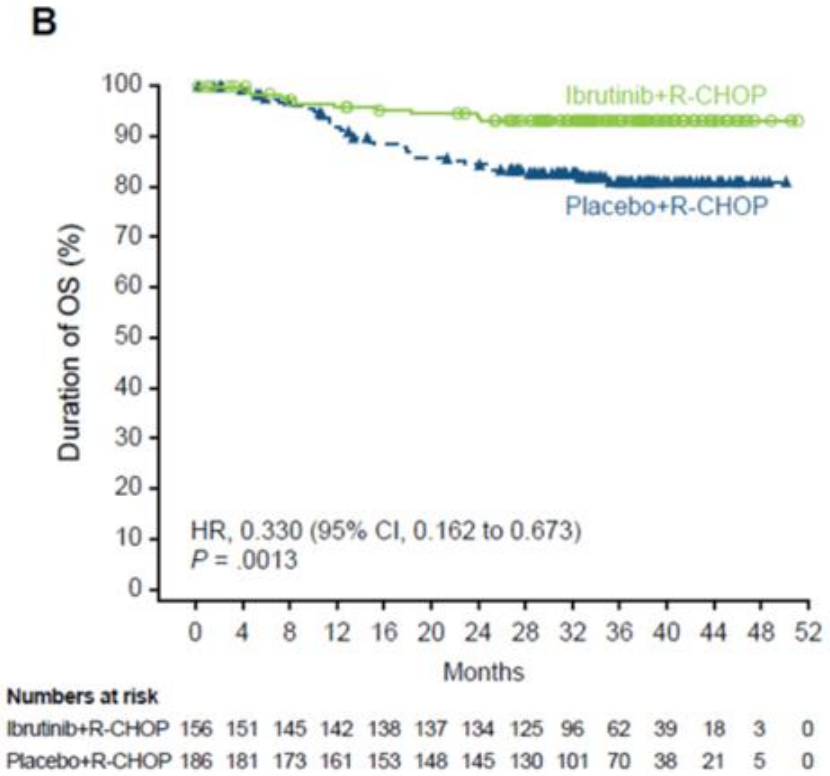
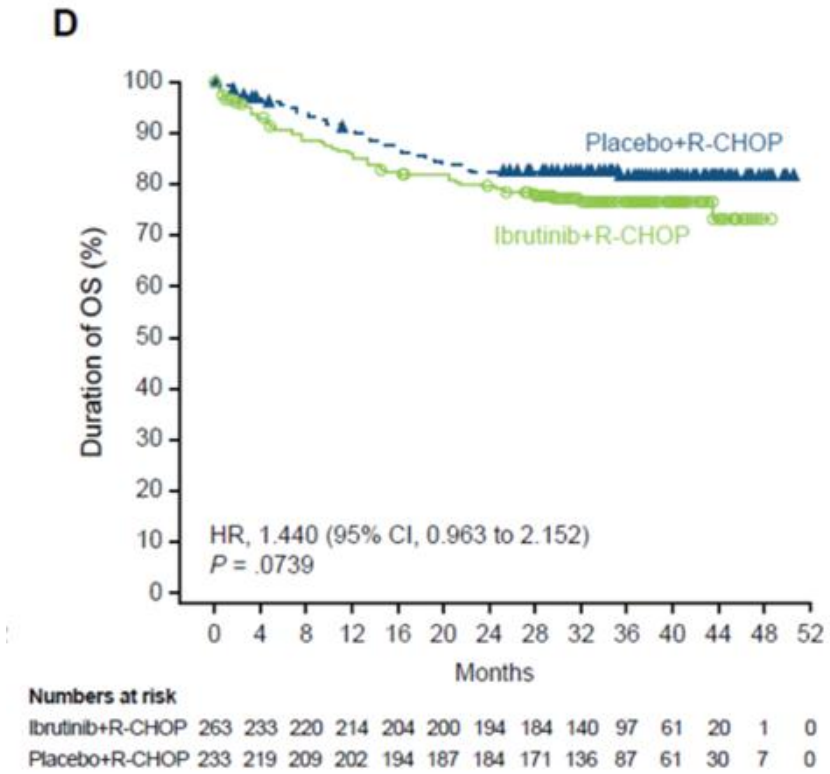
PHOENIX: R-CHOP +/- Ibrutinib in NGCB Subtypes of DLBCL - OS by Age (Subgroup Analysis)

age < 60 years (n = 342).



age ≥ 60 years (n = 496)



Younes. ASH 2018. Abstr 784.

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. ASH 2018. Abstr 784.

DLBCL leczenie I rzutu – refundacja w ramach NFZ

- **Program lekowy z Rituximabem ogranicza prawo chorych do leczenia zgodnie ze standardem, i jest w jawnej sprzeczności choćby z założeniami kart DILO**

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**

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2)

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): Study Design

- Multicenter, randomized, double-blind, active-controlled phase III trial (data cutoff: August 15, 2018)

Stratification for IPI score (0-1 vs 2-3 vs 4-5), histologic subtype (ALK+ sALCL vs other subtypes)

Adult patients with **previously untreated CD30+ (≥ 10% expression) PTCL*** (N = 452)

Brentuximab Vedotin† + **CHP**‡ Q3W for 6-8 cycles + **Placebo for Vincristine** (n = 226)

CHOP‡ Q3W for 6-8 cycles + **Placebo for Brentuximab Vedotin** (n = 226)

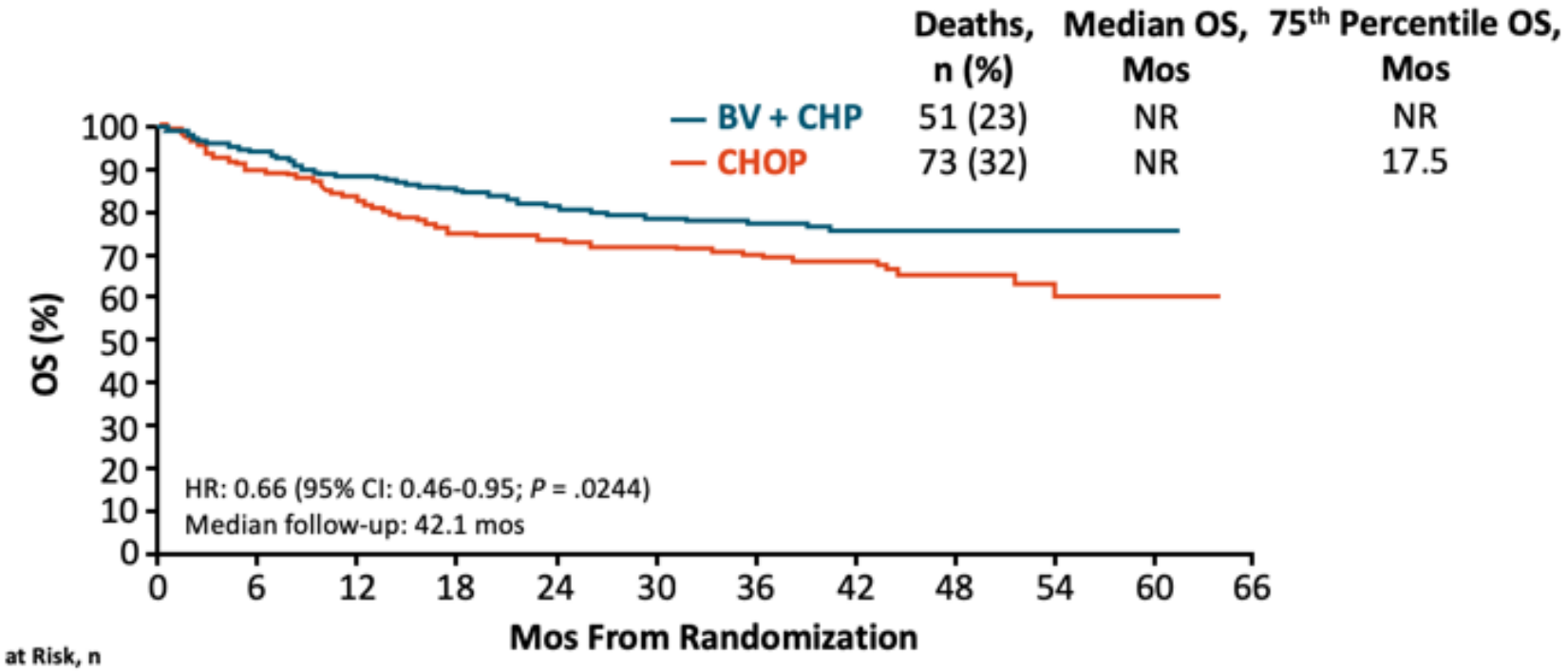
End-of-treatment PET

*PTCL includes sALCL (including ALK+ sALCL with IPI ≥ 2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin: 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL (ECHELON-2): OS (Secondary Endpoint)



Patients at Risk, n (Number Censored)

BV + CHP	226 (0)	208 (14)	193 (27)	184 (33)	159 (42)	128 (47)	108 (49)	83 (51)	45 (51)	20 (51)	4 (51)	0 (51)
CHOP	226 (0)	196 (24)	181 (39)	158 (57)	140 (60)	121 (63)	103 (66)	79 (68)	46 (71)	22 (72)	4 (73)	0 (73)

Horwitz. ASH 2018. Abstr 997. Horwitz. Lancet. 2018;[Epub].

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
- .....

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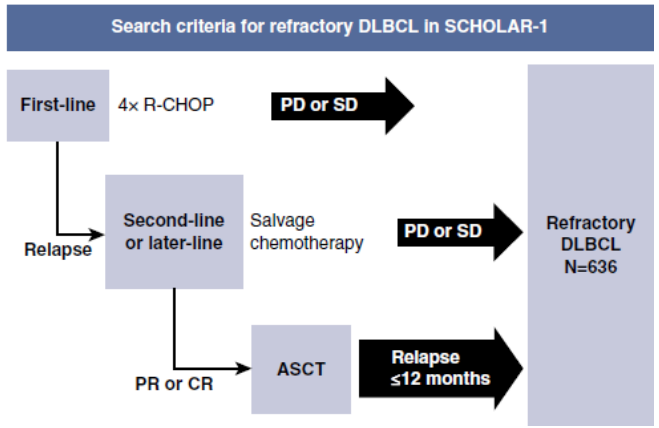
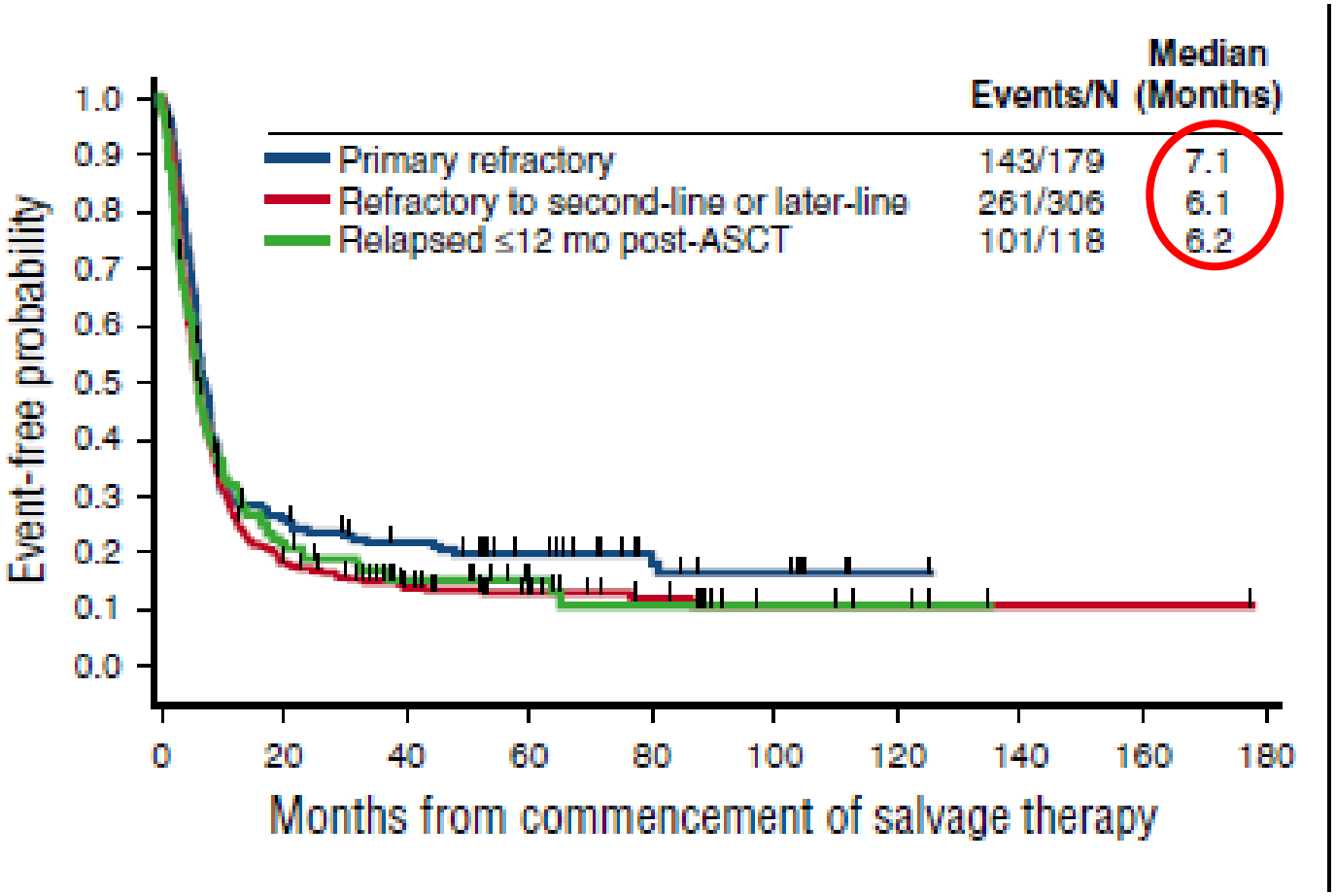
R/R DLBCL – SCHOLAR-1 study





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

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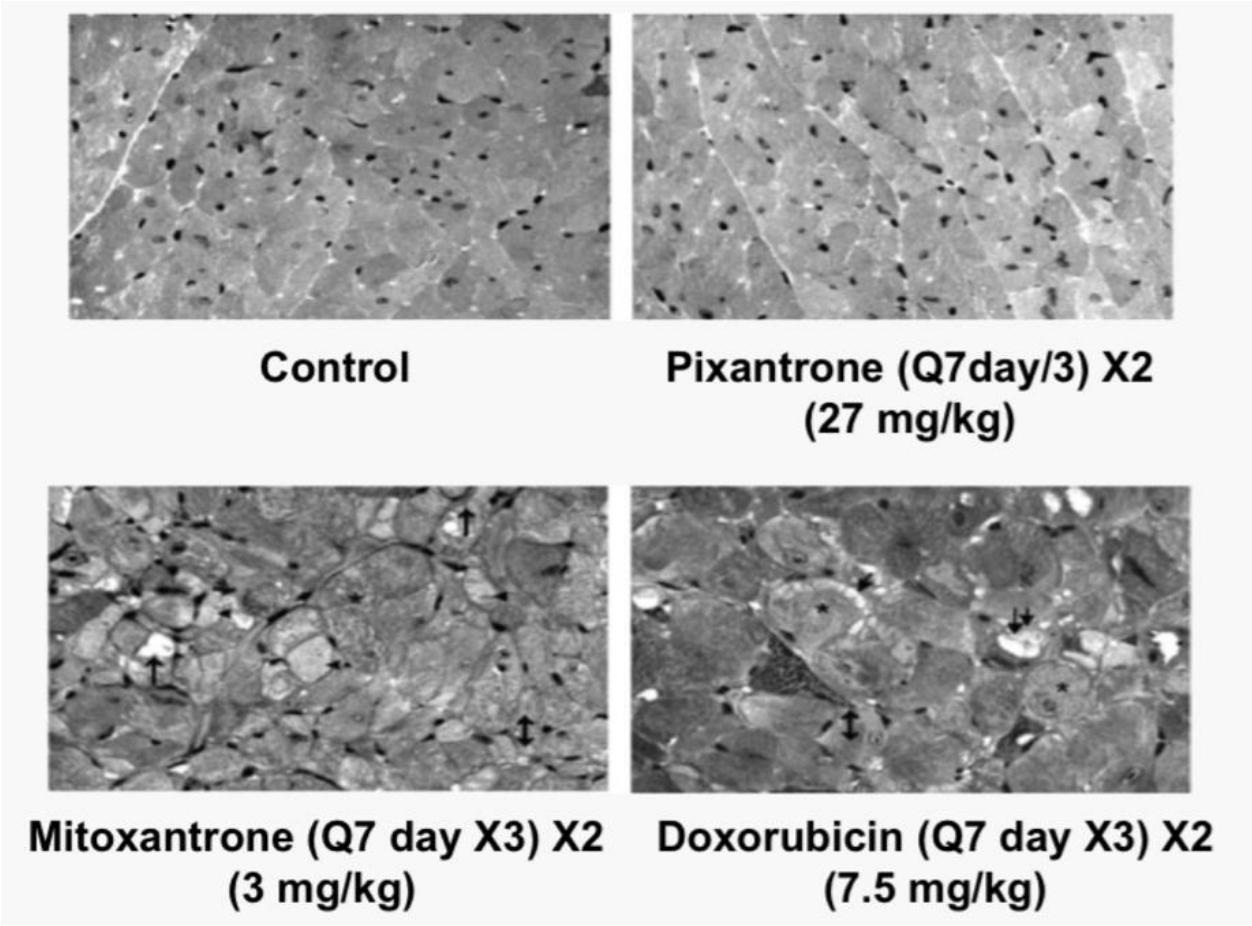
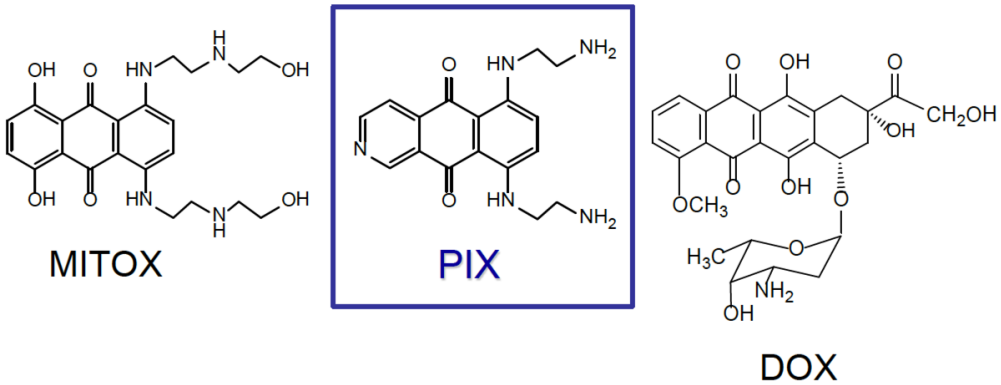
Pixantrone resembles anthracyclins, but is less cardiotoxic





By courtesy of SERVIER

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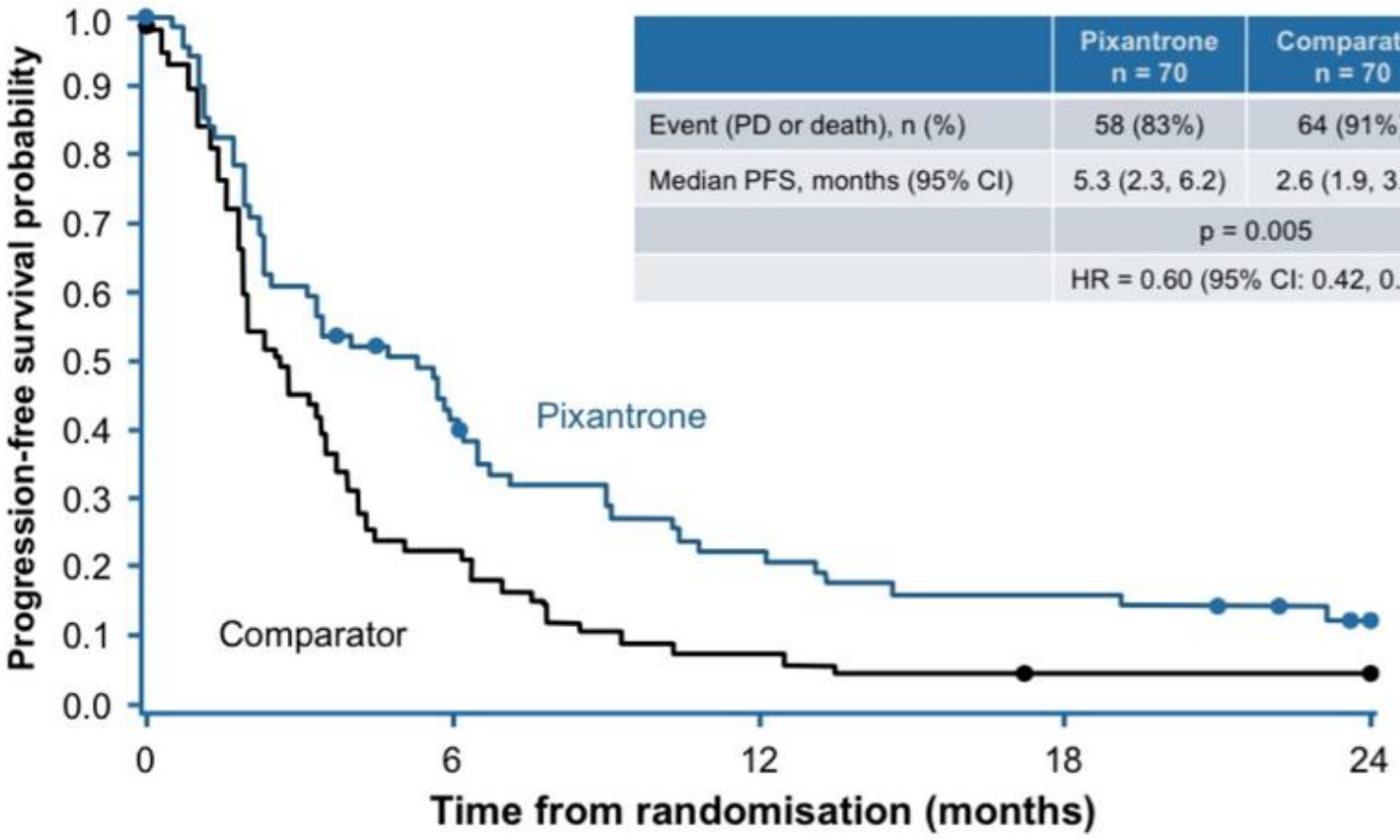
Pixantrone – registered for R/R DLBCL, 3rd line



	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.

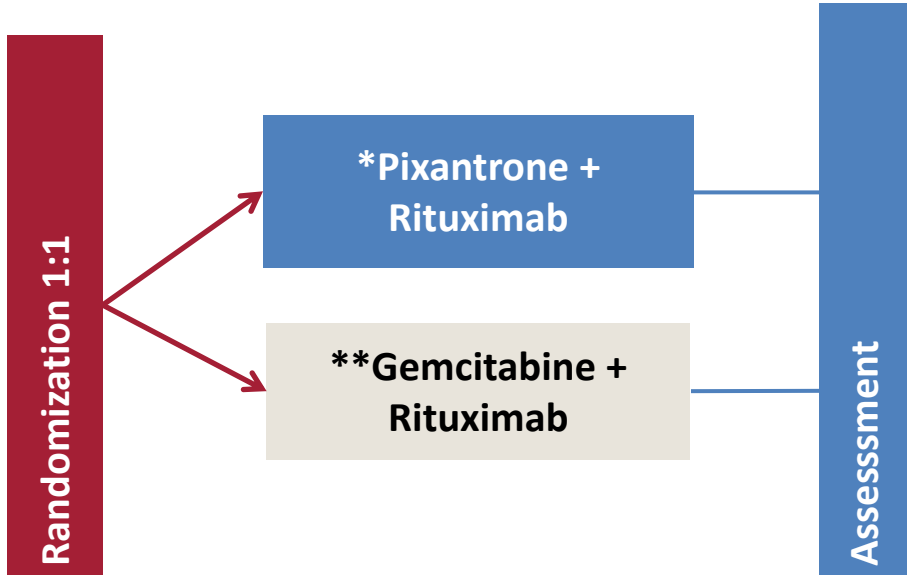
Pixantrone – ongoing phase III in R/R DLBCL, 2nd line

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

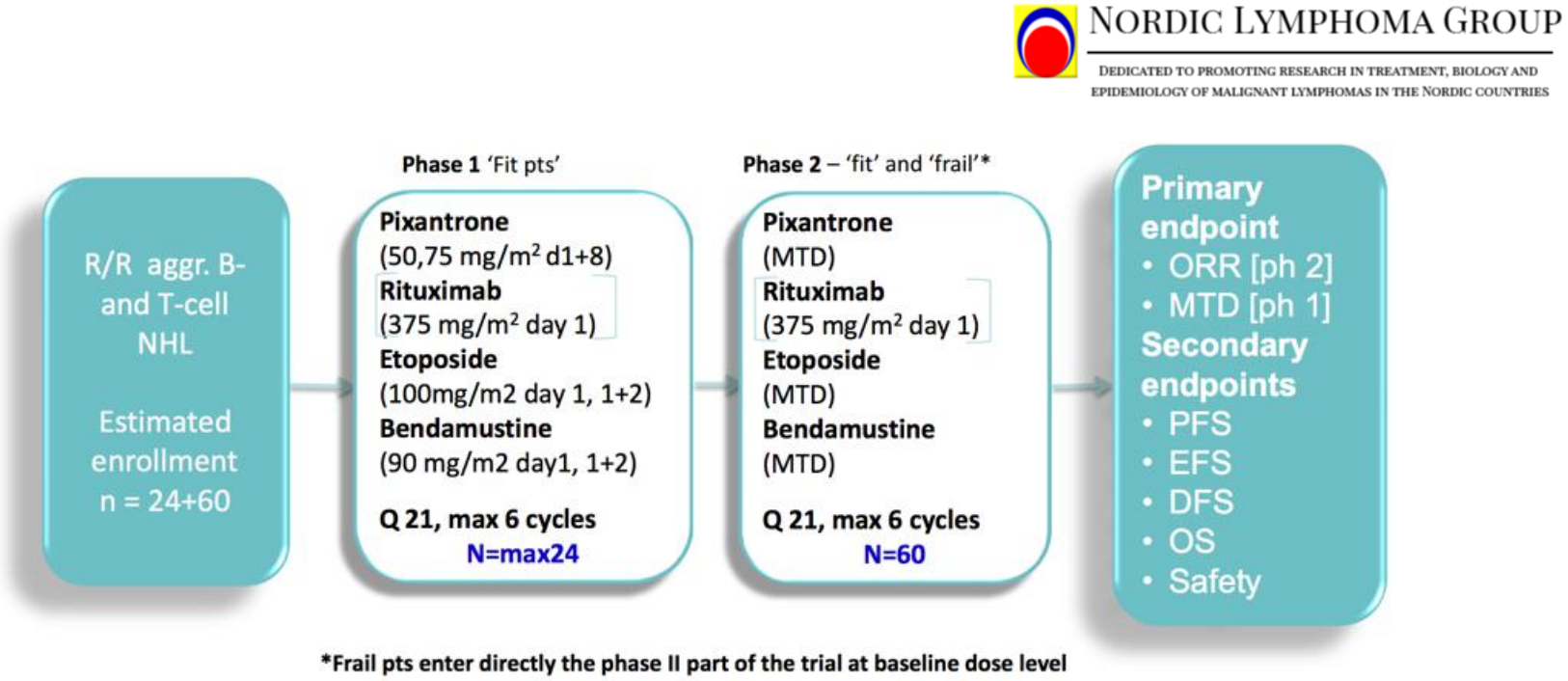


* Pixantrone + R: rituximab 375 mg/m^2 i.v. on Day 1 and pixantrone 50 mg/m2 IV on Days 1, 8, and 15. Regimen is given in 28-day cycles. Up to 6 cycles may be administered.

**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

PREBEN - Pixantrone, Etoposide, Bendamustine (& Rituximab)

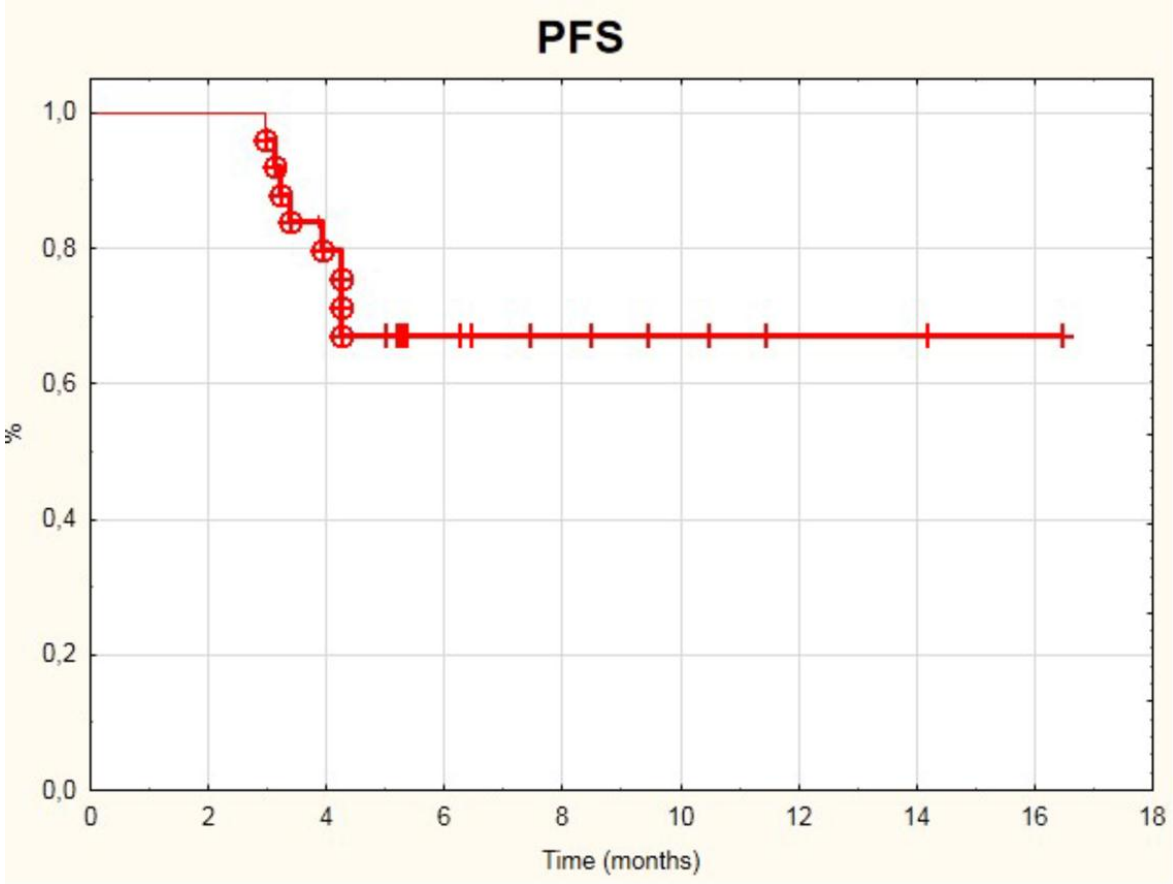


- CR in DLBCL (CR 40%, PR 20%) and PTCL (CR 25%, PR 50%)
- Response durations are in the range 4–17+ months
- Out-patient regimen
- Grade 3-4 infections in 40% of patients

Michael Roost Clausen et al., ASH 2016

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

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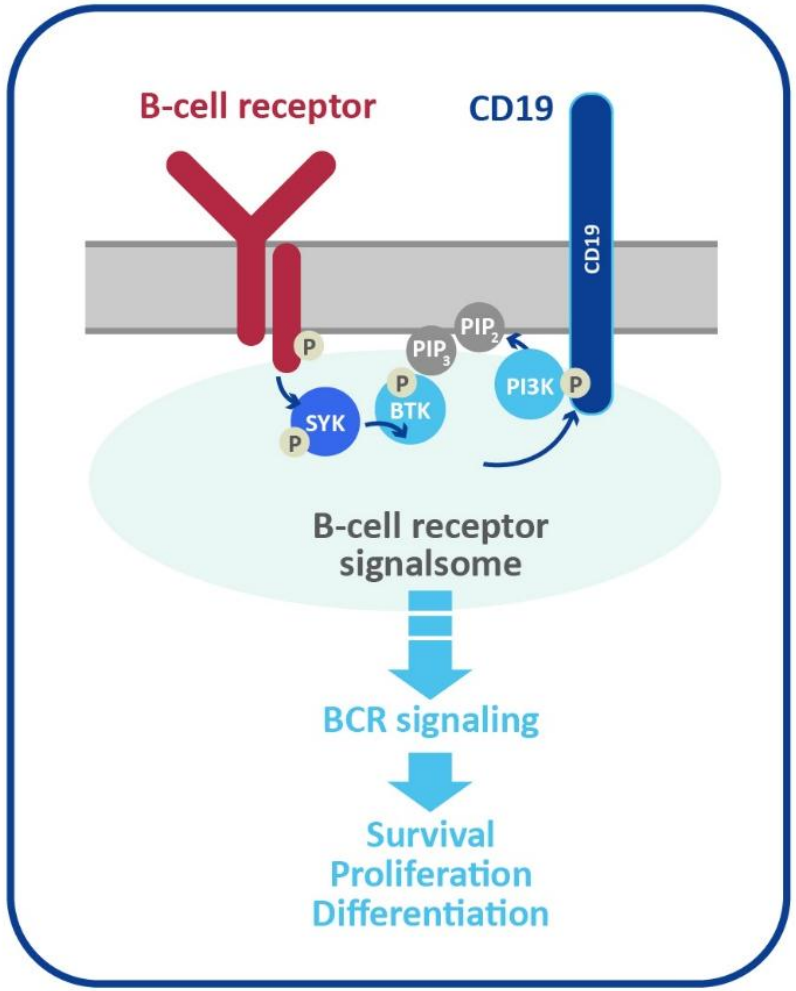
CD19: Role and therapeutic target

- 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]

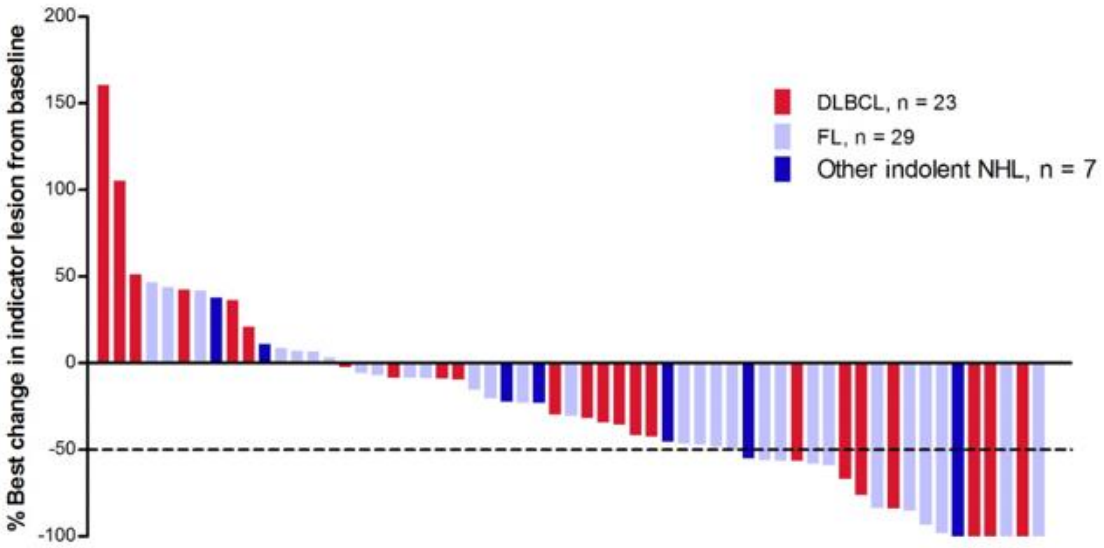
- CD19 expression is **maintained despite loss of CD20 expression** following treatment with CD20 antibodies[2]

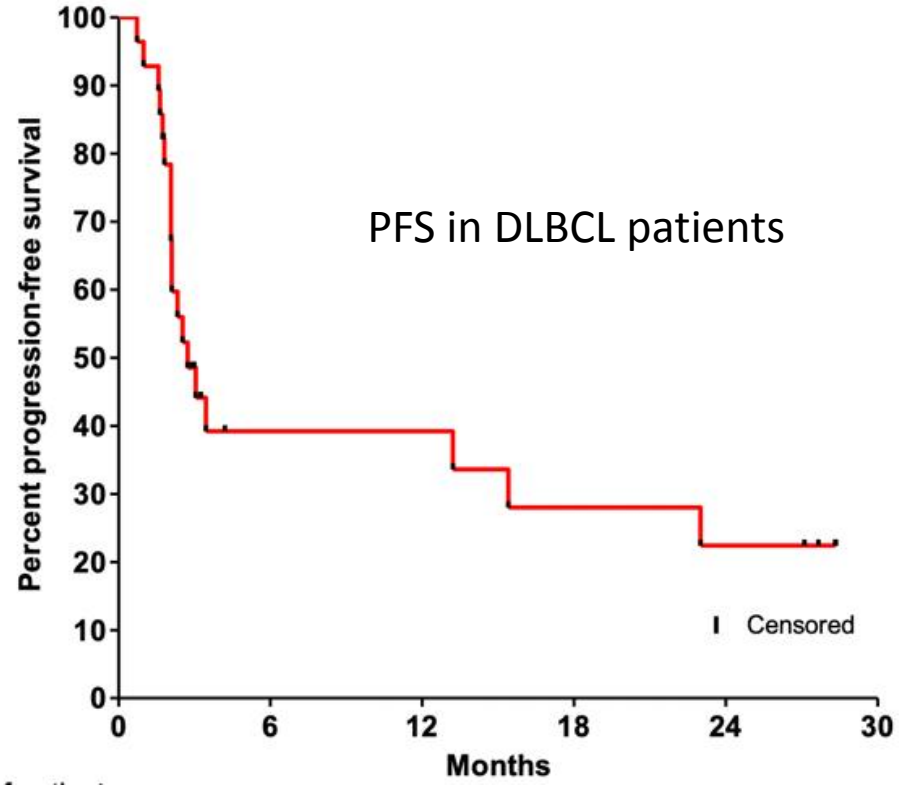
Therefore, **CD19** appears an **attractive target** for **new therapeutic approaches** to B-cell malignancies



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





Jurczak et al. – Ann Oncol 2018

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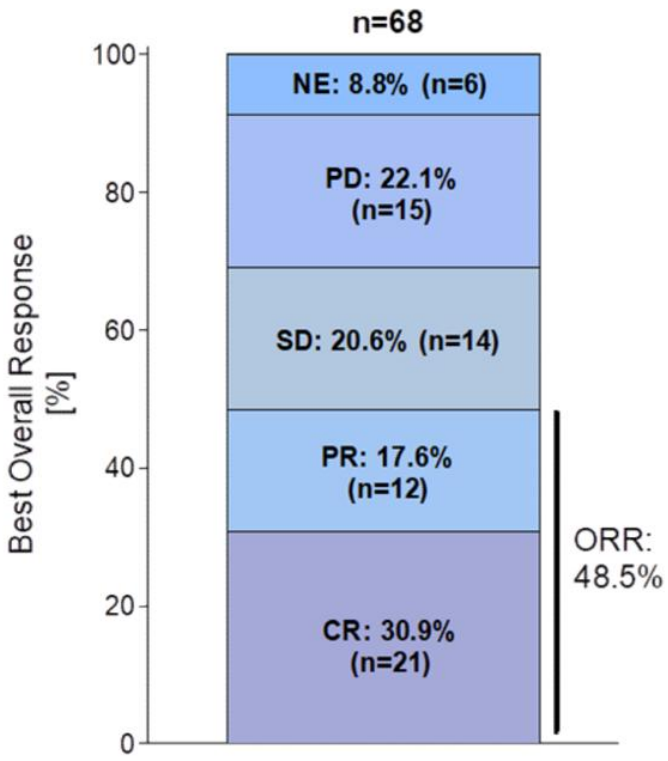
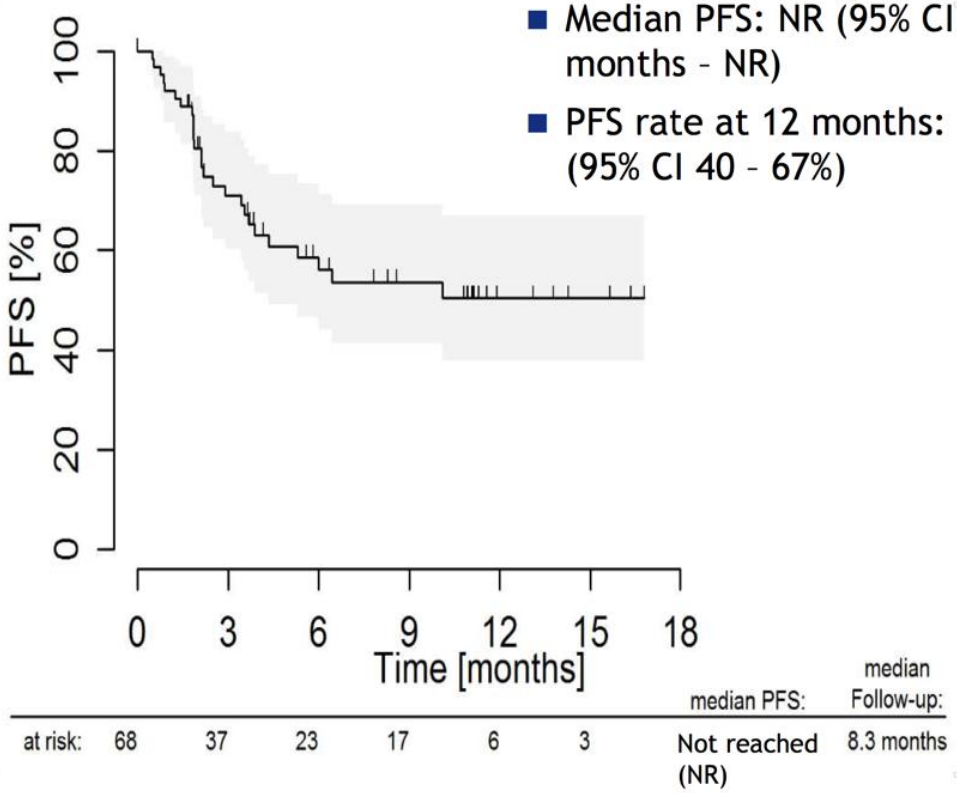
L-MIND trial (Lenalidomide + MOR 208)



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



- Median PFS: NR (95% CI 4.3 months - NR)
- PFS rate at 12 months: 50.4% (95% CI 40 - 67%)

- MOR208 in combination with lenalidomide showed highly encouraging efficacy

Data cut-off: December 12, 2017

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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

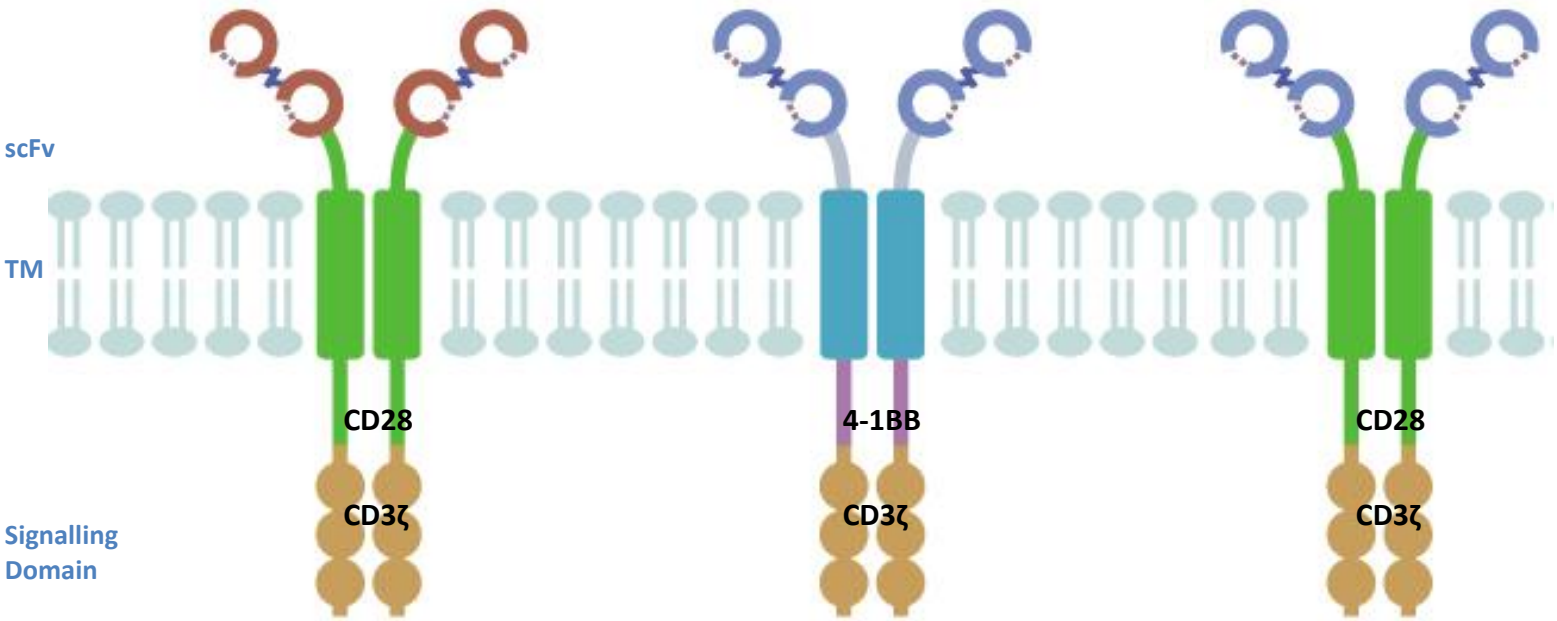
Lenalidomide **+ MOR208** (Phase II; preliminary data)[4]

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			
Gene transfer	Retrovirus	Lentivirus	Retrovirus



NCI
FMC63-28z

UPenn
CD19-BB-z

MSKCC
19-28z

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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

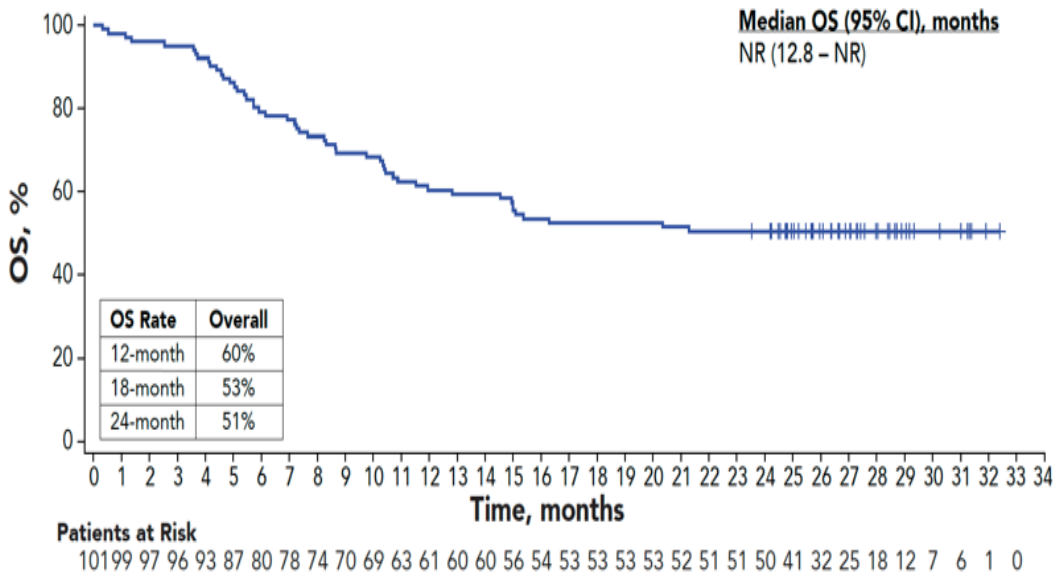
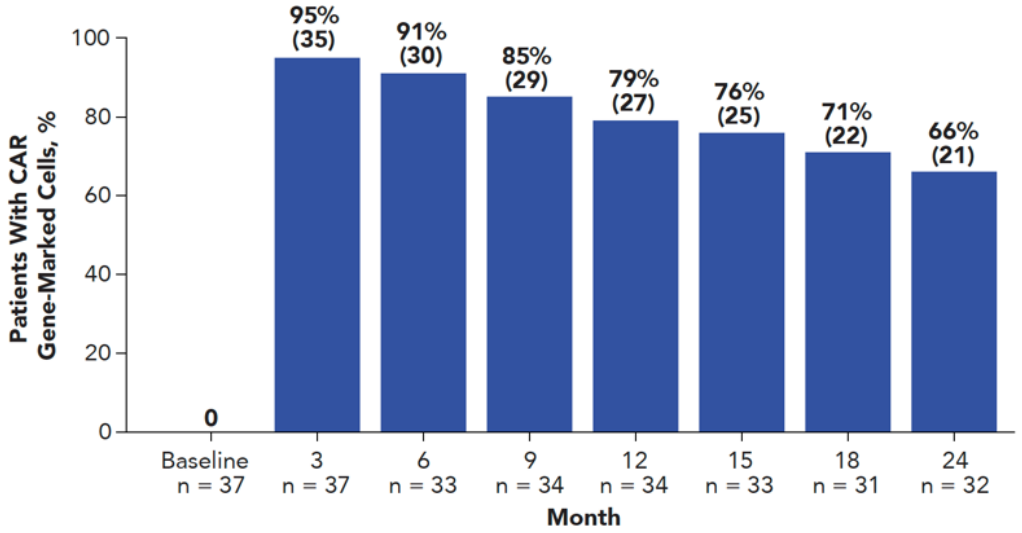


Figure 7. Proportion of Patients With Detectable CAR Gene-Marked T Cells in Blood Among Patients With Ongoing Response Over Time



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

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

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

Characteristic, n (%)	KEYNOTE-013 (N = 21)	KEYNOTE-170† (N = 53)	KEYNOTE-170‡ (N = 53)
OR	**10 (48)**	**24 (45)**	**23 (43)**
▪ **CR**	**7 (33)**	**7 (13)**	**11 (21)**
▪ **PR**	**3 (14)**	**17 (32)**	**12 (22)**
SD	5 (24)	5 (9)	5 (9)
PD	4 (19)	12 (23)	13 (25)
Nonevaluable/ no assessment*	2 (10)	12 (23)	12 (23)

*Insufficient data for response assessment.
†Cheson criteria.
‡Lugano criteria.

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, mos (range)**	**10.4 (3.4-NR)**	**5.5 (2.8-12.1)**
OS		
▪ 12-mo, %	65	58
▪ Median, mos (range)	31.4 (4.9-NR)	NR (7.3-NR)

§2 patients converted from PR to CR after 12 mos; 4 patients maintained CR after 2 yrs on treatment (2.3+, 2.5+, 3+, 3.5+ yrs).
‖No relapses in patients with CR reported at database lock.

Armand. ASH 2018. Abstr 228.

DLBCL w Klinice Hematologii UJCM

Journal of the American Society of Hypertension 8(11) (2014) 791–799

Research Article

Pre-existing arterial hypertension as a risk factor for early left ventricular systolic dysfunction following (R)-CHOP chemotherapy in patients with lymphoma

Sebastian Szmit, MD, PhD[a,*], Wojciech Jurczak, MD, PhD[b], Jan Maciej Zaucha, MD, PhD[c], Joanna Drozd-Sokołowska, MD, PhD[d], Wojciech Spychałowicz, MD, PhD[e], Monika Joks, MD, PhD[f], Monika Długosz-Danecka, MD[b], and Adam Torbicki, MD, PhD, FESC[a]

[a]Department of Pulmonary Circulation and Thromboembolic Diseases, Centre of Postgraduate Medical Education, Otwock, Poland;
[b]Department of Hematology, Jagiellonian University, Krakow, Poland;
[c]Department of Propedeutic Oncology, Medical University of Gdansk and Gdynia Oncology Center, Gdynia, Poland;
[d]Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland;
[e]Internal Medicine and Oncology Clinic, Silesian Medical University, Katowice, Poland; and
[f]Department of Hematology, University of Medical Sciences, Poznan, Poland

Manuscript received April 28, 2014 and accepted August 13, 2014

Abstract

Experimental studies in animals suggest that arterial hypertension may be a specific risk factor predisposing to anthracycline cardiotoxicity. The aim was determination of the effect of pre–existing arterial hypertension on the development of early left ventricular systolic dysfunction (LVSD) directly after rituximab, cyclophosphamide, doxorubicin, vincristin, prednisone ([R]-CHOP) chemotherapy in patients with lymphomas.The study included 208 patients with non-Hodgkin's lymphoma receiving conventional doxorubicin. LVSD was defined as a decrease of left ventricular ejection fraction below 50% and at least by 10 percentage points from baseline value. Patients with pre-existing hypertension more frequently developed new LVSD (19.7% vs. 6.6%; $P = .004$), pitting edema of the ankles (23.9% vs. 9.5%; $P = .005$), and nycturia (21.1% vs. 7.3%; $P = .004$) compared with patients without hypertension. As a consequence, the hypertension subgroup suffered from more delays of subsequent chemotherapy cycles (26.8% vs. 14.6%; $P = .03$), more reductions of doxorubicin doses (18.3% vs. 8.8%; $P = .05$), and premature discontinuations of chemotherapy (16.9% vs. 7.3%; $P = .03$). On logistic regression analyses, hypertension was one of the most important risk factors for developing new LVSD after (R)-CHOP chemotherapy.Arterial hypertension confers a significant risk of early LVSD in lymphoma patients treated with (R)-CHOP chemotherapy, interfering with its recommended schedule of administration. J Am Soc Hypertens 2014;8(11):791–799. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Cardiac damage; doxorubicin; prevention.

ORIGINAL ARTICLE

Role of rituximab in the first-line therapy of high-risk diffuse large B-cell lymphoma: a retrospective analysis by the Polish Lymphoma Research Group

Wojciech Jurczak[1], Bogdan Ochrem[1], Agnieszka Giza[1], Dagmara Zimowska-Curyło[1], Tomasz Górecki[1], Piotr Boguradzki[2], Wanda Knopińska-Posłuszny[3], Beata Stella-Hołowiecka[4], Jan Walewski[5], Monika Joks[6], Tomasz Wróbel[7], Jan M. Zaucha[8]

1 Department of Hematology, The University Hospital in Krakow, Kraków, Poland
2 Department of Hematology, Oncology and Internal Medicine, Central Clinical Hospital of the Ministry of the Interior in Warsaw, Warsaw, Poland
3 Department of Hematology and Transplantation, University Clinical Centre, Gdańsk, Poland
4 Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland
5 Department of Lymphoid Malignancies, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
6 Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznań, Poland
7 Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wrocław Medical University, Wrocław, Poland
8 Department of Propedeutic Oncology, Medical University of Gdansk, Gdańsk, Poland

KEY WORDS

CHOP protocol, diffuse large B-cell lymphoma, immunochemotherapy, International Prognostic Index, rituximab

ABSTRACT

INTRODUCTION R-CHOP immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is a standard first-line treatment for diffuse large B-cell lymphoma (DLBCL). None of the randomized trials have proved a statistically significant overall survival (OS) benefit in high-risk subgroups according to the International Prognostic Index (IPI).

OBJECTIVES We retrospectively investigated the role of adding rituximab to anthracycline-based chemotherapy in patients with high-risk DLBCL according to the IPI.

PATIENTS AND METHODS A total of 371 patients with high-risk DLBCL treated at 15 Polish hematology centers were retrospectively analyzed in 2 distinct age groups: older than 60 years and 60 years old or younger. Response rates, OS, and progression-free survival (PFS) were compared and analyzed.

RESULTS The overall response rate (ORR) of high-risk DLBCL patients significantly improved in rituximab-treated patients compared with patients treated without rituximab (78.7% vs 95.6%, $P < 0.05$). The R-CHOP immunochemotherapy prolonged survival in both older and younger subgroups. The 5-year projected OS and PFS in younger patients treated with rituximab vs chemotherapy alone were 42% vs 38% and 48% vs 27%, respectively ($P < 0.05$), while the 5-year projected OS and PFS in older patients treated with rituximab vs chemotherapy alone were 82% vs 52% and 67% vs 45%, respectively ($P < 0.05$).

CONCLUSIONS With all the limitations of a retrospective analysis, the superiority of adding rituximab to CHOP combination chemotherapy has been clearly demonstrated regarding ORR, OS, and PFS in both age subgroups of patients with high-risk DLBCL.

Correspondence to:
Bogdan Ochrem, MD,
Oddział Kliniczny Hematologii,
Szpital Uniwersytecki w Krakowie,
ul. Mikołaja Kopernika 17,
31-501 Kraków, Poland,
phone: (+48 12) 424 78 02,
fax: (+48 12) 424 78 23,
e-mail: bogdanochrem@gmail.com

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Premature cardiovascular mortality in lymphoma patients treated with (R)-CHOP regimen — A national multicenter study

Wojciech Jurczak [a], Sebastian Szmit [b,*], Marcin Sobociński [a], Maciej Machaczka [c], Joanna Drozd-Sokołowska [d], Monika Joks [e], Justyna Dzietczenia [f], Tomasz Wróbel [f], Beata Kumiega [g], Jan Maciej Zaucha [h], Wanda Knopińska-Posłuszny [i], Wojciech Spychałowicz [j], Anna Prochwicz [a], Anna Drohomirecka [k], Aleksander B. Skotnicki [a]

[a] Department of Hematology, Jagiellonian University, Krakow, Poland
[b] Department of Pulmonary Circulation and Thromboembolic Diseases, The Centre of Postgraduate Medical Education, European Health Centre Otwock, Poland
[c] Karolinska University Hospital Huddinge, Stockholm, Sweden
[d] Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland
[e] Department of Hematology, University of Medical Sciences, Poznan, Poland
[f] Department of Haematology, Wrocław Medical University, Wrocław, Poland
[g] Departament of Hematooncology, Markiewicz Memorial Oncology Center Brzozow, Brzozow, Poland
[h] Department of Propedeutic Oncology, Medical University of Gdansk and Gdynia Oncology Center, Poland
[i] Hematology Department, Independent Public Health Care Ministry of the Interior of Warmia and Mazury Oncology Center, Olsztyn, Poland
[j] Internal Medicine and Oncology Clinic, Silesian Medical University, Katowice, Poland
[k] Independent Researcher, Warsaw, Poland

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ABSTRACT

Background: Premature cardiovascular mortality related to chemotherapy and occurred in lymphoma survivors before disease progression is one of significant clinical failure of modern hematology. The aim of this retrospective analysis was to evaluate early cardiovascular mortality and its predictors in patients treated with the (R)-CHOP regimen.

Methods: The study assessed 610 patients: 581 patients were treated with non-liposomal doxorubicin (cumulative dose of 337 ± 96 mg/m2), and 29 patients with liposomal non-pegylated doxorubicin (cumulative dose of 237 ± 126 mg/m2). Their present status, history of cardiovascular diseases and associated risk factors were recorded.

Results: The analysis identified 93 deaths (15.5%): 51 cases (55%) related to lymphoma disease progression and 28 (30%) to cardiovascular complications. Multivariate Cox analysis revealed history of previous heart diseases (HR = 4.71; CI: 3.82–5.6; p < 0.001), ECG rhythm abnormalities related to chemotherapy (HR = 4.78; CI: 3.63–5.92; p = 0.01), and lack of complete remission (HR = 2.73; CI: 1.78–3.66; p = 0.03), as the independent predictors for cardiovascular death. Neither decreased LVEF nor increasing cumulative dose of anthracyclines had a significant predictive value for cardiovascular prognosis.

Conclusions: The study indicated that cardiovascular mortality in lymphoma patients treated with (R)-CHOP regimen is relatively high and ECG monitoring may be the most effective in cardiological risk assessment. The unfavorable outcome depended on lack of complete remission that seems to be a consequence of patients' individual susceptibility for cardiac events, which should become a purpose of further trials.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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doi:10.1093/annonc/mdy056
Published online 9 February 2018

ORIGINAL ARTICLE

Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma

W. Jurczak[1]*, P. L. Zinzani[2], G. Gaidano[3], A. Goy[4], M. Provencio[5], Z. Nagy[6], T. Robak[7], K. Maddocks[8], C. Buske[9], S. Ambarkhane[10], M. Winderlich[10], M. Dirnberger-Hertweck[10], R. Korolkiewicz[10] & K. A. Blum[8]

[1]Department of Hematology, Jagiellonian University, Kraków, Poland; [2]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna; [3]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy; [4]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, USA; [5]Department of Medical Oncology, University Hospital Puerta De Hierro, Madrid, Spain; [6]First Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [7]Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland; [8]Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, USA; [9]Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital of Ulm, Ulm; [10]MorphoSys AG, Planegg, Germany

*Correspondence to: Dr Wojciech Jurczak, Department of Hematology, Jagiellonian University, Kopernika 17, 30-501 Kraków, Poland. Tel: +48-60233829; E-mail: wojciech.jurczak@uj.edu.pl

Background: This two-stage, phase IIa study investigated the antitumor activity and safety of MOR208, an Fc-engineered, humanized, CD19 antibody, in patients with relapsed or refractory (R-R) B-cell non-Hodgkin's lymphoma (NHL). CD19 is broadly expressed across the B-lymphocyte lineage, including in B-cell malignancies, but not by hematological stem cells.

Patients and methods: Patients aged ≥18 years, with R-R NHL progressing after ≥1 prior rituximab-containing regimen were enrolled into subtype-specific cohorts: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), other indolent (i)NHL and mantle cell lymphoma (MCL). Treatment was MOR208, 12 mg/kg intravenously, weekly, for 8 weeks. Patients with at least stable disease could continue treatment for an additional 4 weeks. Those with a partial or complete response after 12 weeks could receive extended MOR208 treatment (12 mg/kg, either monthly or every second week) until progression. The primary end point was overall response rate.

Results: Ninety-two patients were enrolled: DLBCL ($n = 35$), FL ($n = 34$), other iNHL ($n = 11$) and MCL ($n = 12$). Responses were observed in DLBCL, FL and other iNHL cohorts (26%, 29% and 27%, respectively). They lasted ≥12 months in 5/9 responding patients with DLBCL, 4/9 with FL and 2/3 with other iNHL. Responses in nine patients are ongoing (>26 months in five instances). Patients with rituximab refractory disease showed a similar response rate and progression-free survival time to patients with non-refractory disease. The most common adverse events (any grade) were infusion-related reactions (12%) and neutropenia (12%
neutropenia. No t

Conclusions: MO
in patients with ri
MOR208 in phase

ClinicalTrials.go

Key words: CD1

ORIGINAL ARTICLE

Central nervous system prophylaxis with intrathecal liposomal cytarabine in diffuse large B-cell lymphomas

Katarzyna Krawczyk[1], Wojciech Jurczak[1], Monika Długosz-Danecka[1], Agnieszka Zauska-Giza[1], Justyna Dzietczenia[2], Tomasz Wróbel[2], Aleksander B. Skotnicki[1]

1 Department of Hematology, Jagiellonian University Medical College, Kraków, Poland
2 Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Medical University of Wroclaw, Wroclaw, Poland

KEY WORDS

central nervous system prophylaxis, liposomal cytarabine, non-Hodgkin lymphoma

ABSTRACT

INTRODUCTION Central nervous system (CNS) involvement is a serious and potentially fatal complication in patients with lymphoma because it is associated with a particularly poor prognosis (median progression-free survival [PFS] of 4–8 months). Although CNS prophylaxis is considered necessary, there are no clear guidelines on identifying high-risk patients or selecting treatment regimen.

OBJECTIVES The aim of the study was to assess the safety and efficacy of CNS prophylaxis with intrathecal liposomal cytarabine.

PATIENTS AND METHODS We analyzed the data of 79 patients (46 men and 33 women; median age, 48.5 years [20–79]) with diffuse large B-cell lymphoma (83.5% of the patients) and primary mediastinal large B-cell lymphoma (16.5%). Patients were treated in the departments of hematology in Kraków and Wrocław, Poland, between the years 2009–2012. They were considered to be at a high risk of developing CNS involvement associated with a lymphoma.

RESULTS Adverse reactions after intrathecal liposomal cytarabine were reported in 59 patients (74.7%); in 7 cases, the reactions were severe. The most common side effect was headache (67.1%). During antilymphoma therapy and prophylaxis, the functional status assessed by the Karnofsky score improved in 56 patients (70.9%) and remained unchanged in the remaining cases. A median follow-up time did not exceed 28 months (range, 1.4–52.1); during follow-up, neither median overall survival (OS) nor PFS were reached (projected OS and PFS at 48 months are 86.1% and 90.1%, respectively).

CONCLUSIONS Our results encourage the use of intrathecal liposomal cytarabine in CNS prophylaxis in patients with lymphoma.

Liposomal cytarabine in the prophylaxis and treatment of CNS lymphoma: toxicity analysis in a retrospective case series study conducted at Polish Lymphoma Research Group Centers

Wojciech Jurczak · Renata Kroll-Balcerzak · Sebastian Giebel · Maciej Machaczka · Agnieszka Giza · Tomasz Ogórka · Szymon Fornagiel · Justyna Rybka · Tomasz Wróbel · Beata Kumiega · Aleksander B. Skotnicki · Mieczysław Komarnicki

Received: 11 September 2014 / Accepted: 13 February 2015 / Published online: 26 February 2015

Abstract Lymphomas with primary or secondary involvement of central nervous system (CNS) have poor prognosis despite specific treatment protocols which include whole brain radiotherapy and high-dose systemic and/or intrathecal chemotherapy. Toxicity of intrathecal liposomal cytarabine-based regimens collected between November 2006 and January 2012 was assessed retrospectively. Data from 120 adult lymphoma patients with, or at high risk of CNS involvement who received intrathecal liposomal cytarabine-based regimens at six Polish Lymphoma Research Group centres between November 2006 and January 2012 were assessed retrospectively. Patients were divided into three cohorts: A (high risk of CNS disease, $n = 88$), B (cerebrospinal fluid pleocytosis without neurological symptoms or pathological imaging findings, $n = 7$), and C (CNS disease/neurological involvement; $n = 25$). In all examined groups, toxicity of treatment was found to be acceptable (including the prophylactic setting). None of the patients in cohorts A or B who took intrathecal liposomal cytarabine 50 mg, repeated every 2–4 weeks (mean 3.8 doses) had experienced a CNS relapse at a median follow-up time of 3 years. Patients in cohort C had a 76 % overall neurological response rate (including a 40 % complete response rate) and median overall survival of 4.8 years. Regimens incorporating liposomal cytarabine seem to be safe and effective treatments for lymphomas with CNS involvement.

Keywords Intrathecal liposomal cytarabine · CNS lymphoma · Prophylaxis

Accepted Manuscript

Acute decompensated heart failure as a reason of premature chemotherapy discontinuation may be independent of a lifetime doxorubicin dose in lymphoma patients with cardiovascular disorders

Sebastian Szmit, Wojciech Jurczak, Jan Maciej Zaucha, Monika Długosz-Danecka, Barbara Sosnowska-Pasiarska, Ewa Chmielowska, Monika Joks, Joanna Drozd-Sokołowska, Wanda Knopińska-Posłuszny, Wojciech Spychałowicz, Beata Kumiega, Grzegorz Charliński, Marta Morawska, Grzegorz Słomian

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ELSEVIER

Pharmacological Reports
Available online 6 February 2019
In Press, Accepted Manuscript

Pixantrone, etoposide, bendamustine with or without rituximab (P[R]EBEN) as an effective salvage regimen for relapsed/refractory aggressive non-Hodgkin lymphoma—Polish Lymphoma Research Group (PLRG) real-life analysis

Monika Długosz-Danecka [1], Iwona Hus [2], Bartosz Puła [3], Artur Jurczyszyn [1], Tomasz Chojnacki [4], Beata Blajer-Olszewska [5], Joanna Drozd-Sokołowska [6], Małgorzata Raźny [7], Joanna Romejko-Jarosińska [8], Michał Taszner [9], Wojciech Jurczak [1]

Show more

https://doi.org/10.1016/j.pharep.2019.02.001

Prof. Wojc

R/R DLBCL - podsumowanie

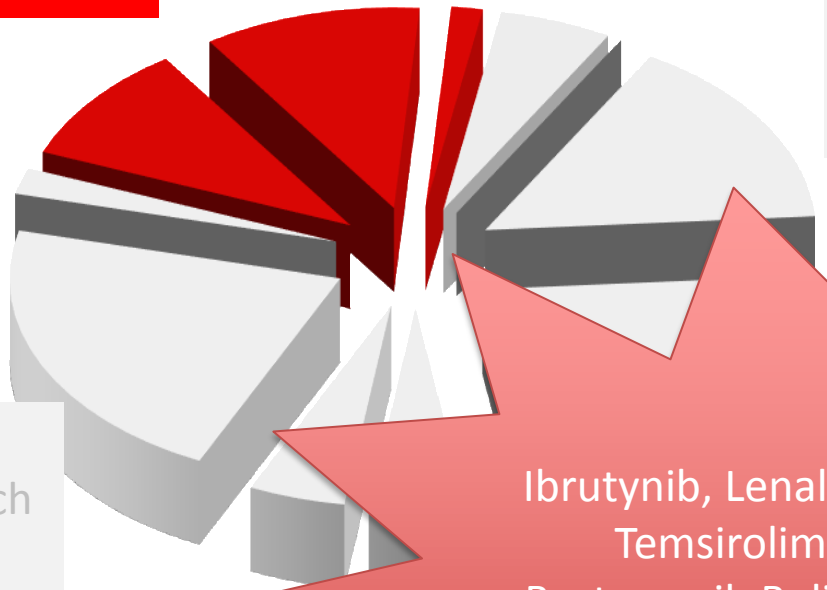
- **Im lepsze są wyniki leczenia I rzutu, tym gorzej rokują chorzy ze wznową/ opornością procesu**
- Małe prawdopodobieństwo wieloletnich remisji chorych leczonych „chemioterapią ratującą”, **spadek znaczenia ASCT**
- **Male prawdopodobieństwo wieloletnich remisji chorych leczonych lekami o alternatywnym do cytosatatyków mechanizmach działania**, w monoterapii można się w większości przypadków 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**


B 591ZM

Chłoniaki o niepewnym rokowaniu – szybkie pojawienie się oporności na chemioterapię

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

Chłoniaki agresywne
Chłoniak Hodgkina
(Ziarnica złośliwa)



Chłoniaki agresywne
- Chłoniak rozlany z dużych komórek B
- Chłoniak limfoblastyczny

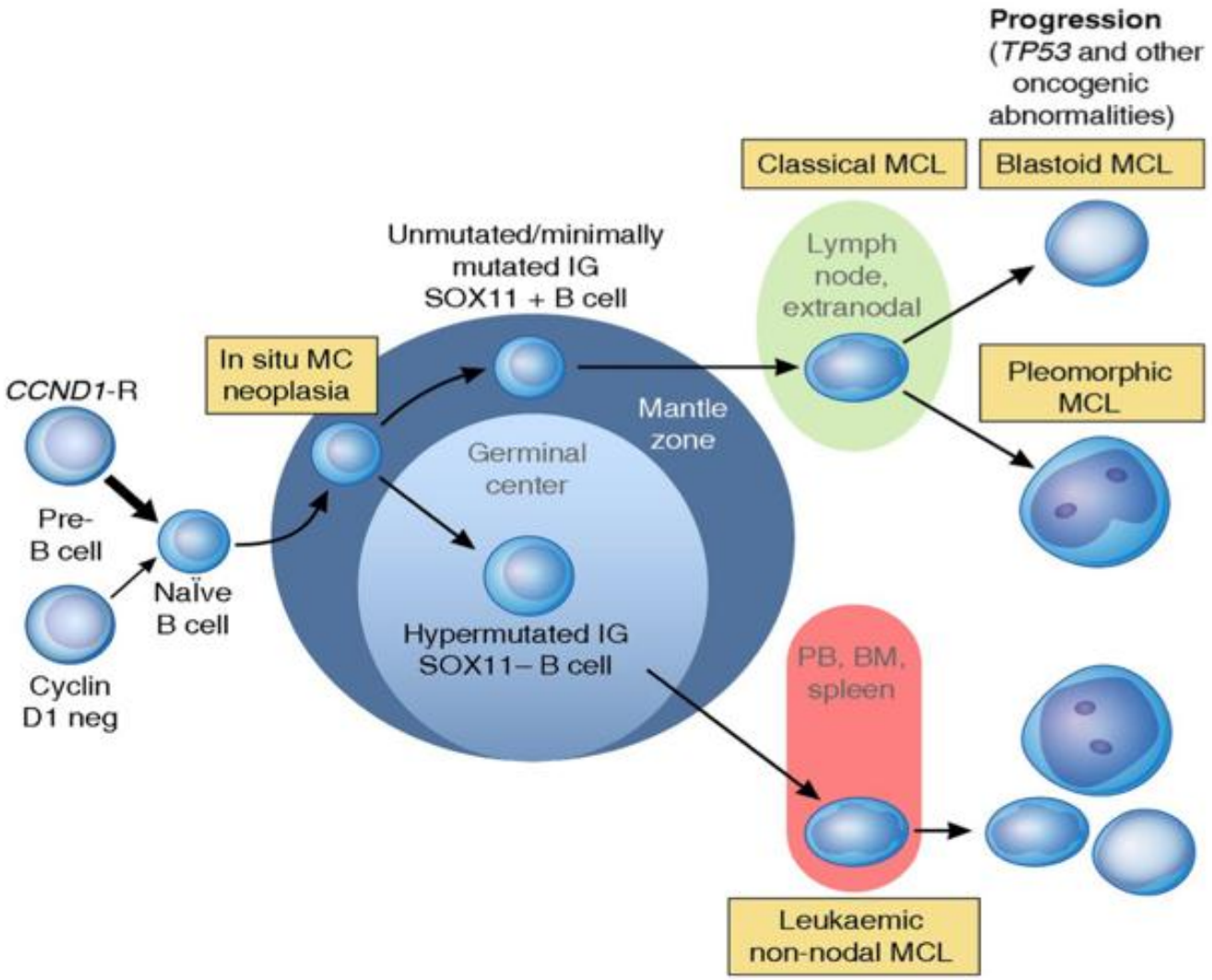
Ibrutynib, Lenalidomid,
Temsirolimus,
Bortezomib Belinost, …

90% chorych

yczna

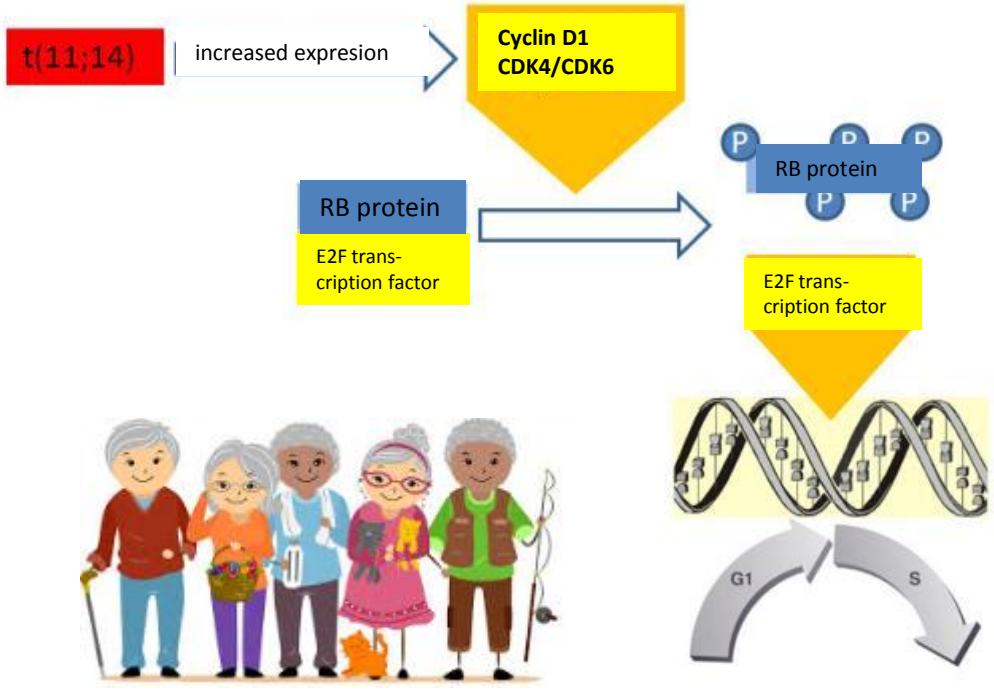
efy b żnej, MALT

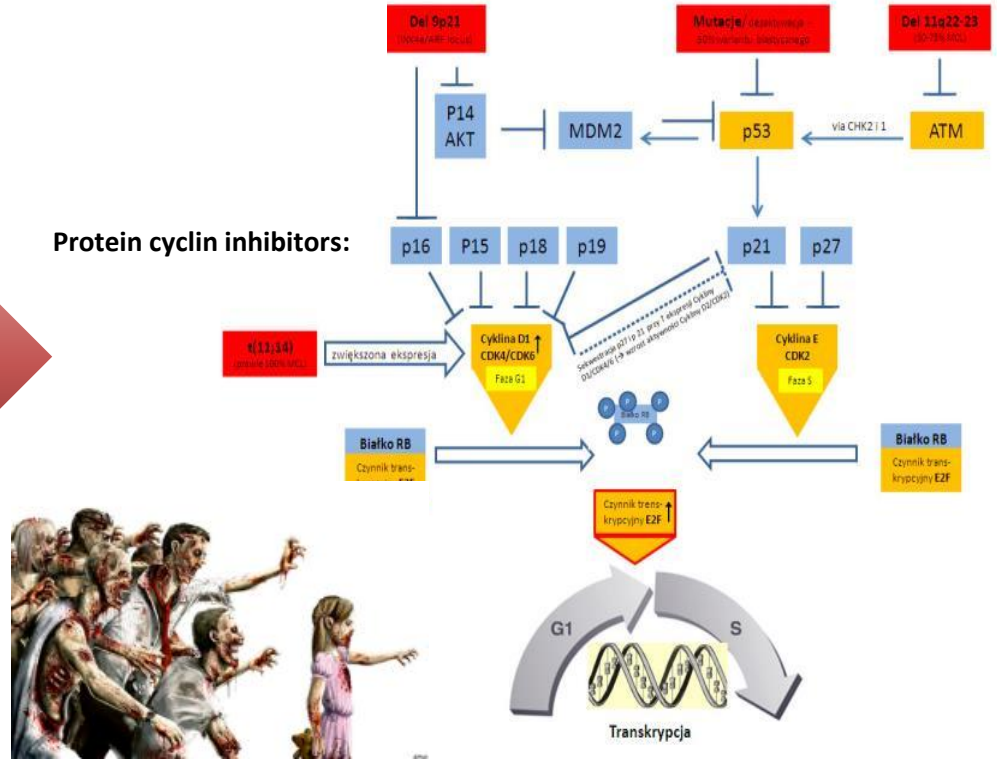
MCL – the disease we know better and better



Courtesy of E Campo

MCL – acumulation of secondary cytogenetic abnormalities





Prognostic Factors: MIPI + Ki67 and MRD status

Figure 4

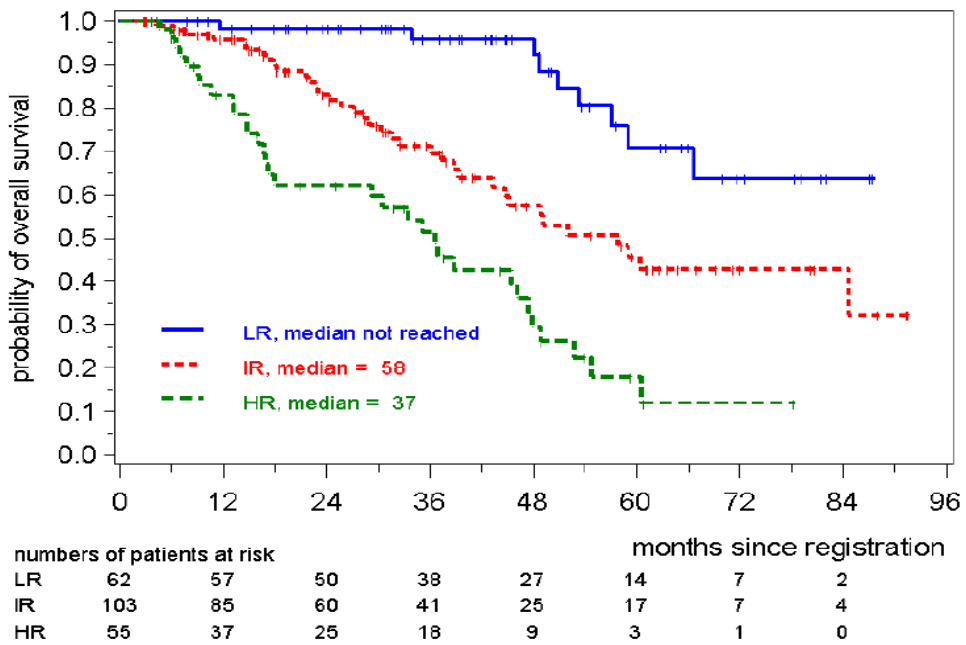
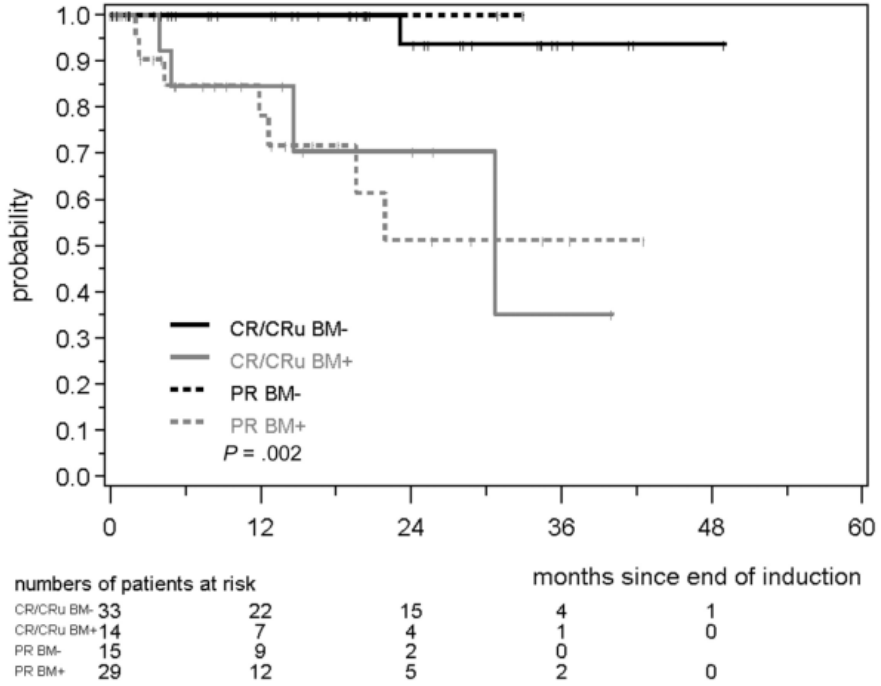


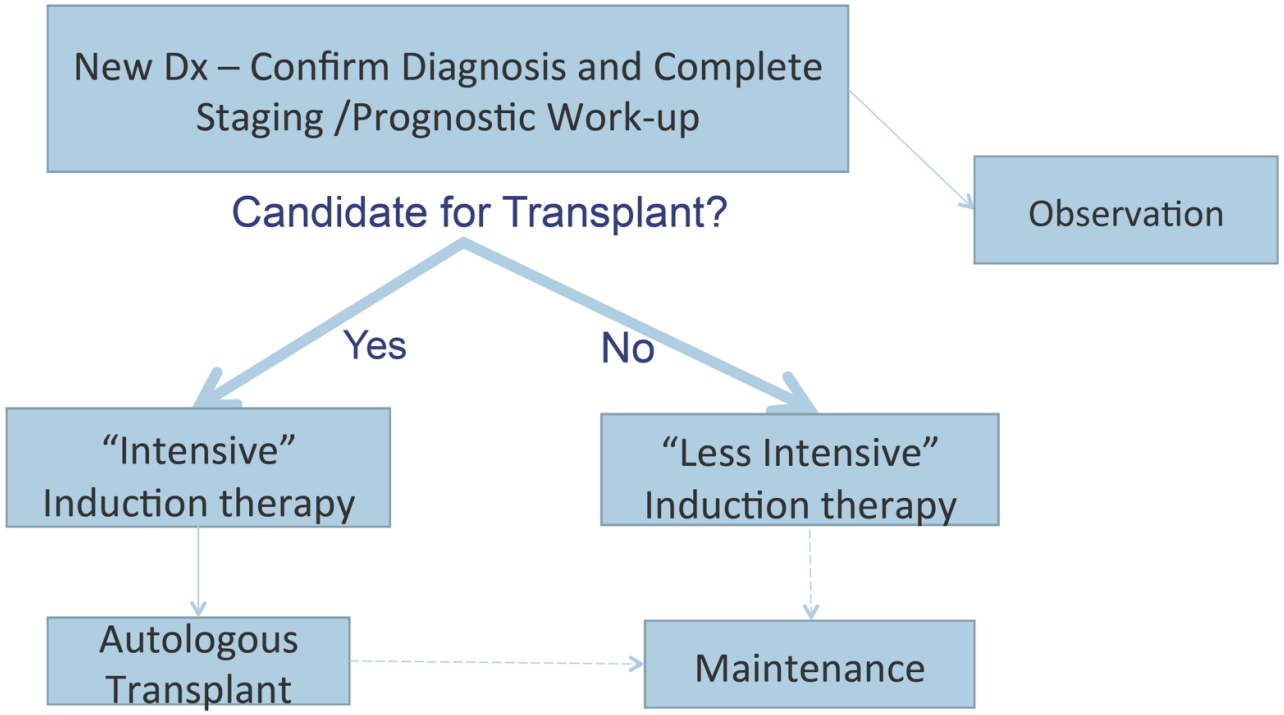
Figure 4: Overall survival according to the combined biological index ($MIPI_b$) in 220 patients with Ki-67 available. LR: low risk, combined biological score (CBS) < 5.7, IR: intermediate risk, 5.7 ≤ CBS < 6.5, HR: high risk, CBS ≥ 6.5. The combined biological score is calculated according to CBS = 0.03535 · age (years) + 0.6978 (if ECOG > 1) + 1.367 · $\log_{10}$(LDH/ULN) + 0.9393 · $\log_{10}$(WBC count) + 0.02142 · Ki-67 (%). ULN: upper limit of normal.

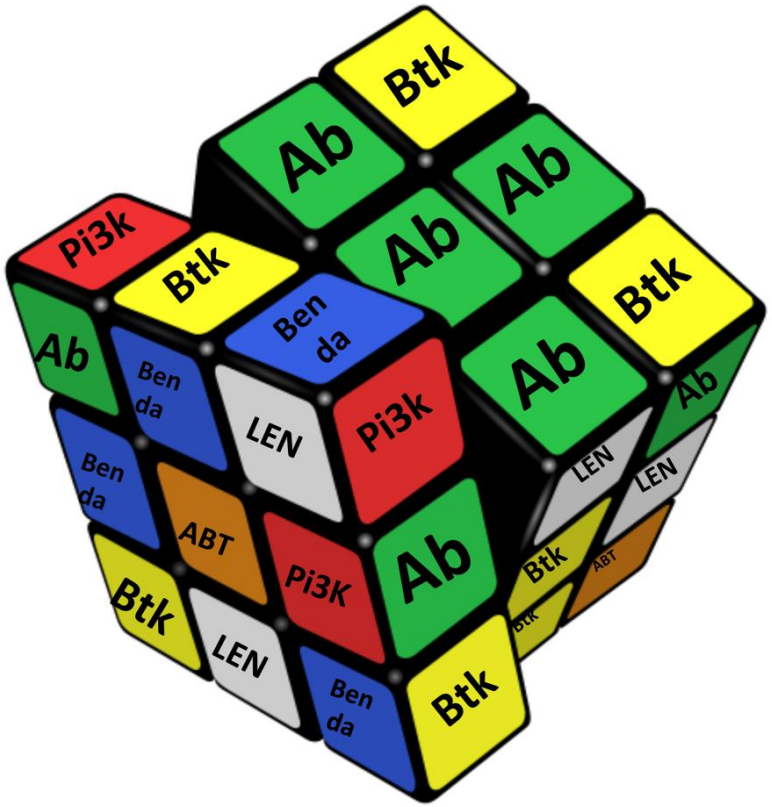


E.Hoster, M Dreyling et al, Blood, 2007; A Pott et al., Blood 2010

Polish Lymphoma Research Group

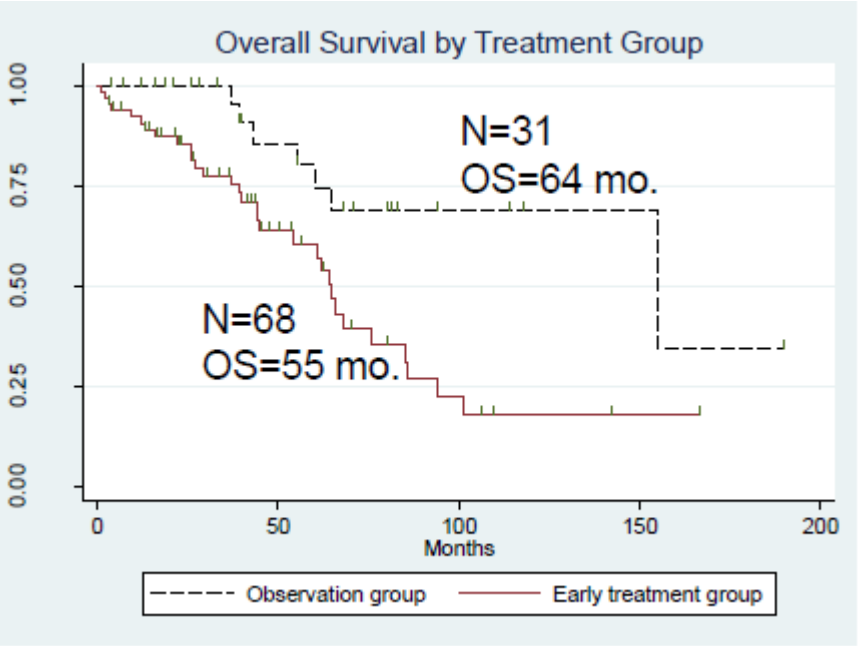
“Traditional” vs „Targeted” Approaches in MCL





Polish Lymphoma Research Group

Outcomes of Deferred Therapy in MCL
- Successful identification of low risk patients



What characteristics are define these patients?

- **Not blastoid morphology1**
- **Normal LDH2**
- **Ki67 <30%3**
- **No B symptoms4**
- **Mutated IGHV5**
- **SOX11-**
- **Non-nodal6**
- **MIPI is NOT a defining characteristic**

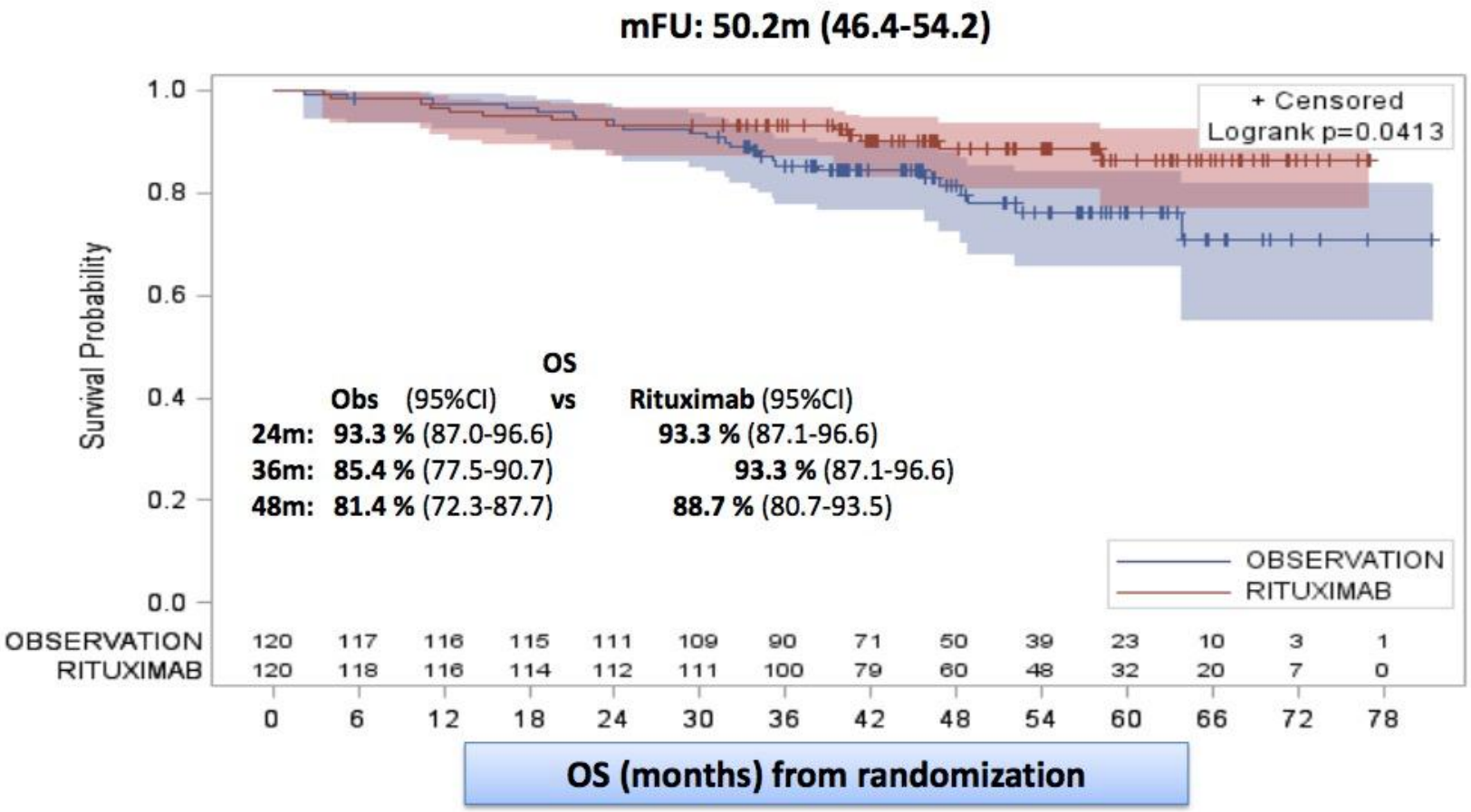
Outcomes of Deferred Therapy in MCL
- Successful identification of low risk patients

Series	Number of Deferred Patients (%)	Median time to treatment (Range)	Median OS (Deferred Pts)	Median OS (Immediate Pts)
Martin 2009 (Cornell)	31 / 97 (32)	12 months (4-128)	Not Reached (4.6 years)	5.3 years
Abrisqueta 2017 (B.C.)	74 / 439 (17)	35.5 months (5-79)	5.5 years	4.2 years
Cohen 2016 (NCDB)	492 / 8029 (6)	4 months (3-38)*	6.6 years	-
Kumar 2015 (MSKCC)	91 / 404 (23)	23 months	10.6 years	9.4 years
Calzada 2016 (Multicenter)	72 / 395 (18)	7.8 months (3-121)*	11.8 years	11.6 years

„Younger” MCL patients - necessity of maintenance after ASCT

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

LyMa trial



Le Gouill et al. NEJM 2017

Polish Lymphoma Research Group

„Younger” MCL patients - necessity of maintenance after ASCT (≠)

MCL0208 study

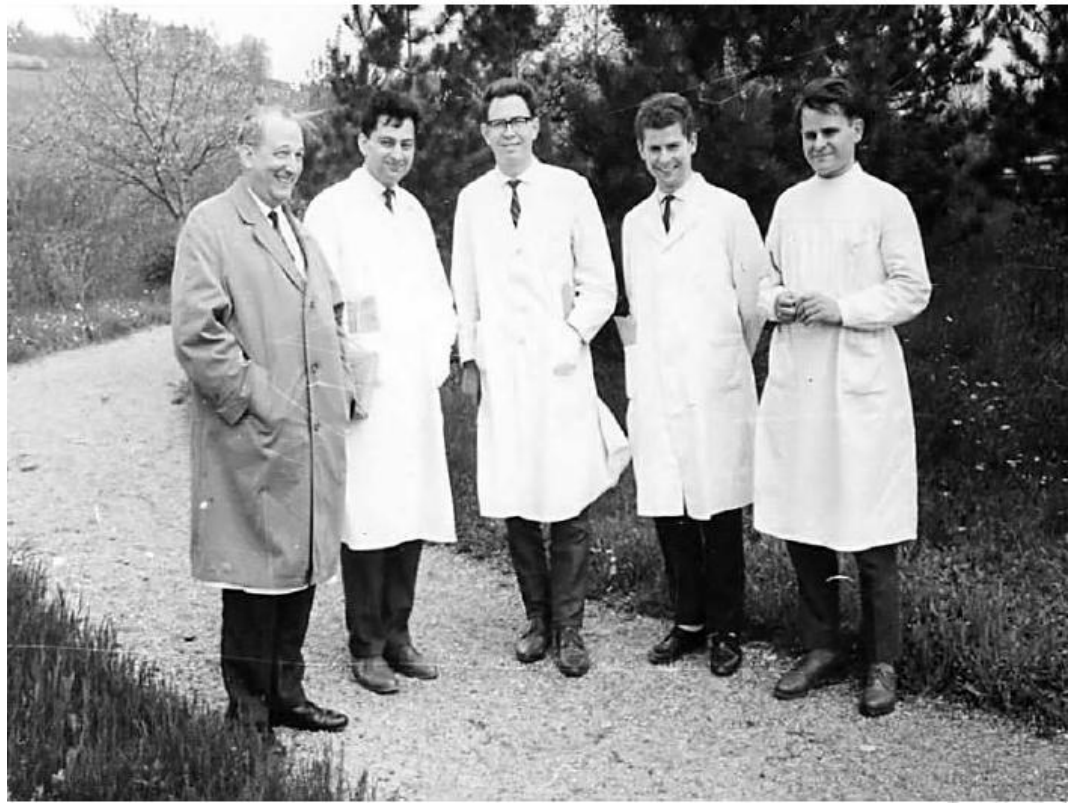
1. Induction: R-CHOP-21 x 3 — Staging
2. Consolidation: CTX 4g/m² — Restaging
   R-HD-Ara-C 2g/m² q12h x 3
   Ritux 375mg/m² d 4, 10 — Harvest CD34+
   R-HD-Ara-C 2g/m² q12h x 3
   Ritux 375mg/m² d 4, 10 — 2° Harvest CD34+
   Restaging
   PR <50%, SD, NR
   Off-study
   BEAM-PBSCT — Restaging
   CR/PR
3. Maintenance: RANDOM observation vs. lenalidomide
   15 mg (plts >100x10⁹/ L) or 10 mg (plts 60-100x10⁹/L) once daily on days 1-21 every 28 day cycle) for 24 months.

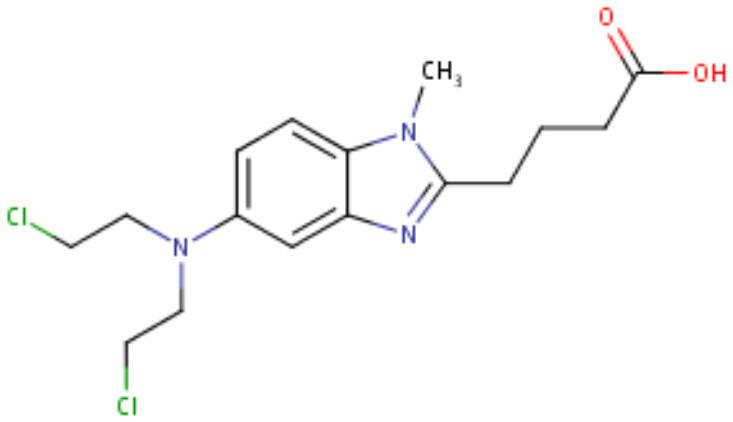
„Triangle” study

R

- Arm A: Alternating 3x R-CHOP / 3x R-DHAP → ASCT → Observation/Follow-up
- Arm A+I: Alternating 3x R-CHOP + I / 3x R-DHAP → ASCT → 2 yrs I-maintenance → Observation/Follow-up
- Arm I: Alternating 3x R-CHOP + I / 3x R-DHAP → 2 yrs I-maintenance → Observation/Follow-up

Bendamustine: An ‘agent’ with a long history

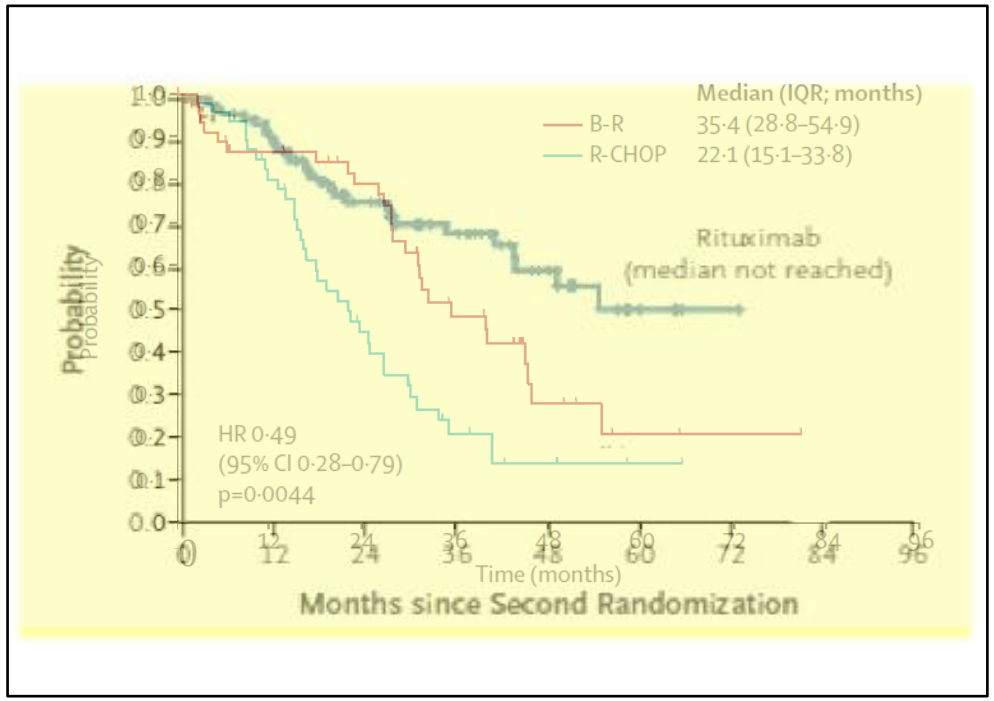




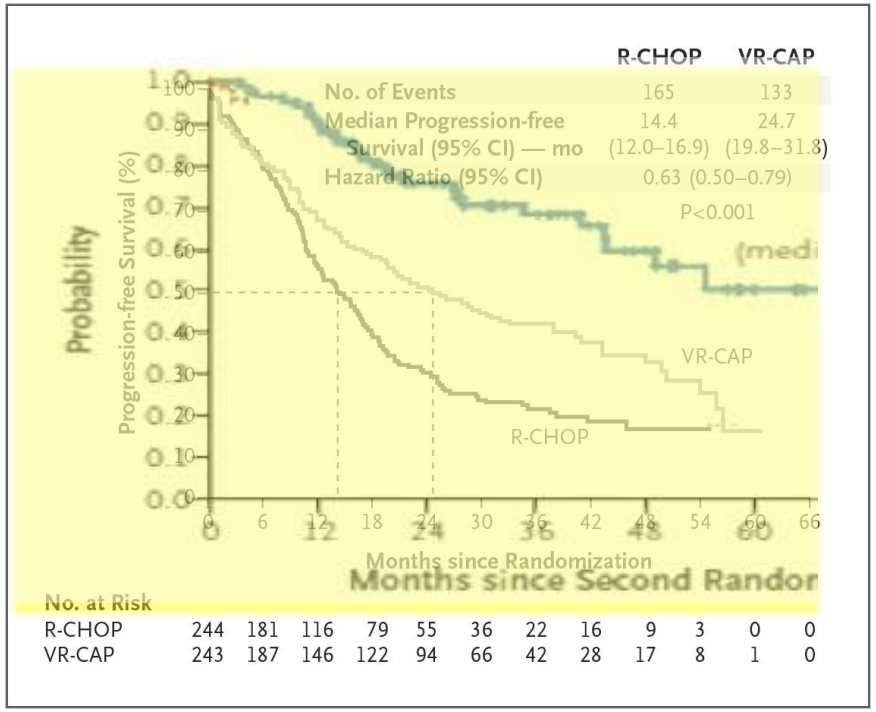
Synthesis : W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)

Praktische Chemie, Vol. 20, issue 3-4, 1963

I line immuno-chemotherapy in elderly MCL patients



Rummel et al, Lancet 2013



Robak et al, NEJM 2015

R-CHOP + Rituximab maintenance was however always better

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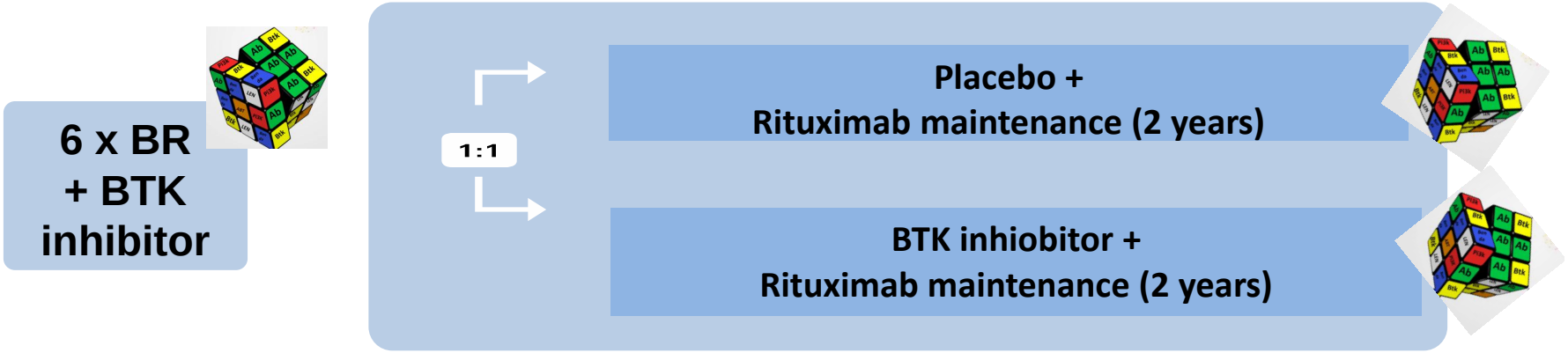
BR and Rituximab maintenance +/- BTK inhibitor *(≠)*



Study	SHINE PCI-32765MCL3002	Acerta 196	Acerta 306
Study details	N=520 Phase III Ibrutinib	N=48 Phase I Acalabrutinib	N=546 Phase III Acalabrutinib
Recruitment status	completed	completed	On - going
Primary Objective	PFS		PFS
Secondary Objectives	**OS**, RR, CR, DOR, Safety		**OS**, RR, CR, DOR

MCL – present European standard of care

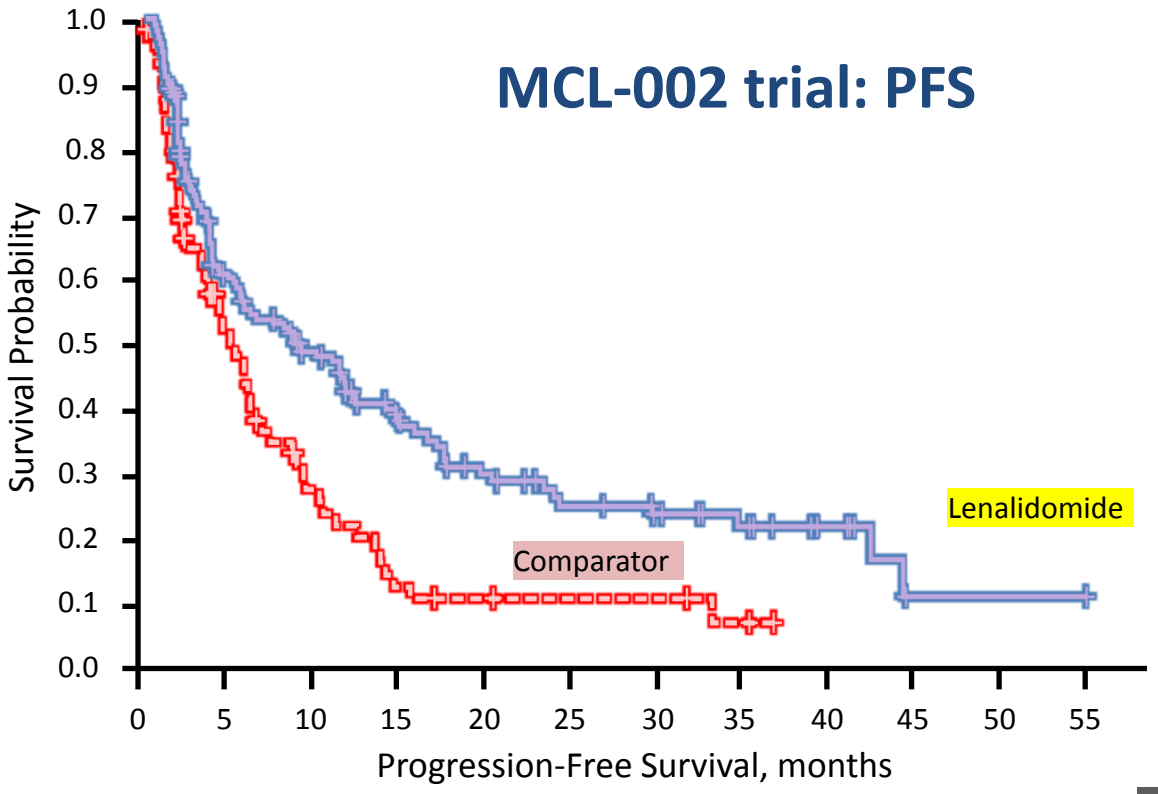
Young Patients (<65)	Elderly (>65)	„Compromised”
I line therpy		
Dose-intensified (R-CHOP + R-high dose Ara-C → ASCT) + Rit Maintenance	Conventional Immuno-chemotherapy (e.g. R-CHOP, BR, VR-CAP,) + Rit maintenance	Best supportive care R-Chlorambucil BR (dose reduced) R-CVP
1 relapse		
Immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches Discuss: - Rit maintenance - Allo SCT	Immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches Discuss: - Rit maintenance - Radioimmunotherapy - Autologous SCT	Immuno-chemotherapy (e.g. BR) or targeted approaches
Higher relapse		
Targeted approaches (Ibrutynib, Lenalidomide, Temsirolimus, Bortezomib (preferably in Combinations) Alternatively – repeat previous therapy if in long remissions		

Dreyling, ESMO 2017

Novel Agents - results in relapsing/refractory (‡)

Regimen	N	ORR% (CR%)	mPFS (months)	mOS	Reference
Idelalisib	40	40 (5)	**3.7**	n/a	Kahl, Blood 2014
Temsirolimus	54	22 (2)	**4.8**	12.8	Hess, JCO 2009
Everolimus	35	20 (6)	**5.5**	n/a	Wang, BJH 2014
Bortezomib	141	33 (8)	**6.7**	23.5	Fisher, JCO 2006
Lenalidomide	134	28 (8)	**8,6**	19	Trneny, Lancet O 2016
Ibrutinib	110	68 (21)	**13.9**	n/a	Wang, NEJM 2013

Lenalidomide in R/R MCL



	Lenalidomide (n = 170)	IC (n = 84)
Median PFS, mo (95% CI)	8.6 (5.5-12.1)	5.2 (3.6-6.9)
HR (95% CI)	0.61 (0.44-0.84); P = 0.004	

Lenalidomide vs IC showed a 39% reduction in the risk of PD or death, reflected as an estimated improvement in median PFS of 3.4 months

Regimen	N	ORR% (CR%)	mPFS	mOS	Reference
Lenalidomide	**134**	**28 (8)**	**8,6**	**19**	**Trneny, L.Oncol 2016**
Len + R	**52**	**56 (36)**	**11.1**	**24.3**	**Wang, Lancet 2012**
Thal+R+PEPC	**25**	**73 (32)**	**10**	**45%@2y**	**Ruan, Cancer 2010**

Trneny et al, Lancet Oncology 2016

Prof. Wojciech Jurczak MD,PhD

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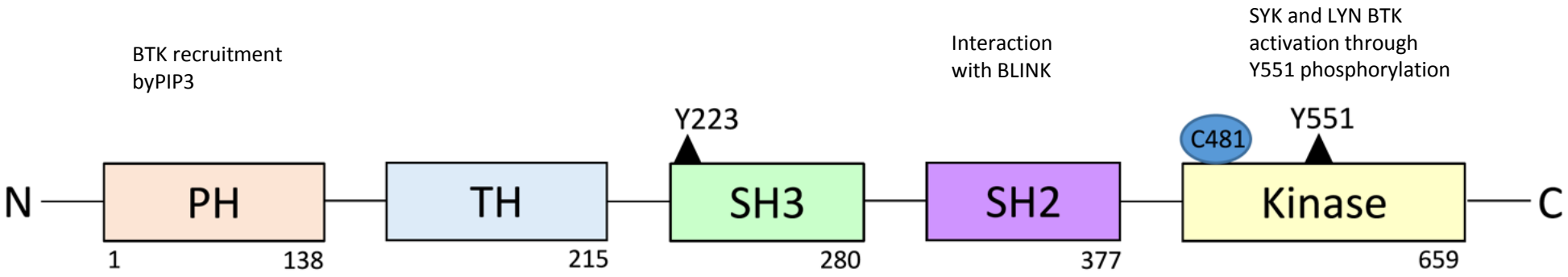
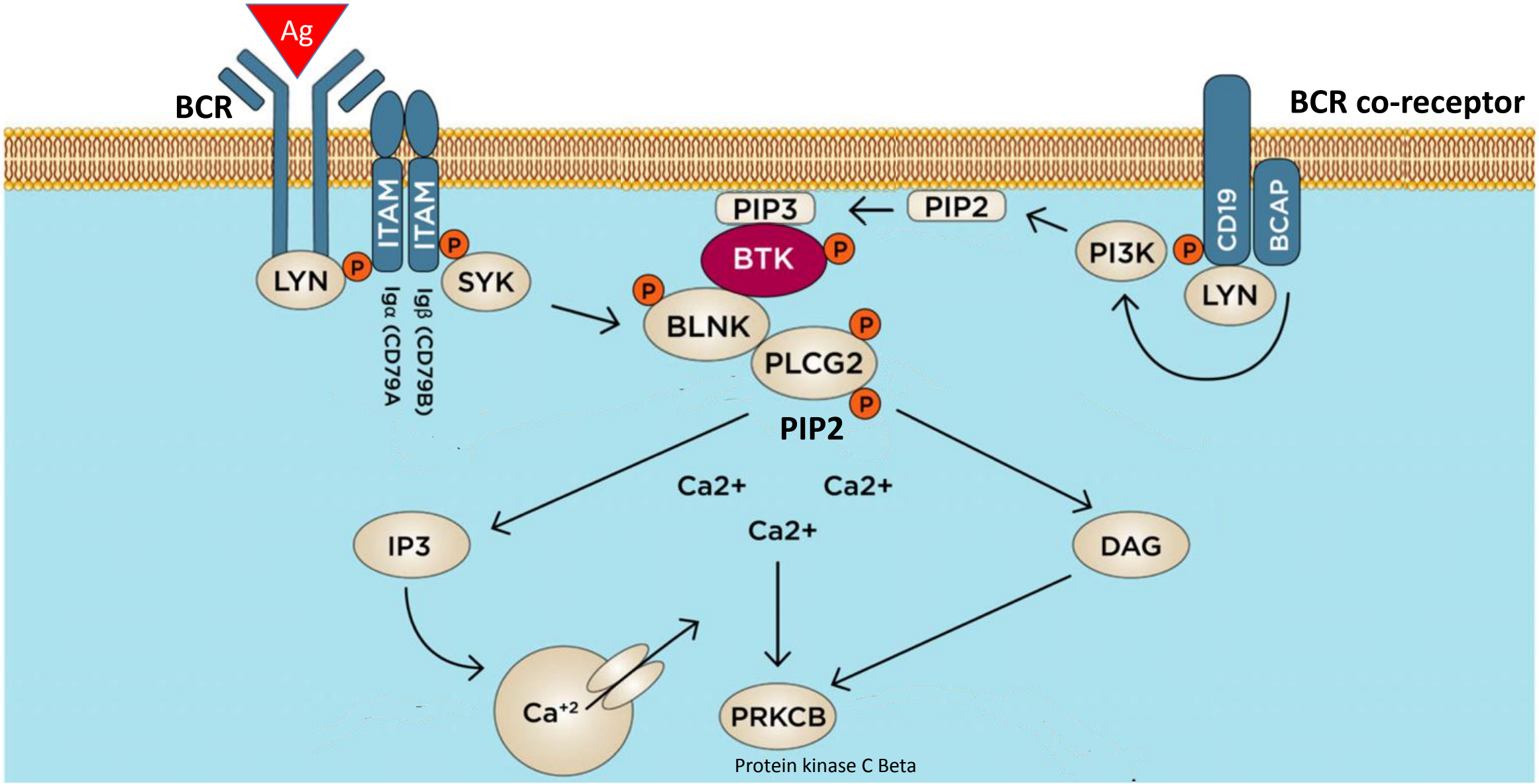
Bruton Throsine Kinase

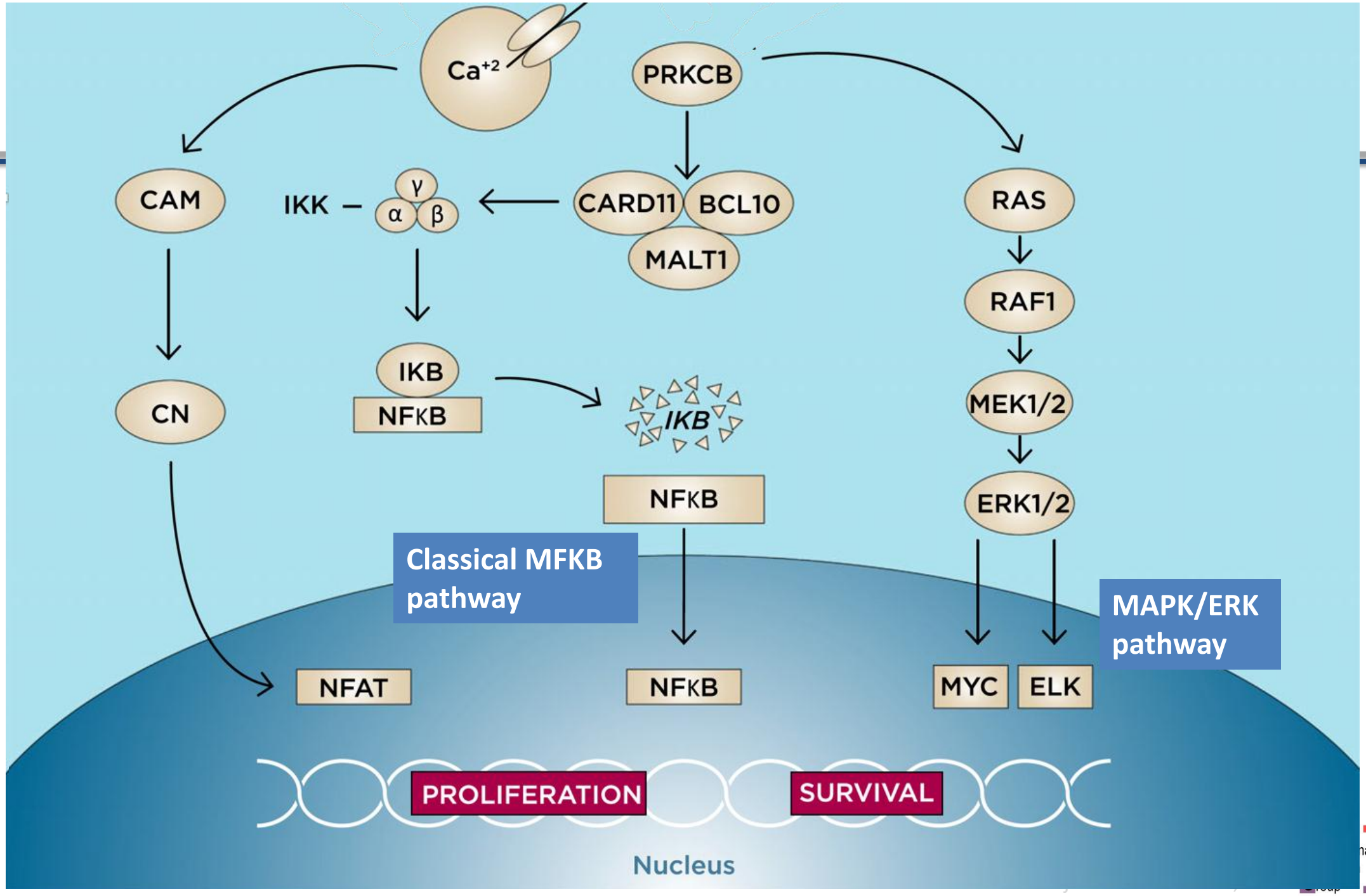


- **BCR signalling**
- CD19, CD38, CD40, G-protein coupled receptors and chemokine receptors, TNF, Toll like receptor signalling

- BTK is essential for B cell maturation, formation of germinal centres, plasma cell proliferation
- BTK activation may provoke autoantibody production and auto-immunopathy
- BTK is defective in primary immunodeficiency X-linked agammaglobulinemia (XLA)

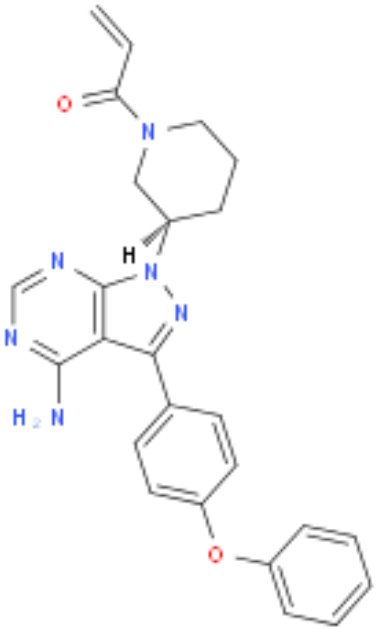


Hershkovitz-Rokah et al., BJH 2018

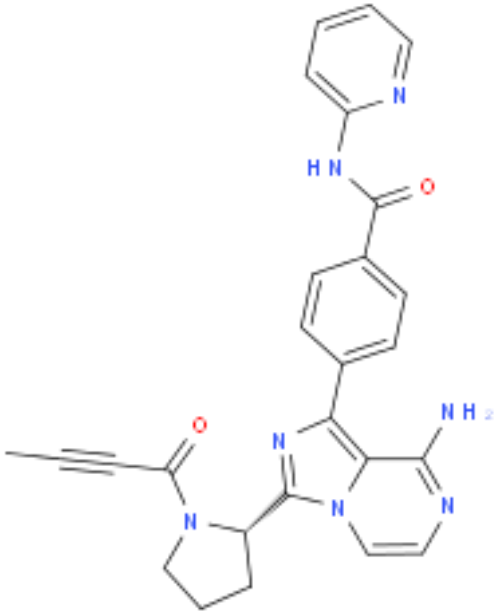

Ca+2
PRKCB
CAM
IKK
γ
α
β
CARD11
BCL10
MALT1
RAS
RAF1
MEK1/2
ERK1/2
IKB
NFKB
IKB
CN
NFKB
Classical MFKB pathway
MAPK/ERK pathway
NFAT
NFKB
MYC
ELK
PROLIFERATION
SURVIVAL
Nucleus

Comparison of BTK inhibitors

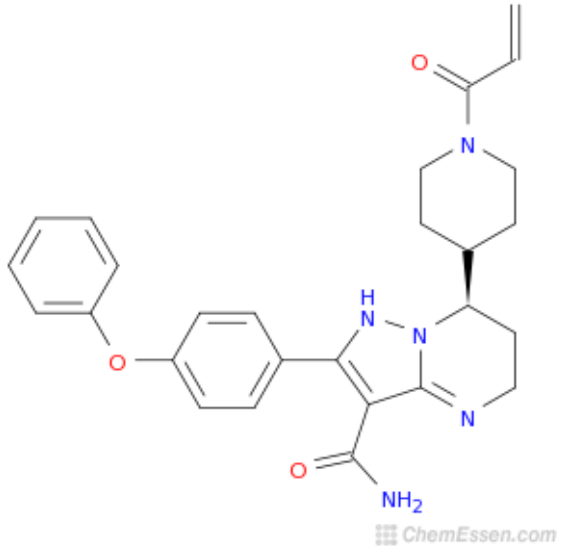
Ibrutynib (PCI 32765)



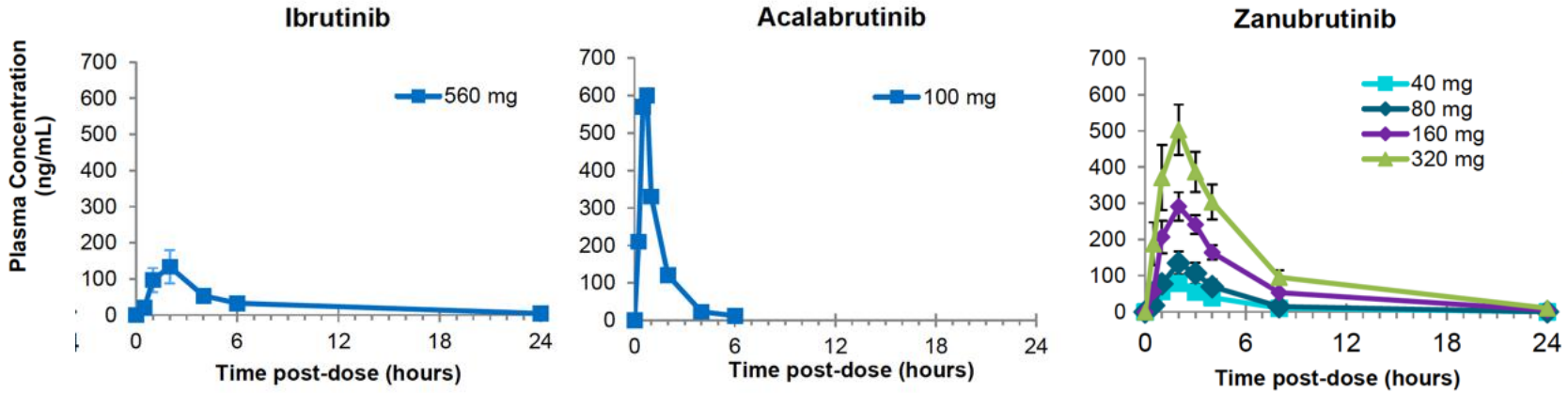
Acalabrutinib (ACP-196)



Zanubrutynib (BGB-311)



Comparison of BTK inhibitors - Plasma Exposure By Dose

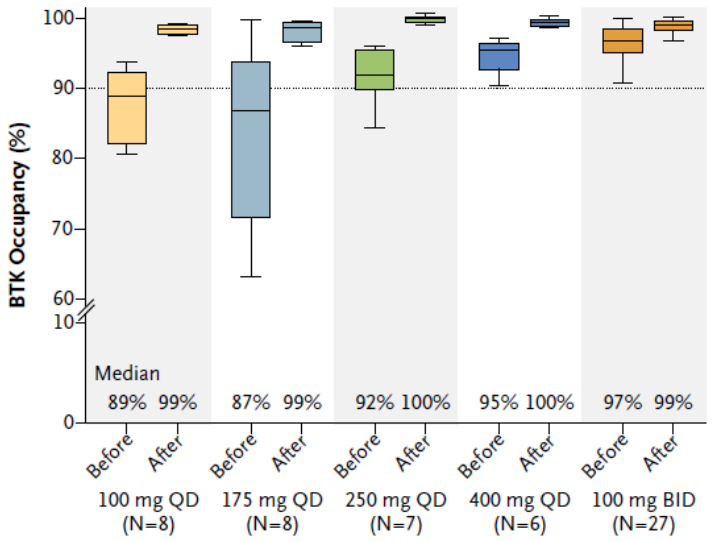


in vitro BTK inhibition IC50 relative to Ibrutinib:	1	3.4-7.2	1
Dose in MCL:	1 x 560 mg	2 x 100 mg	2 x 160 mg

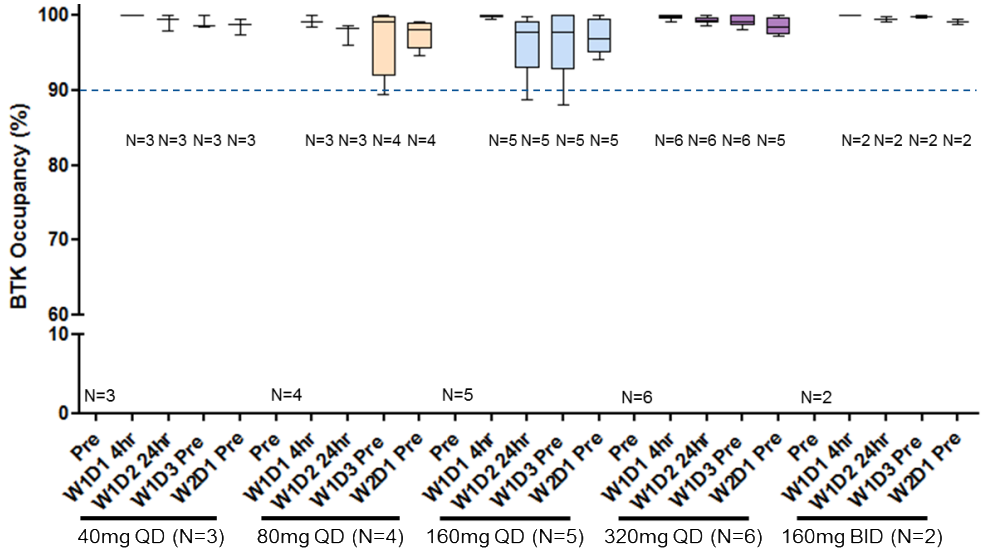
Advani et al., JCO 2013; Byrd et al. NEJM 2015,

Comparison of BTK inhibitors – Target Occupancy

Acalabrutinib (ACP-196)

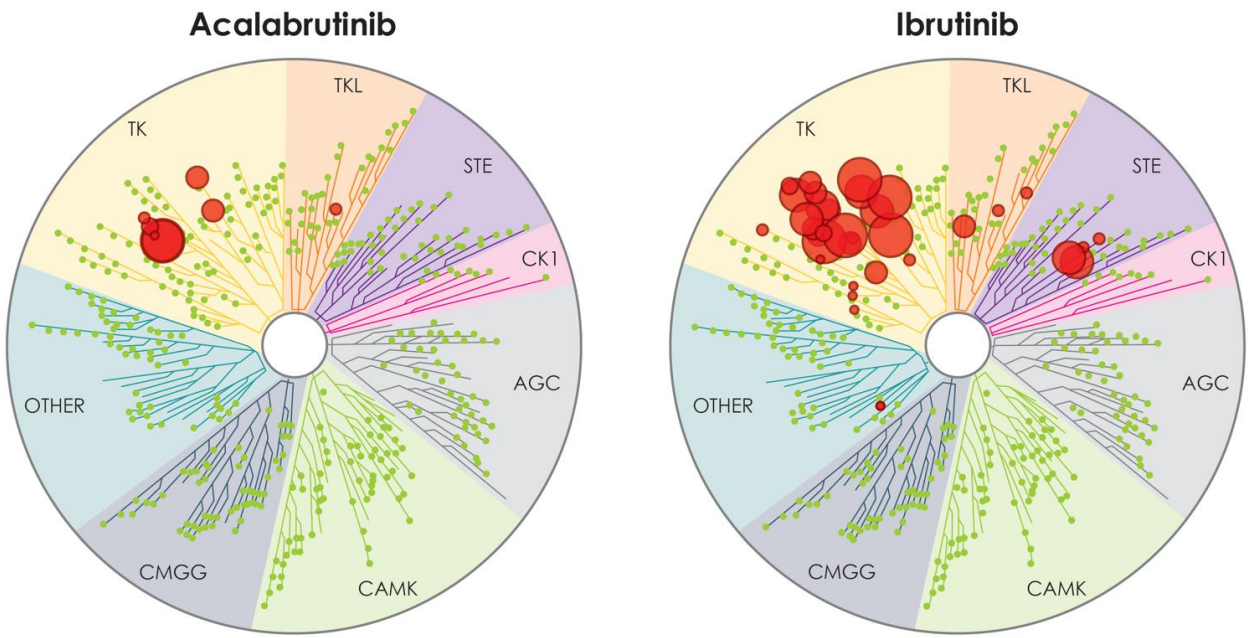


Zanubrutynib (BGB-311)



Advani et al., JCO 2013; Byrd et al. NEJM 2015,

How selective BTK inhibitors are ?



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)[4]										
Kinase	BTK	TEC	ITK	BMX	TXK	EGFR	ERBB2	ERBB4	BLK	JAK3
Acalabrutinib	5.1	126	>1000	46	368	>1000	~1000	16	>1000	>1000
Ibrutinib	1.5	10	4.9	0.8	2.0	5.3	6.4	3.4	0.1	32

TEC kinases: non-receptor tyrosine kinases with a highly conserved carboxyl-terminal kinase domain:

- **BTK (Bruton Tyrosine kinase)**
- **BMX (bone marrow tyrosine kinase on chromosome X)**
- **TXK (tyrosine-protein kinase)**
- **ITK (interleukin 2-inducible T-cell kinase)**
- **TEC (tyrosine kinase expressed in hepatocellular carcinoma)**

Barf et al. Jnl of Pharmacol and Exp Therap 2017

Two uncomparable clinical studies

	PCYC-1104-CA	ACE-LY-004
Study Name	Safety and Efficacy of PCI-32765 in Participants with Relapsed/Refractory MCL	An Open-label, Phase 2 Study of ACP-196 in Subjects with MCL
Study Timeline	February 2011 – January 2014	March 2015 - February 2017
Inclusion Criteria: • Men and women ≥ 18 years of age. • Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions • Relapsed/refractory after at least 1, but no more than 5, prior treatment regimens for MCL • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.		
Number of patients, median age	115, median age 68	124, median age 68

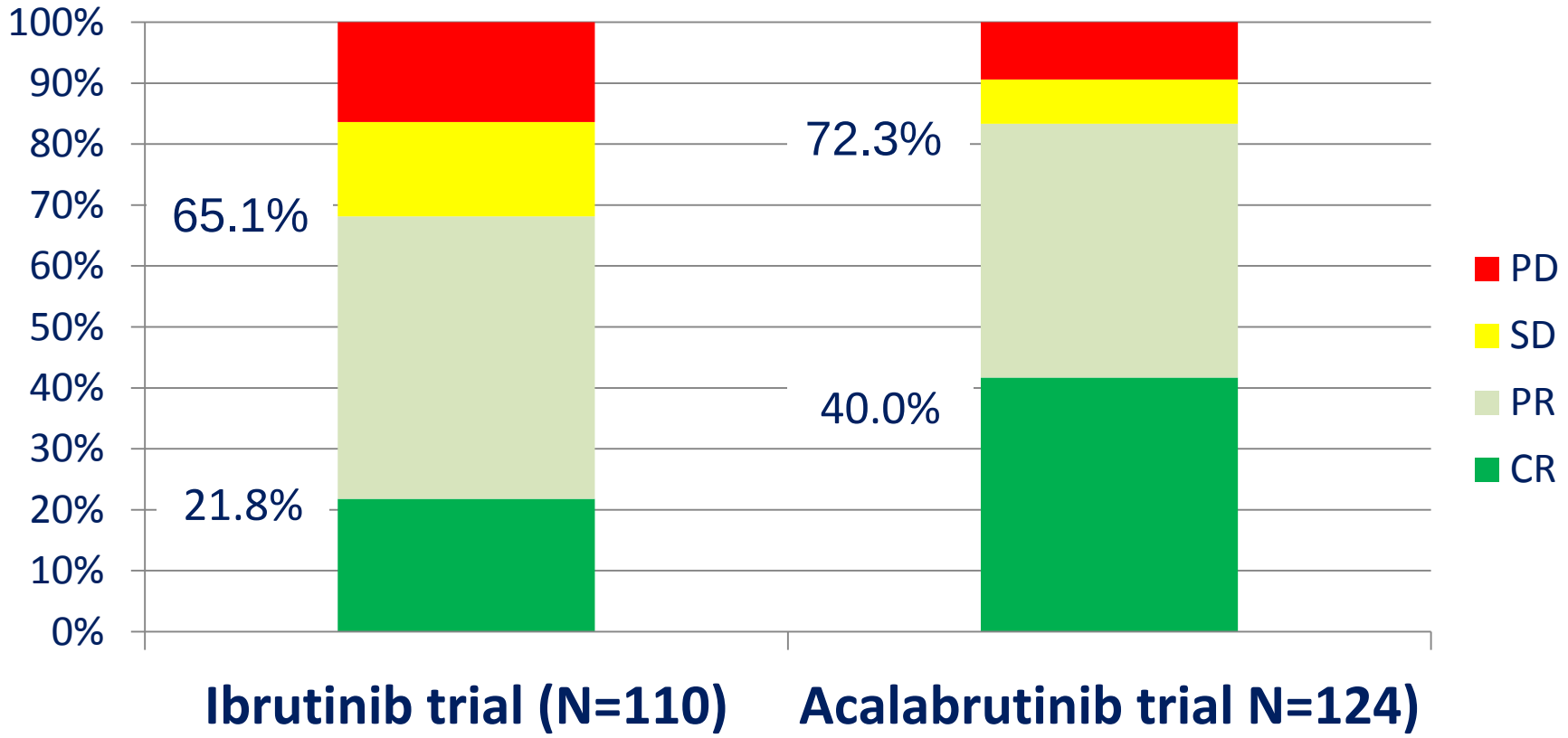
Wang et al., NEJM 2013; Wang et al. Lancet 2018

Two uncomparable clinical studies

	PCYC-1104-CA	ACE-LY-004
Number of previous therapies	**3 (1-5)**	2 (1-5)
Previous ASCT	11%	**18%**
% of patients with intermediate-or high-risk (MIPI)	**86%**	60%
Refractory disease	**45%**	24%
Bulk > 5 and > 10 cm	39% and 8% respectively	37% and 8% respectively
Primary endpoint - ORR (*):	ORR – 68% CR - 21% PR - 47%	**ORR - 81%** **CR - 40%** PR - 41%
Median time to initial response (months)	1.9 (range 1.4-13.7)	1.9 (range 1.5-4.4)
Median time to CR (months)	5.5 (range 1.7-24.7)	**3.4** (range 1.9–5.5)
Duration of Response (DOR) Progression Free Survival (PFS) Overall Survival (OS)	median - 17.5 months median - 13.9 months 58% at 18 months	**72% at 12 months** **67% at 12 months** **87 at 12 months**

Wang et al., NEJM 2013; Wang et al. Lancet 2018

BTK inhibitors in R/R MCL - Response to therapy



CT based follow-up
PET and BM only in CT CR

PET based follow-up
BM only in PET CR

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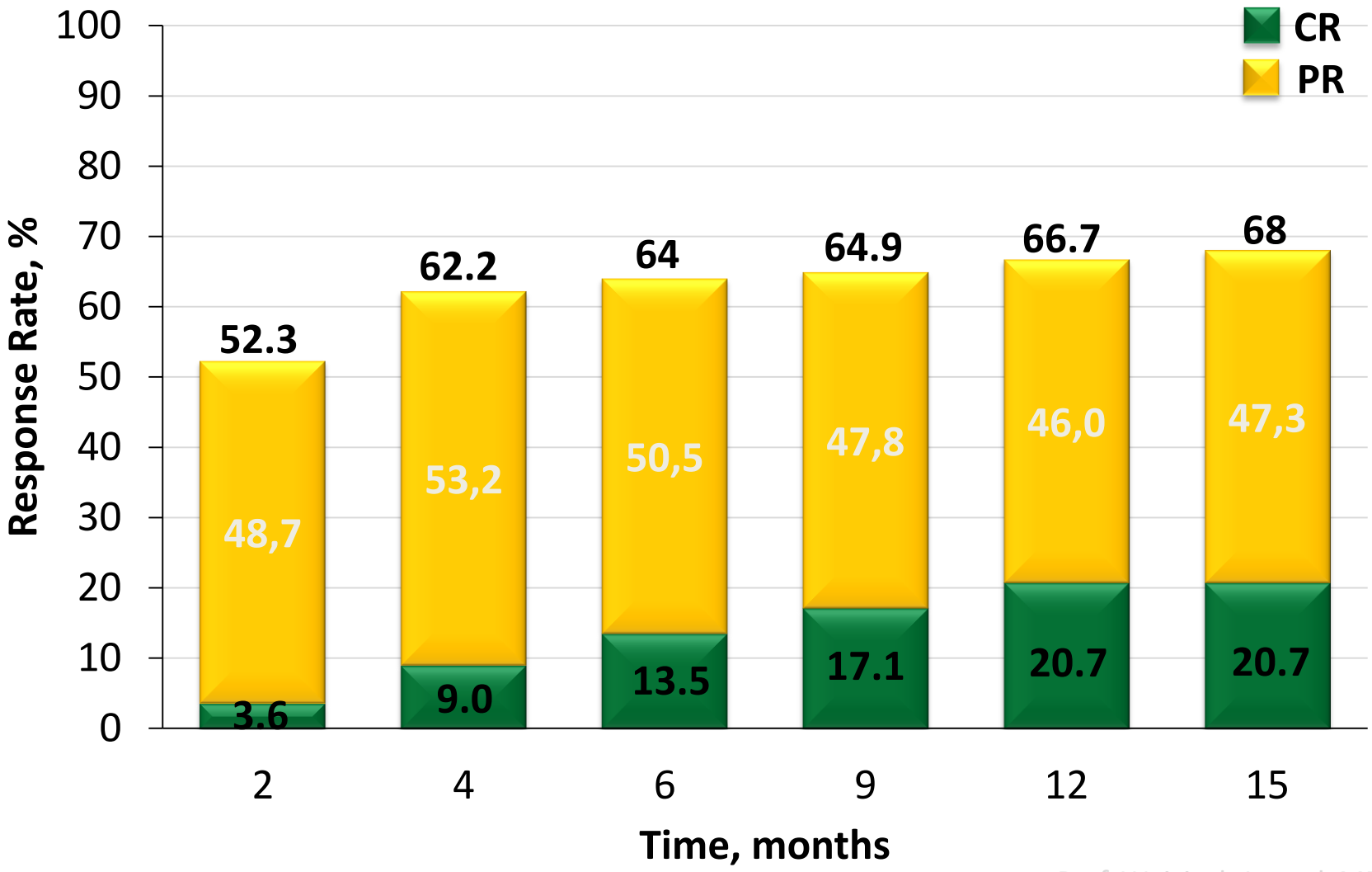
RR of MCL patients treated by Ibrutinib increased with time



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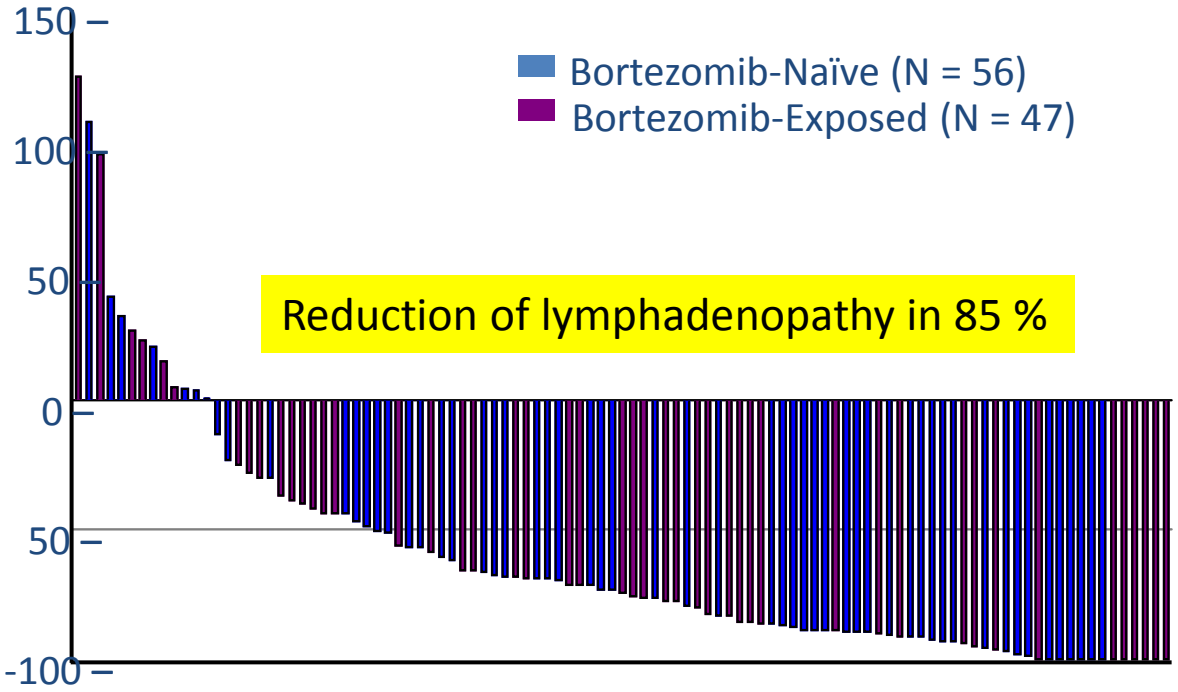
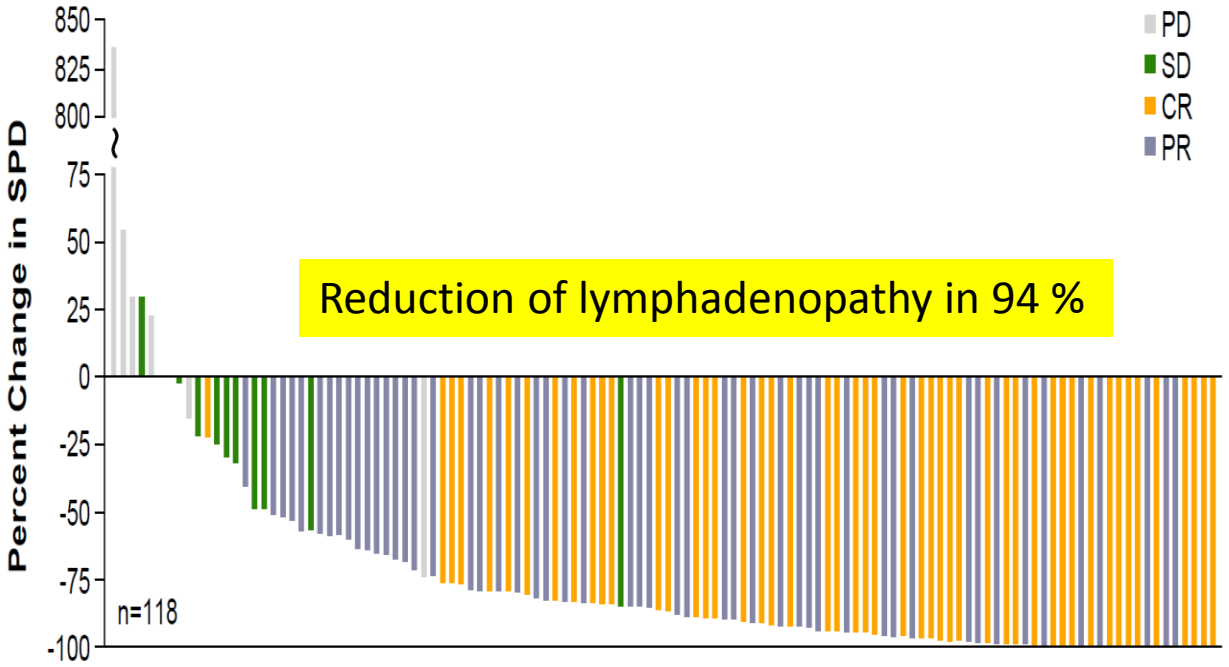
BTK inhibitors in R/R MCL - Response to therapy (SPD)



Ibrutinib trial



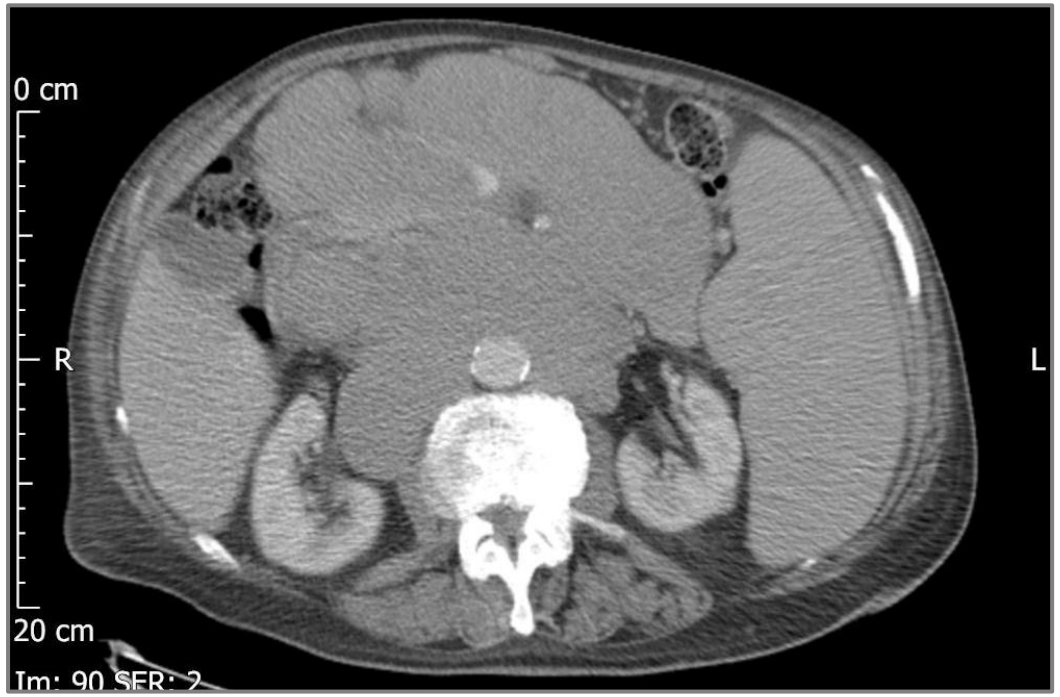
Acalabrutinib trial

Polish Lymphoma Research Group

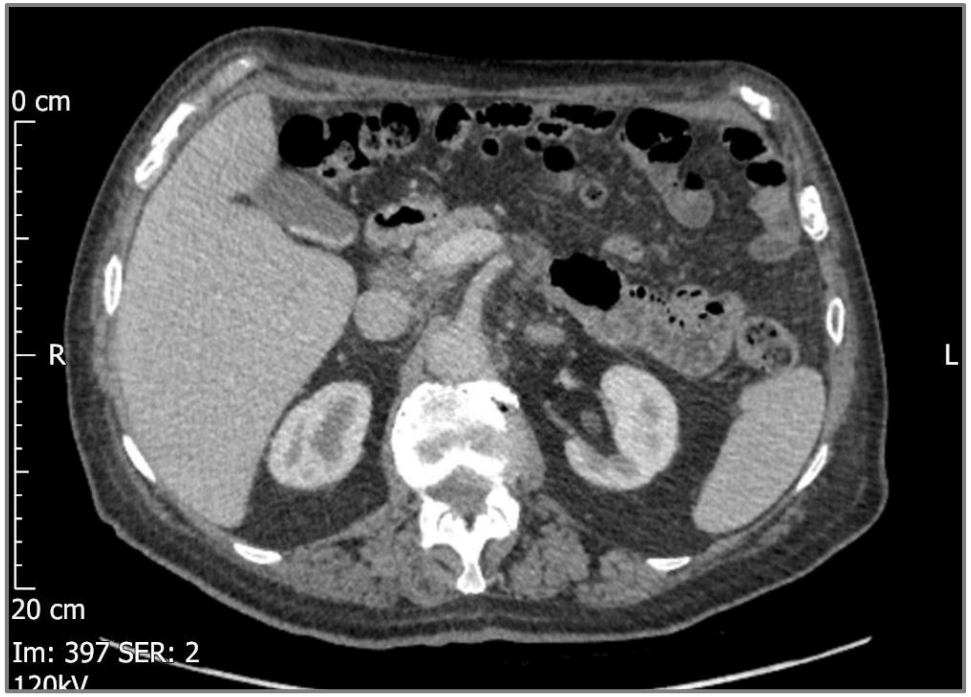
CT Scans of Tumor Response to Acalabrutinib

- Axial images of a 92-year-old male with chemorefractory MCL treated with acalabrutinib

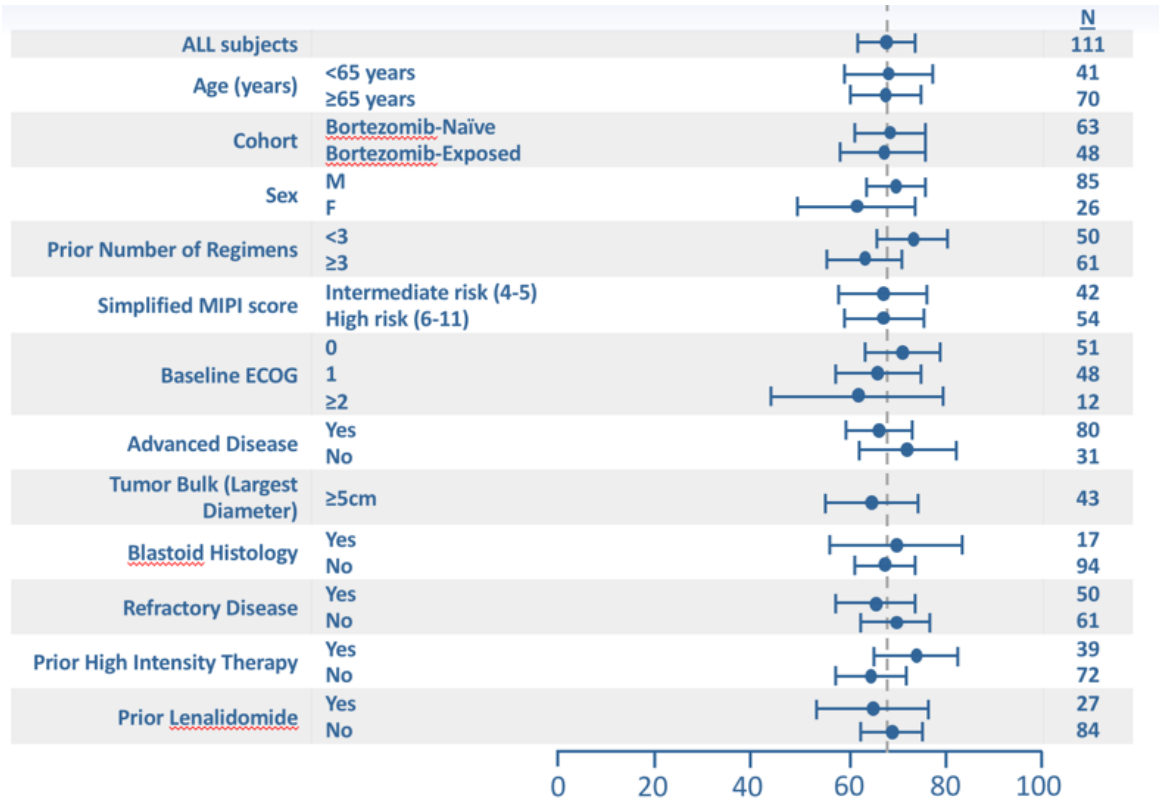
Before Treatment



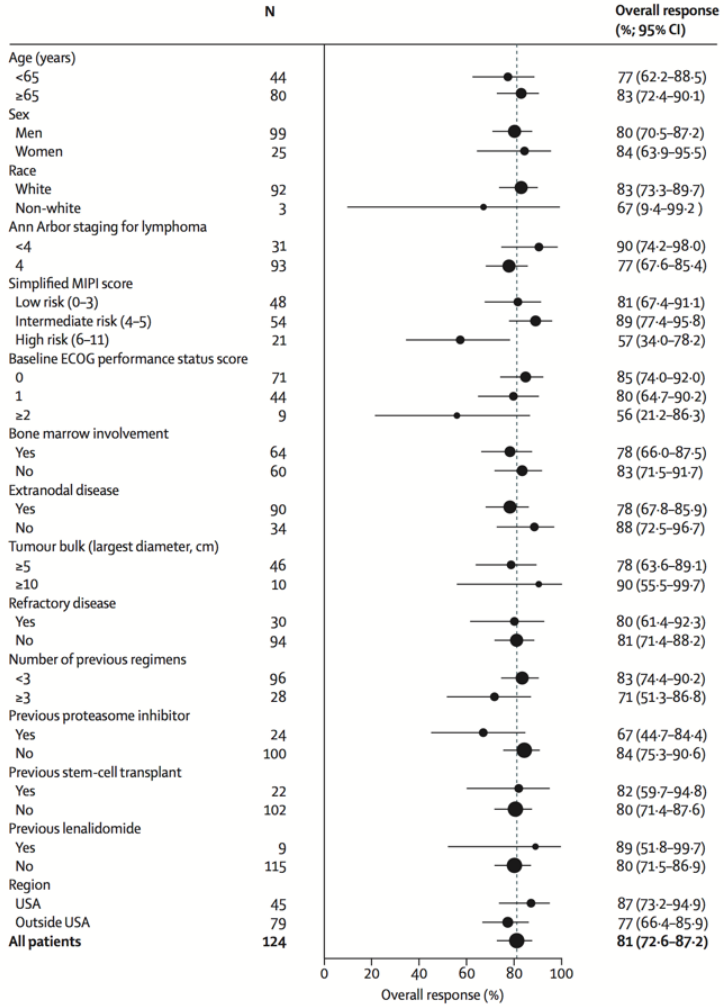
After 7 Months of Treatment



Response to BTK inhibitors is Independent of Patient Characteristics and Risk Factors



Ibrutinib trial



Acalabrutinib trial

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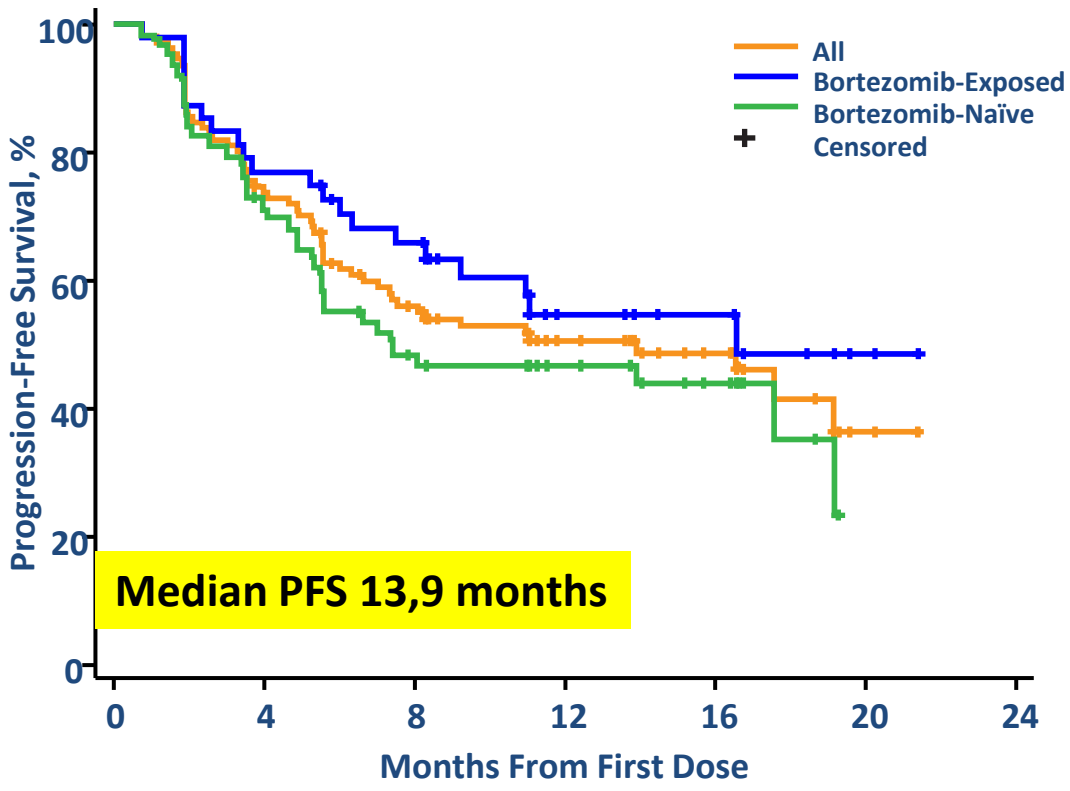
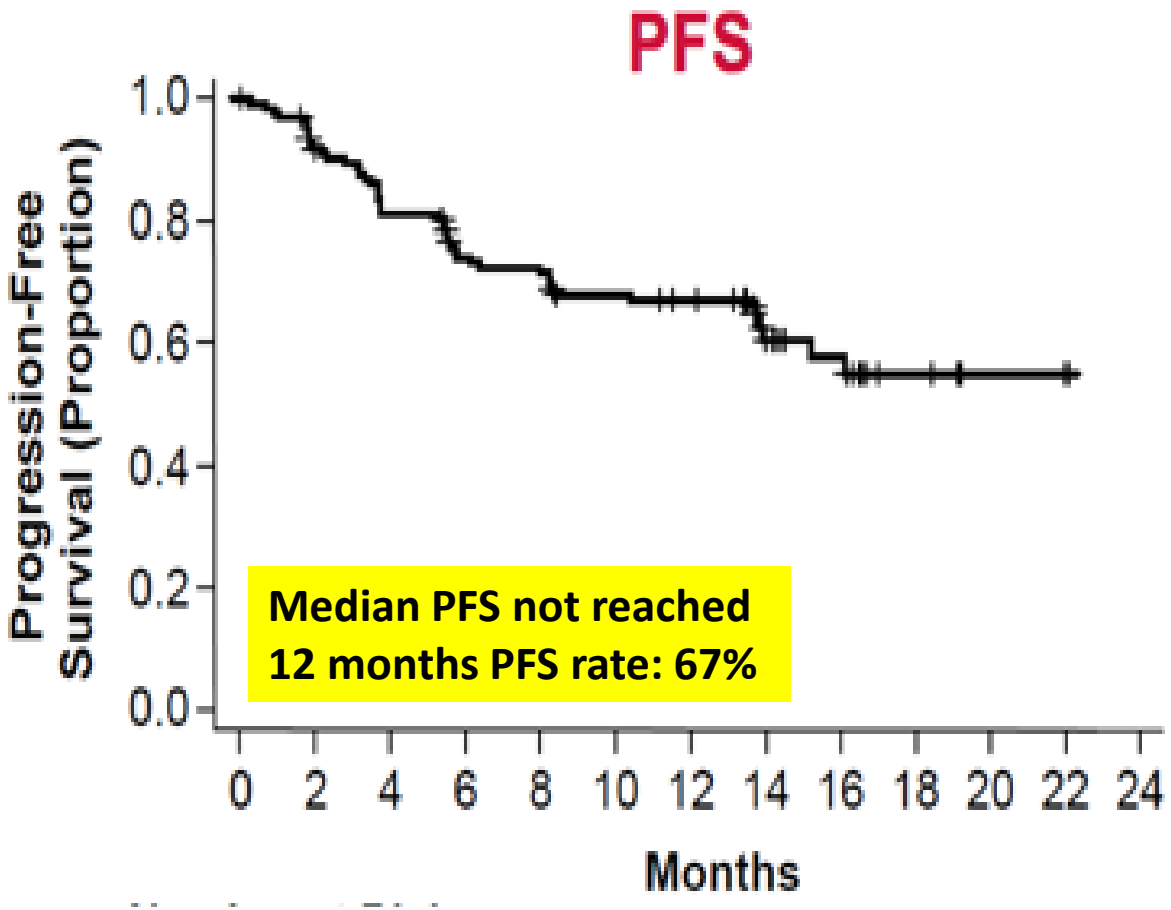
BTK inhibitors in R/R MCL - PFS



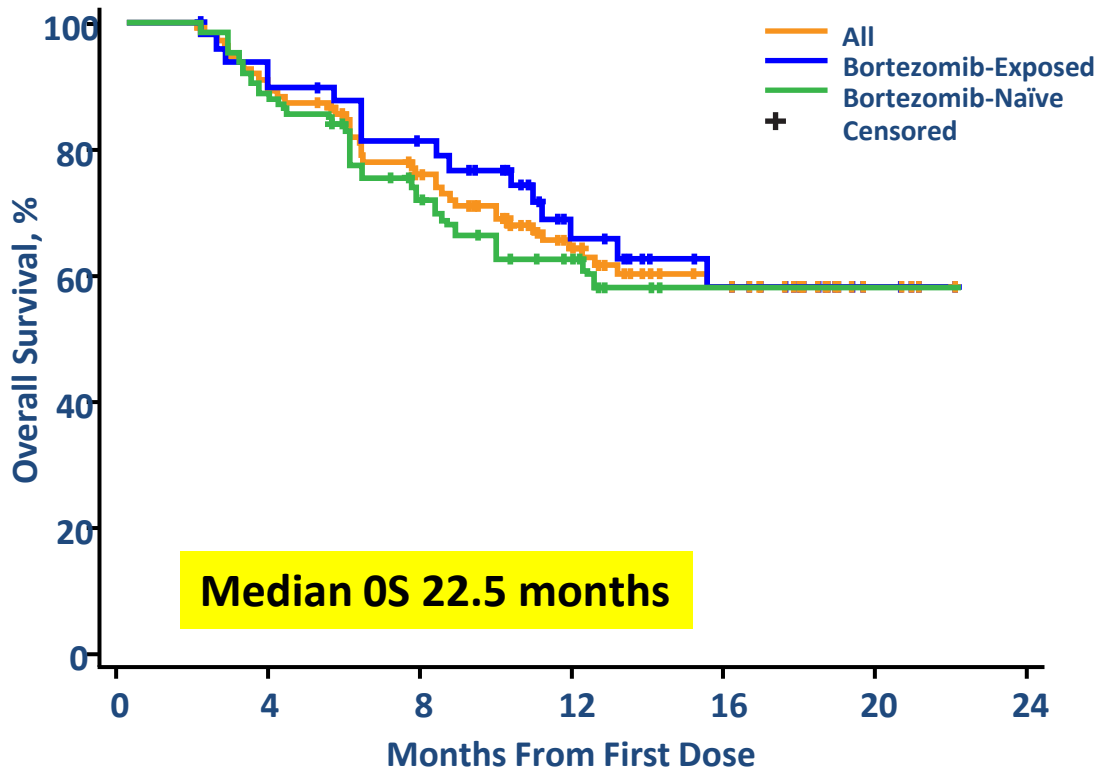
Ibrutinib trial



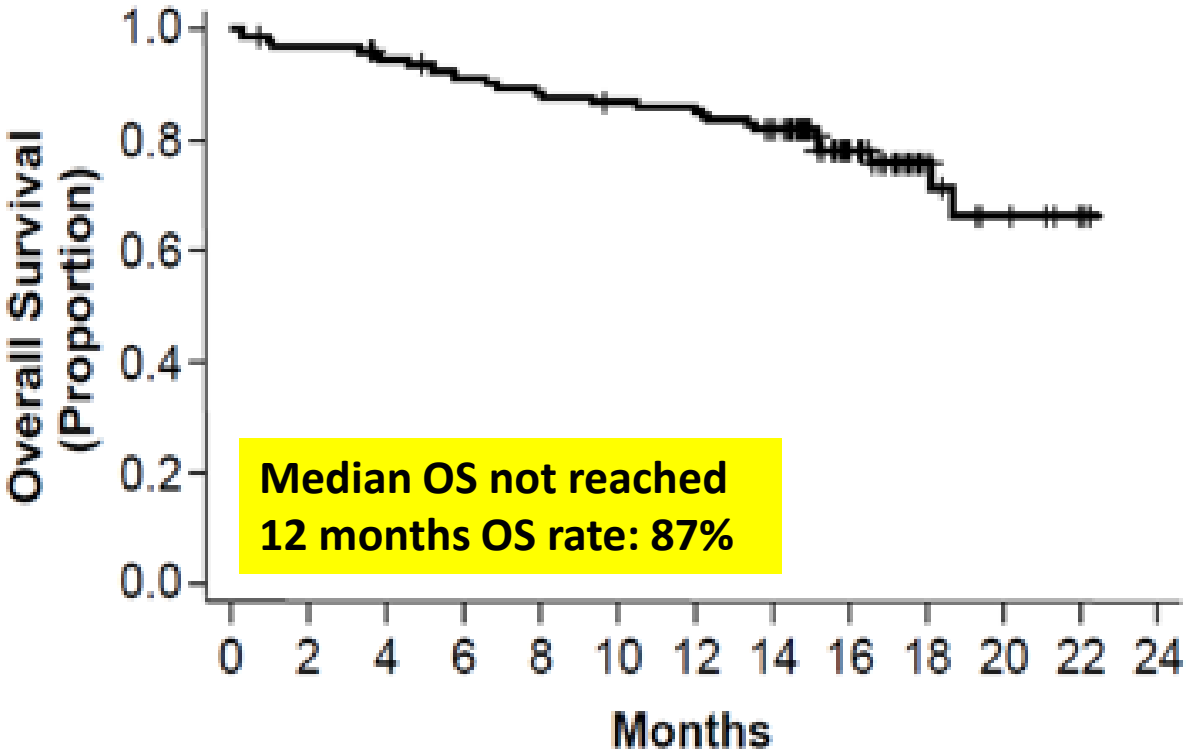
Acalabrutinib trial

Polish Lymphoma Research Group

BTK inhibitors in R/R MCL - OS



Ibrutinib trial



Acalabrutinib trial

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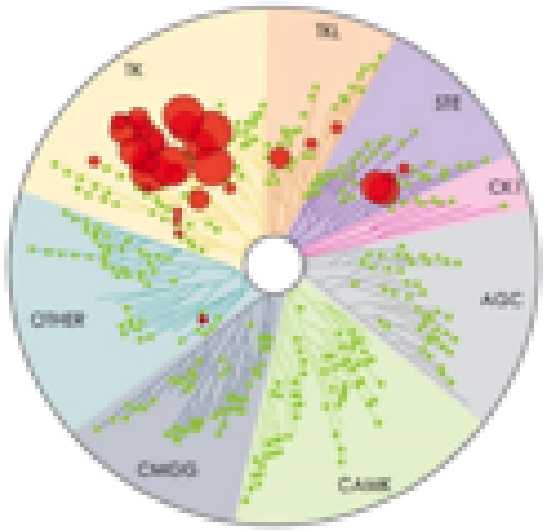
Two uncomparable clinical studies

	PCYC-1104-CA	ACE-LY-004
Hematological AE: any /3-4 grade (%):		
Neutropenia	17 /16	14/14
Anemia	11 / 10	15/11
Thrombocytopenia	**13 /11**	**<5%**
Most Common AE any grade/grade 3-4 (%):		
Headache	0	**38/2**
Diarrhea	**53/6**	31/3
Fatigue	**49/5**	27/1
Myalgia	**17/0**	21/1
Nausea	**33/1**	18/1
AE of special interest any grade/grade 3-4 (%)		
Pneumonia	7 / 6	7/6
Atrial fibrillation	**7/ 6**	0/0
Bleeding events	**41/6**	31/1
Patients discontinuing therapy due to AE (%)	**11**	6

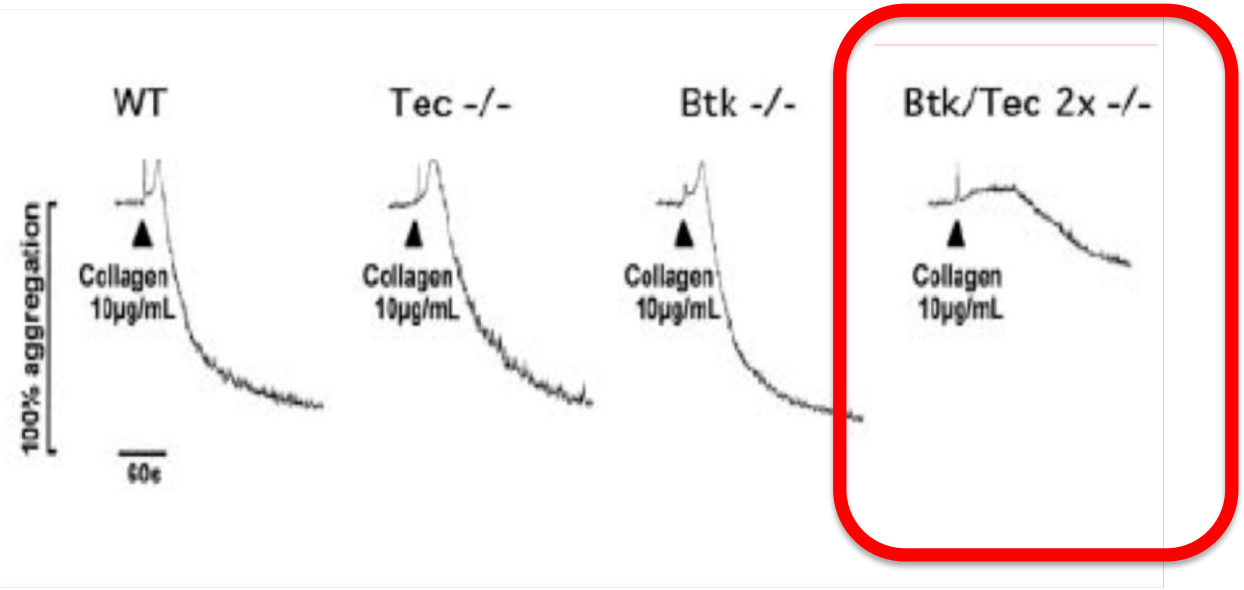
Wang et al., NEJM 2013; Wang et al. Lancet 2017

Ibrutinib - Concurrent BTK/TEC inhibition disrupts collagen-mediated platelet aggregation



Kinase Inhibition IC_5 (nmol/L)[1]

Kinase	Ibrutinib
BTK	1.5
TEC	7.0
BMX	0.8
TXK	2.0
ERBB2	6.4
EGFR	5.3
ITK	4.9
JAK3	32
BLK	0.1

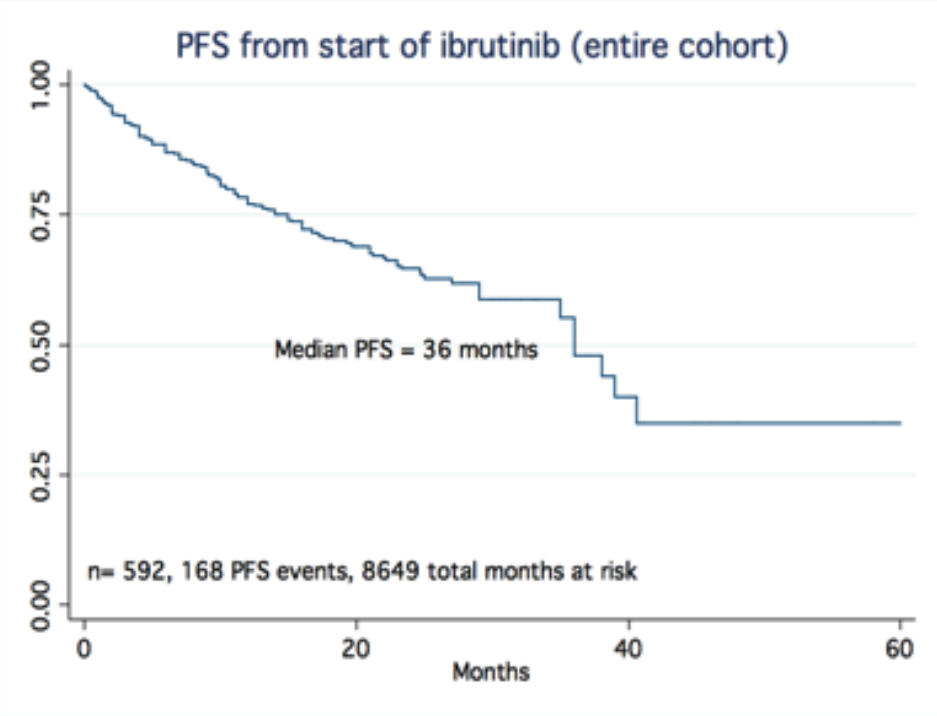


Atkinson et al, 2003

Clinical trials with Ibrutinib in R/R MCL

	Wang et al (2013b)	Cheah et al (2015)	Martin et al (2016)	Dreyling et al (2016)	Epperla et al (2017)
Study design	Prospective, phase 2 (2011–12)	Retrospective (2011–14)	Retrospective (NA)	Prospective, phase 3, (2012–13)	Retrospective (2013–2015)
Sites, n	18	1	15	21	8
Patients, n	111	78	114	280 (139 on Ibrut.)	97
Median prior treatments (range)	3 (1–5)	2 (1–8)	3 (0–10)	2 (1–9)	2 (1–8)
Median Ibrutinib (cycles/duration)	9 cycles	6-5 cycles	4-7 months	14-4 months	NA
CR	NA	30%	11%	NA	NA
ORR to ibrutinib	68%	NA	55%	72%	65%
Median DOR to ibrutinib	17-5 months	6 months	NA	NR	17 months
Ibrutinib discontinuation	58%	54%	NA	53%	50%
Progression (%)	45%	35%	100%	40%	25% PD, 10% SD
Primary resistance	**32%**	**10%**	**32%**	**28%**	**35%**
Acquired resistance	**NA**	**25%**	**54%**	**NA**	**17%**

Ibrutinib discontinuation rate (CLL ”real life”data)



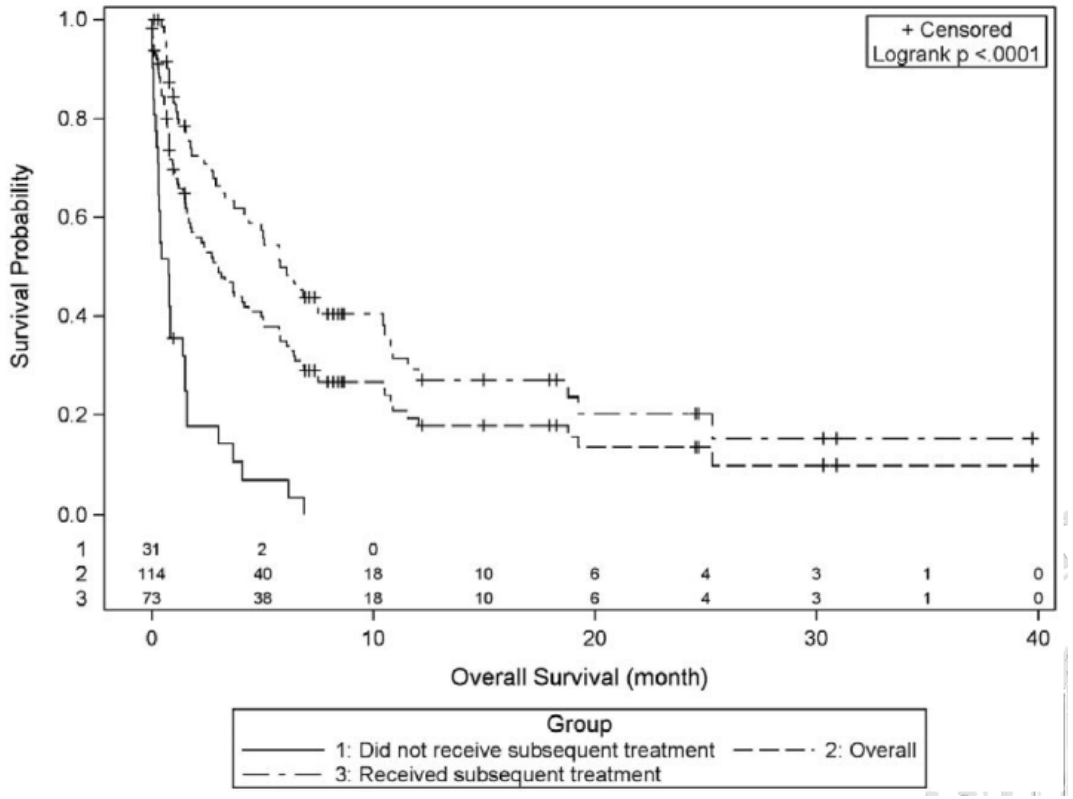
d/c rate = 42% after median f/u of 17 months

Due to PD: 10-20%

Due to Toxicity: 50%

Mato AR et al, ASH2016

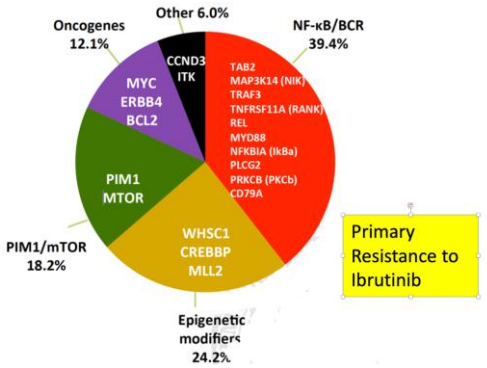
How to treat MCL after BTKi failure ?



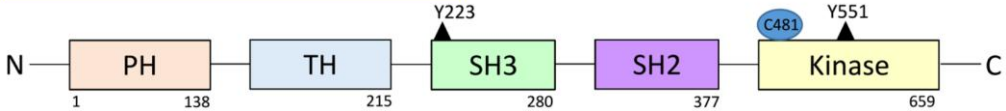
ABSOLUTELY NO IDEA

But it almost certainly depends on when it is used

……Simon Rule



Mechanisms of acquired Ibrutinib resistance



Cysteine to Serine mutation of BTK binding site of Ibrutinib:

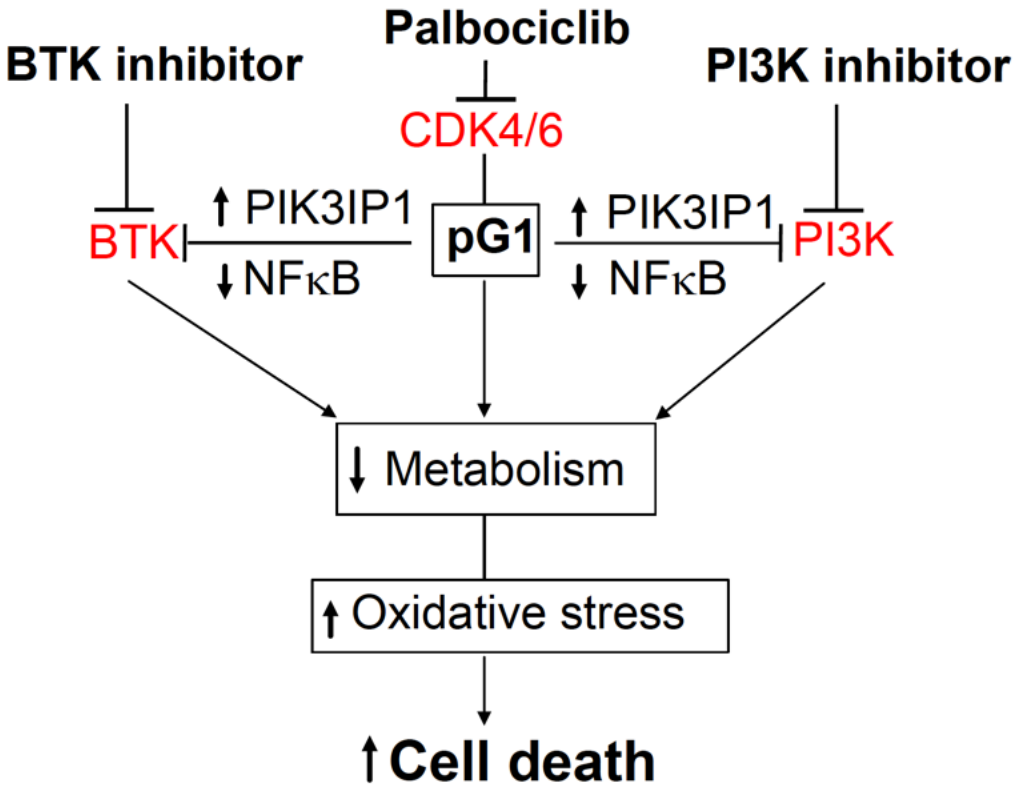
Martin et al., Blood 2016

How to overcome Ibrutinib resistance ?

BTK inhibitor „combos” & „triplets”

Novel BTK inhibitors

Loxo-305 – Loxo Oncology
ARQ 351 – ArQuele
Vecabrutinib – Sunesis
GDC583 - Genethech



IMIDS

Venetoclax

MCL w Klinice Hematologii UJCM

- **Opracowywanie standardów leczenia MCL** w ramach współpracy z European MCL Network (Luek.Lymph 2008)
- Zajęcie **CNS** w przebiegu MCL (Ann.Oncol. 2016)
- **Radioimmunoterapia** jako metoda konsolidacji u chorych z MCL, dysertacja doktorska lek.med. Dagmary Zimowskiej Curyło, temat habilitacji dr.med. Wojciecha Jurczaka, (J.Nucl. Med. 2007, J.Nucl.Med 2011, Bone Marrow Transpl. 2011, konferencje Eur.Nucl Medicine 2007, ASCO 2006, ASH 2007, 2008 , ICML2013)

Leukemia & Lymphoma, September 2010; 51(9): 1612–1622

informa healthcare

REVIEW

Update on the molecular pathogenesis and clinical treatment of Mantle Cell Lymphoma (MCL): minutes of the 9th European MCL Network conference

MARTIN DREYLING[1], EVA HOSTER[1], SILVIA BEA[2], ELENA HARTMANN[3], HEIKE HORN[4], GRIT HUTTER[5], ITZIAR SALAVERRIA[6], CHRISTIANE POTT[7], MAREK TRNENY[8], STEVEN LE GOUILL[9], SERGIO CORTELAZZO[10], MICHAL SZYMCZYK[11], WOJCIECH JURCZAK[12], OFER SHPILBERG[13], VINCENT RIBRAG[14], & OLIVIER HERMINE[15]; FOR THE EUROPEAN MCL NETWORK

[1]*Department of Medicine III, University Hospital Großhadern/LMU Munich, Germany,* [2]*Hematopathology Unit, Department of Pathology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain,* [3]*Institute of Pathology, University of Würzburg, Würzburg, Germany,* [4]*Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology and Department of Clinical Pathology, Robert-Bosch-Hospital, Stuttgart, Germany,* [5]*Helmholtz Zentrum München,German Research Center for Environmental Health, Munich, Germany,* [6]*Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany,* [7]*Second Medical Department, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Germany,* [8]*1st Department of Internal Medicine, University Hospital, Prague, Czech Republic,* [9]*Hematology Department, Hospital Hôtel-Dieu, Nantes, France,* [10]*Department of Hematology, A. O. S. Maurizio, Bolzano, Italy,* [11]*Maria Sklodowska-Curie Institute and Oncology Center, Warsaw, Poland,* [12]*Department of Heamtology, CMUJ, Poland,* [13]*Institute of Hematology, Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center and Sackler School of Medicine, Tel Aviv University, Israel,* [14]*Department of Hematology, Gustave Roussy Institute, Villejuif, France, and* [15]*Department of Pathology, Necker Hospital, Assistance Publique-Hôpitaux de Paris, University Paris-Descartes, Faculté de Médecine, Paris, France*

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Central nervous system involvement in mantle cell lymphoma: clinical features, prognostic factors and outcomes from the European Mantle Cell Lymphoma Network†

C. Y. Cheah[1,12], A. George[1], E. Giné[2], A. Chiappella[3], H. C. Kluin-Nelemans[4], W. Jurczak[5], K. Krawczyk[5], H. Mocikova[6], P. Klener[7], D. Salek[8], J. Walewski[9], M. Szymczyk[9], L. Smolej[10], R. L. Auer[11], D. S. Ritchie[1,12], L. Arcaini[13], M. E. Williams[14], M. Dreyling[15], J. F. Seymour[1,12]* & for the European Mantle Cell Lymphoma Network

[1]*Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia;* [2]*Department of Hematology, Hospital Clinic, Barcelona, Spain;* [3]*Department of Hematology 2, The City of Health and Science Hospital and University, Torino, Italy;* [4]*University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;* [5]*Department of Haematology, Jagiellonian University, Krakow, Poland;* [6]*Third Faculty of Medicine, University Hospital Kralovske Vinohrady, Charles University in Prague, Prague;* [7]*First Faculty of Medicine, General University Hospital, Charles University in Prague, Prague;* [8]*Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Masaryk University, Czech Republic;* [9]*Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland;* [10]*Fourth Department of Internal Medicine—Hematology, University Hospital and Faculty of Medicine, Hradec Kralove, Czech Republic;* [11]*Centre for Haemato-Oncology, Barts Health NHS Trust, London, UK;* [12]*University of Melbourne, Parkville, Victoria, Australia;* [13]*Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, and Department of Molecular Medicine, University of Pavia, Pavia, Italy;* [14]*University of Virginia Health System, Charlottesville, USA;* [15]*University Hospital Munich, Campus Grosshadern, Munich, Germany*

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Background: Central nervous system (CNS) involvement in mantle cell lymphoma (MCL) is uncommon, and the manifestations and natural history are not well described.
Patients and methods: We present the data on 57 patients with MCL who developed CNS involvement, from a database of 1396 consecutively treated patients at 14 institutions.
Results: The crude incidence of CNS involvement was 4.1%, with 0.9% having CNS involvement at diagnosis. Blastoid histology, B-symptoms, elevated lactate dehydrogenase, Eastern Cooperative Group performance status ≥2 and a high Mantle Cell Lymphoma International Prognostic Index score were enriched in the cohort with CNS involvement, and the presence of ≥1 of these features defined a high-risk subset (an actuarial risk of CNS involvement 15% at 5 years) in a single-institution subset. The median time to CNS relapse was 15.2 months, and the median survival from time of CNS diagnosis was 3.7 months. The white blood cell count at diagnosis $<10.9 \times 10^9$/l, treatment of CNS involvement with high-dose anti-metabolites, consolidation with stem cell transplant and achievement of complete response were all associated with improved survival.
Conclusions: In MCL, CNS involvement is uncommon, although some features may predict risk. Once manifest outlook is poor; however, some patients who receive intensive therapy survive longer than 12 months.
Key words: mantle cell lymphoma, central nervous system, prognosis

Radioimmunotherapy Confers Long-Term Survival to Lymphoma Patients with Acceptable Toxicity: Registry Analysis by the International Radioimmunotherapy Network

Karin Hohloch[1], Angelika Bischof Delaloye[2], Christiane Windemuth-Kieselbach[3], Jose Gómez-Codina[4], Werner Linkesch[5], Wojciech Jurczak[6], Roberto Cacchione[7], Cheolwon Suh[8], Pier Luigi Zinzani[9], and Lorenz Trümper[1]

[1]*Göttingen Comprehensive Cancer Center, Georg August University, Göttingen, Germany;* [2]*Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [3]*Alcedis GmbH, Independent CRO, Giessen, Germany;* [4]*Hospital Universitario La Fe, Valencia, Spain;* [5]*Klinische Abteilung für Hämatologie, Medical University Graz, Graz, Austria;* [6]*Department of Haematology, Jagiellonian University, Cracow, Poland;* [7]*CEMIC, Centro de Educación, Médica e Investigaciones Clinical, Norberto Quirno, Buenos Aires, Argentina;* [8]*Ulsan College of Medicine, Seoul, Korea; and* [9]*Istituto di Ematologia e Oncologia Medica, Università di Bologna, Bologna, Italy*

The Radioimmunotherapy Network (RIT-N) is a Web-based, international registry collecting long-term observational data about radioimmunotherapy-treated patients with malignant lymphoma outside randomized clinical studies. The RIT-N collects unbiased data on treatment indications, disease stages, patients' conditions, lymphoma subtypes, and hematologic side effects of radioimmunotherapy treatment. **Methods:** RIT-N is located at the University of Göttingen, Germany, and collected data from 14 countries. Data were entered by investigators into a Web-based central database managed by an independent clinical research organization. **Results:** Patients (1,075) were enrolled from December 2006 until November 2009, and 467 patients with an observation time of at least 12 mo were included in the following analysis. Diagnoses were as follows: 58% follicular lymphoma and 42% other B-cell lymphomas. The mean overall survival was 28 mo for follicular lymphoma and 26 mo for other lymphoma subtypes. Hematotoxicity was mild for hemoglobin (World Health Organization grade II), with a median nadir of 10 g/dL, but severe (World Health Organization grade III) for platelets and leukocytes, with a median nadir of 7,000/μL and 2.2/μL, respectively. **Conclusion:** Clinical usage of radioimmunotherapy differs from the labeled indications and can be assessed by this registry, enabling analyses of outcome and toxicity data beyond clinical trials. This analysis proves that radioimmunotherapy in follicular lymphoma and other lymphoma subtypes is a safe and efficient treatment option.

Key Words: B-cell lymphoma; radioimmunotherapy; registry; treatment; RIT-Network

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Radioimmunotherapy is a highly lymphoma-specific therapeutic approach with low side effects and a good tolerability established in the treatment of relapsed follicular lymphoma (FL) and in consolidation after first-line treatment (*1*). The current standard first-line therapy for FL patients in limited stage consists of involved-field radiation, with a local control rate of 95% and disease-free and overall survival (OS) rates of 37%–94% and 40%–95%, respectively (*2*). In advanced stages, however, FL is deemed incurable by conventional therapy. For asymptomatic patients with advanced-stage FL, watchful waiting is the recommended strategy, whereas for symptomatic patients a variety of single-agent or multiagent chemotherapy options with high response rates are available. The introduction of rituximab, a monoclonal anti-CD20 antibody, when combined with different chemotherapy regimens resulted in a significant superior treatment outcome, compared with chemotherapy alone (*3,4*). Relapses after conventional therapies are frequent, and subsequent treatment approaches are usually hampered by decreased response rates and shorter durations of remission with each successive treatment (*5,6*).

The introduction of radioimmunotherapy in 1993 provided a new and effective treatment option for FL patients. The active principle of radioimmunotherapy in lymphoma is the targeting of lymphoma cells by highly specific antibodies labeled with radioactive isotopes acting primarily by killing lymphoma cells via emission of β-particles (*7*). Antibodies labeled with the radioactive isotopes ^{131}I or

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ELSEVIER — EJC

Review

Consensus conference: Implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice – Report of a European workshop

Pier Luigi Zinzani[a,], Francesco d'Amore[b], Emilio Bombardieri[c], Caroline Brammer[d], José Gómez Codina[e], Tim Illidge[f], Wojciech Jurczak[g], Werner Linkesch[h], Franck Morschhauser[i], Elisabeth Vandenberghe[j], Achiel Van Hoof[k]*

[a]*Institute of Hematology and Oncology 'Seràgnoli', Via Massarenti 9, 40138 Bologna, Italy*
[b]*Department of Hematology, Arhus University Hospital, Arhus, Denmark*
[c]*Fondazione IRCCS 'Istituto Nazionale Tumori', Milano, Italy*
[d]*Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK*
[e]*Hospital Universitario La Fe, Valencia, Spain*
[f]*Paterson Institute Cancer Studies Division, Manchester University Christie Hospital, Manchester, UK*
[g]*Department of Haematology, Collegium Medicum Jagiellonian University, Krakow, Poland*
[h]*Klinische Abteilung für Hämatologie, Universitätsklinik für Innere Medizin Graz, Graz, Austria*
[i]*Centre Hospitalier Universitaire, Lille, France*
[j]*St James's Hospital, Dublin, Ireland*
[k]*Algemeen Ziekenhuis St. Jan, Brugge, Belgium*

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ABSTRACT

Radiolabelled immunotherapy is a significant step forward in the treatment of non-Hodgkin's lymphoma (NHL), with preliminary data suggesting long remissions in some patients. ^{90}Y-ibritumomab tiuxetan is the only therapy approved for use after rituximab failure and is currently indicated in the EU for the treatment of adults with rituximab-relapsed or refractory CD20-positive follicular B-cell NHL. However, retrospective analyses confirm better responses when ^{90}Y-ibritumomab tiuxetan is used earlier in the disease course. An expert panel of oncologists, haematologists and nuclear medicine physicians met at an European workshop to discuss proposed therapeutic algorithms for follicular lymphoma and the preliminary medical evidence supporting the incorporation of ^{90}Y-ibritumomab tiuxetan as an early therapeutic option. Phase II data indicate that ^{90}Y-ibritumomab tiuxetan either alone as primary therapy or as consolidation therapy following induction chemotherapy with or without rituximab achieves high response rates in follicular lymphoma, with complete remission rates of 62–80%. Phase III data are warranted, but based on preliminary observations the expert panel recommended incorporation of radiolabelled immunotherapy into national lymphoma treatment algorithms across Europe. This approach would maximise the therapeutic potential of this agent by encouraging its use early in the disease course of follicular lymphomas.

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Polish Lymphoma Research Group

MCL w Klinice Hematologii UJCM – inhibitory kinazy Brutona

- **Inhibitory Kinazy Brutona w leczeniu MCL: Ibrutynib** (NEJM 2013, Blood 2015, Lancet 2016, Blood 2016, Leuk.Lymphoma 2016, Leukaemia 2018) **, Acalabrutynib** (Lancet 2018)

NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., Stephan Stilgenbauer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, M.D., Peter Johnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., Liang Zhang, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., Nancy Cheng, M.S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, Sc.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., Ph.D., Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

ABSTRACT

BACKGROUND

Bruton's tyrosine kinase (BTK) is a mediator of the B-cell–receptor signaling pathway implicated in the pathogenesis of B-cell cancers. In a phase 1 study, ibrutinib, a BTK inhibitor, showed antitumor activity in several types of non-Hodgkin's lymphoma, including mantle-cell lymphoma.

METHODS

In this phase 2 study, we investigated oral ibrutinib, at a daily dose of 560 mg, in 111 patients with relapsed or refractory mantle-cell lymphoma. Patients were enrolled into two groups: those who had previously received at least 2 cycles of bortezomib therapy and those who had received less than 2 complete cycles of bortezomib or had received no prior bortezomib therapy. The primary end point was the overall response rate. Secondary end points were duration of response, progression-free survival, overall survival, and safety.

RESULTS

The median age was 68 years, and 86% of patients had intermediate-risk or high-risk mantle-cell lymphoma according to clinical prognostic factors. Patients had received a median of three prior therapies. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). A response rate of 68% (75 patients) was observed, with a complete response rate of 21% and a partial response rate of 47%; prior treatment with bortezomib had no effect on the response rate. With an estimated median follow-up of 15.3 months, the estimated median response duration was 17.5 months (95% confidence interval [CI], 15.8 to not reached), the estimated median progression-free survival was 13.9 months (95% CI, 7.0 to not reached), and the median overall survival was not reached. The estimated rate of overall survival was 58% at 18 months.

CONCLUSIONS

Ibrutinib shows durable single-agent efficacy in relapsed or refractory mantle-cell lymphoma. (Funded by Pharmacyclics and others; ClinicalTrials.gov number, NCT01236391.)

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ORIGINAL ARTICLE: CLINICAL

Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus

Georg Hess[a], Simon Rule[b], Wojciech Jurczak[c], Mats Jerkeman[d], Rodrigo Santucci Silva[e], Chiara Rusconi[f], Dolores Caballero[g], Cristina Joao[h], Mathias Witzens-Harig[i], Isabelle Bence-Bruckler[j], Seok-Goo Cho[k], Wenjiong Zhou[l], Jenna D. Goldberg[l], Cristina Trambitas[m], Christopher Enny[l], Jessica Vermeulen[n], Shana Traina[l], Chiun-Fang Chiou[l], Joris Diels[o] and Martin Dreyling[p]

[a]Department of Hematology, Oncology and Pneumology, University Medical School of the Johannes Gutenberg University, Mainz, Germany; [b]Derriford Hospital, Plymouth University Medical School, Plymouth, UK; [c]Department of Hematology, Jagiellonian University, Krakow, Poland; [d]Skånes University Hospital, Lund University, Lund, Sweden; [e]Instituto de Ensino e Pesquisa Sao Lucas, Sao Paulo, Brazil; [f]Division of Hematology, Department of Hematology and Oncology, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy; [g]Instituto Biosanitario de Salamanca, Hospital Clinico Universitario Salamanca, Salamanca, Spain; [h]Instituto Português de Oncologia de Lisboa, Portugal and Champalimaud Centre for the Unknown, Hematology, Lisbon, Portugal; [i]Klinikum der Ruprechts-Karls-Universität Heidelberg – Med. Klinik u. Poliklinik V, Heidelberg, Germany; [j]The Ottawa Hospital, General Campus, Ottawa, ON, Canada; [k]Seoul St. Mary's Hospital, Seocho-gu, Seoul, South Korea; [l]Janssen Research & Development, Raritan, NJ, USA; [m]Janssen Inc, Ontario, Canada; [n]Janssen Research & Development, LLC, Leiden, The Netherlands; [o]Janssen Pharmaceuticals, Beerse, Belgium; [p]Department of Medicine III, Klinikum der Universität München, LMU, Munich, Germany

ABSTRACT

Mantle cell lymphoma (MCL) is a rare, aggressive, incurable B-cell malignancy. Ibrutinib has been shown to be highly active for patients with relapsed/refractory (R/R) MCL. The RAY trial (MCL3001) was a phase 3, randomized, open-label, multicenter study that compared ibrutinib with temsirolimus in patients with R/R MCL. Active disease is frequently associated with impaired functional status and reduced well-being. Therefore, the current study employed two patient-reported outcome instruments, the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and the EQ-5D-5L, to assess symptoms, well-being, health status, and health-related quality of life of patients on treatment within the RAY trial. We found that patients on ibrutinib had substantial improvement in FACT-Lym subscale and total scores, and had improvement in EQ-5D-5L utility and VAS scores compared with temsirolimus patients, indicating a superior well-being. These improvements in well-being correlated with clinical response, indicating that better health-related quality of life was associated with decreased disease burden.

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KEYWORDS
Bruton's tyrosine kinase inhibitor; EQ-5D-5L; FACT-Lym; ibrutinib; mantle cell lymphoma; patient-reported outcomes

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Genetic heterogeneity in primary and relapsed mantle cell lymphomas: Impact of recurrent *CARD11* mutations

Chenglin Wu[1], Noel FCC de Miranda[1,*], Longyun Chen[1,2,*], Agata M. Wasik[3,*], Larry Mansouri[4], Wojciech Jurczak[5], Krystyna Galazka[6], Monika Dlugosz-Danecka[5], Maciej Machaczka[7], Huilai Zhang[8], Roujun Peng[9], Ryan D. Morin[10], Richard Rosenquist[4], Birgitta Sander[3], Qiang Pan-Hammarström[1]

[1]Division of Clinical Immunology and Transfusion Medicine, Karolinska Institutet at Karolinska University Hospital, Huddinge, Stockholm, Sweden
[2]Beijing Genomics Institute, Shenzhen, China
[3]Division of Pathology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital, Huddinge, Stockholm, Sweden
[4]Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[5]Department of Hematology, Jagiellonian University Collegium Medicum, Kraków, Poland
[6]Department of Pathology, Jagiellonian University Collegium Medicum, Kraków, Poland
[7]Faculty of Health Sciences, Jagiellonian University Collegium Medicum, Michalowskiego, Krakow, Poland
[8]Department of Lymphoma, Tianjin Medical University Cancer Hospital and Institutet, China
[9]Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China
[10]Department of Molecular Biology and Biochemistry, Simon Fraser Univers
*These authors contributed equally to this work

Correspondence to: Qiang Pan-Hammarström, **e-mail:** Qiang.Pan-Hamm

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ABSTRACT

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THE LANCET

Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D Smith, Gandhi Damaj, Jeanette Doorduijn, Thierry Lamy, Franck Morschhauser, Carlos Panizo, Bijal Shah, Andrew Davies, Richard Eek, Jehan Dupuis, Eric Jacobsen, Arnon P Kater, Steven Le Gouill, Lucie Oberic, Tadeusz Robak, Todd Covey, Richa Dua, Ahmed Hamdy, Xin Huang, Raquel Izumi, Priti Patel, Wayne Rothbaum, J Greg Slatter, Wojciech Jurczak

Summary

Background Bruton tyrosine kinase is a clinically validated target in mantle cell lymphoma. Acalabrutinib (ACP-196) is a highly selective, potent Bruton tyrosine kinase inhibitor developed to minimise off-target activity.

Methods In this open-label, phase 2 study, oral acalabrutinib (100 mg twice per day) was given to patients with relapsed or refractory mantle cell lymphoma, until disease progression or unacceptable toxicity. The primary endpoint was overall response assessed according to the Lugano classification, and safety analyses were done in all participants. This trial is registered with ClinicalTrials.gov, number NCT02213926.

Findings From March 12, 2015, to Jan 5, 2016, 124 patients with relapsed or refractory mantle cell lymphoma were enrolled and all patients received treatment; median age 68 years. Patients received a median of two (IQR 1–2) previous therapies. At a median follow-up of 15·2 months, 100 (81%) patients achieved an overall response and 49 (40%) patients achieved a complete response. The Kaplan-Meier estimated medians for duration of response, progression-free survival, and overall survival were not reached; the 12-month rates were 72% (95% CI 62–80), 67% (58–75), and 87% (79–92%), respectively. The most common adverse events were primarily grade 1 or 2 and were headache (47 [38%]), diarrhoea (38 [31%]), fatigue (34 [27%]), and myalgia (26 [21%]). The most common grade 3 or worse adverse events were neutropenia (13 [10%]), anaemia (11 [9%]), and pneumonia (six [5%]). There were no cases of atrial fi ... 8 months. Treatmen ... verse events (seven [6 ...

Interpreta ... y profile in patients w ... calabrutinib in the tre ...

Funding ...

AUTHOR VERSION

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Leukemia

Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study

S Rule, W Jurczak, M Jerkeman, C Rusconi, M Trneny, F Offner, D Caballero, C Joao, M Witzens-Harig, G Hess, I Bence-Bruckler, S-G Cho, C Thieblemont, W Zhou, T Henninger, J Goldberg, J Vermeulen, M Dreyling

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THE LANCET

Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study

Martin Dreyling, Wojciech Jurczak*, Mats Jerkeman*, Rodrigo Santucci Silva, Chiara Rusconi*, Marek Trneny*, Fritz Offner*, Dolores Caballero*, Cristina Joao*, Mathias Witzens-Harig*, Georg Hess*, Isabelle Bence-Bruckler, Seok-Goo Cho, John Bothos, Jenna D Goldberg, Christopher Enny, Shana Traina, Sriram Balasubramanian, Nibedita Bandyopadhyay, Steven Sun, Jessica Vermeulen, Aleksandra Rizo, Simon Rule**

Summary

Background Mantle-cell lymphoma is an aggressive B-cell lymphoma with a poor prognosis. Both ibrutinib and temsirolimus have shown single-agent activity in patients with relapsed or refractory mantle-cell lymphoma. We undertook a phase 3 study to assess the efficacy and safety of ibrutinib versus temsirolimus in relapsed or refractory mantle-cell lymphoma.

Methods This randomised, open-label, multicentre, phase 3 clinical trial enrolled patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology in 21 countries who had received one or more rituximab-containing treatments. Patients were stratified by previous therapy and simplified mantle-cell lymphoma international prognostic index score, and were randomly assigned with a computer-generated randomisation schedule to receive daily oral ibrutinib 560 mg or intravenous temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles). Randomisation was balanced by using randomly permuted blocks. The primary efficacy endpoint was progression-free survival assessed by a masked independent review committee with the primary hypothesis that ibrutinib compared with temsirolimus significantly improves progression-free survival. The analysis followed the intention-to-treat principle. The trial is ongoing and is registered with ClinicalTrials.gov (number NCT01646021) and with the EU Clinical Trials Register, EudraCT (number 2012-000601-74).

Findings Between Dec 10, 2012, and Nov 26, 2013, 280 patients were randomised to ibrutinib (n=139) or temsirolimus (n=141). Primary efficacy analysis showed significant improvement in progression-free survival (p<0·0001) for patients treated with ibrutinib versus temsirolimus (hazard ratio 0·43 [95% CI 0·32–0·58]; median progression-free survival 14·6 months [95% CI 10·4–not estimable] *vs* 6·2 months [4·2–7·9], respectively). Ibrutinib was better tolerated than temsirolimus, with grade 3 or higher treatment-emergent adverse events reported for 94 (68%) versus 121 (87%) patients, and fewer discontinuations of study medication due to adverse events for ibrutinib versus temsirolimus (9 [6%] *vs* 36 [26%]).

Interpretation Ibrutinib treatment resulted in significant improvement in progression-free survival and better tolerability versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma. These data lend further support to the positive benefit–risk ratio for ibrutinib in relapsed or refractory mantle-cell lymphoma.

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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Postibrutinib outcomes in patients with mantle cell lymphoma

Peter Martin,[1] Karni Maddocks,[2] John P. Leonard,[1] Jia Ruan,[1] Andre Goy,[3] Nina Wagner-Johnston,[4] Simon Rule,[5] Ranjana Advani,[6] David Iberri,[6] Tycel Phillips,[7] Stephen Spurgeon,[8] Eliana Kozin,[8] Katherine Noto,[1] Zhengming Chen,[9] Wojciech Jurczak,[10] Rebecca Auer,[11] Ewa Chmielowska,[12] Stephan Stilgenbauer,[13] Johannes Bloehdorn,[13] Craig Portell,[14] Michael E. Williams,[14] Martin Dreyling,[15] Paul M. Barr,[16] Belina Chen-Kiang,[17] Maurizio DiLiberto,[17] Richard R. Furman,[1] and Kristie A. Blum[2]

[1]Department of Medicine, Weill Cornell Medical College, New York, NY; [2]Ohio State University Comprehensive Cancer Center, Columbus, OH; [3]Hackensack University Medical Center, Hackensack, NJ; [4]Division of Oncology, Washington University School of Medicine, St. Louis, MO; [5]Department of Haematology, Plymouth University Peninsula Schools of Medicine and Dentistry and Derriford Hospital, Plymouth, United Kingdom; [6]Stanford Cancer Institute, Stanford, CA; [7]Department of Internal Medicine, University of Michigan, Ann Arbor, MI; [8]Center for Hematologic Malignancies, Oregon Health and Science University, Portland, OR; [9]Department of Healthcare Policy and Research, Weill Cornell Medical College, New York, NY; [10]Department of Hematology, Jagiellonian University, Krakow, Poland; [11]St. Bartholomew's Hospital, London, United Kingdom; [12]Oddział Kliniczny Onkologii, Bydgoszcz, Poland; [13]Universitätsklinikum Ulm, Ulm, Germany; [14]University of Virginia Cancer Center, Charlottesville, VA; [15]Klinikum der Universität München, Munich, Germany; [16]Department of Medicine, University of Rochester Medical Center, Rochester, NY; and [17]Department of Pathology, Weill Cornell Medical College, New York, NY

Key Points

- Patients with mantle cell lymphoma who progressed during treatment with ibrutinib have a poor outcome.
- There are no therapies that appear to be uniquely successful in the postibrutinib setting. The postibrutinib setting is an unmet need.

Despite unprecedented clinical activity in mantle cell lymphoma (MCL), primary and acquired resistance to ibrutinib is common. The outcomes and ideal management of patients who experience ibrutinib failure are unclear. We performed a retrospective cohort study of all patients with MCL who experienced disease progression while receiving ibrutinib across 15 international sites. Medical records were evaluated for clinical characteristics, pathological and radiological data, and therapies used pre- and postibrutinib. A total of 114 subjects met eligibility criteria. The median number of prior therapies was 3 (range, 0-10). The Mantle Cell Lymphoma International Prognostic Index (MIPI) scores at the start of ibrutinib were low, intermediate, and high in 46%, 31%, and 23% of patients, respectively. Of patients with available data prior to ibrutinib and postibrutinib, 34 of 47 and 11 of 12 had a Ki67 >30%. The median time on ibrutinib was 4.7 months (range 0.7-43.6). The median overall survival (OS) following cessation of ibrutinib was 2.9 months (95% confidence interval [CI], 1.6-4.9). Of the 104 patients with data available, 73 underwent subsequent treatment an average of 0.3 months after stopping ibrutinib with a median OS of 5.8 months (95% CI, 3.7-10.4). Multivariate Cox regression analysis of MIPI before postibrutinib treatment, and subsequent treatment with bendamustine, cytarabine, or lenalidomide failed to reveal any association with OS. Poor clinical outcomes were noted in the majority of patients with primary or secondary ibrutinib resistance. We could not identify treatments that clearly improved outcomes. Future trials should focus on understanding the mechanisms of ibrutinib resistance and on treatment after ibrutinib. (*Blood.* 2016;127(12):1559-1563)

Prof. Wojciech Jurczak MD,PhD

Polish Lymphoma Research Group

MCL w Klinice Hematologii UJCM

- **IMIDy w R/R MCL**
  Lenalidomid w leczeniu przypadków opornych (Lancet Oncol 2016, Br J Haemat 2018)

- **Inhibitory mTOR w MCL**
  (Leuk.Lymphoma 2017)

THE LANCET Oncology

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

Marek Trněný, Thierry Lamy, Jan Walewski, David Belada, Jiri Mayer, John Radford, Wojciech Jurczak, Franck Morschhauser, Julia Alexeeva, Simon Rule, Boris Afanasyev, Kamil Kaplanov, Antoine Thyss, Alexej Kuzmin, Sergey Voloshin, Kazimierz Kuliczkowski, Agnieszka Giza, Noel Milpied, Caterina Stelitano, Reinhard Marks, Lorenz Trümper, Tsvetan Biyukov, Meera Patturajan, Marie-Laure Casadebaig Bravo, Luca Arcaini, on behalf of the SPRINT trial investigators and in collaboration with the European Mantle Cell Lymphoma Network

Summary

Background Lenalidomide, an immunomodulatory drug with antineoplastic and antiproliferative effects, showed activity in many single-group studies in relapsed or refractory mantle cell lymphoma. The aim of this randomised study was to examine the efficacy and safety of lenalidomide versus best investigator's choice of single-agent therapy in relapsed or refractory mantle cell lymphoma.

Methods The MCL-002 (SPRINT) study was a randomised, phase 2 study of patients with mantle cell lymphoma aged 18 years or older at 67 clinics and academic centres in 12 countries who relapsed one to three times, had Eastern Cooperative Oncology Group performance status of 0–2, at least one measurable lesion to be eligible, and who were ineligible for intensive chemotherpy or stem-cell transplantation. Using a centralised interactive voice response system, we randomly assigned (2:1) patients in a permuted block size of six to receive lenalidomide (25 mg orally on days 1–21 every 28 days) until progressive disease or intolerability, or single-agent investigator's choice of either rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine. Randomisation was stratified by time from diagnosis, time from last anti-lymphoma therapy, and previous stem-cell transplantation. Individual treatment assignment between lenalidomide and investigator's choice was open label, but investigators had to register their choice of comparator drug before randomly assigning a patient. Patients who progressed on investigator's choice could cross over to lenalidomide treatment. We present the prespecified primary analysis results in the intention-to-treat population for the primary endpoint of progression-free survival, defined as the time from randomisation to progressive disease or death, whichever occurred first. Patient enrolment is complete, although treatment and collection of additional time-to-event data are ongoing. This study is registered with ClinicalTrials.gov, number NCT00875667.

Findings Between April 30, 2009, and March 7, 2013, we enrolled 254 patients in the intention-to-treat population (170 [67%] were randomly assigned to receive lenalidomide, 84 [33%] to receive investigator's choice monotherapy). Patients had a median age of 68·5 years and received a median of two previous regimens. With a median follow-up of 15·9 months (IQR 7·6–31·7), lenalidomide significantly improved progression-free survival compared with investigator's choice (median 8·7 months [95% CI 5·5–12·1] *vs* 5·2 months [95% CI 3·7–6·9]) with a hazard ratio of 0·61 (95% CI 0·44–0·84; p=0·004). In the 167 patients in the lenalidomide group and 83 patients in the investigator's choice group who received at least one dose of treatment the most common grade 3–4 adverse events included neutropenia (73 [44%] of 167 *vs* 28 [34%] of 83) without increased risk of infection, thrombocytopenia (30 [18%] *vs* 23 [28%]), leucopenia (13 [8%] *vs* nine [11%]), and anaemia (14 [8%] *vs* six [7%]).

Interpretation Patients with relapsed or refractory mantle cell lymphoma ineligible for intensive chemotherapy or stem-cell transplantation have longer progression-free survival, with a manageable safety profile when treated with lenalidomide compared with monotherapy investigator's choice options.

bjh research paper

Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide *versus* investigator's choice in relapsed or refractory mantle cell lymphoma

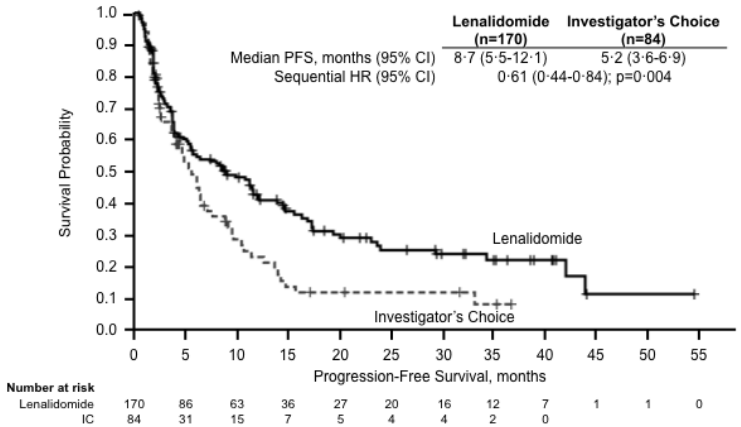
Luca Arcaini,[1,2] Thierry Lamy,[3] Jan Walewski,[4] David Belada,[5] Jiri Mayer,[6] John Radford,[7] Wojciech Jurczak,[8] Franck Morschhauser,[9] Julia Alexeeva,[10] Simon Rule,[11] José Cabeçadas,[12] Elias Campo,[13] Stefano A. Pileri,[14] Tsvetan Biyukov,[15] Meera Patturajan,[16] Marie-Laure Casadebaig Bravo,[15] and Marek Trněný,[17] on behalf of the SPRINT Trial Investigators

[1]Department of Molecular Medicine, University of Pavia, Pavia, Italy, [2]Department of Haematology-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [3]Department of Haematology, Hôpital Pontchaillou, Rennes, France, [4]Department of Lymphoid Malignancies, Maria Skłodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, [5]Fourth Department of Internal Medicine, Haematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic, [6]Department of Internal Medicine, Haematology and Oncology, University Hospital Brno, Brno, Czech Republic, [7]The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [8]Department of Haematology, Jagiellonian University Medical College, Kraków, Poland, [9]Department of Haematology, Hôpital Claude Huriez, EA 2365 GRITA, Lille, France, [10]Department of Hematolgy Research, Federal

Summary

In the mantle cell lymphoma (MCL)-002 study, lenalidomide demonstrated significantly improved median progression-free survival (PFS) compared with investigator's choice (IC) in patients with relapsed/refractory MCL. Here we present the long-term follow-up data and results of preplanned subgroup exploratory analyses from MCL-002 to evaluate the potential impact of demographic factors, baseline clinical characteristics and prior therapies on PFS. In MCL-002, patients with relapsed/refractory MCL were randomized 2:1 to receive lenalidomide (25 mg/day orally on days 1–21; 28-day cycles) or single-agent IC therapy (rituximab, gemcitabine, fludarabine, chlorambucil or cytarabine). The intent-to-treat population comprised 254 patients (lenalidomide, $n = 170$; IC, $n = 84$). Subgroup analyses of PFS favoured lenalidomide over IC across most characteristics, including risk factors, such as high MCL International Prognostic Index score, age ≥65 years, high lactate dehydrogenase (LDH), stage III/IV disease, high tumour burden, and refractoriness to last prior therapy. By multivariate Cox regression analysis, factors associated with significantly longer PFS (other than lenalidomide treatment) included normal LDH levels ($P < 0·001$), nonbulky disease ($P = 0·045$), <3 prior antilymphoma treatments ($P = 0·005$), and ≥6 months since last prior treatment ($P = 0·032$). Overall, lenalidomide improved PFS *versus* single-agent IC therapy in patients with relapsed/refractory MCL, irrespective of many demographic factors, disease characteristics and prior treatment history.

Keywords: lenalidomide, mantle cell lymphoma, non-Hodgkin lymphoma.



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Comparison of two doses of intravenous temsirolimus in patients with relapsed/refractory mantle cell lymphoma

Wojciech Jurczak[a], Sundra Ramanathan[b], Pratyush Giri[c], Alessandra Romano[d], Heidi Mocikova[e], Jill Clancy[f], Mariajose Lechuga[g], Michelle Casey[h], Joseph Boni[h], Agnieszka Giza[a] and Georg Hess[i]

[a]Department of Haematology, Jagiellonian University, Kraków, Poland; [b]Haematology Department, Cancer Care Centre, The St George Hospital, Kogarah, Australia; [c]Lyell McEwin Hospital (LMH), Royal Adelaide Hospital (RAH), Adelaide, Australia; [d]Division of Hematology, A.O.U. Policlinico-Vittorio Emanuele, University of Catania, Catania, Italy; [e]Department of Clinical Hematology, University Hospital Královské Vinohrady, Third Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; [f]InVentiv Health Clinical, Princeton, NJ, USA; [g]Pfizer S.r.l, Milan, Italy; [h]Pfizer Inc, Collegeville, PA, USA; [i]Department of Hematology/Oncology, Johannes Gutenberg University, Mainz, Germany

ABSTRACT

Temsirolimus 175 mg once-weekly for 3 weeks, followed by 75 mg once-weekly intravenously dosed (175/75 mg) is approved in the European Union for treatment of relapsed/refractory mantle cell lymphoma (MCL). A phase IV study explored whether similar efficacy, but improved safety could be achieved with 75 mg without 175 mg loading doses (ClinicaTrials.gov: NCT01180049). Patients with relapsed/refractory MCL were randomized to once-weekly temsirolimus 175/75 mg ($n = 47$) or 75 mg ($n = 42$). Treatment continued until objective disease progression. Primary endpoint: progression-free survival (PFS). Secondary endpoints included overall survival (OS) and adverse events (AEs). Median PFS was 4.3 versus 4.5 months (hazard ratio [HR] 0.731; 80% confidence interval [CI], 0.520–1.027), and median OS 18.7 versus 11.0 months (HR 0.681; 80% CI, 0.472–0.982) with 175/75 mg versus 75 mg. There were fewer patients with serious AEs, dose reduction, or death with 175/75 mg (57.4%, 48.9%, and 48.9%) versus 75 mg (73.8%, 64.3%, and 65.1%). Temsirolimus 175/75 mg remains the preferred dosing regimen for relapsed/refractory MCL.

ARTICLE HISTORY
Received 21 April 2017
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KEYWORDS
Temsirolimus; mantle cell lymphoma; progression-free survival; overall survival; safety

MCL – present European standard of care

Young Patients (<65)	Elderly (>65)	„Compromised”
I line therpy		
Dose-intensified (R-CHOP + R-high dose Ara-C → ASCT) + Rit Maintenance	Conventional Immuno-chemotherapy (e.g. R-CHOP, BR, VR-CAP,) + Rit maintenance	Best supportive care R-Chlorambucil BR (dose reduced) R-CVP
1 relapse		
Immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches Discuss: - Rit maintenance - Allo SCT	Immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches Discuss: - Rit maintenance - Radioimmunotherapy - Autologous SCT	Immuno-chemotherapy (e.g. BR) or targeted approaches
Higher relapse		
Targeted approaches (Ibrutynib, Lenalidomide, Temsirolimus, Bortezomib (preferably in Combinations) Alternatively – repeat previous therapy if in long remissions		

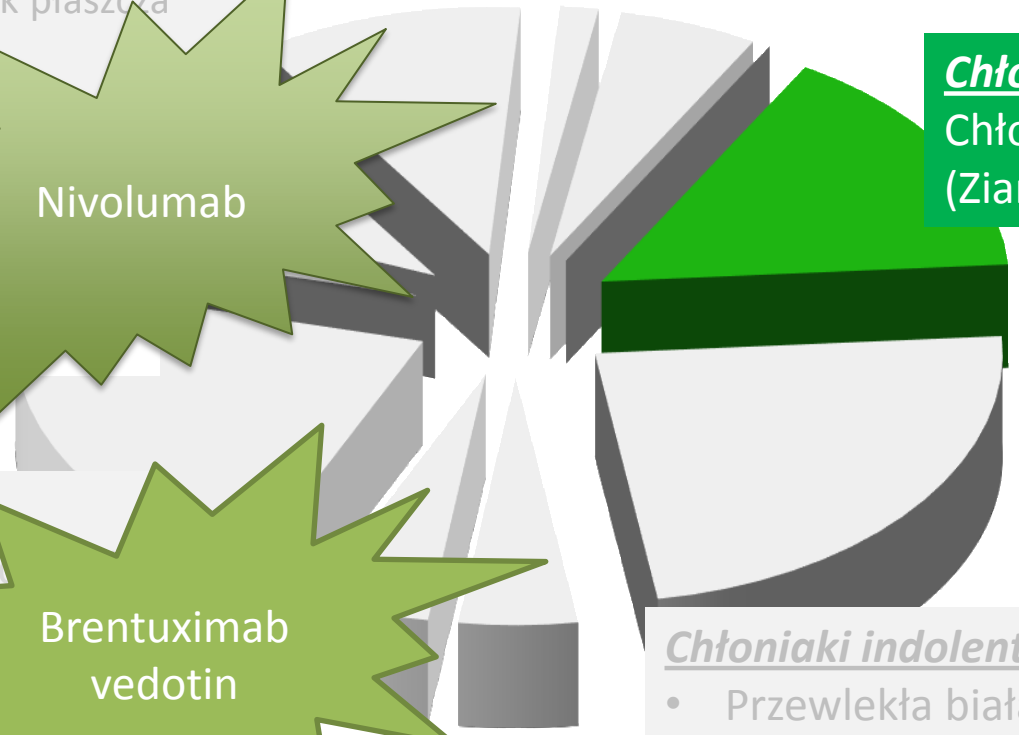
Dreyling, ESMO 2017


B 591ZM

Chłoniaki o dużej dynamice – duża szansa na całkowite wyleczenie choroby

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

Nivolumab



Chłoniaki agresywne
Chłoniak Hodgkina
(Ziarnica złośliwa)

Chłoniaki agresywne
- Chłoniak rozlany z komórek B
- Chłoniak lim

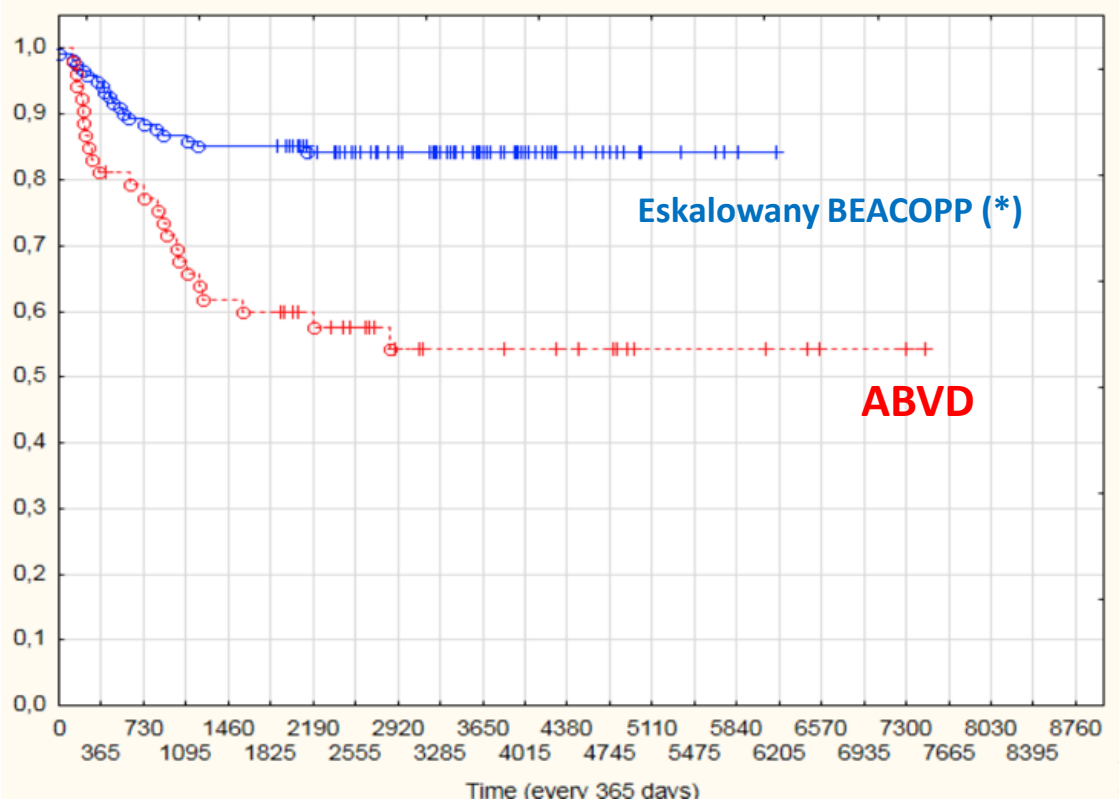
Brentuximab vedotin

Chłoniaki indolentne
- Przewlekła białaczka limfatyczna
- Chłoniak grudkowy
- Chłoniak strefy brzeżnej, MALT

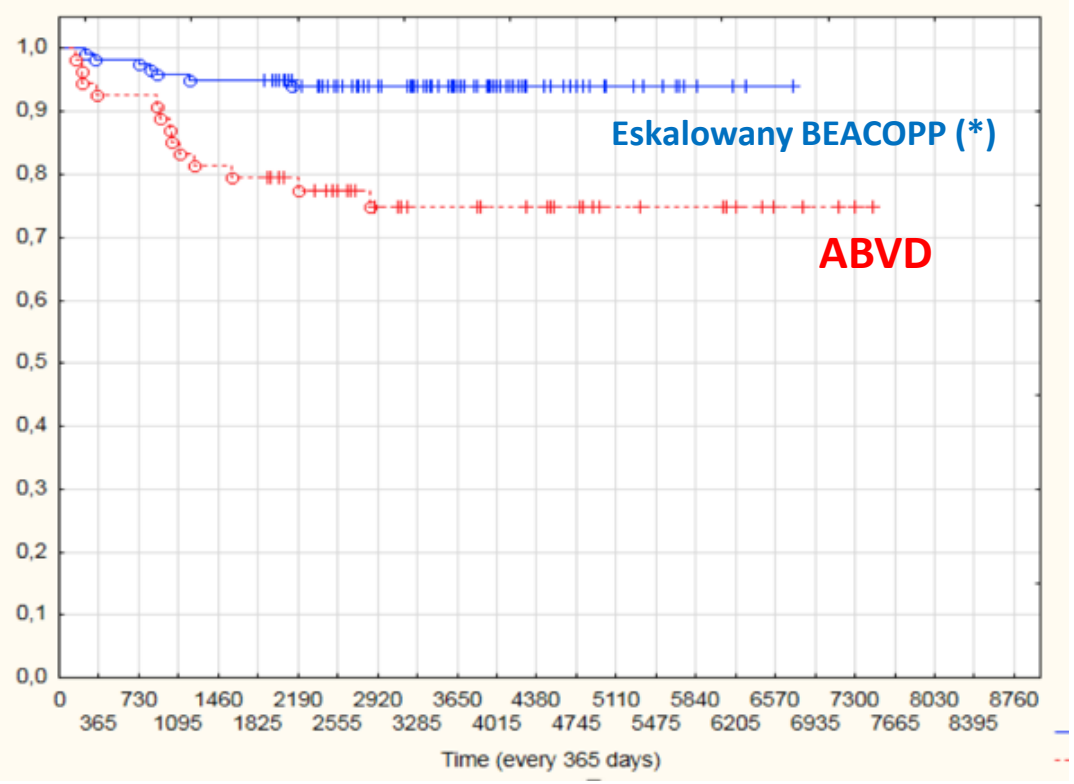
Polish Lymphoma Research Group

Wyniki leczenia HD (IIBX-IV) w Klinice Hematologii UJCM

PFS



OS

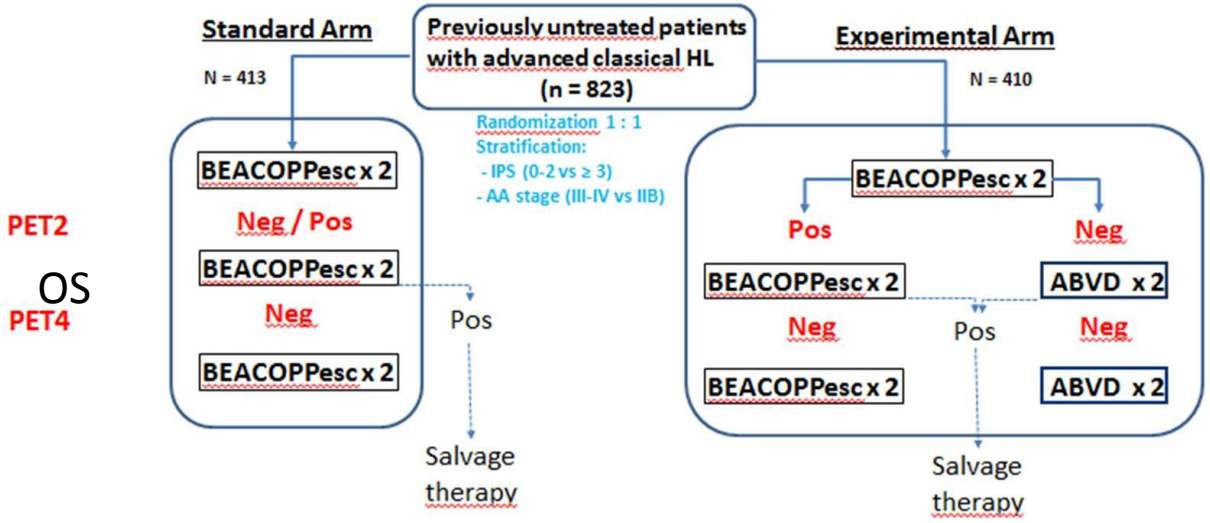


(*) – u 80% chorych, po 2 cyklach eskalowanego BEACOPP, możliwe było zmniejszenie intensywności leczenia i zmiana schematu na ABVD

Wyniki leczenia HD (IIBX-IV) – eskalowany BEACOPP

PFS

AHL 2011: study design

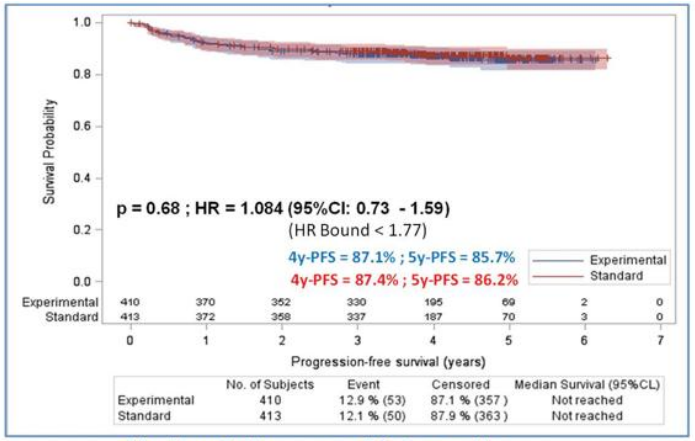


PET2

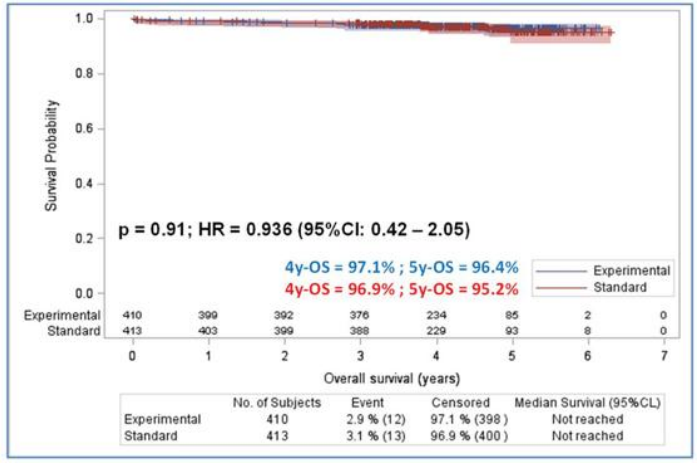
OS

PET4

Non-inferiority 5y-PFS design: Standard arm: 85%; Experimental arm: >75% (HR=1.77)

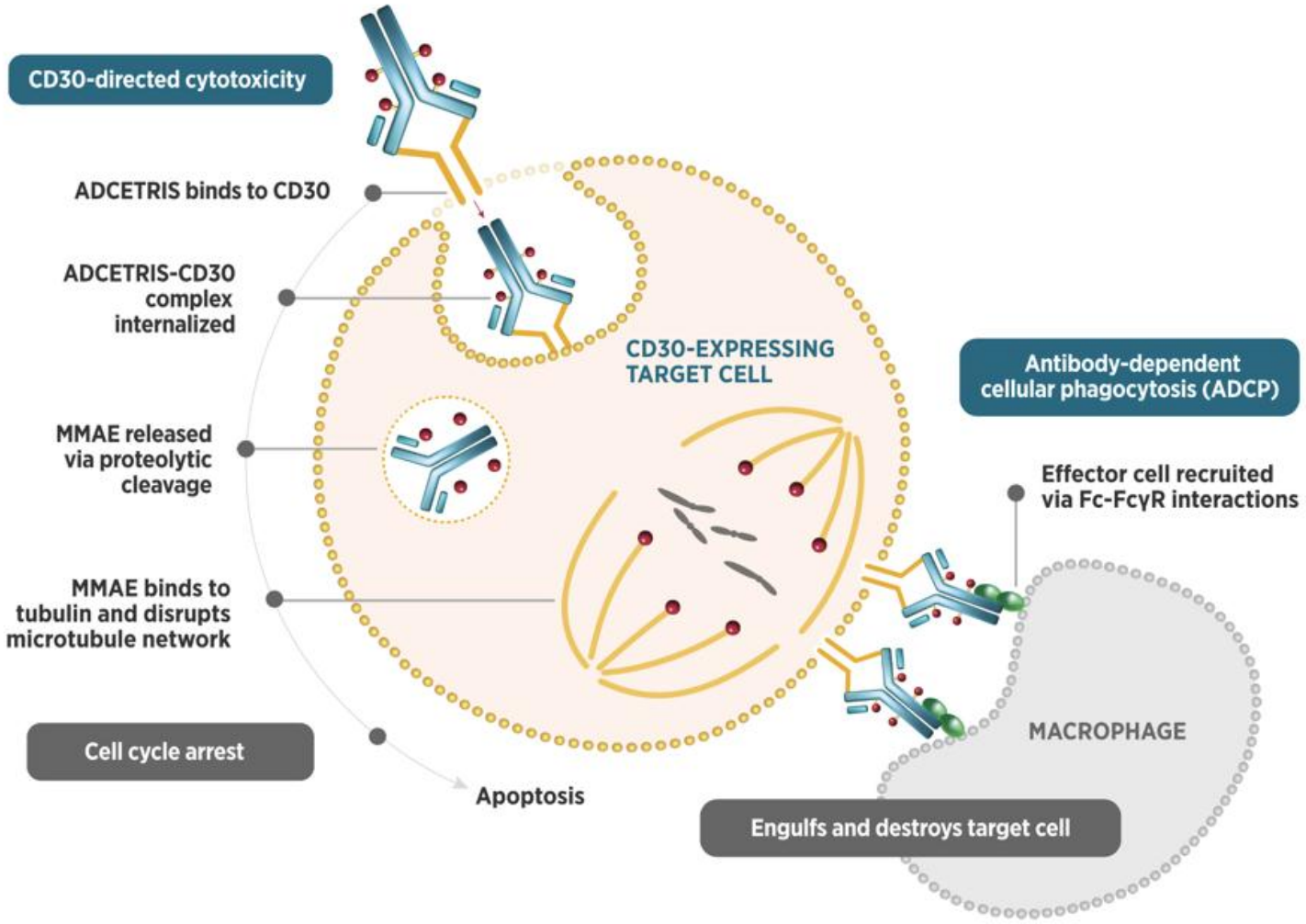


Median follow-up = 50.4 months



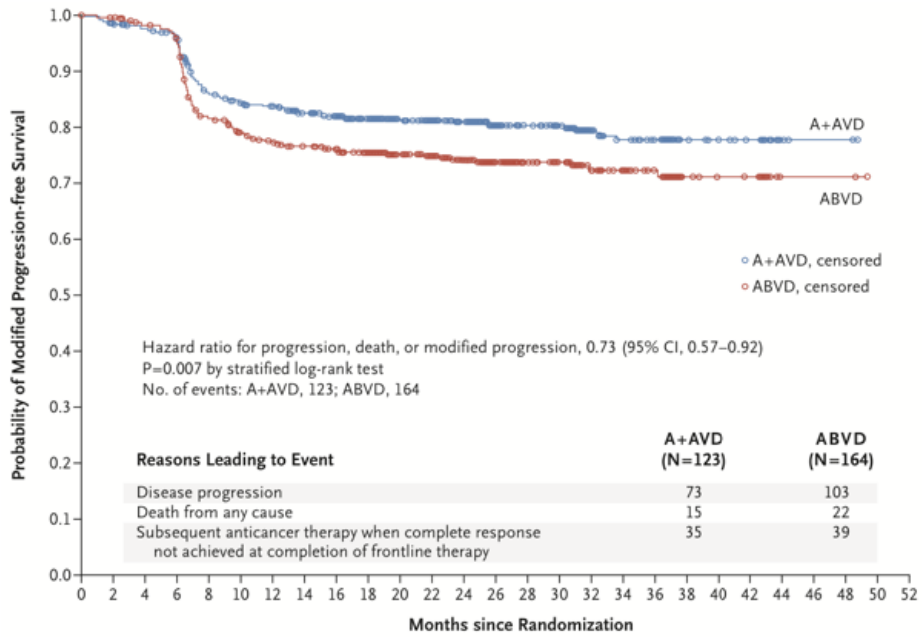
Olivier Casasnovas at 2018 ASCO

Brentuximab vedotin

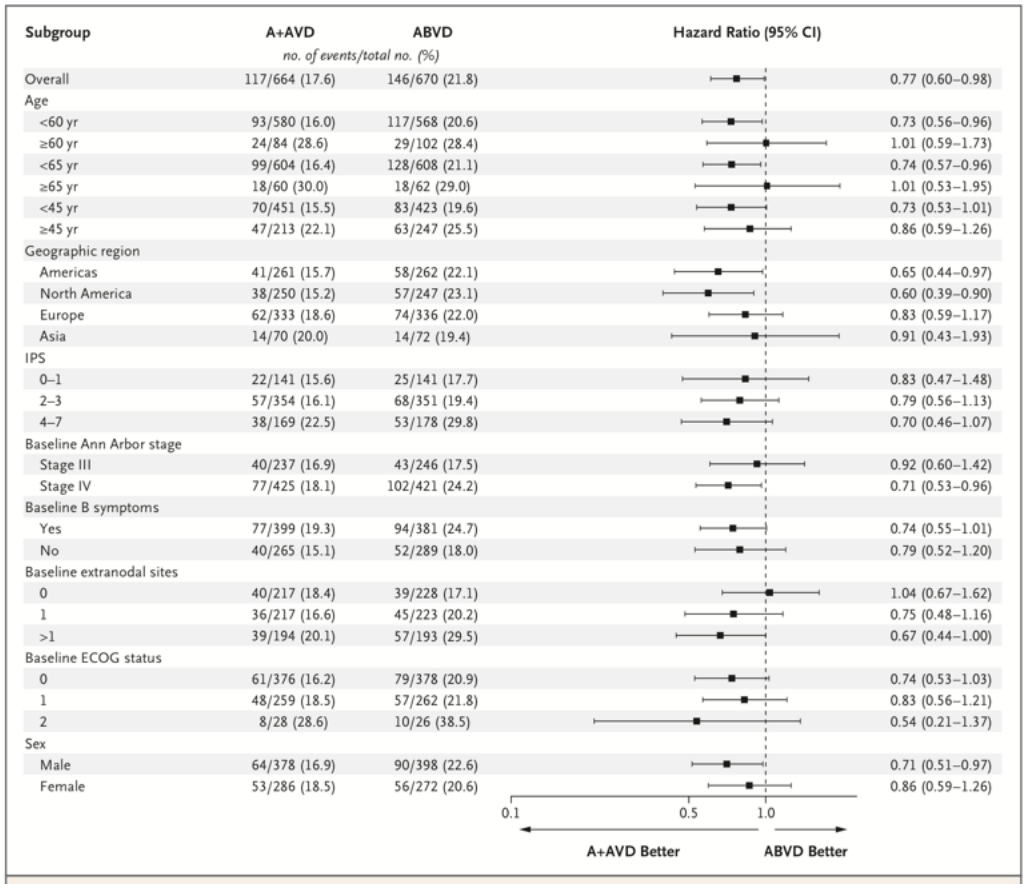


Wyniki leczenia HD (IIBX-IV) – Brentuximab-AVD

NEJM



Reasons Leading to Event	A+AVD (N=123)	ABVD (N=164)
Disease progression	73	103
Death from any cause	15	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	35	39



Subgroup	A+AVD	ABVD	Hazard Ratio (95% CI)
	no. of events/total no. (%)		
Overall	117/664 (17.6)	146/670 (21.8)	0.77 (0.60–0.98)
Age			
<60 yr	93/580 (16.0)	117/568 (20.6)	0.73 (0.56–0.96)
≥60 yr	24/84 (28.6)	29/102 (28.4)	1.01 (0.59–1.73)
<65 yr	99/604 (16.4)	128/608 (21.1)	0.74 (0.57–0.96)
≥65 yr	18/60 (30.0)	18/62 (29.0)	1.01 (0.53–1.95)
<45 yr	70/451 (15.5)	83/423 (19.6)	0.73 (0.53–1.01)
≥45 yr	47/213 (22.1)	63/247 (25.5)	0.86 (0.59–1.26)
Geographic region			
Americas	41/261 (15.7)	58/262 (22.1)	0.65 (0.44–0.97)
North America	38/250 (15.2)	57/247 (23.1)	0.60 (0.39–0.90)
Europe	62/333 (18.6)	74/336 (22.0)	0.83 (0.59–1.17)
Asia	14/70 (20.0)	14/72 (19.4)	0.91 (0.43–1.93)
IPS			
0–1	22/141 (15.6)	25/141 (17.7)	0.83 (0.47–1.48)
2–3	57/354 (16.1)	68/351 (19.4)	0.79 (0.56–1.13)
4–7	38/169 (22.5)	53/178 (29.8)	0.70 (0.46–1.07)
Baseline Ann Arbor stage			
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42)
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96)
Baseline B symptoms			
Yes	77/399 (19.3)	94/381 (24.7)	0.74 (0.55–1.01)
No	40/265 (15.1)	52/289 (18.0)	0.79 (0.52–1.20)
Baseline extranodal sites			
0	40/217 (18.4)	39/228 (17.1)	1.04 (0.67–1.62)
1	36/217 (16.6)	45/223 (20.2)	0.75 (0.48–1.16)
>1	39/194 (20.1)	57/193 (29.5)	0.67 (0.44–1.00)
Baseline ECOG status			
0	61/376 (16.2)	79/378 (20.9)	0.74 (0.53–1.03)
1	48/259 (18.5)	57/262 (21.8)	0.83 (0.56–1.21)
2	8/28 (28.6)	10/26 (38.5)	0.54 (0.21–1.37)
Sex			
Male	64/378 (16.9)	90/398 (22.6)	0.71 (0.51–0.97)
Female	53/286 (18.5)	56/272 (20.6)	0.86 (0.59–1.26)

Connors, Jurczak et al – NEJM 2018

HD w Klinice Hematologii UJCM

NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Involved-Field Radiotherapy for Advanced Hodgkin's Lymphoma

Berthe M.P. Aleman, M.D., Jo
Umberto Tirelli, M.D., Ph.D
Mars B. van 't Veer, M.D., Ph.D., Marnix
Patrice Carde, M.D., Ph.D.,
Richard W.M. van der Maazer
Marjeta Vovk, M.D., Ph.D., Achilles van H
Pieternella J. Lugtenburg, M.D
Wilfried Schroyens, M.D., P
Johanna W. Baars, M.D., Ph.D., Jo
Christian Carrie, M.D., Malek Aoudj
Houchingue Eghbali, M.
Jacobus H. Meerwaldt, M.D., Ph.D., Ant
and Michel Henry-Amar, M.D., Ph.D.,
and Treatment of C

ABS

BACKGROUND
The use of involved-field radiotherapy
lymphoma is controversial.

METHODS
We randomly assigned patients with p
lymphoma who were in complete remiss
ethamine, vincristine, procarbazine, p
blastine (MOPP-ABV) to receive either n
apy. Radiotherapy consisted of 24 Gy to a
to all initially involved extranodal sites.
30 Gy to nodal areas and 18 to 24 Gy to e

RESULTS
Of 739 patients, 421 had a complete rem
no further treatment, and 172 to involved
79 months. The five-year event-free surv
receive radiotherapy and 79 percent in th
apy (P=0.35). The five-year overall surv
(P=0.07). Among the 250 patients in par
event-free and overall survival rates were 79 and 87 percent, respectively.

CONCLUSIONS
Involved-field radiotherapy did not improve the outcome in patients with advanced-stage Hodgkin's lymphoma who had a complete remission after MOPP-ABV chemotherapy. Radiotherapy may benefit patients with a partial response after chemotherapy.

Bone Marrow Transplantation (2002) 30, 29–34

www.nature.com/bmt

Hodgkin's disease

High-dose chemotherapy with autologous stem cell transplantation is an effective treatment of primary refractory Hodgkin's disease. Retrospective study of the Polish Lymphoma Research Group

J Czyż[1], A Hellmann[1], R Dziadziuszko[1], J Hansz[2], J Goździk[2], J Hołowiecki[3], B Stella-Ho
Ł Kachel[3], W Knopińska-Posłuszny[1], A Nagler[4], J Meder[5], J Walewski[5], E Lampka[5],
W Sawicki[6], A Lange[7], K Forgacz[7], K Suchnicki[7], T Pacuszko[7], A Skotnicki[8], P Mens
W Jurczak[8], K Kuliczkowski[9], T Wróbel[9], G Mazur[9], A Dmoszyńska[10], M Wach[10], T
and K Warzocha[11]

[1]Medical University, Gdańsk, Poland; [2]University of Medical Sciences, Poznań, Poland; [3]Silesian Medical Univers
Poland; [4]The Chaim Sheba Medical Centre, Tel-Hashomer, Israel; [5]Maria Skłodowska-Curie Memorial Cancer Ce
Oncology, Warsaw, Poland; [6]Central Military Hospital, Warsaw, Poland; [7]K Dluski Hospital-Institute of Immunolo
Experimental Therapy, Wrocław, Poland; [8]Collegium Medicum Jagiellonian University, Cracow, Poland; [9]Medical
Wrocław, Poland; [10]Medical University, Lublin, Poland; and [11]Copernicus Memorial Hospital-Medical University,

Summary:

We analysed the treatment outcome of primary refractory HD patients managed with high-dose chemotherapy and haematopoietic cell transplantation. Data of 65 adult patients who underwent HDC/ASCT in nine Polish centres for primary resistant Hodgkin's disease between June 1991 and July 2000 were collected retrospectively. Response rate to HDC/ASC: CR, 54%; PR, 20%; less than PR, 15%; early deaths, 11%. Actuarial 3-year OS and PFS were 55% and 36%, respectively. In multivariate analysis, lack of bulky lymph nodes and use of immunotherapy were favourable factors for both OS and PFS. IPF <3 at the time of transplantation was predictive for PFS. However, the prognostic impact of immunotherapy should be interpreted with caution since this group included more patients who achieved CR after HDC/ASCT. The results of HDC/ASCT are encouraging and confirm earlier findings. The role of immunotherapy should be further investigated in prospective trials.
Bone Marrow Transplantation (2002) **30**, 29–34. doi: 10.1038/sj.bmt.1703590
Keywords: high-dose chemotherapy; primary refractory Hodgkin's disease

occasionally.[3,4] For selected patients, salva
apy may be considered as an alternative op
has not been previously irradiated.[5]

Recently, encouraging reports on hi
therapy with autologous stem cell
(HDC/ASCT) in this group of patients hav
by European and American institutions,
trials comparing this treatment with stan
still lacking.[6–10]

At present, autologous bone marrow tra
cedures are performed in adult patients
Poland. Data from nine of them, which w
1999, were collected retrospectively and
current study. The aim of the study was
ment results and prognostic factors in univ
variate models for overall and progressio

Patients and methods

Data of 65 adult patients who underwent
primary resistant Hodgkin's disease betwe
July 2000 were collected retrospectively.
for this study included: disease progressio
chemotherapy, or partial remission after

Original article

Annals of Oncology 15: 1222–1230, 200
DOI: 10.1093/annonc/mdh30

Outcome and prognostic factors in advanced Hodgkin's disease treated with high-dose chemotherapy and autologous stem cell transplantation: a study of 341 patients

J. Czyż*, R. Dziadziuszko, W. Knopińska-Postuszuy, A. Hellmann, Ł. Kachel, J. Hołowiecki, J. Goździk, J. Hansz, A. Avigdor, A. Nagler, M. Osowiecki, J. Walewski, P. Mensah, W. Jurczak, A. Skotnicki, M. Sędzimirska, A. Lange, W. Sawicki, K. Sułek, M. Wach, A. Dmoszyńska, A. Kuś, T. Robak & K. Warzocha
On behalf of the Polish Lymphoma Research Group

Medical University of Gdansk, Gdansk, Poland

Leukemia & Lymphoma, March 2007; 48(3): 535–541

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Two autologous transplants in the treatment of patients with Hodgkin's lymphoma: Analysis of prognostic factors and comparison with a single procedure

J. CZYŻ[1], R. DZIADZIUSZKO[2]*, W. KNOPIŃSKA-POSŁUSZNY[2], A. HELLMANN[2], Ł. KACHEL[3], J. HOŁOWIECKI[3], A. CZYŻ[4], M. KOMARNICKI[4], M. OSOWIECKI[5], J. WALEWSKI[5], W. JURCZAK[6], & A. SKOTNICKI FOR POLISH LYMPHOMA RESEARCH GROUP[6]

[1]*Huddersfield Royal Infirmary, United Kingdom,* [2]*Department of Oncology*, Department of Haematology, Medical University of Gdansk, Poland,* [3]*Department of Haematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland,* [4]*Department of Haematology and Bone Marrow Transplantation, University of Medical Science, Poznań, Poland,* [5]*Department of Haematology and Bone Marrow Transplantation, Maria Skłodowska-Curie Center and Institute of Oncology, Warszawa, Poland, and* [6]*Department of Haematology and Bone Marrow Transplantation, Jagiellonian University, Collegium Medicum, Kraków, Poland*

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Abstract
We summarized registry data of the long term observation of 35 patients treated with two autologous transplants. Prognostic factors for overall survival (OS) and DFS were analyzed. The OS was compared with 105 patients from a single transplant group. Two factors were significant in univariate analysis of DFS after the second transplant: response to the first transplant (complete remission (CR) versus progressive disease (PD) $p = 0.041$) and the disease status at the time of the second autologous stem cell transplantation (ASCT) (CR versus partial remission (PR) $p = 0.004$; CR versus PD $p = 0.0002$). In the multivariate analysis only the last of the parameters remain significant (RR 2.30, $p = 0.004$, 95% CI; 1.30–4.04). In the analysis of OS, two factors were significant in univariate analysis: status of the disease at the first transplant (PR versus PD $p = 0.008$) and response to the first transplant (CR versus PD $p = 0.025$). None of those factors remained significant in a multivariate analysis. A probability of 5-year survival after the first transplant in patients treated with two transplants was 83% (95% CI; 70–97%). A tendency towards better survival was seen in patients treated with two transplants ($p = 0.01$). The trend toward better survival from the time of diagnosis is kept for those who entered CR or PR after standard chemotherapy ($p = 0.097$) but not for the whole group ($p = 0.13$).

Keywords: *Hodgkin lymphoma, second autologous transplant*

NEJM

NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

J.M. Connors, W. Jurczak, D.J. Straus, S.M. Ansell, W.S. Kim, A. Gallamini, A. Younes, S. Alekseev, Á. Illés, M. Picardi, E. Lech-Maranda, Y. Oki, T. Feldman, P. Smolewski, K.J. Savage, N.L. Bartlett, J. Walewski, R. Chen, R. Ramchandren, P.L. Zinzani, D. Cunningham, A. Rosta, N.C. Josephson, E. Song, J. Sachs, R. Liu, H.A. Jolin, D. Huebner, and J. Radford, for the ECHELON-1 Study Group*

ABSTRACT

BACKGROUND
Brentuximab vedotin is an anti-CD30 antibody–drug conjugate that has been approved for relapsed and refractory Hodgkin's lymphoma.

METHODS
We conducted an open-label, multicenter, randomized phase 3 trial involving patients with previously untreated stage III or IV classic Hodgkin's lymphoma, in which 664 were assigned to receive brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) and 670 were assigned to receive doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The primary end point was modified progression-free survival (the time to progression, death, or noncomplete response and use of subsequent anticancer therapy) as adjudicated by an independent review committee. The key secondary end point was overall survival.

RESULTS
At a median follow-up of 24.9 months, 2-year modified progression-free survival rates in the A+AVD and ABVD groups were 82.1% (95% confidence interval [CI], 78.7 to 85.0) and 77.2% (95% CI, 73.7 to 80.4), respectively, a difference of 4.9 percentage points (hazard ratio for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60 to 0.98; P=0.03). There were 28 deaths with A+AVD and 39 with ABVD (hazard ratio for interim overall survival, 0.72 [95% CI, 0.44 to 1.17]; P=0.19). All secondary efficacy end points trended in favor of A+AVD. Neutropenia occurred in 58% of the patients receiving A+AVD and in 45% of those receiving ABVD; in the A+AVD group, the rate of febrile neutropenia was lower among the 83 patients who received primary prophylaxis with granulocyte colony-stimulating factor than among those who did not (11% vs. 21%). Peripheral neuropathy occurred in 67% of patients in the A+AVD group and in 43% of patients in the ABVD group; 67% of patients in the A+AVD group who had peripheral neuropathy had resolution or improvement at the last follow-up visit. Pulmonary toxicity of grade 3 or higher was reported in less than 1% of patients receiving A+AVD and in 3% of those receiving ABVD. Among the deaths that occurred during treatment, 7 of 9 in the A+AVD group were associated with neutropenia and 11 of 13 in the ABVD group were associated with pulmonary-related toxicity.

CONCLUSIONS
A+AVD had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin's lymphoma, with a 4.9 percentage-point lower combined risk of progression, death, or noncomplete response and use of subsequent anticancer therapy at 2 years. (Funded by Millennium Pharmaceuticals and Seattle Genetics; ECHELON-1 ClinicalTrials.gov number, NCT01712490; EudraCT number, 2011-005450-60.)

Badania Kliniczne u chorych z chłoniakami

- Szansa na skuteczne leczenie w przypadkach opornych
- Coraz częściej jedyna możliwość leczenia zgodne z europejskim standardem
- Inne niż chemioterapia skutki działań niepożądanych
- Znaczne oszczędności dla NFZ i budżetu Państwa

Chłoniaki w Klinice Hematologi UJCM










Prof. Wojciech Jurczak MD,PhD

Polish Lymphoma Research Group

Prof. Wojciech Jurczak, M.D., Ph.D.
Dpt of Hematology, Jagiellonian University
wojciech.jurczak@uj.edu.pll, (+48 602 338290)

Polish Lymphoma Research Group

Hodgkin Lymphoma Clinical Case

Monika Długosz-Danecka

Prof. Wojciech Jurczak MD,PhD

Polish Lymphoma Research Group

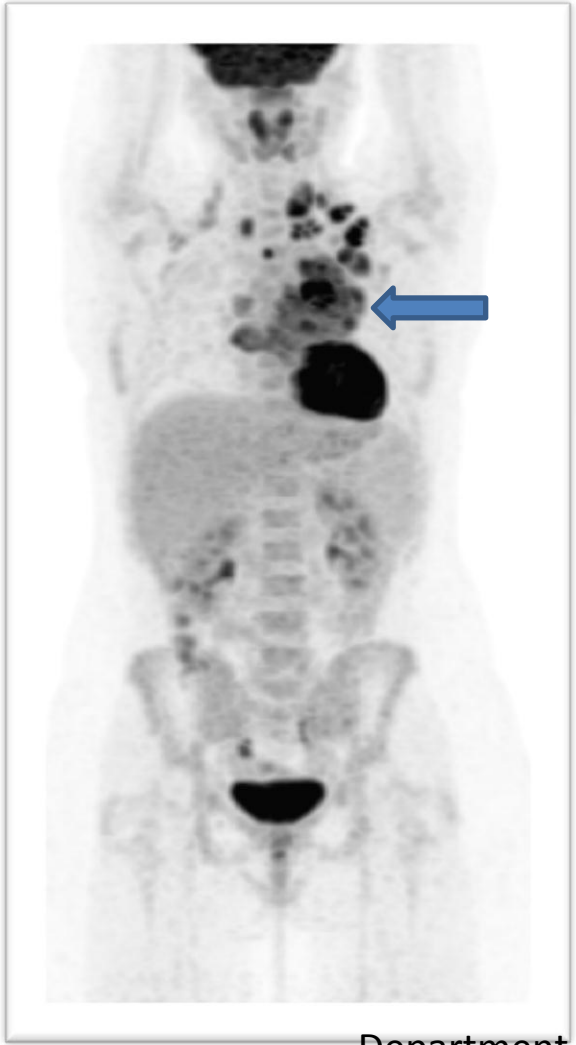
PET-CT staging at the diagnosis – 08.2014

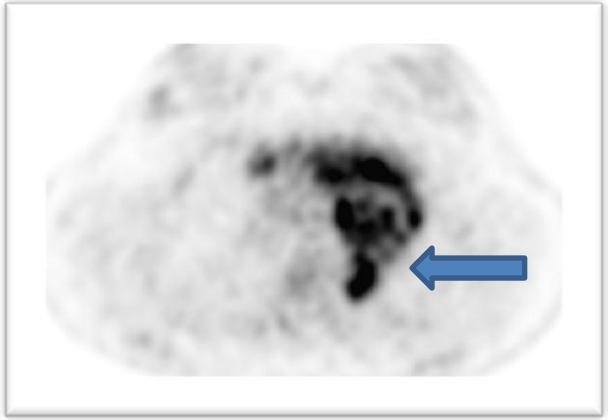
Female – age 31

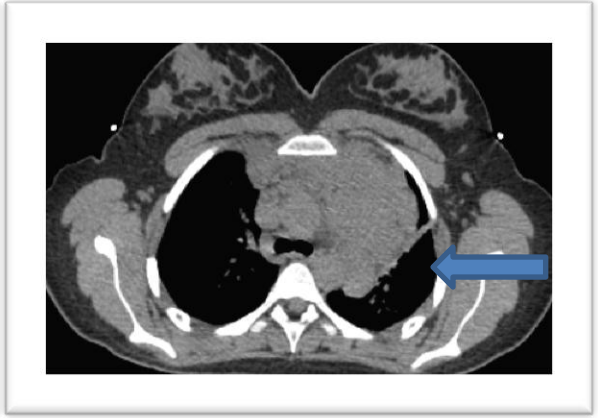
Ann Arbor IV

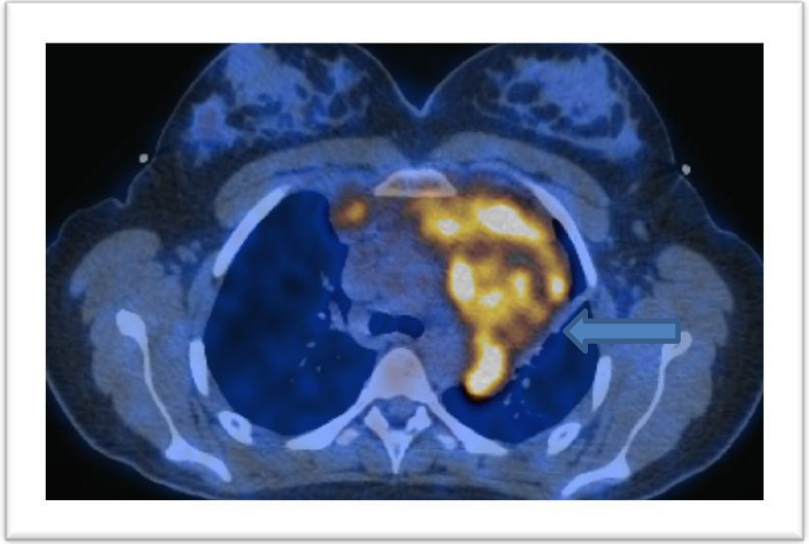
HD IPI 4:

- Hb< 10 g/dl,
- Albumin < 40 g/l
- Limphopaenia < 6%
- CS IV









I-III line therapy

I line: ABVD (6x) 03.2014 – 08.2014

- after 2nd cycle PET PR
- after 6th cycle – progressive disease (PD)

II line: ESHAP (2x) with PBSCC (19.10.2014) - PD

III line: Brentuximab vedotin (16x) 11.2014 - 12.2015

CR followed by PD

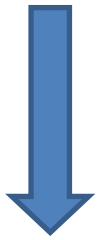
ASCT

12.2015 – progressive disease (PD) in PET-CT

IV line: BeGeV (2x) - CR
BEAM ASCT consolidation (07.03.2016)

Nivolumab and MUD allo SCT

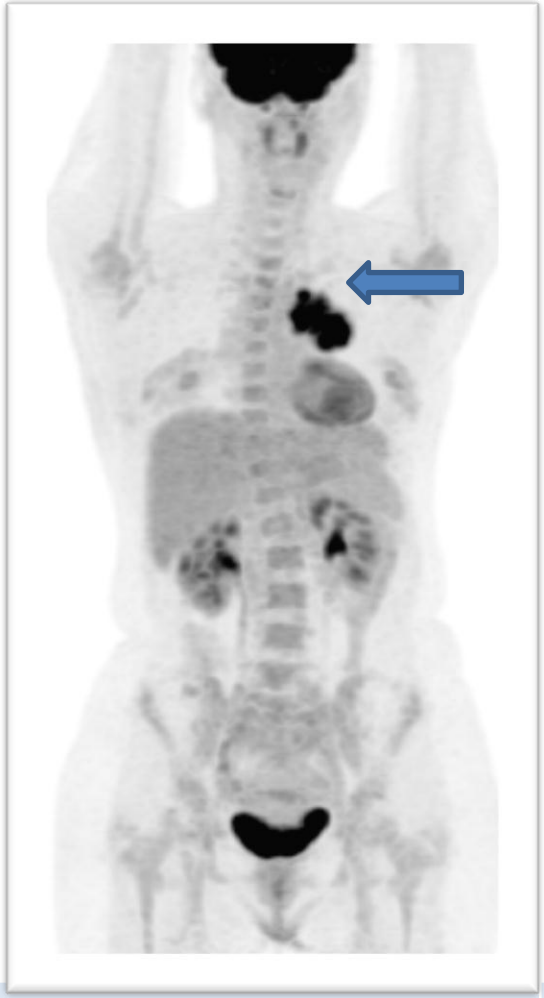
31.11.2016– relapse in PET-CT



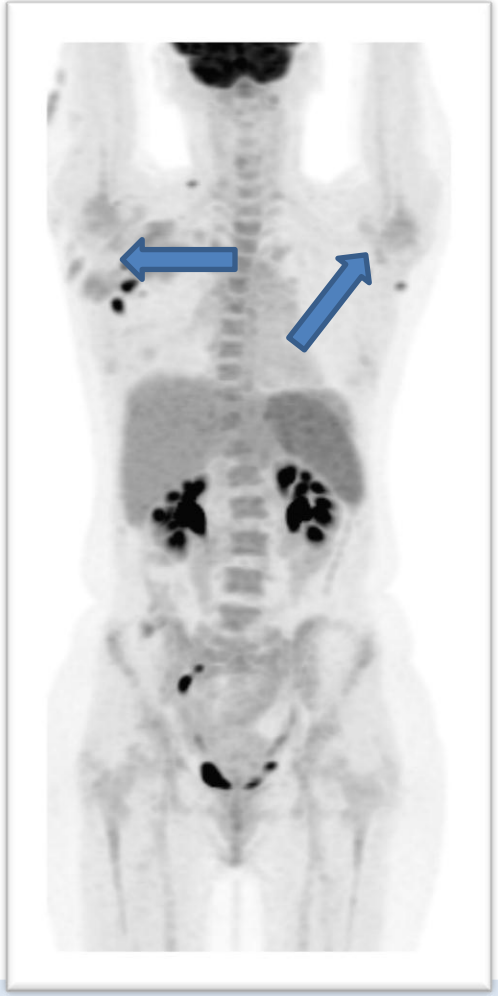
V line: Nivolumab as (12.2016 – 11.2017)
(23 doses a 3 mg /m^2) – PET CR
Conolidated with MUD SCT (Feb 2018)

Feb 2019 – Alive in CR

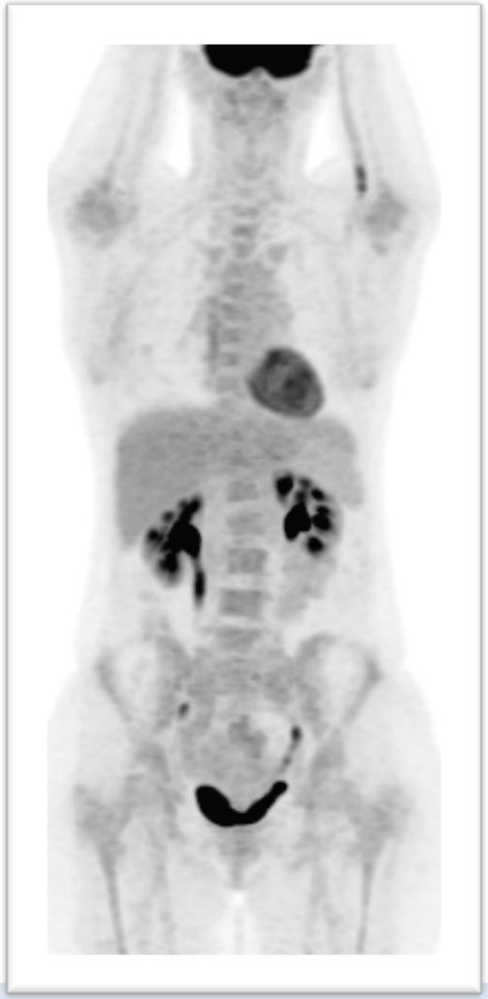
PET-CT during Nivolumab therapy



12.2016
Before Nivolumab



04.2017
After 8th doses



09.2017
After 20th doses

Polish Lymphoma Research Group

Thank you for your attention

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