Le novità nella biologia e terapia dei DLBCL

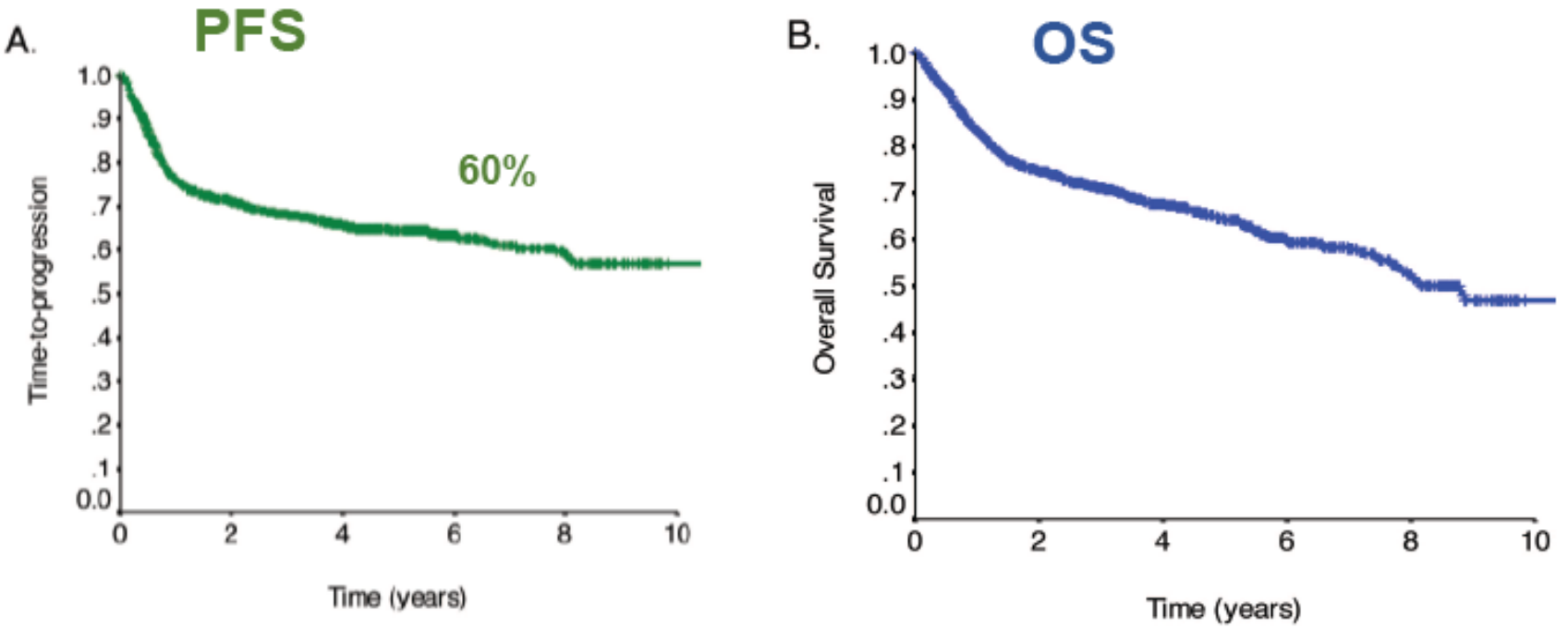
Prof. Marco Gobbi

IRCCS A.O.U. SAN MARTINO – IST GENOVA

What outcome can we expect with R-CHOP in DLBCL ?

BC Cancer Agency
CARE & RESEARCH

Patients with DLBCL treated with R-CHOP-21 at BCCA (n=1476)



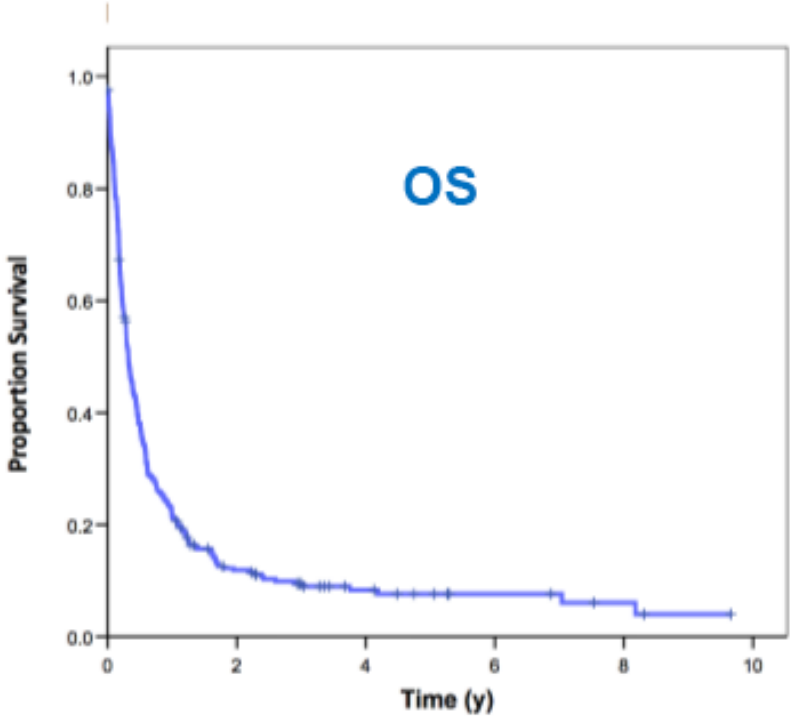
Main role of first line therapy and low activity of salvage treatment

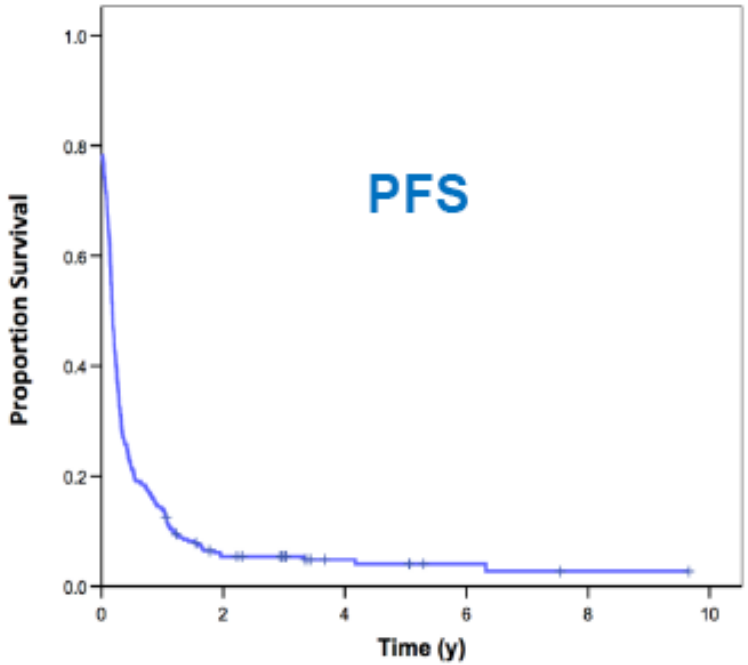
BC Cancer Agency Database Sehn Hematology 2012

What outcome can we expect with R-CHOP in DLBCL ?

Outcome of primary or early relapsed patients to R-CHOP

BC Cancer Agency
CARE & RESEARCH





We need to identifie at diagnosis these group patients and improve their first line treatment

Hitz et al ASH 2010

How can we improve the treatment of DLBCL ?

- New monoclonal antibodies combined with CHOP
- Cell of origin (COO) oriented therapy in DLBCL combining new biological drugs to conventional chemotherapy
- Hystopathological subtypes: Myc positive, double Hit (DHIT) and double Expressor (DE)
- When should we consider an alternative to R-CHOP?

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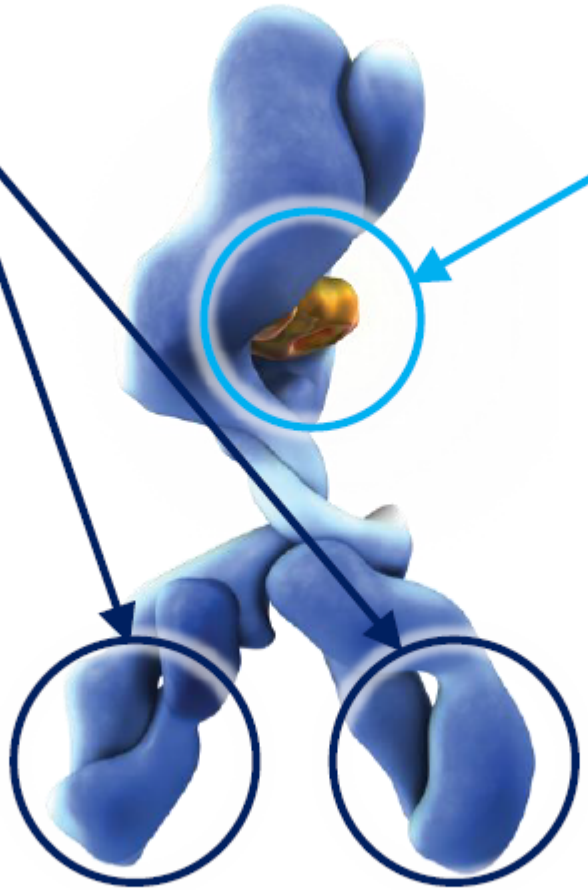
GA101: Designed for increased antibody-dependent cellular cytotoxicity (ADCC) and Direct Cell Death

Type II anti-CD20 mAb[1]

Increased Direct Cell Death[2]



Glycoengineered Fc region[2]

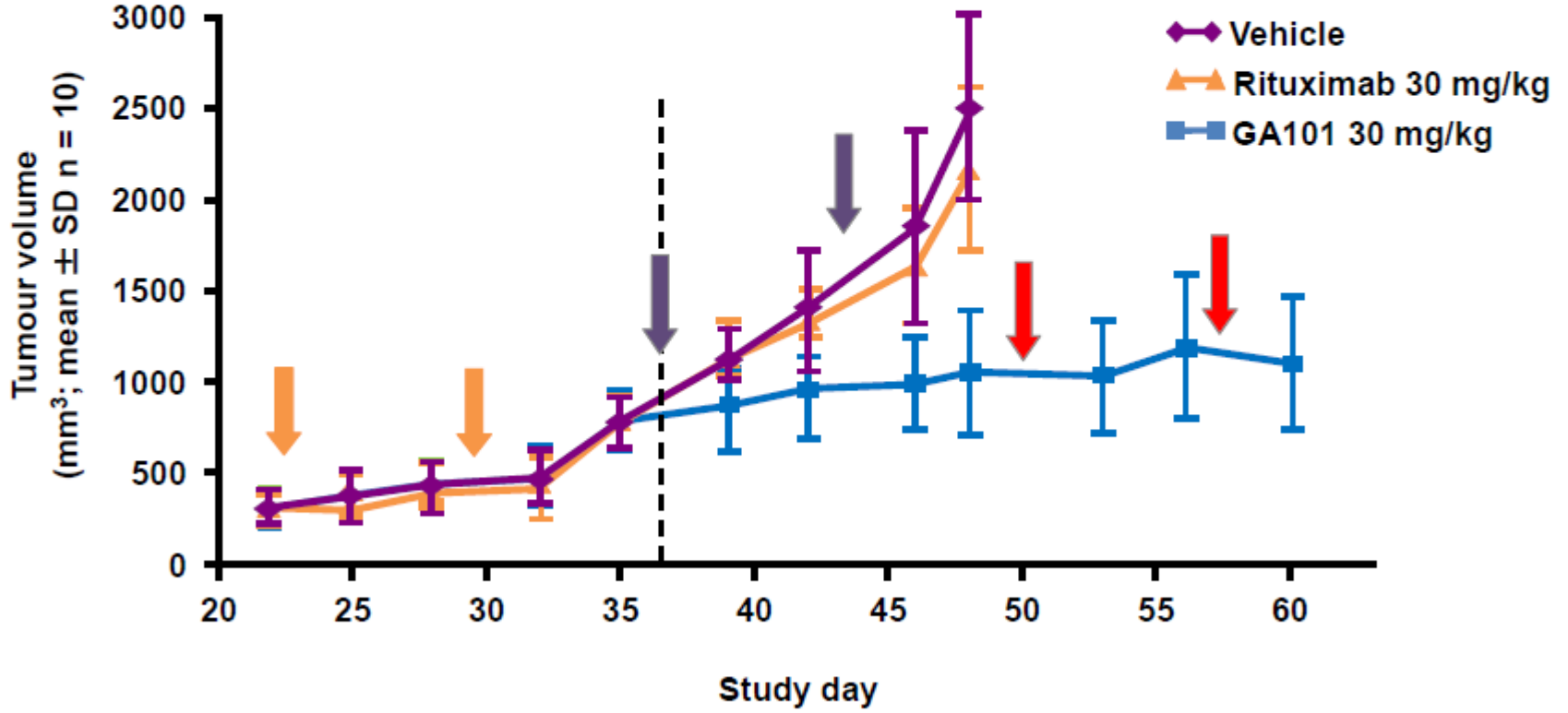
Increased antibody-dependent cellular cytotoxicity (ADCC)[2]

Extensive clinical development program to evaluate the superiority of GA101 over rituximab in multiple head-to-head trials

1. Niederfellner G, et al. Blood 2011; 118:358–367. 2. Mössner E, et al. Blood 2010; 115:4393–4402.

GA101 showed response in a rituximab-refractory DLBCL xenograft model

While tumours remained refractory and did not respond to further rituximab, GA101 was able to control tumour progression



Female SCID mice transplanted with established subcutaneous SU-DHL4 (DLBCL) tumours (250 mm³). Orange arrows = rituximab therapy; grey arrows = vehicle, rituximab or GA101 therapy
DLBCL, diffuse large B-cell lymphoma
Mössner E, *et al. Blood* 2010;115:4393–4402.

GOYA (BO21005) Phase III: Study design

GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
Rituximab: 375 mg/m² d1, cycles 1–8, every 21 days

Primary endpoint

- PFS

Secondary endpoints

- PFS (assessed by IRC)
- ORR and CR
- ORR and CR (assessed by IRC)
- Overall survival
- EFS
- Disease-free survival
- Response duration
- Time to next lymphoma treatment
- Safety
- Quality of life
- Medical resource utilisation

This trial is currently ongoing. Recruitment closed

This trial is being conducted in collaboration with the **Fondazione Italiana Linfomi (FIL) study group**

CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; IRC, Independent Review Committee; ORR, overall response rate; PFS, progression-free survival
www.clinicaltrials.gov NCT01287741

How can we improve the treatment of DLBCL ?

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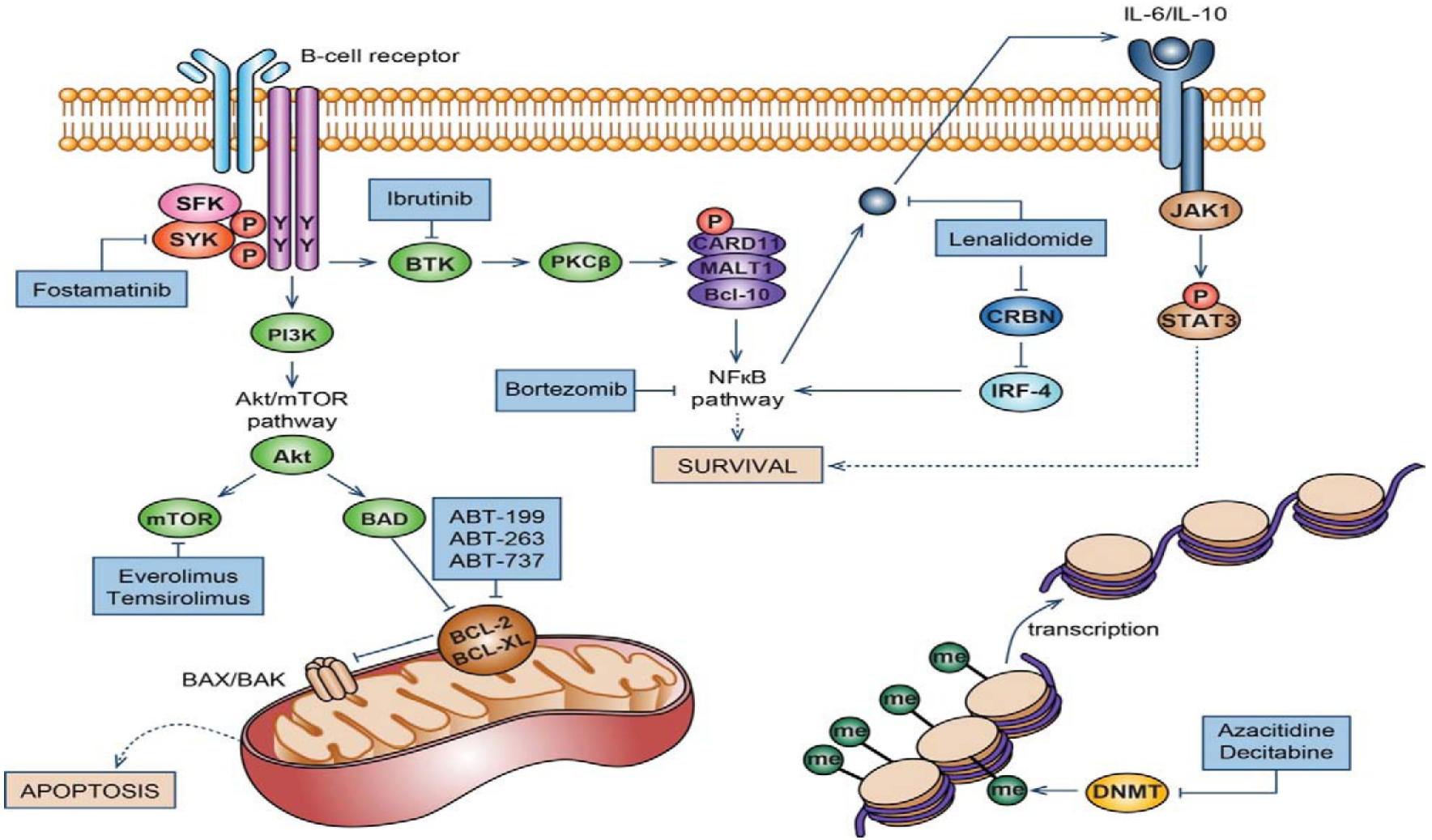
- **Cell of origin (COO) oriented therapy in DLBCL combining new biological drugs to conventional chemotherapy**
- Hystopathological subtypes: Myc positive, double Hit (DHIT) and double Expressor (DE)
- When should we consider an alternative to R-CHOP?

Pathways Targeted By Treatments Currently in Development for Patients with DLBCL



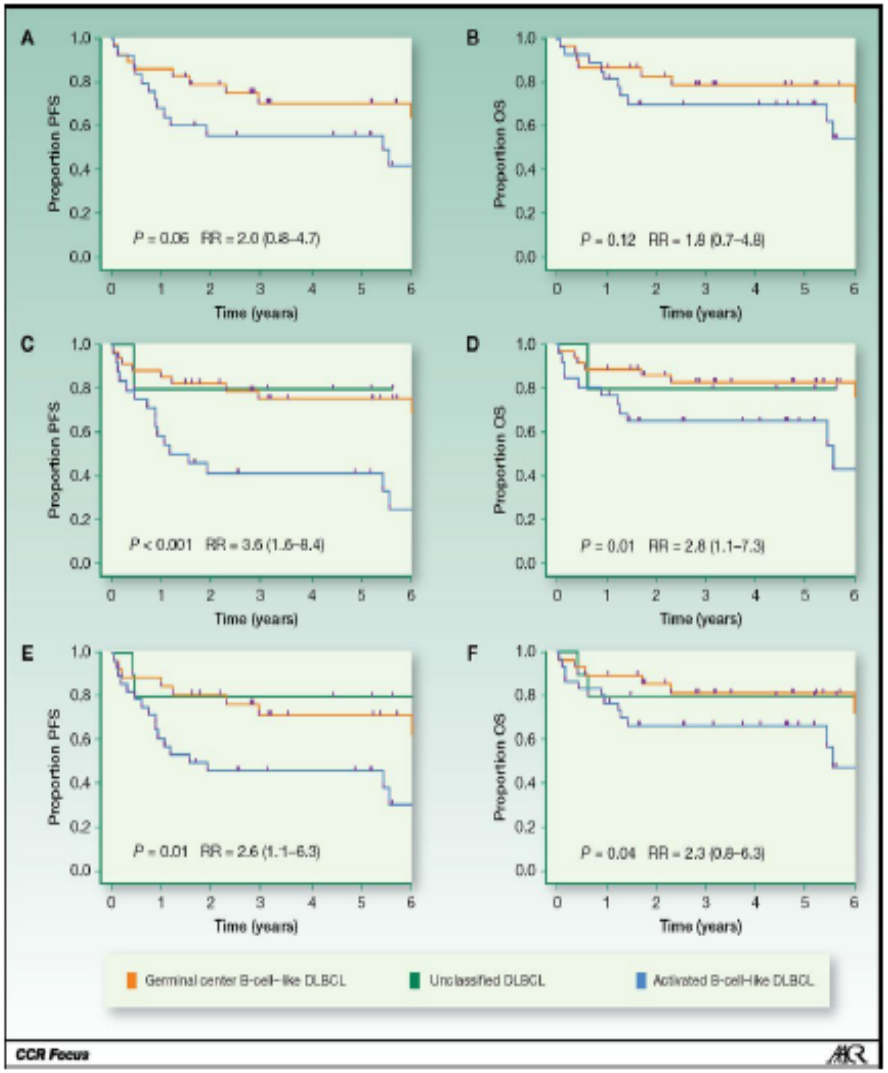
DLBCL outcomes following R-CHOP by Cell of Origin

Method

Hans IHC

Lymph2cx
nanostring

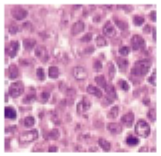
Frozen GEP
Gold standard

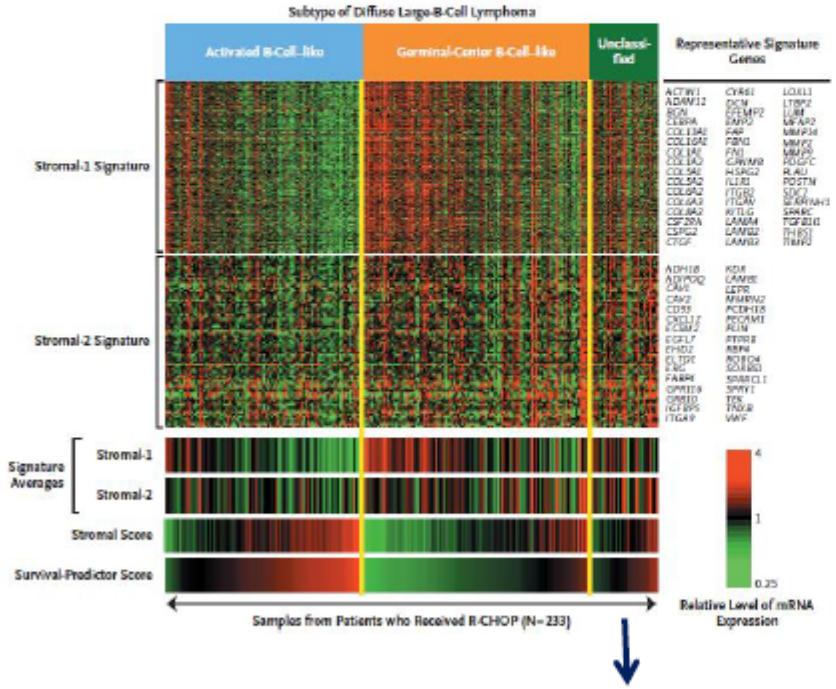


Kieron Dunleavy et al. Clin Cancer Res 2014;20:5182-5193

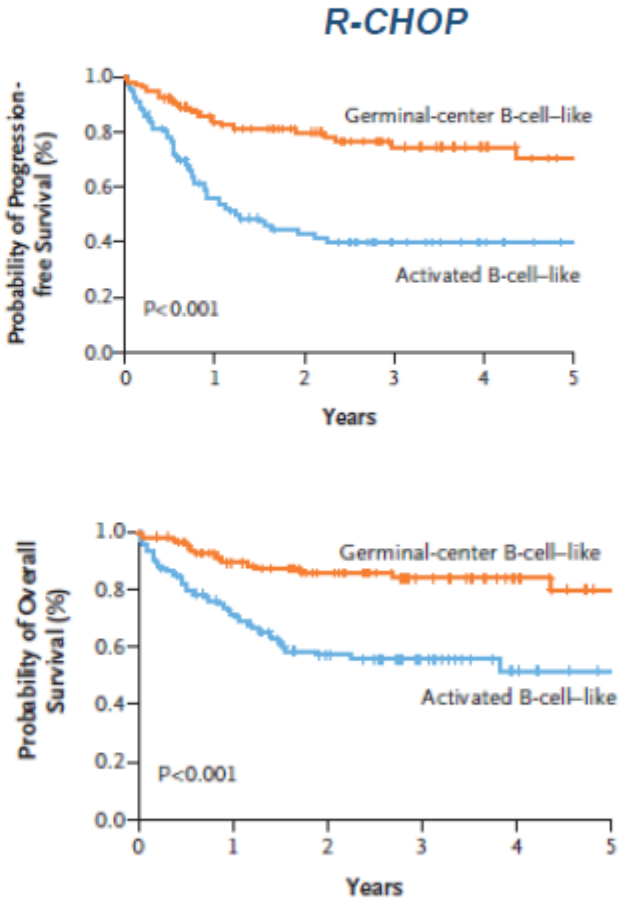
A better evaluation of unfavorable DLBCL subsets: COO profile subgroups

Diffuse Large B- Cell Lymphoma





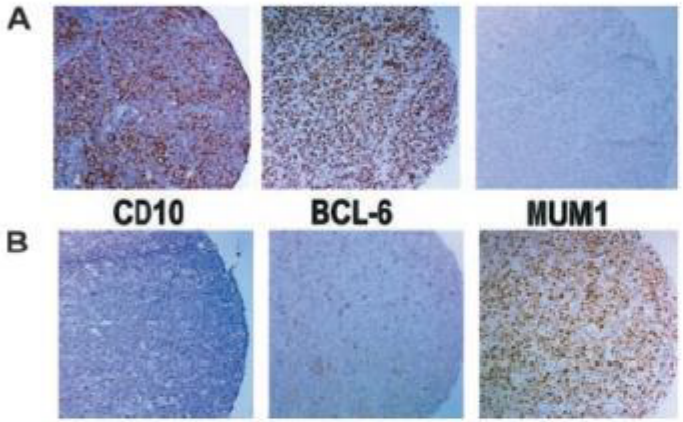
15% Unclassificable

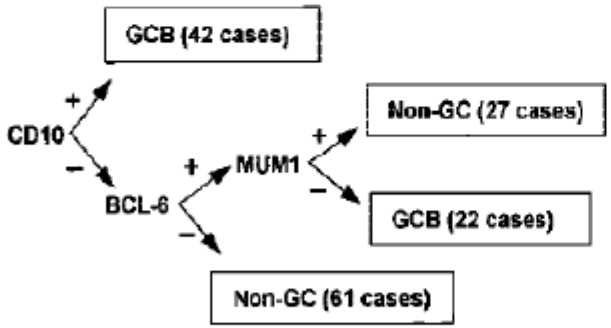


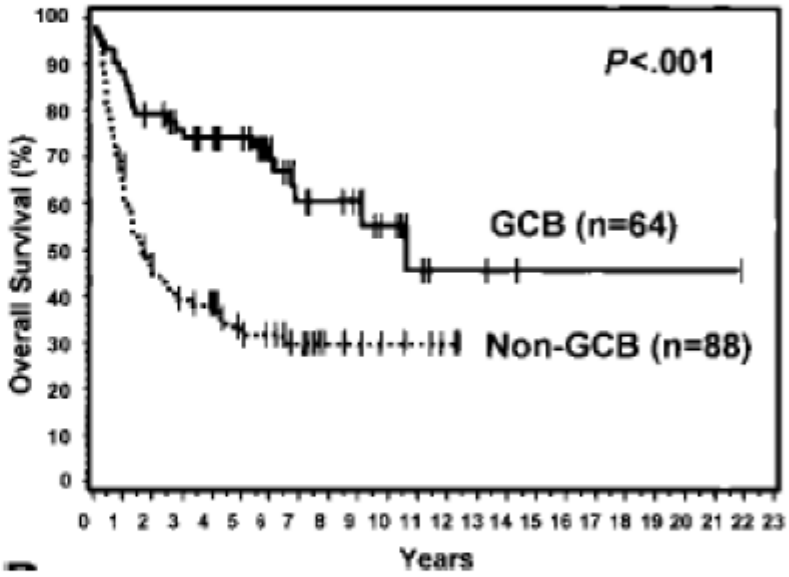
The GEP classification is not available in the daily clinical practice

Lenz G et al. N Engl J Med 2008;359:2313

A better evaluation of unfavorable DLBCL subsets: COO profile subgroups assessed by IHC (Hans)







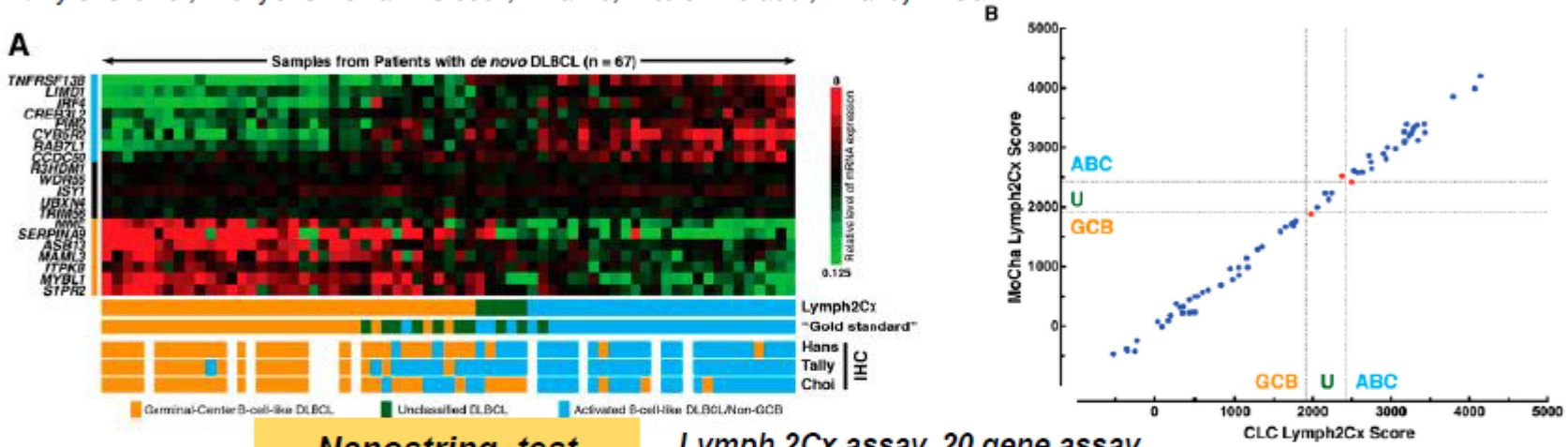
Hans et al. Blood 2004; 103: 275-82

...The prognostic role of COO assessed by IHC is poorly reproducible with controversial results in the Rituximab era!

BLOOD, 20 FEBRUARY 2014 • VOLUME 123, NUMBER 8

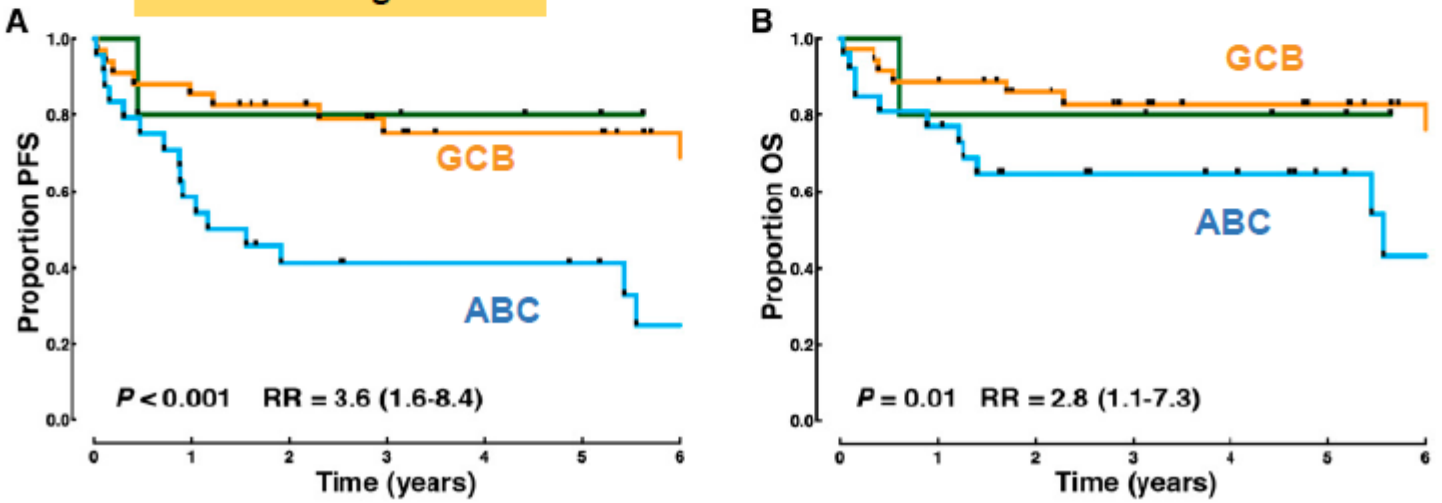
Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue

David W. Scott,[1] George W. Wright,[2] P. Mickey Williams,[3] Chih-Jian Lih,[3] William Walsh,[3] Elaine S. Jaffe,[4] Andreas Rosenwald,[5] Elias Campo,[6] Wing C. Chan,[7] Joseph M. Connors,[1] Erlend B. Smeland,[8] Anja Mottok,[1] Rita M. Braziel,[9] German Ott,[10] Jan Delabie,[11] Raymond R. Tubbs,[12] James R. Cook,[13] Dennis D. Weisenburger,[14] Timothy C. Greiner,[7] Betty J. Glinsmann-Gibson,[15] Kai Fu,[7] Louis M. Staudt,[16] Randy D. Gascoyne,[1,17] and Lisa M. Rimsza[15]

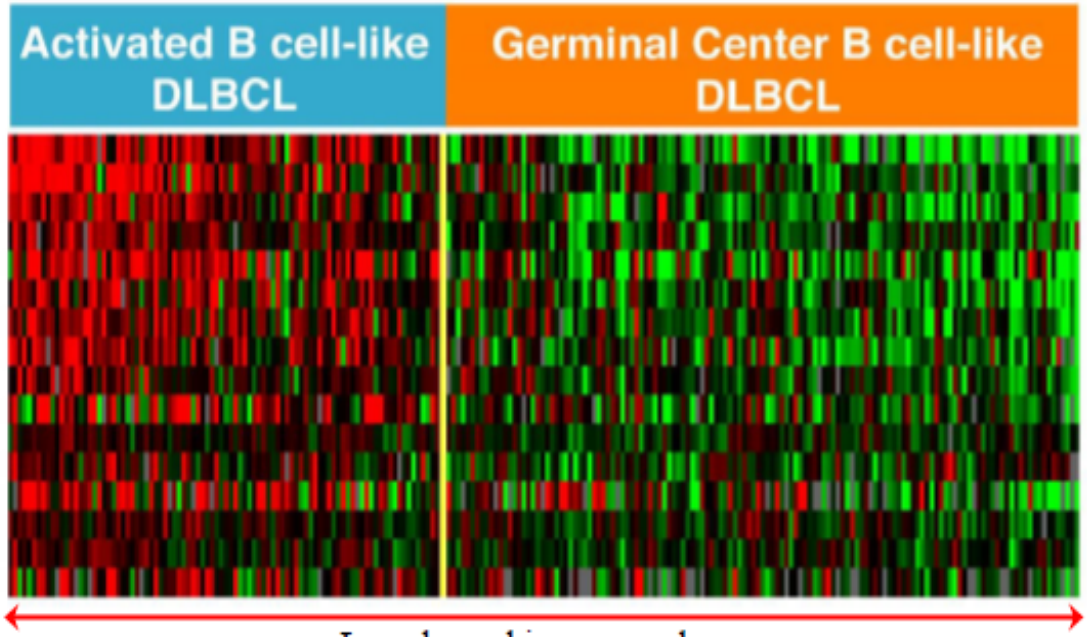


Nanostring test

Lymph 2Cx assay, 20 gene assay

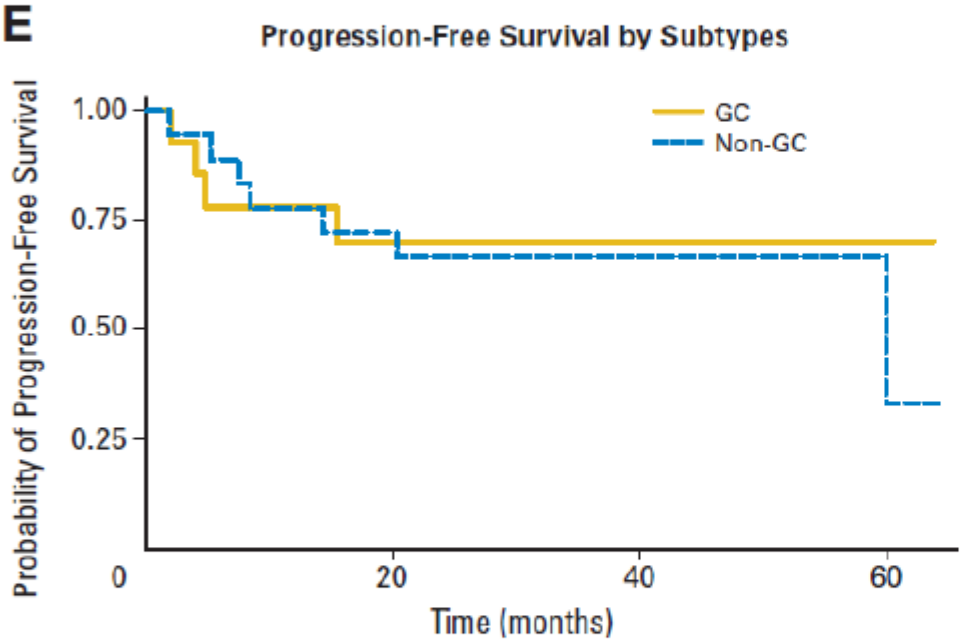


Constitutive Expression of NFKB in ABC DLBCL



NF-kB target gene	p value
IRF-4	6.23 E-29
Cyclin D2	1.28 E-16
Pim-1	2.69 E-19
Lyn	5.34 E-19
BIC	6.49 E-18
CD44	2.35 E-13
FLICE	3.30 E-14
IM684838	8.74 E-14
IkB ε	7.64 E-09
EBI2	2.77 E-07
NCF2	6.67 E-07
DIFF48	2.86 E-06
CCR7	1.55 E-05
SNF2L2	1.16 E-05
NFkB1	6.68 E-05
IL-6	4.01 E-04

Is it possible to reverse the adverse outcomes of ABC DLBCL? R-CHOP+ Bortezomib

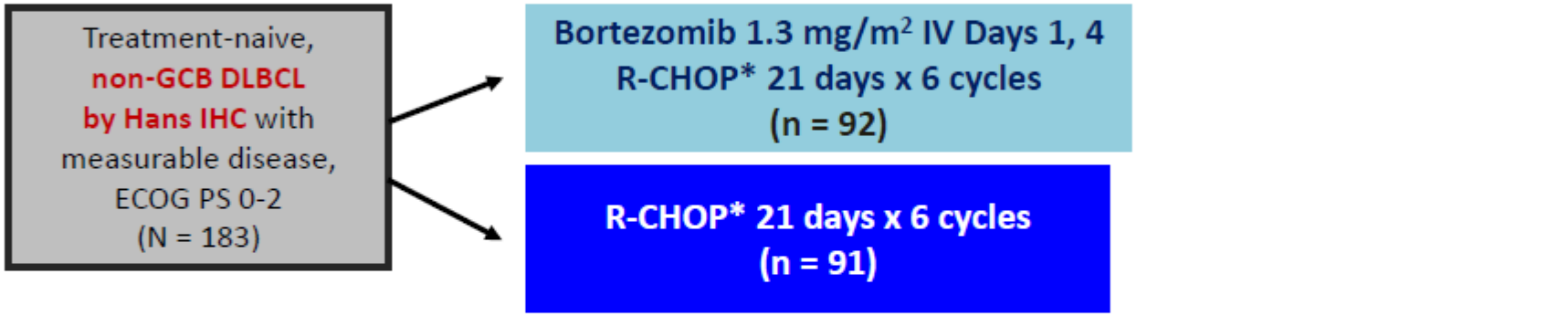


- The nuclear factor-kB (NF-kB) pathway is constitutively activated in ABC DLBCL[1]
- ***The proteasome inhibitor bortezomib*** is a potent inhibitor of NF-κB[2]; may overcoming the negative prognosis associated with non-GCB phenotype[3,4]

Ruan J et al. J Clin Oncol. 2011;29(6):690-697

PYRAMID: Study Design

- Prospective randomized, open-label phase II study



*Rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (max 2 mg), all IV Day 1; prednisone 100 mg, PO Days 1-5.

- ***Primary endpoint: PFS***
- Secondary endpoints: OS, ORR, CR, toxicity
  - Evaluated response, disease progression by CT and FDG-PET at end of cycles 2 and 6
  - Follow-up scans every 3 mos until disease progression

Leonard JP, et al. ASH 2015. Abstract 811.
Hans CP, et al. Blood 2004;103:275-282.

Leonard P.J et al. ASH 2015 oral session abs 811

Response and survival outcomes

Characteristic, %	VR-CHOP (n = 90)	R-CHOP (n = 86)
CR	56	49
CR/PR (ORR)	96	98
Negative FDG-PET at EOT visit	59	53

Outcome, %	VR-CHOP (n = 92)	R-CHOP (n = 91)	HR (95% CI)	*P* Value
2-yr PFS rate	**82**	**78**	**0.73 (0.43-1.24)**	**.611**
2-yr PFS rate by IPI risk group				
▪ Low and Low/Intermediate	89 (n = 51)	90 (n = 45)	0.85 (0.35-2.10)	.958
▪ Intermediate/High and High	72 (n = 41)	65 (n = 46)	0.67 (0.34-1.29)	.606
2-yr OS rate	93	88	0.75 (0.38-1.45)	.763

Leonard JP, et al. ASH 2015. Abstract 811.

A Prospective Randomised Trial of Targeted Therapy for Diffuse Large B-Cell Lymphoma (DLBCL) Based upon Real-Time Gene Expression Profiling.

The REMoDL-B Study of the UK NCRI and SAKK Lymphoma Groups

Andrew J Davies[1], Josh Caddy[2], Tom Maishman[2], Sharon Barrans[3], Christoph Mamot[4], Matthew Care[5], Christopher Pocock[6], Louise Stanton,[2], Debbie Hamid[2], Keith Pugh[2], Andrew McMillan,[7], Paul Fields[8], Anton Kruger[9], Andrew Jack[10] and Peter W.M. Johnson[1]

CANCER RESEARCH UK

NCRI National Cancer Research Institute

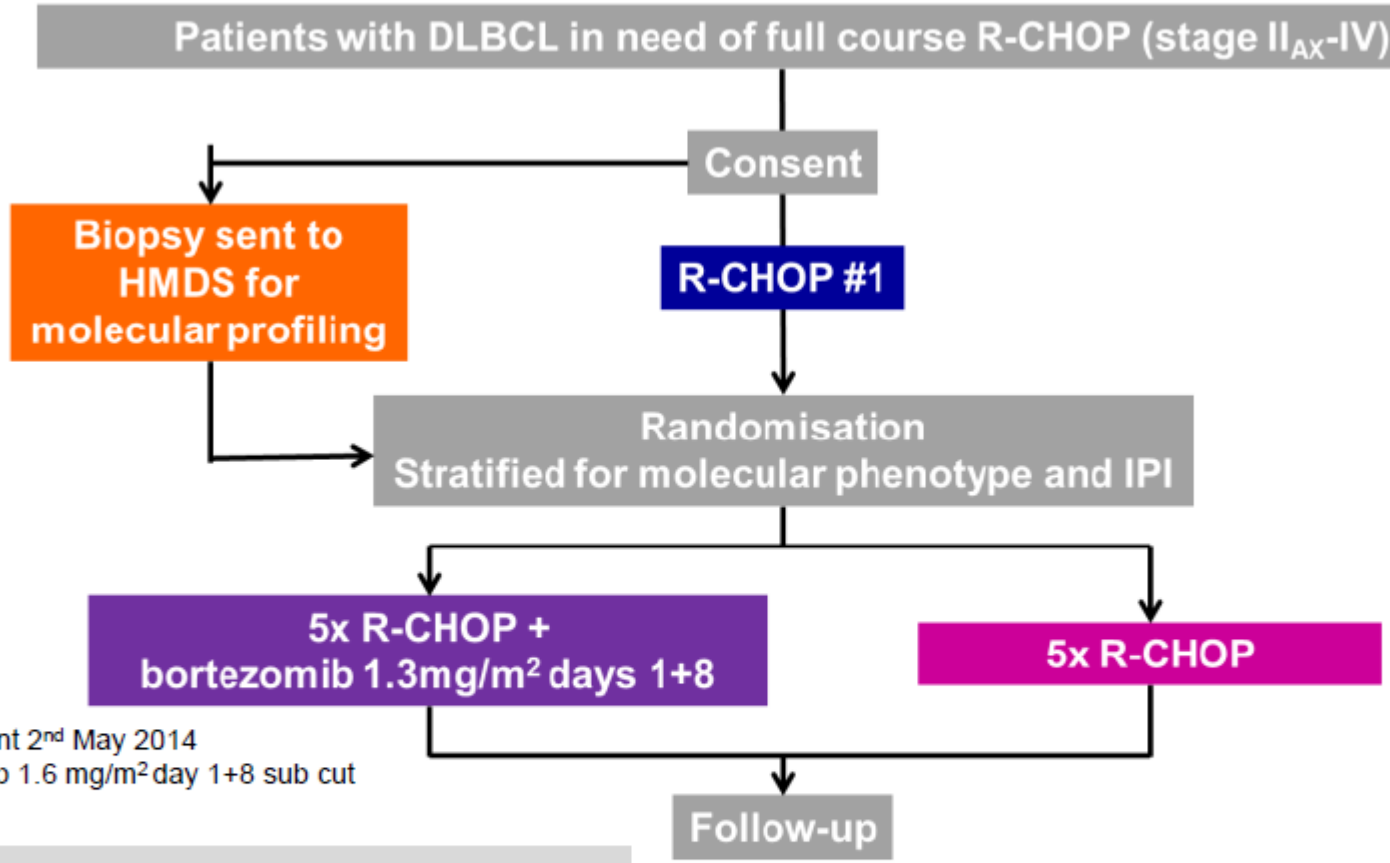
REMoDL-B

SAKK

NHS National Institute for Health Research

REMoDL-B

Study design



Inclusion criteria

- Age ≥18 years
- Untreated CD20 DLBCL (excluding PMBL)
- Adequate FFPE material for molecular profiling
- Stage IA bulky, IB, II, III and IV

Primary endpoints

- PFS at 30 months of RB-CHOP versus RCHOP
- ABC or GCB, of DLBCL molecular phenotype

determines the benefit from the addition of bortezomib

REMoDL-B

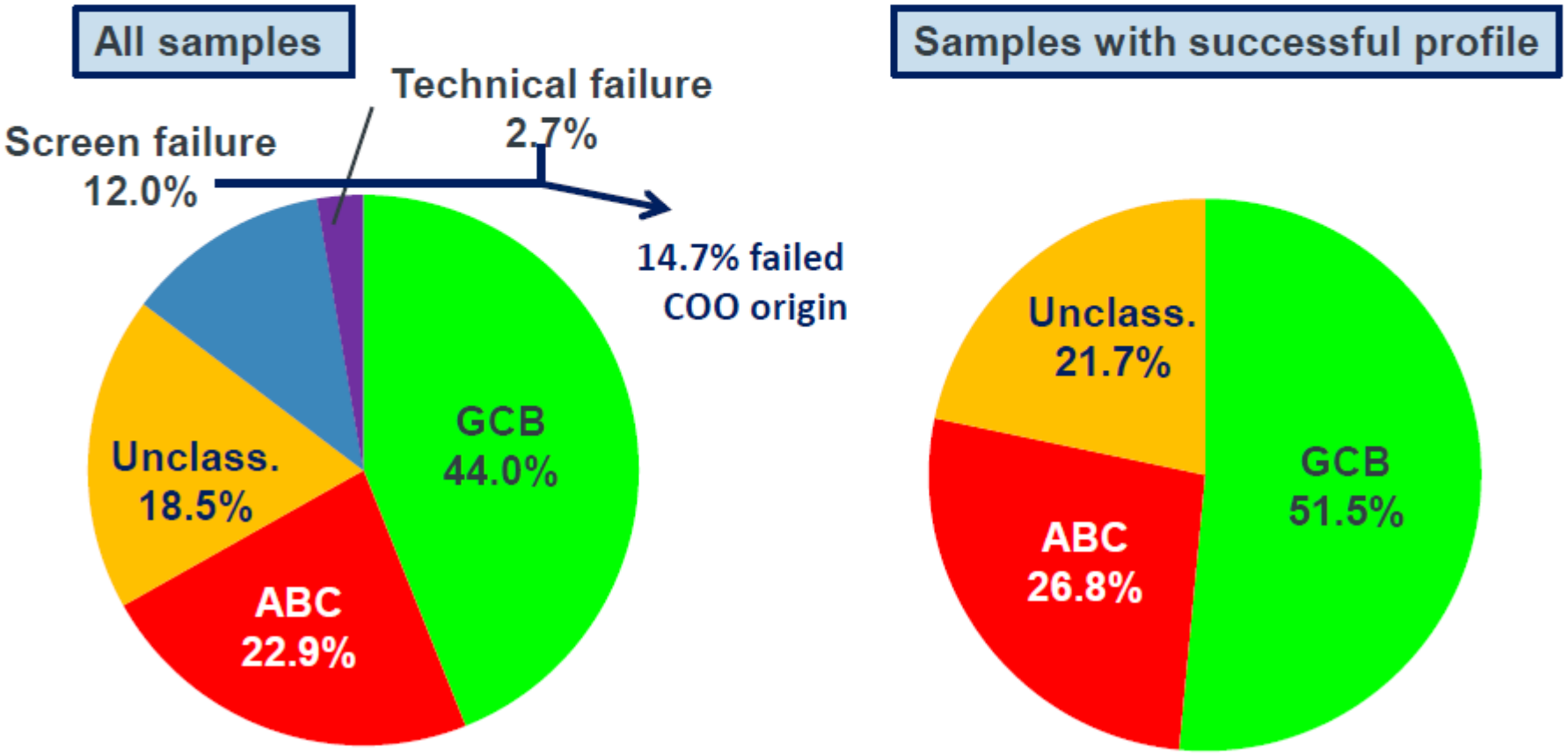
Disposition by cell of origin

1132 patients registered. ***1085 patients eligible and randomised***

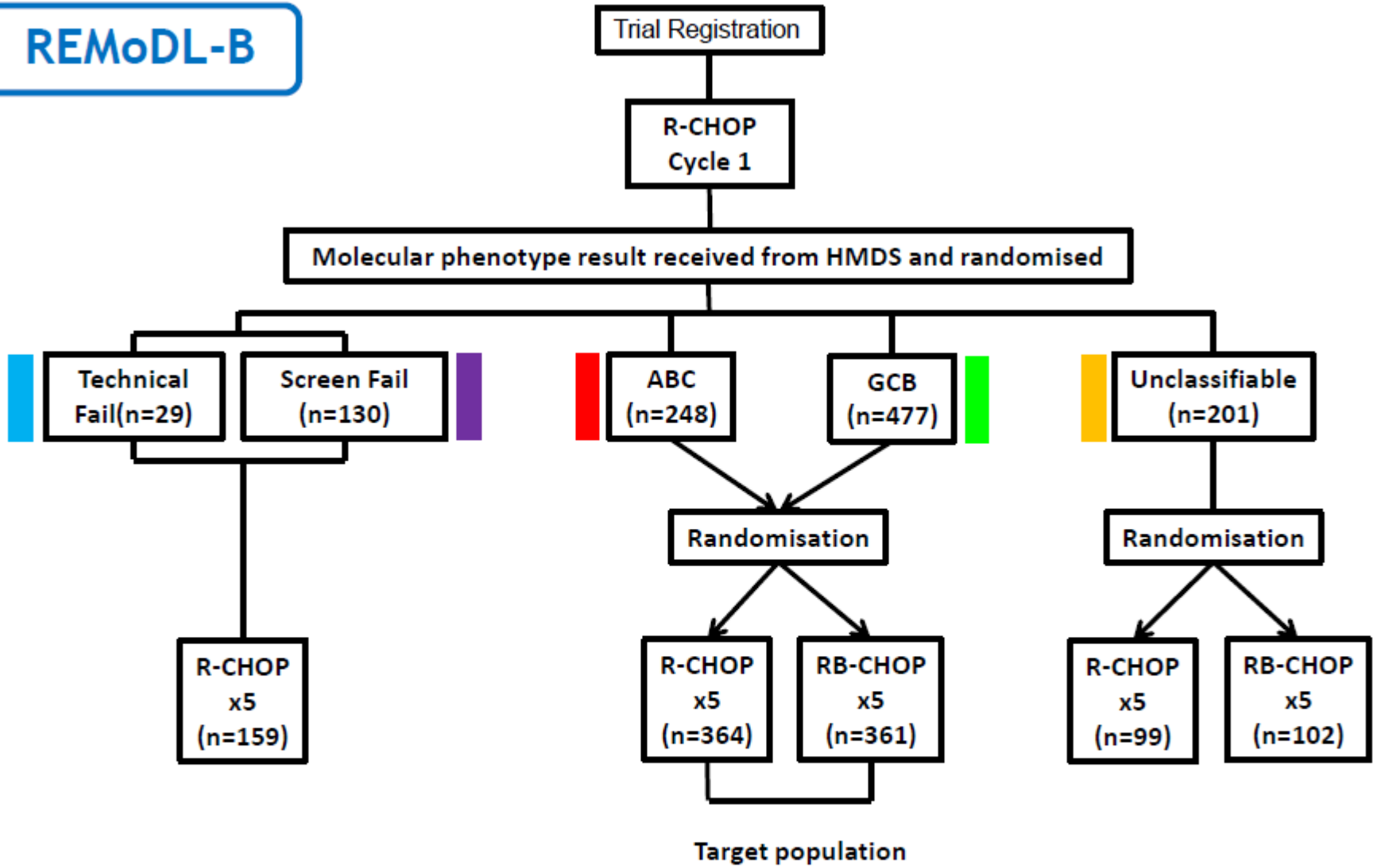
(incorrect histology; did not meet eligibility criteria; no block; 2 early deaths before profile)

Median turn around = 10 days

Similar success rate with both surgical and core biopsies



REMoDL-B



320 pts. treated at 1.3 mg/m^2 IV

143 pts treat at 1.6 mg/m^2 subcutaneous

R-CHOP+ Bortezomib: conclusions

- Similar survival outcomes with VR-CHOP and R-CHOP in treatment-naive pts with non-GCB DLBCL (Hans IHC) ***PYRAMID trial***
- Real time gene expression profiling is feasible in a clinically relevant timeframe from FFPE material. Failure rates are low (14%).***REMoDL-B***
- The addition of bortezomib to R-CHOP chemotherapy does not appear to impact upon early treatment failure rates.***REMoDL-B***
- Bortezomib, at these doses, did not appear to significantly increase the toxicity of R-CHOP. ***PYRAMID trial and REMoDL-B***
- Analysis of primary endpoint PFS at 30 months of RB-CHOP versus RCHOP in ***REMoDL-B*** is awaited.

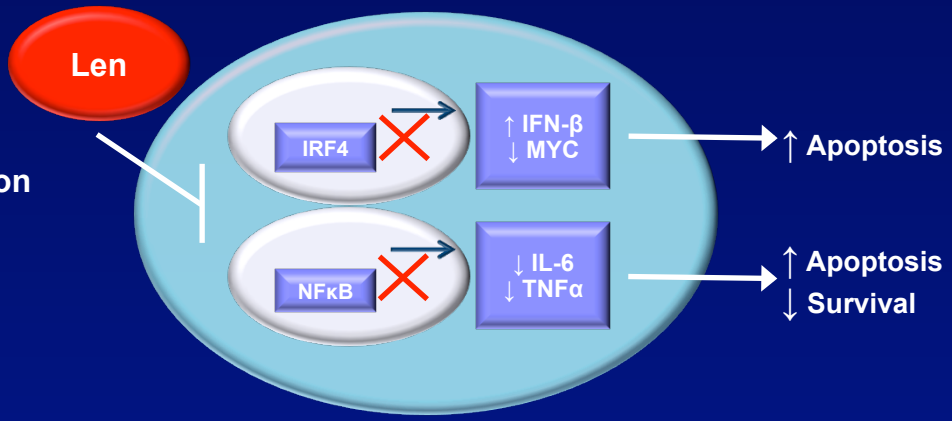
A Phase 2/3 Multicenter, Randomized Study Comparing the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Relapsed/Refractory DLBCL

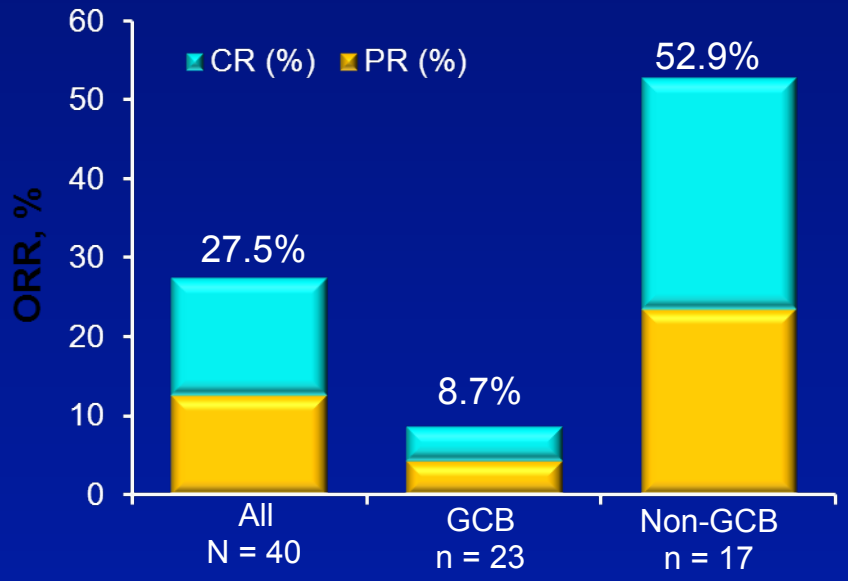
Myron S. Czuczman,[1] Andrew Davies,[2] Simon Rule,[3] Kim Linton,[4] Nina Wagner-Johnston,[5] Randy D. Gascoyne,[6] Graham W. Slack,[6] Pierre Brousset,[7] David A. Eberhard,[8] Gilles Salles,[9] Thomas Witzig,[10] Pier Luigi Zinzani,[11] George Wright,[12] Louis M. Staudt,[13] P. Mickey Williams,[14] Chih-Jian Lih,[14] Jacqueline Repici,[15] Pierre Fustier,[16] Dale Song,[15] Oliver Manzke,[15] Ian D. Lewis[17]

[1]Roswell Park Cancer Institute, Buffalo, NY; [2]University of Southampton, Southampton General Hospital, Southampton, UK; [3]Derriford Hospital, Plymouth, UK; [4]The Christie Foundation Trust, Manchester, UK; [5]Washington University School of Medicine, Division of Oncology, St. Louis, MO; [6]Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver, BC; [7]Laboratoire D'Anatomie Pathologique, Centre Hospitalier Universitaire Purpan, Toulouse, France; [8]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [9]Centre Hospitalier Lyon-Sud, Pierre-Benite, France; [10]Mayo Clinic, Rochester, MN; [11]Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; [12]Biometric Research Branch, DCTD, National Cancer Institute, NIH, Bethesda, MD; [13]Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD; [14]Frederick National Laboratory for Cancer Research, Frederick, MD; [15]Celgene Corporation, Summit, NJ; [16]Celgene Corporation, Boudry, Switzerland; [17]Royal Adelaide Hospital, Adelaide, Australia

DLBCL and Lenalidomide Activity

- DLBCL is an aggressive form of NHL, composed of 2 main subtypes:
  - GCB
  - ABC/non-GCB (subtype classification based on the use of GEP or IHC, respectively)
- Less than 10% of DLBCL patients with refractory disease achieve durable remissions with secondary therapies[1]
- ABC patients have a poorer prognosis compared to GCB subpopulations[2]
  - NFκB activity has been associated with survival in ABC DLBCL cells[3]
- Lenalidomide is an immunomodulatory agent (IMiD®) with antitumor functions such as decreasing IRF4 and NFκB activity[4,5]
- Retrospective analysis suggests that patients with non-GCB subtype had higher response compared to GCB (*P* = .006) when treated with lenalidomide monotherapy[6]



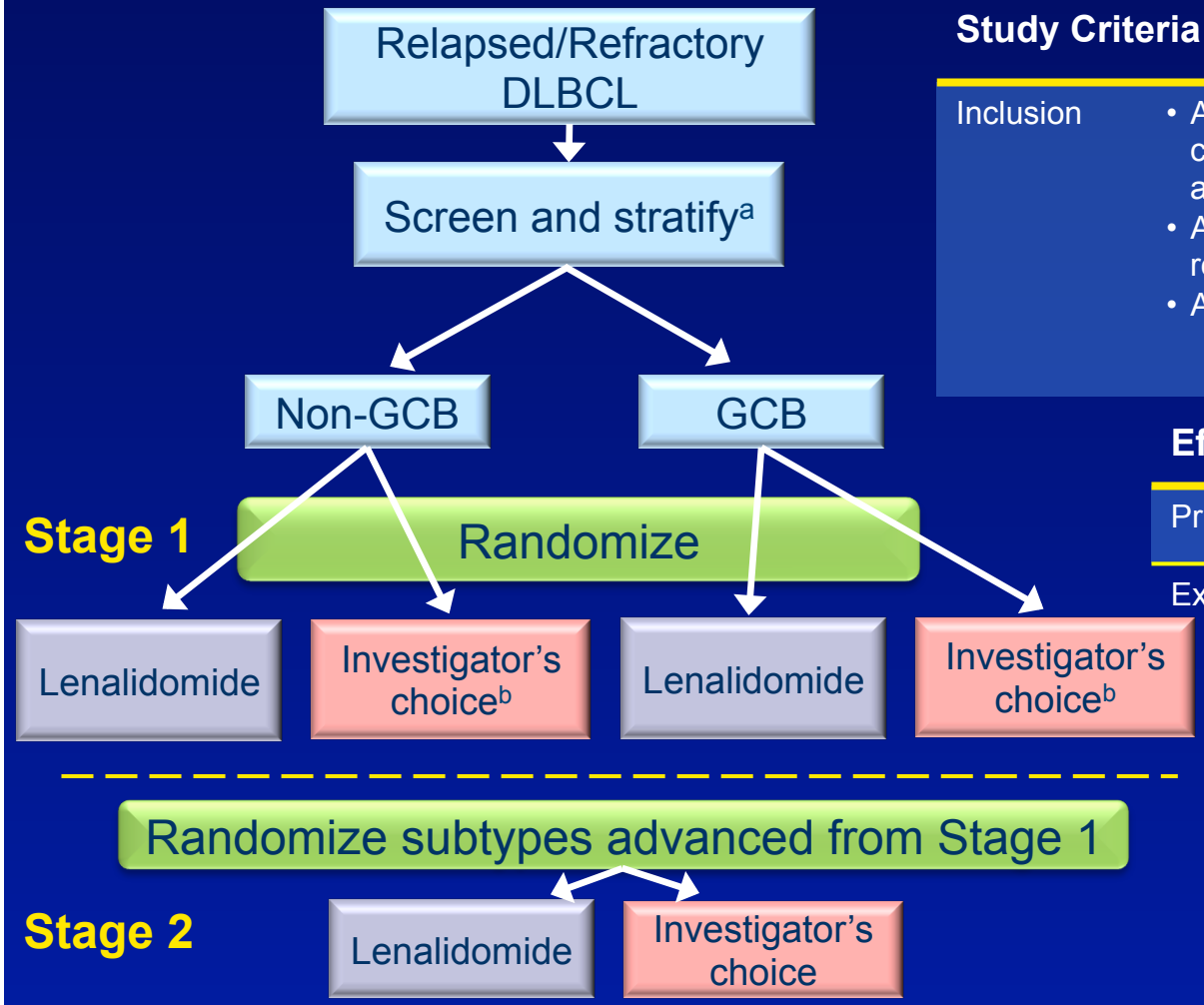


Abbreviations: ABC, activated B-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GEP, gene expression profiling; IFN-β, interferon beta; IHC, immunohistochemistry; IL-6, interleukin-6; IMiD, immunomodulatory agent; IRF4, interferon regulatory factor 4; Len, lenalidomide; NFκB, nuclear factor kappa B; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PR, partial response; TNFα, tumor necrosis factor alpha.

1. Hitz F, et al. *Blood* (ASH). 2010;116(21): Abstract 1751; 2. Hans CP, et al. *Blood*. 2004;103:275-282; 3. Davis RE and Brown KD. *J Exp Med*. 2001;194(12):1861-1874;
4. Zhang LH, et al. *Br J Haematol*. 2013;160(4):487-502; 5. Martiniani R, et al. *Adv Hematol*. 2012;2012:842945; 6. Hernandez-Ilizaliturri FJ, et al. *Cancer*. 2011;117(22):5058-5066.

DLC-001: Single-Agent Lenalidomide in R/R DLBCL

Phase 2/3 Trial



Study Criteria

Inclusion	• Adults with DLBCL relapsed/refractory to chemotherapy regimen containing rituximab and anthracycline or equivalent AND • At least 1 other treatment or conditioning regimen followed by SCT • Adequate renal, hepatic, bone marrow function

Efficacy Endpoints

Primary	ORR per IRAC
Exploratory	PFS, OS, subtype per GEP

Stage 1

To select adequate ($P < .15$ in favor of Len) subtype(s)

Stage 2

Compare PFS of Len versus IC in selected subtype(s)

Investigator's choice was single agent gemcitabine, rituximab, etoposide, or oxaliplatin

[a] Confirm diagnosis; lymph node biopsy collected to determine subtype by IHC.
[b] At the time of PD, patients receiving IC had the option to crossover and receive lenalidomide.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GEP, gene expression profiling; IC, investigator's choice; IHC, immunohistochemistry; IRAC, Independent Response Assessment Committee; Len, lenalidomide; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; SCT, stem cell transplantation.

DLC-001: DLBCL Subtype Analysis
IHC Versus GEP

Immunohistochemistry

- Immunohistochemistry assessment to distinguish GCB versus non-GCB was conducted on fresh or FFPE lymph node tissue
- Based on the Hans algorithm[1]
  - Markers CD10, BCL6, and MUM1
- Assessments conducted by central pathology lab

Gene Expression Profiling

- In an exploratory analysis, GEP was used distinguish GCB versus ABC in fresh or FFPE lymph node tissue
- Used Affymetrix U133 Plus 2.0 GeneChip Microarray

Abbreviations: ABC, activated B-cell; FFPE, formalin-fixed paraffin-embedded; GCB, germinal center B-cell; GEP, gene expression profiling; IHC, immunohistochemistry; R/R, relapsed/refractory.

1. Hans CP, et al. *Blood*. 2004;103(1):275-282.

DLC-001: Heavily Pretreated Patients

Demographics of mITT[a] Population

	All		GCB Subtype[b]		Non-GCB Subtype[b]	
	Len n = 51	IC n = 51	Len n = 23	IC n = 25	Len n = 28	IC n = 26
Age, median years (range)	69 (28, 84)	65 (20, 84)	70 (37, 84)	64 (28, 84)	68 (28, 78)	67 (20, 80)
Male, n (%)	30 (58.8)	31 (60.8)	13 (56.5)	16 (64.0)	17 (60.7)	15 (57.7)
Patients with ≥3 systemic anticancer therapies, n (%)	25 (49.0)	32 (62.7)	14 (60.9)	15 (60.0)	11 (39.3)	17 (65.4)
Patients with 1 SCT, n (%)	13 (25.5)	17 (33.3)	6 (26.1)	8 (32.0)	7 (25.0)	9 (34.6)
ECOG performance status, n (%)						
0	18 (35.3)	15 (29.4)	6 (26.1)	9 (36.0)	12 (42.9)	6 (23.1)
1	24 (47.1)	28 (54.9)	12 (52.2)	12 (48.0)	12 (42.9)	16 (61.5)
2	7 (13.7)	8 (15.7)	4 (17.4)	4 (16.0)	3 (10.7)	4 (15.4)
Most common prior regimens, n (%)[c]						
R-CHOP	38 (74.5)	35 (68.6)	15 (65.2)	12 (48.0)	23 (82.1)	23 (88.5)
R-ICE	9 (17.6)	15 (29.4)	3 (13.0)	6 (24.0)	6 (21.4)	9 (34.6)
R-DHAP	8 (15.7)	9 (17.6)	4 (17.4)	6 (24.0)	4 (14.3)	3 (11.5)

[a]mITT population defined as patients with DLBCL diagnosis and subtype analysis confirmed by central pathology and received at least 1 dose of study drug.
[b]Subtype analysis conducted using immunohistochemistry.
[c] Received by ≥10% of patients in the mITT population.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; IC, investigator's choice; Len, lenalidomide; mITT, modified intent-to-treat; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP, rituximab-dexamethasone, high-dose cytarabine, cisplatin; R-ICE, rituximab-ifosfamide, carboplatin, etoposide; SCT, stem cell transplantation.

DLC-001: Crossover Phase

- At the time of PD, patients receiving investigator's choice had the option to cross over to lenalidomide
- A total of 29 patients entered the crossover phase
  - 1 patient achieved PR (3.4%)[a]
  - 5 patients had SD (17.2%)
  - 22 patients had PD/death (75.9%)
- Median treatment duration was 6 weeks (maximum 27.4 weeks)
- At least 1 dose interruption due to AE was reported in 15 patients (51.7%)
- 19 patients entered the follow-up phase

[a]Patient had non-GCB DLBCL and previously received gemcitabine in investigator's choice arm.
Abbreviations: AE, adverse event; DLBCL, diffuse large B-cell lymphoma; GCB; germinal center B-cell; PD, progressive disease; PR, partial response; SD, stable disease.

DLC-001: Lenalidomide in R/R DLBCL

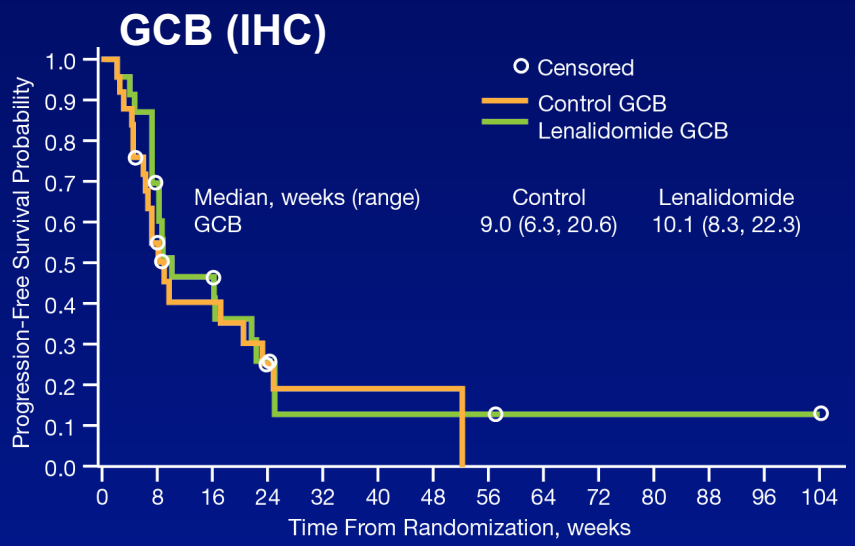
IHC Versus GEP

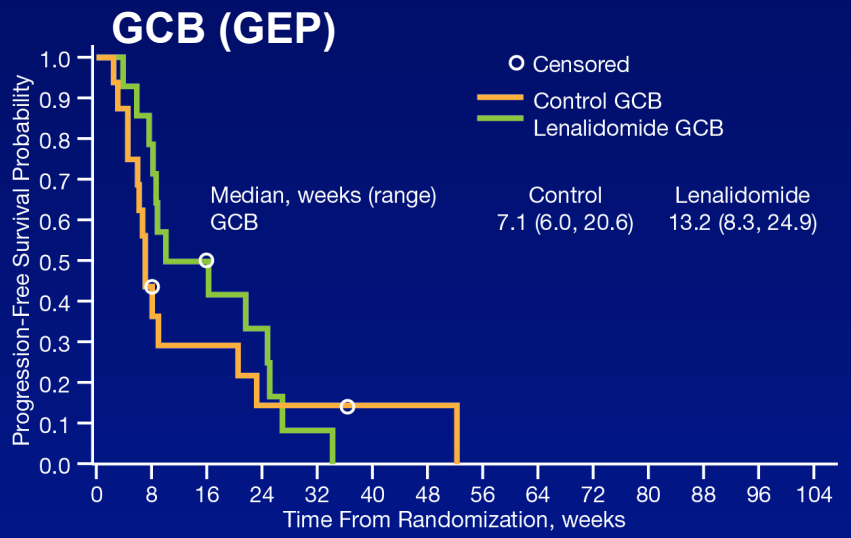
	IHC						GEP			
	All		GCB		Non-GCB		GCB		ABC	
	Len	IC	Len	IC	Len	IC	Len	IC	Len	IC
Patients, n	51	51	23	25	28	26	14	16	11	16
ORR, %	28	12	26	12	29	12	21	13	46	19
PFS, med wk	13.6	7.9	10.1	9.0	15.1	7.1	13.2	7.1	82.0	6.2
HR **95% CI**	0.64 0.41, 0.99		0.82 0.43, 1.57		0.50 0.27, 0.92		0.77 0.35, 1.68		0.44 0.15, 1.23	
***P* value**	.041		.550		.021		.506		.105	
OS, med wk	31.0	24.6	30.0	24.9	32.3	20.4	30.0	20.1	108.4	18.6
HR **95% CI**	0.91 0.59, 1.41		1.23 0.65, 2.34		0.70 0.38, 1.30		1.12 0.52, 2.42		0.47 0.17, 1.33	
***P* value**	.673		.526		.253		.767		.144	

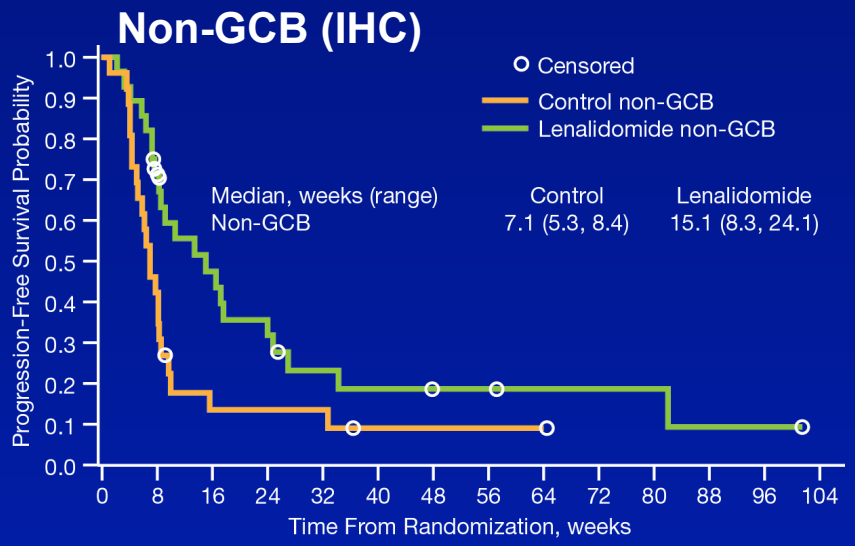
Abbreviations: ABC, activated B-cell; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GEP, gene expression profiling; HR, hazard ration; IC, investigator's choice; IHC, immunohistochemistry; Len, lenalidomide; med, median; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; wk, weeks.

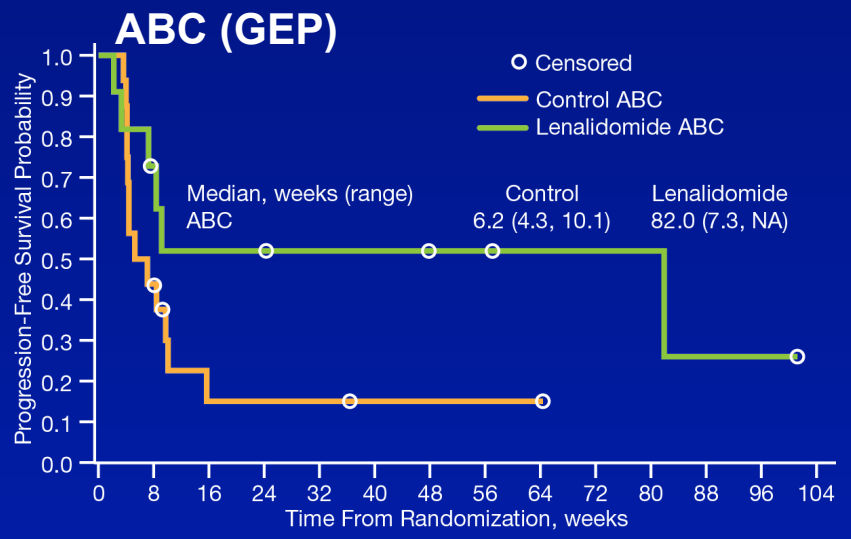
DLC-001: Lenalidomide in R/R DLBCL Subtypes

Progression-free Survival (IHC versus GEP)









Abbreviations: ABC, activated B-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GEP, gene expression profiling; IC, investigator's choice; IHC, immunohistochemistry; L, lenalidomide; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; wk, weeks.

DLC-001 Summary and Conclusions

- These data demonstrate a promising enrichment of responses (ORR, OS, PFS) in patients with ABC DLBCL treated with single-agent lenalidomide, thus validating prior retrospective data[1]
  - However, IRAC assessment of Stage 1 results determined that neither subtype met the prespecified criteria to advance to Stage 2
- Lenalidomide has demonstrated promising results in R/R DLBCL, and combination with other agents warrants further investigation, especially in patients with ABC DLBCL
  - Stratification of patients by GEP subtyping suggests a higher response rate to lenalidomide in patients with the ABC subtype and supports GEP-guided treatment in DLBCL patients
- The use of lenalidomide in combination with other agents for treatment in DLBCL is currently under investigation
  - ROBUST: Phase 3 randomized study comparing the efficacy and safety of lenalidomide in combination with R-CHOP (R^2-CHOP) in previously untreated ABC DLBCL patients[2]

Abbreviations: ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; IRAC, Independent Response Assessment Committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone; R-GEM, rituximab-gemcitabine, cisplatin, methylprednisolone; R/R, relapsed/refractory.

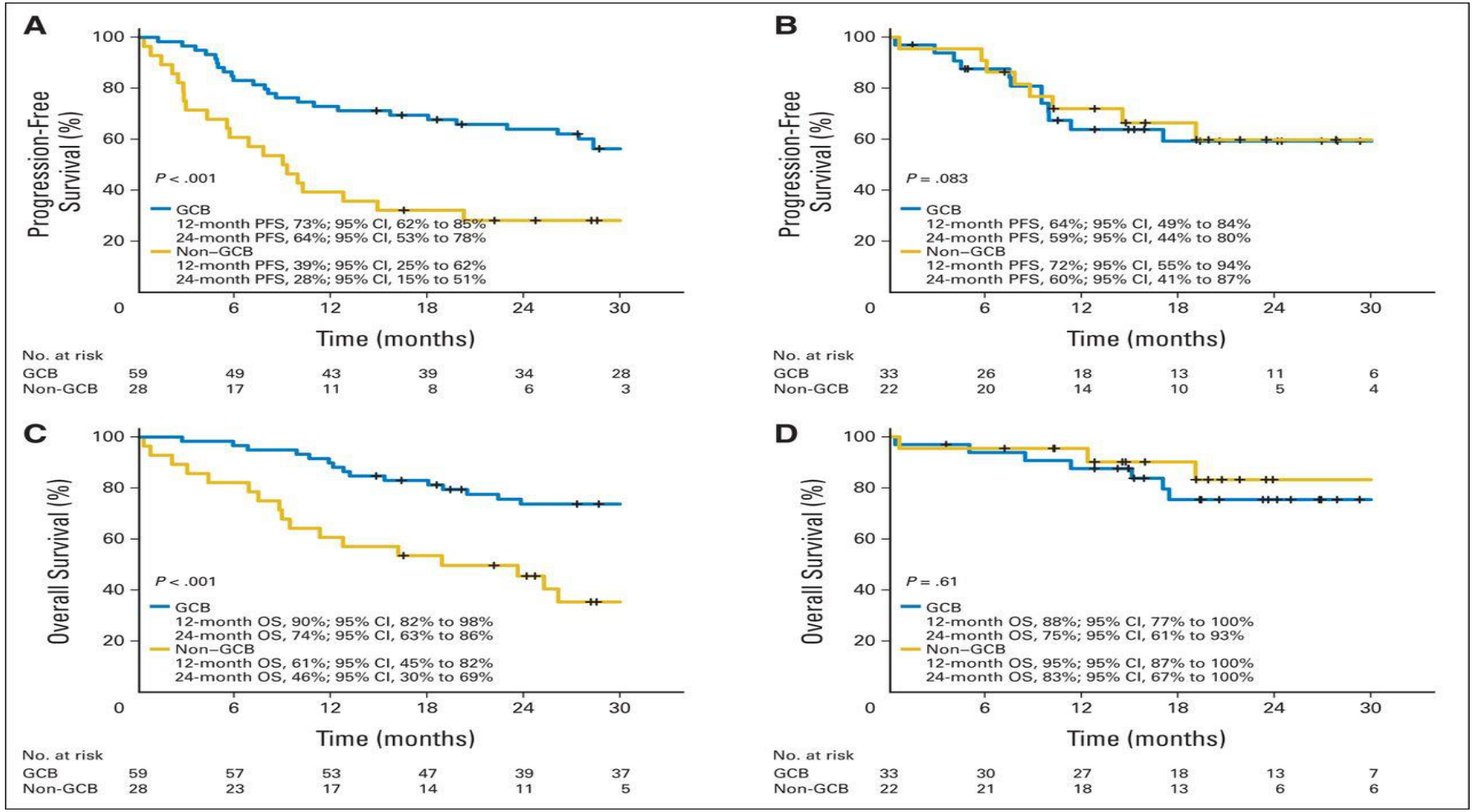
1. Hernandez-Ilizaliturri FJ, et al. *Cancer*. 2011;117(22):5058-5066; 2. NCT02285062: http://clinicaltrials.gov/ct2/show/NCT02285062.

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non–Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study

Grzegorz S. Nowakowski, Betsy LaPlant, William R. Macon, Craig B. Reeder, James M. Foran, Garth D. Nelson, Carrie A. Thompson, Candido E. Rivera, David J. Inwards, Ivana N. Micallef, Patrick B. Johnston, Luis F. Porrata, Stephen M. Ansell, Randy D. Gascoyne, Thomas M. Habermann, and Thomas E. Witzig

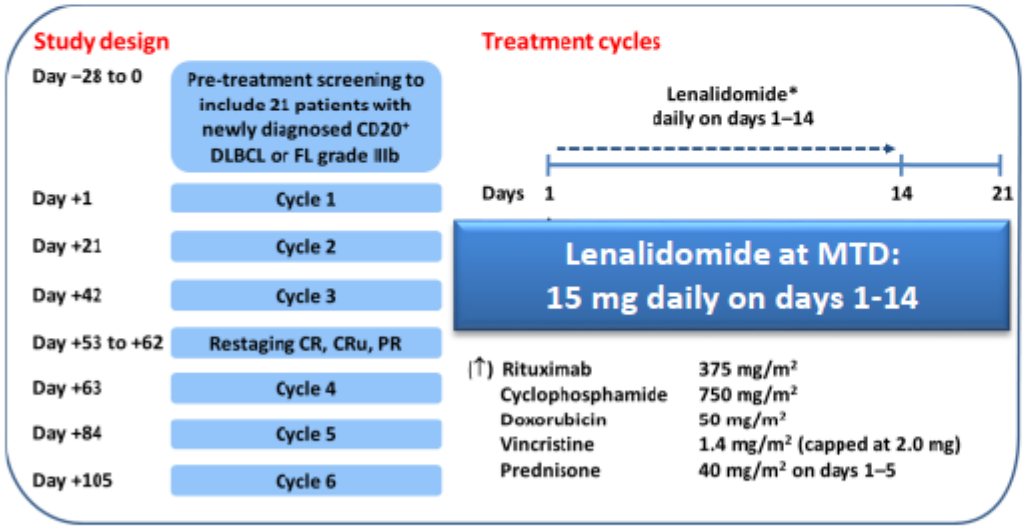


Lancet Oncol 2014

Articles

Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, Vincenza Pavone, Marco Ladetto, Anna Marina Liberati, Anna Lia Molinari, Pierluigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Martin Dreyling, Barbara Botto, Alessia Castellino, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi



CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

	Enrolled patients (n=49)
Age (years)	69 (64–71)
Sex	
Men	29 (59%)
Women	20 (41%)
Eastern Cooperative Oncology Group performance status	
0–1	42 (86%)
2	7 (14%)
Ann Arbor stage	
II	6 (12%)
III	8 (16%)
IV	35 (71%)
International Prognostic Index risk	
Low-intermediate risk	19 (39%)
High-intermediate or high risk	30 (61%)
Lymphoma type	
Diffuse large B-cell lymphoma	45 (92%)
Follicular lymphoma grade 3b	4 (8%)
Bone marrow involvement	17 (35%)
B symptoms	21 (43%)
Increased lactate dehydrogenase concentration*	22 (45%)
Increased β_2 microglobulin*	34 (69%)

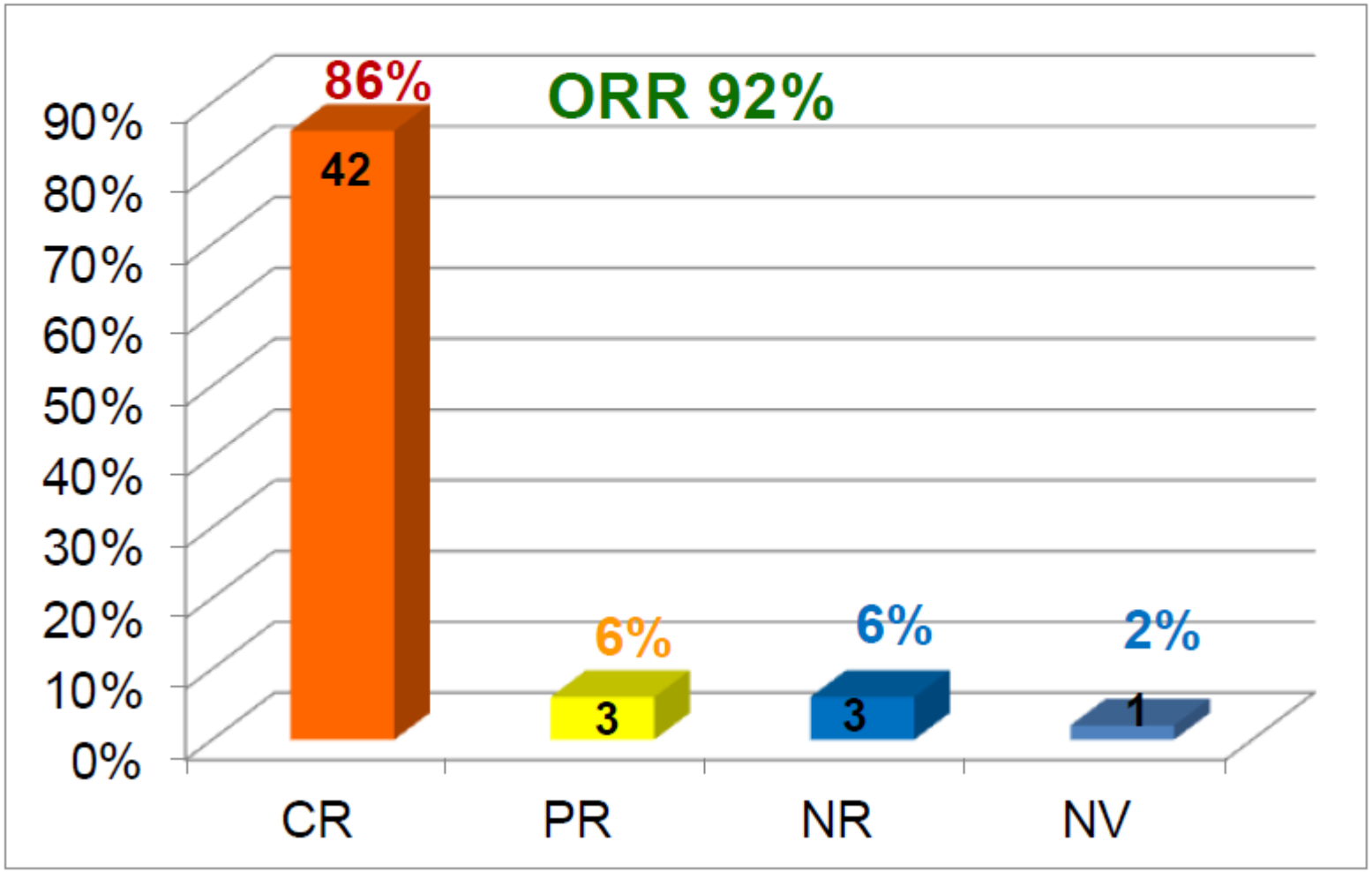
Data are median (IQR) or n (%). *Higher than the upper limit of normal.

Table 1: **Baseline clinical characteristics**

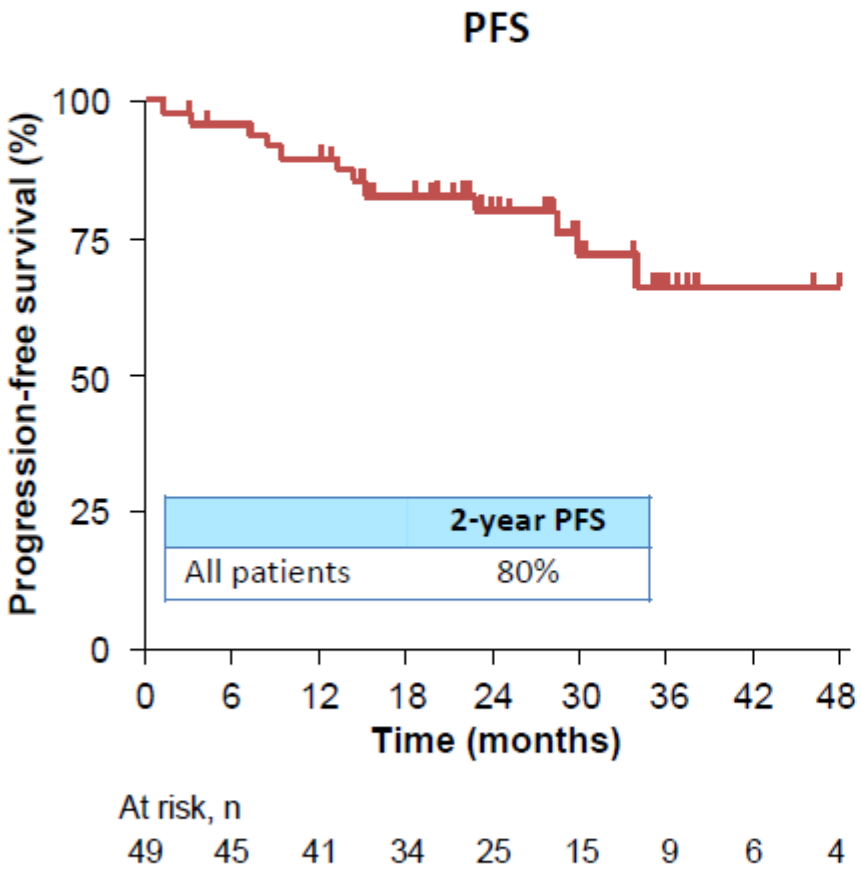
Final response assessed with PET-CT scan

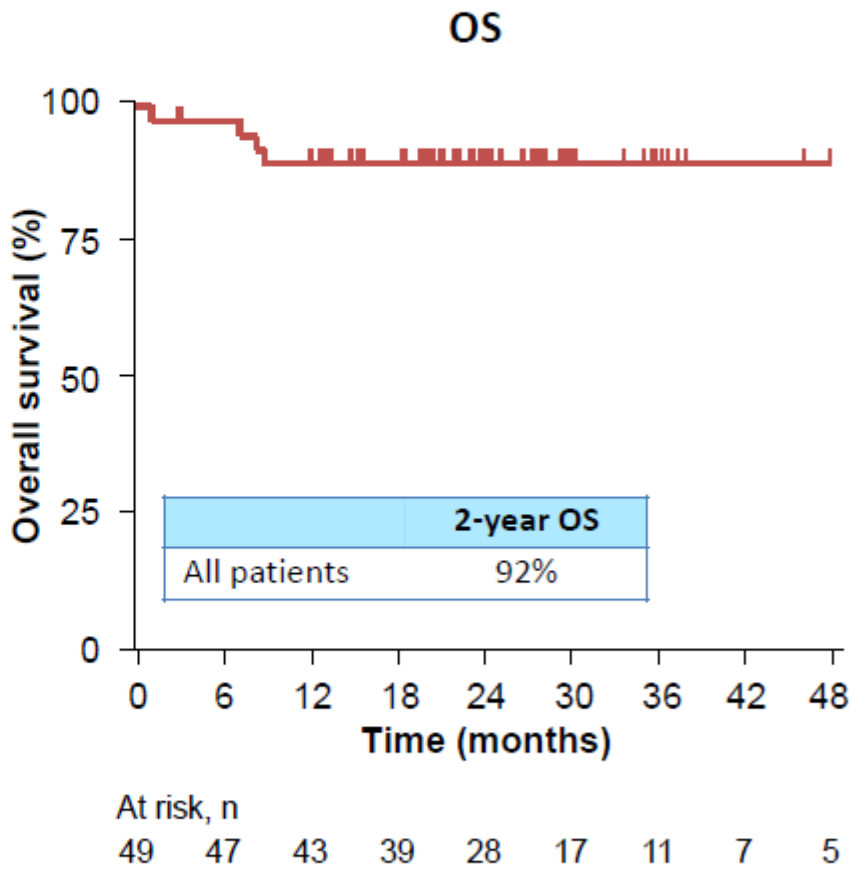
(IWC Cheson 2007)

ITT response in the 49 elderly (>65 years) IPI= LI/HI/H



REAL07 phase II R2-CHOP21 in elderly high risk untreated DLBCL

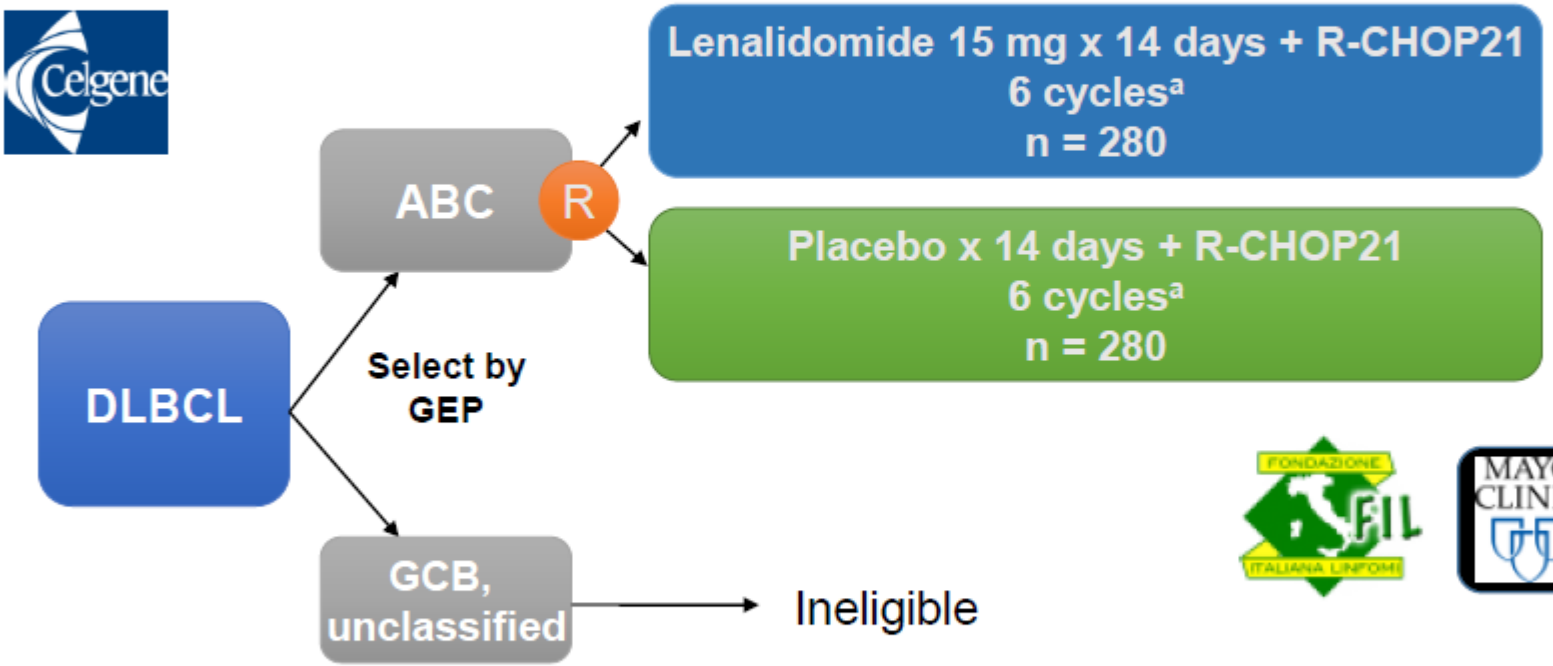




Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

DLC-002 (ROBUST) study design: COO categorization made on nanostring

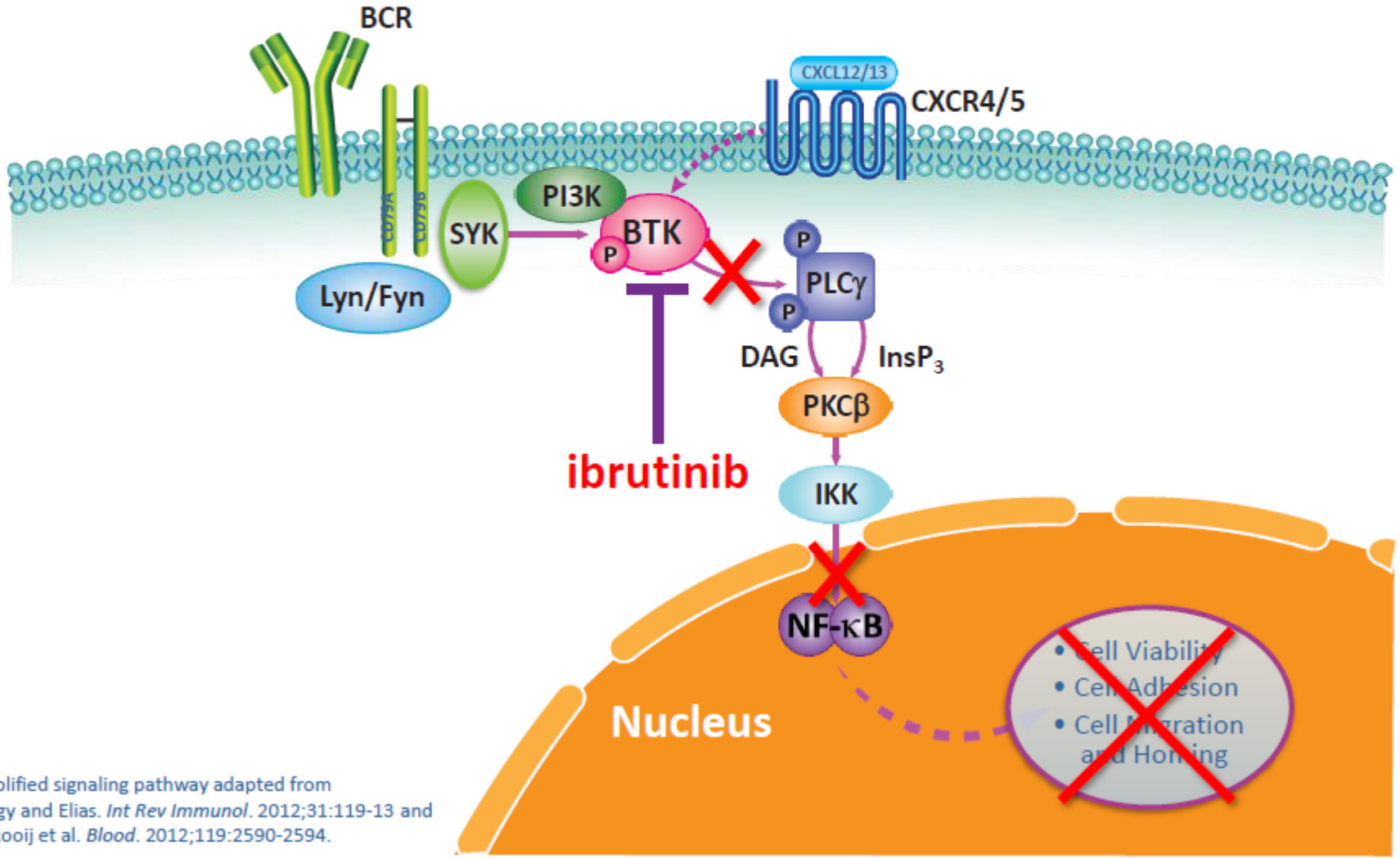
Sponsor: Celgene Corporation. Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.
Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.



- Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age 18–80 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)
- 208 sites expected to be involved

NCT02285062.

BCR-Signaling Pathway & Inhibition of BTK with Ibrutinib



Simplified signaling pathway adapted from Buggy and Elias. *Int Rev Immunol*. 2012;31:119-13 and de Rooij et al. *Blood*. 2012;119:2590-2594.

Ibrutinib in DLBCL

VOLUME 31 · NUMBER 1 · JANUARY 1 2013

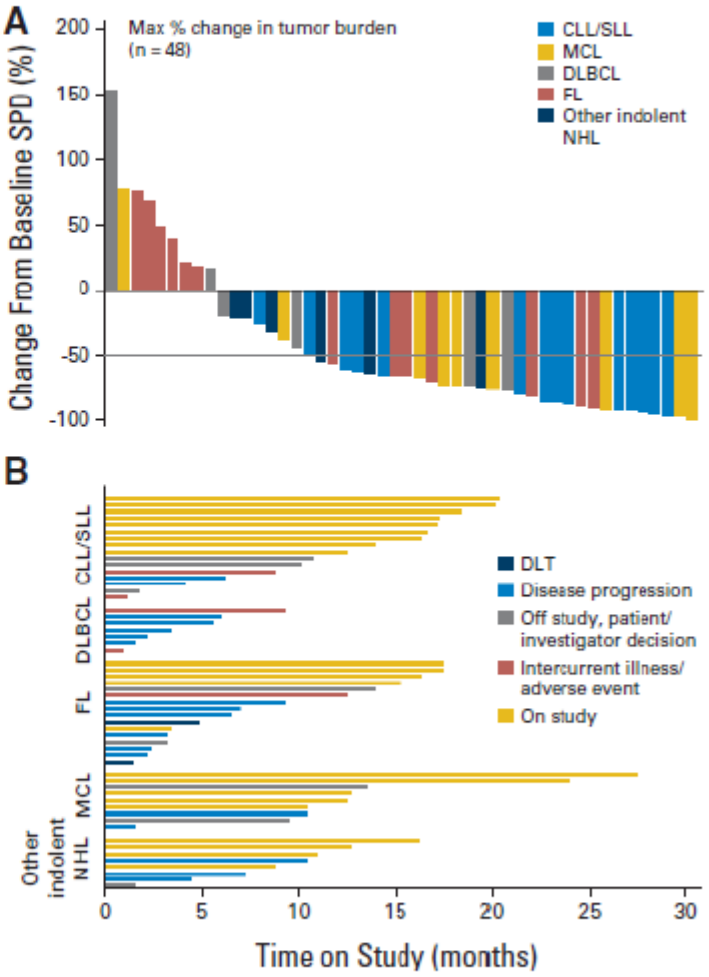
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies

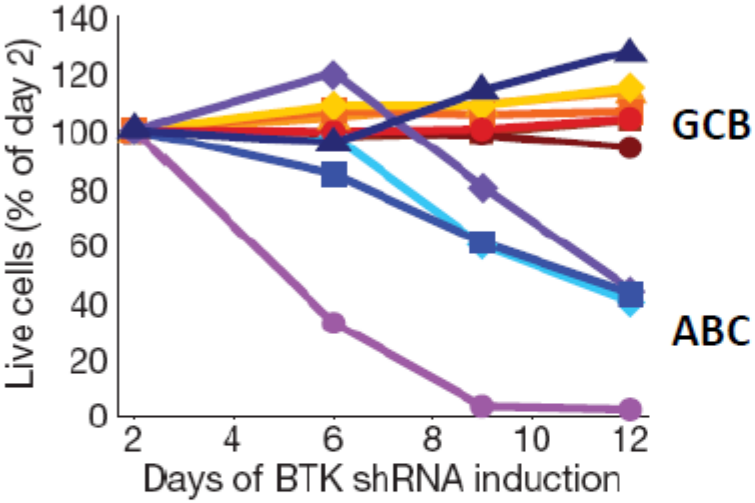
Ranjana H. Advani, Joseph J. Buggy, Jeff P. Sharman, Sonali M. Smith, Thomas E. Boyd, Barbara Grant, Kathryn S. Kolibaba, Richard R. Furman, Sara Rodriguez, Betty Y. Chang, Juthamas Sukbuntherng, Raquel Izumi, Ahmed Hamdy, Eric Hedrick, and Nathan H. Fowler

TOTAL N^ PATIENTS	**56**
FL	16
CLL/SLL	16
MCL	**9**
DLBCL	**7**
MZL/MALT	4
WM	4



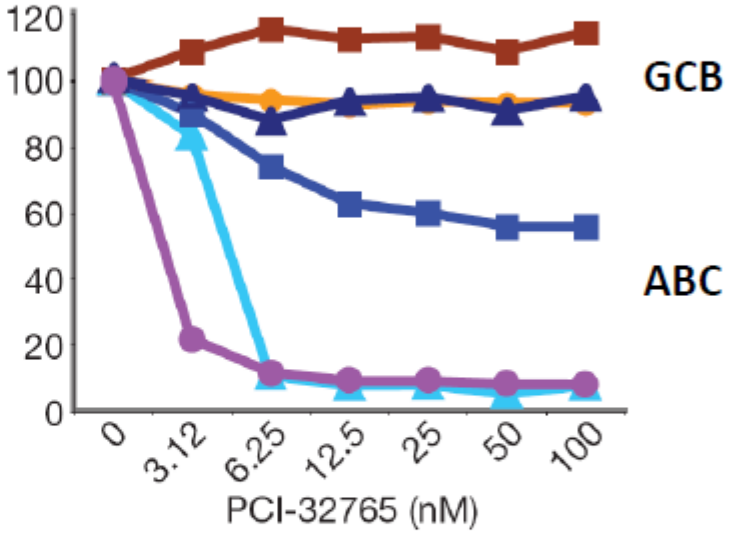
Switch-off of BTK is lethal for ABC-DLBCL

Genetic inhibition of BTK is lethal for ABC-DLBCL



Cell line	DLBCL subtype	CARD11 status
OCI-Ly3	ABC	Mutant
HBL-1	ABC	WT
TMD8	ABC	WT
U2932	ABC	WT
OCI-Ly10	ABC	WT
BJAB	GCB	WT
OCI-Ly19	GCB	WT
SUDHL-6	GCB	WT
SUDHL-10	GCB	WT
SUDHL-4	GCB	WT
OCI-Ly7	GCB	WT

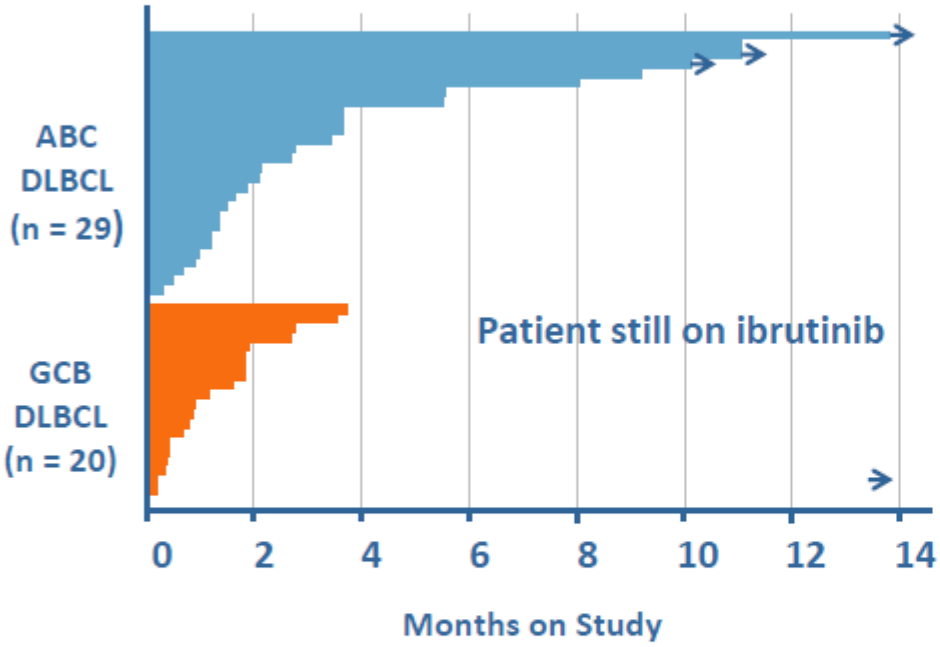
Pharmacologic inhibition of BTK is lethal for ABC-DLBCL

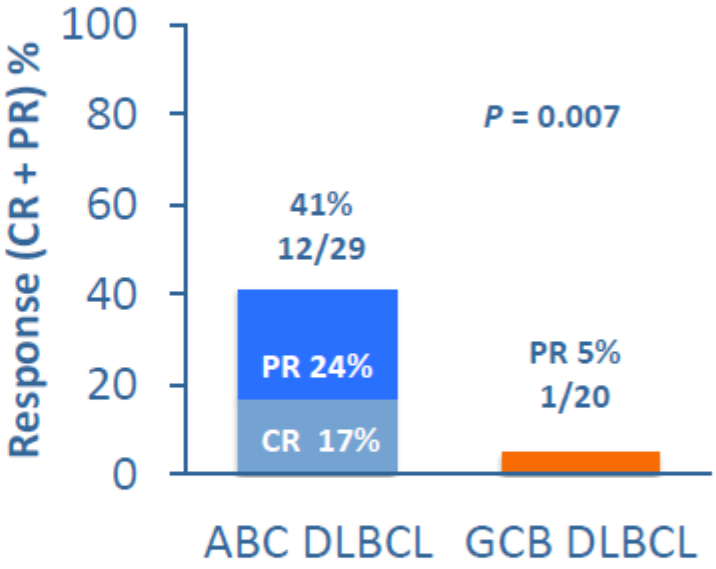


	DLBCL subtype	Chronic active BCR signalling
OCI-Ly10	ABC	+
HBL1	ABC	+
TMD8	ABC	+
OCI-Ly3	ABC	–
BJAB	GCB	–
OCI-Ly19	GCB	–

Davis et al, Nature 2010

Response in ABC and GCB refractory DLBCL



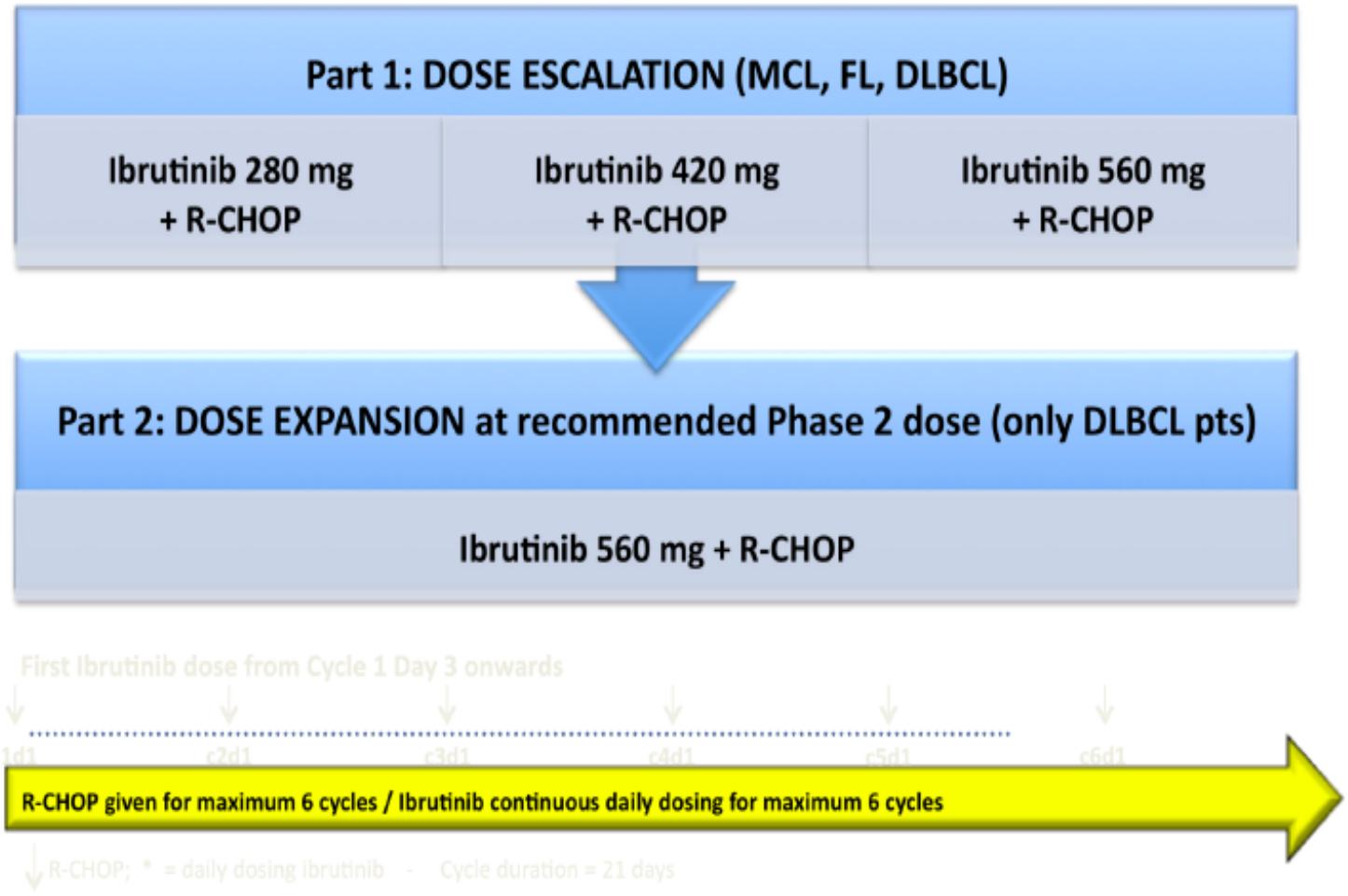


- **Ibrutinib activity will be restricted to ABC DLBCL**
- **Ibrutinib activity will be dependent on pathogenetic events within the BCR pathway**

Wilson et al, ASH 2012

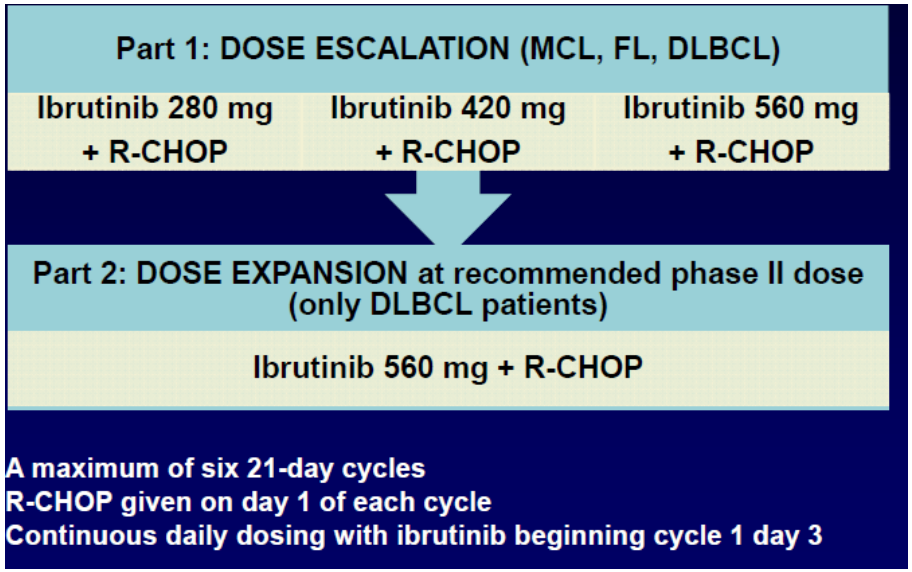
Ibrutinib + RCHOP

Study Design



Younes A, et al: The Lancet Oncology 2014

Phase 1b Ibrutinib + R-CHOP in CD20^{+} B-Cell NHL



Efficacy Evaluable Patients (N = 22)

ORR 100% (91% CR, 9% PR)

- 4 non-GCB patients (All CR)
- 14 GCB patients (86% CR, 14% PR)
- 4 patients subtype analysis pending (all CR)

Dose reduction:

- 4 patients required dose reduction for ibrutinib
  - Febrile neutropenia G3 (n = 2)
  - Diarrhea G3 (n = 1)
  - Prolonged bleeding time (n = 1)
- 2 patients required dose reduction for doxorubicin due to febrile neutropenia
- 7 patients required a dose reduction in vincristine with the majority occurring in cycle 4/5

Younes A, et al. ASH 2013. Abstract 852.

Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study

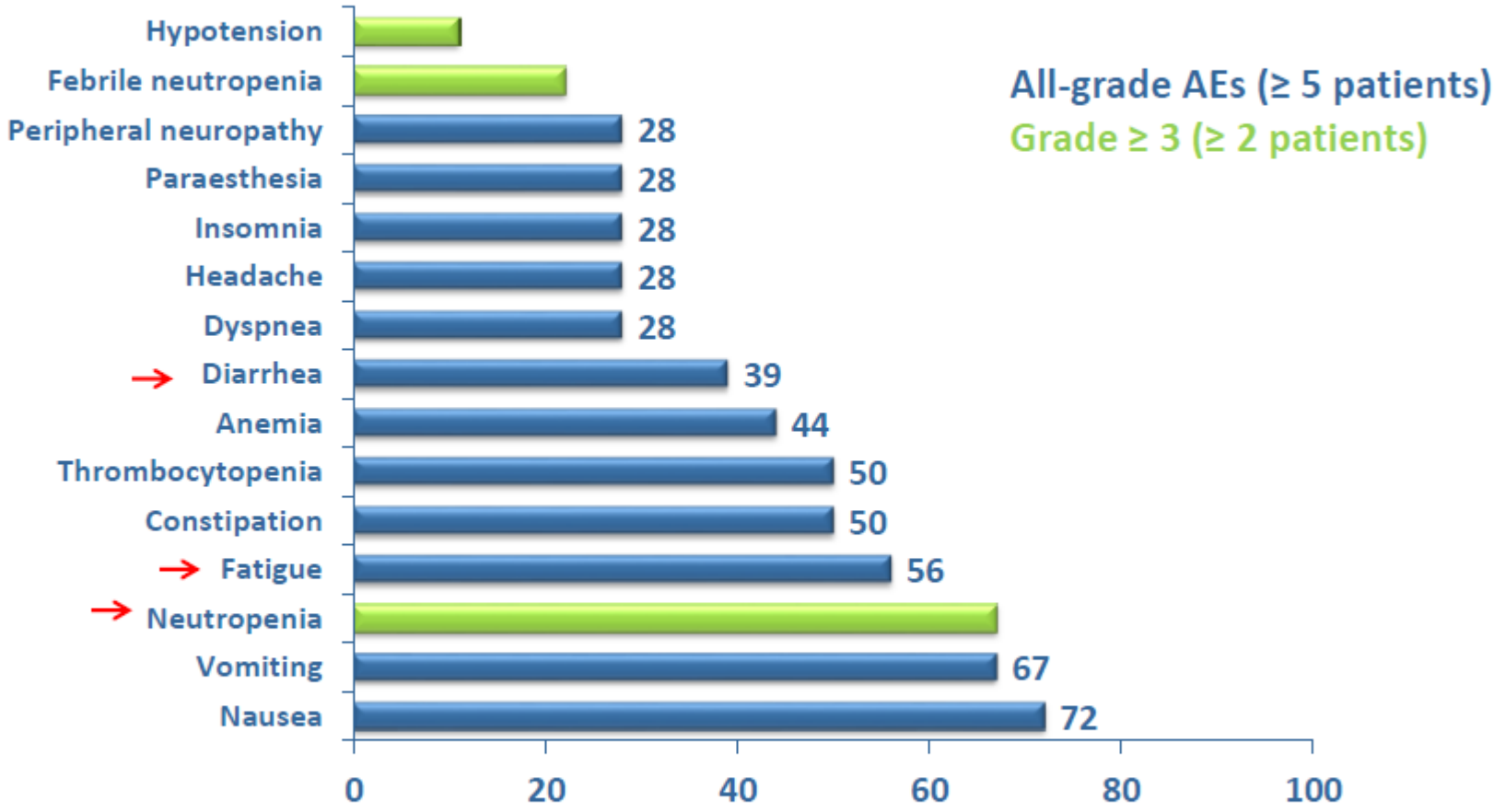
Anas Younes, Catherine Thieblemont, Franck Morschhauser, Ian Flinn, Jonathan W Friedberg, Sandy Amorim, Benedicte Hivert, Jason Westin, Jessica Vermeulen, Nibedita Bandyopadhyay, Ronald de Vries, Sriram Balasubramanian, Peter Hellemans, Johan W Smit, Nele Fourneau, Yasuhiro Oki

Best response to treatment, assessed by Revised Response Criteria for Malignant Lymphoma

n (%)	280 mg (n = 7)	420 mg (n = 4)	560 mg (n = 21)	Combined (n = 32)	All (n = 33)[a]
Overall response	6 (86)	4 (100)	20 (95)	30 (94)	30 (91)
Complete response	5 (71)	3 (75)	15 (71)	23 (72)	23 (70)
Partial response	1 (14)	1 (25)	5 (24)	7 (22)	7 (21)
Stable disease	0	0	0	0	0
Progressive disease	0	0	0	0	0
Not evaluable	1 (14)	0	1 (5)	2 (6)	3 (9)

Younes A, et al. Lancet Oncol. 2014;15:1019-26.

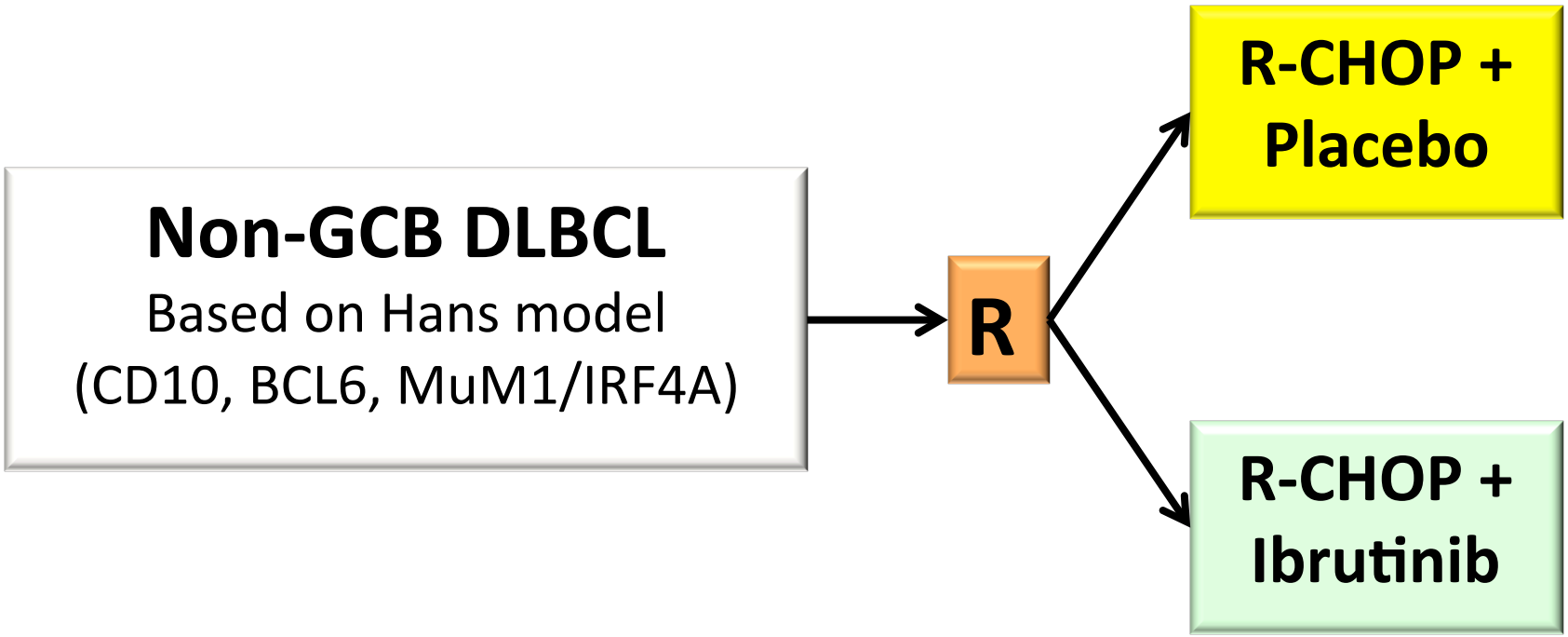
Adverse Events in DLBCL in Patients Treated With Ibrutinib 560 mg + R-CHOP



SAEs were reported in 12 patients. The most commonly reported SAE was febrile neutropenia (17%)

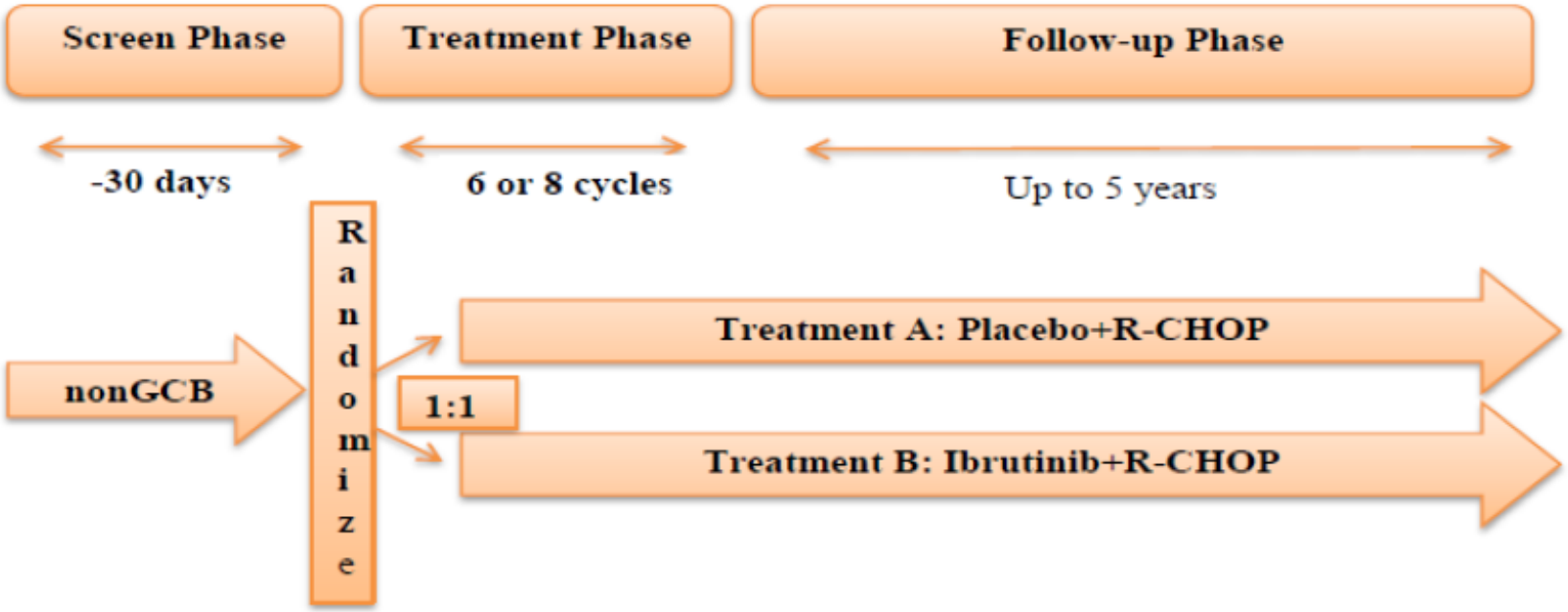
A. Younes et al . Lancet Oncol 2014

Phase III Validation: R-CHOP ± Ibrutinib for Non-GCB DLBCL



www.clinicaltrials.gov: NCT01855750.

PCI-32765 DBL3001 Phase III randomized trial



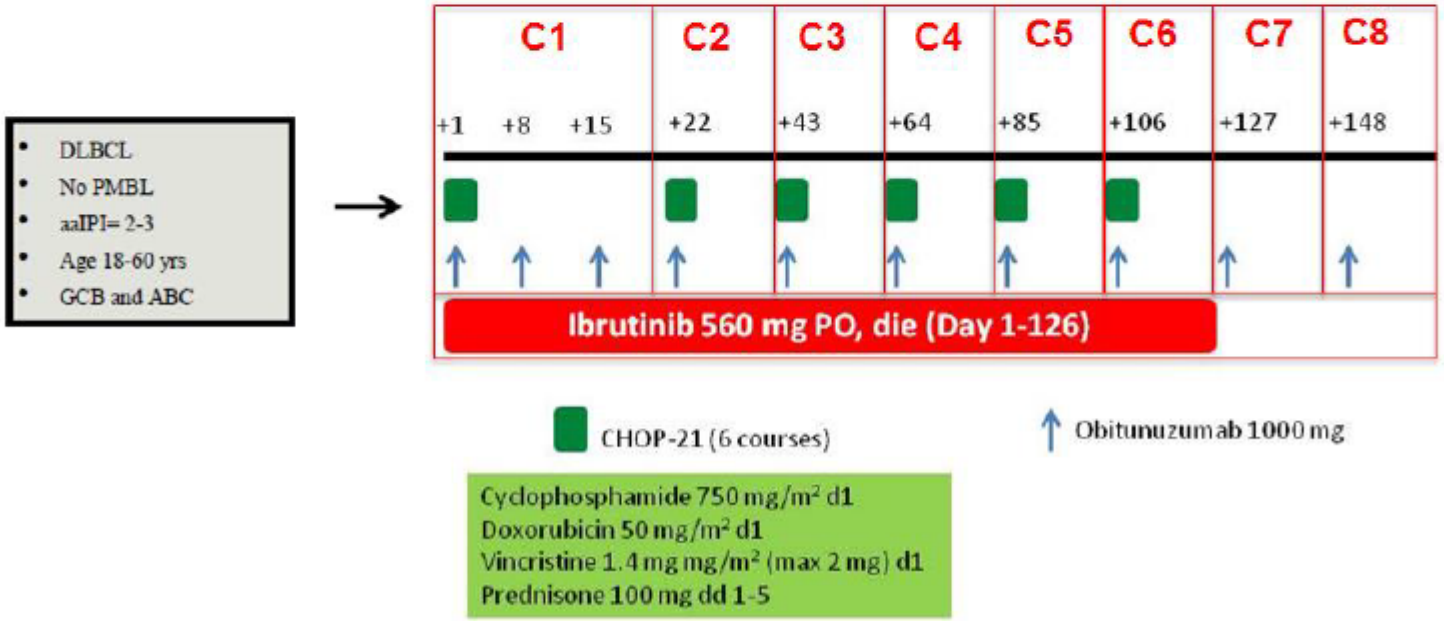
Population:
Subjects with DLBCL who in non-GCB sub-population determined by central IHC

Stratification factors:

- R-IPI score low risk (1) vs. intermediate risk (2-3) vs. high risk (4-5)
- Region (United States/Western Europe vs. Rest of World)
- Number of treatment cycles (6 vs. 8 cycles)

Multicenter phase II open-label study on the feasibility and efficacy of combination of CHOP supplemented with Obinutuzumab (GA101) and Ibrutinib in untreated younger high risk Diffuse Large B-cell Lymphoma (DLBCL). *GALIleo study*

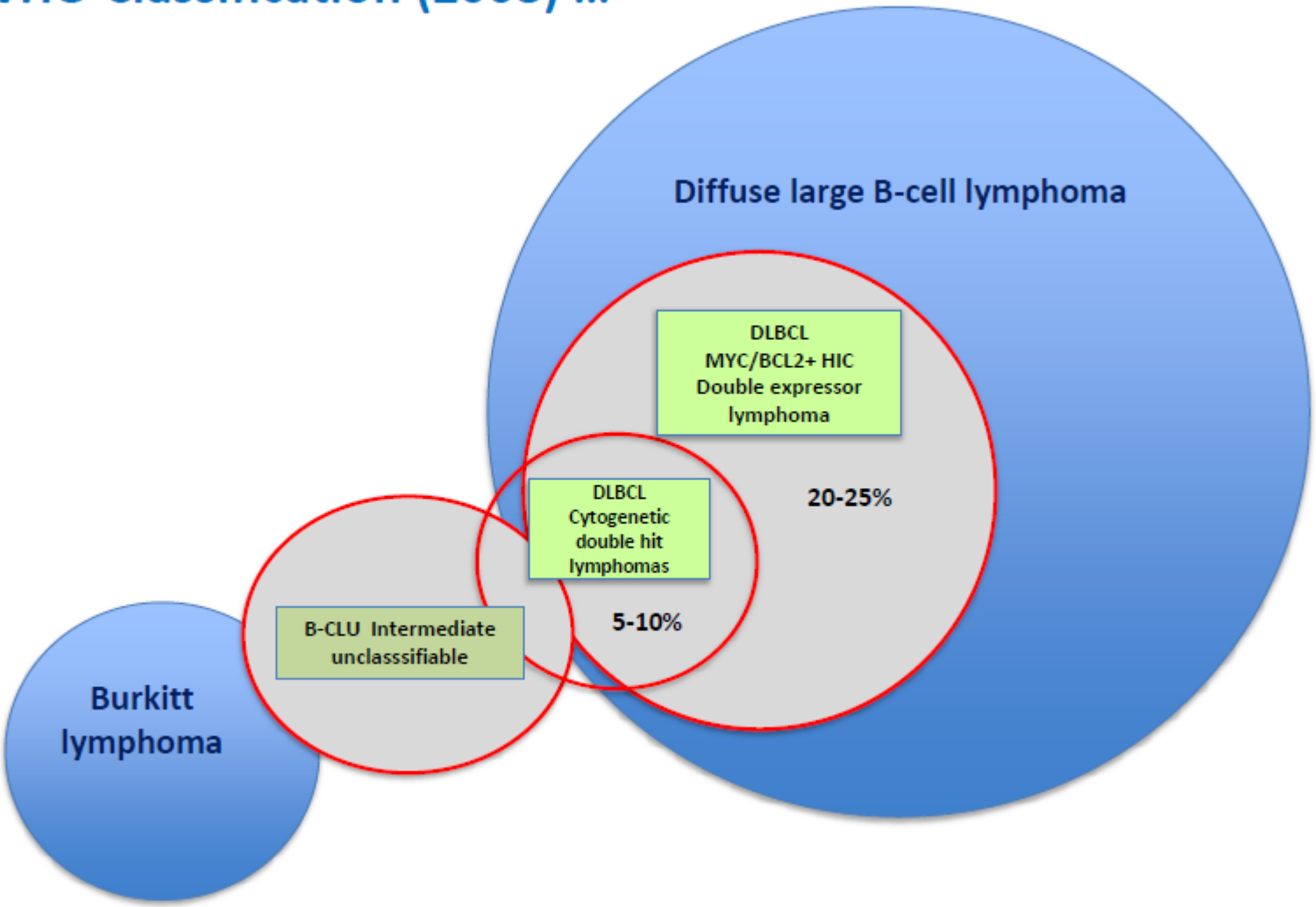
- One arm phase II trial 90 pts to be enrolled
- Aim: to evaluate if the treatment GA101 + CHOP21 + Ibrutinib is able to increase PFS compared to historical R-CHOP14/21 data
- Primary Endpoints: - efficay in terms of 2-years PFS
  - safety of the combination G- CHOP21 + Ibrutinib



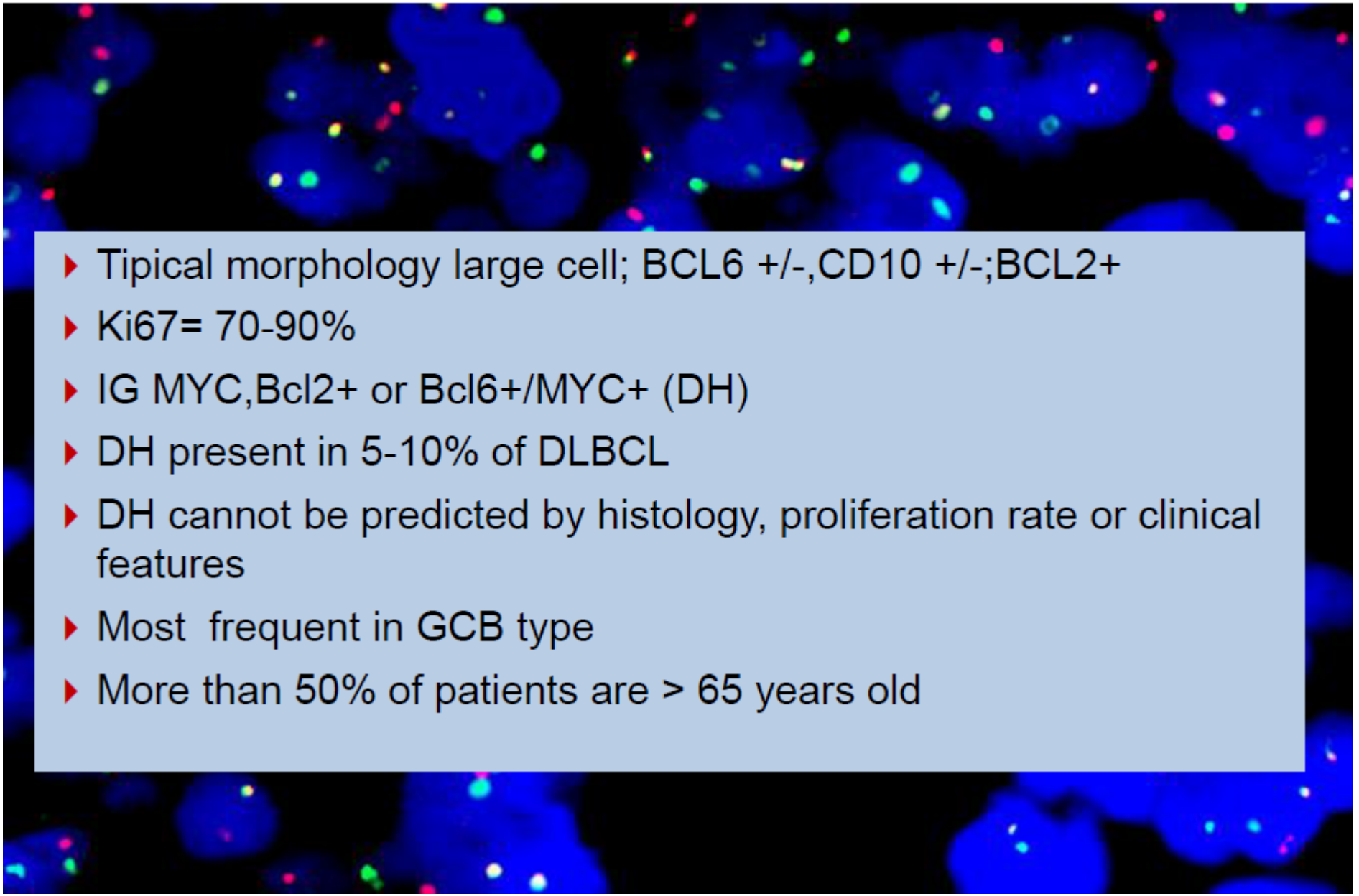
How can we improve the treatment of DLBCL ?

- New monoclonal antibodies combined with CHOP
- Cell of origin (COO) oriented therapy in DLBCL combining new biological drugs to conventional chemotherapy
- **Hystopathological subtypes: Myc positive, double Hit (DHIT) and double Expressor (DE)**
- When should we consider an alternative to R-CHOP?

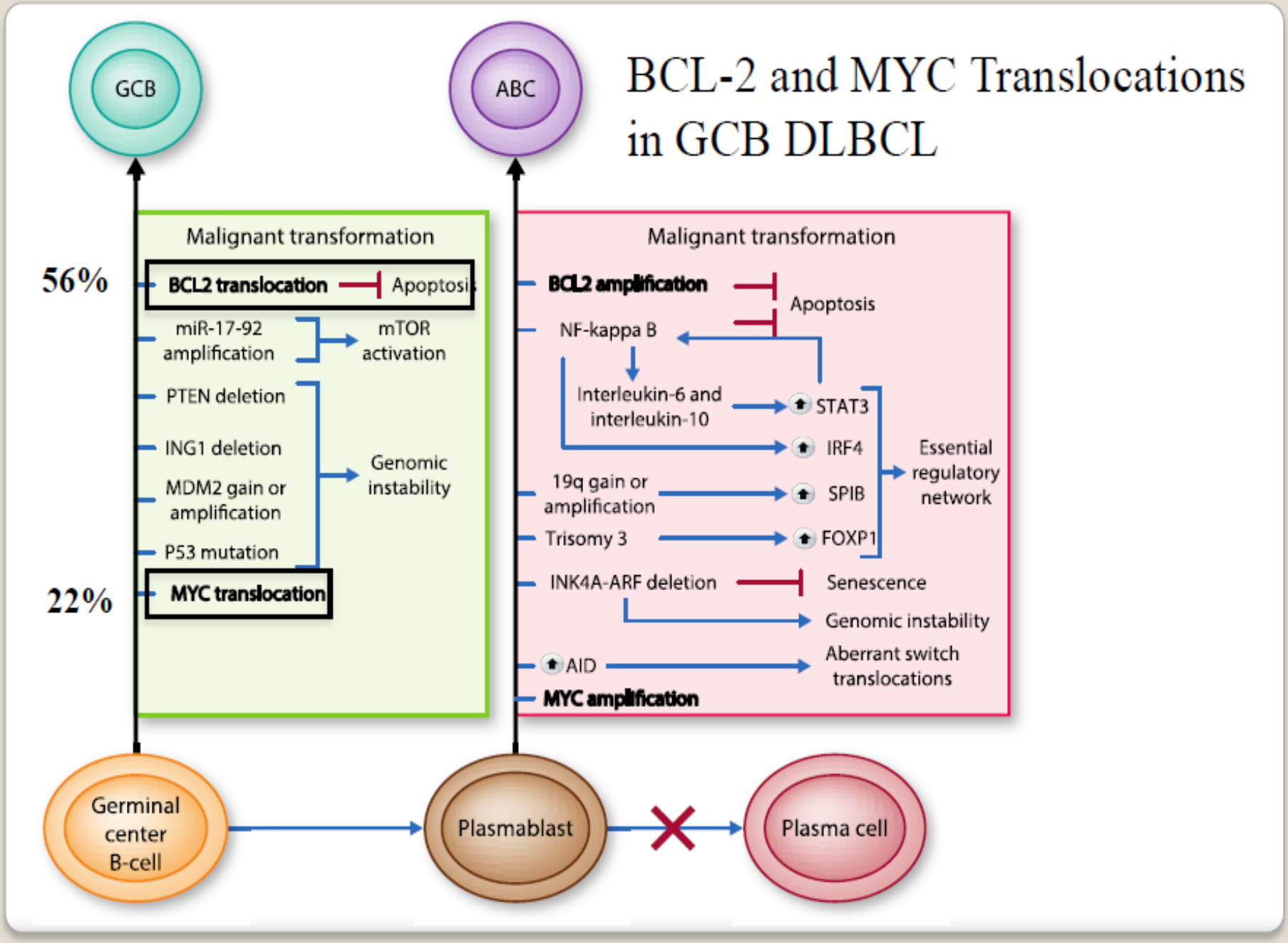
Aggressive B-cell Lymphomas in the WHO Classification (2008) …



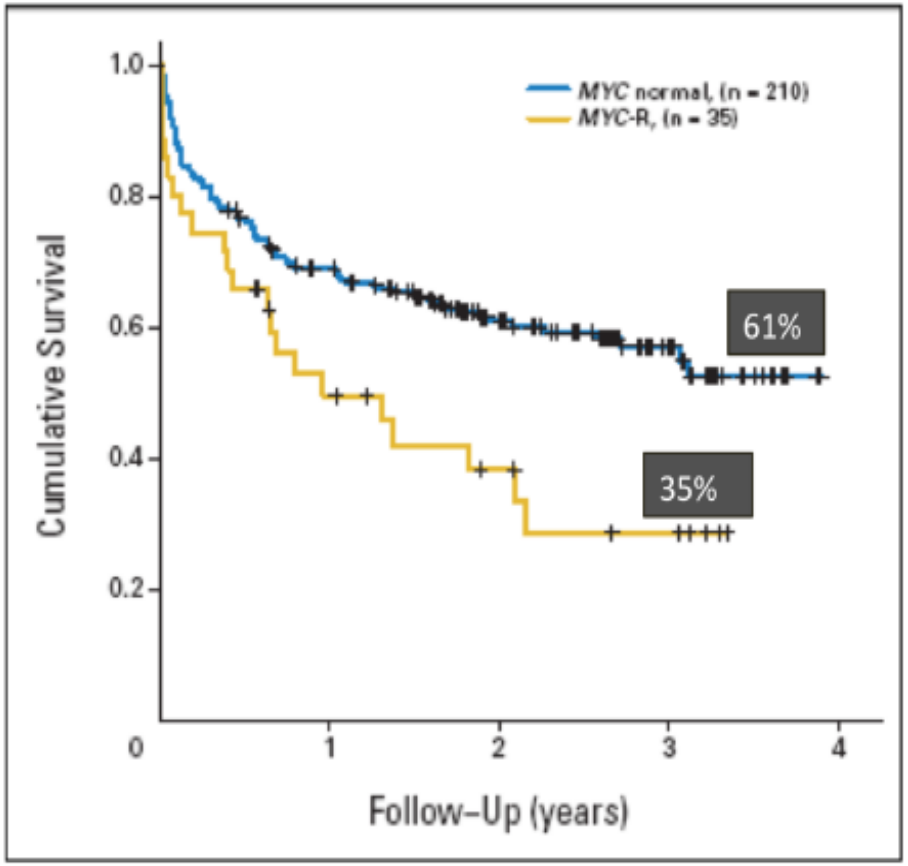
MYC or double HIT DLBCL



- Tipical morphology large cell; BCL6 +/-,CD10 +/-;BCL2+
- Ki67= 70-90%
- IG MYC,Bcl2+ or Bcl6+/MYC+ (DH)
- DH present in 5-10% of DLBCL
- DH cannot be predicted by histology, proliferation rate or clinical features
- Most frequent in GCB type
- More than 50% of patients are > 65 years old


GCB
ABC
BCL-2 and MYC Translocations in GCB DLBCL
Malignant transformation
56%
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
22%
MYC translocation
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
Essential regulatory network
19q gain or amplification
SPIB
Trisomy 3
FOXP1
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
Germinal center B-cell
Plasmablast
Plasma cell

MYC-R DLBCL –Inferior Outcome with R-CHOP



303 patients with DLBCL
- 245 with FISH data

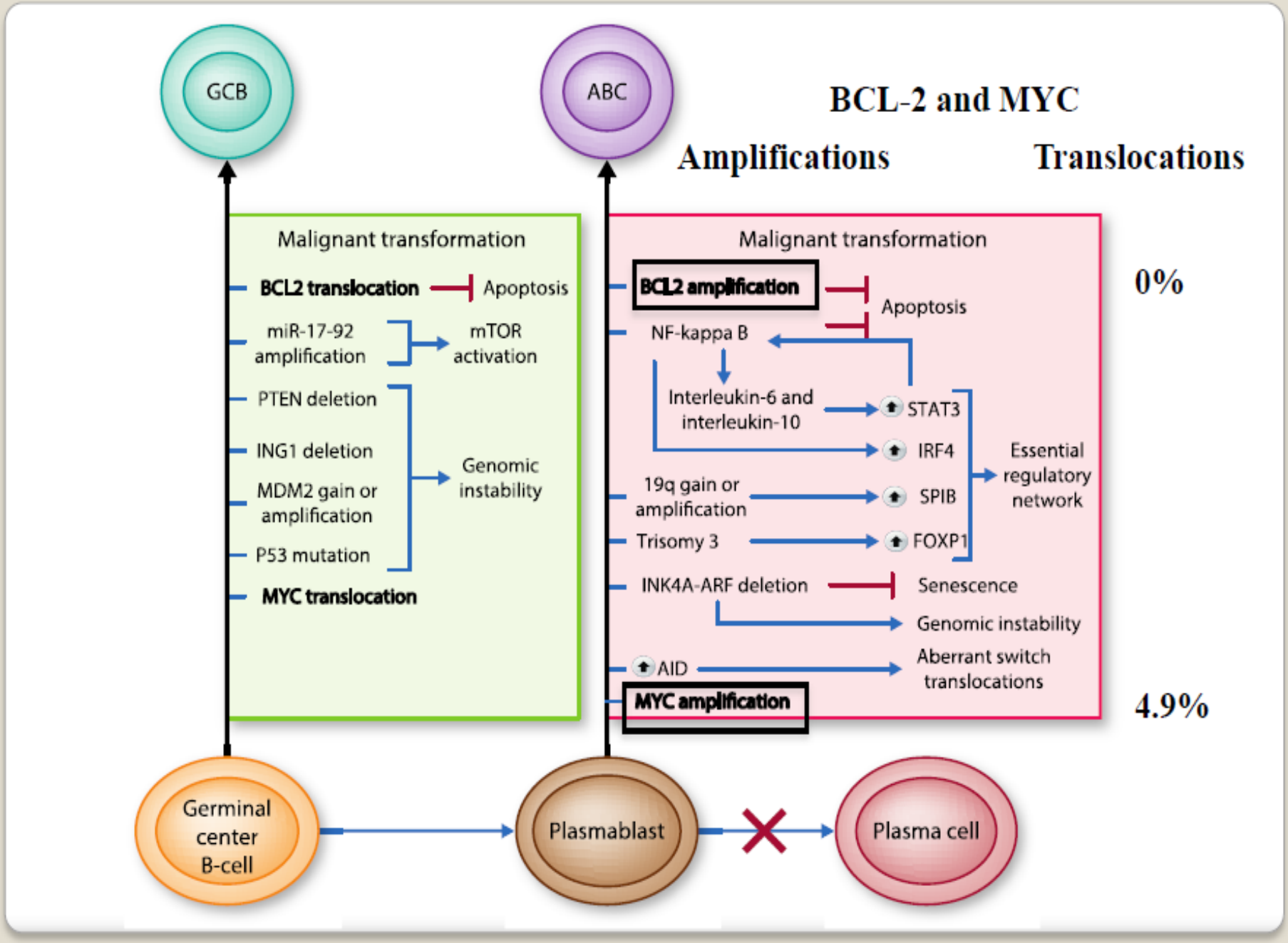
35 (14%) with c-MYC R

19 (54%) also with BCL2 R
3 (8%) also with BCL6 R
7 (20%) had MYC, BCL2 & BCL6

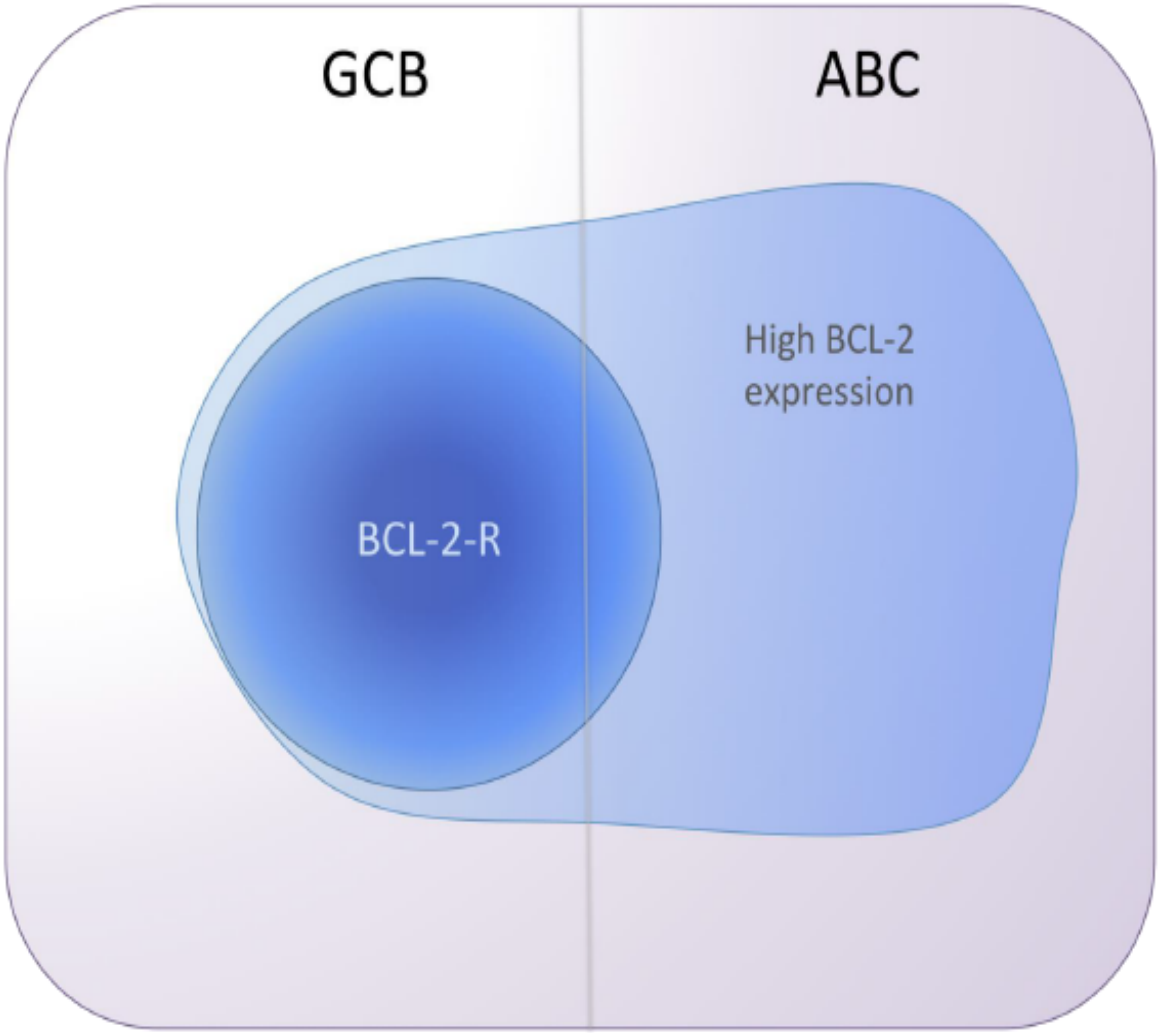
6 (17%) MYC as the sole abnormality

MYC-R cases: high IPI and GCB origin

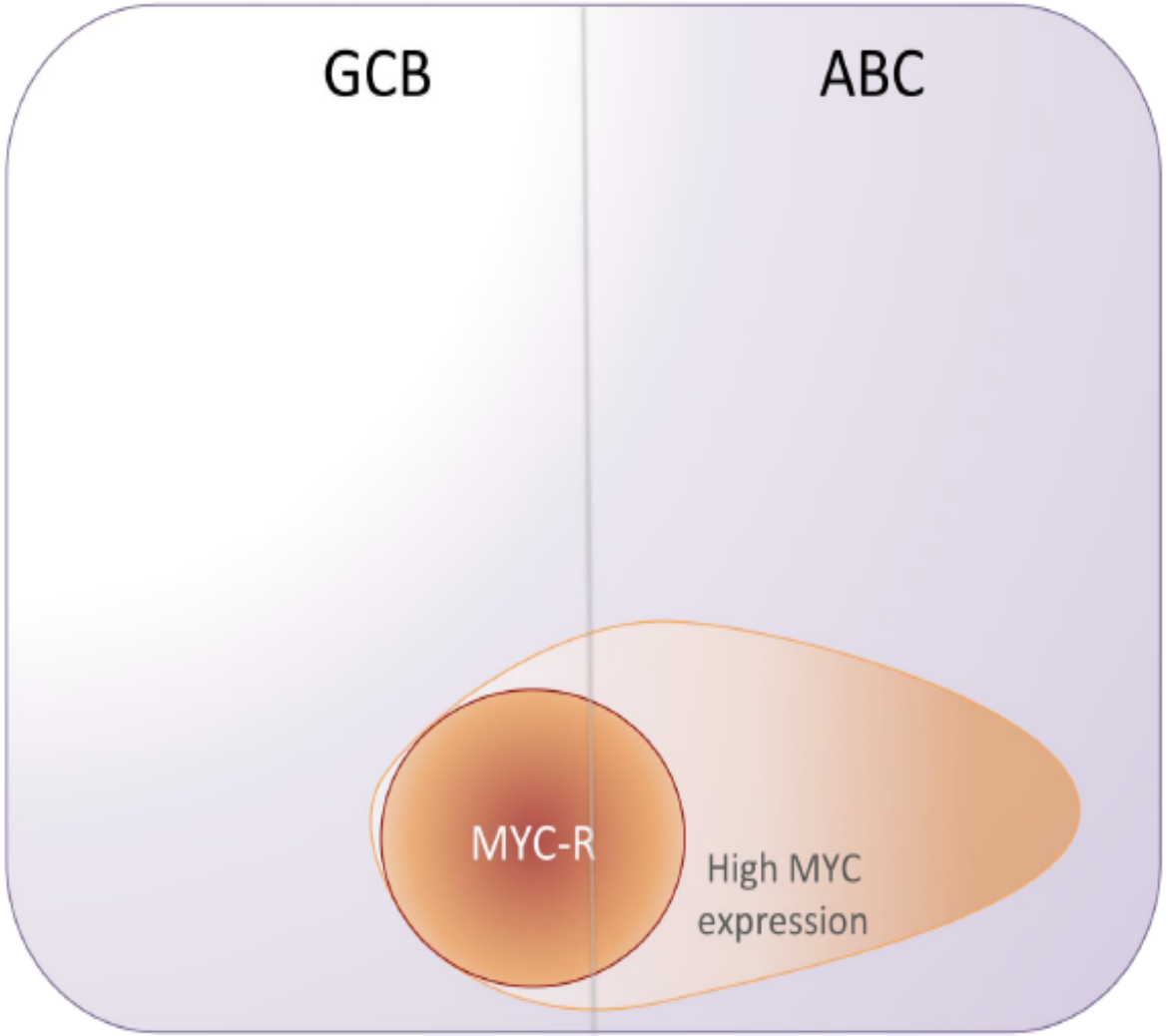
Barrans S et al. JCO 2010

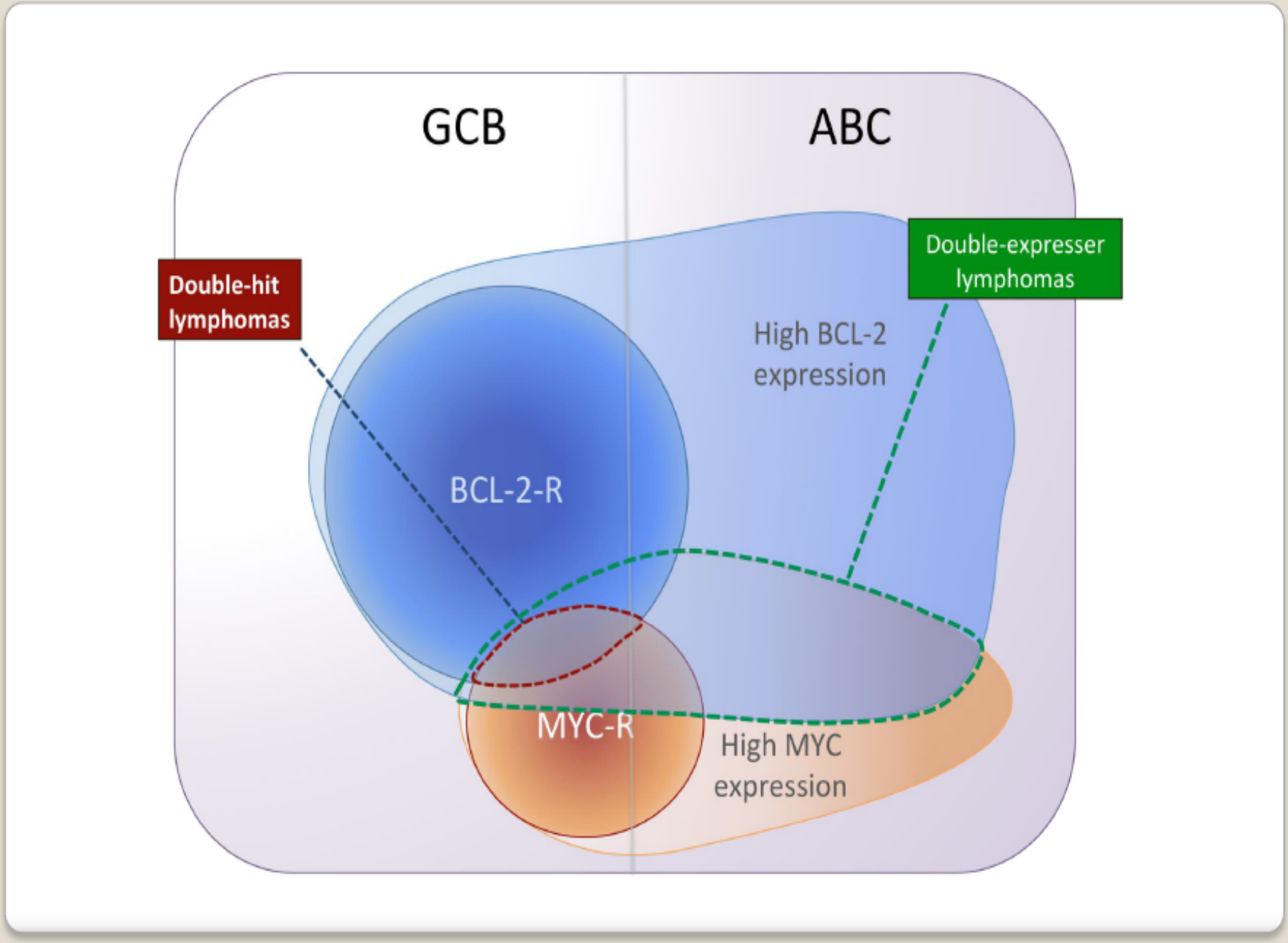

GCB
ABC
BCL-2 and MYC
Amplifications
Translocations
Malignant transformation
BCL2 translocation
Apoptosis
miR-17-92 amplification
mTOR activation
PTEN deletion
ING1 deletion
MDM2 gain or amplification
P53 mutation
Genomic instability
MYC translocation
Malignant transformation
BCL2 amplification
Apoptosis
NF-kappa B
Interleukin-6 and interleukin-10
STAT3
IRF4
19q gain or amplification
SPIB
Trisomy 3
FOXP1
Essential regulatory network
INK4A-ARF deletion
Senescence
Genomic instability
AID
Aberrant switch translocations
MYC amplification
0%
4.9%
Germinal center B-cell
Plasmablast
Plasma cell

BCL-2-Rearrangement versus Expression



MYC-Rearrangement versus Expression




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

MYC gene rearrangements are associated with a poor prognosis in DLBCL patients treated with R-CHOP

DLBCL MYC positive 12/123 (8,8%)

BC Cancer Agency
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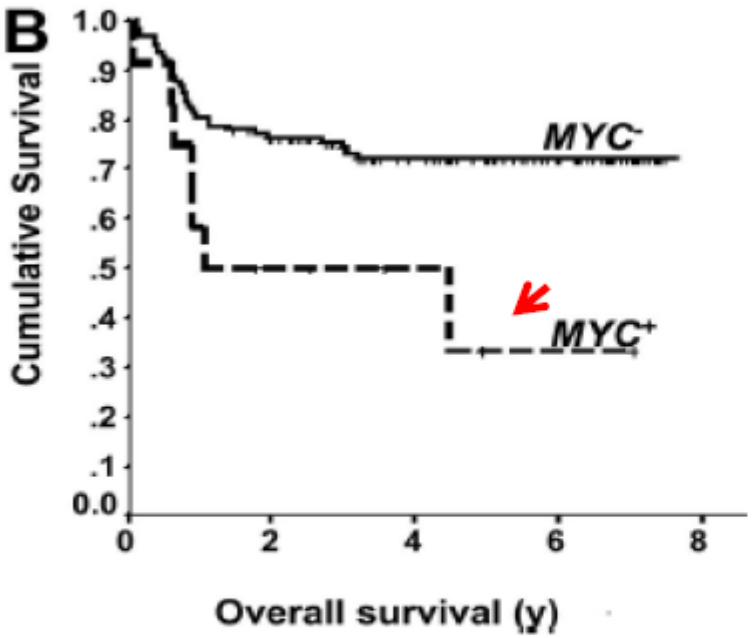
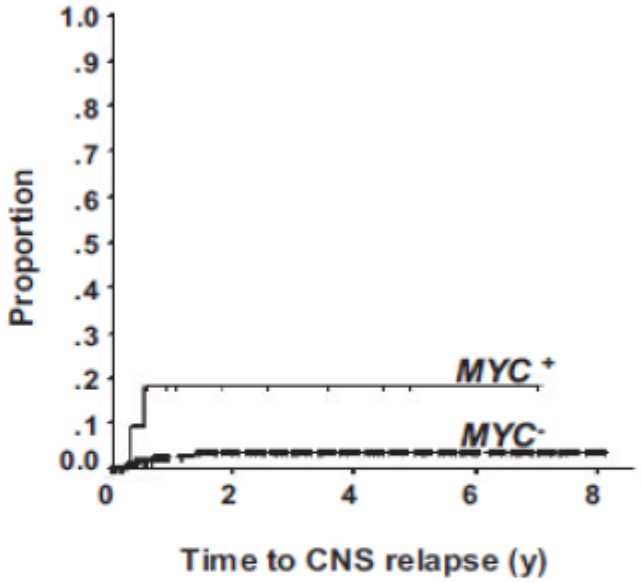
An agency of the Provincial Health Services Authority



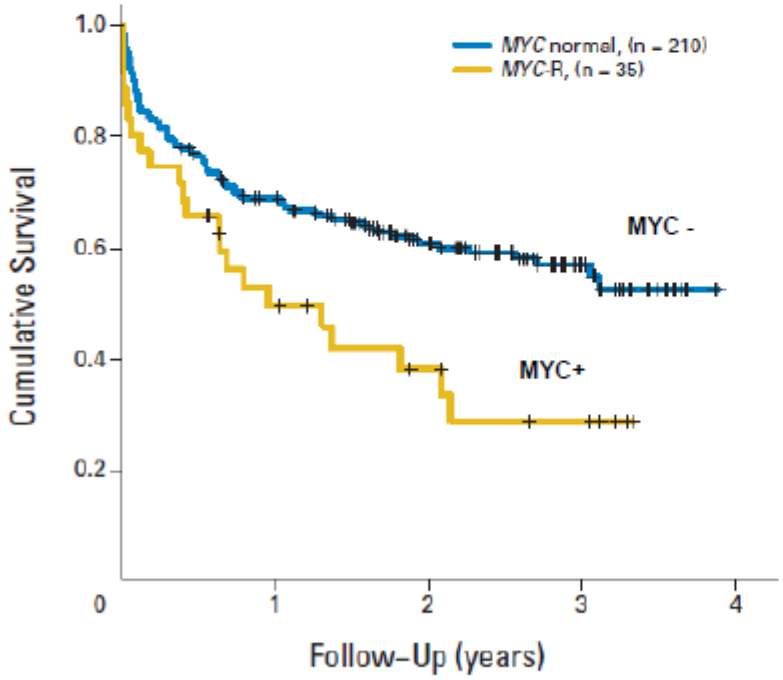


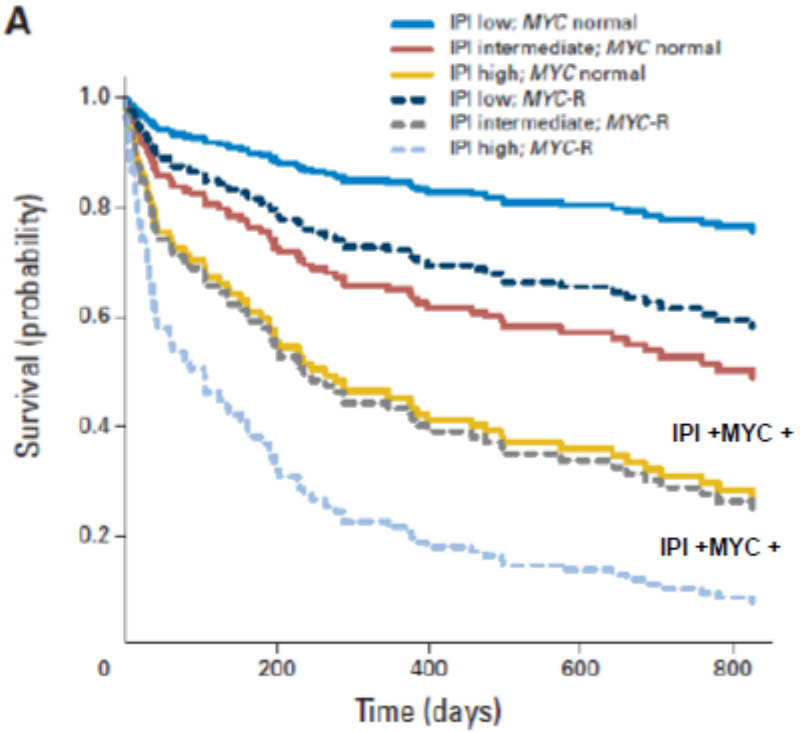
Risk factor	PFS		OS	
	Hazard ratio (CI)	*P*	Hazard ratio (CI)	*P*
MYC+	3.28 (1.49-7.21)	.003	2.98 (1.28-6.95)	.011
IPI ≥ 3	2.69 (1.48-4.86)	.001	3.29 (1.68-6.46)	.001
Non-GCB phenotype*	1.86 (1.04-3.34)	.038	—	NS
Bone marrow DLBCL+	3.74 (1.67-8.36)	.001	4.06 (1.72-9.58)	.001

Savage KJ et al. Blood 2009

Rearrangement of MYC in R-CHOP treated DLBCL

- **303 DLBCL previously untreated no follicular evidence.**
- **MYC, BCL6, t(14;18)/ BCL2 rearrangements**
- **245 evaluable, 35 (14%) MYC rearrangements of these 26 (74%) double HIT**





Barrans S. et al JCO 2010

blood
2015 126: 2466-2474
doi:10.1182/blood-2015-05-647602 originally published
online September 15, 2015

MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study

Christiane Copie-Bergman, Peggy Cuillière-Dartigues, Maryse Baia, Josette Briere, Richard Delarue, Danielle Canioni, Gilles Salles, Marie Parrens, Karim Belhadj, Bettina Fabiani, Christian Recher, Tony Petrella, Nicolas Ketterer, Frederic Peyrade, Corinne Haioun, Inga Nagel, Reiner Siebert, Fabrice Jardin, Karen Leroy, Jean-Philippe Jais, Herve Tilly, Thierry Jo Molina and Philippe Gaulard

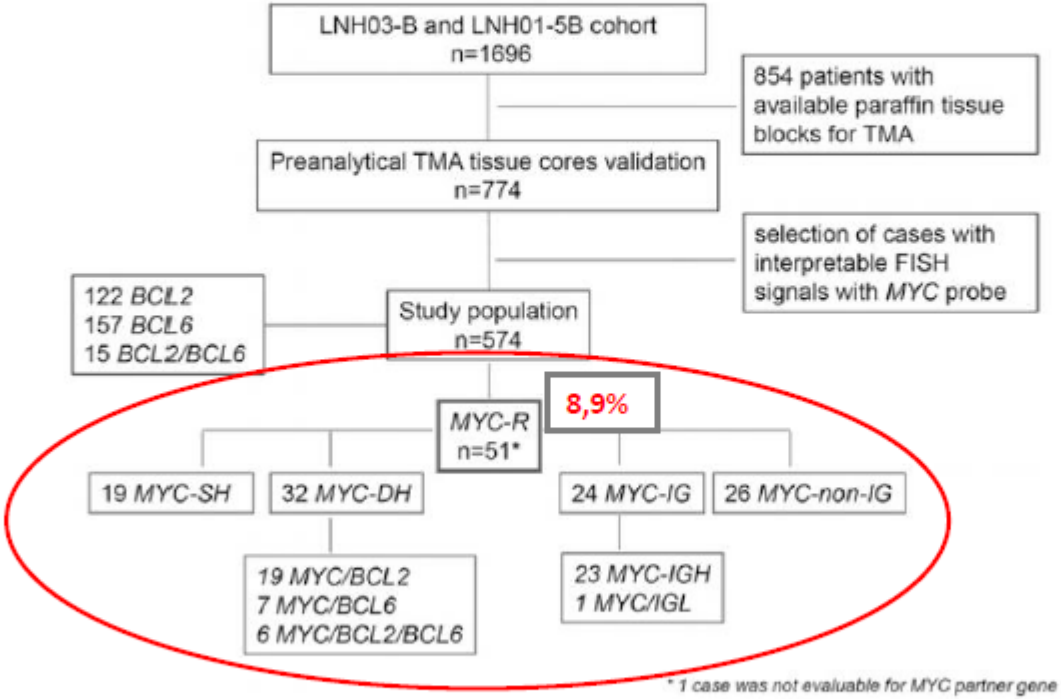


Figure 1. Flow-chart of LNH03-B and LNH01-5B cohort, case selection, and FISH results. *BCL2-R*, DLBCL with *BCL2* gene rearrangement; *BCL6-R*, DLBCL with *BCL6* gene rearrangement; *MYC-R*, DLBCL with *MYC* gene rearrangement; *MYC-IG*, *MYC* gene rearrangement with *IG* partner gene; *MYC*-non-*IG*, *MYC* gene rearrangement with non-*IG* partner gene.

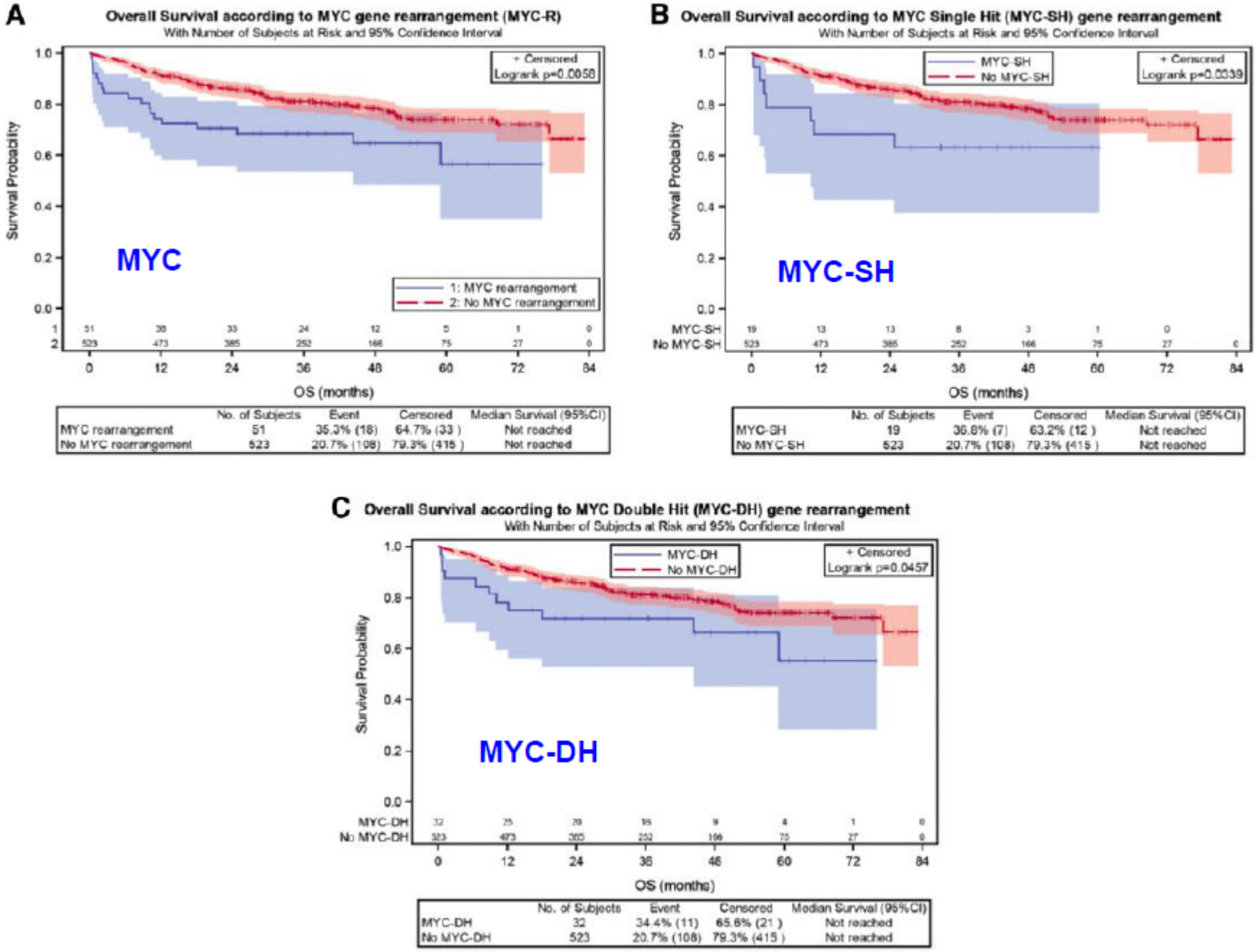
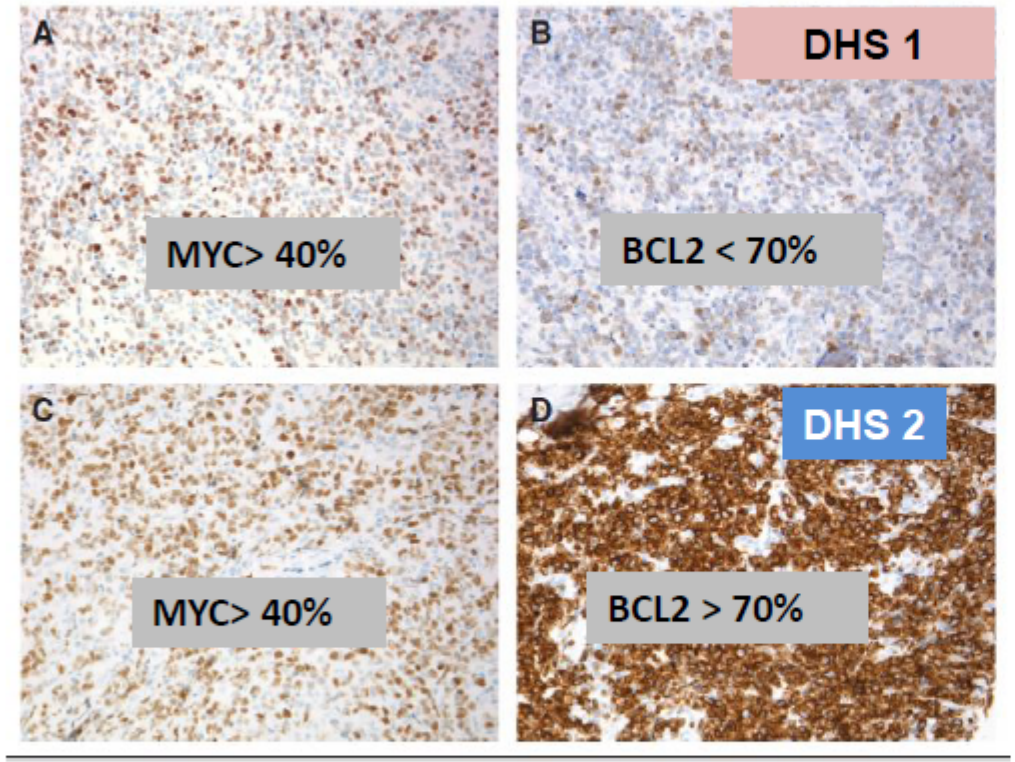


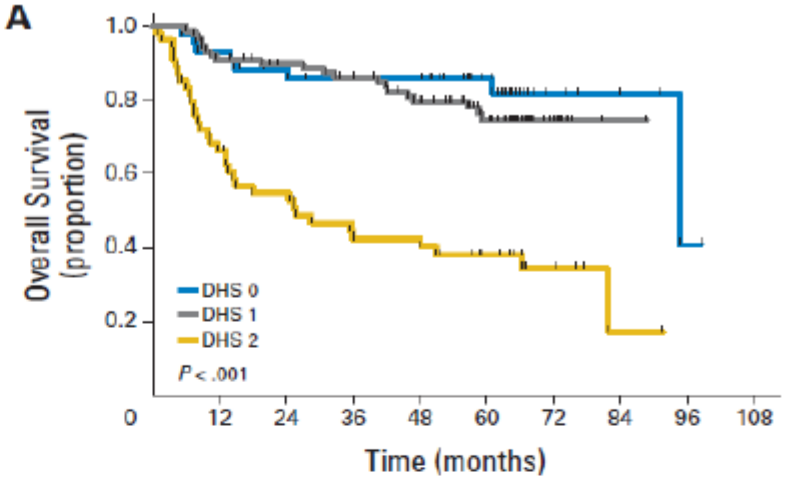
Figure 2. Univariate analysis of *MYC*-R for OS. (A) The global population, (B) SH, and (C) subgroups of DLBCL patients.

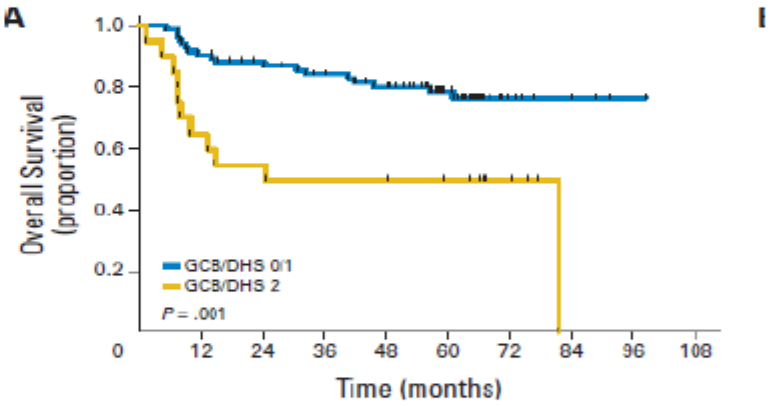
Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

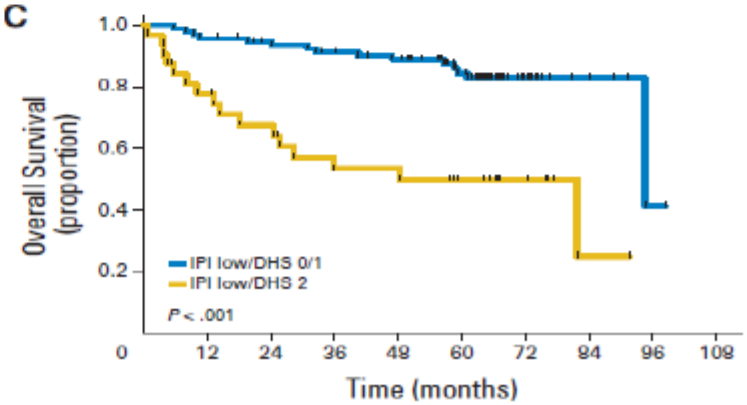
Tina Marie Green, Ken H. Young, Carlo Visco, Zijun Y. Xu-Monette, Attilio Orazi, Ronald S. Go, Ole Nielsen, Ole V. Gaidenberg, Torben Mourits-Andersen, Mikael Frederiksen, Lars Møller Pedersen, and Michael Boe Møller



DHS 2 = 29%







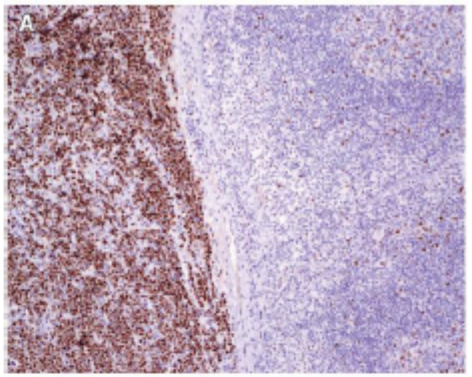
Green T.M et al JCO 2012

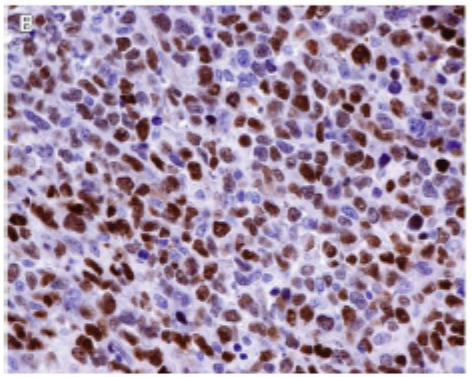
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

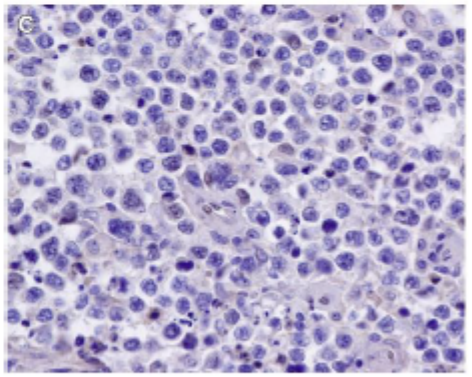
Nathalie A. Johnson, Graham W. Slack, Kerry J. Savage, Joseph M. Connors, Susana Ben-Neriah, Sanja Rogic, David W. Scott, King L. Tan, Christian Steidl, Laurie H. Sehn, Wing C. Chan, Javeed Iqbal, Paul N. Meyer, Georg Lenz, George Wright, Lisa M. Rimsza, Carlo Valentino, Patrick Brunhoeber, Thomas M.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

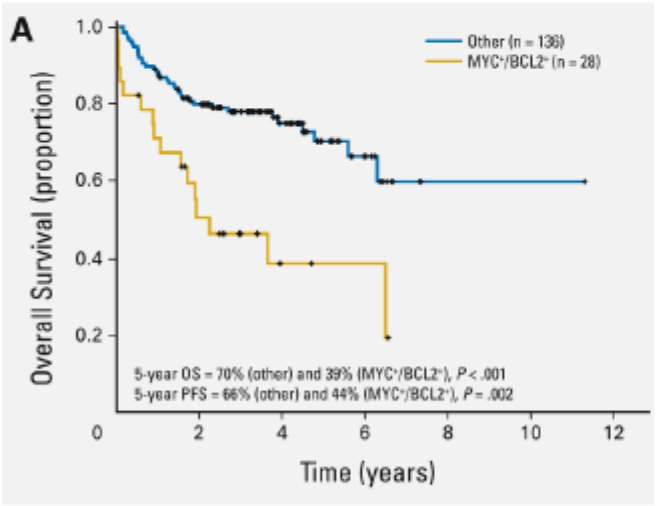
BC Cancer Agency CARE & RESEARCH

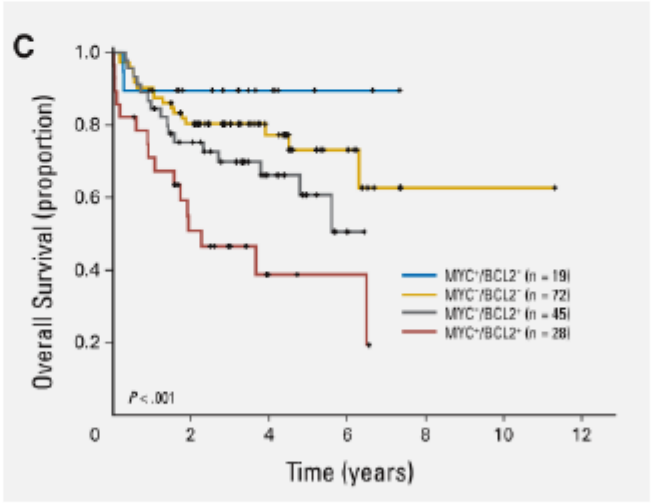
J Clin Oncol 30. © 2012







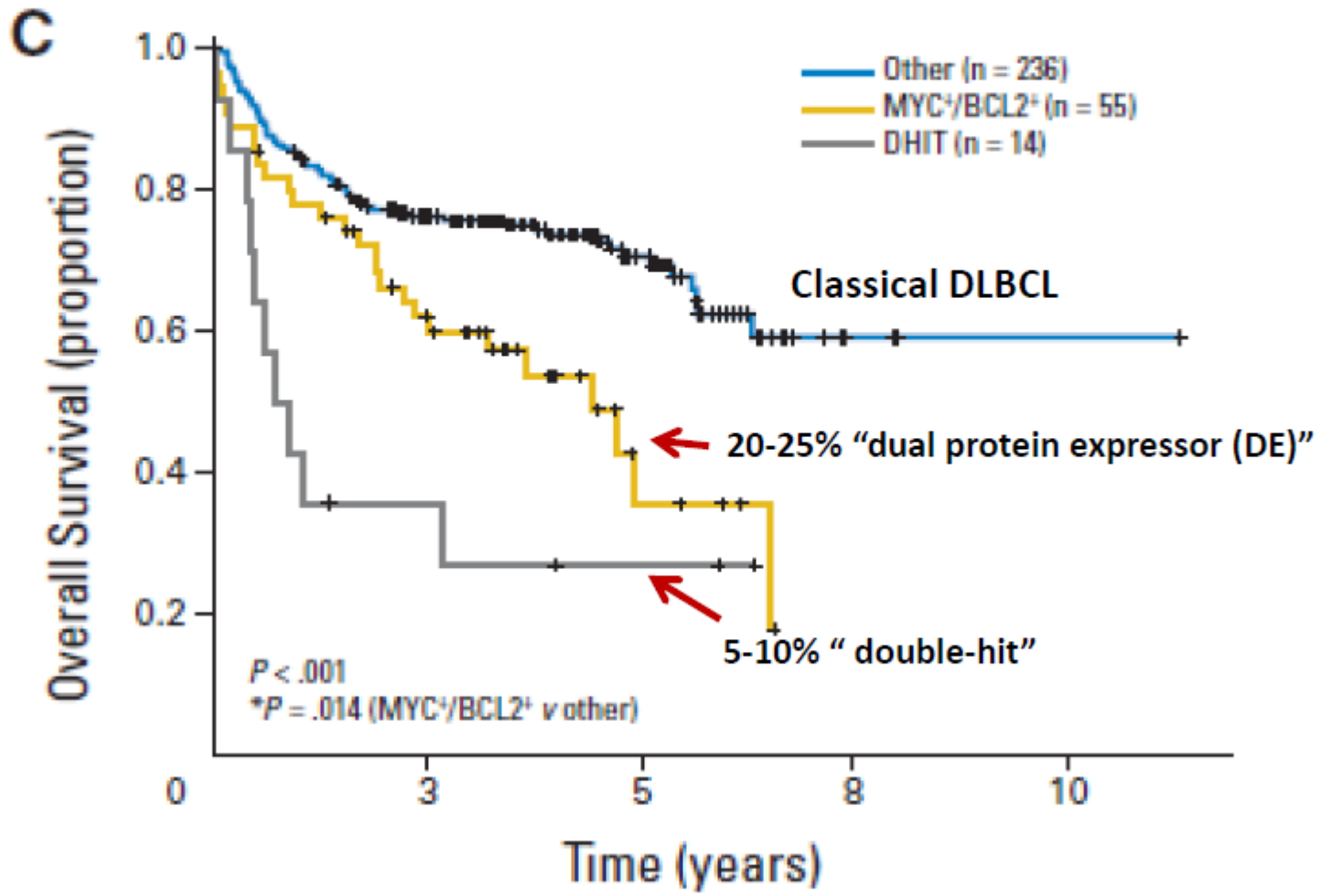




Myc+: ≥ 40% pos.
Bcl2+: ≥ 50% pos.

Johnson et al J.Clin. Oncol 2012

Overall survival of patients with DLBCL according MYC and BCL2 translocation (DHIT) or MYC and BCL2 protein expression (DE)



Johnson et al J.Clin. Oncol 2012

How can we improve the treatment of DLBCL ?

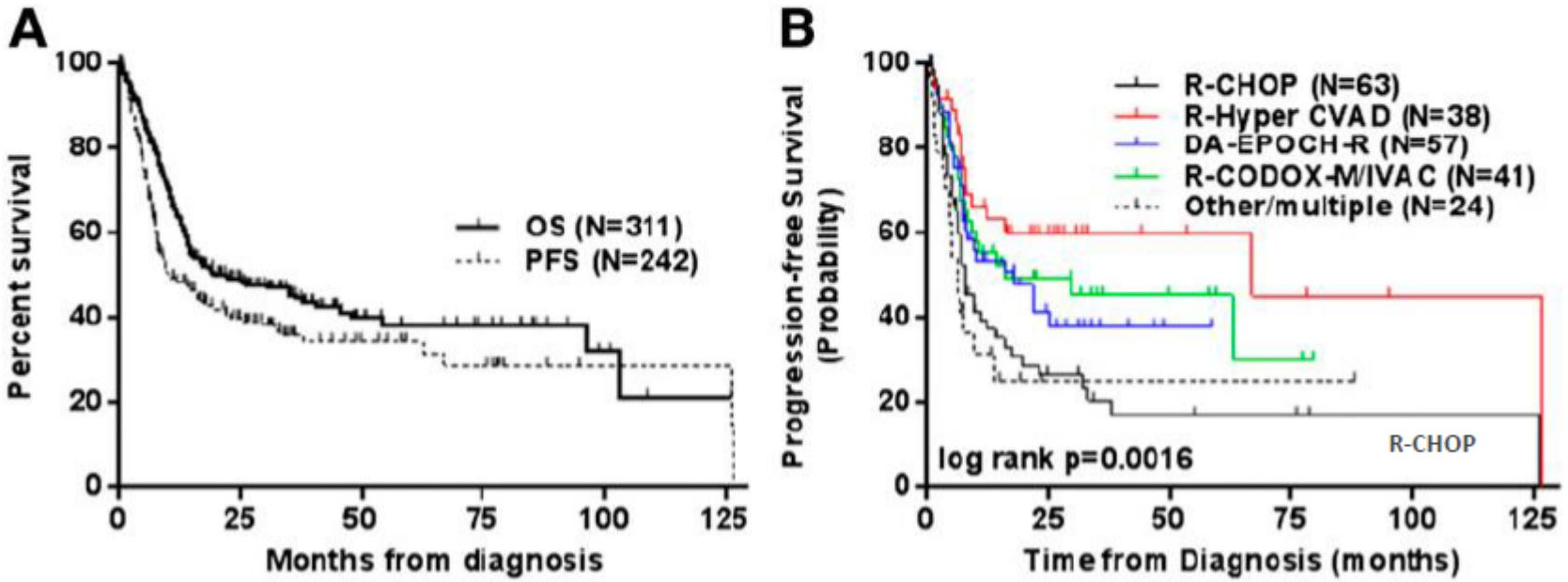
- New monoclonal antibodies combined with CHOP
- Cell of origin (COO) oriented therapy in DLBCL combining new biological drugs to conventional chemotherapy
- Hystopathological subtypes: Myc positive, double Hit (DHIT) and double Expressor (DE)
- **When should we consider an alternative to R-CHOP?**

blood 2014 124: 2354-2361

CLINICAL TRIALS AND OBSERVATIONS

Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

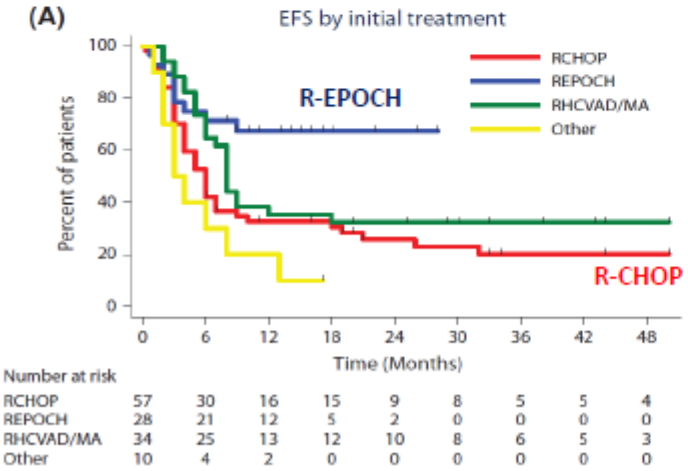
DH-DLBCL= 311 pts

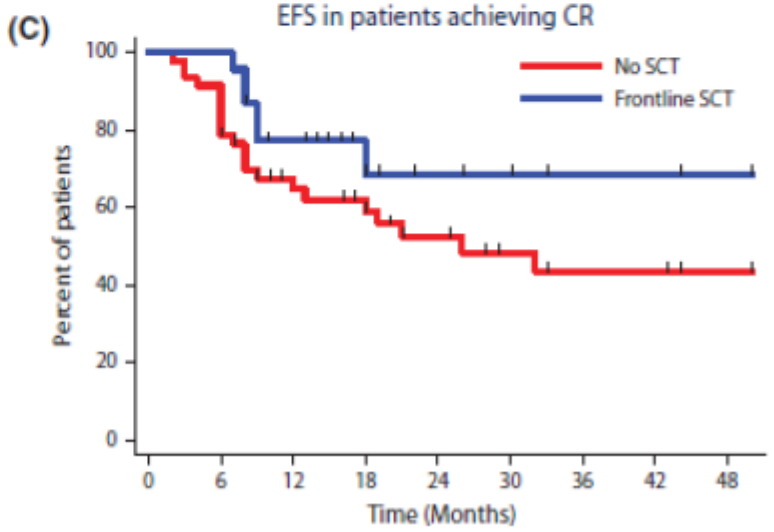


Petrich M, Gandhi M et al 2014

D-Hit DLBCL: MDACC experience

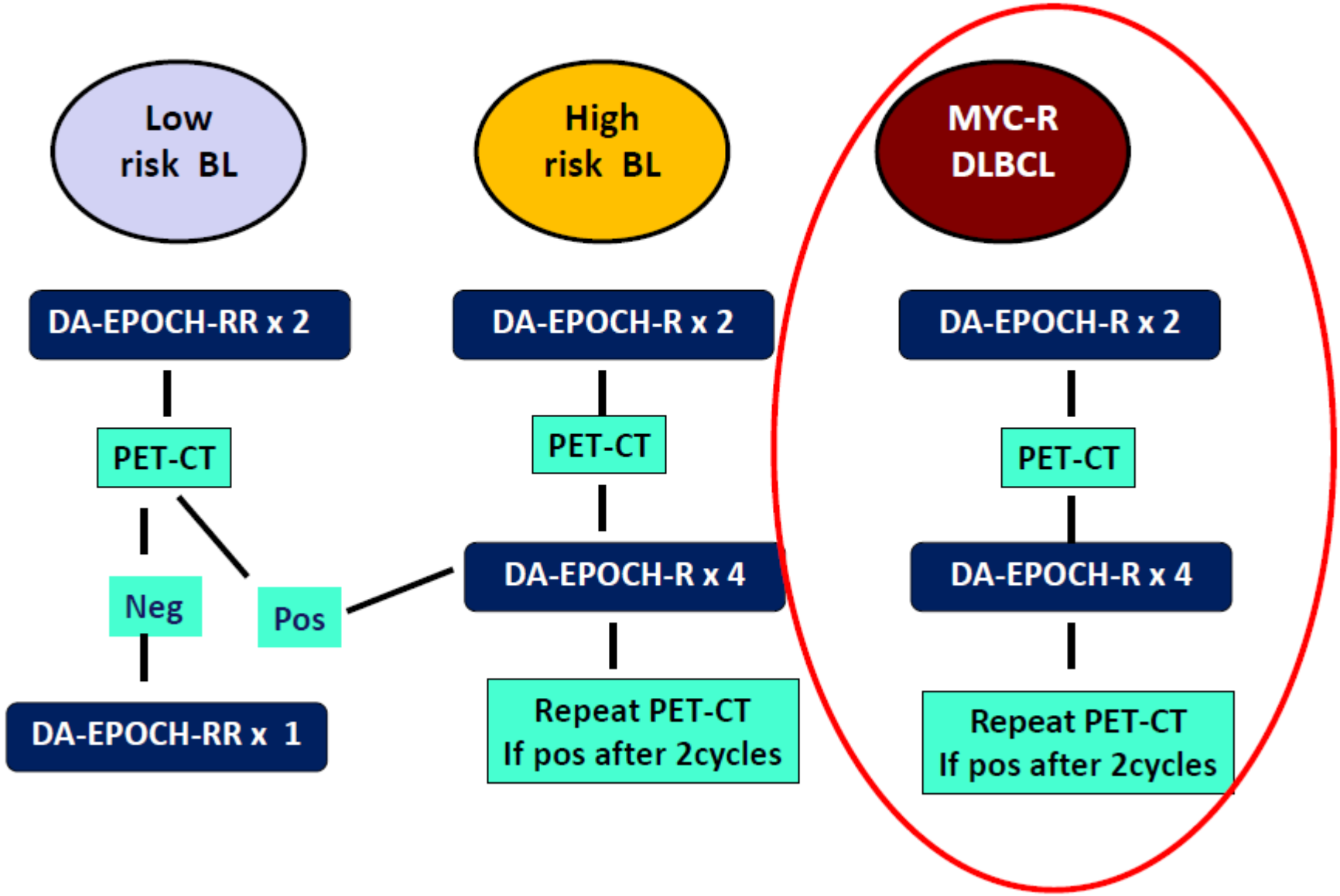
Characteristic	RCHOP n = 54	R-EPOCH n = 28	RHCVAD/MA n = 34	Other n = 10	All n = 129
CR after initial therapy (%)	23 (40)	19 (68)	23 (68,)	6 (60)	71 (55)
Frontline SCT (%)					
Any (auto+allo)	2 (4)	14 (50)	8 (24)	2 (20)	26 (20)
Allo	1 (2)	0	1 (3)	0	2 (2)





Oki et al Br. J. Hematol. 2014

Preliminary report of a multicenter phase II study of DA-EPOCH-R in MYC rearranged Aggressive B Lymphoma



Dunleavy et al ASH 2014 abs 395 (oral session)

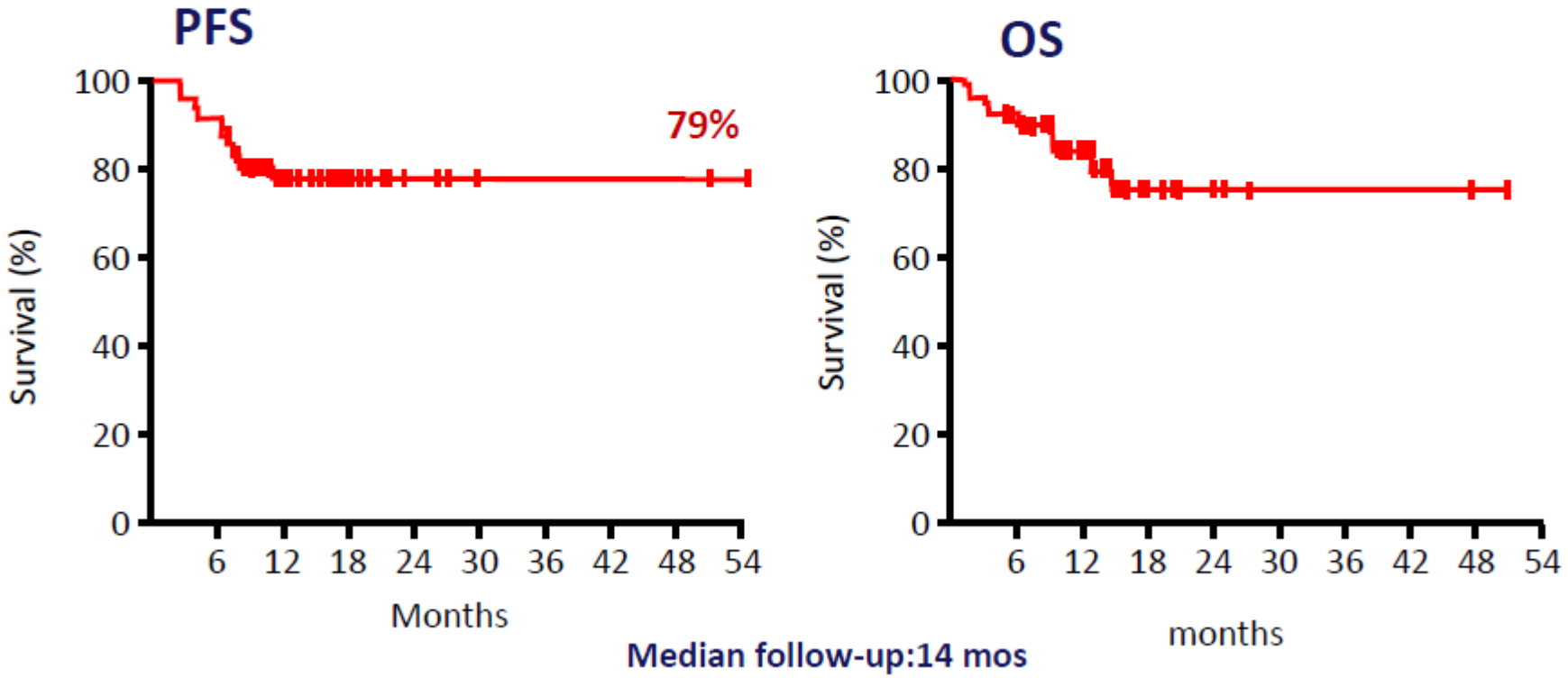
Preliminary report of a multicenter phase II study of DA-EPOCH-R in MYC rearranged Aggressive B Lymphoma

N= 52

Characteristic	n (%)
Median age y (range)	61 (29-80)
Male sex	71%
Stage III/IV	73%
Elevated LDH	53%
CNS disease	6%
IPI score 0-2 3-5	 35% 65%
Histology DLBCL BCL-U	 86% 14%
MYC by FISH	100%
BCL2 by FISH	45%
BCL2 high IHC	55%

Dunleavy et al ASH 2014 abs 395 (oral session)

DA-EPOCH-R in *MYC*-Rearranged Aggressive B-Cell Lymphoma: PFS and OS



Median follow-up:14 mos

Dunleavy et al ASH 2014 abs 395 (oral session)

The Oral Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) Demonstrates Broad and Durable Clinical Activity in Relapsed / Refractory Non Hodgkin's Lymphoma

John Kuruvilla[1], John C. Byrd[2], Joseph Flynn[2], Ramiro Garzon[2], Pierluigi Porcu[2], Nina Wagner-Johnston[3], Lynn Savoie[4], Richard Stone[5], Eric Jacobsen[5], Morten Mau-Sorensen[6], Peter de Nully Brown[6], Rachid Baz[7], Bijal Shal[7], Ian Flinn[8], Nashat Gabrail[9], Vishal Kukreti[1], Rodger Tiedemann[1], Yosef Landesman[10], Boris Klebanov[10], Eran Shacham[10], Jean-Richard Saint-Martin[10], Tracey Marshall[10], John McCartney[10], Dilara McCauley[10], Robert Carlson[10], Sasha Norori[11], Michael Savona[10], Tami Rashal[10], Mansoor R Mirza[10], Michael Kauffman[10], Sharon Shacham[10]

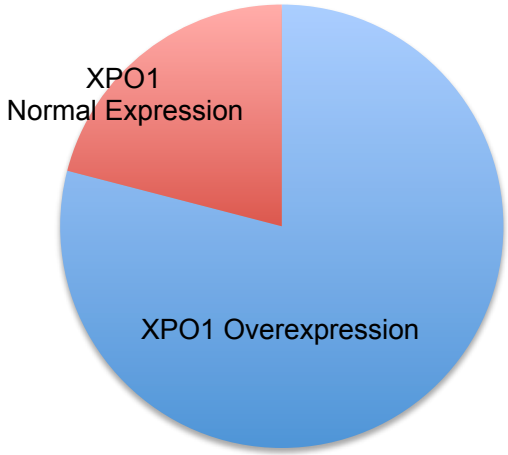
(1) Princess Margaret Cancer Center, Toronto, Canada;
(2) The Ohio State University, James Cancer Hospital, OH, USA;
(3) Washington University School of Medicine, St. Louis, MO, USA;
(4) University of Calgary Division of Hematology, Calgary, Canada
(5) Dana-Farber Cancer Institute, Boston, MA, USA;
(6) Dept. of Oncology, Rigshospitalet, Copenhagen, Denmark;
(7) H. Lee Moffitt Cancer Center & Research Institute Inc., Tampa, FL, USA;
(8) Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA;
(9) Gabrail Cancer Center, Canton, OH;
(10) Karyopharm Therapeutics Inc, Newton, MA, USA;
(11) Ozmosis Research Toronto, Ontario, Canada

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

Oral Selinexor as Novel Therapy for NHL

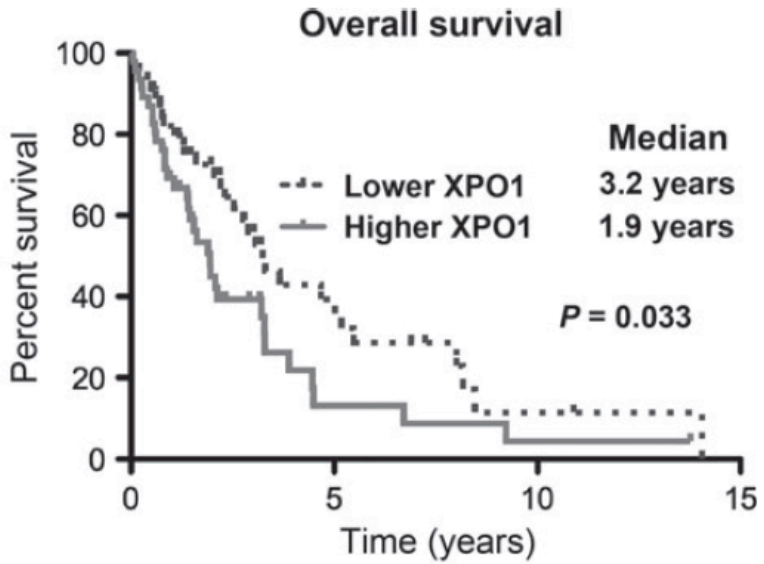
- Exportin 1 (XPO1/Crm1) is the major nuclear export protein with >200 protein and a few RNA cargos
- XPO1 is overexpressed in many hematological and solid tumor cancers and correlates with poor prognosis or resistance to chemotherapy

XPO1 overexpression in DLBCL cell lines and primary specimens
(Kuruvilla et al. (2014) EHA 19th Annual Congress)



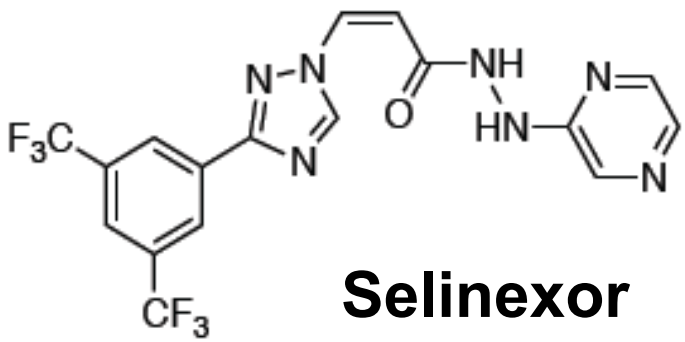
XPO1 protein expression in 62 primary DLBCL samples

Poorer prognosis in XPO1 overexpressing MCL
(Yoshimura et al. (2014) Cancer Sci 105: 795)



Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)

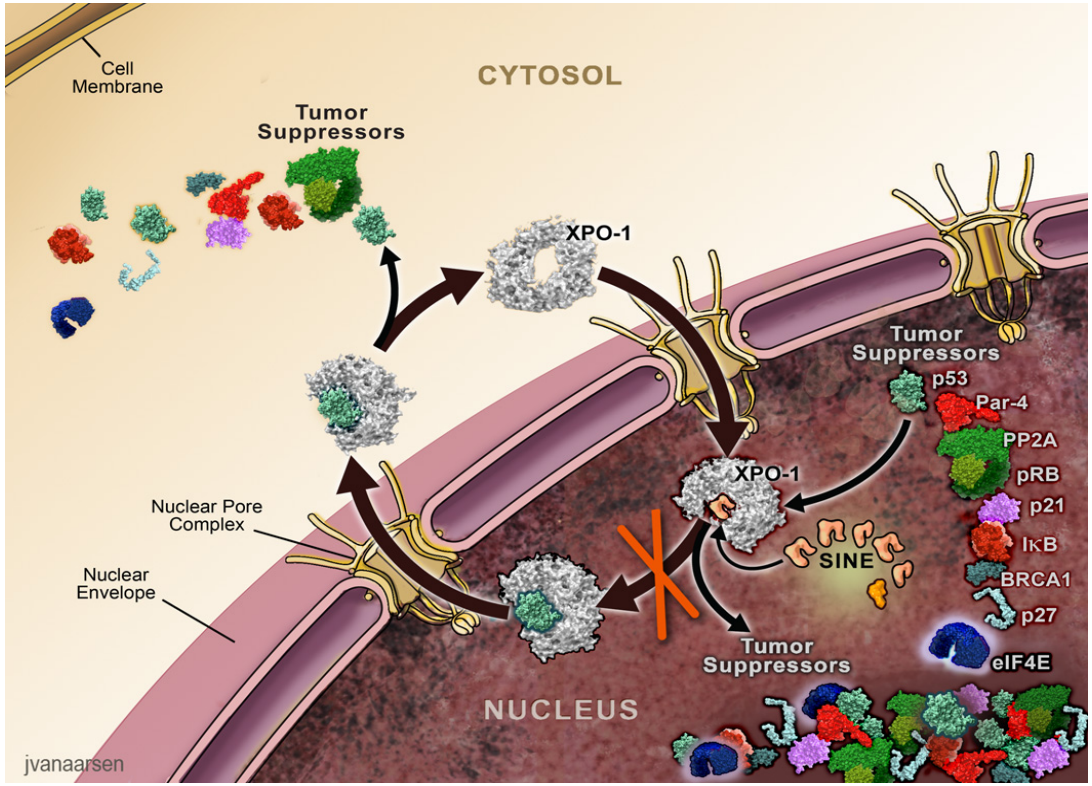
- Novel, small molecule selective inhibitor of XPO1
- Oral drug given 1x, 2x, or 3 times per week
- No known drug-drug interactions through CYP450s
- Potent anti-lymphoma effects in vitro and in vivo in NHL models
- Anti-tumor activity in ongoing Phase I and II studies in advanced hematologic and solid tumors



Selinexor

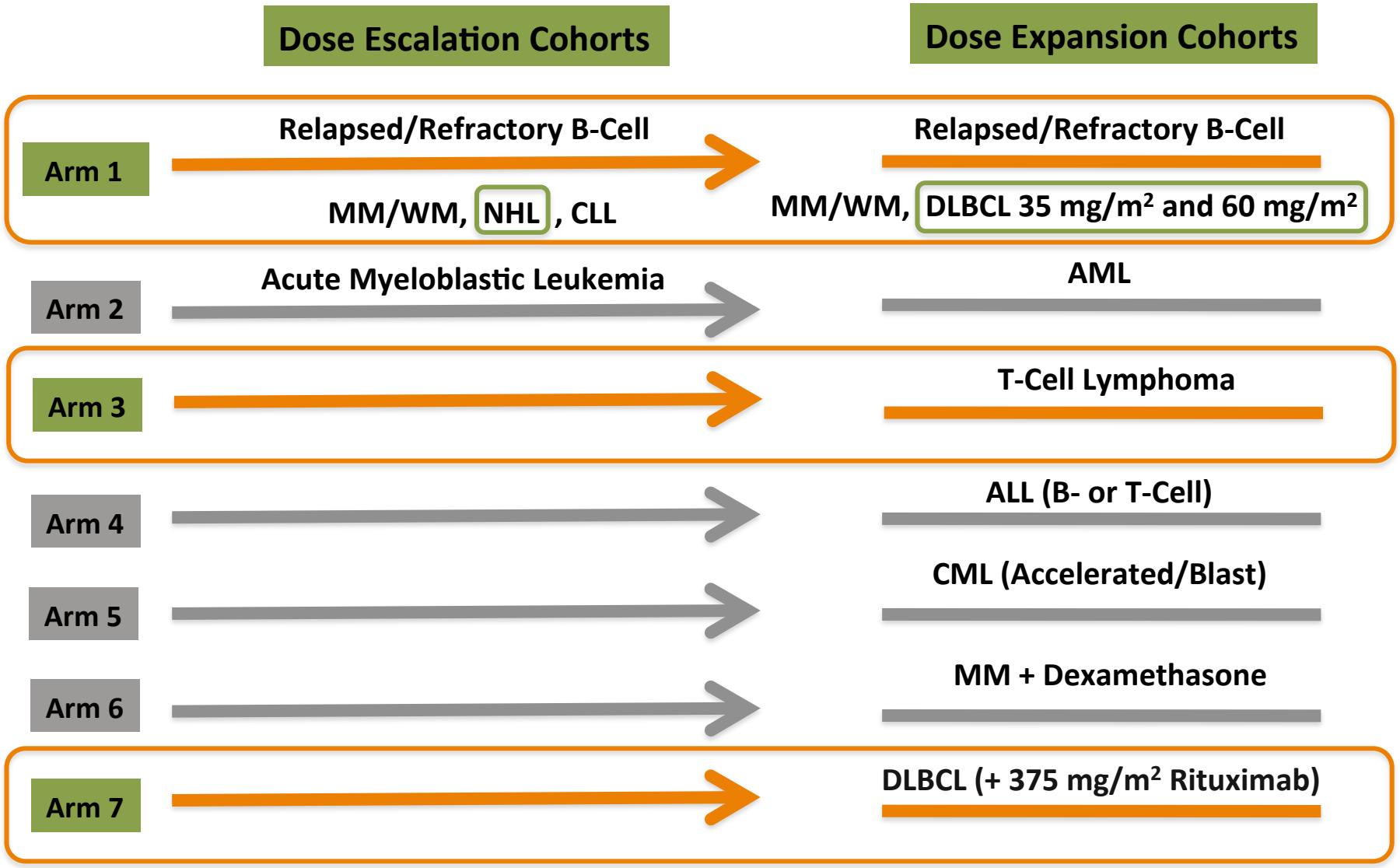
Selinexor is a Rational Therapy for NHL

- Selinexor interferes with activity of proteins known to play critical roles in NHL
  - Reduces expression of the proto-oncogene proteins c-myc, Bcl-2, Bcl-6, Mdm2, BTK, Cyclin D and survivin for which overexpression correlates with poor prognosis
  - Blocks NF-κB activation, which is required for ABC DLBCL cell survival
  - Reactivates p53, for which mutation is associated with poor prognosis



- Selinexor shows robust anti-cancer activity in multiple preclinical models of NHL, including canines with spontaneous lymphoma, largely independent of genotype

Selinexor Phase 1 Study Design (NCT01607892)



Selinexor Phase 1 Study: Patient Characteristics

Characteristics	N* = 71
Mean Age (Range)	63 (23 – 79)
Male to Female	43 : 28
Mean Prior Treatment Regimens (Range)	3 (1–12)
ECOG Performance Status (0:1:2)	24 : 45 : 02
Non Hodgkin's Lymphoma (NHL)	
-Aggressive B-Lymphoma (DLBCL, Follicular Grade 3b, Transformed)	DLBCL N=31, Trans N=11, Follicular Grade 3b N=1
-Follicular Lymphoma & Other Indolent	10 Patients
-Mantle Cell	4 Patients
-T Cell Lymphoma	5 Patients
-Burkitt's Lymphoma	1 Patient
-Richter's Transformation	8 Patients

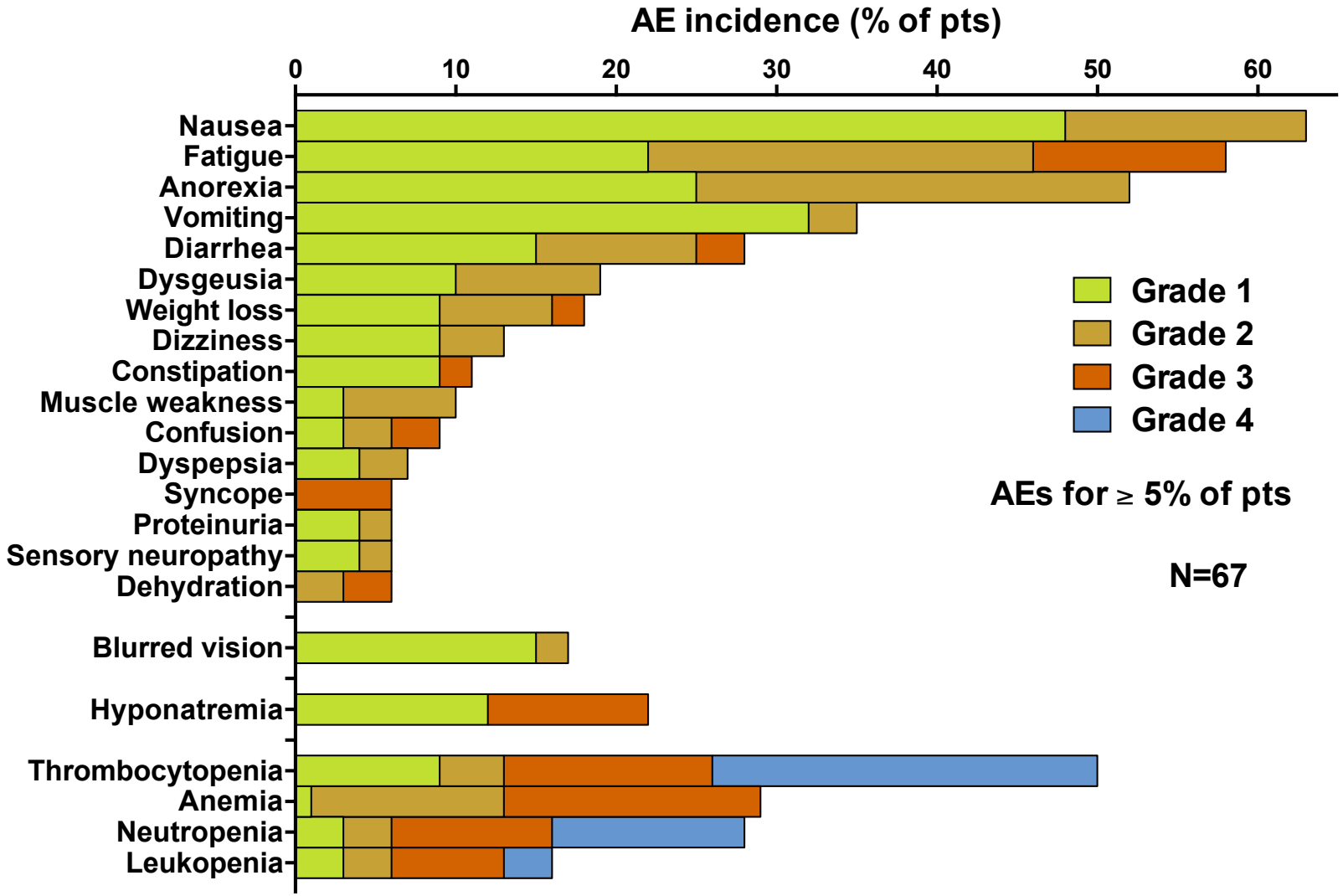
* As of 1-December-2014

Selinexor Phase 1 Study: Doses, DLT and MTD

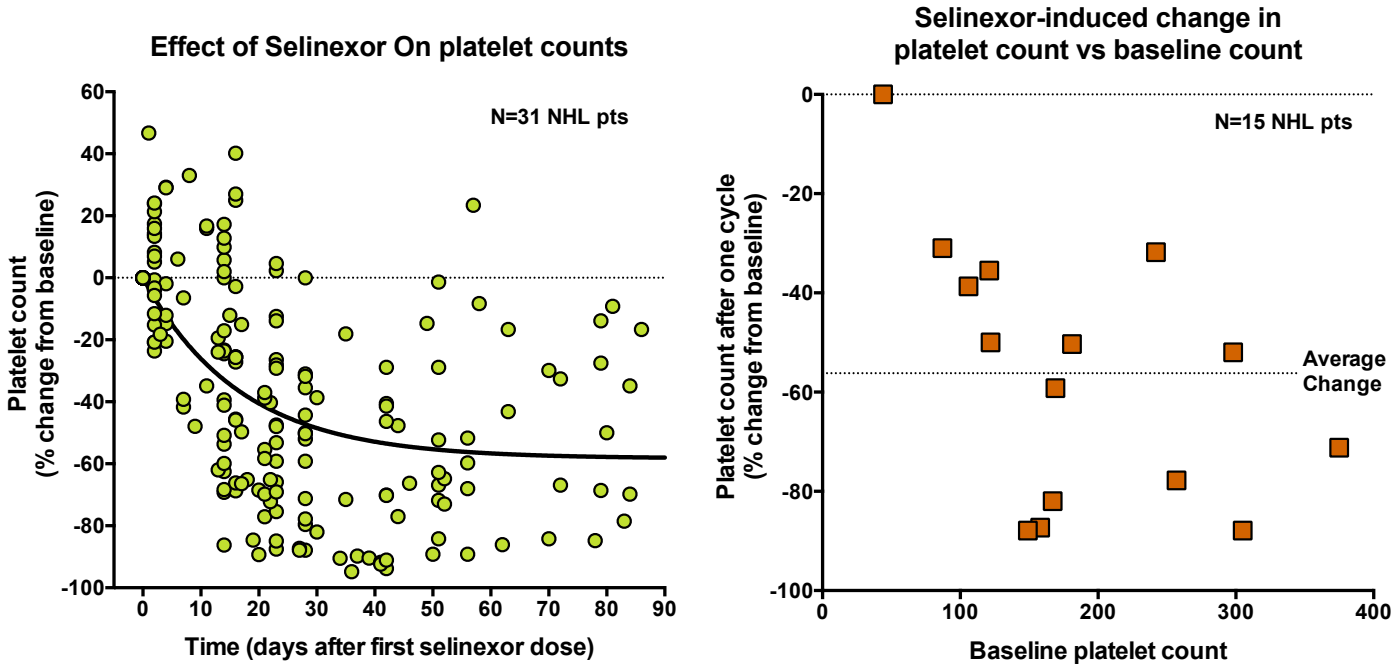
- **10 Cohorts Evaluated:**
  - Doses Ranging from 3 – 80 mg/m^2
- **3 DLTs* Have Been Seen (Only in 10 doses/cycle schedule):**
  - Dose Level: 16.8 mg/m^2; MM pt with Grade 4 thrombocytopenia
  - Dose Level: 23 mg/m^2; FL pt with Grade 4 thrombocytopenia
  - Dose Level: 30 mg/m^2; CLL pt with Grade 2 fatigue, pt missed 3 doses
- **Expansion Cohort 1**
  - 35 mg/m^2; DLBCL – MM – WM patients
- **Expansion Cohort 2**
  - 60 mg/m^2; DLBCL patients

*All patients in Arm 1 (NHL, CLL, MM and WM) were included for DLT evaluation

Selinexor Phase 1 Study: Drug Related AEs



Selinexor Phase 1 Study: Effects on Platelet Count



Data from pts maintained at a set dose from the start (3-80 mg/m^2, QOD x2-3/wk), over the period of platelet count measurement.

- Selinexor induced ~50% decrease in platelet count over the first cycle, without further significant loss over subsequent cycles
- Platelet loss is due to inhibition of megakaryocyte progenitor maturation*
- Platelet loss percentage was independent of baseline platelet count
- TPO agonist or IL-11 treatment can be effective at increasing platelet count

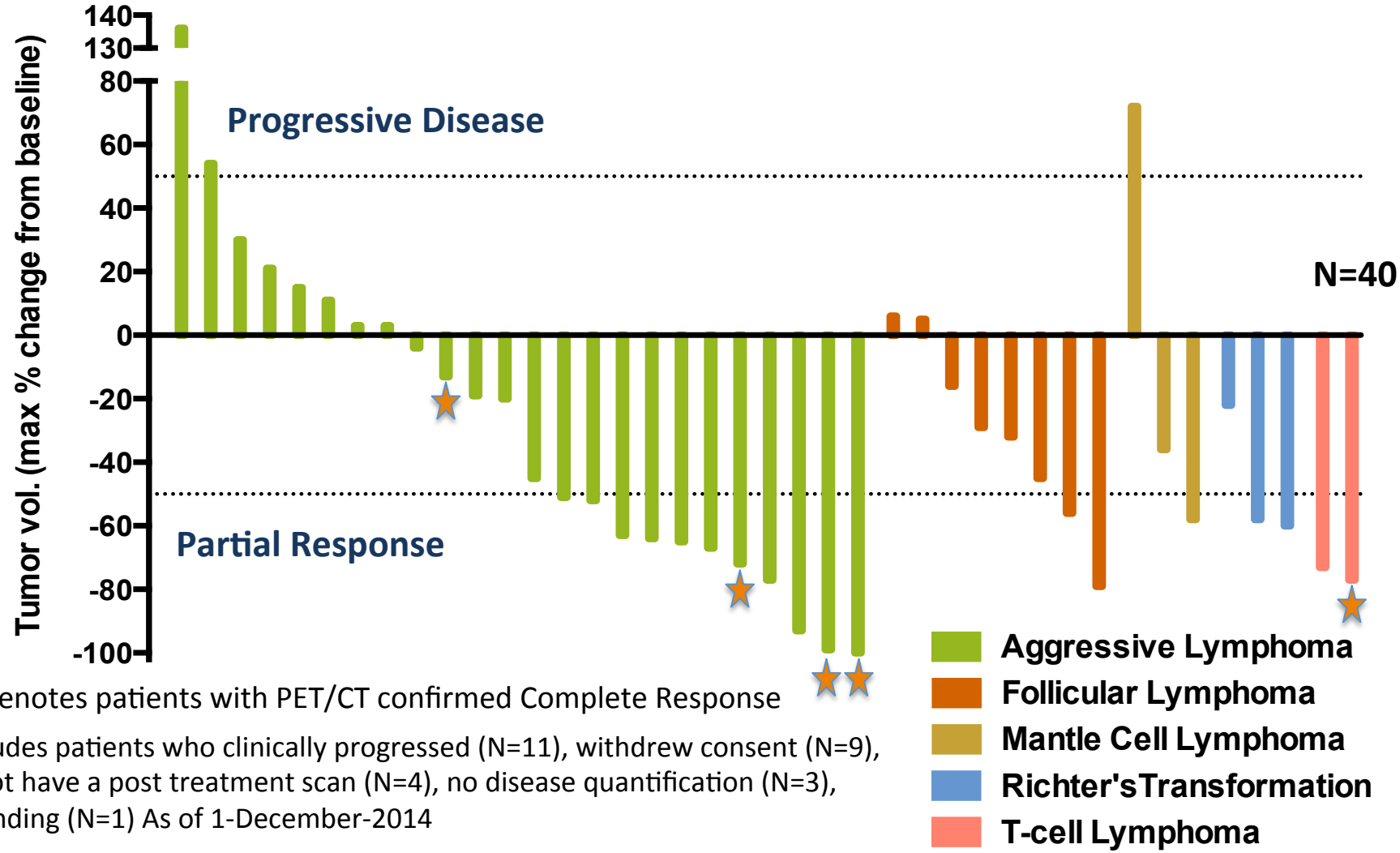
*See Poster: “Selinexor-Induced Thrombocytopenia Results from the Inhibition of Megakaryocyte …” Abstract No. 1458, ASH 2014

Selinexor Phase 1 Study: Responses in Heavily Pretreated Patients with NHL

Cancer Type	Selinexor Dose (mg/m^2)	N*	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
Aggressive B-NHL (DLBCL, FLgrd3b, Transformed)	≤ 20	4	1 (25%)	--	1 (25%)	1 (25%)	2 (50%)
	20 – 50	19	7 (37%)	4 (21%)	3 (16%)	5 (26%)	7 (37%)
	≥ 60	10	4 (40%)	--	4 (40%)	4 (40%)	2 (20%)
Follicular & Other Indolent NHL	≤ 30	4	--	--	--	4 (100%)	--
	≥ 35	4	2 (50%)	--	2 (50%)	1 (25%)	1 (25%)
Burkitt's Lymphoma	≥ 60	1	--	--	--	--	1 (100%)
Mantle Cell Lymphoma	≤ 30	2	1 (50%)	--	1 (50%)	1 (50%)	--
	≥ 35	1	--	--	--	--	1 (100%)
T-Cell Lymphoma	≤ 30	2	1 (50%)	--	1 (50%)	1 (50%)	--
	≥ 35	1	1 (100%)	1 (100%)	--	--	--
Richter's Transformation	≤ 30	3	1 (33%)	--	1 (33%)	2 (67%)	--
	≥ 35	1	1 (100%)	--	1 (100%)	--	--
TOTAL		52	19 (37%)	5 (10%)	14 (27%)	19 (37%)	14 (27%)

ORR=Overall Response Rate, CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease
1 patient is pending response; 15 patients were not evaluable for response (Responses as of 1-December-2014)

Selinexor Phase 1 Study: Evaluable Patients*
Maximal % Change in Lymph Node from Baseline



★ Denotes patients with PET/CT confirmed Complete Response

*Excludes patients who clinically progressed (N=11), withdrew consent (N=9), did not have a post treatment scan (N=4), no disease quantification (N=3), or pending (N=1) As of 1-December-2014

Selinexor Phase 1 Study: Responses Across Subtypes of Relapsed / Refractory DLBCL

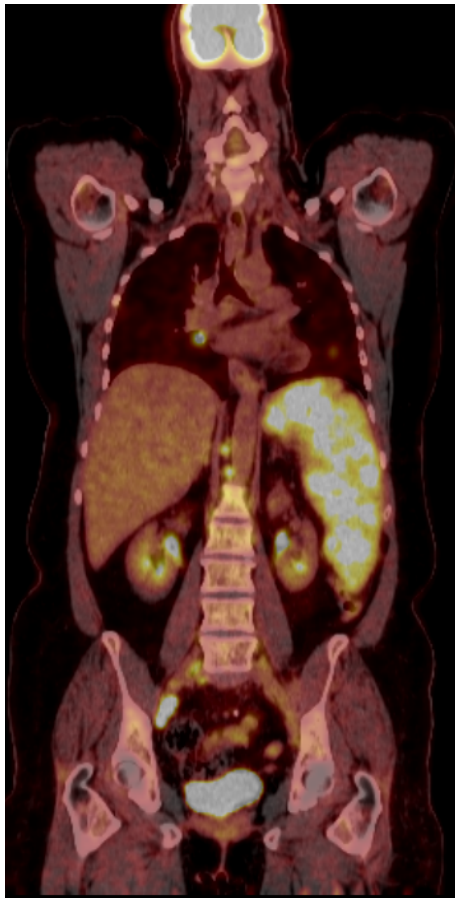
Responses in Diffuse Large B-Cell Patients as of 1-December-2014							
Type	**N**	**DCR (%)**	**ORR (%)**	**CR (%)**	**PR (%)**	**SD (%)**	**PD (%)**
GCB	11	9 (82%)	4 (36%)	1 (9%)	3 (27%)	5 (45%)	2 (18%)
Non GCB	5	4 (80%)	2 (40%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)

Subtyping was available for 16 evaluable patients

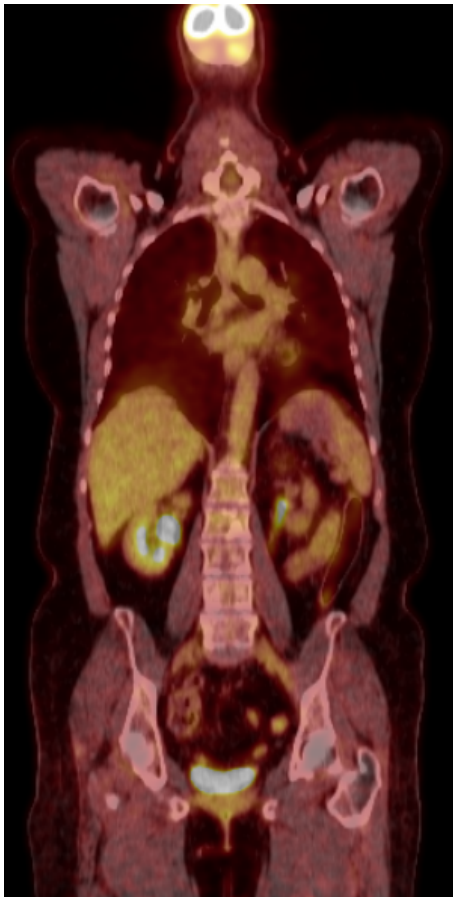
Patients with "Double Hit" DLBCL as of 1-December-2014				
Patient ID	**Best Response**	**% Reduction in Lymph Nodes**	**Days on Study**	**Prior Therapies**
046	**CR**	73% (PET Negative)	429+	**CHOP-R, RICE**
058	**PD**	--	57	**CHOP-R, RICE**
072	**PR**	-65%	214	**R-CHOP, Benda, RICE, DHAP-R, BEAM**
086	**SD**	-45%	104	**CHOP-R, GDP, Ibrutinib +Lenalidomide**

DCR=Disease Control Rate (CR+PR+SD), ORR=Overall Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease (+ patient remains on study)

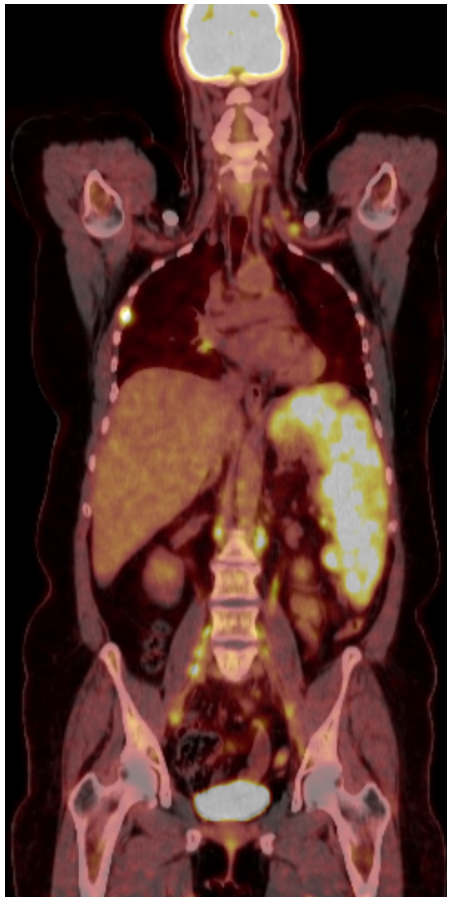
Rel/Ref DLBCL 040-050: PET Confirmed Complete Response



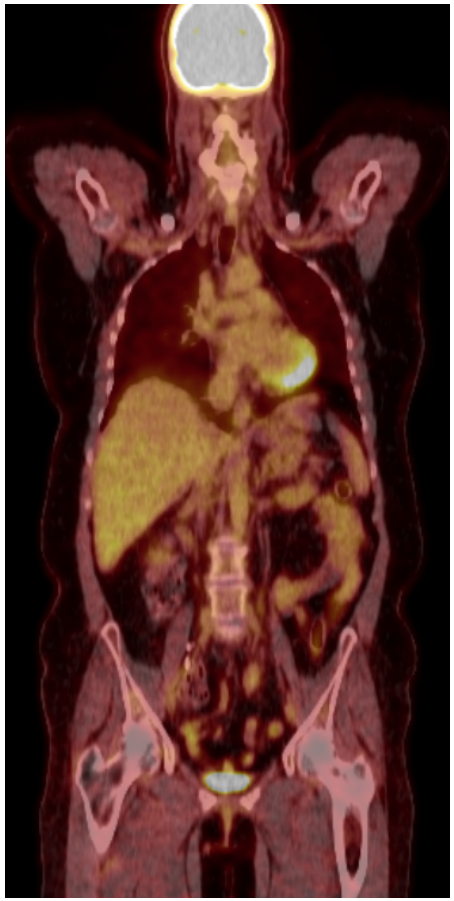
Baseline



Cycle 14



Baseline



Cycle 14