La terapia dei Linfomi DLBCL può cambiare nei diversi sottotipi della nuova WHO?

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Disclosures, Annalisa Chiappella

Research Support/P.I.	N/A
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Consultant	N/A
Major Stockholder	N/A
Conferences/Educational Activities	Amgen, Celgene, Janssen, Nanostring, Pfizer, Roche, Teva
Scientific Advisory Board	Celgene

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

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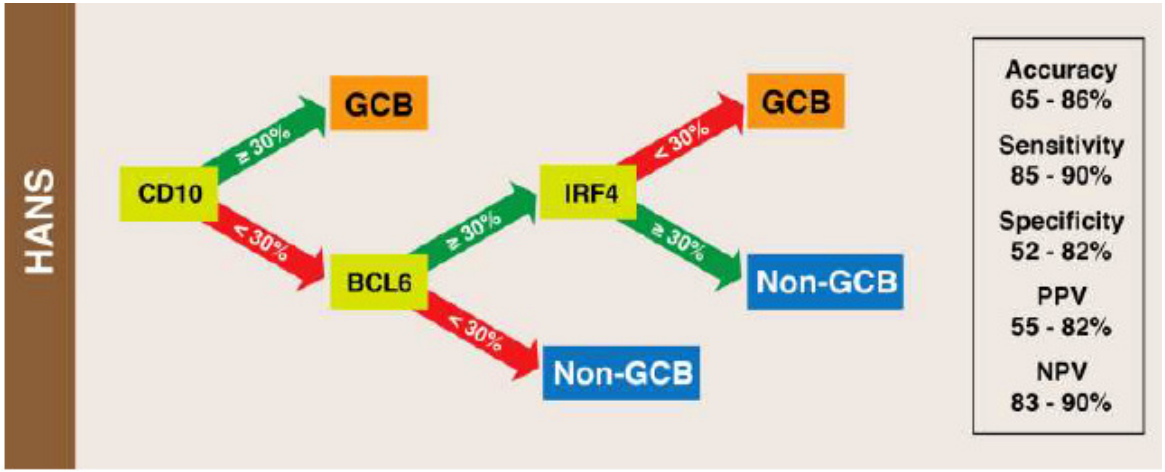
Table 2. Highlights of changes in 2016 WHO classification of lymphoid, histiocytic, and dendritic neoplasms

Diffuse large B-cell lymphoma, NOS	• Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy. • Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma). • Mutational landscape better understood but clinical impact remains to be determined.
EBV$^+$ DLBCL, NOS	• This term replaces EBV$^+$ DLBCL of the elderly because it may occur in younger patients. • Does not include EBV$^+$ B-cell lymphomas that can be given a more specific diagnosis.
EBV$^+$ mucocutaneous ulcer	• Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence.
Burkitt lymphoma	• *TCF3* or *ID3* mutations in up to ~70% of cases.
Burkitt-like lymphoma with 11q aberration	• New provisional entity that closely resembles Burkitt lymphoma but lacks *MYC* rearrangement and has some other distinctive features.
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations	• New category for all "double-/triple-hit" lymphomas other than FL or lymphoblastic lymphomas.
High-grade B-cell lymphoma, NOS	• Together with the new category for the "double-/triple-hit" lymphomas, replaces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU). • Includes blastoid-appearing large B-cell lymphomas and cases lacking *MYC* and *BCL2* or *BCL6* translocations that would formerly have been called BCLU.

DLBCL: GCB vs ABC/non-GCB: IHC

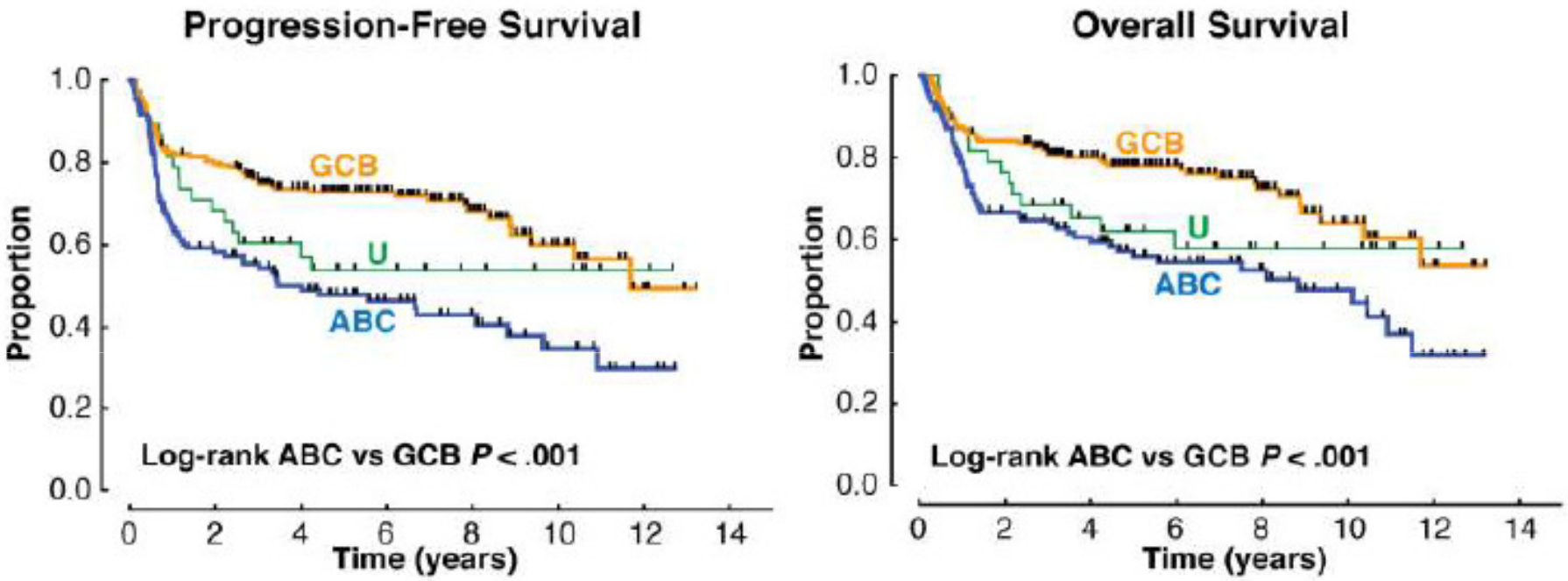


- ✓ Do not capture the concept of unclassified;
- ✓ impact of inter-laboratory variability

	GCB	Non-GCB/ABC
HANS	38%	62%
CHOI	45%	55%
VISCO-YOUNG	37%	63%
TALLY	21%	78%

Courtesy of David Scott

DLBCL: GCB vs ABC/non-GCB: Nanostring

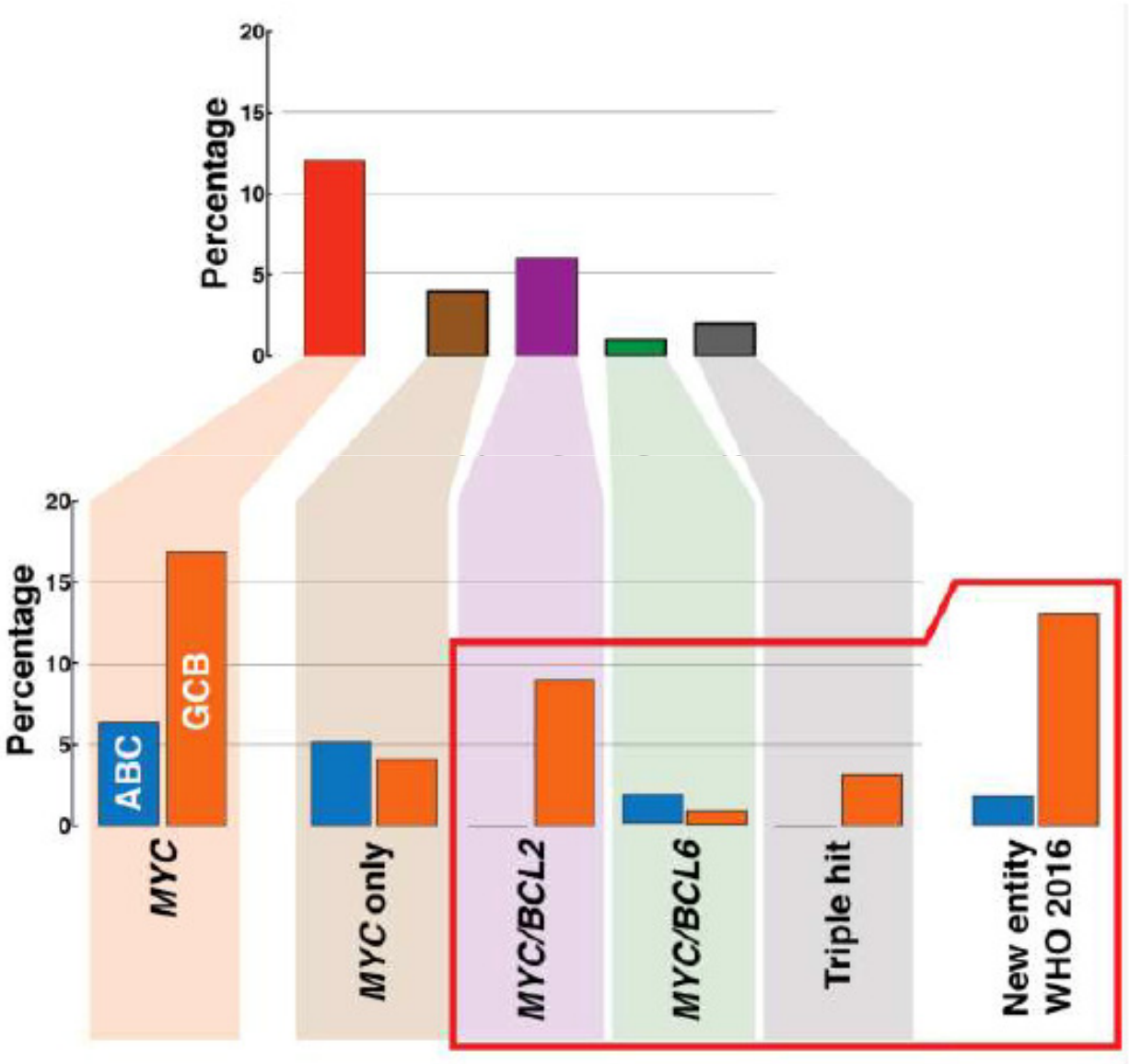


Lymph2Cx applied to biopsies from 339 patients with *de novo* DLBCL (BCCA)
Uniformly treated with R-CHOP

1% assay failure rate

Scott D et al, Blood 2014; Scott D et al, J Clin Oncol 2015.

Recurrent translocations in DLBCL: the new WHO 2016 entities



Courtesy of David Scott

DLBCL: the new WHO 2016 entities

How I treat?

✓GCB vs ABC/non-GCB
✓High grade B-cell lymphoma

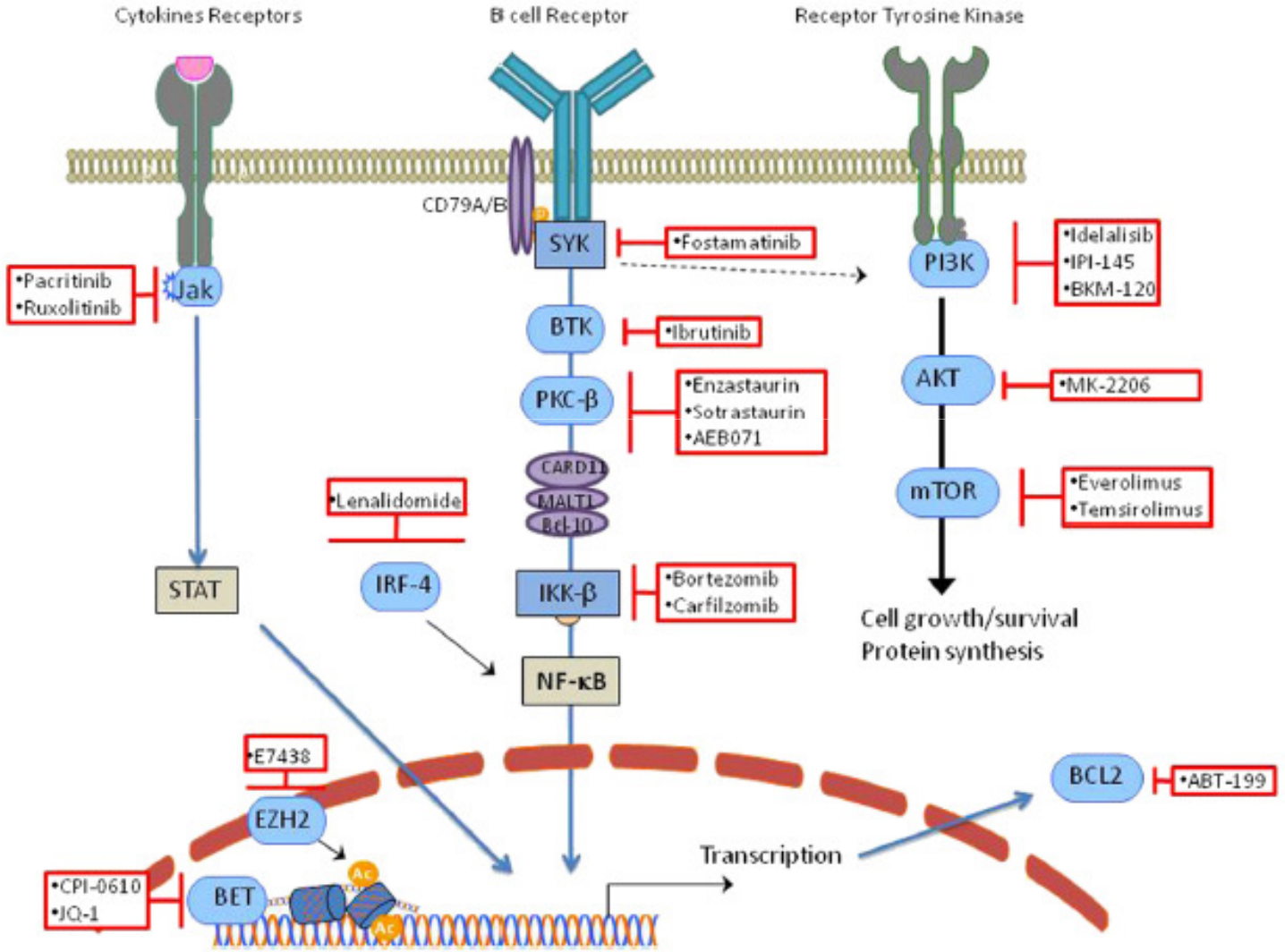
DLBCL: the new WHO 2016 entities

How I treat?

✓GCB vs ABC/non-GCB

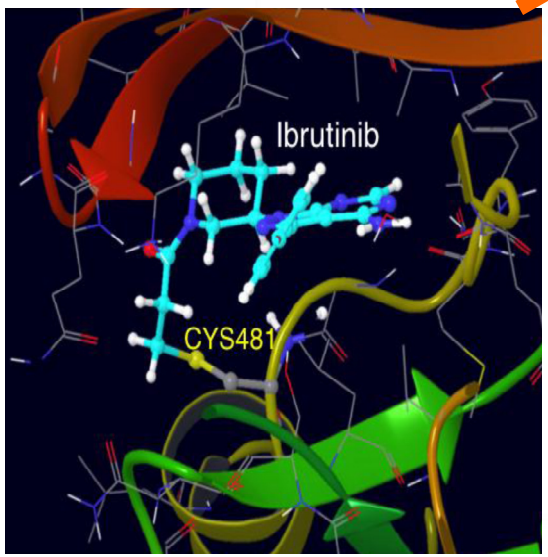
✓High grade B-cell lymphoma

Pathways Targeted By Treatments in ABC and GCB DLBCL



Mehta-Shah et Younes, Semin Hematol 2015.

Targeting B-Cell Receptor Signaling Through Inhibition of Bruton Tyrosine Kinase (BTK)



Daily oral dosing produces 24-hour BTK inhibiton

It blocks NF-κB

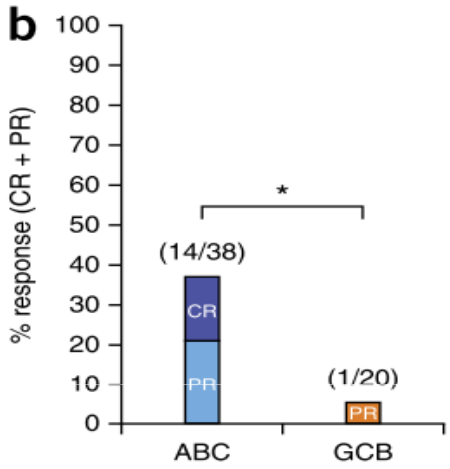
inhibition of proliferation
adhesion disruption
apoptosis

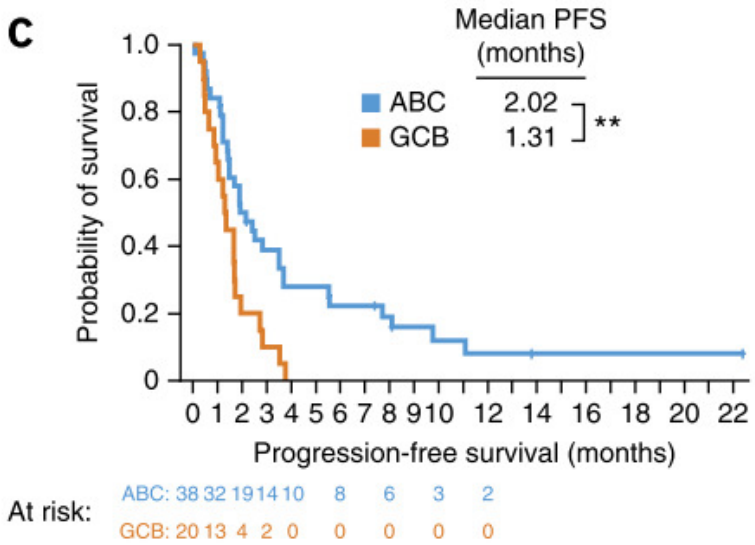
Ibrutinib in DLBCL, by COO subgroups

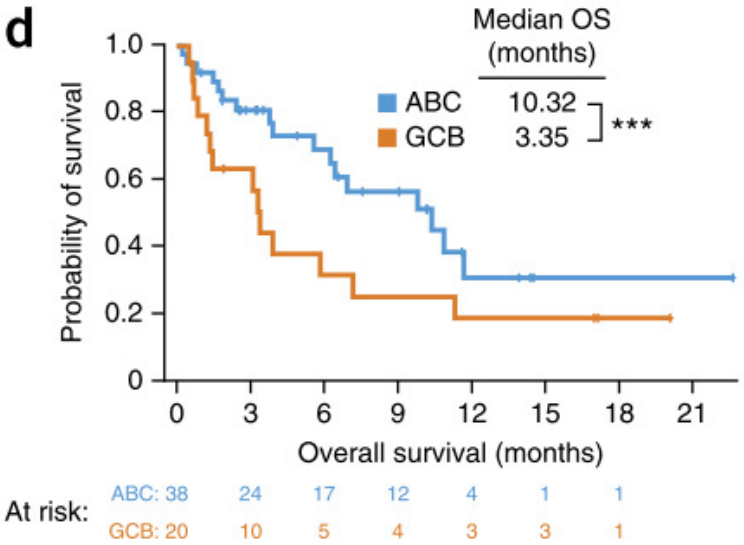
The Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib (PCI-32765) has a preferential activity in ABC DLBCL: phase II interim results

Table 1 Baseline characteristics by DLBCL subtype

Characteristics	ABC (*N* = 38)	GCB (*N* = 20)	Unclassified (*N* = 17)	Unknown (*N* = 5)
Median age, years (range)	60 (34–89)	65 (28–92)	63 (44–85)	65 (58–78)
Sex (male)	66%	70%	82%	60%
ECOG performance score ≥ 2	5%	20%	24%	40%
RIPI (poor)	63%	59%	50%	60%
Median time from diagnosis, months (range)	19 (4–118)	17 (11–104)	21 (7–332)	19 (9–57)
Median number of prior regimens (range)	3 (1–7)	3.5 (1–7)	3 (1–4)	3 (1–3)
Prior ASCT	13%	30%	24%	40%
Chemotherapy-refractory disease	66%	65%	59%	50%



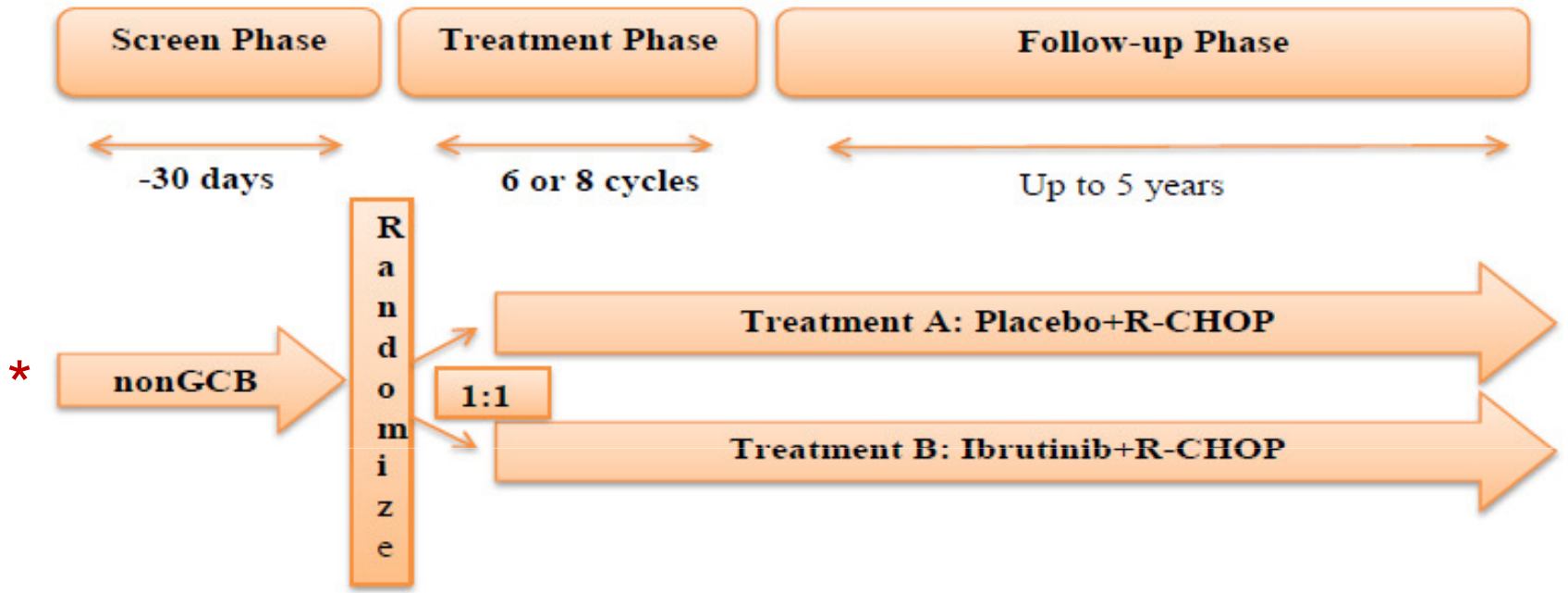




PR, partial response; SPD, sum of the products of the greatest perpendicular diameter.

Wilson WH, et al. Nat Med. 2015;21:922-6.

R-CHOP + iBtk for untreated DLBCL, non GCB



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

Stratification factors:

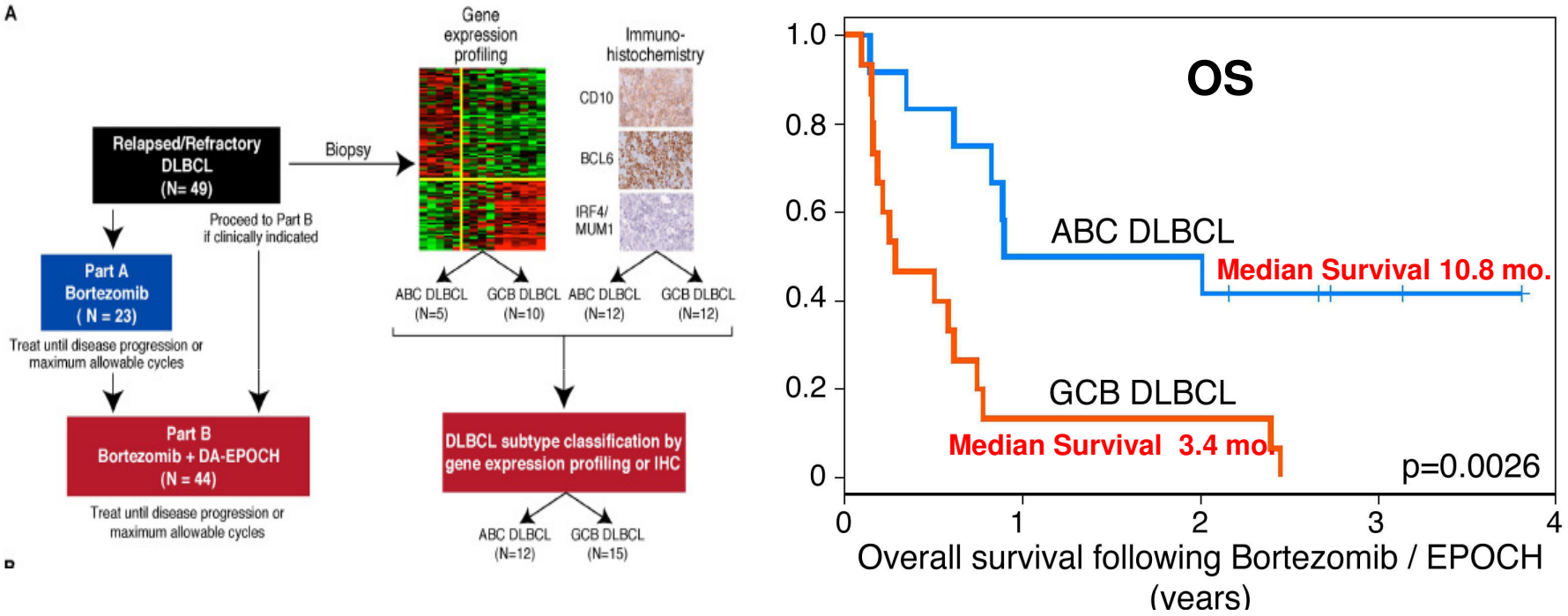
- R-IPI score low risk (1) vs. intermediate risk (2-3) vs. high risk (4-5)
- Region (United States/Western Europe vs. Rest of World)
- Number of treatment cycles (6 vs. 8 cycles)

PHOENIX
PCI-32765DBL3001

***IHC based on Hans' algorithm.**

Janssen
PHARMACEUTICAL COMPANIES of Johnson & Johnson

Efficacy of bortezomib combinations in different subtypes of DLBCL

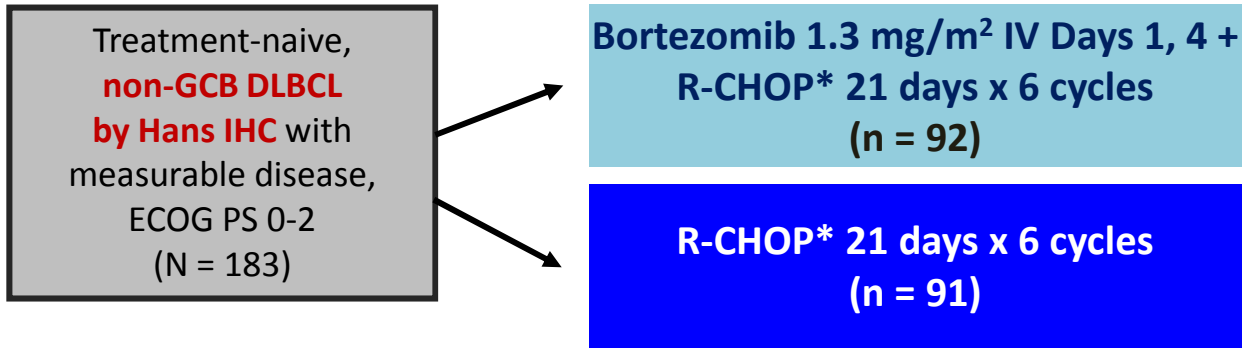


Subtype	Total	Complete response	Partial response	No response	p-value
ABC DLBCL	12	5 (41.7%)	5 (41.7%)	2 (17%)	0.0004
GCB DLBCL	15	1 (6.5%)	1 (6.5%)	13 (87%)	

Dunleavy et al. Blood 2009

PYRAMID: Study Design, non-GCB DLBCL

Prospective randomized, open-label phase II study



Outcome, %	VR-CHOP (n = 92)	R-CHOP (n = 91)	HR (95% CI)	*P* Value
CR	56	49		
2-yr PFS rate	**82**	**78**	**0.73 (0.43-1.24)**	**.611**
2-yr OS rate	93	88	0.75 (0.38-1.45)	.763

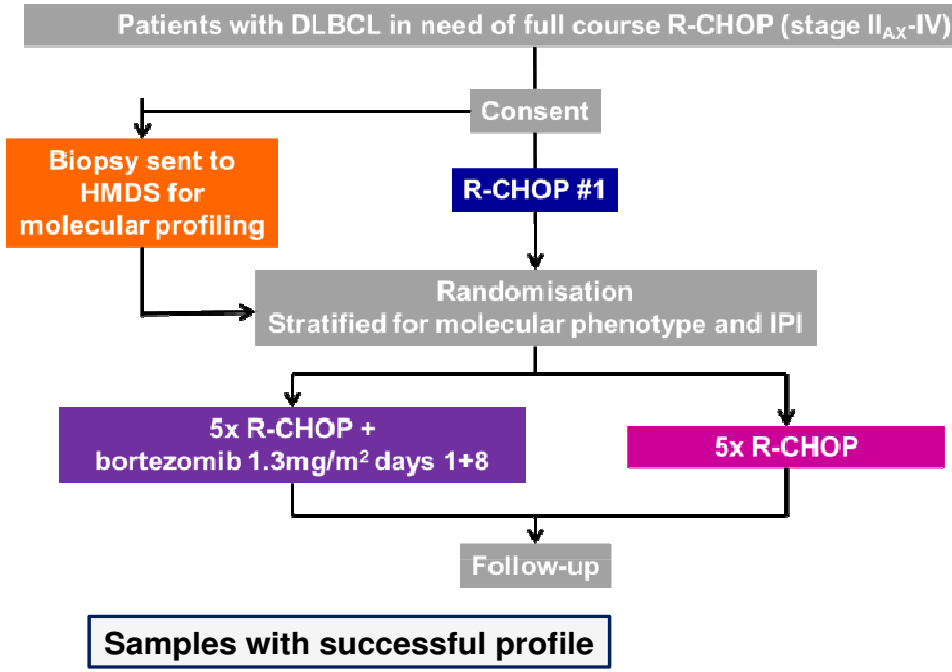
Limits:

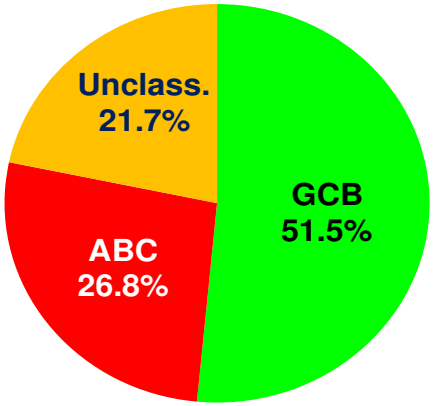
-a probable patient selection in the PYRAMID trial → R-CHOP alone better outcomes than expected

-IHC based on Hans algorithm

Leonard P.J et al, ASH 2015

REMoDL trial

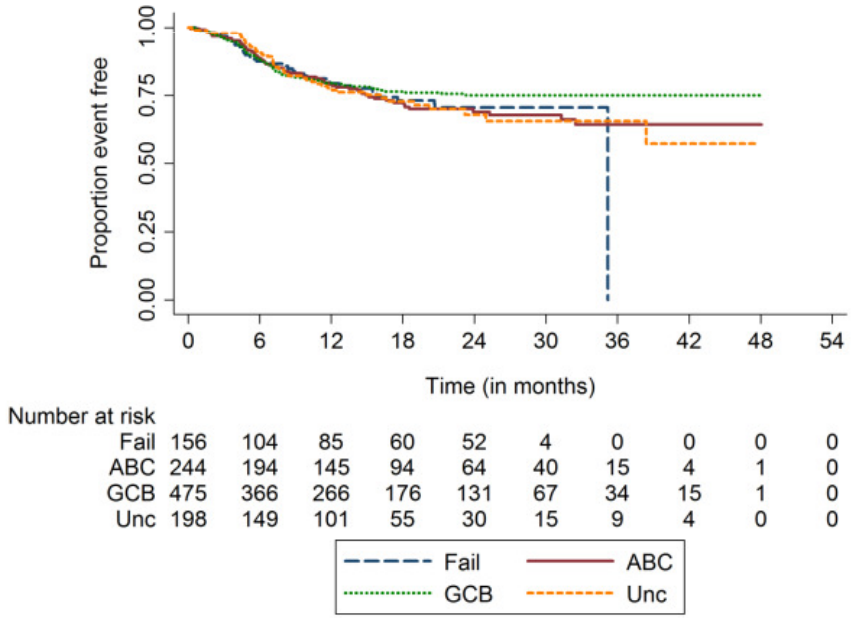




1132 patients registered.
1085 patients eligible and randomised.
Median turn around = 10 days

Treatment-naive,
ABC DLBCL
by DASL assay

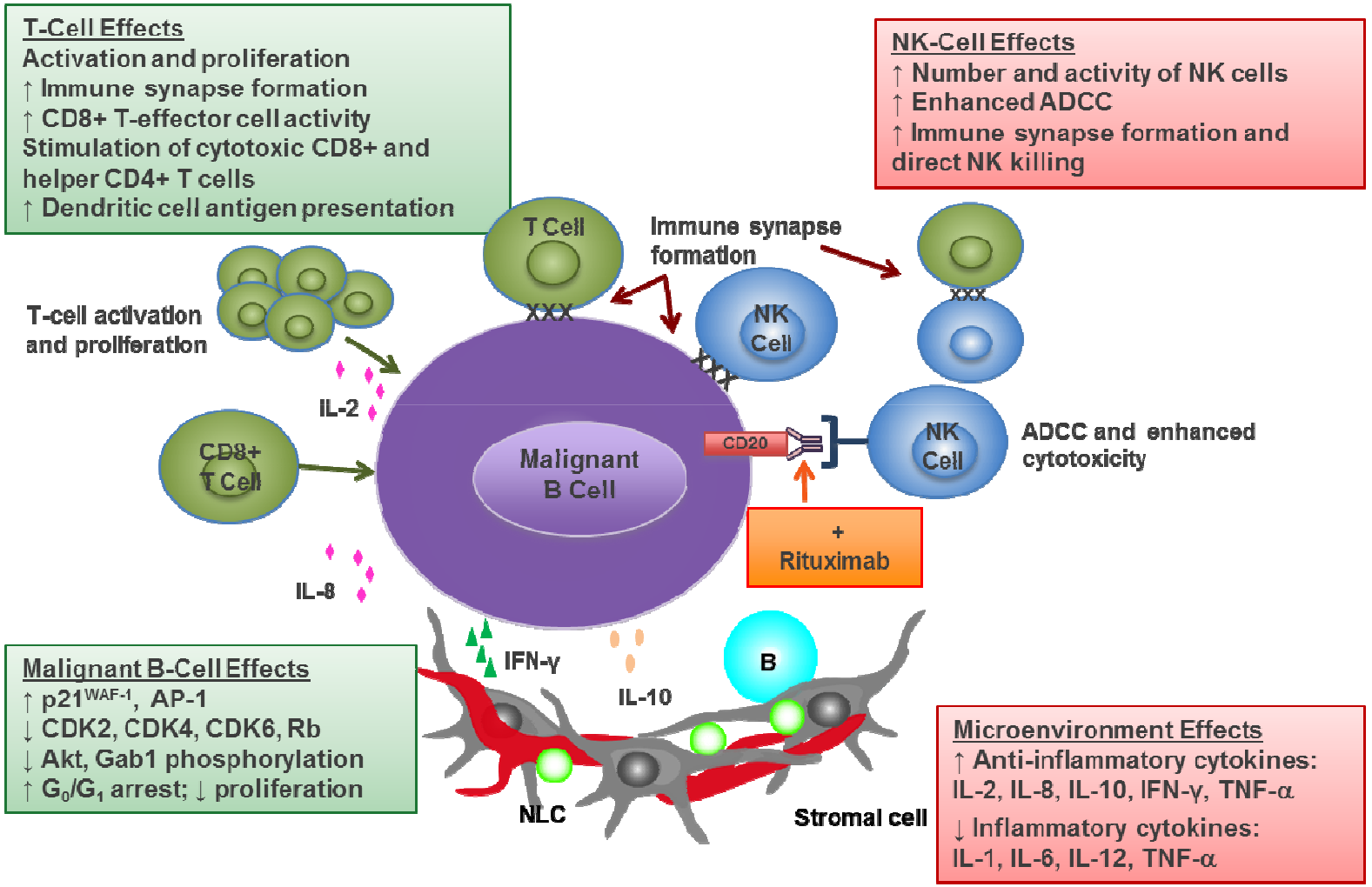
REMoDL-B



DASL, cDNA-mediated annealing, selection, extension and ligation;
HMDS, Haematological Malignancy Diagnostic Service.

Davies A, et al. Blood 2015;126:812a.
(Updated data presented in oral presentation at ASH annual meeting.)

Mechanisms of action of lenalidomide in lymphoma cells and nodal microenvironment



Gribben JG, et al. J Clin Oncol. 2015;33:2803-11.

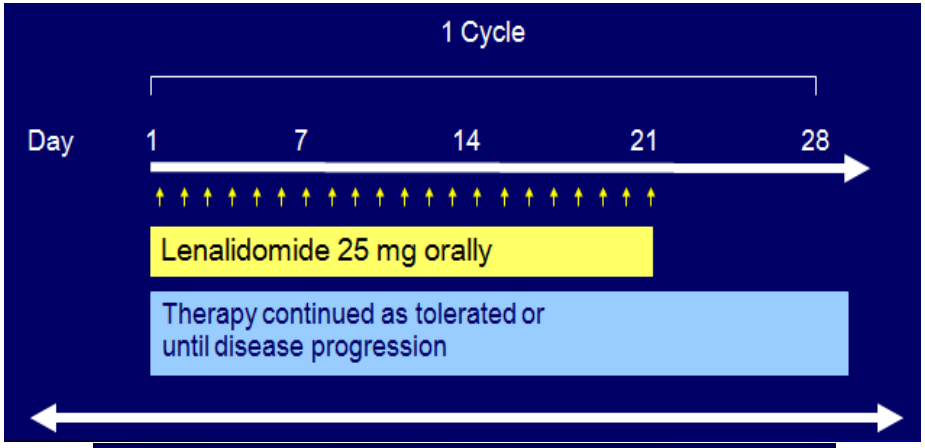
Activity of Lenalidomide in R/R DLBCL

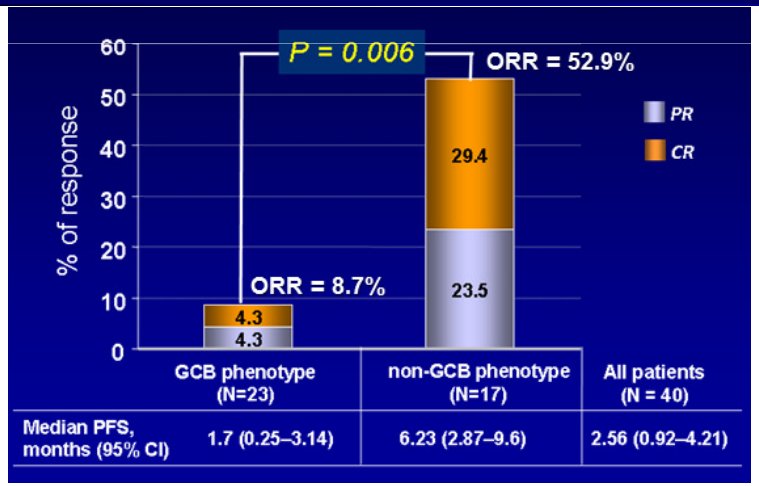
R/R DLBCL	n	ORR	CR/CRu	Median PFS, mo
All patients[1]	26	19%	12%	4.0*
All patients[2]	108	28%	7%	2.7
All patients[3] GCB by IHC Non-GCB by IHC	40 23 17	28% 9% 53%	15%† 4% 29%	2.6 1.7 6.2
All patients[4] GCB by IHC Non-GCB by IHC GCB by GEP ABC by GEP	51 23 28 14 11	27% 26% 29% 21% 46%	N/A N/A N/A N/A N/A	3.1 2.3 3.5 3.0 18.9

*Included all patients in mixed NHL population.

†CR only (not CRu)

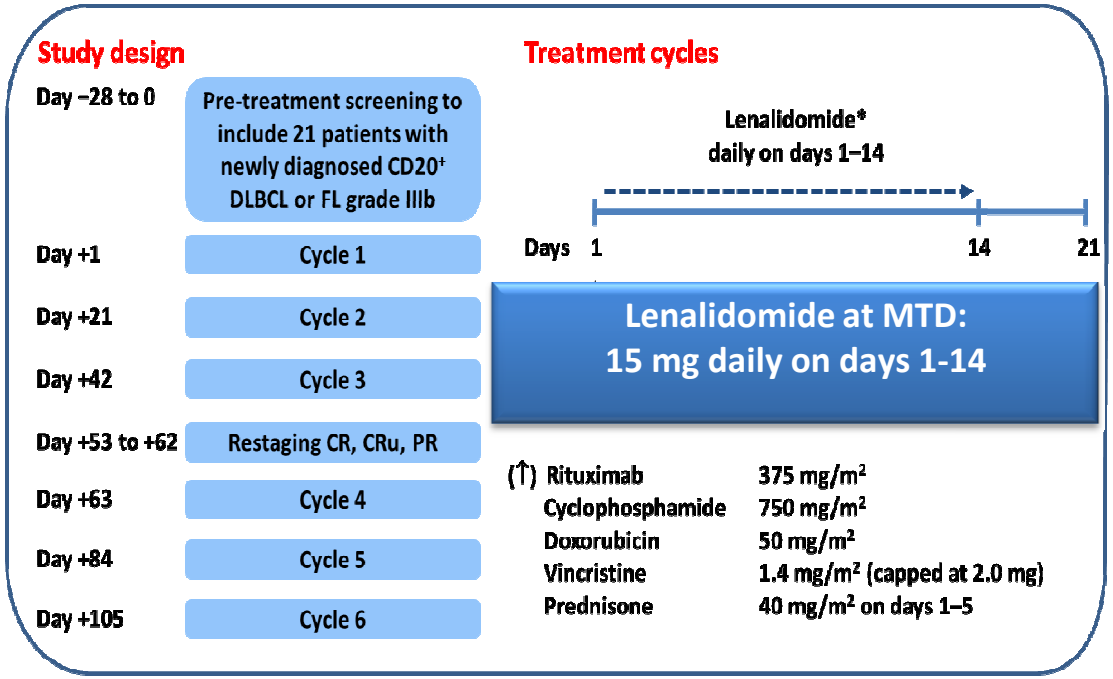
Please note: Direct comparisons between trial designs should not be made due to differences between trial designs and patient characteristics.





1. Wiernik PH, et al. J Clin Oncol. 2008;26:4952-7.
2. Witzig TE, et al. Ann Oncol. 2011;22:1622-7.
3. Hernandez-Ilizaliturri FJ, et al. Cancer. 2011;117:5058-66.
4. Czuczman MS, et al. ASH 2014. Abstract 628.

Lenalidomide + R-CHOP in elderly patients with untreated DLBCL, REAL07 phase I-II trial



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

Lenalidomide provided free by Celgene

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.

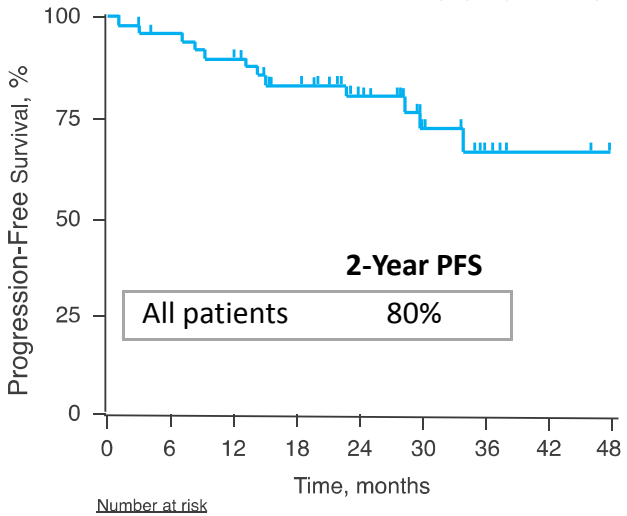
Table 1: **Baseline clinical characteristics**

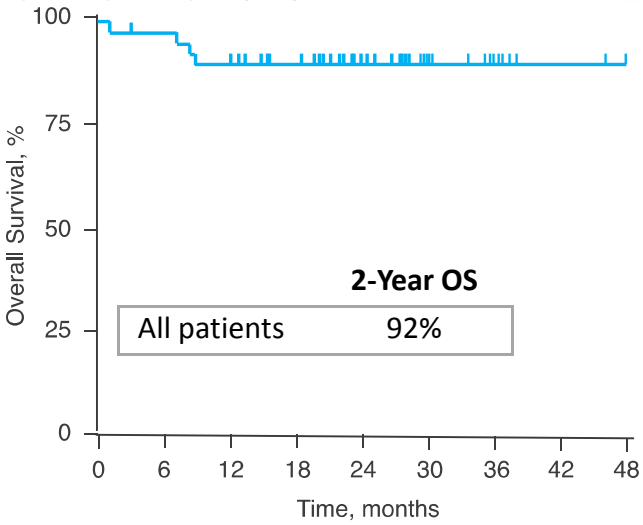
G-CSF, granulocyte-colony stimulating factor; DVT, deep vein thrombosis;
FL, follicular lymphoma; MTD, maximum tolerated dose;

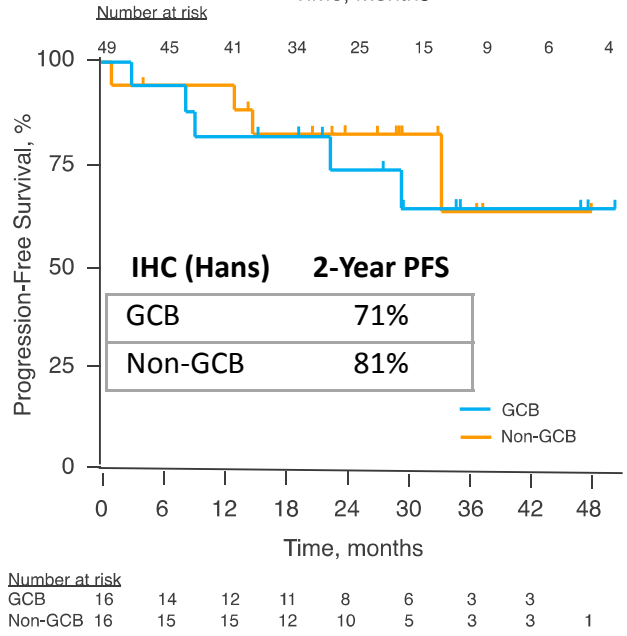
Chiappella A, et al. Haematologica. 2013;98:1732-8.
Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

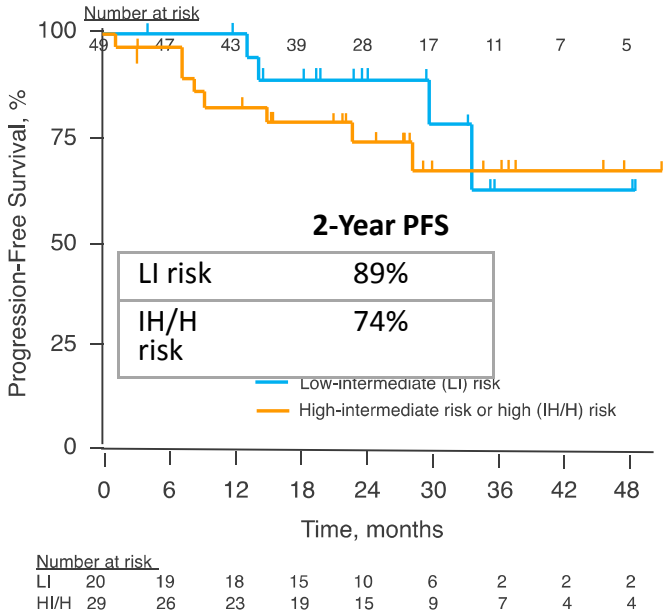
REAL07 Phase II R2-CHOP21 in Elderly Untreated DLBCL: PFS and OS; PFS by COO and PFS by IPI

Median follow-up of 28 months







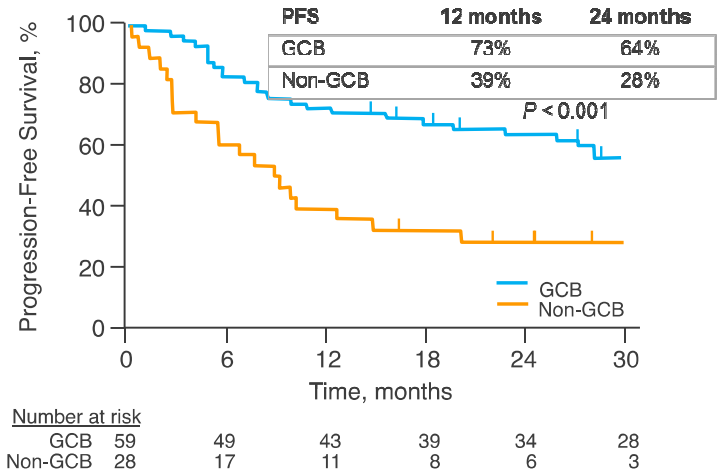


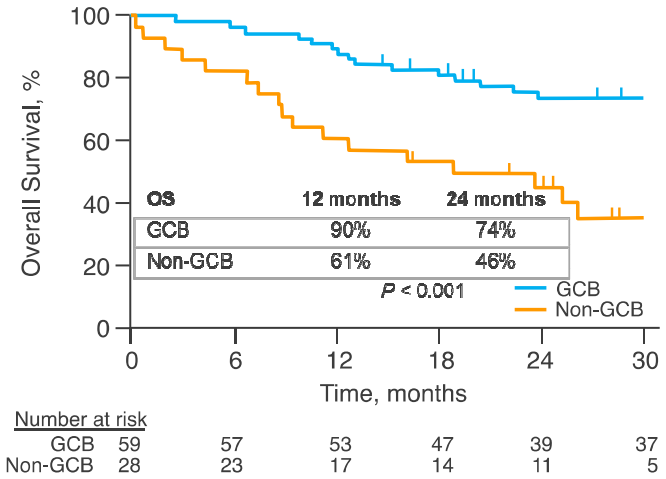
Vitolo U et al, Lancet Oncol 2014

Phase II R2-CHOP21 in Untreated DLBCL and comparison with historical R-CHOP21 group

MAYO CLINIC

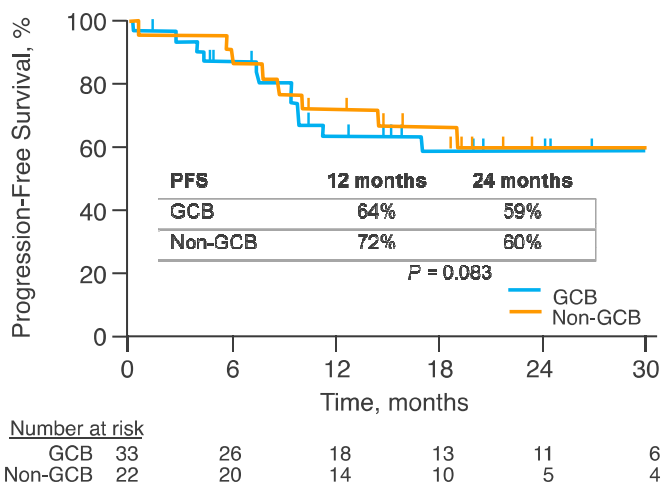
Historical R-CHOP

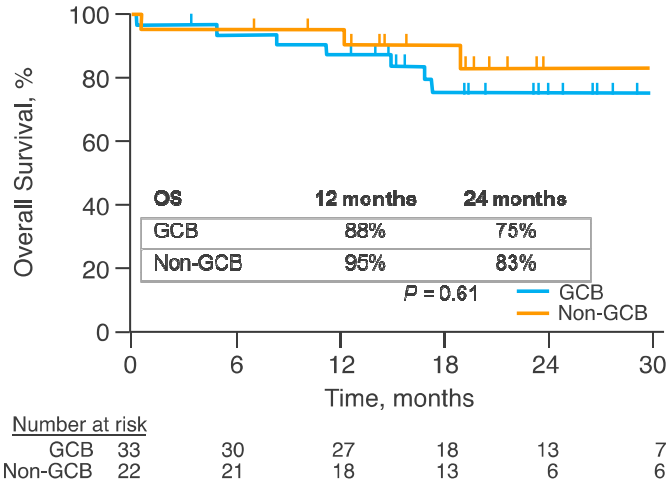




IHC (Hans)

R²-CHOP

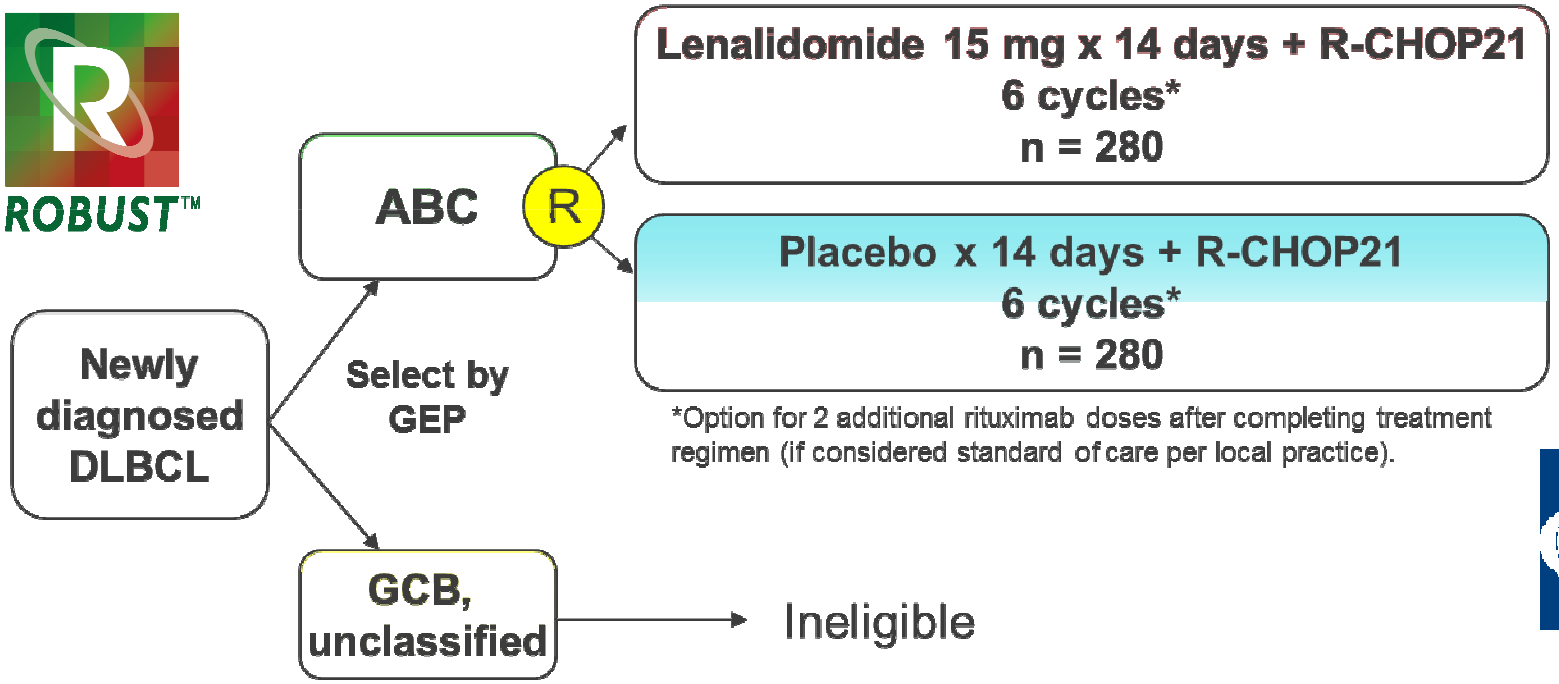




Nowakowski et al, J Clin Oncol 2015

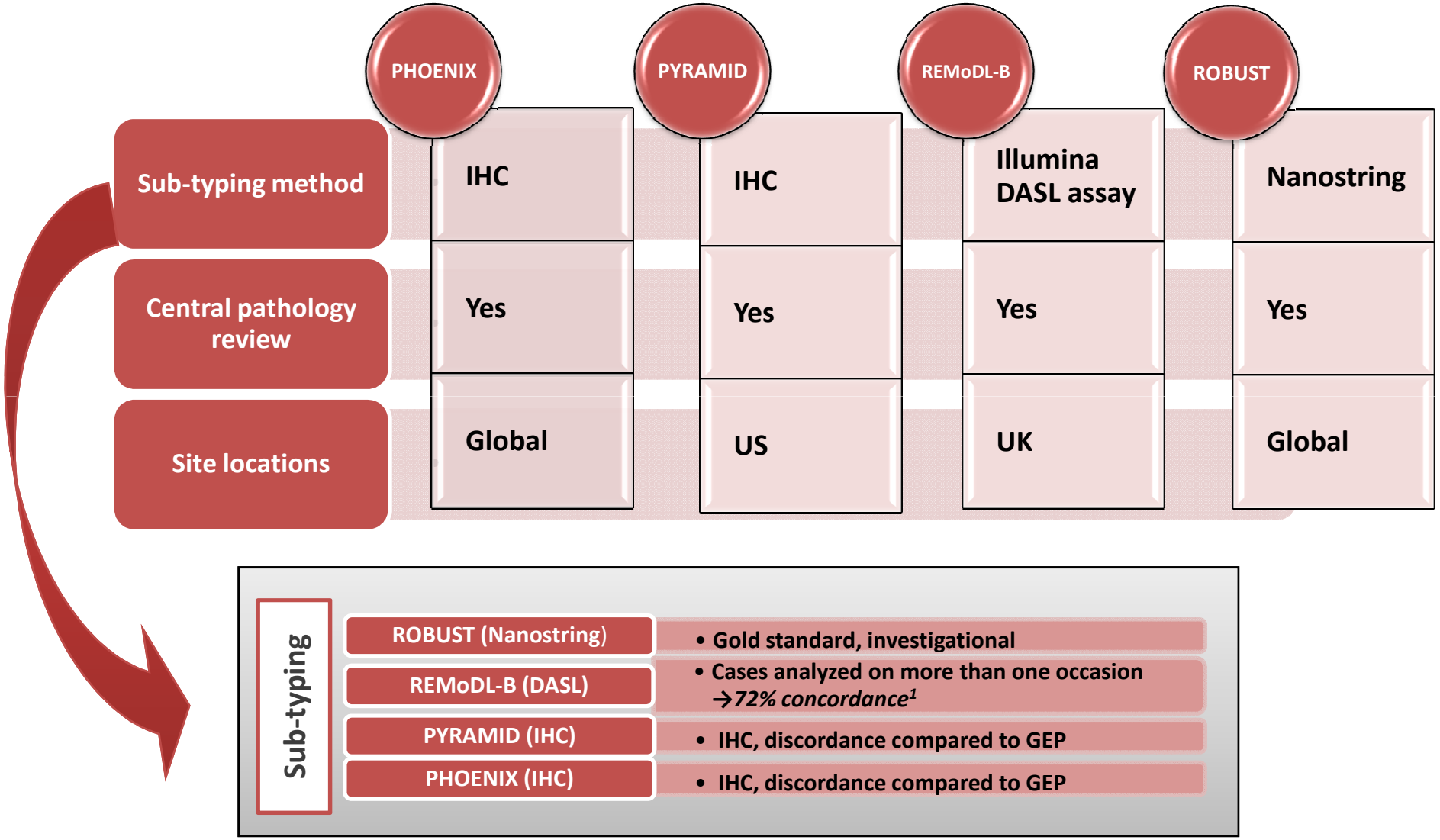
DLC-002 (ROBUST): Phase III Randomized Efficacy and Safety Study of Lenalidomide Plus R-CHOP vs. Placebo Plus R-CHOP in Patients With Untreated ABC-type Diffuse Large B-cell Lymphoma

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 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)

Comparison of COO determination between trials



Barrans SL, et al. Br J Haematol. 2012;159(4):441-53.

Take home messages

- R-CHOP21 is still the standard of care in DLBCL
- COO determined by investigational NanoString assay should identify ABC as a poor prognosis subgroup
- The addition of novel drug to R-CHOP may be an option
- The real role of lenalidomide in first line setting, in addition to standard R-CHOP, in ABC-DLBCL or ibrutinib in addition to R-CHOP in non-GCB DLBCL, should be demonstrated in randomized phase III clinical trials

DLBCL: the new WHO 2016 entities

How I treat?

✓GCB vs ABC/non-GCB

✓**High grade B-cell lymphoma**

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

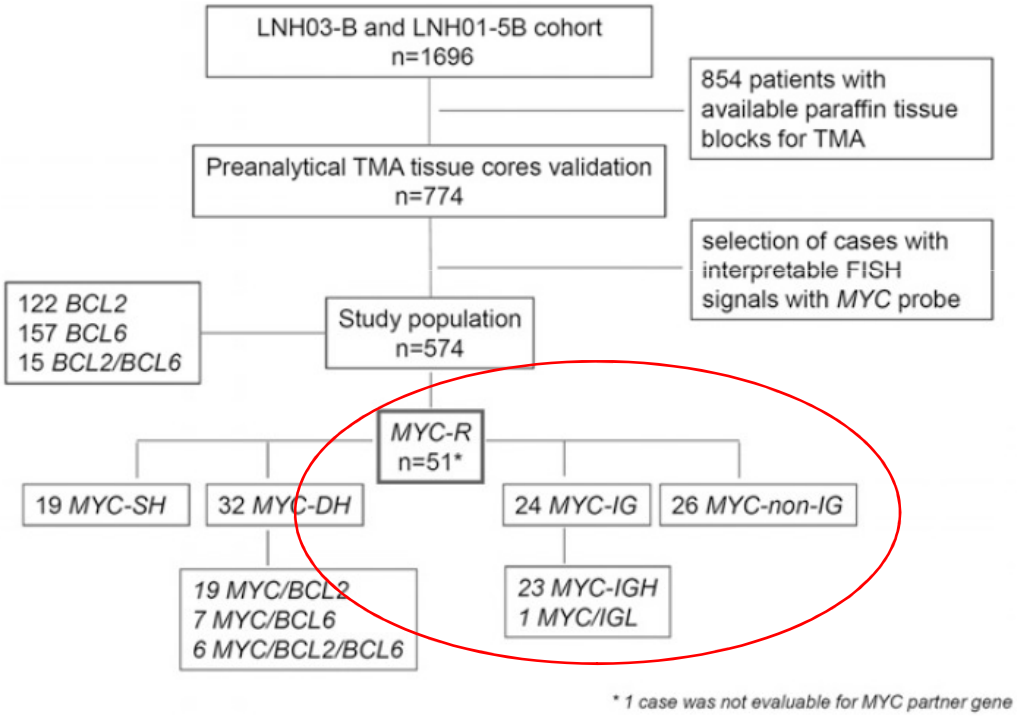


Figure 1. Flow-chart of LNH03-B and LNH01-5B cohort, case selection, and FISH results. *BCL2-R*, DLBCL with *BCL2* gene rearrangement; *BCL6-R*, DLBCL with *BCL6* gene rearrangement; *MYC-R*, DLBCL with *MYC* gene rearrangement; *MYC-IG*, *MYC* gene rearrangement with *IG* partner gene; *MYC*-non-*IG*,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

- ✓ Prospective, homogeneously treated (R-CHOP/R-ACVBP)
- ✓ 774 DLBCL
- ✓ 51 MYC-R(FISH)
- ✓ MYC translocation partner:
  - Gene-IG (MYC-IG) in 24
  - MYC-non-IG in 26

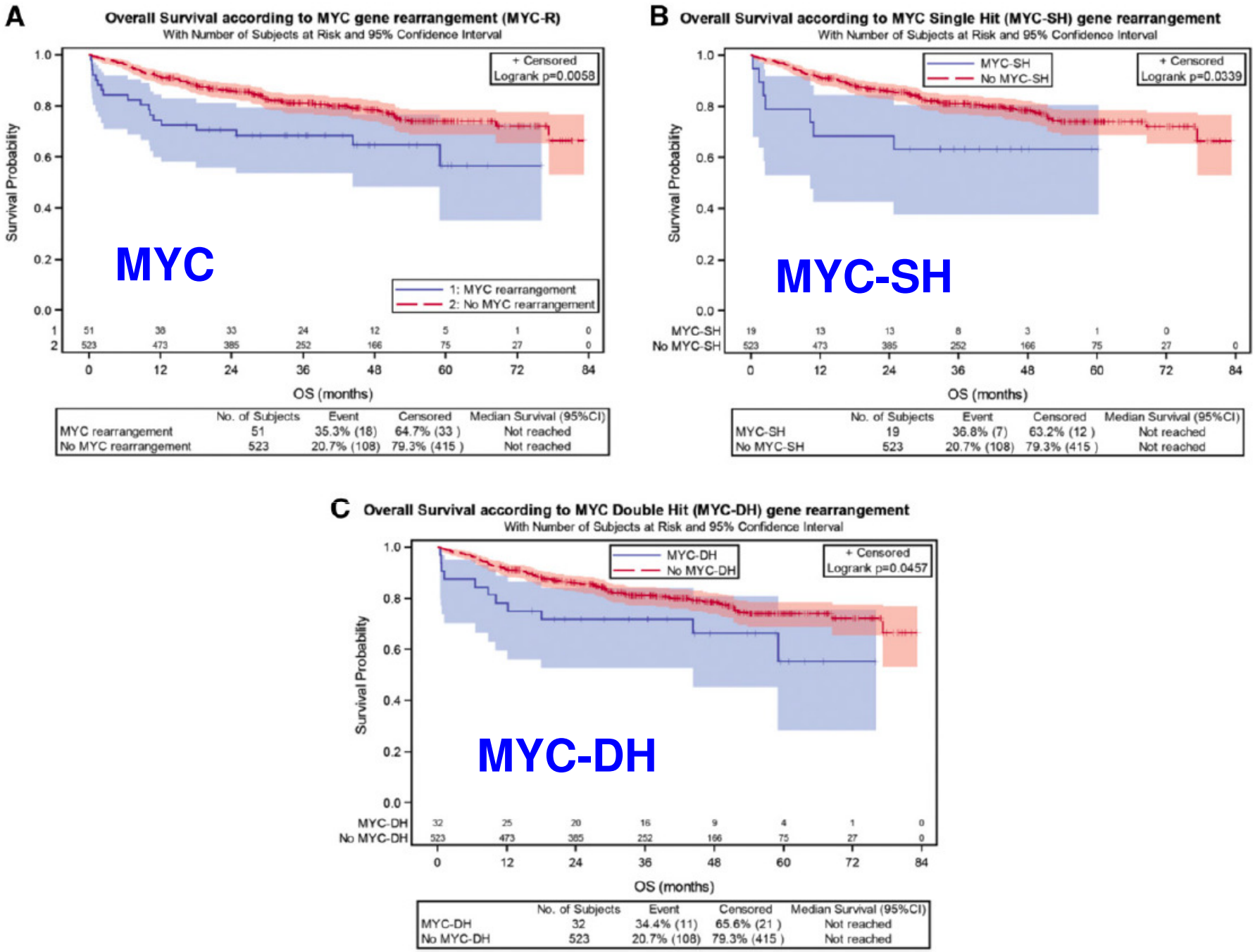


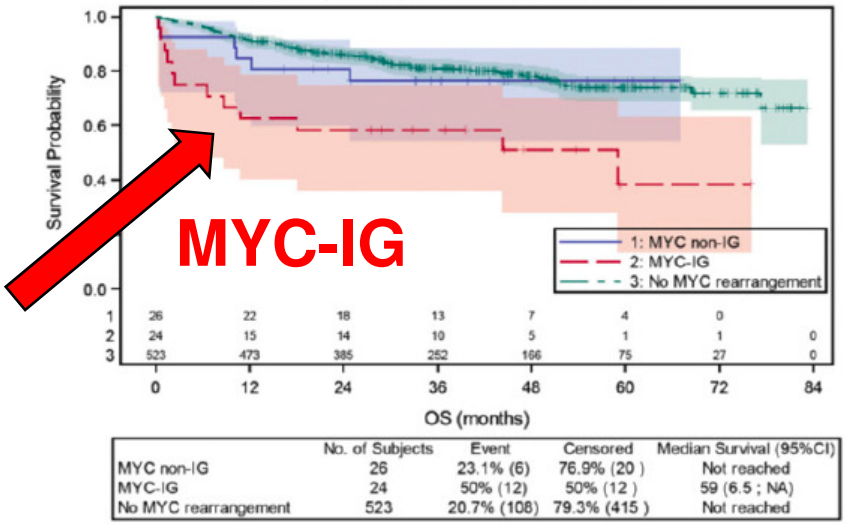
Figure 2. Univariate analysis of *MYC*-R for OS. (A) The global population, (B) SH, and (C) subgroups of DLBCL patients.

Copie-Bergman C et al, Blood 2015

MYC-IG

Overall survival according to MYC partner gene including patients with no MYC rearrangement

With Number of Subjects at Risk and 95% Confidence Interval

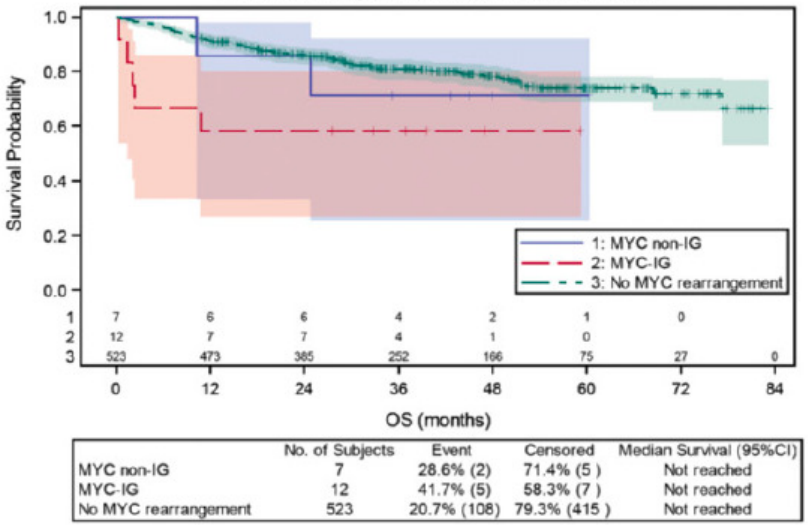


	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	26	23.1% (6)	76.9% (20)	Not reached
MYC-IG	24	50% (12)	50% (12)	59 (6.5 ; NA)
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

MYC-SH-IG

Overall survival according to MYC-SH partner gene including patients with no MYC rearrangement

With Number of Subjects at Risk and 95% Confidence Interval

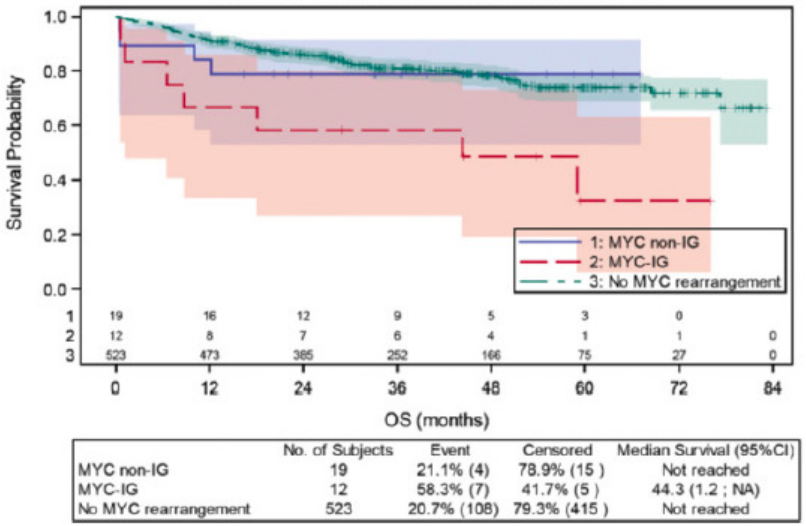


	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	7	28.6% (2)	71.4% (5)	Not reached
MYC-IG	12	41.7% (5)	58.3% (7)	Not reached
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

MYC-DH-IG

Overall survival according to MYC-DH partner gene including patients with no MYC rearrangement

With Number of Subjects at Risk and 95% Confidence Interval



	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	19	21.1% (4)	78.9% (15)	Not reached
MYC-IG	12	58.3% (7)	41.7% (5)	44.3 (1.2 ; NA)
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

- ✓ MYC-IG patients had shorter OS (P=.0002) compared with MYC-negative
- ✓ no survival difference was observed between MYC-non-IG and MYC-neg.
- ✓ In multivariate analyses, MYC-IG predicted poor PFS (P=.0051) and OS (P=.0006) independently from the IPI and the Hans classifier.

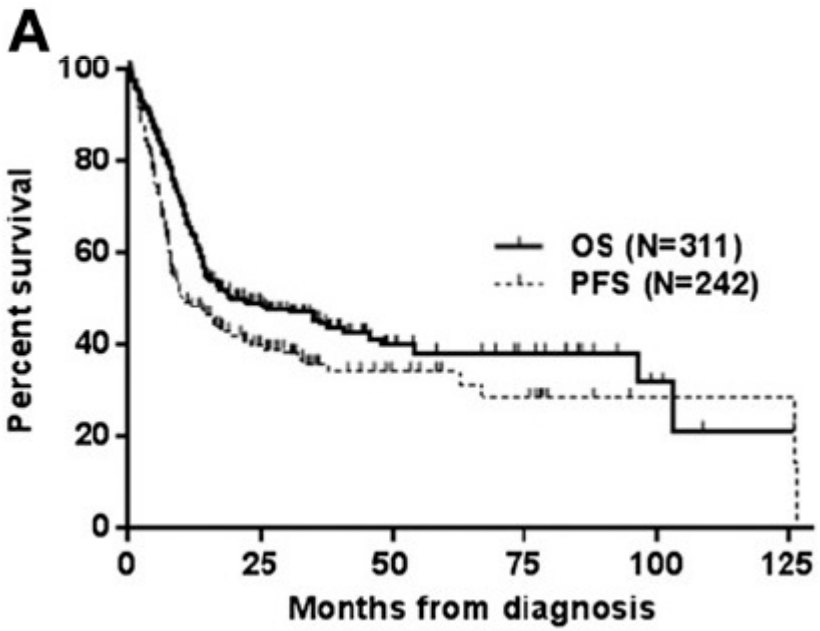
Copie-Bergman C et al, Blood 2015

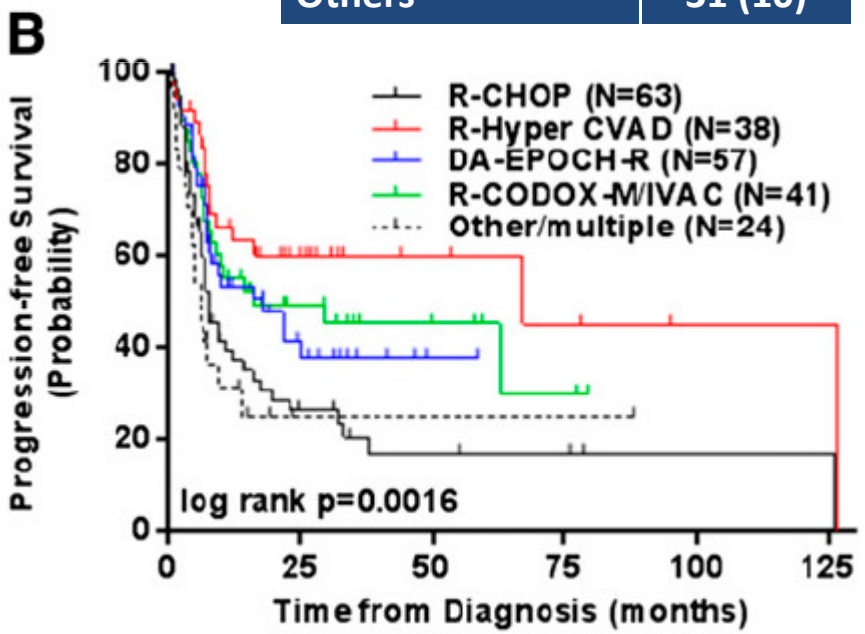
Double Hit Lymphoma (DHL)

DOUBLE HYT LYMPHOMA

- ✓311 pts DHL ; median age 60 (19-87);
- ✓DLBCL= 154 (50%) BCLU= 150(48%)
- ✓BCL2 += 87%; BCL6+ =6% triple Hit= 6%;
- ✓GCB= 58 %

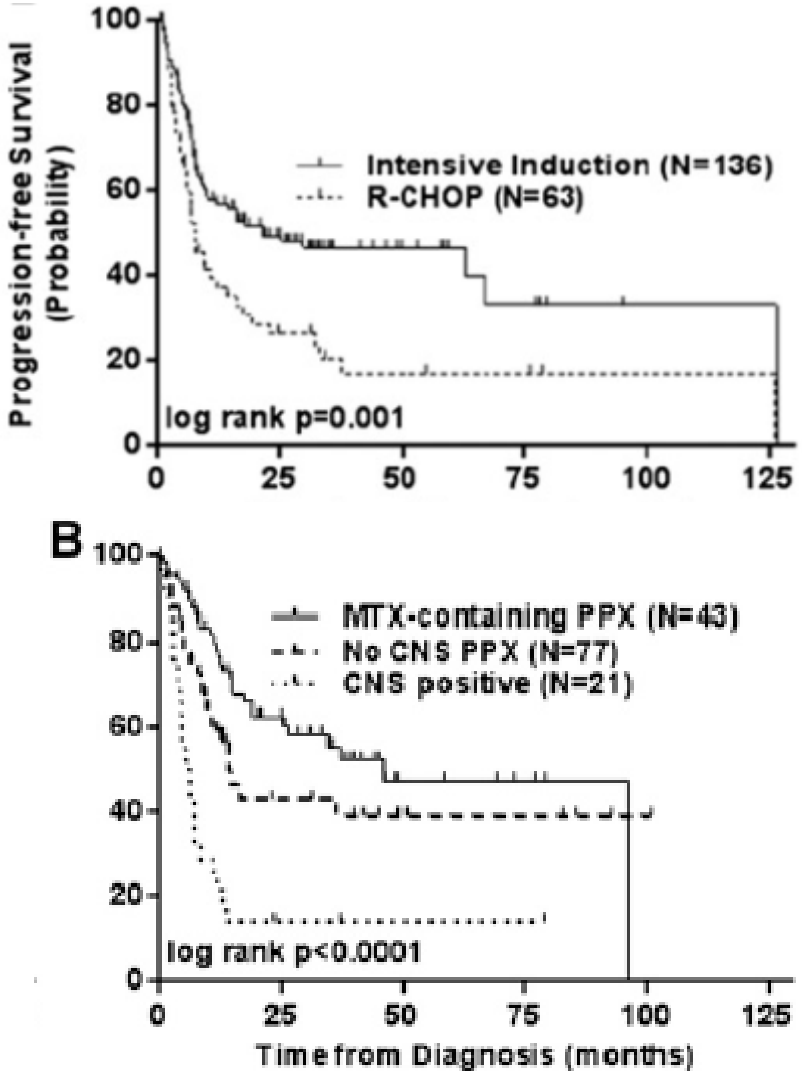
R-CHOP	100 (32)
R-Hyper-CVAD	66 (21)
DA-EPOCH-R	64 (21)
R-CODOX-M/IVAC	42 (14)
R-ICE	9 (3)
Others	31 (10)

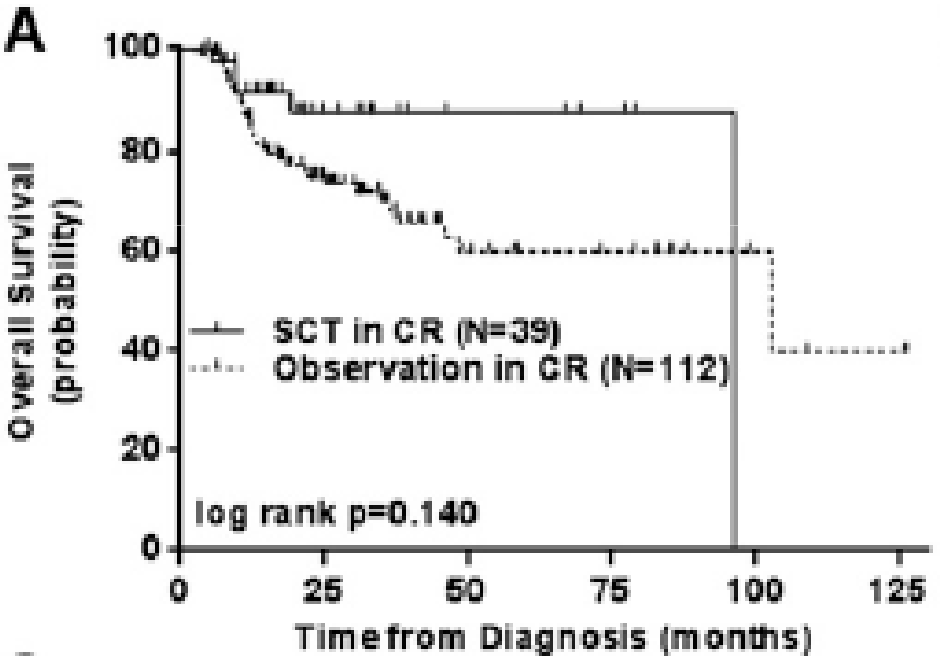




Petrich M, Gandhi M et al Blood 2014

Double Hit Lymphoma (DHL)

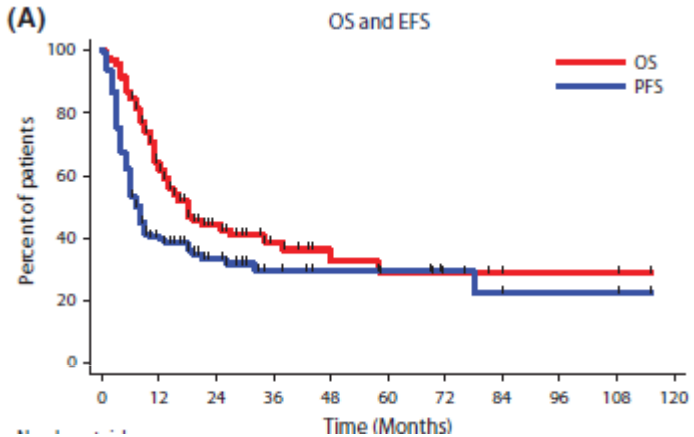


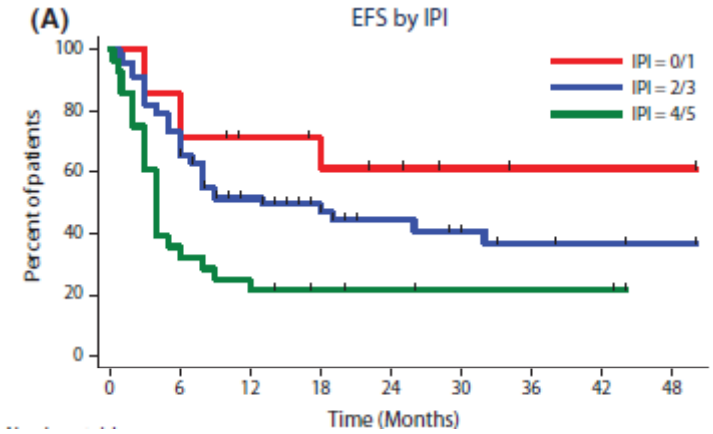


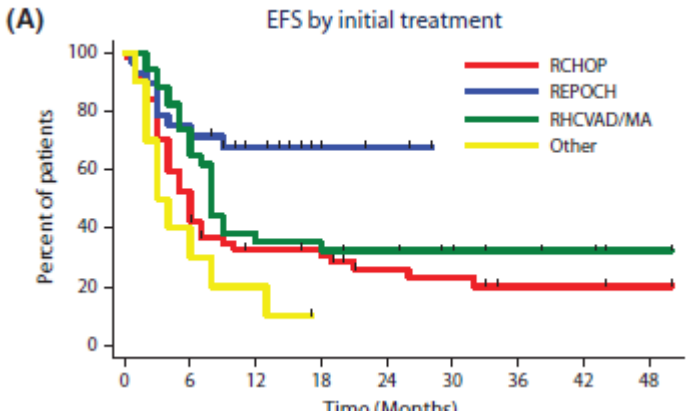
Petrich M, Gandhi M et al Blood 2014

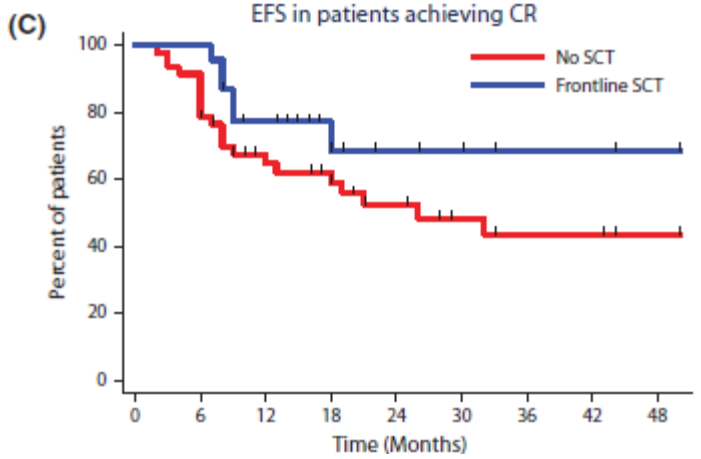
Double Hit Lymphoma (DHL)

129 pts DHL ; median age 62; IPI 2-3 =61%; MYC/BCL2 pos=72%; triple Hit= 11%; GCB 90%





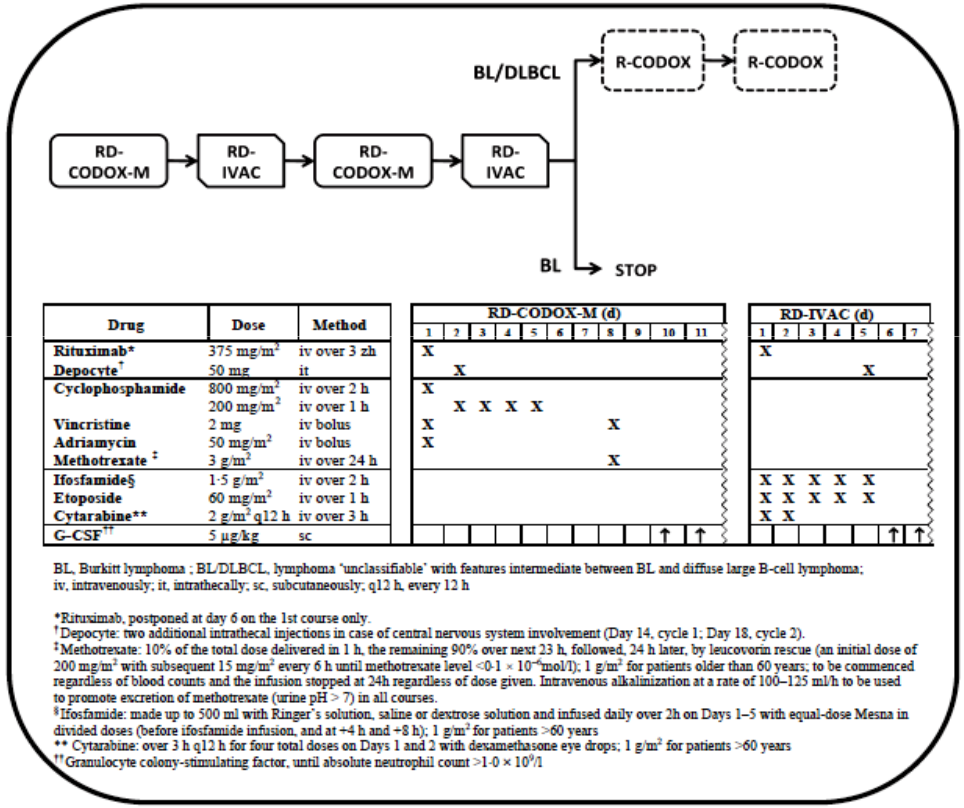




Oki et al, Br J Haematol 2014

bjh
British Journal of Haematology

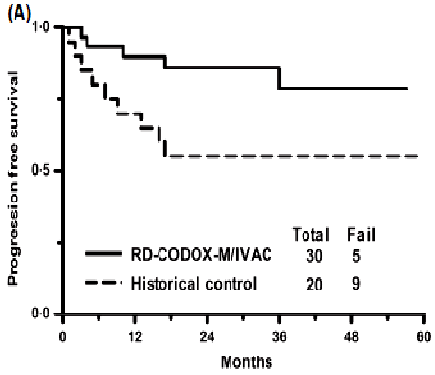
RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma

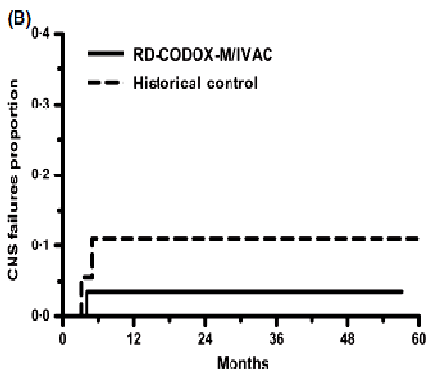


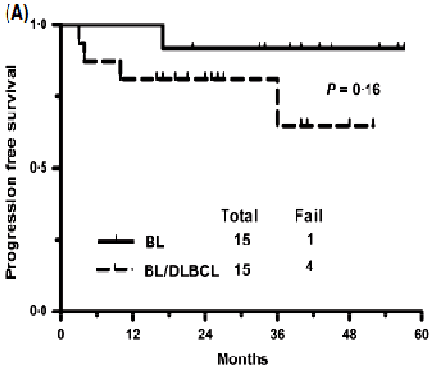
Drug	Dose	Method	RD-CODOX-M (d) 1 2 3 4 5 6 7 8 9 10 11	RD-IVAC (d) 1 2 3 4 5 6 7
Rituximab*	375 mg/m²	iv over 3 zh	X	X
Depocyte†	50 mg	it	X	X
Cyclophosphamide	800 mg/m²	iv over 2 h	X	
	200 mg/m²	iv over 1 h	X X X X	
Vincristine	2 mg	iv bolus	X X	
Adriamycin	50 mg/m²	iv bolus	X	
Methotrexate ‡	3 g/m²	iv over 24 h	X	
Ifosfamide§	1·5 g/m²	iv over 2 h		X X X X X
Etoposide	60 mg/m²	iv over 1 h		X X X X X
Cytarabine**	2 g/m² q12 h	iv over 3 h		X X
G-CSF††	5 µg/kg	sc	↑ ↑	↑ ↑

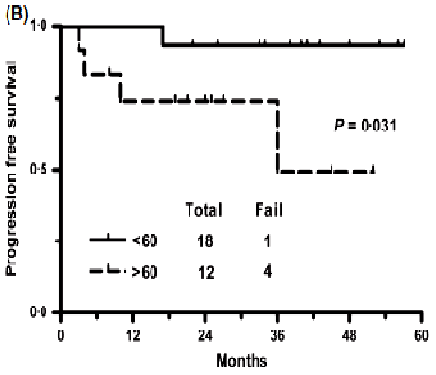
BL, Burkitt lymphoma ; BL/DLBCL, lymphoma 'unclassifiable' with features intermediate between BL and diffuse large B-cell lymphoma; iv, intravenously; it, intrathecally; sc, subcutaneously; q12 h, every 12 h

*Rituximab, postponed at day 6 on the 1st course only.
†Depocyte: two additional intrathecal injections in case of central nervous system involvement (Day 14, cycle 1; Day 18, cycle 2).
‡Methotrexate: 10% of the total dose delivered in 1 h, the remaining 90% over next 23 h, followed, 24 h later, by leucovorin rescue (an initial dose of 200 mg/m² with subsequent 15 mg/m² every 6 h until methotrexate level <0·1 × 10^{-6}mol/l); 1 g/m² for patients older than 60 years; to be commenced regardless of blood counts and the infusion stopped at 24h regardless of dose given. Intravenous alkalinization at a rate of 100–125 ml/h to be used to promote excretion of methotrexate (urine pH > 7) in all courses.
§Ifosfamide: made up to 500 ml with Ringer's solution, saline or dextrose solution and infused daily over 2h on Days 1–5 with equal-dose Mesna in divided doses (before ifosfamide infusion, and at +4 h and +8 h); 1 g/m² for patients >60 years
** Cytarabine: over 3 h q12 h for four total doses on Days 1 and 2 with dexamethasone eye drops; 1 g/m² for patients >60 years
††Granulocyte colony-stimulating factor, until absolute neutrophil count >1·0 × 10^9/l





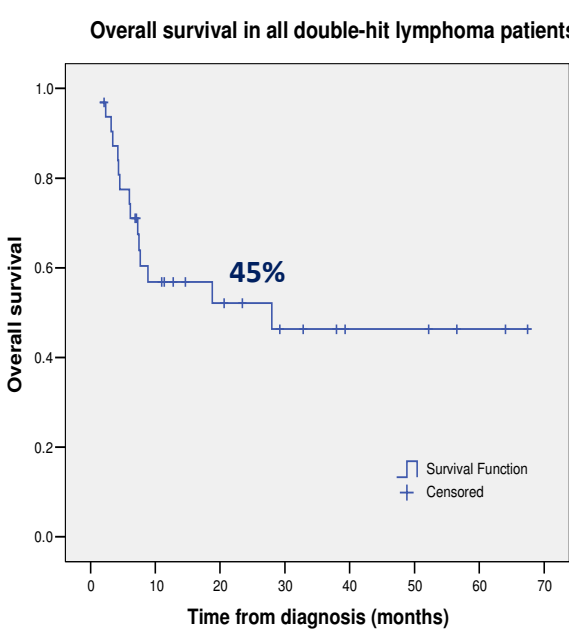


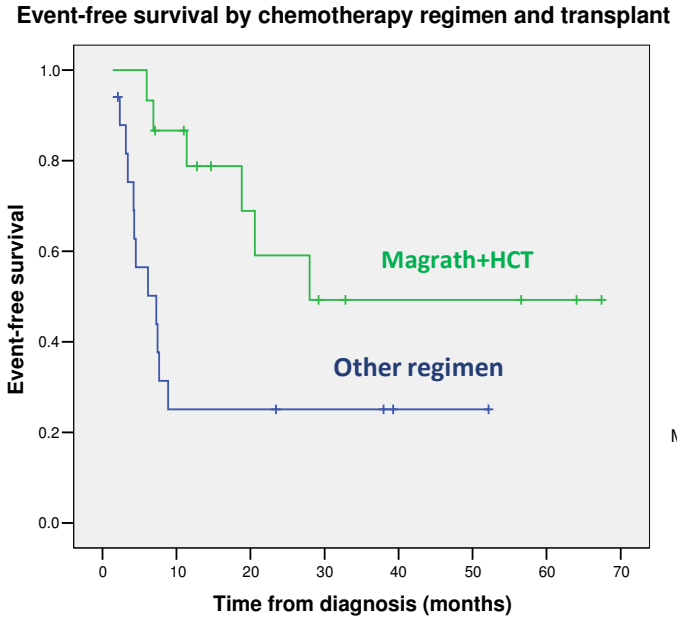


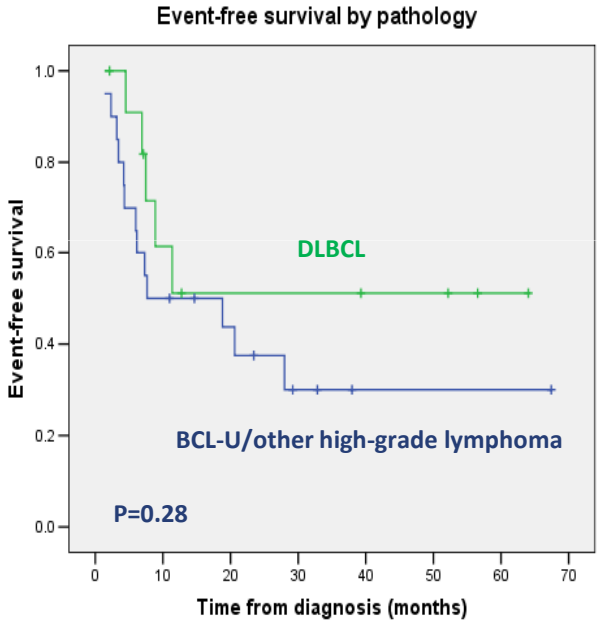
Corazzelli et al, Br J Haematol 2011

Double Hit Lymphoma (DHL)

Outcome of Patients with Double-hit Lymphomas Treated with CODOX-M/IVAC + R followed by HSCT in British Columbia



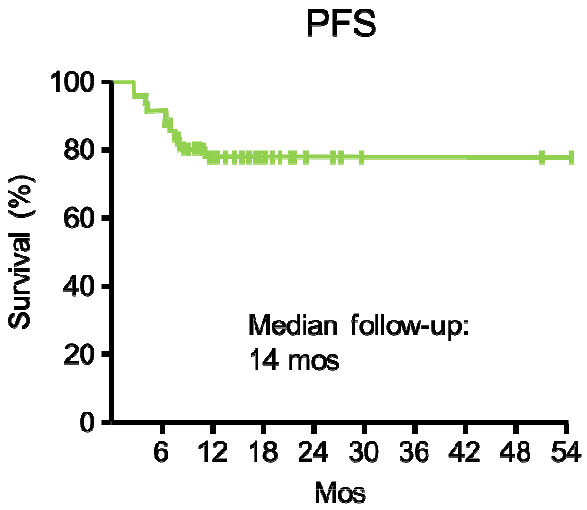


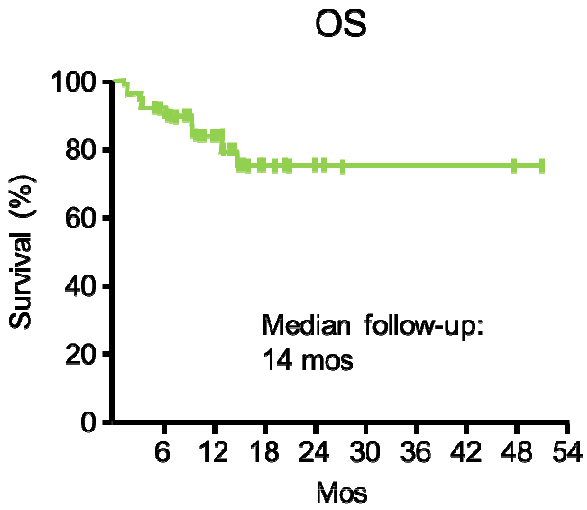


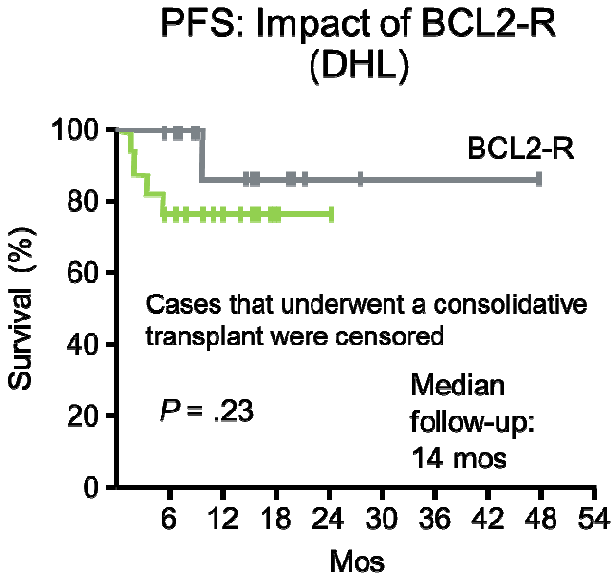
- ✓ Patients with DHIT NHL treated with R-CODOX-M/IVAC plus SCT can have durable CR
- ✓ Patients with DLBCL histology may have a more favorable outcome than those with BCL-U
- ✓ Progression during initial therapy prior to SCT remains a significant problem

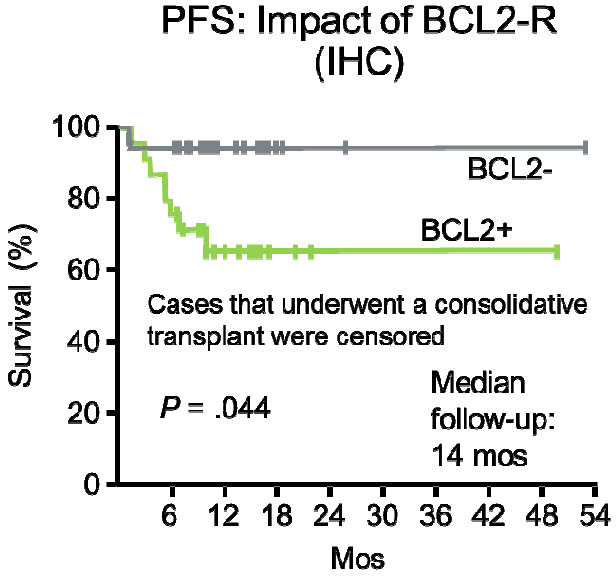
Savage et al, ASH 2013

Double Hit Lymphoma (DHL)







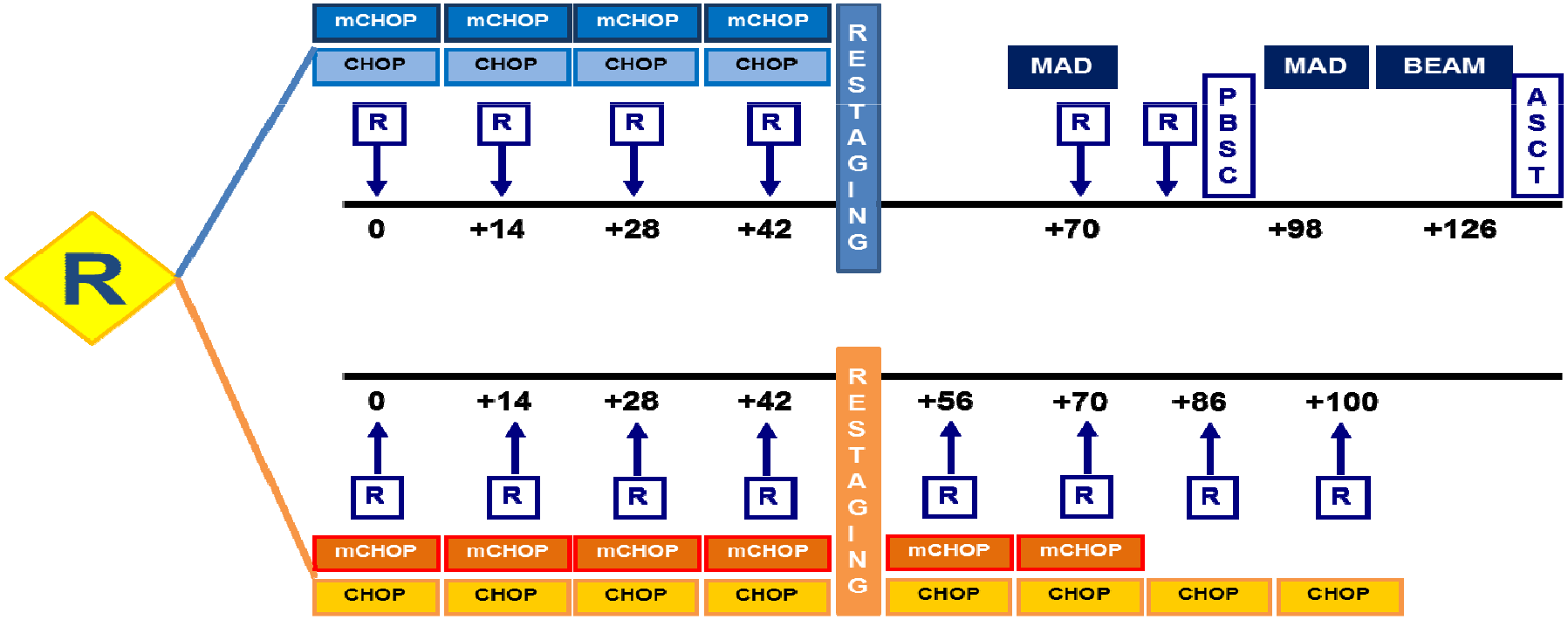


DA-EPOCH-R in MYC-Rearranged Aggressive B-Cell Lymphoma: Early data suggest that DA-EPOCH-R showed good efficacy in MYC-R DLBCL and BCL-U

Dunleavy K, ASH 2014

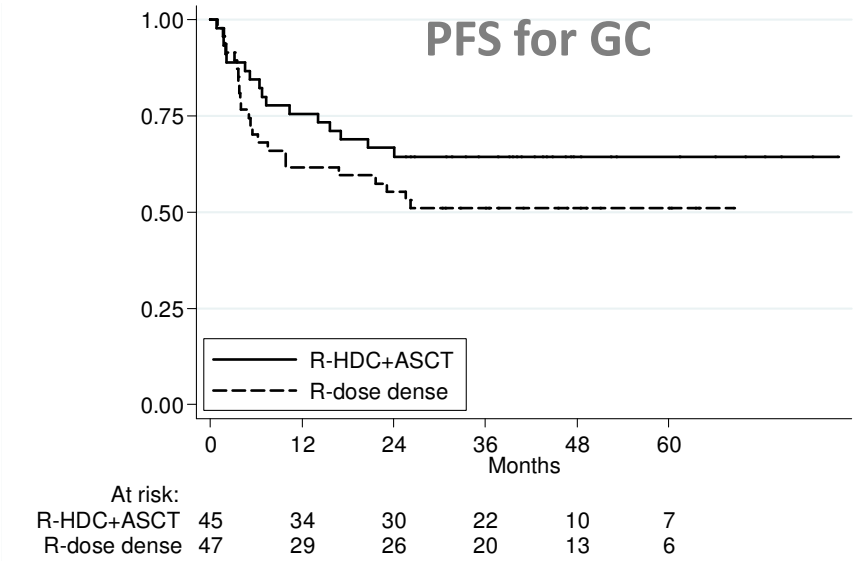
FIL experience – DLCL04

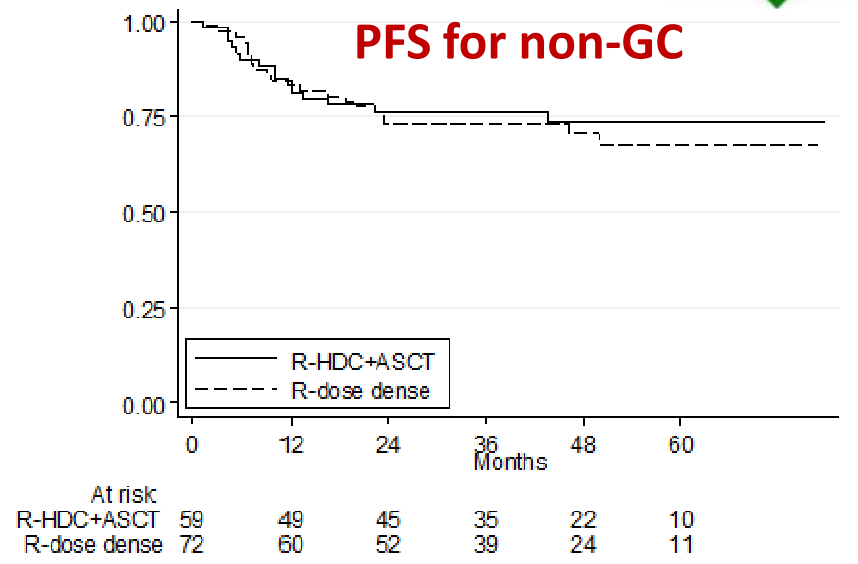
From 2005 to 2010, 412 untreated DLBCL were enrolled into the FIL-DLCL04 phase III randomized trial aimed at investigating the benefit of intensification with high dose therapy + autotransplant (R-HDC+ASCT) compared to R-dose-dense therapy as first line in young DLBCL at poor risk (aa-IPI 2-3).

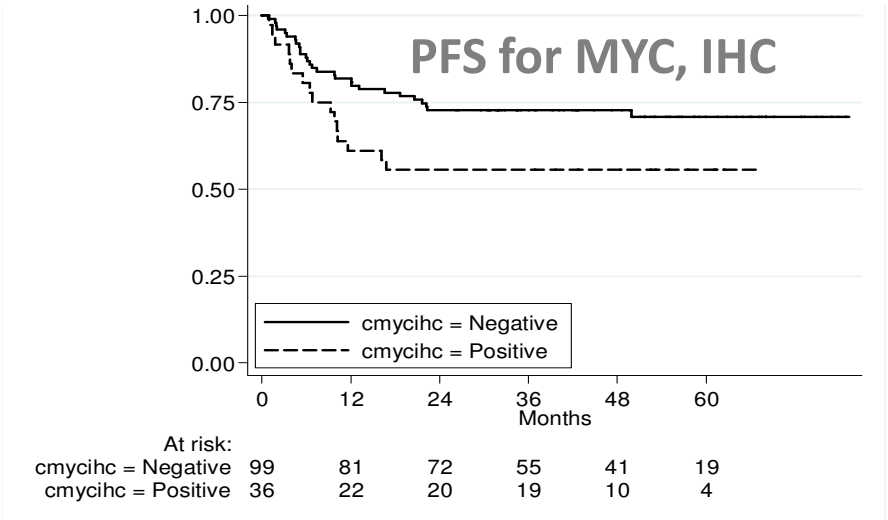


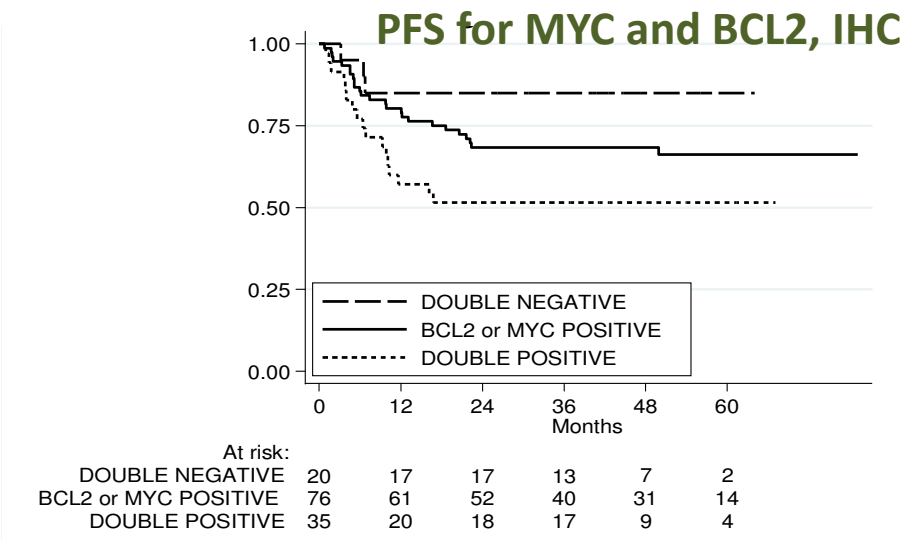
Vitolo U, ASH 2012; Chiappella A, SIE 2013.

FIL experience – DLCL04









Chiappella A, Agostinelli C, SIE 2015.

Take home messages

High-Grade B-cell lymphomas

✓It is important a correct diagnosis performed by expert hemopathologists.

✓A consensus has not yet been reached to provide specific guidelines as to which DLBCL should have FISH.

✓Some believe that all DLBCL should have genetic studies for the detection of MYC, BCL2, and BCL6 rearrangements, whereas others would limit them, for example, to cases with a GCB phenotype and/or high-grade morphology or to cases with 40% MYC cells.

✓HGBL with MYC and BCL2 and/or BCL6 rearrangement should be treated with intensified schemes.

✓The treatment of HGBL in the elderly is still an unmeet clinical need.

Take home messages – PDTA 2016

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

DLBCL AGGRESSIVI MYC+, DOUBLE/TRIPLE HIT

I LINEA

Se FISH positiva solo per myc: trattamento come DLBCL classico o come linfoma aggressivo a seconda della presentazione clinica

Se double/triple hit (FISH positiva per myc e per bcl2 +/- bcl6), trattare come linfoma aggressivo:

→ < 65 anni o elegibili a terapia ad alte dosi + ASCT:
- protocolli Burkitt-like +FEAM/BEAM + ASCT
- R-Magrath (R-CODOX-M + R-IVAC) + PL con Depocyte (off label) o con PL triplice + FEAM/BEAM + ASCT

→ > 65 anni o non elegibili a terapia ad alte dosi + ASCT:
- R-Magrath al 75% della dose (FIT)
- R-DA-EPOCH a dosi piene o ridotte o R-EPOCH (FIT/UNFIT)
- R-CHOP-Metotrexate (UNFIT)
- regimi a intensità ridotta o palliazione (UNFIT o frail)

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