Rimini May 20°, 2016

Aggressive Lymphomas: DLBCL young patients, therapy for high risk

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Disclosures – Umberto Vitolo

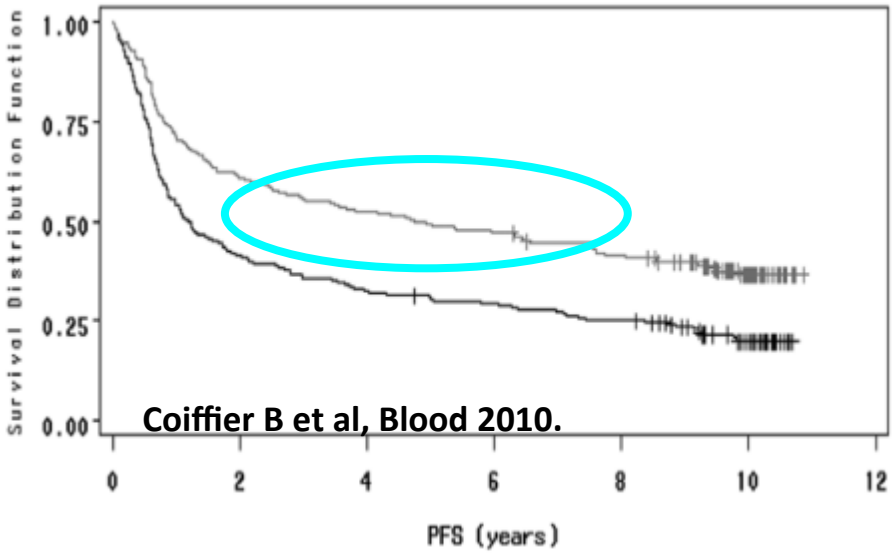
Research Support/P.I.	Roche, Celgene
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Conferences/ Educational Activities	Janssen, Roche, Celgene, Takeda, Gilead
Scientific Advisory Board	Janssen, Roche

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma:

- **30-40% of all NHL**
- **Distribution by age: 53% > 60 years**

CHOP21 vs. R-CHOP21



Coiffier B et al, Blood 2010.

Do we need to improve R-CHOP results in DLBCL?

Do we need to improve R-CHOP results in DLBCL …intensifying chemotherapy?

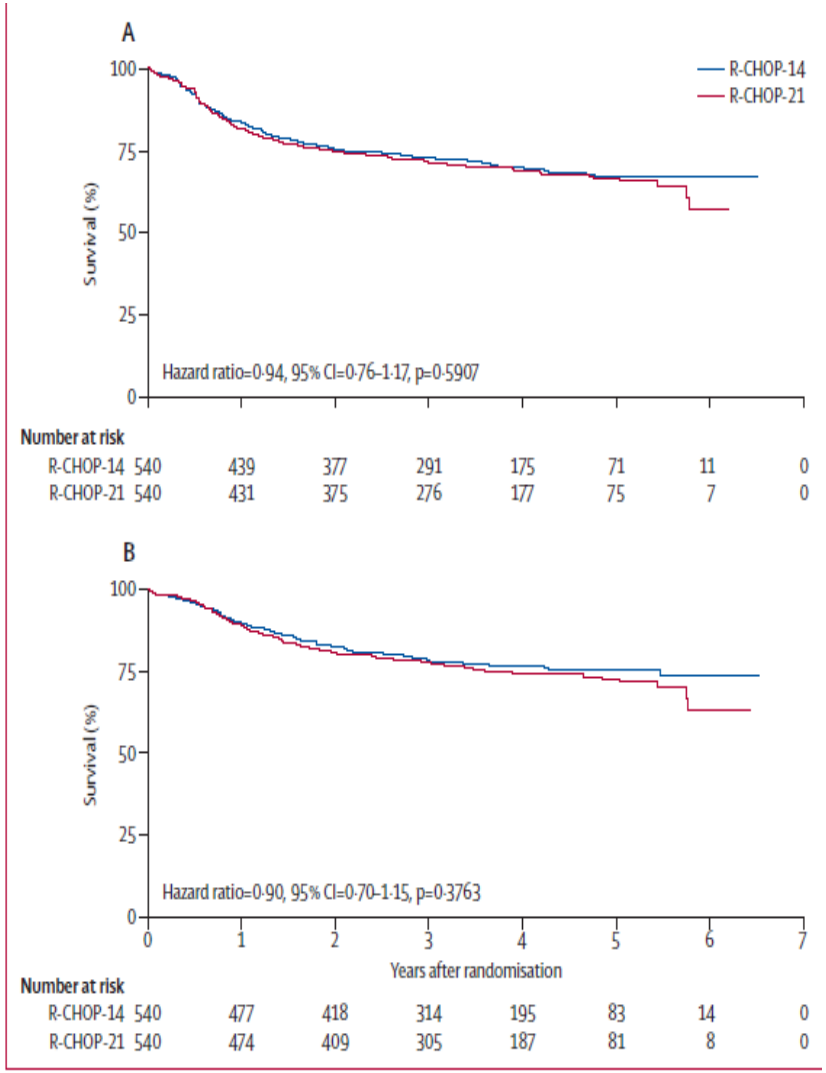
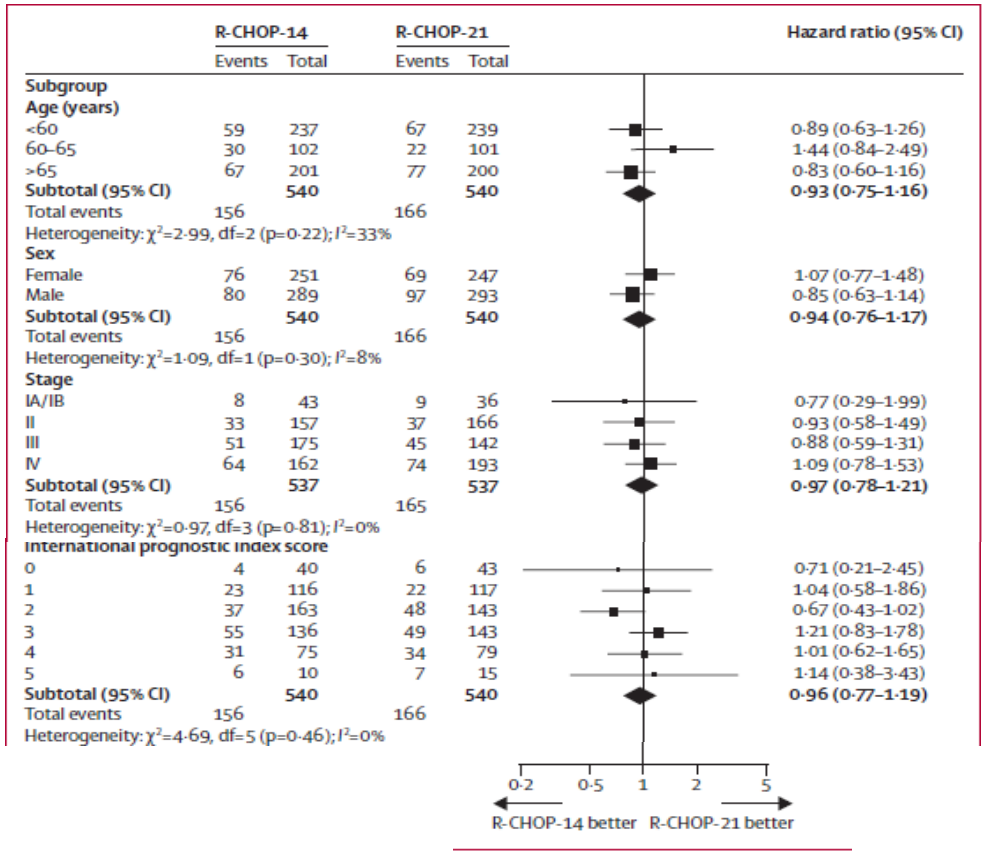


Figure 2: Progression-free survival (A) and overall survival (B) according to treatment

RCHOP21 vs. RCHOP14

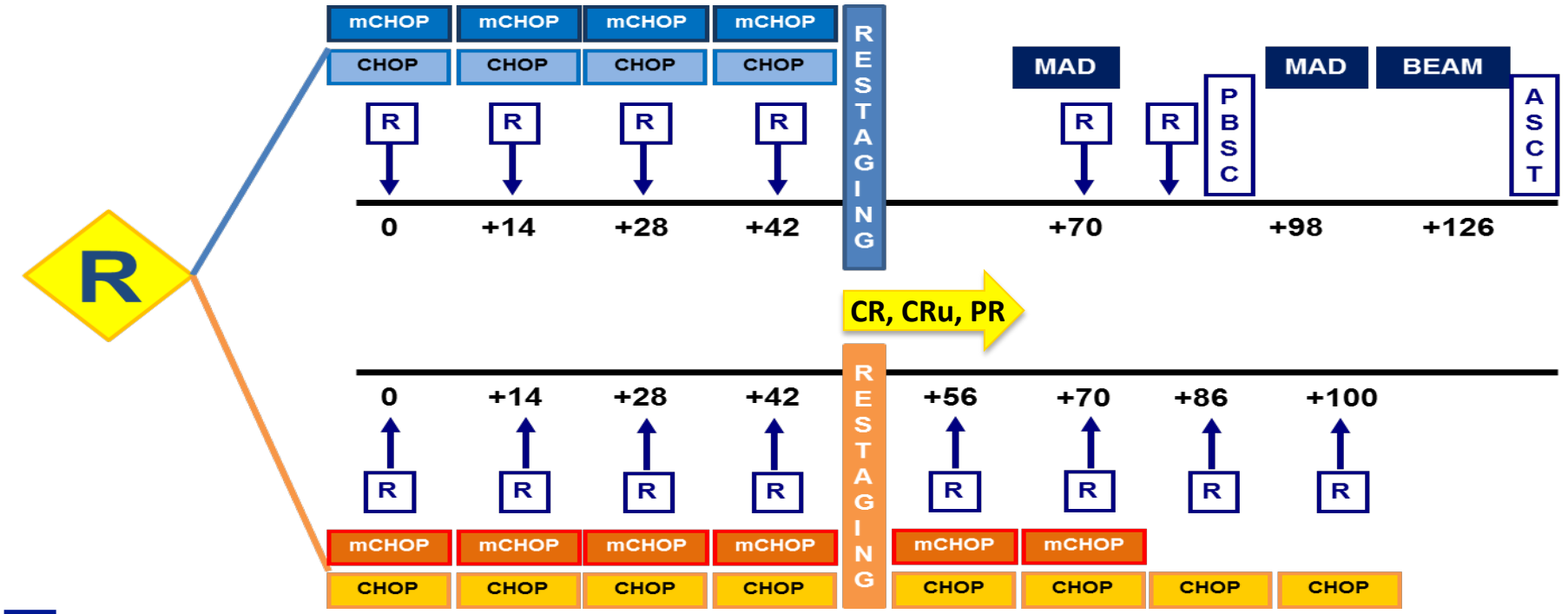


Cunningham D et al, Lancet 2013

Improving DLBCL outcome: intensifying chemotherapy?

High-dose chemotherapy and ASCT?

Untreated DLBCL de novo or Follicular gIIIb or PMBCL with extrathoracic localization; age 18-65 years; aa-IPI 2-3; CNS negative



R Rituximab 375 mg/sqm

mCHOP
mCHOP
MegaCHOP14: Cyclophosphamide 1200 mg/sqm d 1
Doxorubicine 70 mg/sqm d 1
Vincristine 1,4 mg/sqm (capped at 2 mg) d 1
Prednisone 100 mg dd 1-5

CHOP
CHOP
CHOP14: Cyclophosphamide 750 mg/sqm d 1
Doxorubicine 50 mg/sqm d 1
Vincristine 1,4 mg/sqm (capped at 2 mg) d 1
Prednisone 100 mg dd 1-5

MAD
Mitoxantrone 8 mg/sqm dd 1-3
Citarabine 2000 mg/sqm/bid dd 1-3
Dexametasone 4 mg/sqm/bid dd 1-3

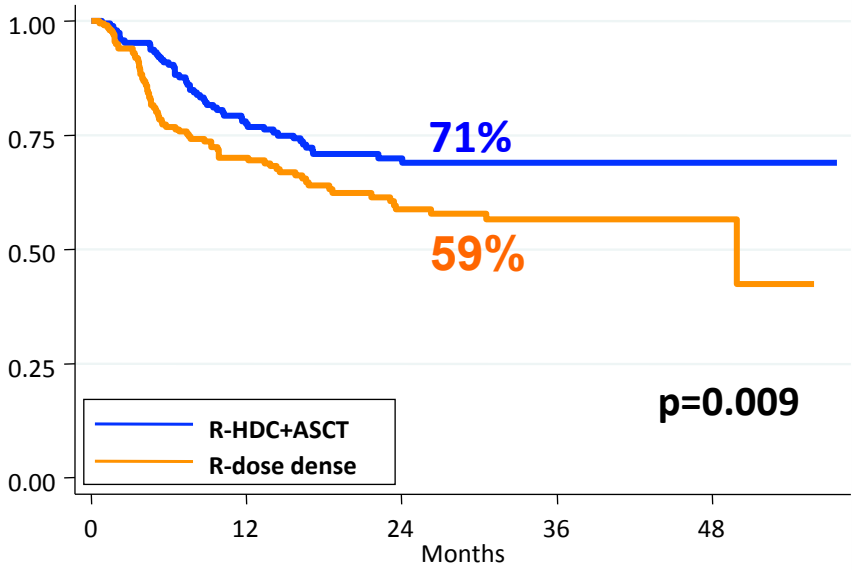
BEAM
BCNU 300 mg/sqm d -7
Cytarabine 200 mg/sqm/bid dd -6,-5,-4,-3
Etoposide 100 mg/sqm/bid dd -6,-5,-4,-3
Melphalan 140 mg/sqm d -2

Umberto Vitolo

Intention-to-treat analysis on 399 patients; median follow-up 25 months overall 2-year PFS: 65% (95% CI:59-70)

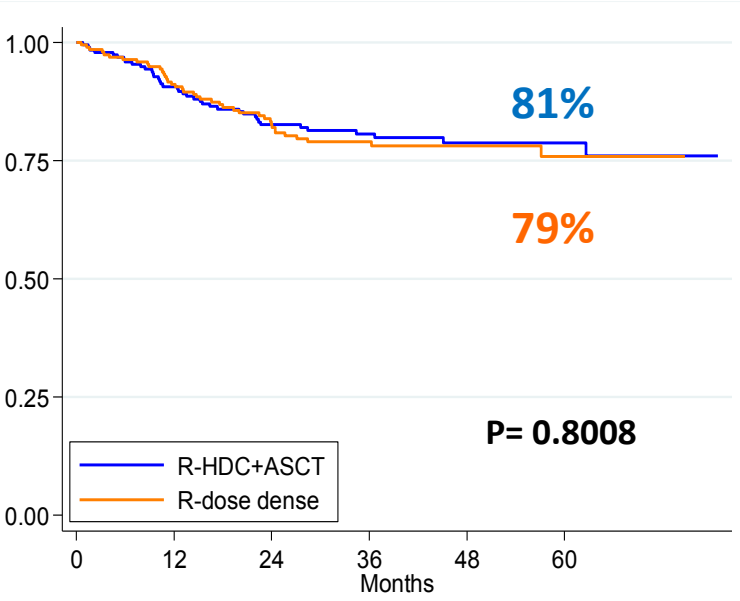
Response	R-HDC+ASCT n = 199	R-dose dense n = 200
CR/CRu	76%	72%

2-year PFS: R-HDC+ASCT vs R-CHOP/R-MegaCHOP



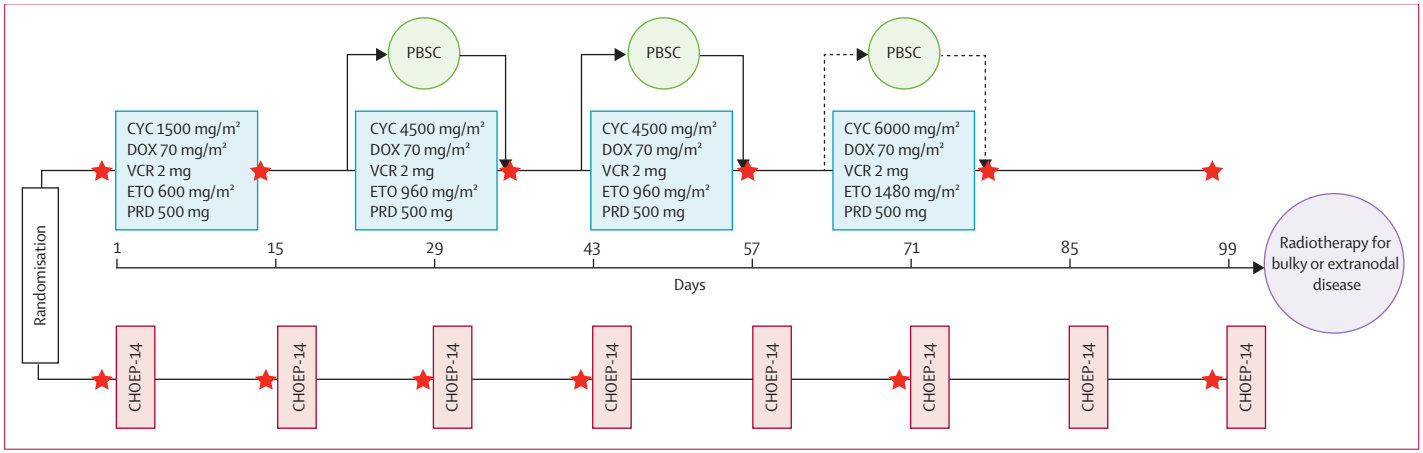
At risk:									
R-HDC+ASCT	199	176	130	101	78	65	51	34	14
R-dose dense	200	145	116	79	65	51	33	20	6

2-year OS: R-HDC+ASCT vs R-CHOP/R-MegaCHOP

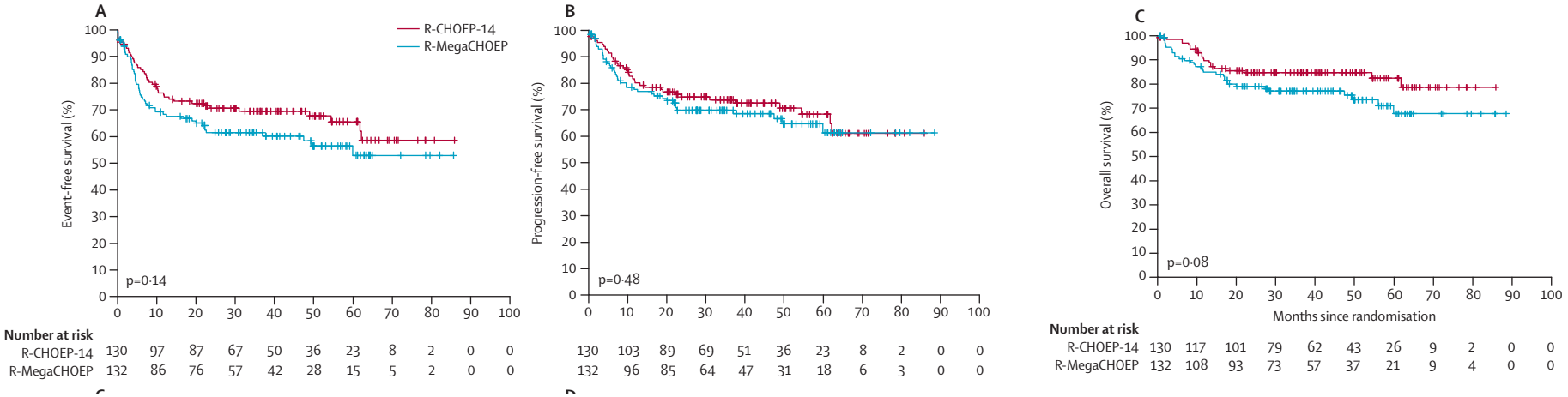


At risk:											
R-HDC+ASCT	199	186	172	161	146	130	106	83	63	52	35
R-dose dense	200	188	172	149	136	119	95	73	58	44	26

R-CHOEP-14 or R-Mega-CHOEP in young high-risk patients with aggressive lymphoma: DSHNHL 2002-1 trial >2



EFS **PFS** **OS**



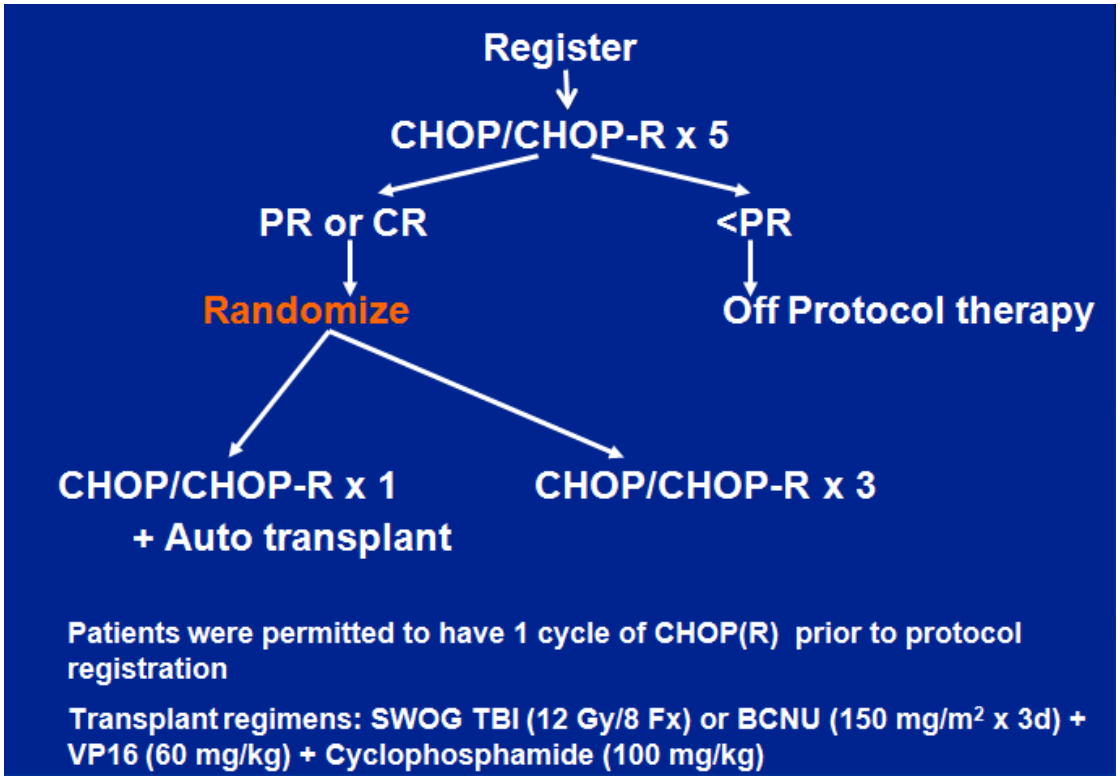
Schmitz N, et al Lancet Oncology 2012

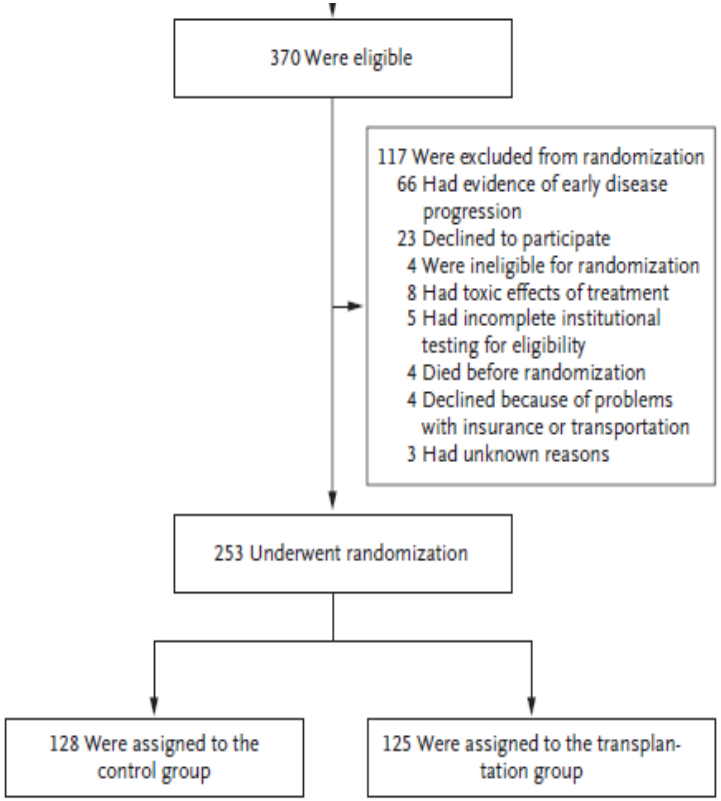
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 31, 2013 VOL. 369 NO. 18

Autologous Transplantation as Consolidation for Aggressive Non-Hodgkin's Lymphoma

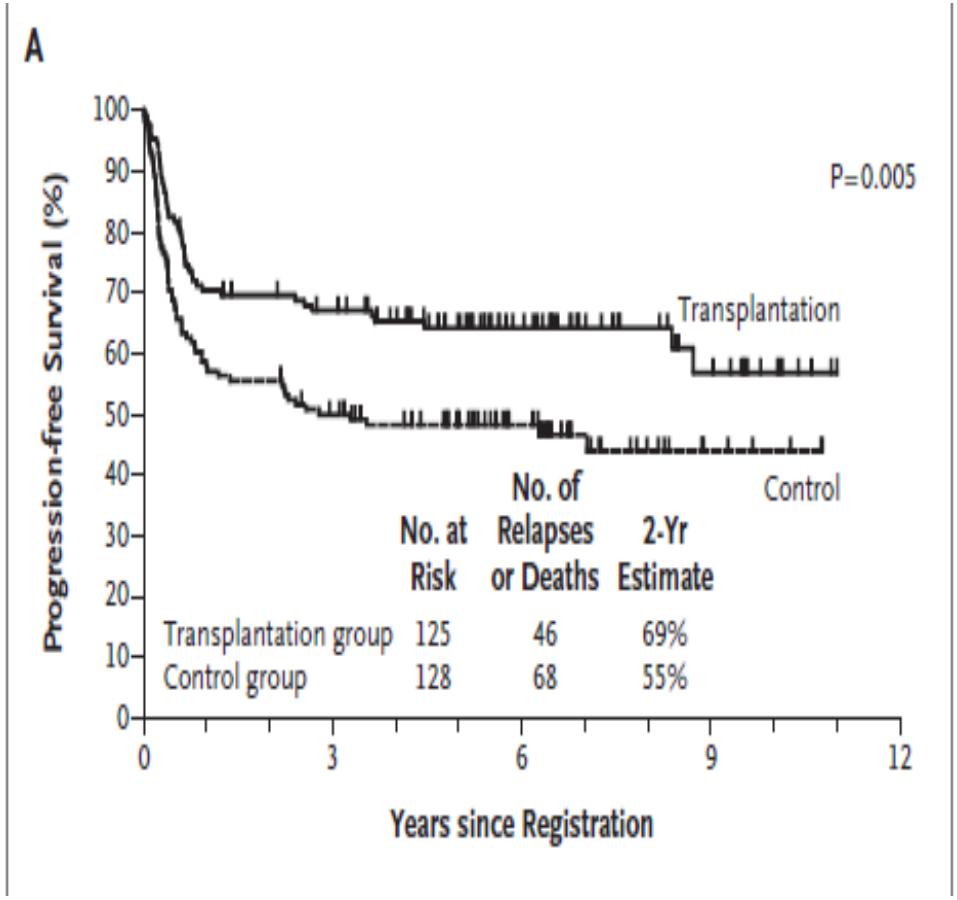
Patrick J. Stiff, M.D., Joseph M. Unger, Ph.D., James R. Cook, M.D., Ph.D., Louis S. Constine, M.D., Stephen Couban, M.D., Douglas A. Stewart, M.D., Thomas C. Shea, M.D., Pierluigi Porcu, M.D., Jane N. Winter, M.D., Brad S. Kahl, M.D., Thomas P. Miller, M.D., Raymond R. Tubbs, D.O., Deborah Marcellus, M.D., Jonathan W. Friedberg, M.D., Kevin P. Barton, M.D., Glenn M. Mills, M.D., Michael LeBlanc, Ph.D., Lisa M. Rimsza, M.D., Stephen J. Forman, M.D., and Richard I. Fisher, M.D.

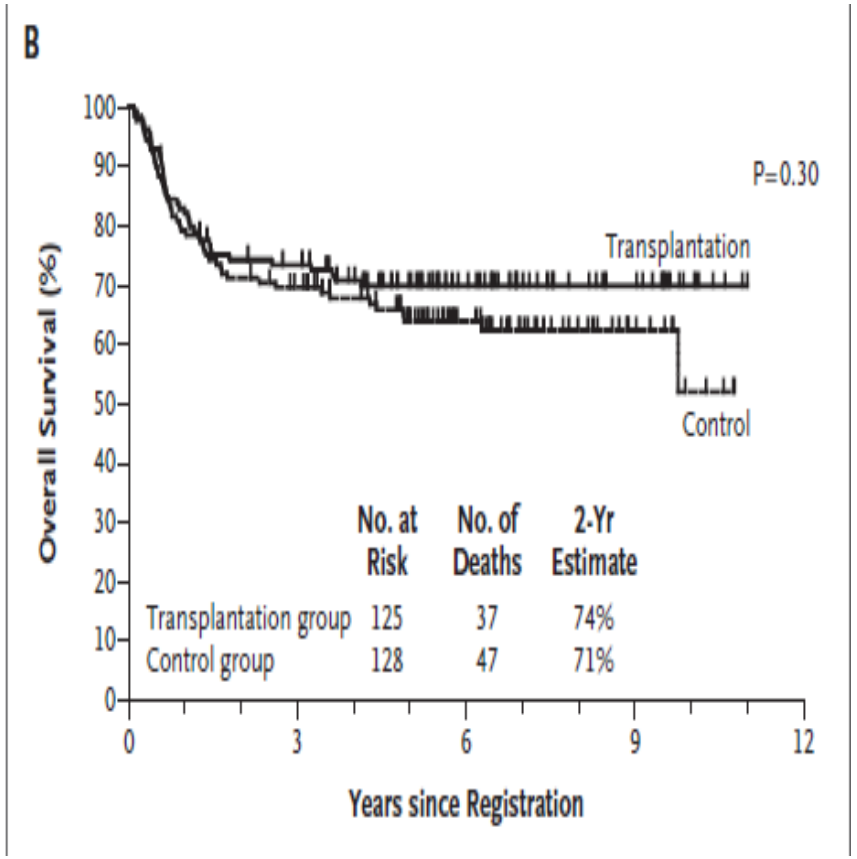




Stiff PJ, NEJM 2013

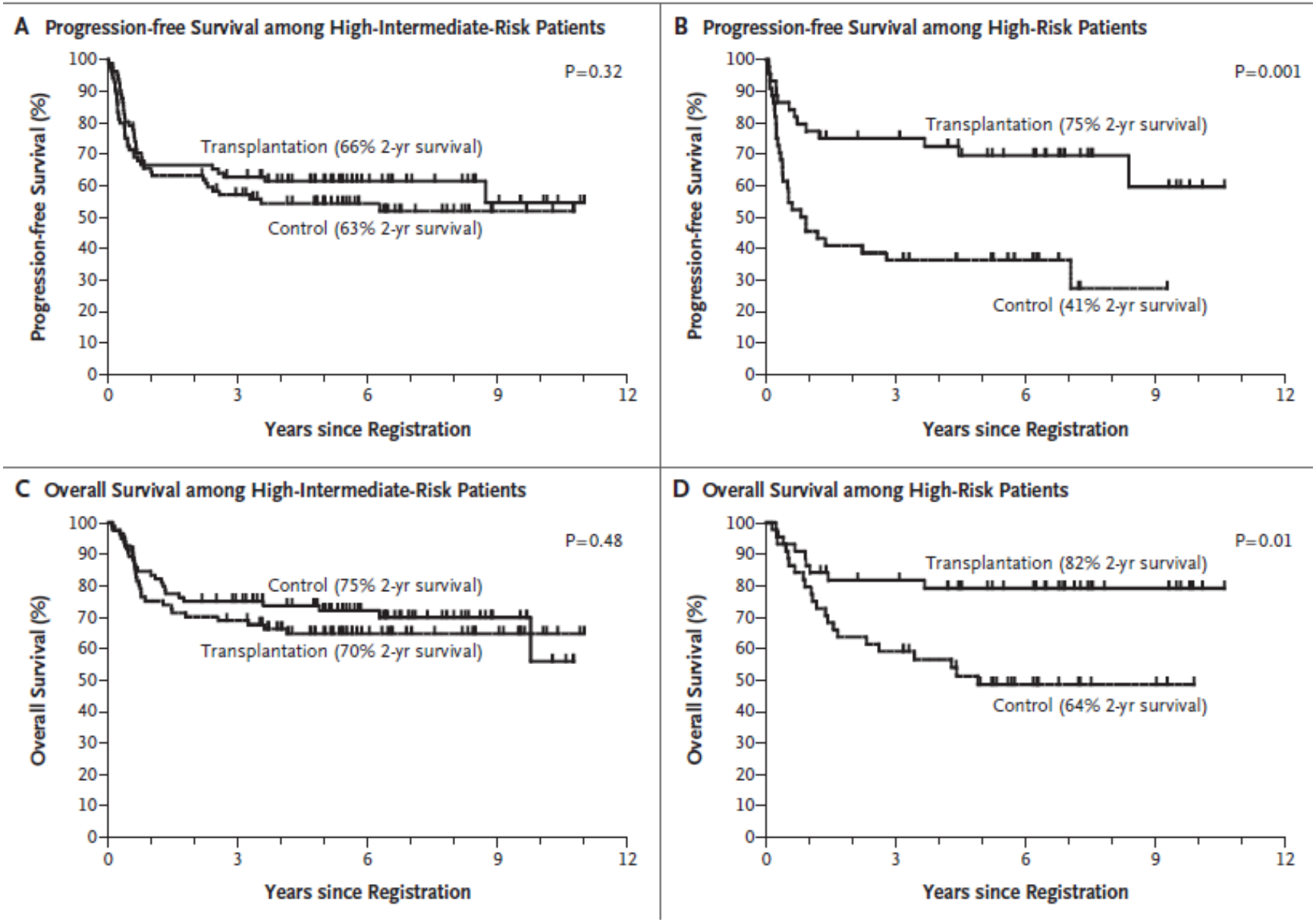
Enrolled: 370 patients.
Randomized: 253 patients in CR after CHOP +/- R x 5
CR 68% after RCHOP x 5





Stiff PJ, NEJM 2013

Survival rates according to IPI risk categories



Stiff PJ, NEJM 2013

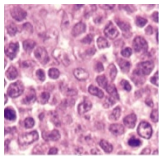
Do we need to improve R-CHOP results in DLBCL?

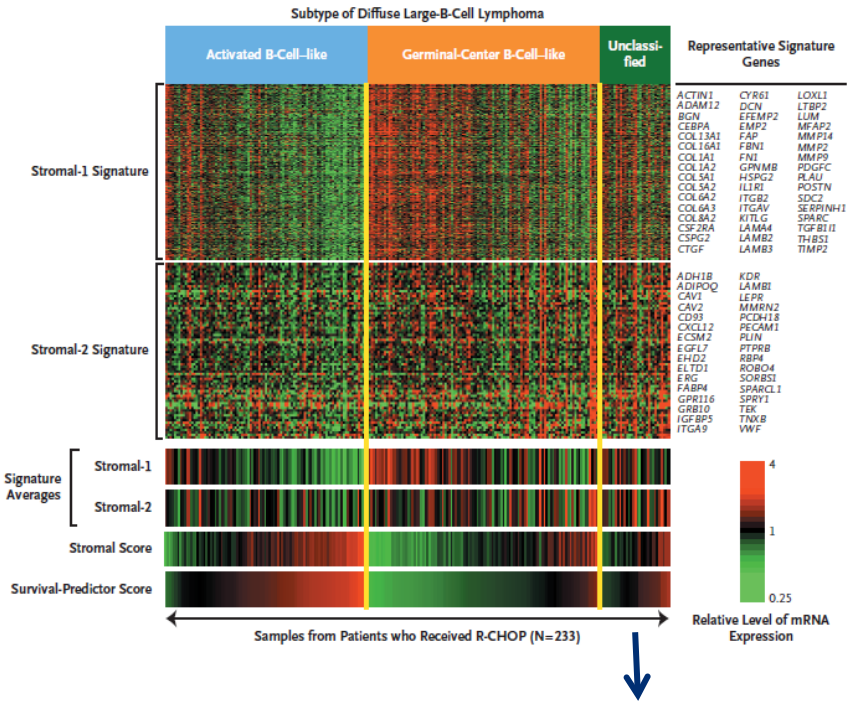
R-CHOP is the backbone…

- ✓ A better recognition based of hystopathological subtypes
- ✓ Combining novel drugs to standard chemoimmunotherapy

A better evaluation of unfavorable DLBCL subsets: COO profile subgroups

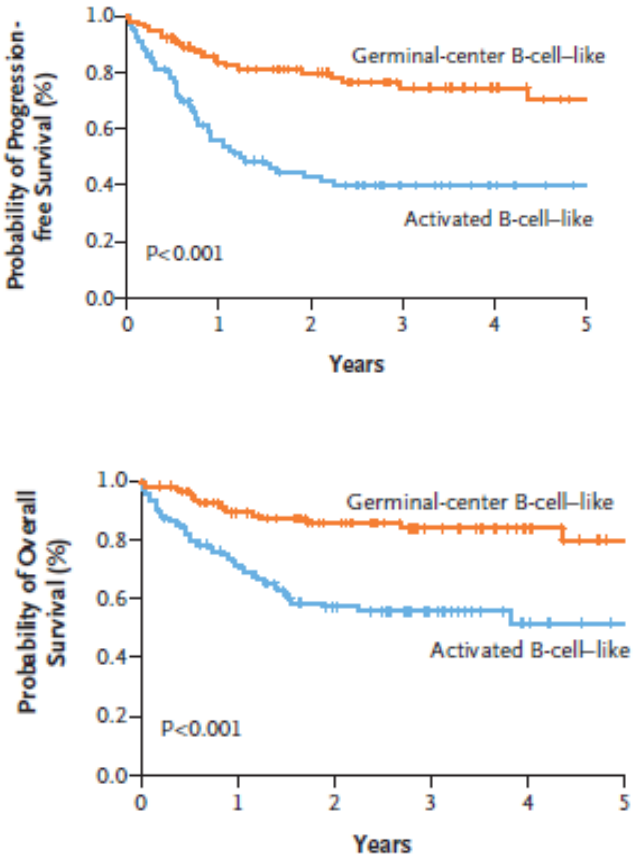
Diffuse Large B- Cell Lymphoma





15% Unclassificable

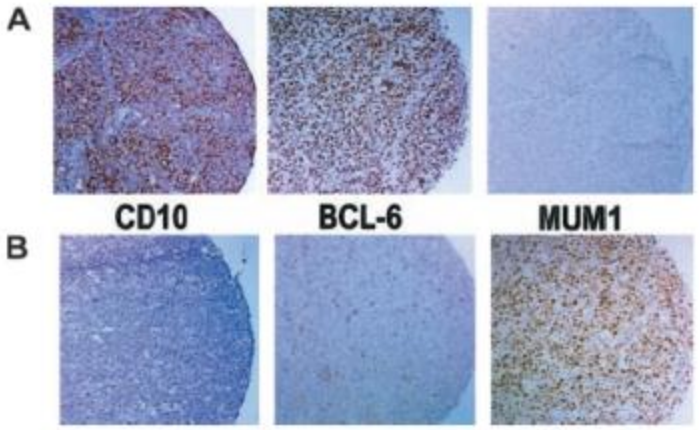
R-CHOP

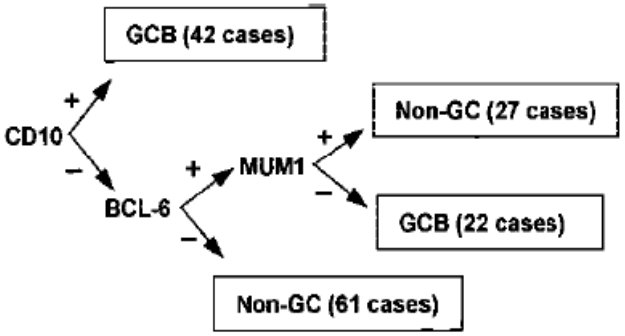


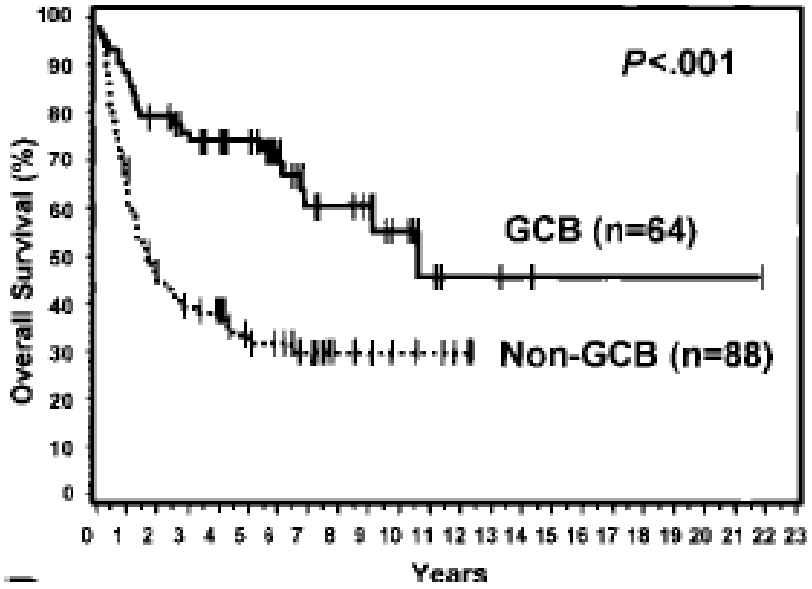
The GEP classification is not available in the daily clinical practice

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

Immunoistochemistry as a surrogate technique to identify Cell of Origin





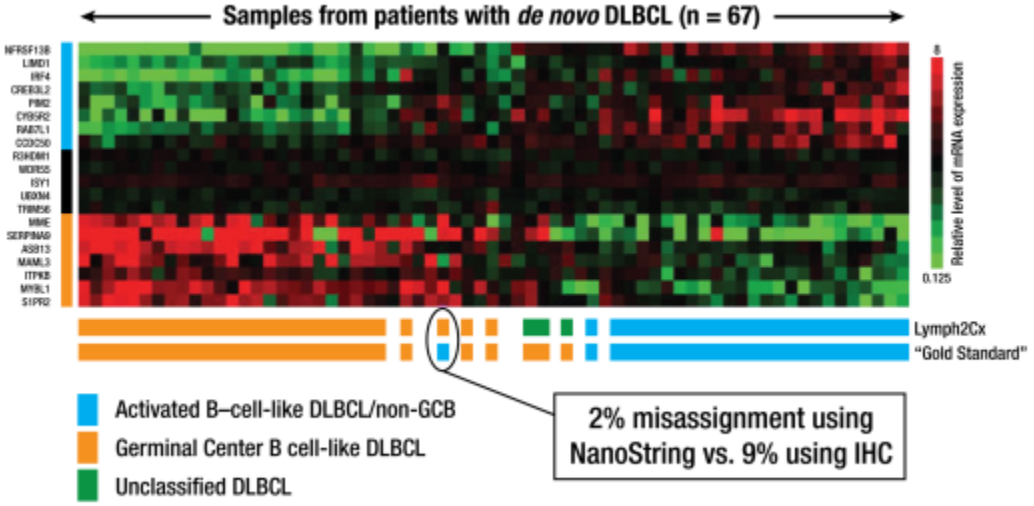


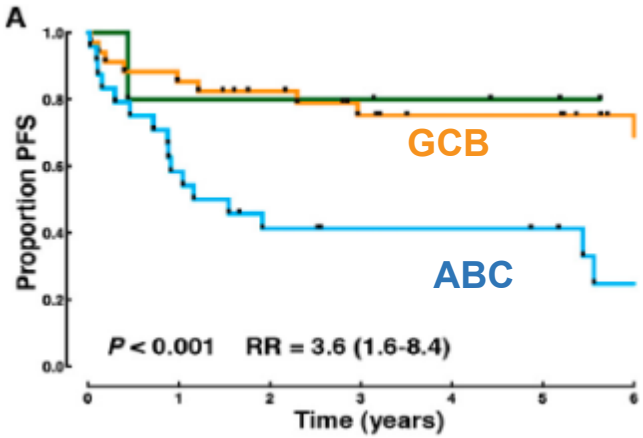
…The prognostic role of COO assessed by IHC is poorly reproducible with controversial results in the Rituximab era!

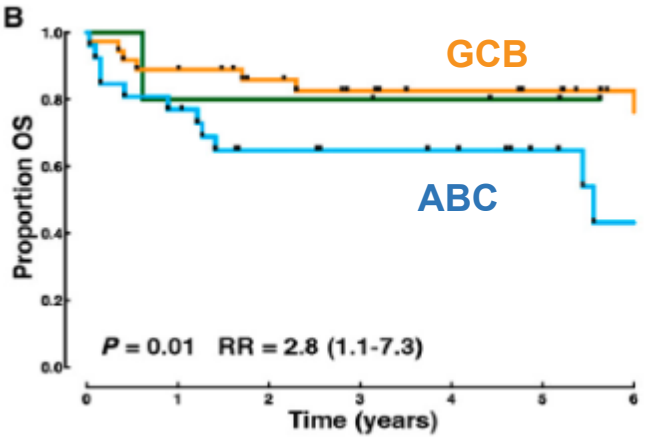
Hans et al. Blood 2004; 103: 275-82

A better recognition of unfavorable DLBCL subsets: COO profile subgroups

Nanostring technology







Scott D et al. Blood 2014; 123: 1214-1217

VOLUME 33 · NUMBER 26 · SEPTEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies

David W. Scott, Anja Mottok, Daisuke Ennishi, George W. Wright, Pedro Farinha, Susana Ben-Neriah, Robert Kridel, Garrett S. Barry, Christoffer Hother, Pau Abrisqueta, Merrill Boyle, Barbara Meissner, Adele Telenius, Kerry J. Savage, Laurie H. Sehn, Graham W. Slack, Christian Steidl, Louis M. Staudt, Joseph M. Connors, Lisa M. Rimsza, and Randy D. Gascoyne

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

Pts 344 R-CHOP

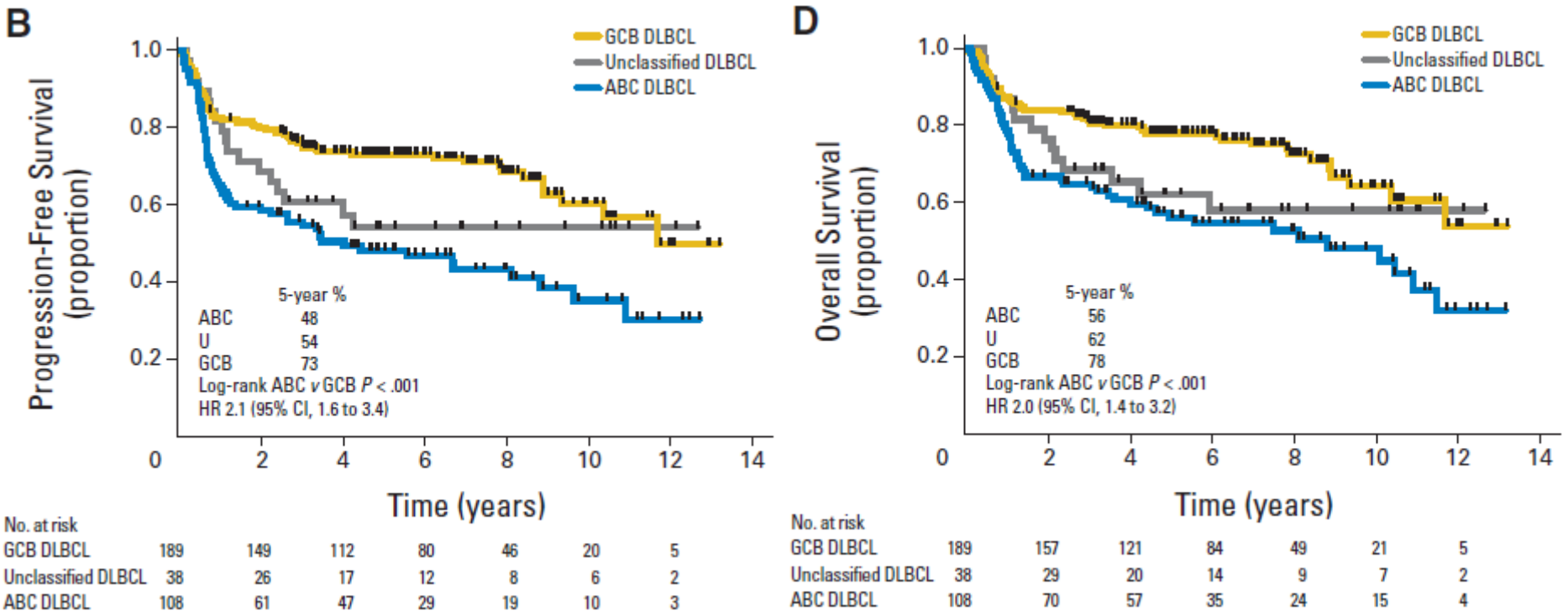
Characteristic	ABC DLBCL (n = 108)	GCB DLBCL (n = 189)	Unclassified DLBCL (n = 38)	*P* (ABC *v* GCB)
Age, years				.30
Median (range)	66.5 (16-86)	62 (16-92)	60.5 (20-87)	
Sex, No. (%)				.31
Male	71 (66)	113 (60)	25 (66)	
Female	37 (34)	76 (40)	13 (34)	
B symptoms, No. (%)				.61
Absent	66 (62)	122 (65)	22 (58)	
Present	40 (38)	65 (35)	16 (42)	
Missing	2	2	0	
Bulk (> 10 cm), No. (%)				.54
Absent	82 (77)	135 (74)	28 (74)	
Present	24 (23)	47 (26)	10 (26)	
Missing	2	7	0	
Disease stage, No. (%)				.61
Limited	32 (30)	61 (33)	10 (26)	
Advanced	75 (70)	125 (67)	28 (74)	
Missing	1	3	0	

ABC=108 (31%) **GCB=189 (55%)** **Unclassicable=38 (11%)**

VOLUME 33 · NUMBER 26 · SEPTEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Nanostring technology predicts survival in DLBCL treated with R-CHOP

Scott D et al. J Clin Oncol 2015; 33: 2848-56

Different targets and agents in GBC and ABC DLBCL subtypes

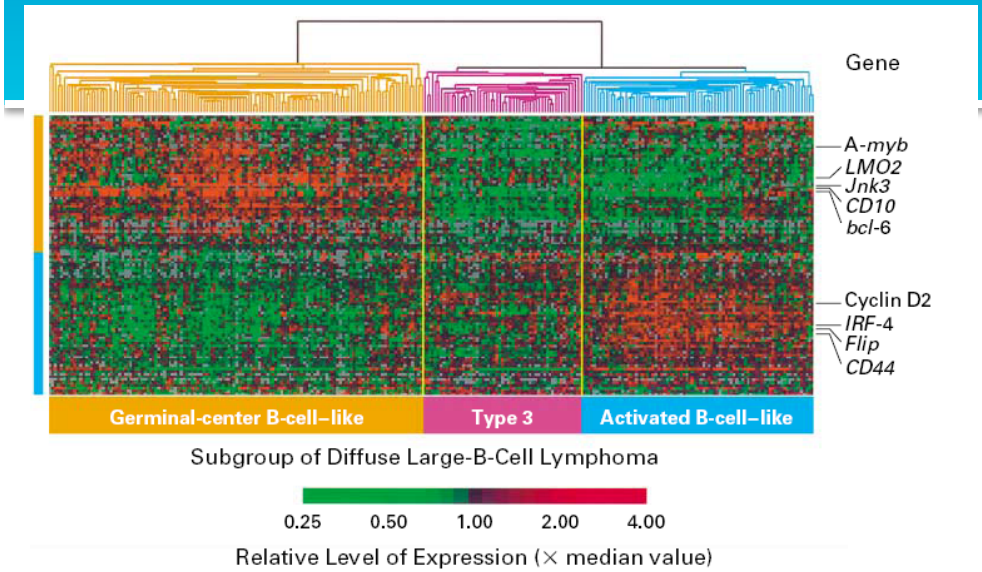
- **Gene Expression Profiling Subsets: histologically indistinguishable ; molecularly distinct; differential sensitivity to targeted agents**

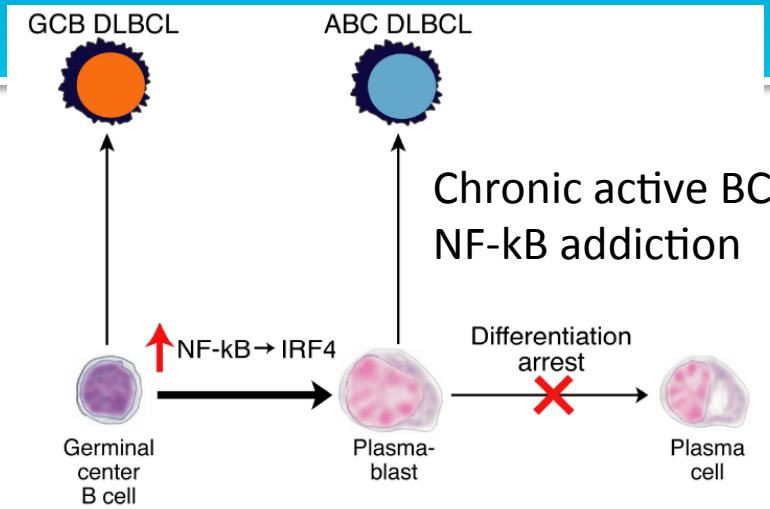
Molecular Aberration	GBC	ABC
BCL2 translocation	++	-
c-rel amplification	++	-
EZ2H mutation	++	-
MYD88 mutation	+	+++
CD79A, CD79B mutation	-	++
BCL6 translocation	+	++
BCL6 pathway	+++	++
MYC pathway	+	+++
NF-κB pathway	-	+++
BCR pathway	-	++
IRF4 pathway	-	+++

Targets	Agents	GCB	ABC
proteasome (NFκB)	*bortezomib* *MLN4924*		++
mTOR/ PI3 kinase	*BKM120* *SAR245409* *everolimus*		++
PKCβ	*sotrastaurin*		++
BTK	*ibrutinib*		++
SYK	GS9973		++
AKT	*MK2206*		++
Microenvironment	*lenalidomide*	+	++

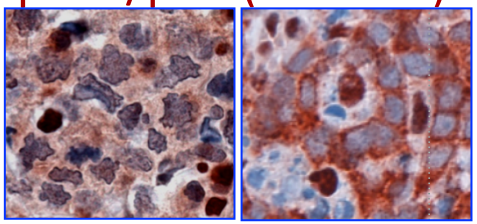
Lenz et al. N Eng J Med 2010;362(15):1417-1429

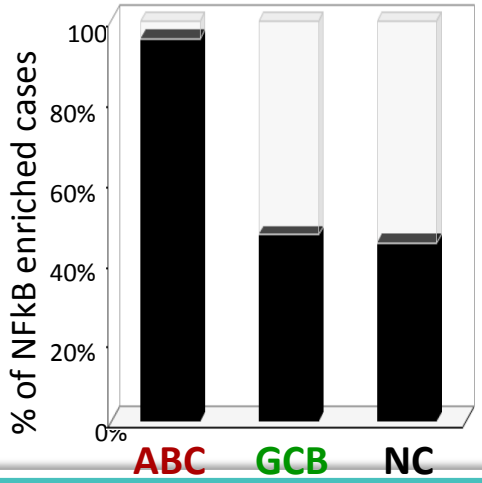
ABC-DLBCL is addicted to NF-kB



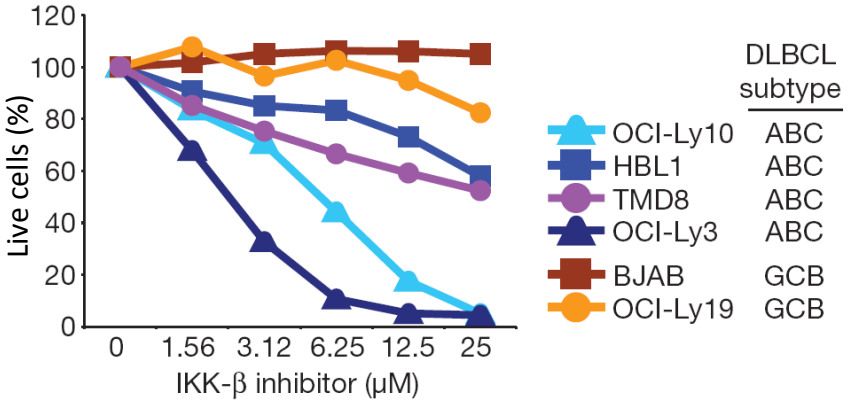


100% ABC-DLBCL have NF-kB activation





NF-kB inhibition is lethal for ABC DLBCL



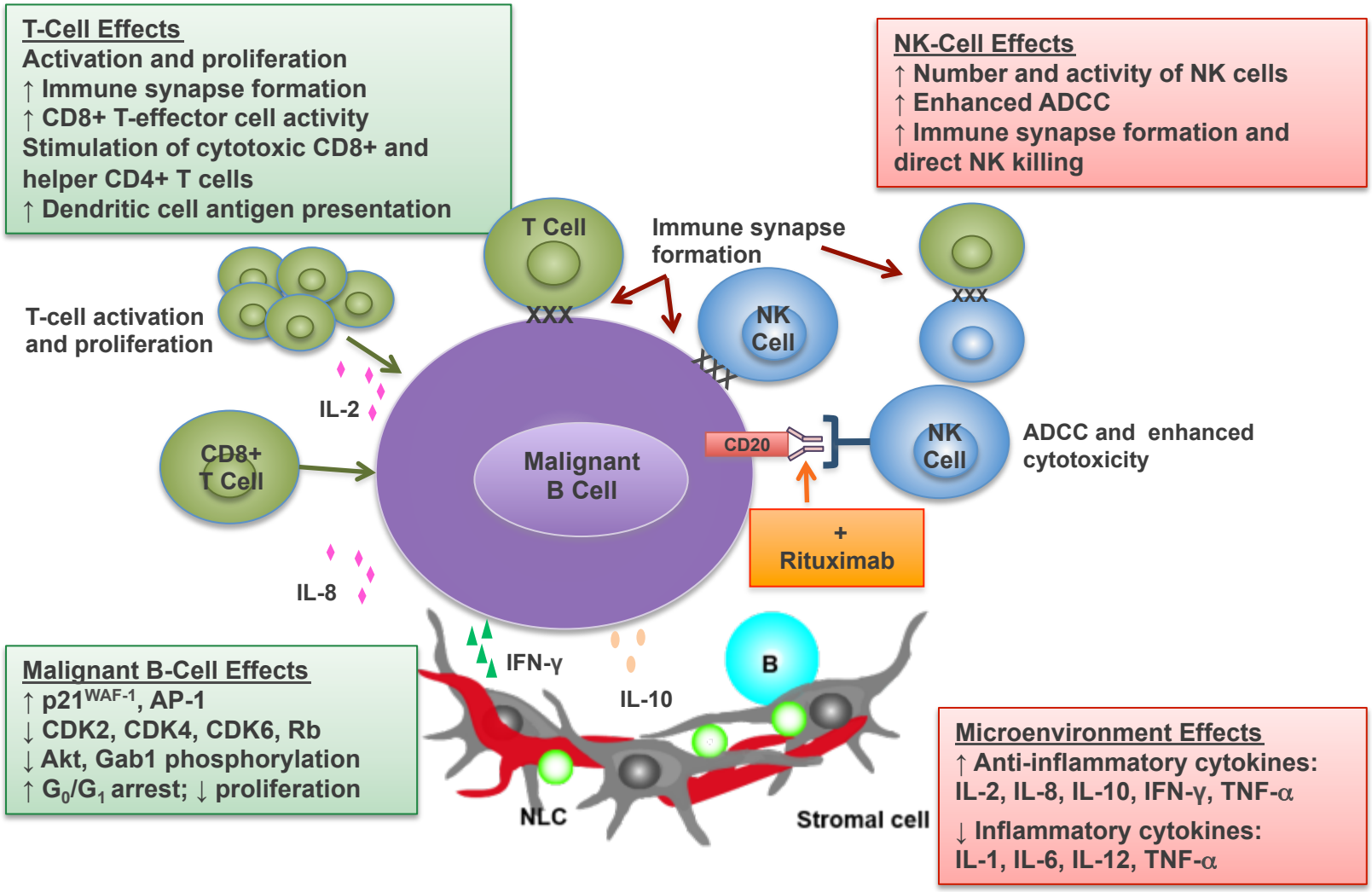
Lenz et al. NEJM, 2008
Compagno et al, Nature 2009
Davis et al, Nature 2010

Do we need to improve R-CHOP results in DLBCL?

R-CHOP is the backbone…

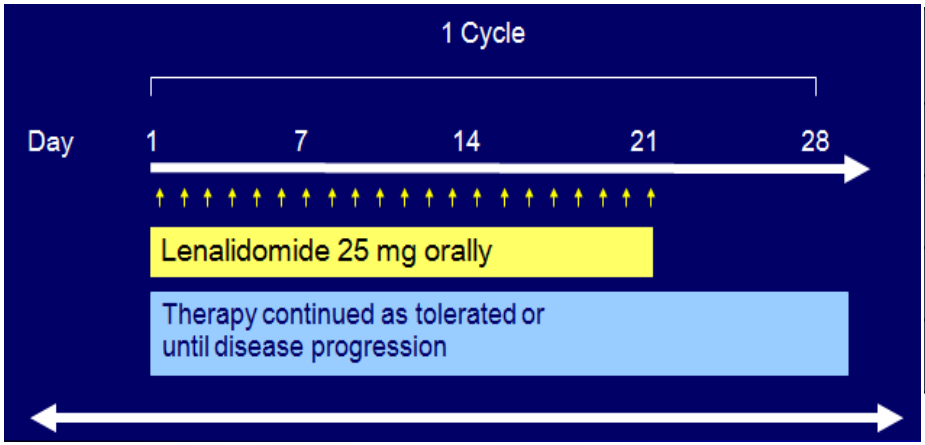
- ✓ A better recognition based of hystopathological subtypes
- ✓ Combining novel drugs to standard chemoimmunotherapy

Mechanisms of Action of Lenalidomide in Lymphoma Cells and Nodal Microenvironment



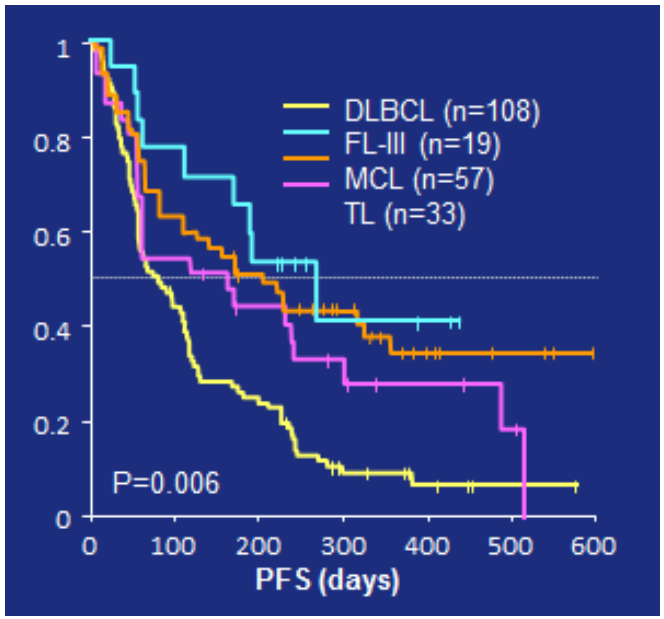
Presented with permission from J. Gribben.

Lenalidomide in relapsed/refractory DLBCL



Histology, n (%)	ORR
Aggressive NHL, 49 (100%)	17 (35%)
DLBCL, 26 (53%)	5 (19%)
MCL, 15 (31%)	8 (53%)
Follicular g3, 5 (10%)	3 (60%)

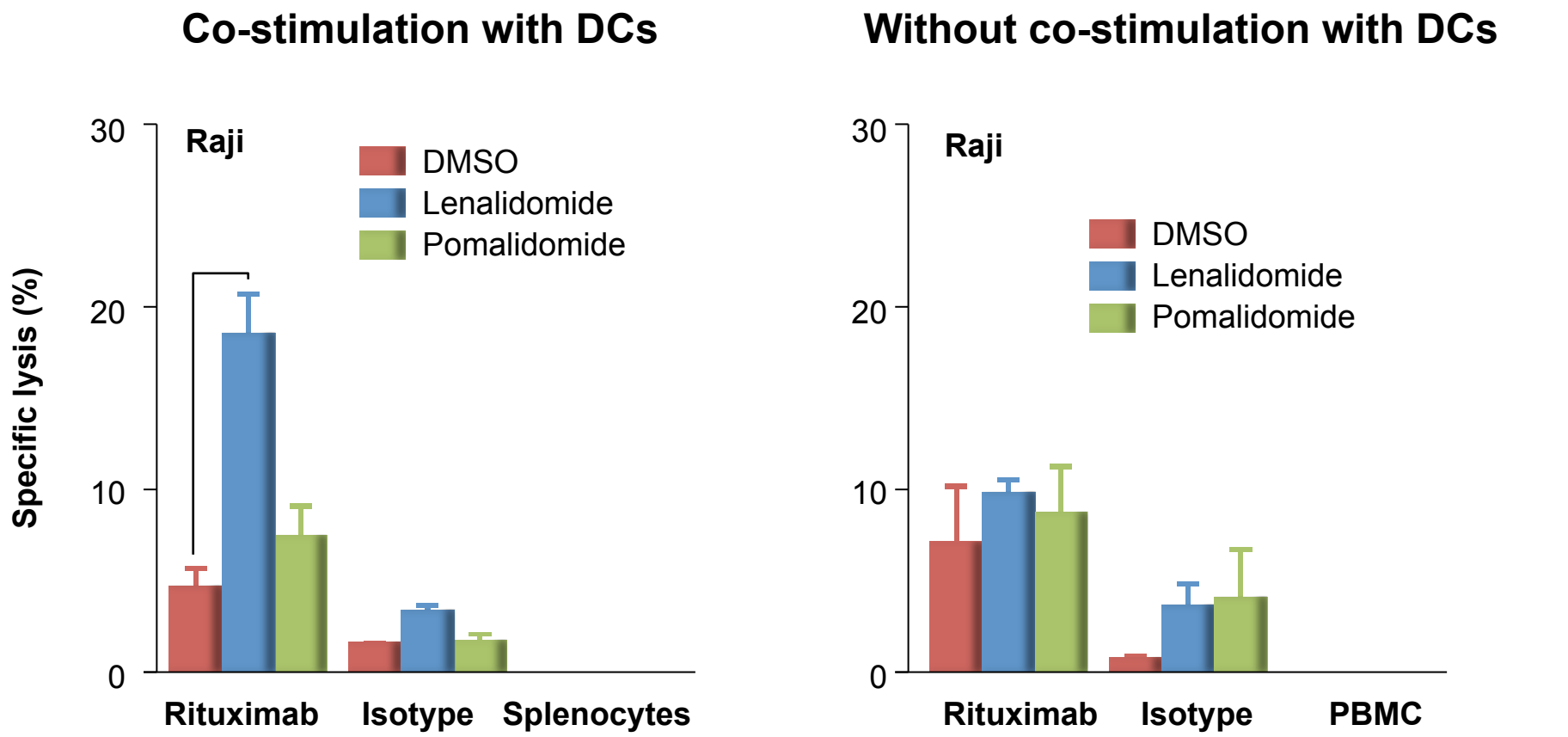
Wiernik PH et al, J Clin Oncol 2008.



Witzig et al 2011

Author	N.	ORR	CR/Cru	Median PFS (months)	Median DOR (months)
Wiernik 2008	26	19%	15%	2-3	
Witzig 2011	108	28%	7%	2.7	4.6
REVEAL 2013	77	43%	18%	3.5	

IMiD enhancement of rituximab-dependent ADCC ex vivo is mediated via co-stimulation of NK-cells by DCs



Provides rationale for R2 regimen

Data is represented by means with error bars showing mean ± 1.0 SE.

ADCC, antibody-dependent cellular cytotoxicity; DC, dendritic cell; DMSO, dimethyl sulfoxide; IMiD, immunomodulatory drug; NK, natural killer; PBMC, peripheral blood mononuclear cells; SE, standard error.

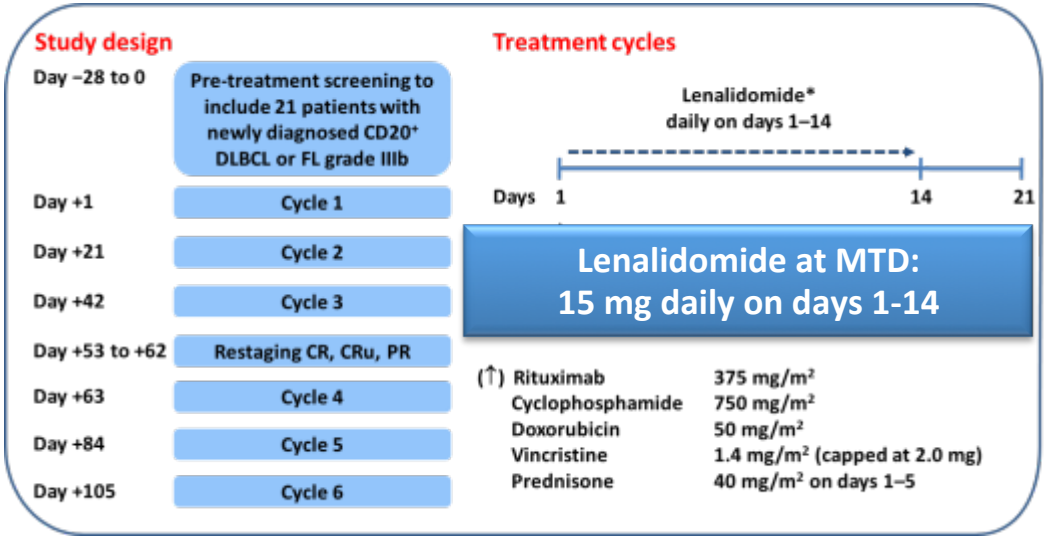
Reddy N, et al. Br J Haematol. 2007;140:36-45.

Articles

Lancet Oncol 2014

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, Vincenzo 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



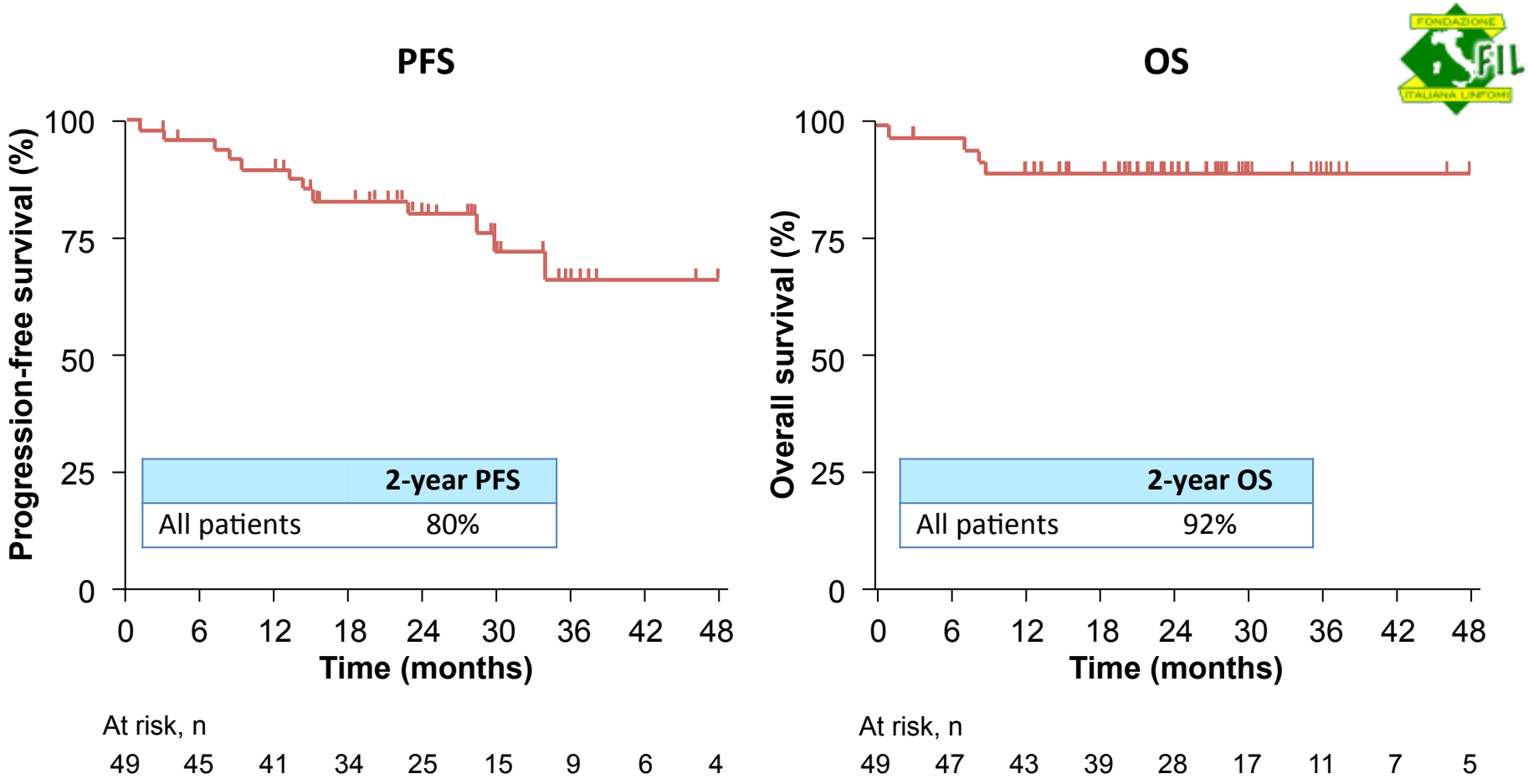
CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

	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**

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: ORR 92%, CR 86%; PFS and OS



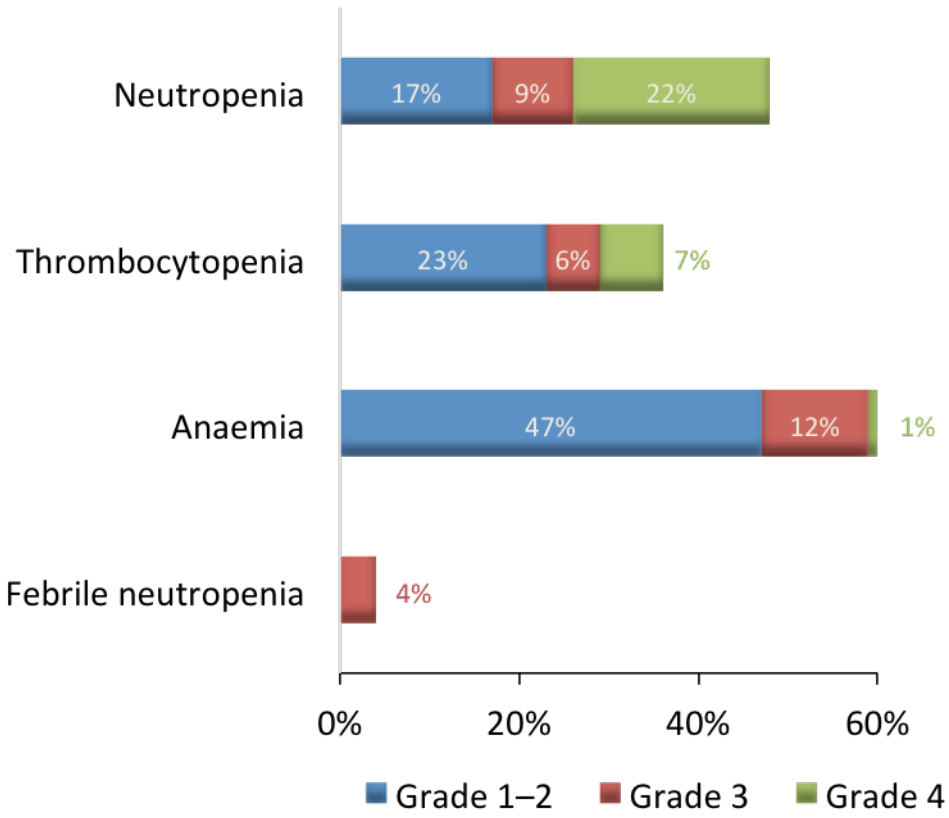
Median follow-up of 28 months. N = 49 elderly DLBCL patients.

DLBCL, diffuse large B-cell lymphoma ; PFS, progression-free survival; OS, overall survival; R2-CHOP, lenalidomide and rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

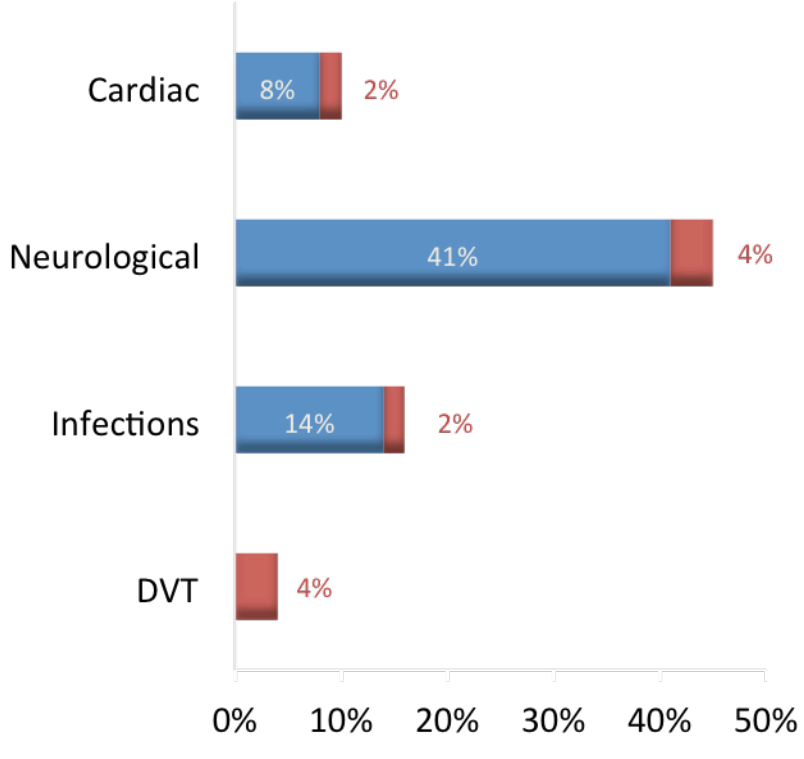
Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: safety data – all grades AEs

Haematological AEs by % of treatment cycles (n = 277)



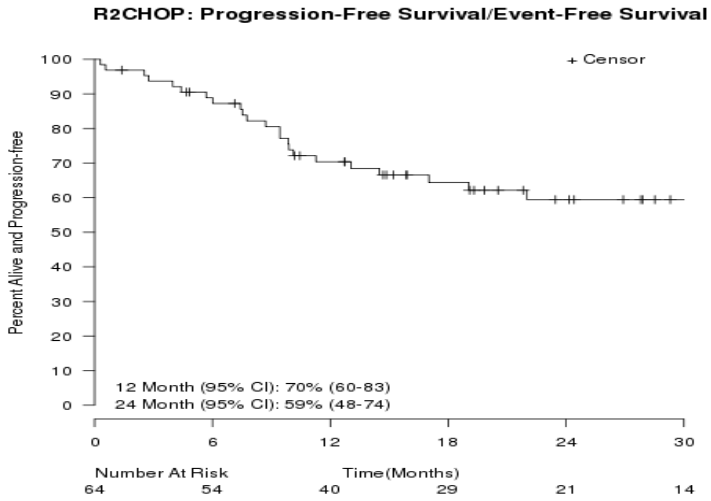
Non-haematological AEs by % of patients (n = 49)

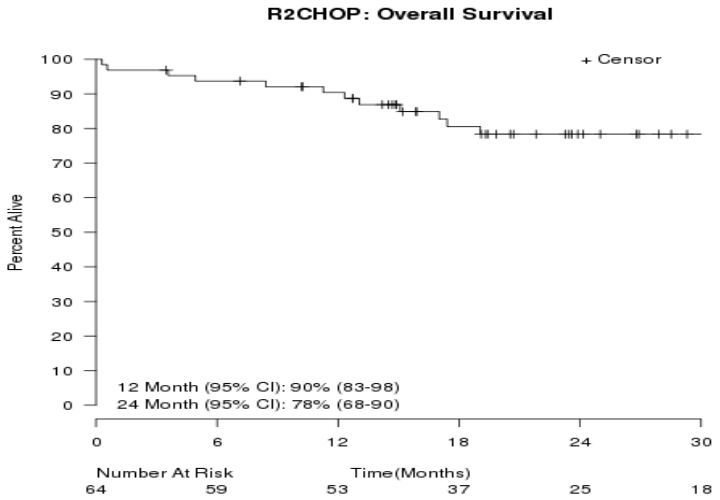


AEs, adverse events; DLBCL, diffuse large B-cell lymphoma; DVT, deep-vein thrombosis.

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

R2CHOP 64 patients median age 65 (22-87), IPI int-high and high 52% : PFS and OS

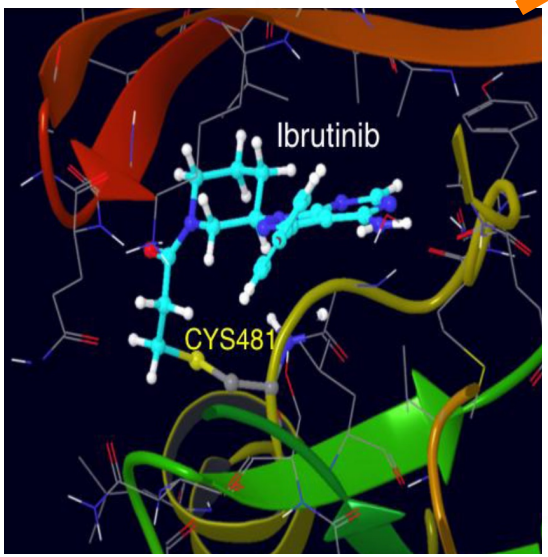




Agent	Dose	Route	Day of cycle
Lenalidomide	**25 mg**	**p.o.**	**1–10**
Rituximab	375 mg/ m^2	i.v.	1
Cyclophosphamide	750 mg/ m^2	i.v.	1
Doxorubicin	50 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2	i.v.	1
Prednisone	100 mg/ m^2	p.o.	1-5
Pegfilgrastim	*6 mg*	*s.c.*	*2*
Aspirin	*81 mg*	*p.o.*	*daily*

Nowakowski GS, et al. J Clin Oncol. 2015;33:251-7.

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

VOLUME 31 · NUMBER 1 · JANUARY 1 2013

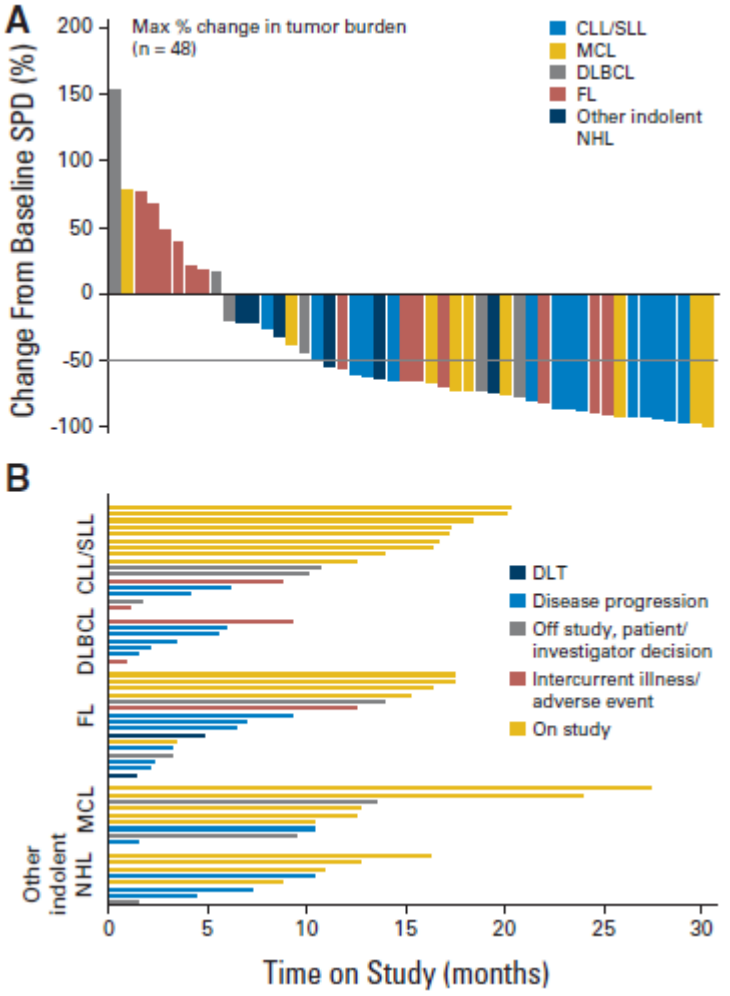
JOURNAL OF CLINICAL ONCOLOGY

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



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)

[a]One patient received rituximab only.
R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

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

Ibrutinib and R-CHOP for untreated CD20+ B-cell NHL: adverse events

Adverse events that occurred in ≥ 10% of patients, and all Grade 3–5 events

	Ibrutinib plus R-CHOP (N = 33)[a]			
n (%)	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	22 (67)	1 (3)	-	-
Vomiting	19 (58)	1 (3)	-	-
Fatigue	15 (45)	-	-	-
Constipation	14 (42)	-	-	-
Thrombocytopenia	**14 (42)**	**7 (21)**	-	-
Diarrhoea	12 (36)	1 (3)	-	-
Headache	11 (33)	-	-	-
Peripheral sensory neuropathy	10 (30)	-	-	-
Alopecia	9 (27)	-	-	-
Dyspnoea	9 (27)	-	-	-
Anaemia	**8 (24)**	**6 (18)**	-	-
Febrile neutropenia	-	**6 (18)**	-	-
Leukocytosis	-	**1 (3)**	-	-
Neutropenia	**1 (3)**	**1 (3)**	**23 (70)**	-
Parainfluzae virus infection	-	1 (3)	-	-
Periorbital cellulitis	-	1 (3)	-	-
Pyrexia	3 (9)	1 (3)	-	-
Testicular oedema	-	1 (3)	-	-
Urinary tract infection	2 (6)	1 (3)	-	-
Comitted suicide	-	-	-	1 (3)

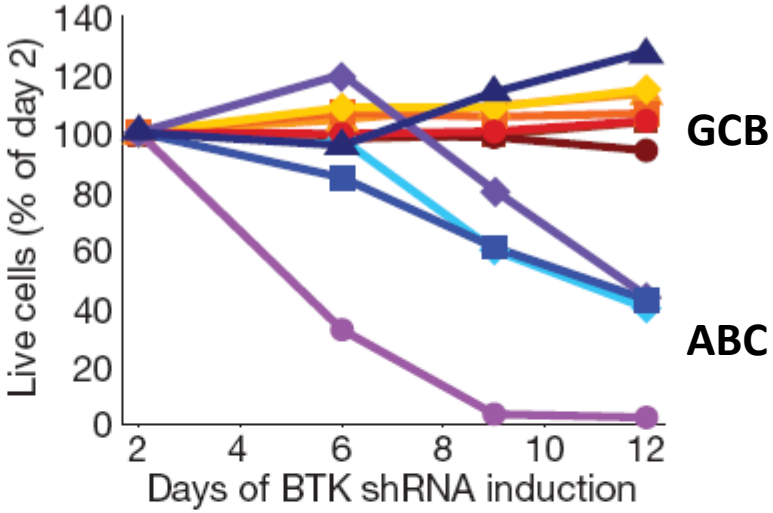
[a]One patient received rituximab only.
R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

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

Selective activity of Lenalidomide and Ibrutinib in ABC subtype?

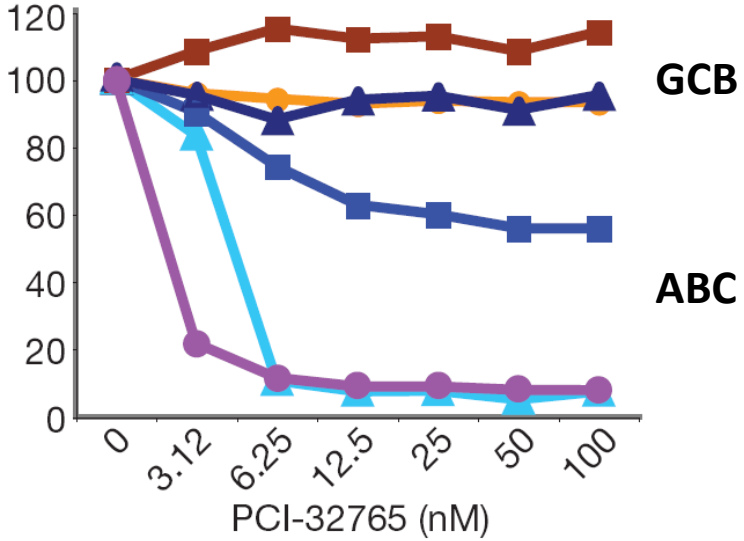
Switch-off of BTK is lethal for ABC-DLBCL

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

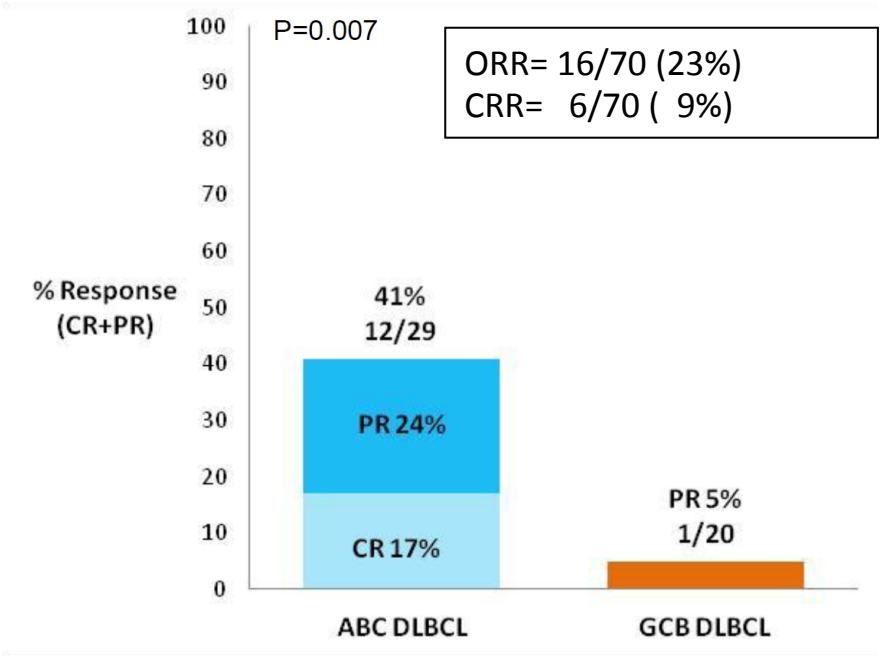


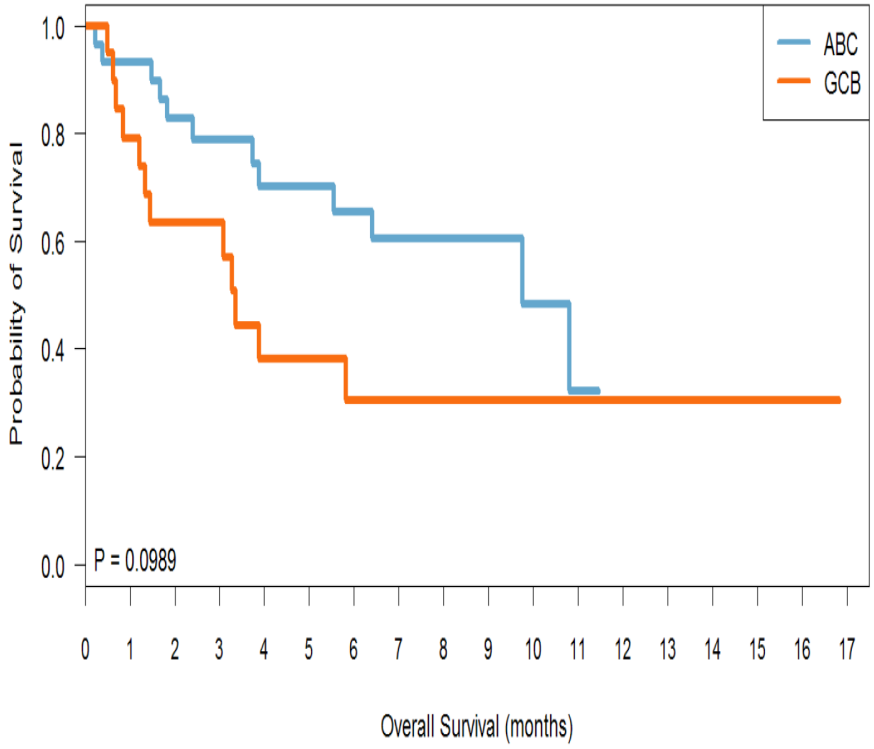
	DLBCL subtype	Chronic active BCR signalling
OCI-Ly10	ABC	+
HBL1	ABC	+
TMD8	ABC	+
OCI-Ly3	ABC	–
BJAB	GCB	–
OCI-Ly19	GCB	–

Davis et al, Nature 2010

IBRUTINIB IN DLBCL

TOTAL N^ 70	ABC	GCB
ABC/GCB	29	20
Median prior Tx	3 (1-7)	3.5 (1-7)
Prior ASCT	17%	30%
Refractory	41%	70%





Wilson W, ASH 2012

A phase II/III multicentre, randomized study comparing lenalidomide with investigator's choice in R/R DLBCL: efficacy

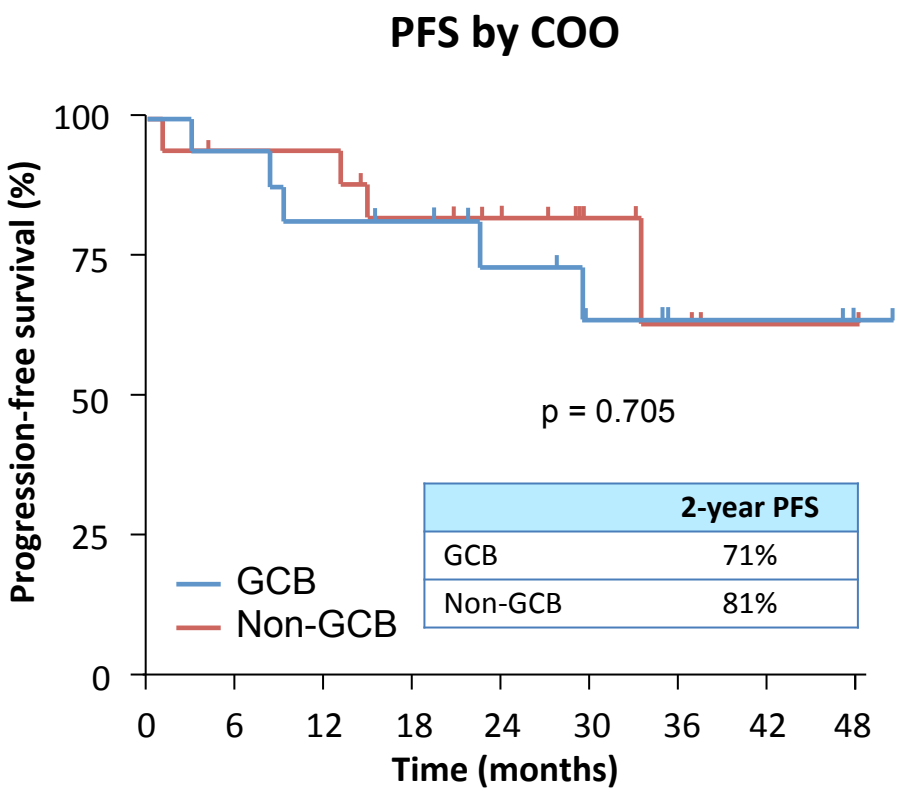
- Patients had received ≥ 2 prior therapies, or were ineligible for ASCT
- Median age 67 years

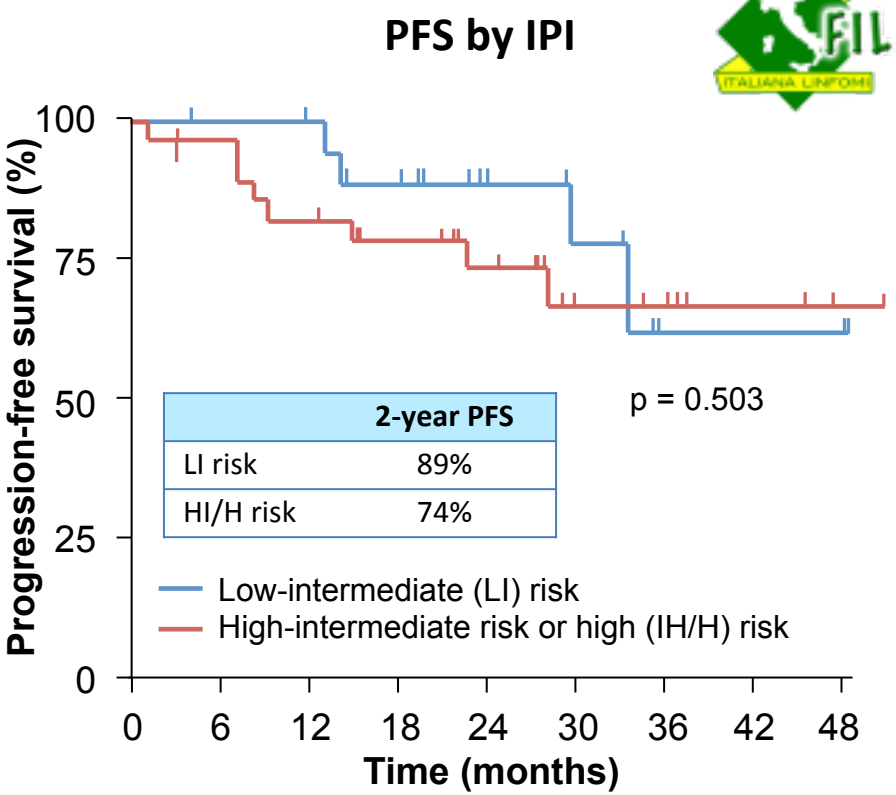
	Overall		By GEP			
			GCB		ABC	
	LEN (n = 51)	IC (n = 51)	LEN (n = 14)	IC (n = 16)	LEN (n = 11)	IC (n = 16)
ORR, %	27.5	11.8	21.4	12.5	45.5	18.8
p value	0.079		0.642		0.206	
PFS, median, weeks	13.6	7.9	13.2	7.1	82.0	6.2
p value	0.041		0.506		0.105	

ABC, activated B-cell like; ASCT, autologous stem cell transplantation; GCB, germinal centre B-cell like; GEP, gene expression profiling; IC, investigator's choice; LEN, lenalidomide; ORR, overall response rate; PFS, progression-free survival; R/R DLBCL, relapsed/refractory diffuse large B-cell lymphoma.

Czuczman MS, et al. Blood. 2014;124:abstract 628.

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: PFS by COO and IPI





Median follow-up of 28 months.

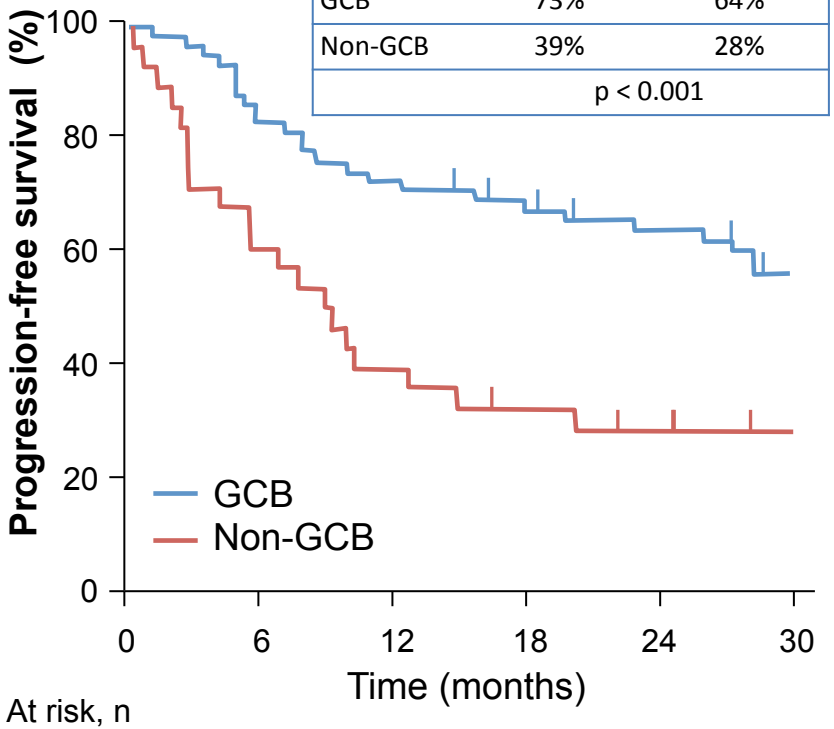
COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal centre B-cell like; HI/H, high-intermediate or high risk; IPI, International Prognostic Index; LI, low-intermediate risk; PFS, progression-free survival; R2-CHOP, lenalidomide and rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

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

PFS in GCB and non-GCB DLBCL for patients treated with R-CHOP and R2-CHOP

Historical R-CHOP PFS[1]

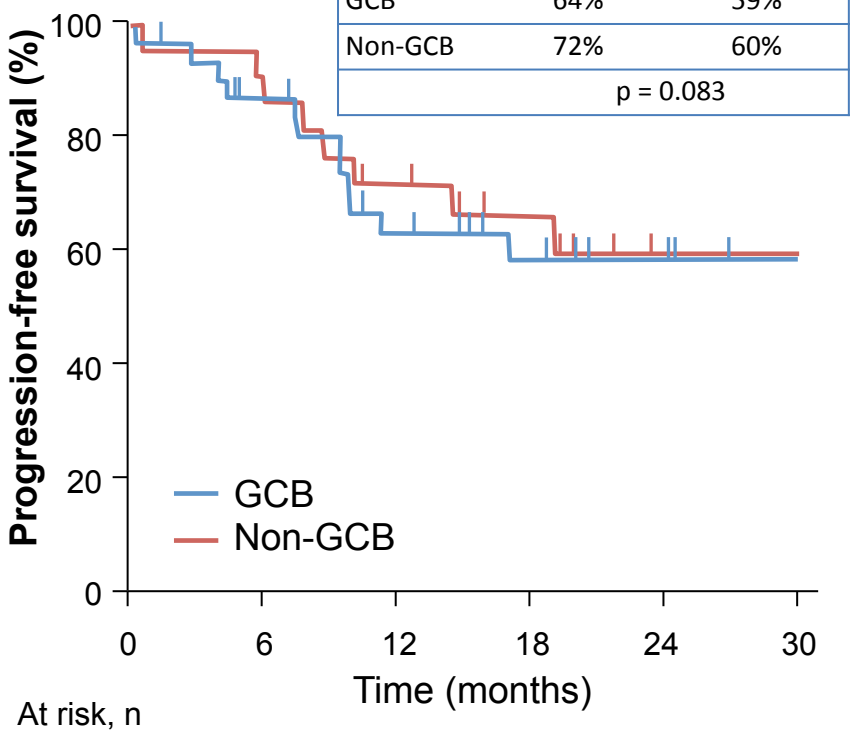
PFS	12 months	24 months
GCB	73%	64%
Non-GCB	39%	28%
	p < 0.001	



At risk, n						
GCB	59	49	43	39	34	28
Non-GCB	28	17	11	8	6	3

R2-CHOP PFS[1]

PFS	12 months	24 months
GCB	64%	59%
Non-GCB	72%	60%
	p = 0.083	



At risk, n						
GCB	33	26	18	13	11	6
Non-GCB	22	20	14	10	5	4

Non-GCB subtype was defined by the Hans algorithm.[2]

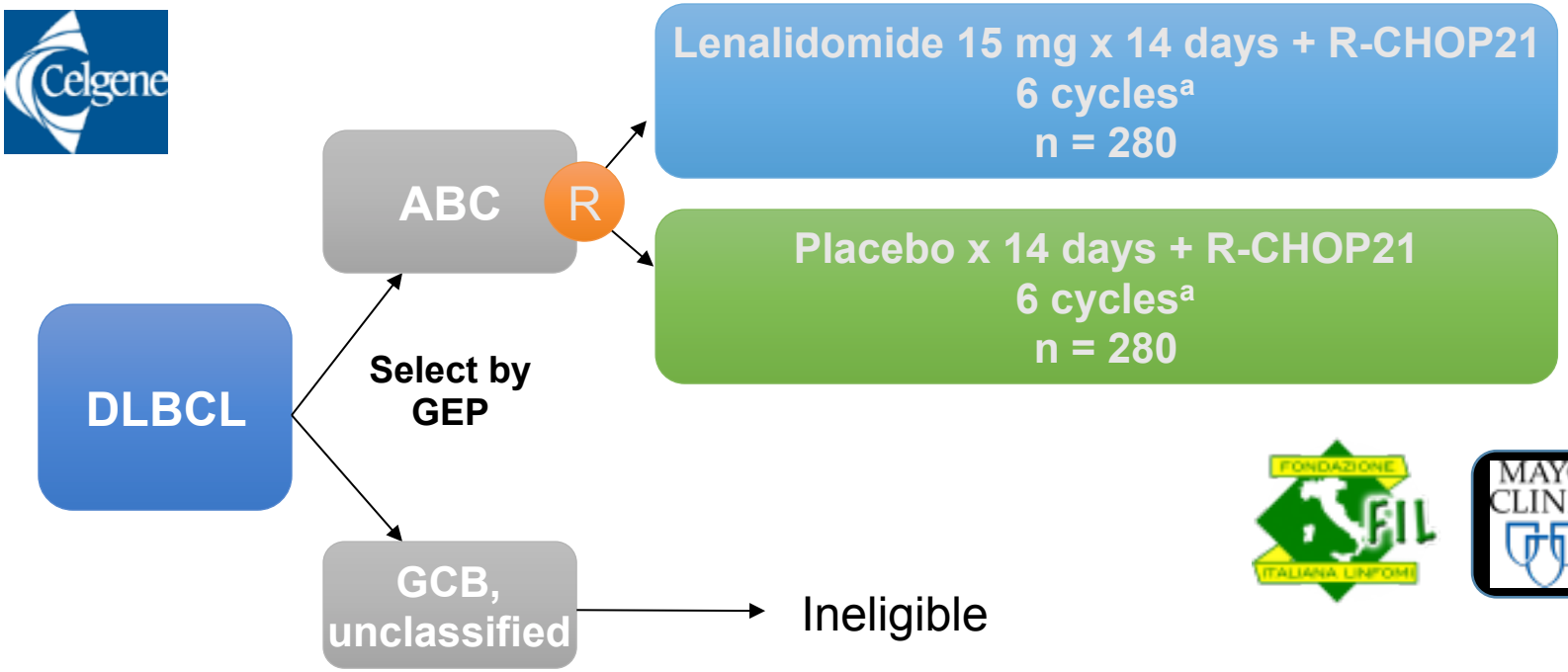
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; GCB, germinal centre B-cell like; PFS, progression-free survival; R-CHOP, rituximab plus CHOP; R2-CHOP, lenalidomide and rituximab plus CHOP.

1. Nowakowski GS, et al. J Clin Oncol. 2015; 33:251-7.
2. Hans CP, et al. Blood. 2004;103:275-82.

MAYO CLINIC

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

[a]Option for 2 additional rituximab doses after completing treatment regimen (if considered standard of care per local practice). ABC, activated B-cell like; COO, cell of origin ; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell like; GEP, gene expression profile; IPI, International Prognostic Index; PFS, progression-free survival; PI, principle investigator; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

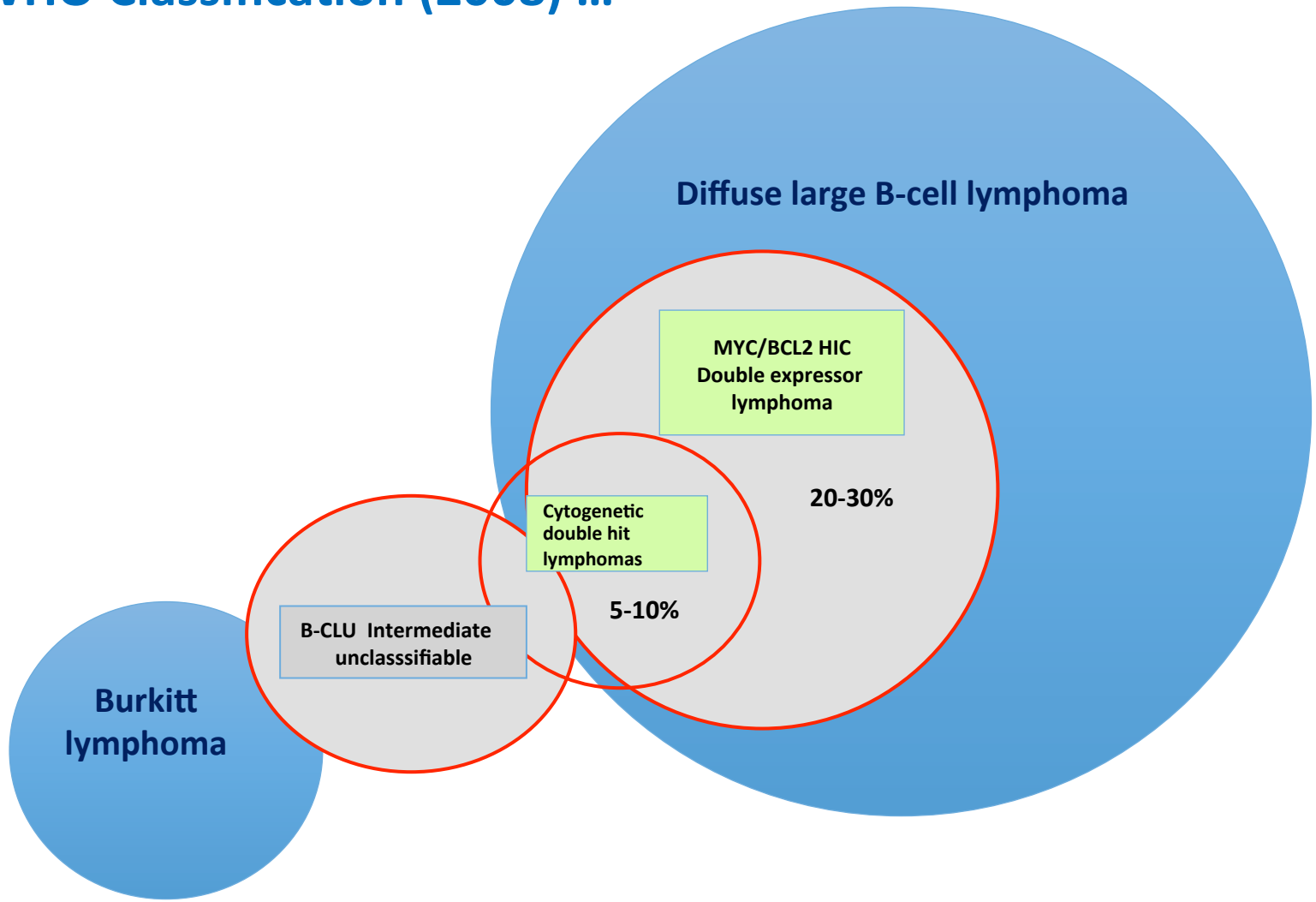
NCT02285062.

Do we need to improve R-CHOP results in DLBCL?

R-CHOP is the backbone…

- ✓ A better recognition based of hystopathological subtypes
- ✓ Combining novel drugs to standard chemoimmunotherapy

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



Genetic alterations identifiy high risk DLBCL

Translocations involving *MYC*, *BCL2* and *BCL6*

BCL2 t(14;18)(q32;q21) in 18–20% of patients with de novo DLBCL.

BCL6 t(3;14)(q21;q27) in 30–40 % DLBCL, more often in ABC

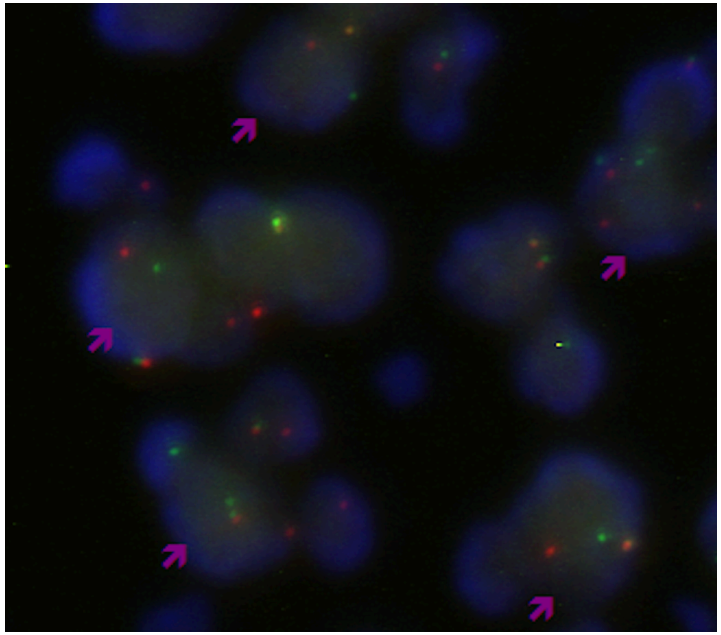
BCL2 and MYC translocations are usually associated with GCB DLBCL

MYC translocations in 5-14% of DLBCL.

Double hit lymphoma

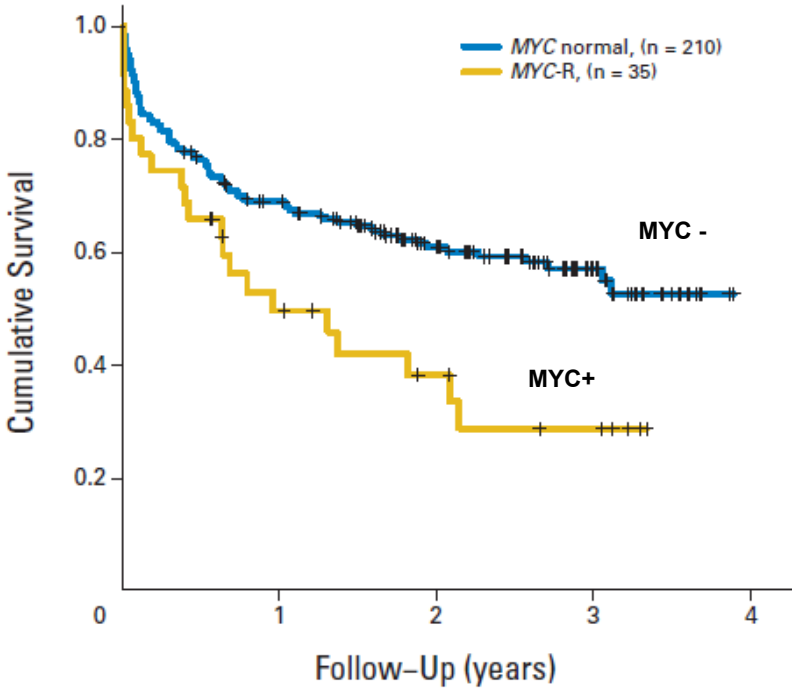
- (*BCL2/MYC*) or triple hit (*BCL2/BCL6/MYC*) have worse prognosis
- Cannot be predicted by histology, proliferation rate or clinical features
- Most frequent in GCB type
- More than 50% of patients are > 65 years old

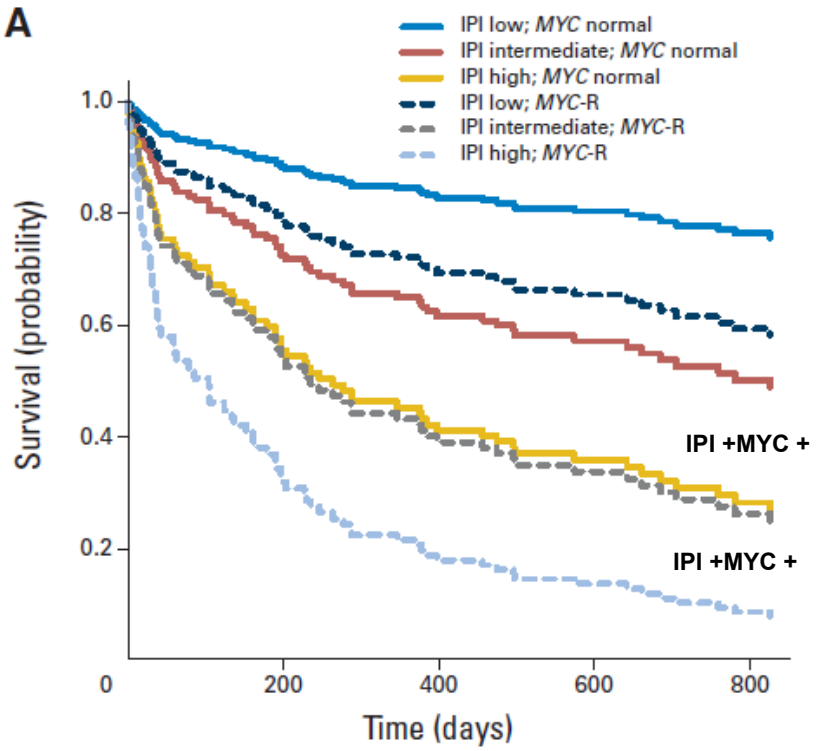
(*key point: DHL include cases with one gene translocated and the second gene with gain or amplification*)



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

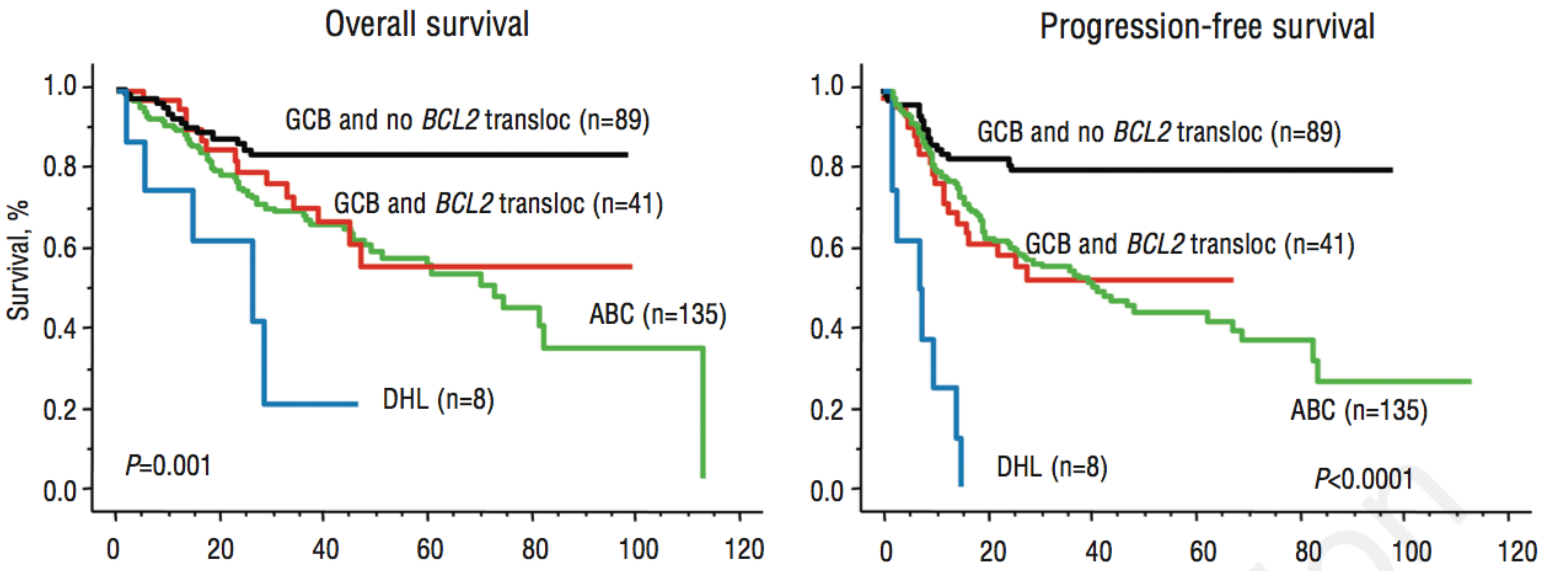




Barrans S. et al JCO 2010

Double or triple hit lymphomas have the worst outcome

Double hit lymphoma (*BCL2/MYC*) or triple hit (*BCL2/BCL6/MYC*) have worse prognosis

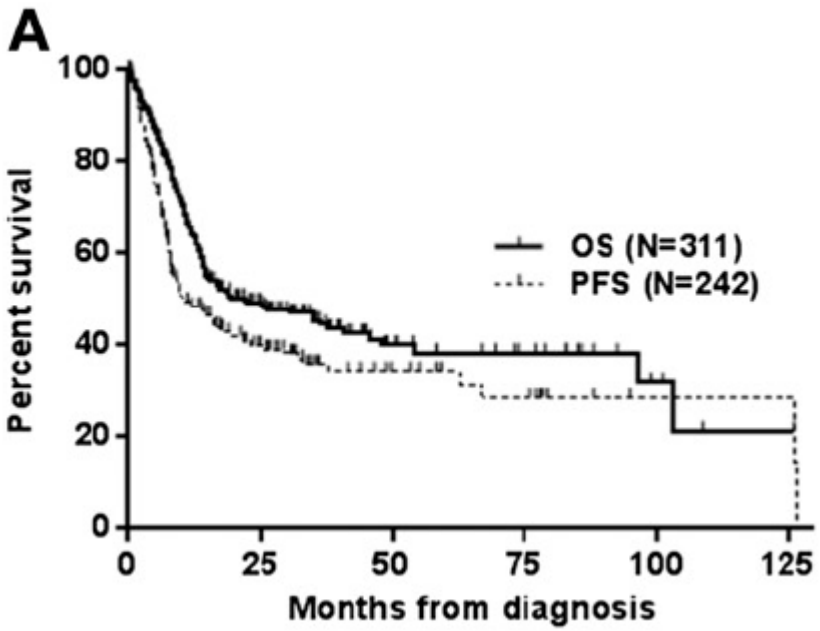


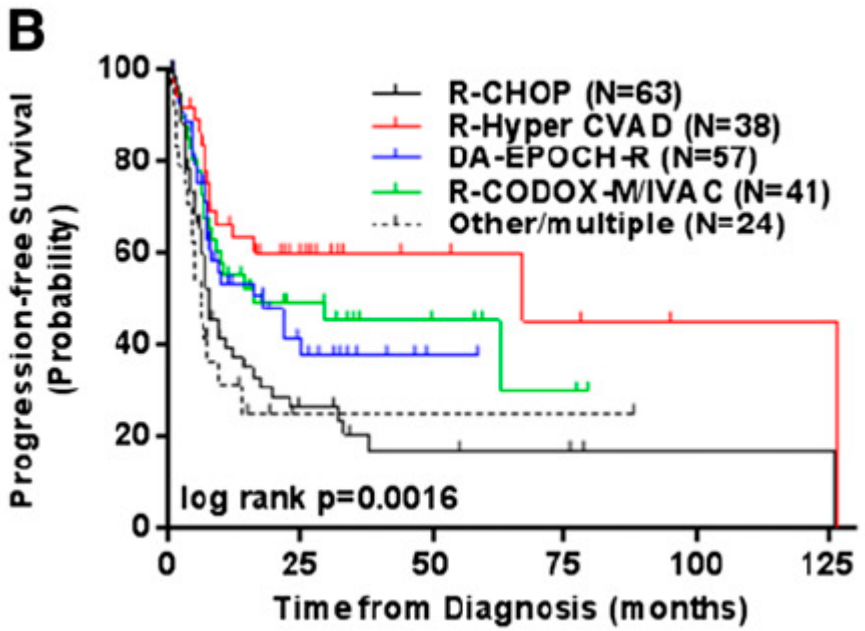
Visco et al., Hematologica 2013

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

- 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)

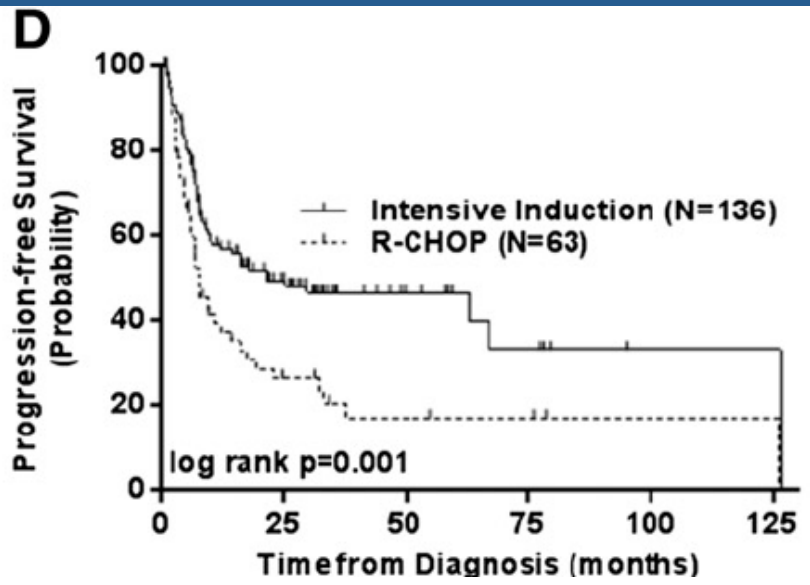


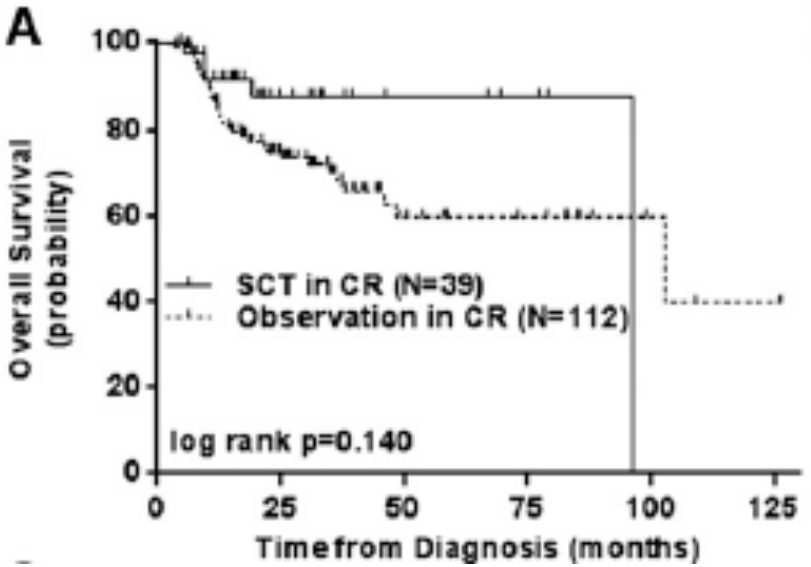


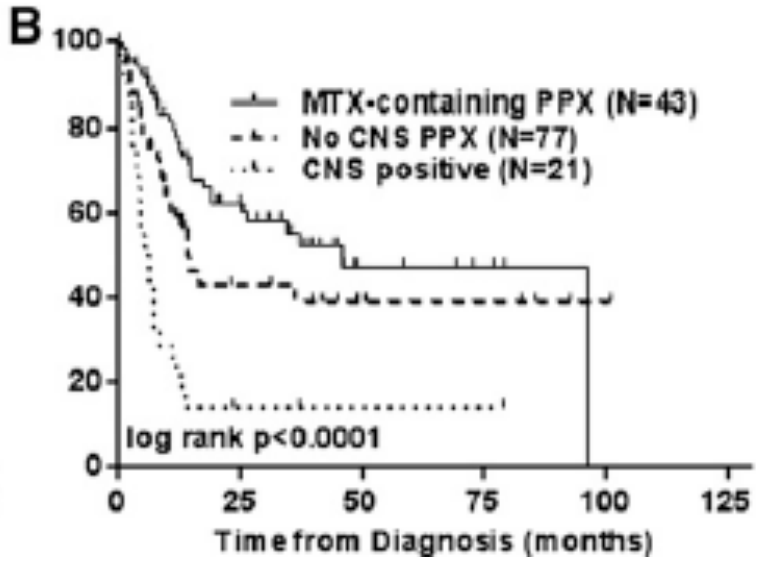
Educational ASH 2014

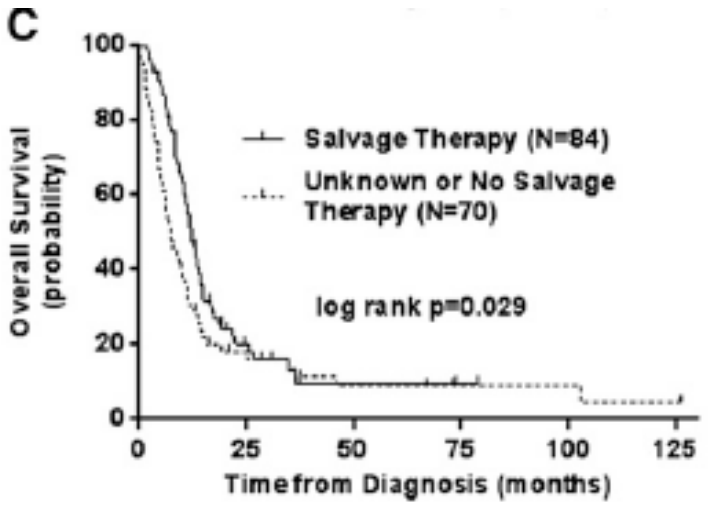
Petrich M, Gandhi M et al Blood 2014

Double Hit Lymphoma (DHL)









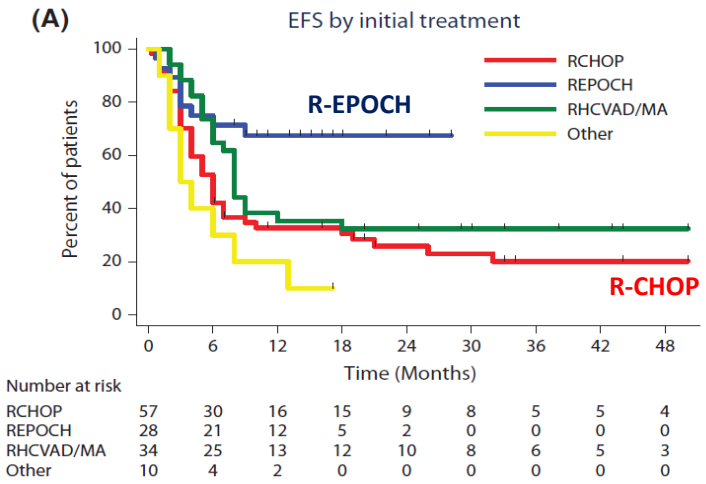
Educational ASH 2014

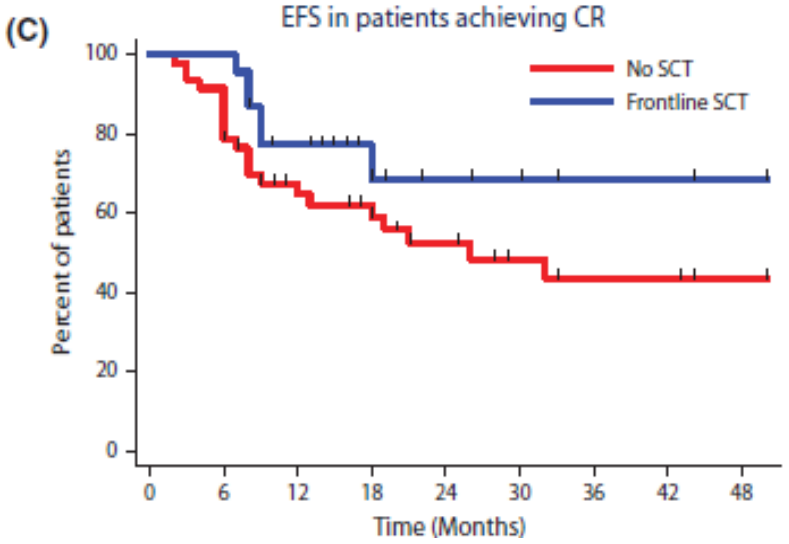
Petrich M, Gandhi M et al Blood 2014

Double Hit lymphoma: MDACC experience

129 pts DHL ; median age 62 (17-84); IPI 2-3 =61%;
MYC/BCL2 pos=72%; triple Hit= 11%; GCB 90%

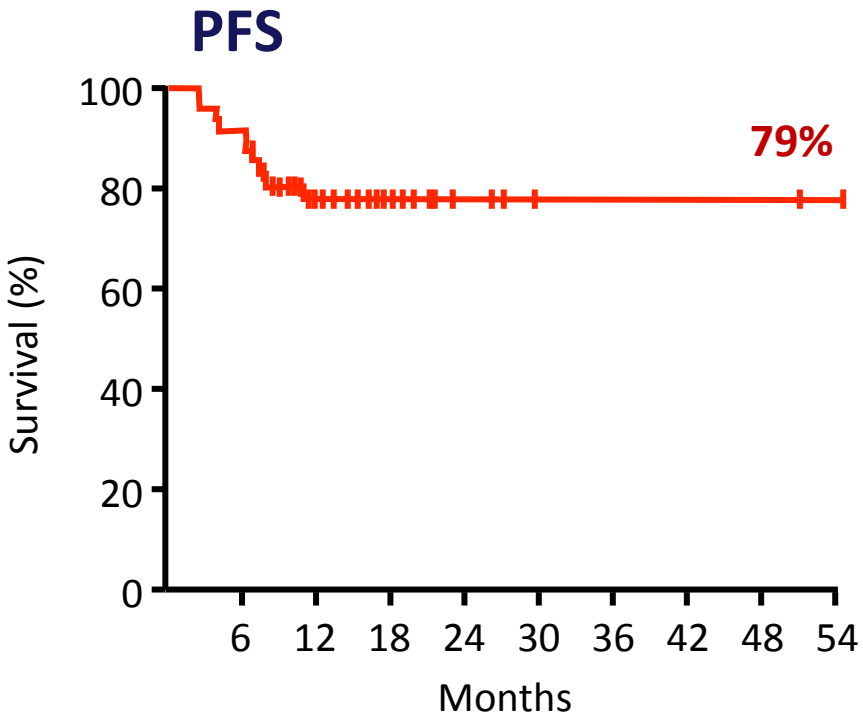
Characteristic	RCHOP n = 54	R-EPOCH n = 28	RHCVAD/MA n = 34	Other n = 10	All n = 129
CR after initial therapy (%)	23 (40)	19 (68)	23 (68,)	6 (60)	71 (55)
Frontline SCT (%)					
Any (auto+allo)	2 (4)	14 (50)	8 (24)	2 (20)	26 (20)
Allo	1 (2)	0	1 (3)	0	2 (2)





Oki et al Br.J.Hematol. 2014

DA-EPOCH-R in MYC-Rearranged Aggressive B-Cell Lymphoma: PFS and OS 52 patients



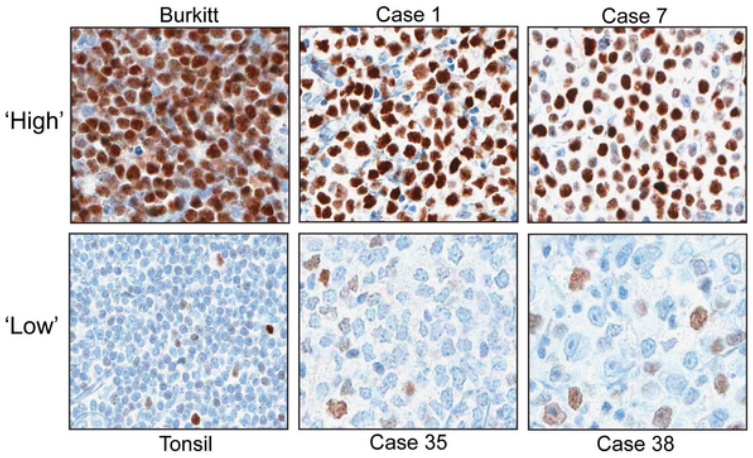
Median follow-up:14 mos

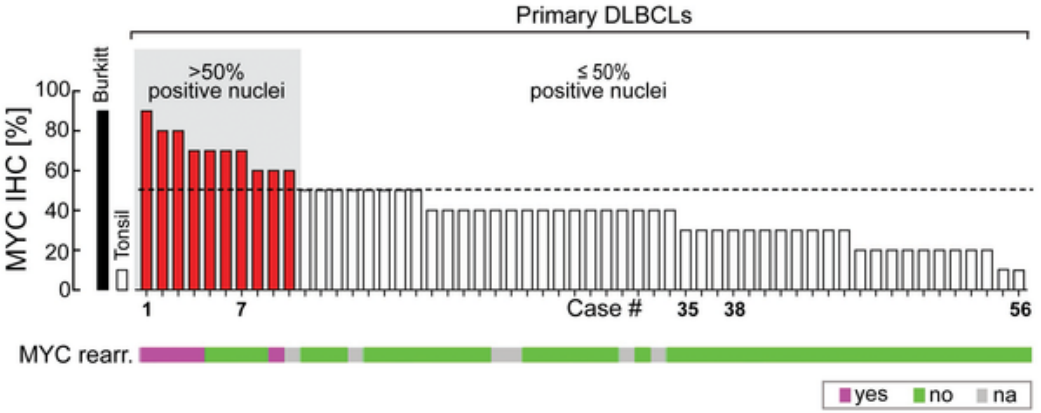
Characteristic	n (%)
Median age y (range)	61 (29-80)
Male sex	71%
Stage III/IV	73%
Elevated LDH	53%
CNS disease	6%
IPI score 0-2 3-5	 35% 65%
Histology DLBCL BCL-U	 86% 14%
MYC by FISH	100%
BCL2 by FISH	45%
BCL2 high IHC	56%

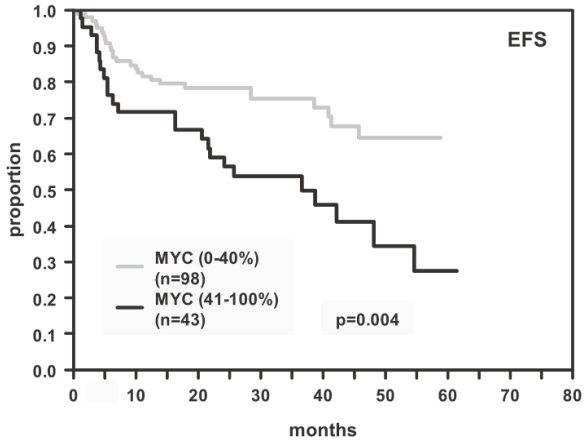
Dunleavy et al ASH 2014 abs 395 (oral session)

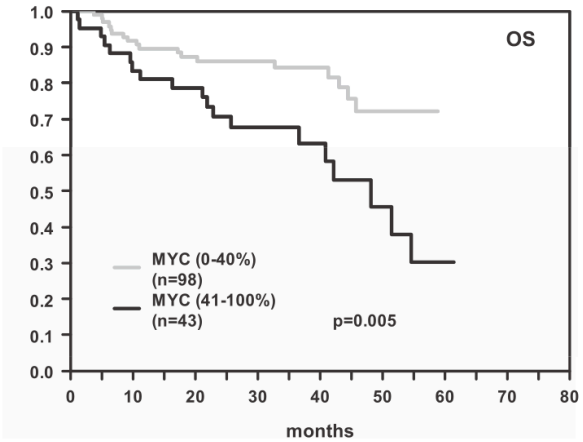
Himmunoistochemistry expression of Myc and BCL2 in DLBCL

c-Myc expression





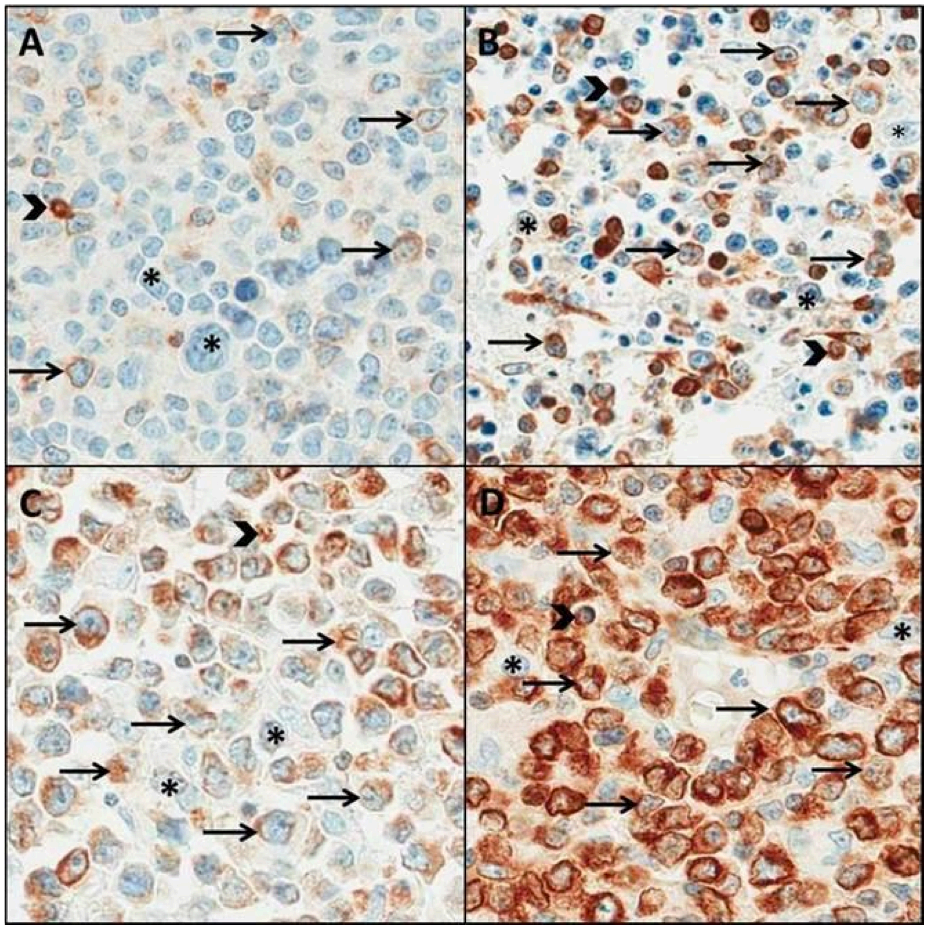




Kluk MJ et al. PLoS ONE 2012 Horn et al., Blood 2013

Himmunoistochemistry expression of Myc and BCL2 in DLBCL

BCL2 expression

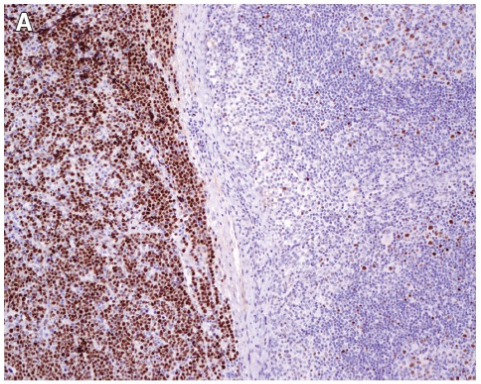


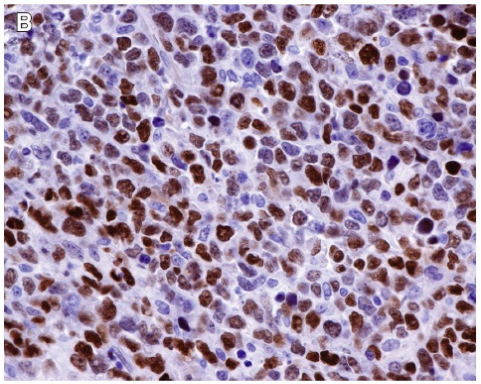
Schneider et al., Leukemia & Lymph 2015

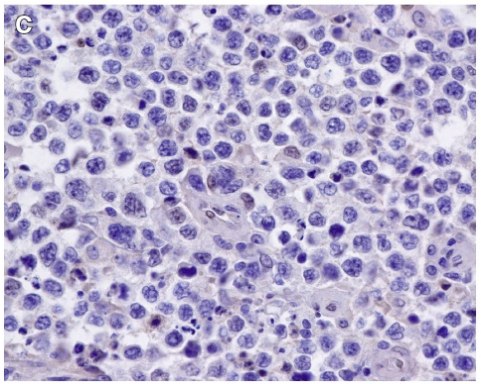
Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

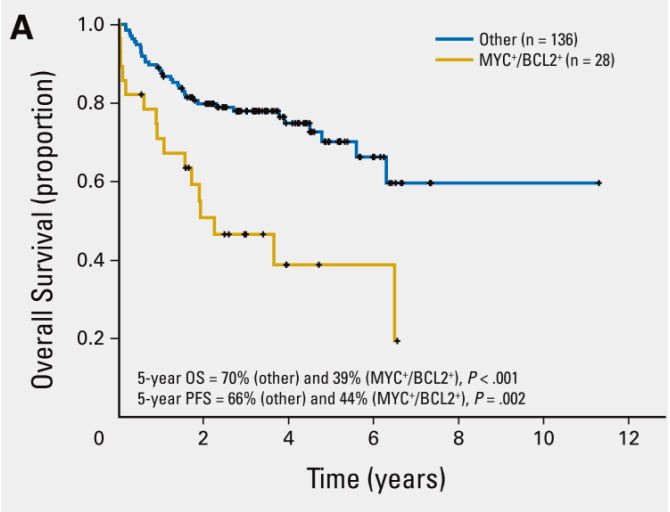
Nathalie A. Johnson, Graham W. Slack, Kerry J. Savage, Joseph M. Connors, Susana Ben-Neriah, Sanja Rogic, David W. Scott, King L. Tan, Christian Steidl, Laurie H. Sehn, Wing C. Chan, Javeed Iqbal, Paul N. Meyer, Georg Lenz, George Wright, Lisa M. Rimsza, Carlo Valentino, Patrick Brunhoeber, Thomas M. 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

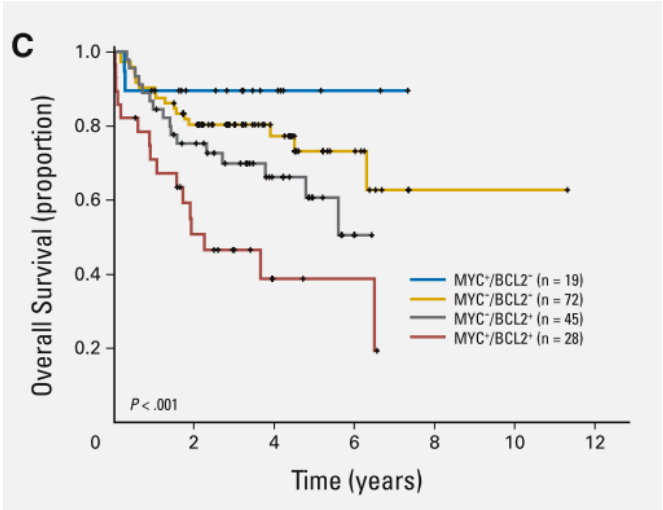
J Clin Oncol 30. © 2012







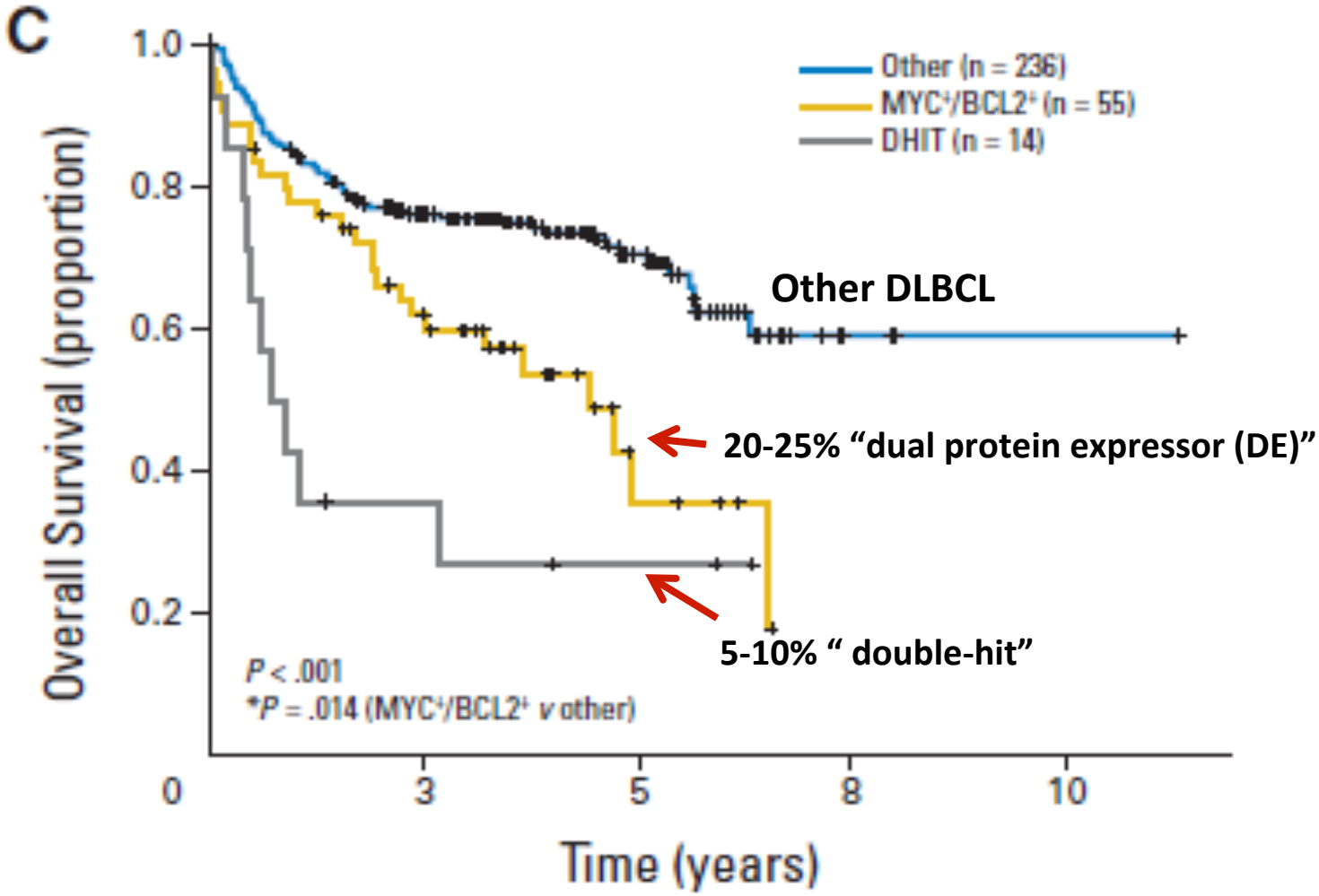




Myc+: ≥ 40% pos.
Bcl2+: ≥ 50% pos.

Johnson et al J.Clin. Oncol 2012

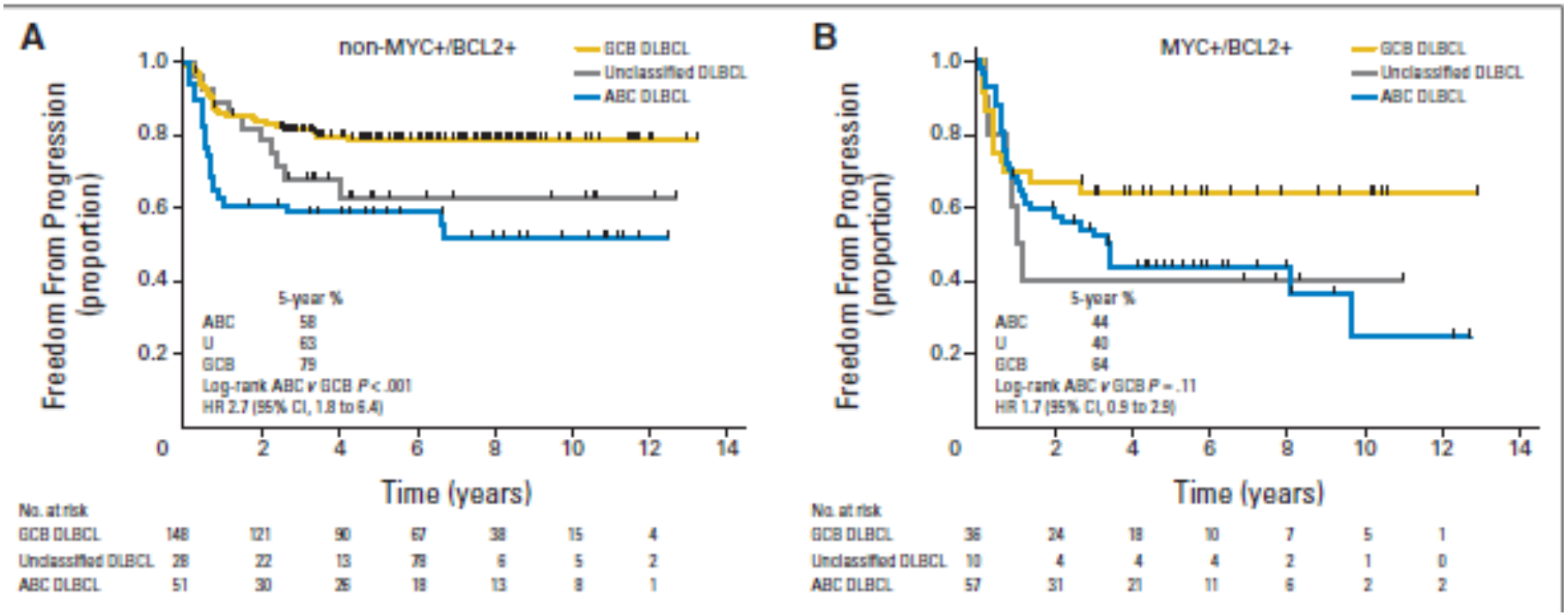
Overall survival of patients with DLBCL according MYC and BCL2 translocation (DHIT) or MYC and BCL2 protein expression (DE)



Johnson et al J.Clin. Oncol 2012

Factors Affecting Treatment Decision
High risk patients by COO profile, myc, bcl2…

- ✓ In the non–MYC-positive/BCL2-positive group, patients with ABC DLBCL had significantly inferior outcomes compared with those with GCB DLBCL.
- ✓ COO did not provide statistically significant risk stratification within the MYC-positive/BCL2-positive group.



Scott D et al. J Clin Oncol 2015; 33: 2848-56

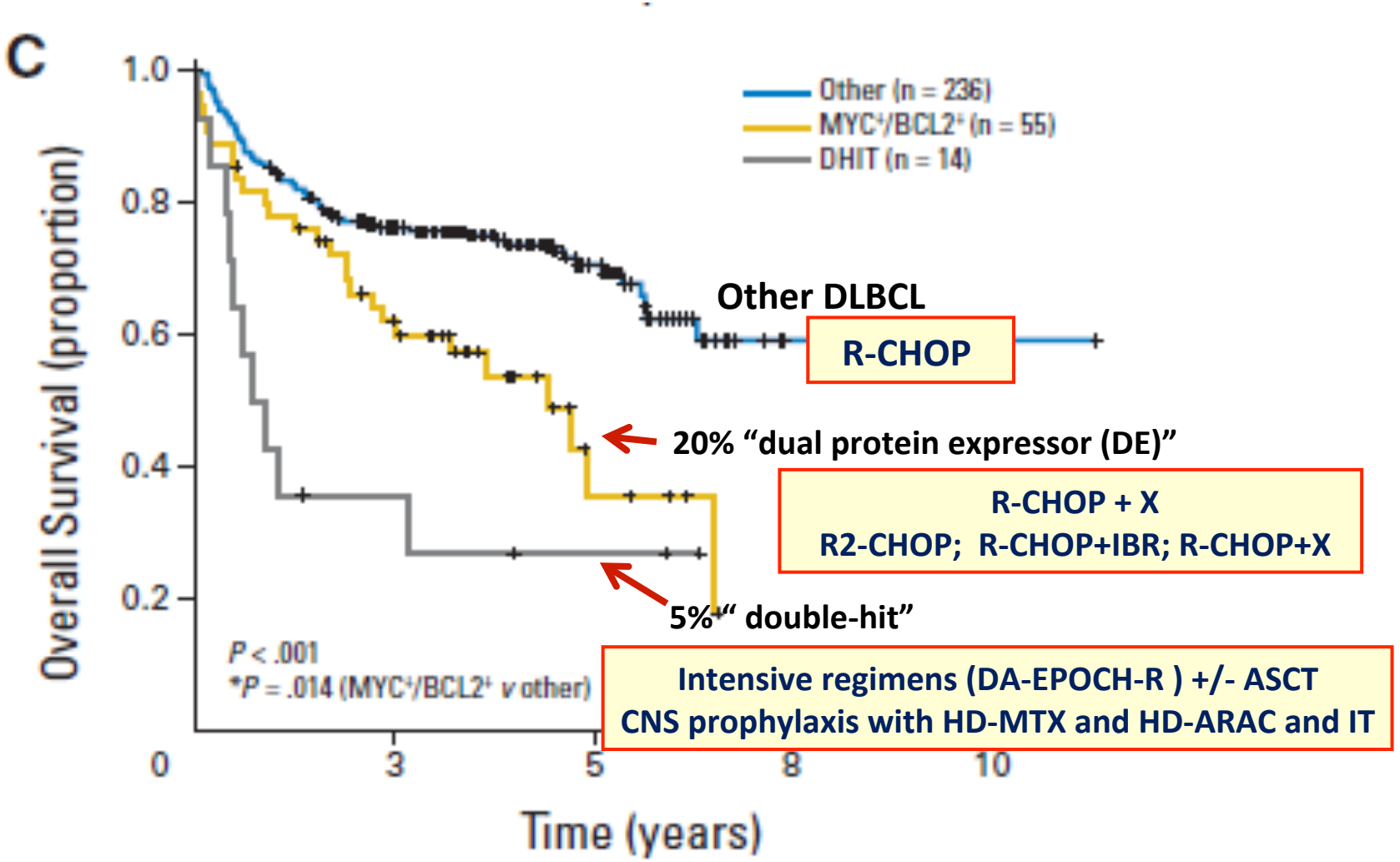
What we (do not) know

- R-CHOP inadequate
- No evidence that DH-DLBCL fare better with more aggressive therapies (i.e. Burkitt-type CT)
- Suggestions that DLBCL/BL may fare better with Burkitt-type CT
- Too small numbers of DH patients treated with upfront HDT-ASCT to suggest any role for transplant procedure (…same for DLBCL/BL)
- DA-EPOCH very active in Myc-only but not in DH-DLBCL (Ann Oncol 19:iv83, 2008)
- Optimal Targets for Targeted-agents ?

New agents in development with potential activity in MYC-driven and double hit lymphoma

Class of drug	Examples	References	Phase	n	Population	ORR
Selective inhibitor of nuclear export (SINE)	Selinexor (KPT-330)	Gutierrez et al (2014)	I	28	R/R NHL	25%
BH3-mimetic	ABT-199 (GDC-0199)	Davids et al (2014)	I/II	44	R/R NHL	44%
BET bromodomain inhibitors	GSK525762 CPI-0610	NCT01943851 NCT01949883	I I	* *	R/R haematological cancers R/R NHL	* *

Future treatment for high risk DLBCL?



Conclusions

- ✓ R-CHOP is still the standard of care in DLBCL and is the backbone of new treatments with novel drugs
- ✓ A better recognition of unfavourable DLBCL subsets is now recommended to better tailor the treatment
- ✓ MYC should be tested in all DLBCL patients (expression and translocation)
- ✓ MYC positive patients (cytogenetic, FISH+) and namely double hit patients positive should be treated with intensified regimens different from RCHOP +/- HDC and ASCT
- ✓ ABC subtype should be included in clinical trials testing the addition of novel drugs to R-CHOP