con il patrocinio di

CIPOMO

rete oncologica

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

Stato dell'arte in terapia oncologica. Linfomi a cellule B.

Umberto Vitolo

Ematologia,

AOU Città della Salute e della Scienza, Torino

Torino, 13-14 ottobre 2017

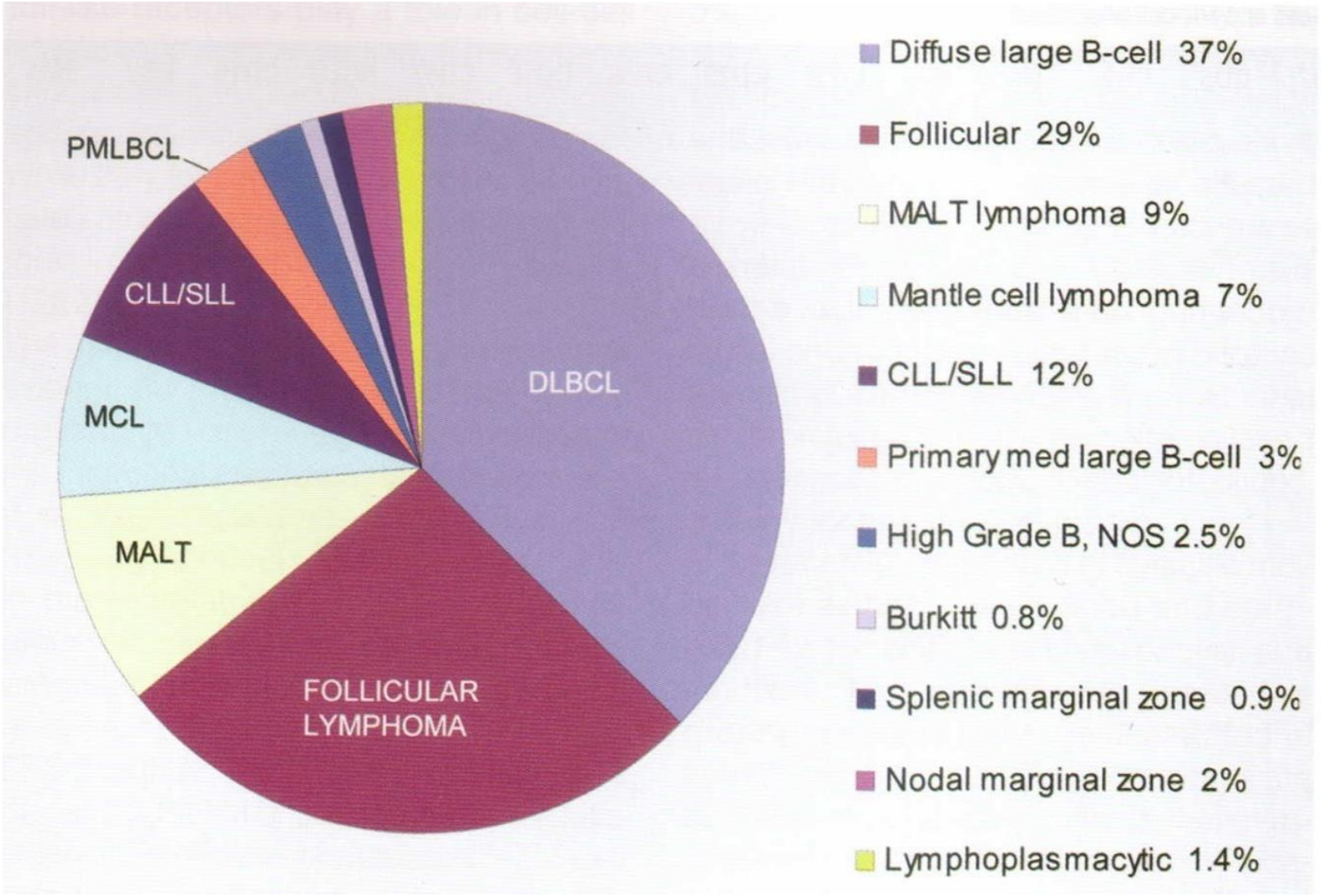
Disclosures – Umberto Vitolo

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

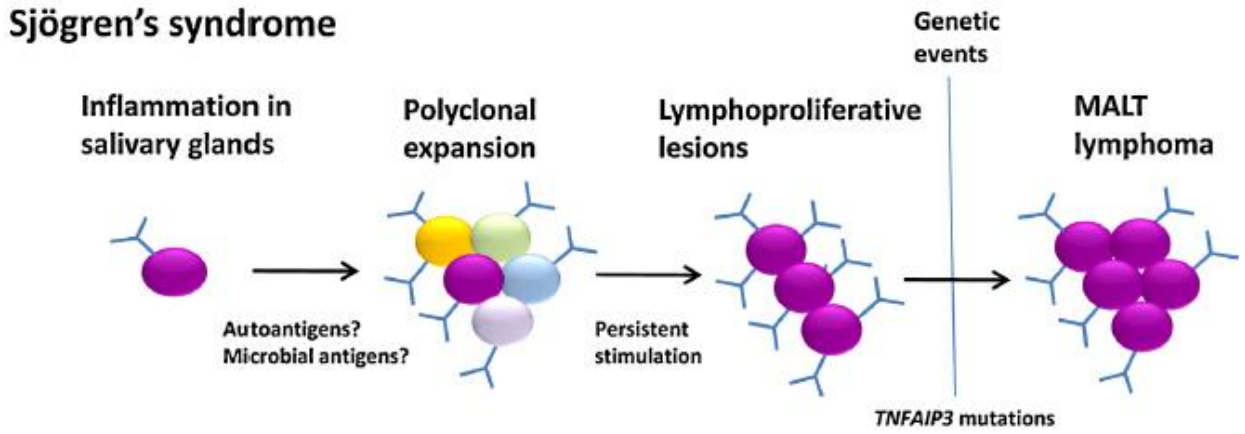
Incidence of B-cell NHL in adults.

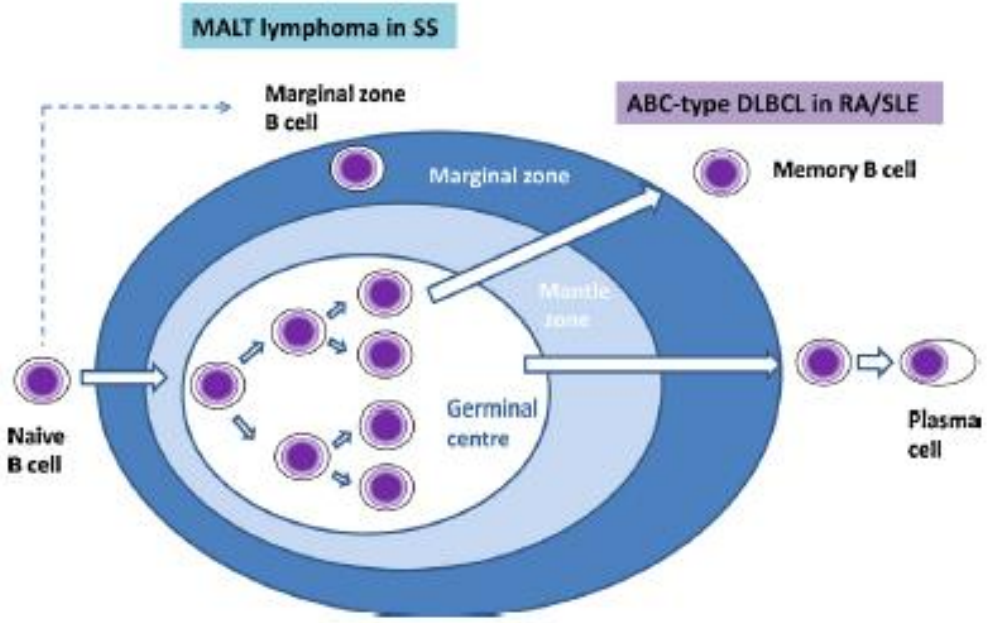
ISTAT 2016:

16.500 diagnosis of lymphomas in Italy: 4.5% of all tumors.



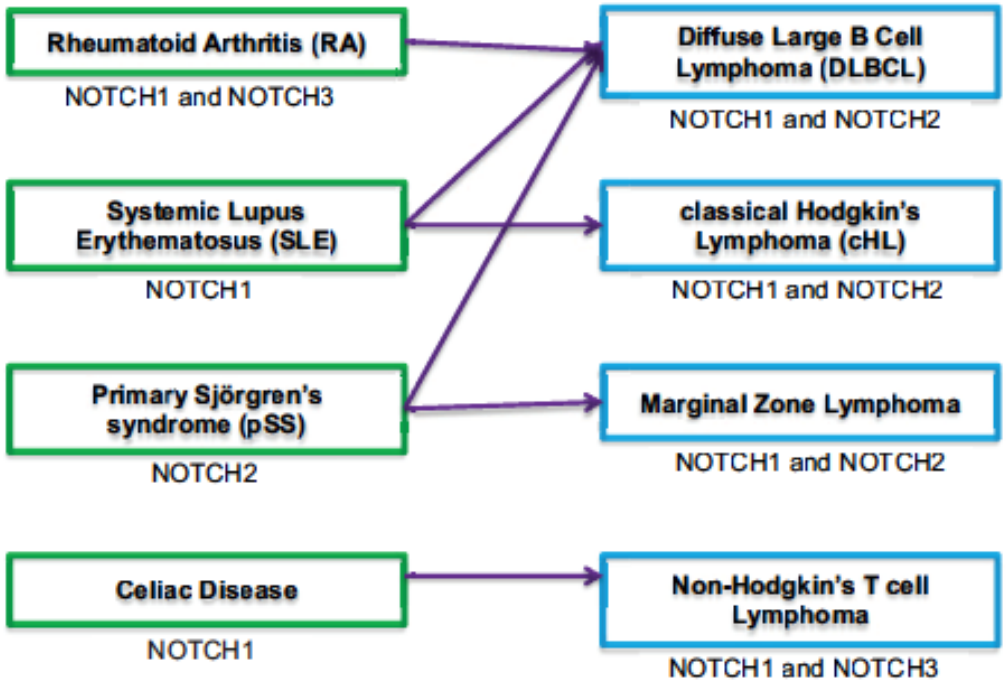
Lymphoma and autoimmunity





Baecklund E et al, Seminars Cancer Biol 2014

Lymphoma and autoimmunity



Disorder	NHL OR (95% CI)	Proportion of exposed NHL case patients	Population-attributable fraction†
Rheumatoid arthritis	1.5 (1.1 to 1.9)	4.2%	1.3%
Primary Sjögren syndrome	6.1 (1.4 to 27)	0.4%	0.4%
Systemic lupus erythematosus	4.5 (1.0 to 21)	0.3%	0.2%
Celiac disease	2.1 (1.0 to 4.8)	0.6%	0.4%

Disease	Associated lymphoma subtype
Rheumatoid arthritis (RA)	Diffuse large B-cell lymphoma (DLBCL)
Primary Sjögren's syndrome (pSS)	Mucosa-associated lymphoid tissue (MALT) Diffuse large B-cell lymphoma (DLBCLs)
Systemic lupus erythematosus (SLE)	Diffuse large B-cell lymphoma (DLBCL)
Inflammatory myositis	No specific association
Psoriasis	T-cell lymphoma Mycosis fungoides

Smedby KE et al, J Natl Cancer Inst 2006
Kuksin CA et al, Frontiers Oncol 2015
Yadlapaty S et al, BioMed Res Int 2016

JOURNAL OF CLINICAL ONCOLOGY

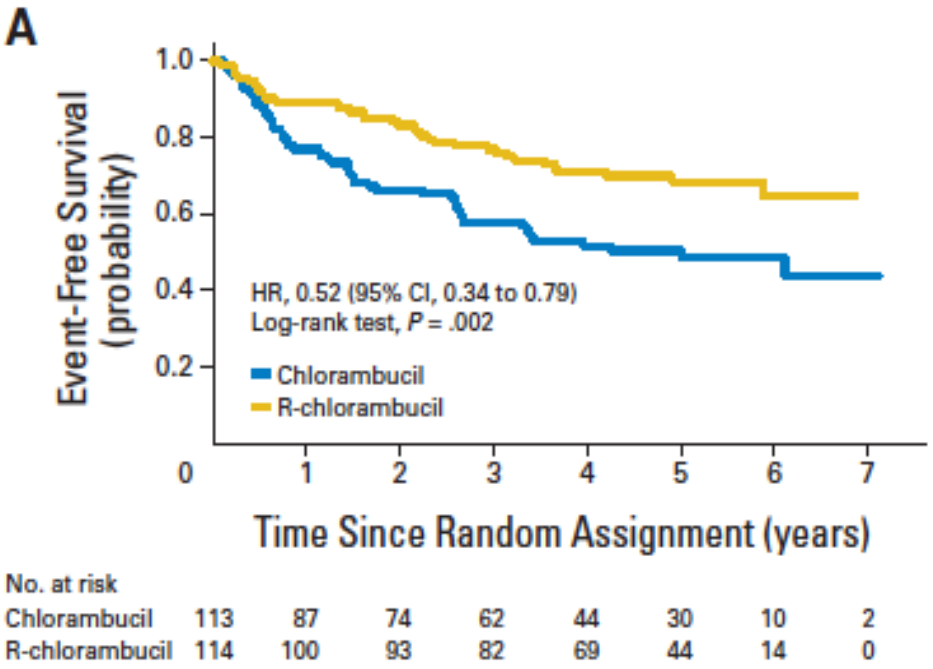
ORIGINAL REPORT

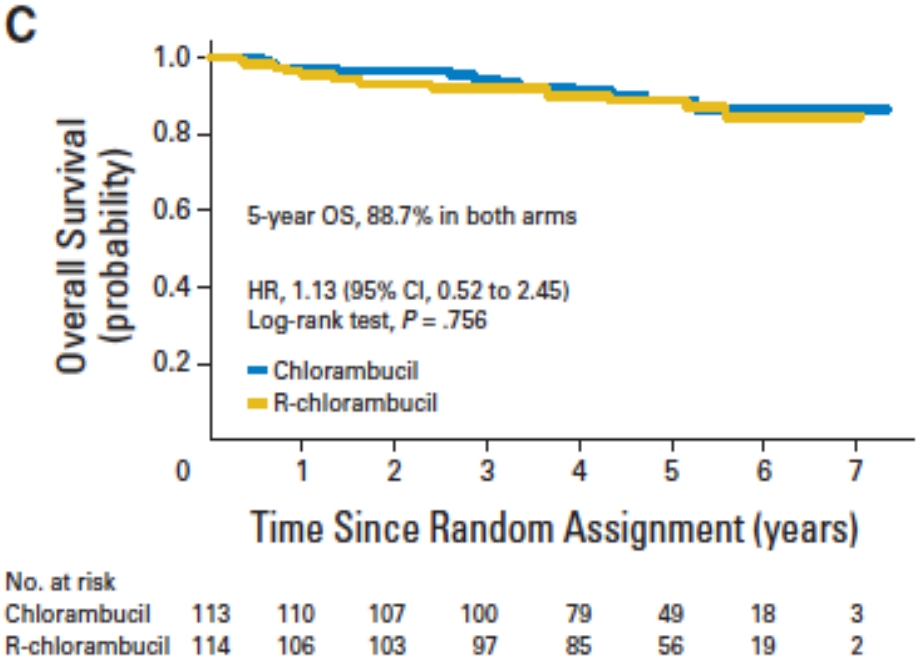
Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study

Emanuele Zucca, Annarita Conconi, Daniele Laszlo, Armando López-Guillermo, Reda Bouabdallah, Bertrand Coiffier, Catherine Sebban, Fabrice Jardin, Umberto Vitolo, Franck Morschhauser, Stefano A. Pileri, Christiane Copie-Bergman, Elias Campo, Andrew Jack, Irene Floriani, Peter Johnson, Maurizio Martelli, Franco Cavalli, Giovanni Martinelli, and Catherine Thieblemont

231 patients, median age 60 (26-81), male 53%

116 Chlorambucil; 115 Rituximab+Chlorambucil.

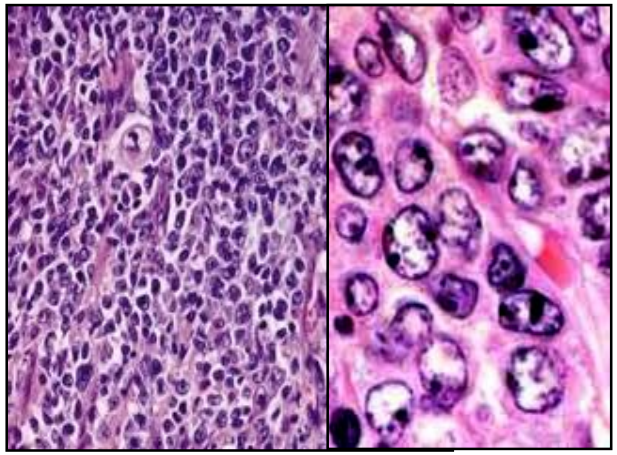




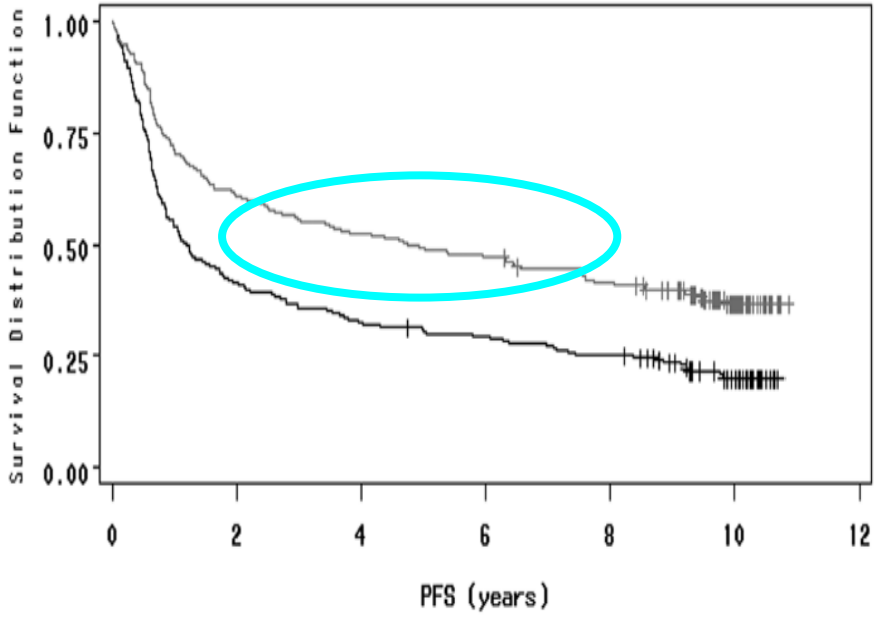
Zucca E et al, J Clin Oncol 2013.

Diffuse Large B-cell Lymphoma

- ✓ Is the most common NHL: 40%
- ✓ Peak incidence in the sixth decade
- ✓ Median survival: weeks to months if not treated



CHOP21 vs R-CHOP21



Standard treatment is R-CHOP21; but 40-50% of patients still relapse

We need to better define DLBCL in order to improve R-CHOP results

Coiffier B et al, NEJM 2002. Coiffier B et al, Blood 2010.

DLBCL: factors affecting treatment decision

Lymphoma

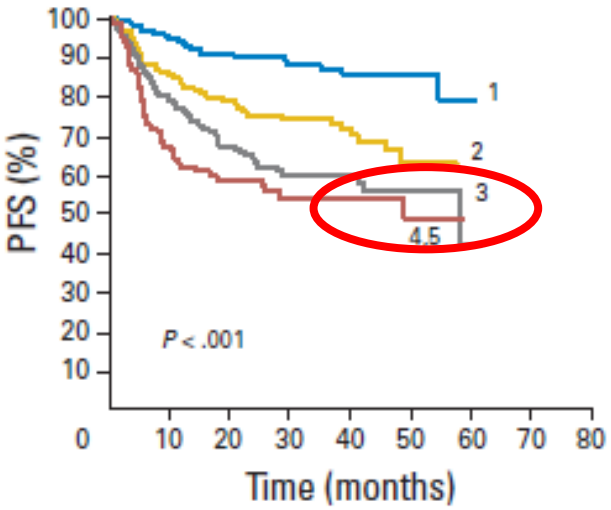
- IPI score
- Histology
- Stage
- Tumoral mass
- Site

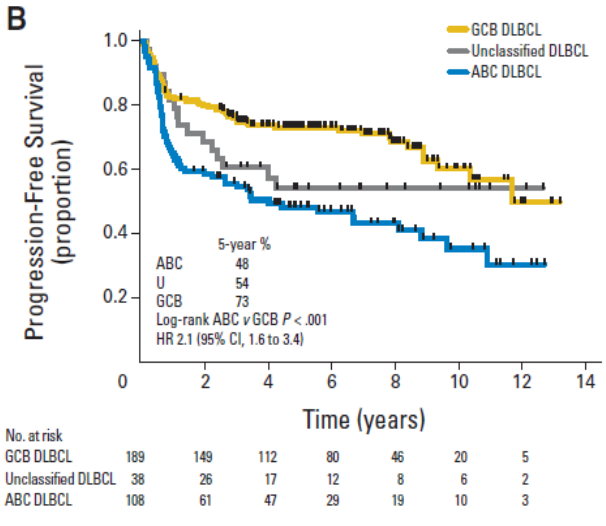
"High risk Patients"

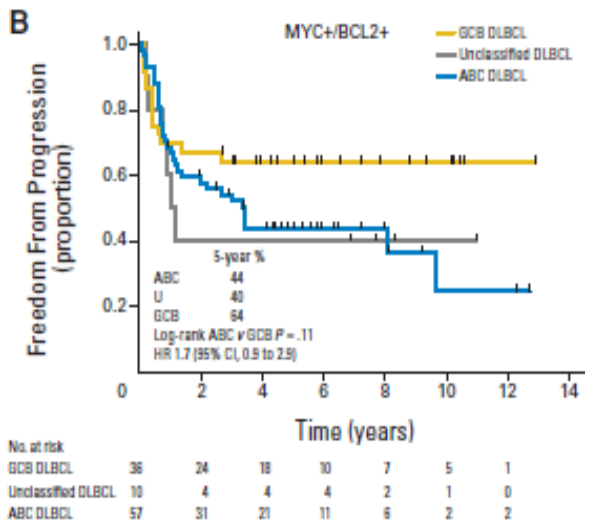
✓**According to IPI**

✓**By COO profile subgroups**

✓**By IHC or FISH expression of MYC and BCL-2**



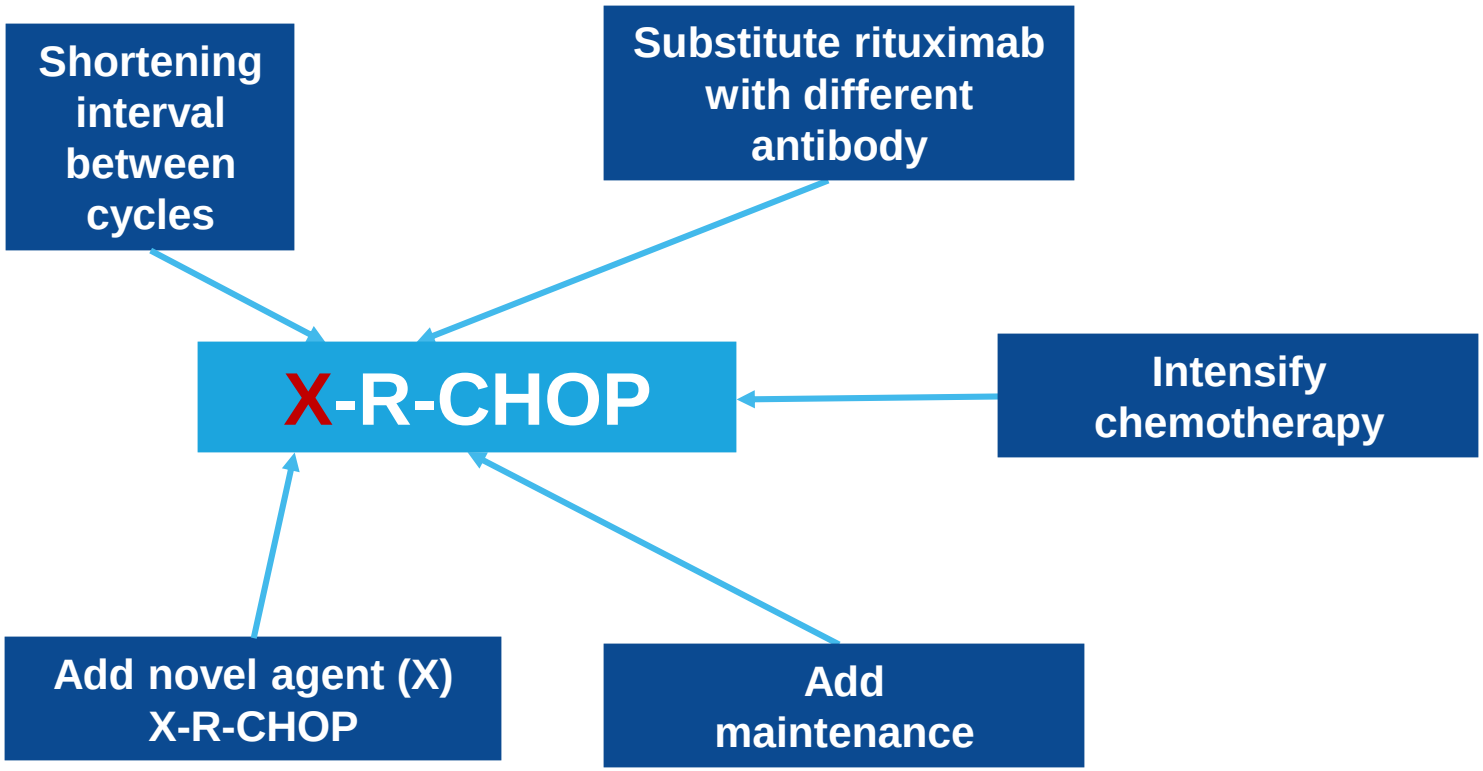




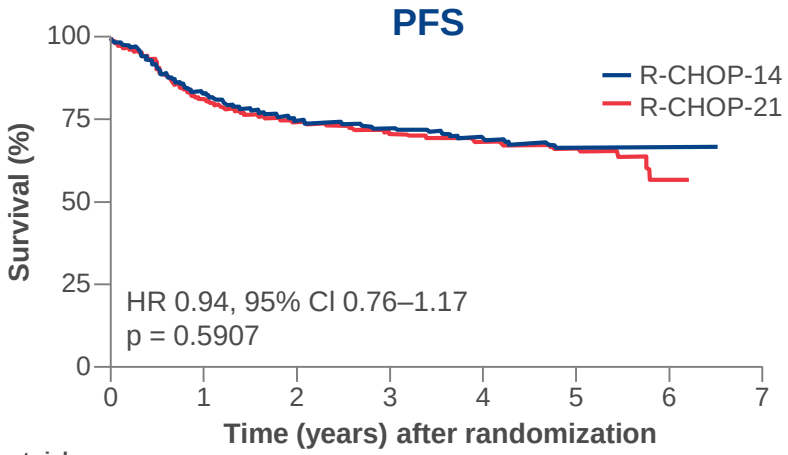
Ziepert M et al, J Clin Oncol 2010.

Scott D et al. J Clin Oncol 2015.

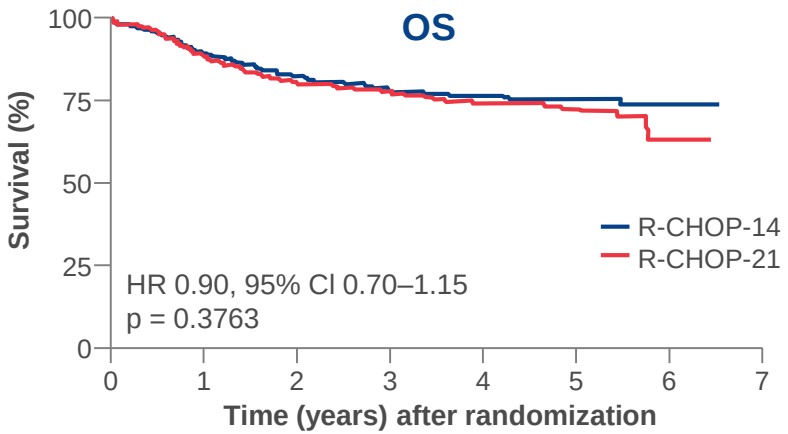
Potential strategies to improve R-CHOP results in DLBCL



How to improve R-CHOP results in DLBCL
Shorten interval between cycles?



No. at risk							
R-CHOP-14 540	439	377	291	175	71	11	0
R-CHOP-21 540	431	375	276	177	75	7	0

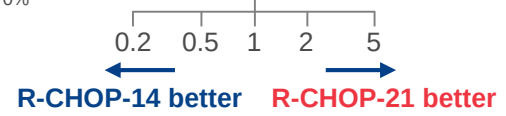


No. at risk							
R-CHOP-14 540	477	418	314	195	83	14	0
R-CHOP-21 540	474	409	305	187	81	8	0

CI, confidence interval; HR, hazard ratio.

R-CHOP-21 vs R-CHOP-14

Subgroup	R-CHOP-14 Events	R-CHOP-14 Total	R-CHOP-21 Events	R-CHOP-21 Total	HR (95% CI)
Age, years					
< 60	59	237	67	239	0.89 (0.63–1.26)
60–65	30	102	22	101	1.44 (0.84–2.49)
> 65	67	201	77	200	0.83 (0.60–1.16)
Subtotal (95% CI)		**540**		**540**	**0.93 (0.75–1.16)**
Total events	156		166		
Heterogeneity: X^2 = 2.99, df = 2 (p = 0.22); I^2 = 33%					
Sex					
Female	76	251	69	247	1.07 (0.77–1.48)
Male	80	289	97	293	0.85 (0.63–1.14)
Subtotal (95% CI)		**540**		**540**	**0.94 (0.76–1.17)**
Total events	156		166		
Heterogeneity: X^2 = 1.09, df = 1 (p = 0.30); I^2 = 8%					
Stage					
IA/IB	8	43	9	36	0.77 (0.29–1.99)
II	33	157	37	166	0.93 (0.58–1.49)
III	51	175	45	142	0.88 (0.59–1.31)
IV	64	162	74	193	1.09 (0.78–1.53)
Subtotal (95% CI)		**537**		**537**	**0.97 (0.78–1.21)**
Total events	156		165		
Heterogeneity: X^2 = 0.97, df = 3 (p = 0.81); I^2 = 0%					
International prognostic index score					
0	4	40	6	43	0.71 (0.21–2.45)
1	23	116	22	117	1.04 (0.58–1.86)
2	37	163	48	143	0.67 (0.43–1.02)
3	55	136	49	143	1.21 (0.83–1.78)
4	31	75	34	79	1.01 (0.62–1.65)
5	6	10	7	15	1.14 (0.38–3.43)
Subtotal (95% CI)		**540**		**540**	**0.96 (0.77–1.19)**
Total events	156		166		
Heterogeneity: X^2 = 4.69, df = 5 (p = 0.46); I^2 = 0%					



R-CHOP-14 is not superior to R-CHOP-21 chemotherapy in previously untreated DLBCL

Cunningham D, et al. Lancet 2013;381:1817-26.

How to improve R-CHOP results in DLBCL
Substitute with different anti-CD20 antibody?

The GOYA study

International, open-label, randomized phase 3 study in previously untreated DLBCL patients

Scientific support from the Fondazione Italiana Linfomi

Previously untreated DLBCL

- Age ≥ 18 years
- IPI ≥ 2 or IPI 1 not due to age alone or IPI 0 with bulky disease (1 lesion ≥ 7.5 cm)
- Adequate haematological function
- ≥ 1 bi-dimensionally measurable lesion
- ECOG PS ≤ 2
- **Target enrolment: 1400**

Randomized 1:1

G-CHOP

G 1,000 mg C1 D1/8/15 and C2–8 D1

CHOP 6 or 8 cycles every 21 days

R-CHOP

R 375 mg/m^2 C1–8 D1

CHOP 6 or 8 cycles every 21 days

- Number of CHOP cycles pre-planned in advance for all patients at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region
- Primary endpoint: investigator-assessed PFS

C, cycle; ECOG, Eastern Cooperative Oncology Group; G, obinutuzumab; IPI, International Prognostic Index; PS, performance status.

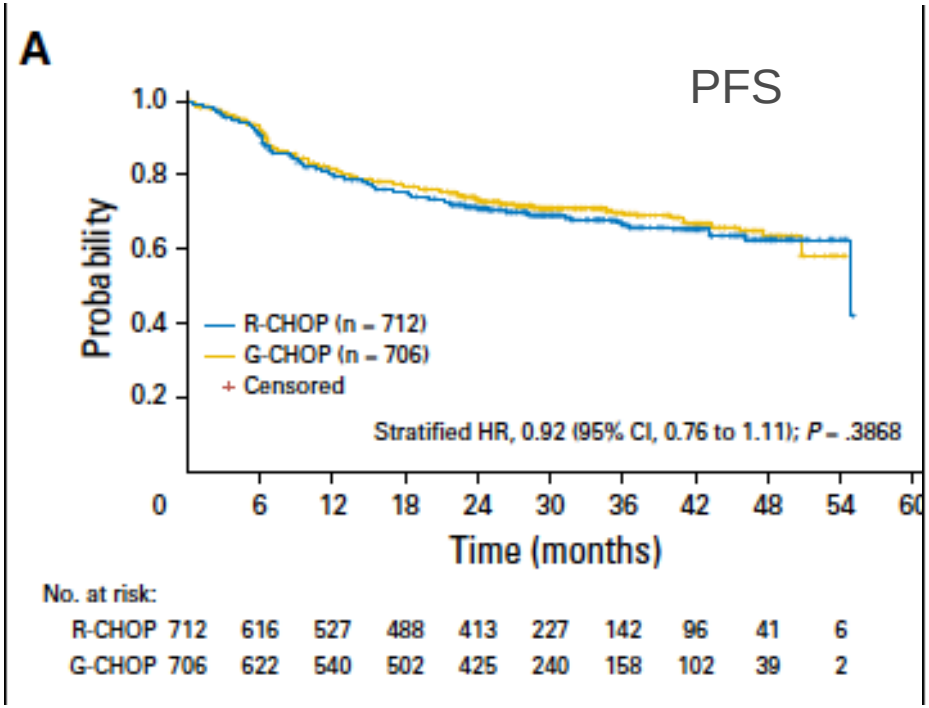
Vitolo U, et al. J Clin Oncol 2017

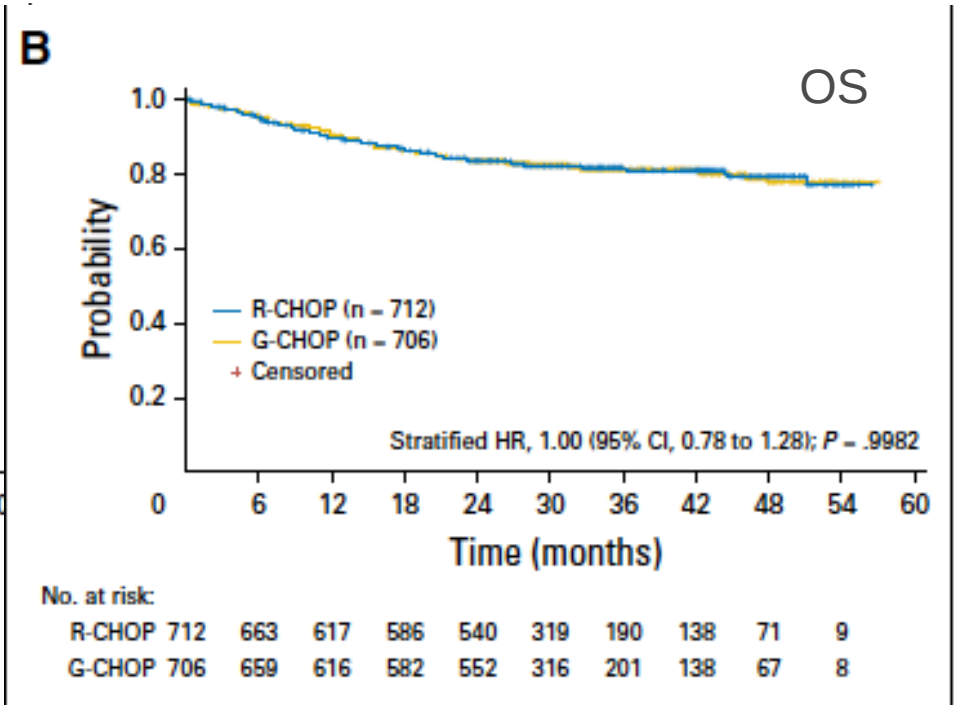
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma

Umberto Vitolo, Marek Trněný, David Belada, John M. Burke, Angelo Michele Carella, Neil Chua, Pau Abrisqueta, Judit Demeter, Ian Flinn, Xiaonan Hong, Won Seog Kim, Antonio Pinto, Yuan-Kai Shi, Yoichi Tatsumi, Mikkel Z. Oestergaard, Michael Wenger, Günter Fingerle-Rowson, Olivier Catalani, Tina Nielsen, Maurizio Martelli, and Laurie H. Sehn

No clinically meaningful differences observed between G-CHOP and R-CHOP

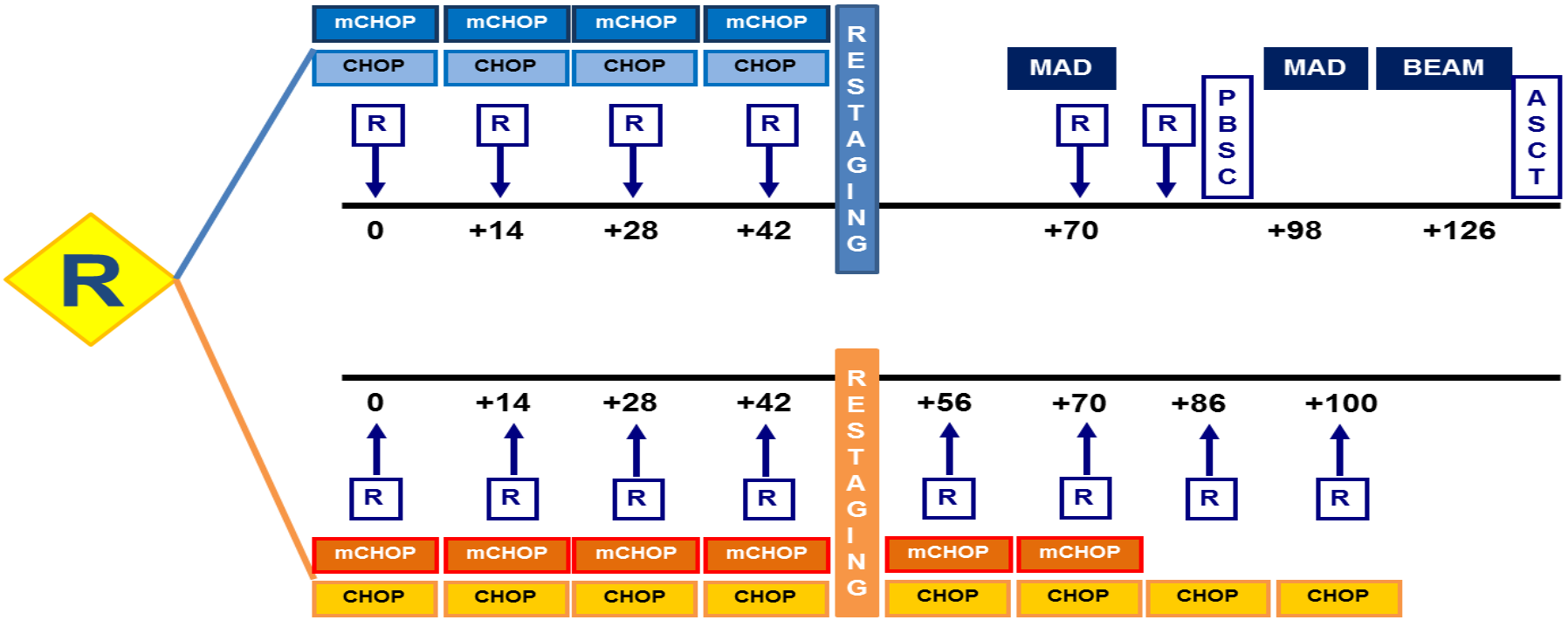




Vitolo U, et al. J Clin Oncol 2017

How to improve R-CHOP results in DLBCL
Intensify chemotherapy?

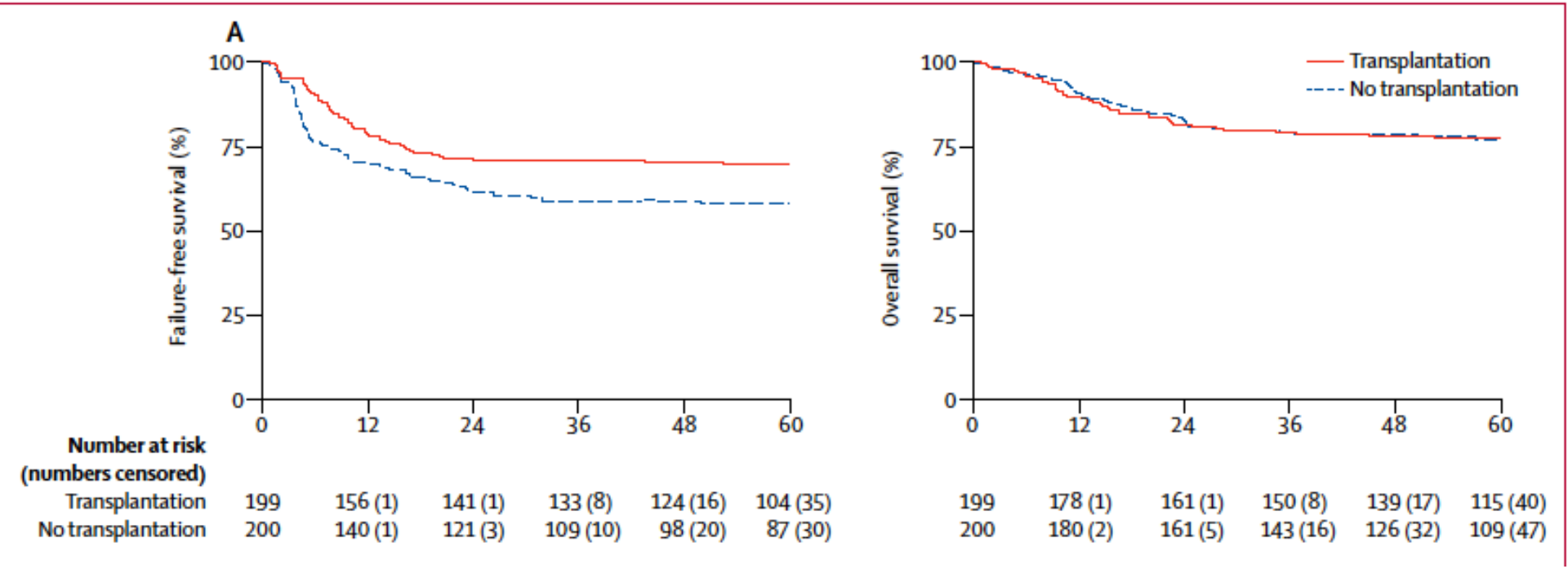
From 2005 to 2010, 412 untreated DLBCL were enrolled into the FIL-DLCL04 phase III randomized trial aimed at investigating the benefit of intensification with high dose therapy + autotransplant (R-HDC+ASCT) compared to R-dose-dense therapy as first line in young DLBCL at poor risk (aa-IPI 2-3).



Chiappella A, et al. Lancet Oncol 2017

Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study

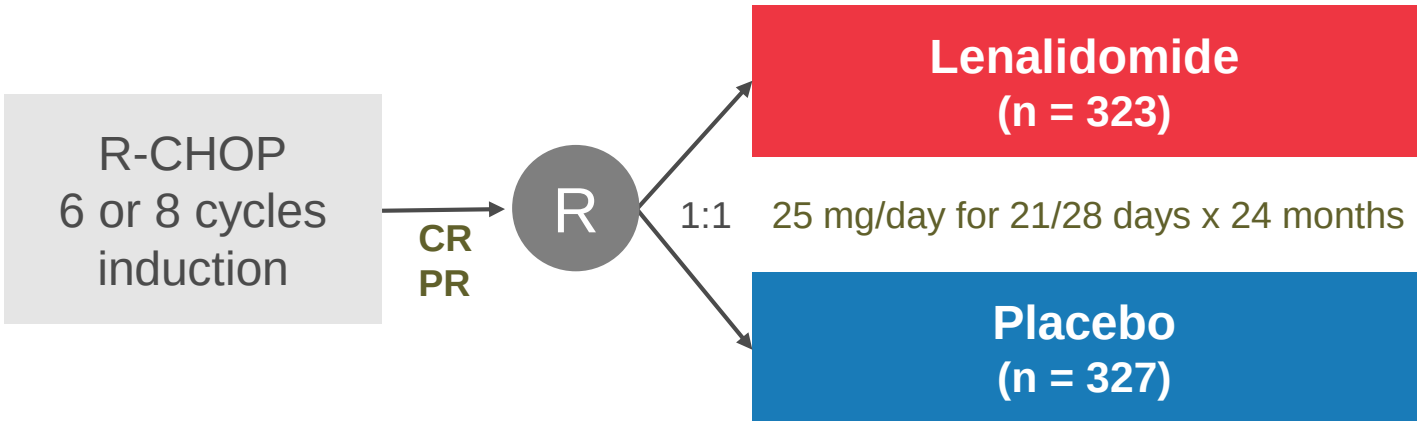
Annalisa Chiappella, Maurizio Martelli*, Emanuele Angelucci, Ercole Brusamolino†, Andrea Evangelista, Angelo Michele Carella, Caterina Stelitano, Giuseppe Rossi, Monica Balzarotti, Francesco Merli, Gianluca Gaidano, Vincenzo Pavone, Luigi Rigacci, Francesco Zaja, Alfonso D'Arco, Nicola Cascavilla, Eleonora Russo, Alessia Castellino, Manuel Gotti, Angela Giovanna Congiu, Maria Giuseppina Cabras, Alessandra Tucci, Claudio Agostinelli, Giovannino Ciccone, Stefano A Pileri, Umberto Vitolo*



Chiappella A, et al. Lancet Oncol 2017

How to improve R-CHOP results in DLBCL
Add maintenance?

- **Lenalidomide maintenance after R-CHOP in elderly DLBCL patients: phase 3 study (REMARC)**
- Patients aged 60–80 years, DLBCL CD20+, follicular lymphoma grade 3B, or de novo transformed follicular or indolent lymphoma



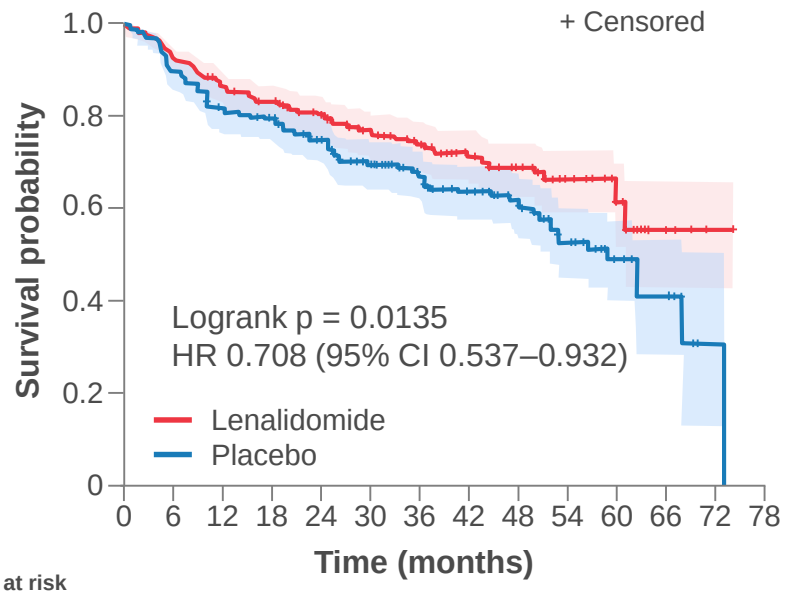
- Primary endpoint: PFS (central review)
  - based on an overall 2-year PFS of 80% and a HR of 0.65, with 80% power and overall alpha level of 5%
  - 160 events required for PFS analysis
- Secondary endpoints: OS, EFS, PFS2, RR, safety

CR, complete response;
PFS2, progression-free survival 2; PR, partial response.

Thieblemont C, et al. J Clin Oncol 2017.

Lenalidomide maintenance after R-CHOP in elderly DLBCL patients: efficacy

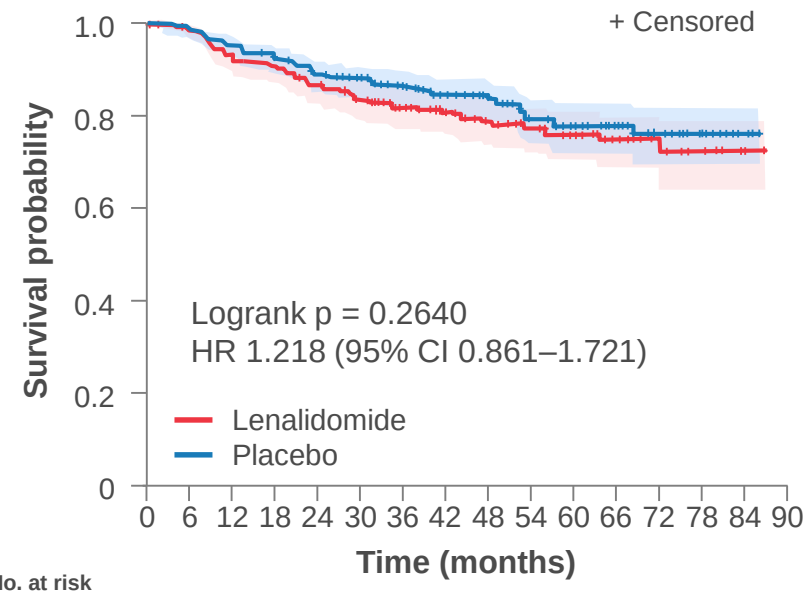
PFS



No. at risk														
Lenalidomide	323	291	265	250	214	172	137	97	70	42	23	6	1	0
Placebo	327	291	259	250	213	173	137	94	62	42	19	8	1	0

Follow-up: 40 months

OS



No. at risk															
Lenalidomide	323	312	292	285	271	250	217	188	152	112	79	50	27	12	1	0
Placebo	327	319	308	299	285	272	240	209	164	117	83	58	34	12	3	0

Follow-up: 52 months

Median PFS was not reached for lenalidomide at a median follow-up of 40 months. Median PFS for placebo was 58.9 months.

Thieblemont C, et al. J Clin Oncol 2017.

How to improve R-CHOP results in DLBCL
Add a novel agent to R-CHOP?

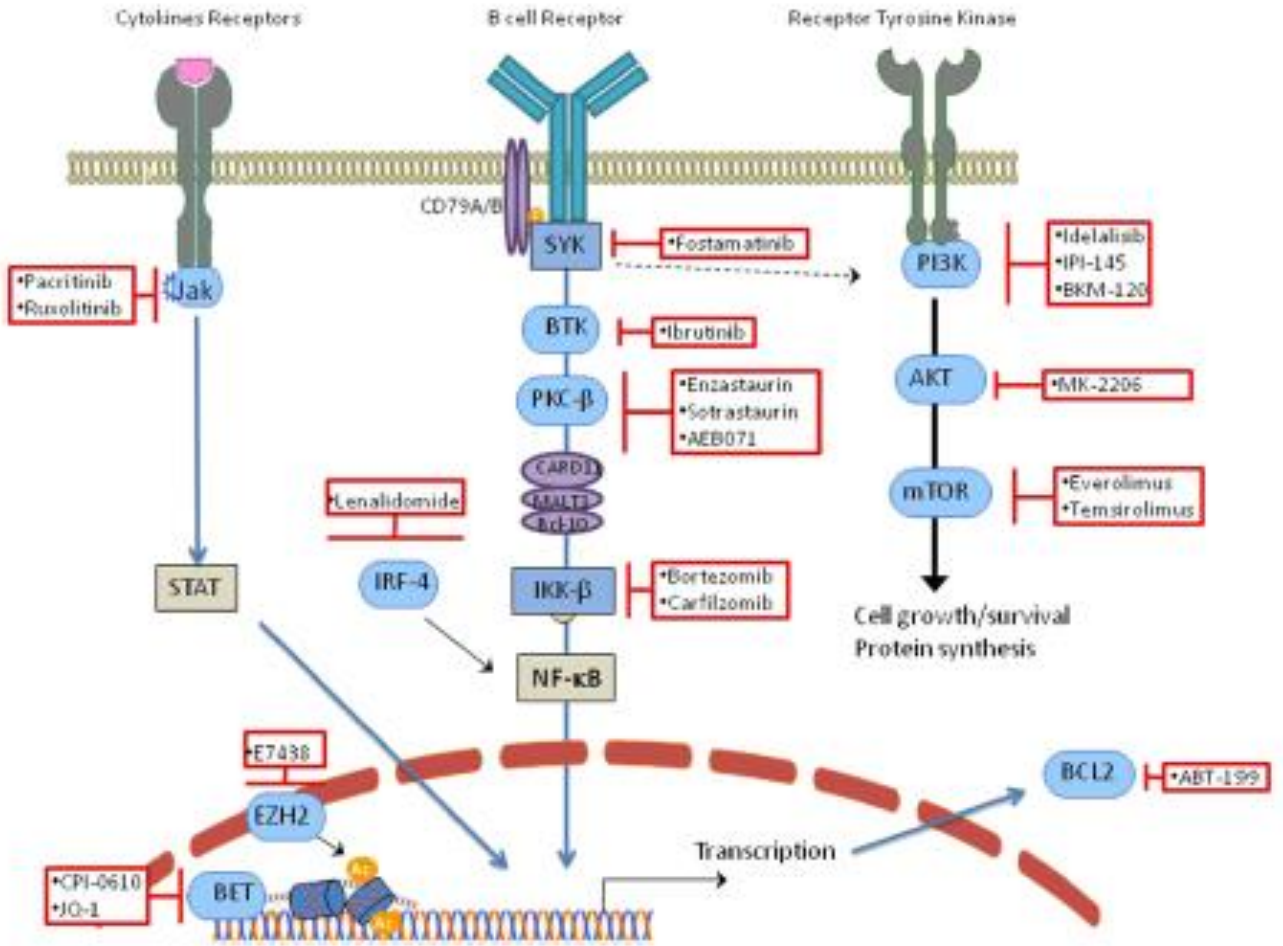
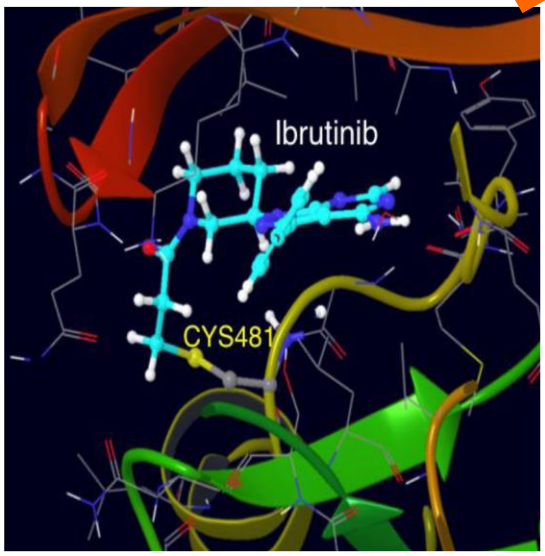


Figure 1. Schematic representation of key pathways in both ABC and GCB DLBCL.

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

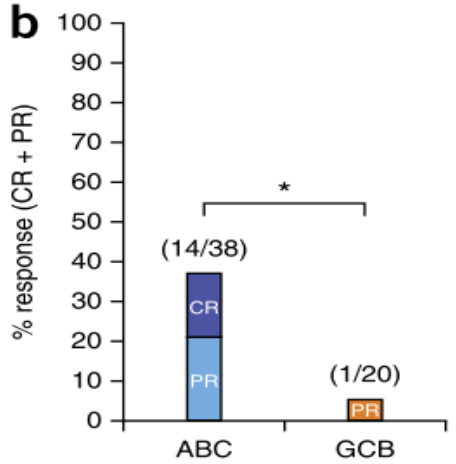
inhibition of proliferation
adhesion disruption
apoptosis

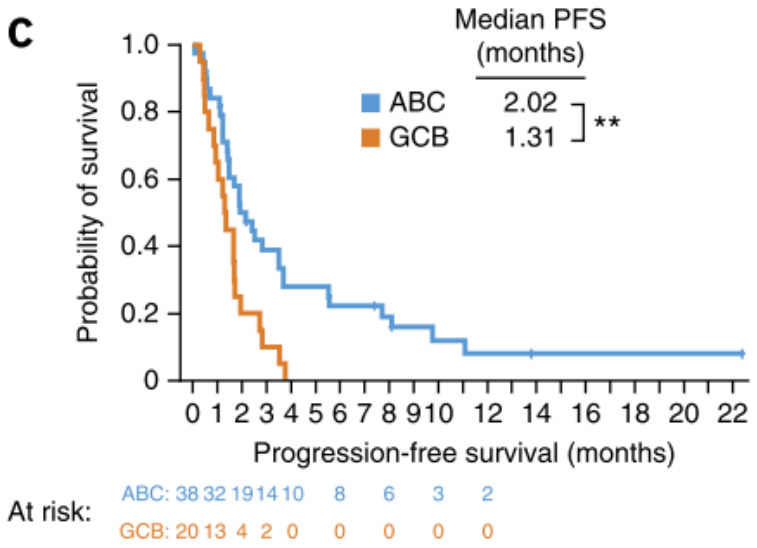
Ibrutinib in DLBCL, by COO subgroups

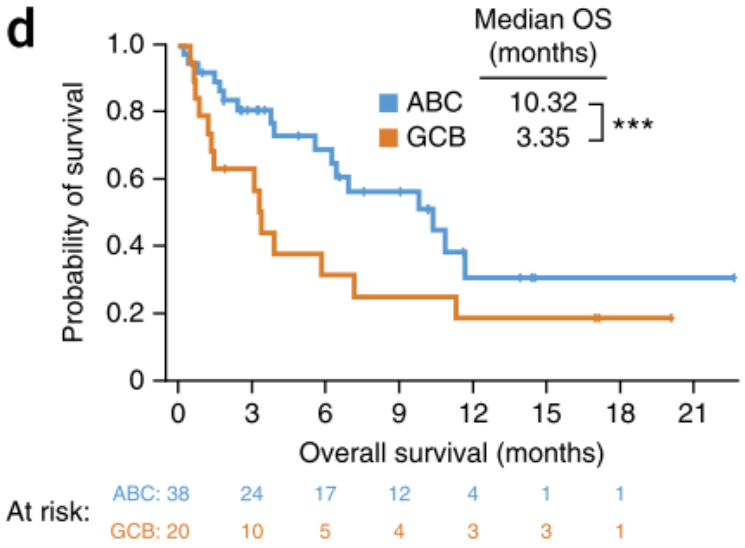
The Bruton's Tyrosine Kinase (BTK) inhibitor, ibrutinib (PCI-32765) has a preferential activity in ABC DLBCL: phase II interim results

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%



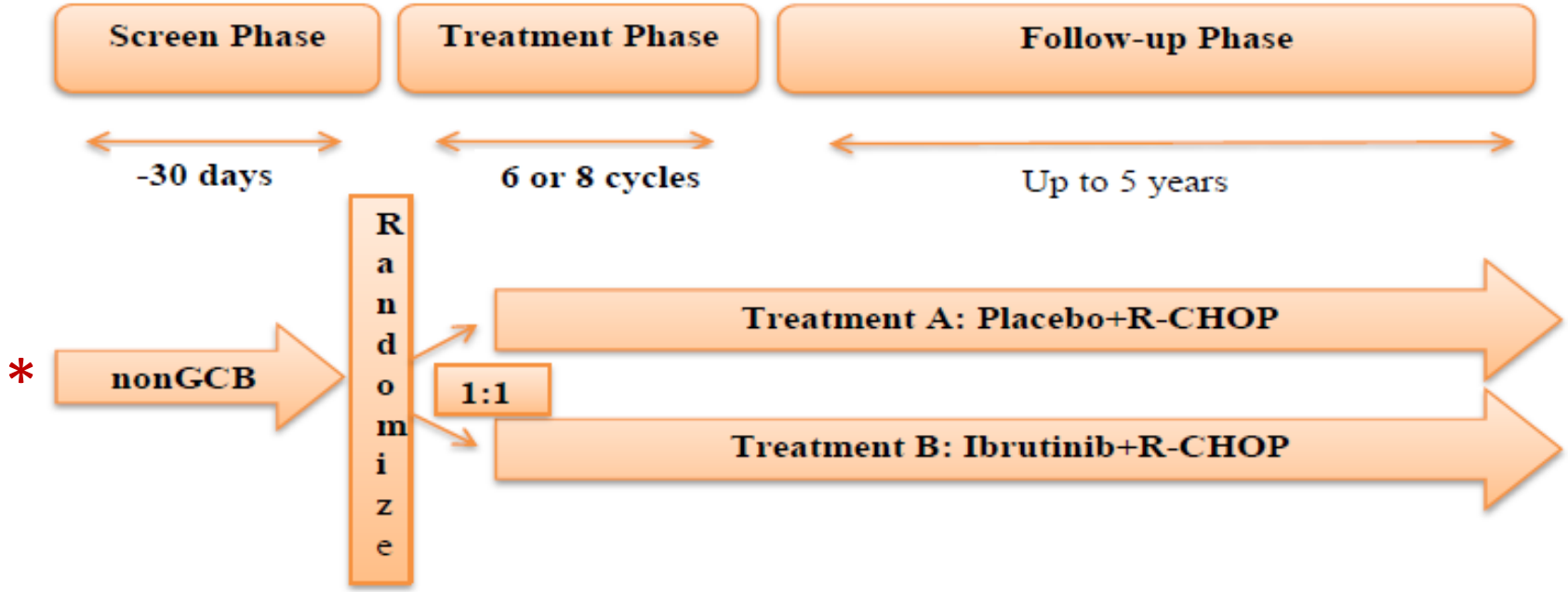




PR, partial response; SPD, sum of the products of the greatest perpendicular diameter.

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:

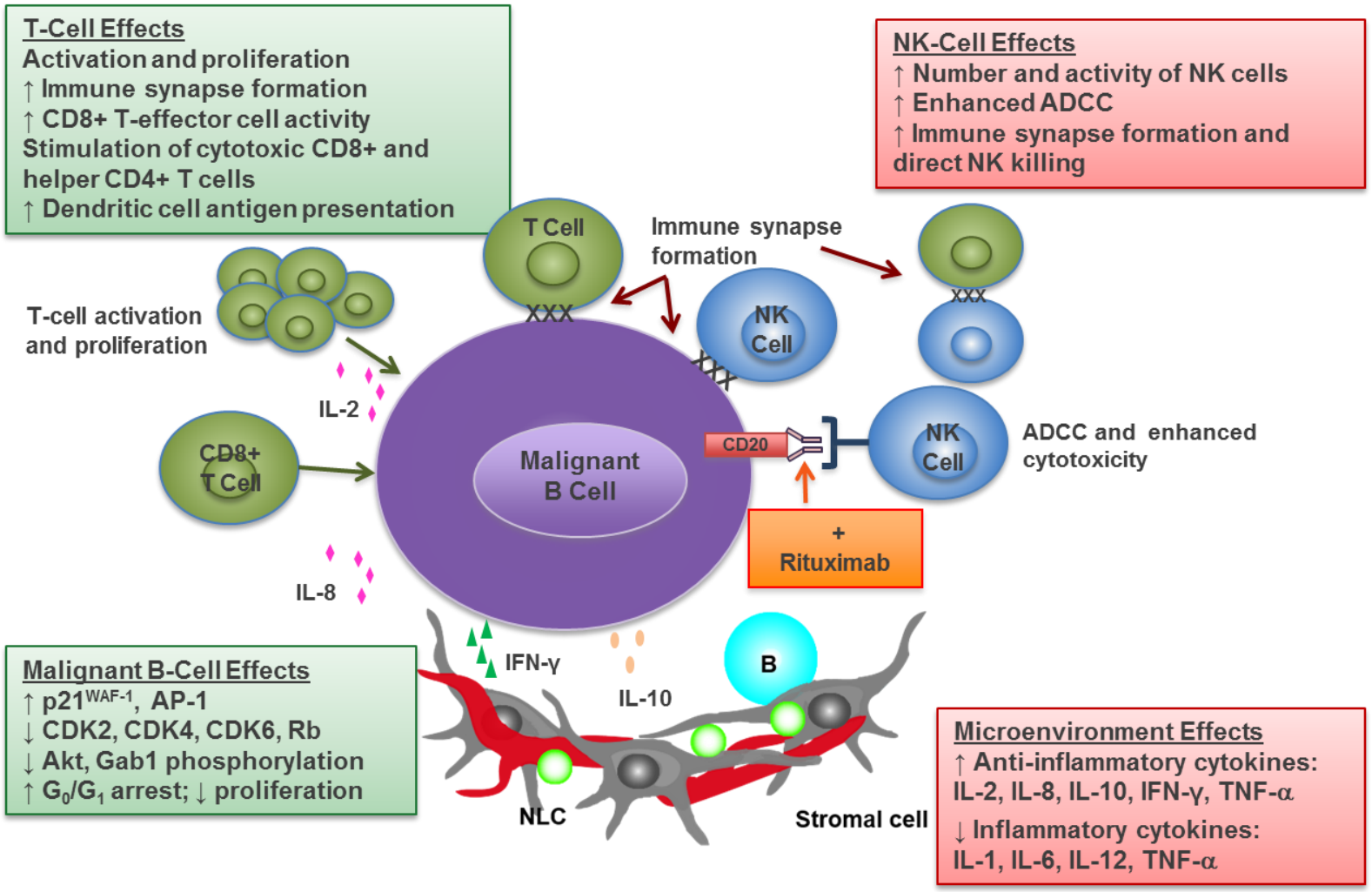
- R-IPI score low risk (1) vs. intermediate risk (2-3) vs. high risk (4-5)
- Region (United States/Western Europe vs. Rest of World)
- Number of treatment cycles (6 vs. 8 cycles)

PHOENIX
PCI-32765DBL3001

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

Janssen
PHARMACEUTICAL COMPANIES of Johnson & Johnson

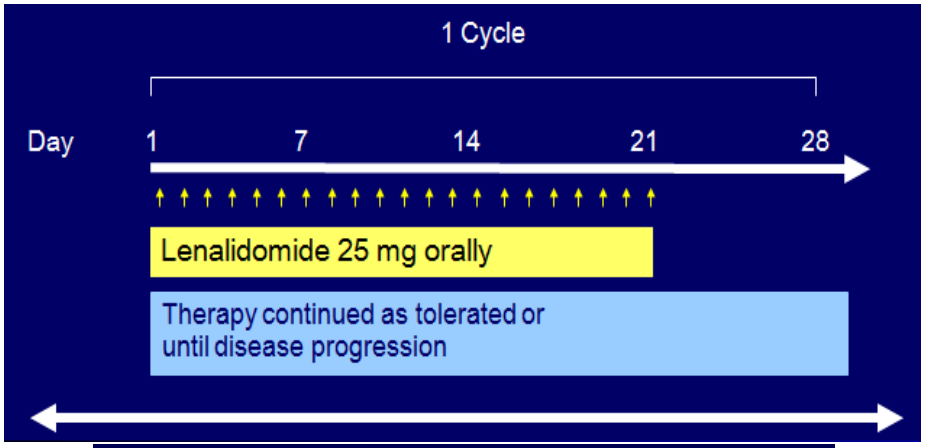
Mechanisms of action of lenalidomide in lymphoma cells and nodal microenvironment

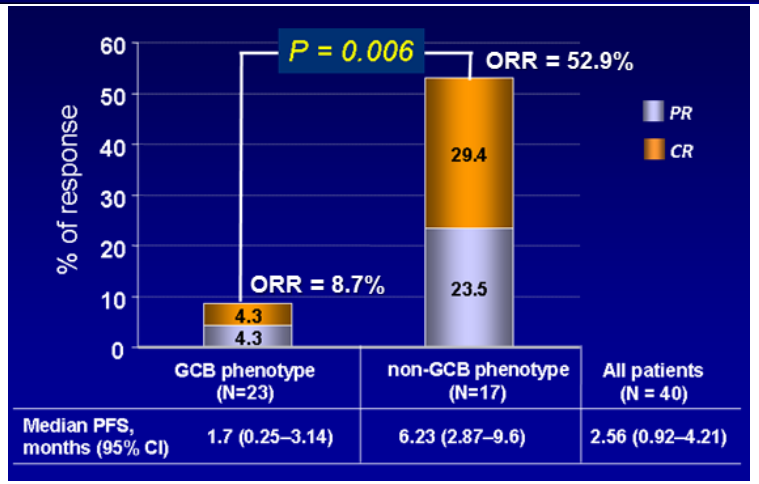


Gribben JG, et al. J Clin Oncol. 2015;33:2803-11.

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]	40	28%	15%†	2.6
GCB by IHC	23	9%	4%	1.7
Non-GCB by IHC	17	53%	29%	6.2
All patients[4]	51	27%	N/A	3.1
GCB by IHC	23	26%	N/A	2.3
Non-GCB by IHC	28	29%	N/A	3.5
GCB by GEP	14	21%	N/A	3.0
ABC by GEP	11	46%	N/A	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.

Wiernik PH, et al. J Clin Oncol 2008.

Witzig TE, et al. Ann Oncol 2011.

3. Hernandez-Ilizaliturri FJ, et al. Cancer 2011.

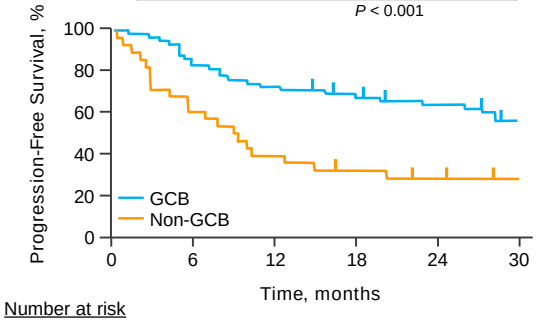
4. Czuczman MS, et al. Blood 2014.

Phase II R2-CHOP21 in Untreated DLBCL, and PFS by Cell Of Origin

Historical R-CHOP

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

P < 0.001



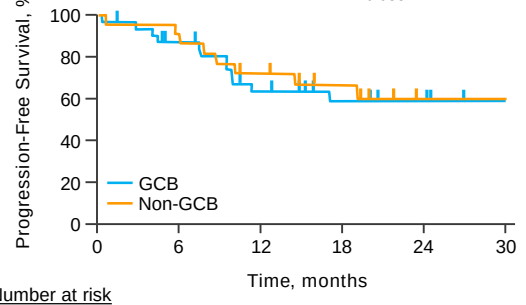
Number at risk

GCB	59	49	43	39	34	28
Non-GCB	28	17	11	8	6	3

R2-CHOP

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

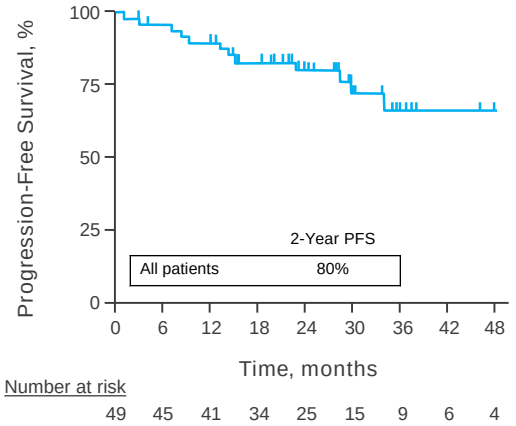
P = 0.083



Number at risk

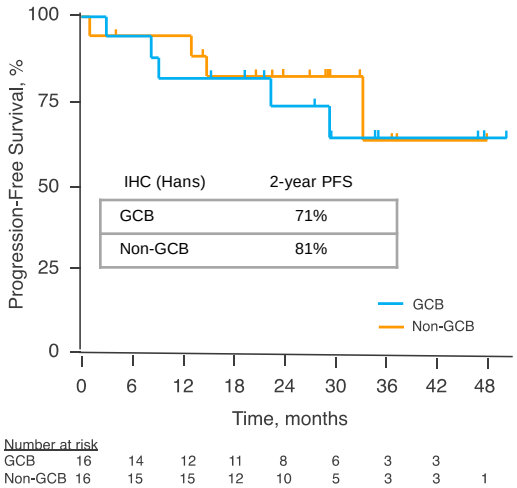
GCB	33	26	18	13	11	6
Non-GCB	22	20	14	10	5	4

R2-CHOP



Number at risk

	49	45	41	34	25	15	9	6	4



Number at risk

GCB	16	14	12	11	8	6	3	3	
Non-GCB	16	15	15	12	10	5	3	3	1

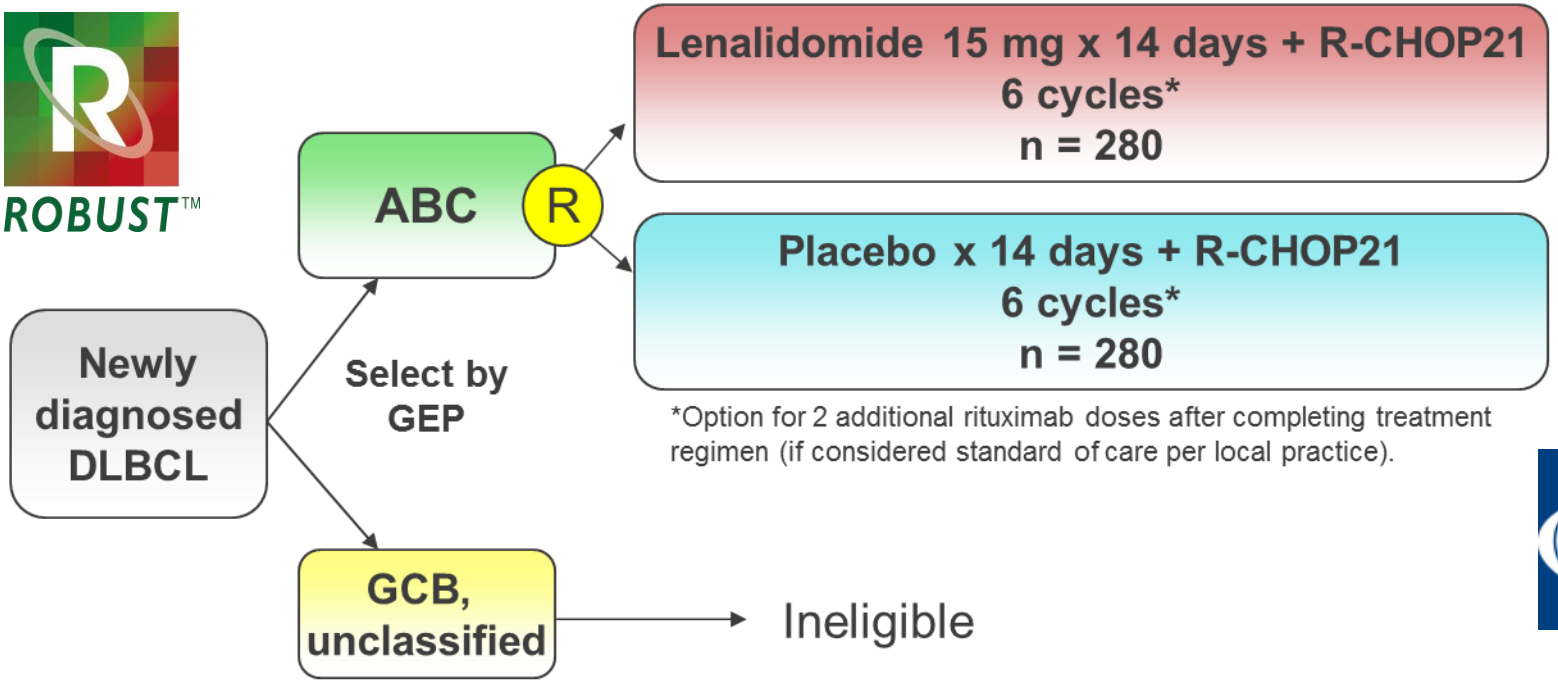
Nowakowski G et al. J Clin Oncol 2015.

Vitolo U et al. Lancet Oncol 2014.

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.

ROBUST™



*Option for 2 additional rituximab doses after completing treatment regimen (if considered standard of care per local practice).

- 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)

Conclusions

- ✓ An association between certain autoimmune conditions and increased risk of developing lymphoma is well documented.
- ✓ The most frequent NHL associated to autoimmune conditions are indolent Marginal Zone Lymphoma/MALT, and aggressive Diffuse Large B-cell Lymphoma/DLBCL
- ✓ R-CHOP is still the standard of care in DLBCL and is the backbone of new treatments with novel drugs
- ✓ A more accurate recognition of unfavorable DLBCL subsets is now recommended to better tailor the treatment
- ✓ ABC subtype should be included in clinical trials testing the addition of novel drugs to R-CHOP

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