

Quali novità per il paziente DLBCL alla diagnosi?



Dr. Guido Gini

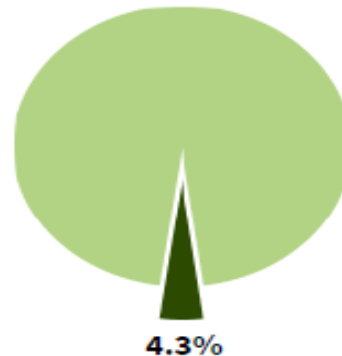
**Clinica di Ematologia
AOU "Ospedali Riuniti"
Università Politecnica delle
Marche**

Bologna, 5 Novembre 2018

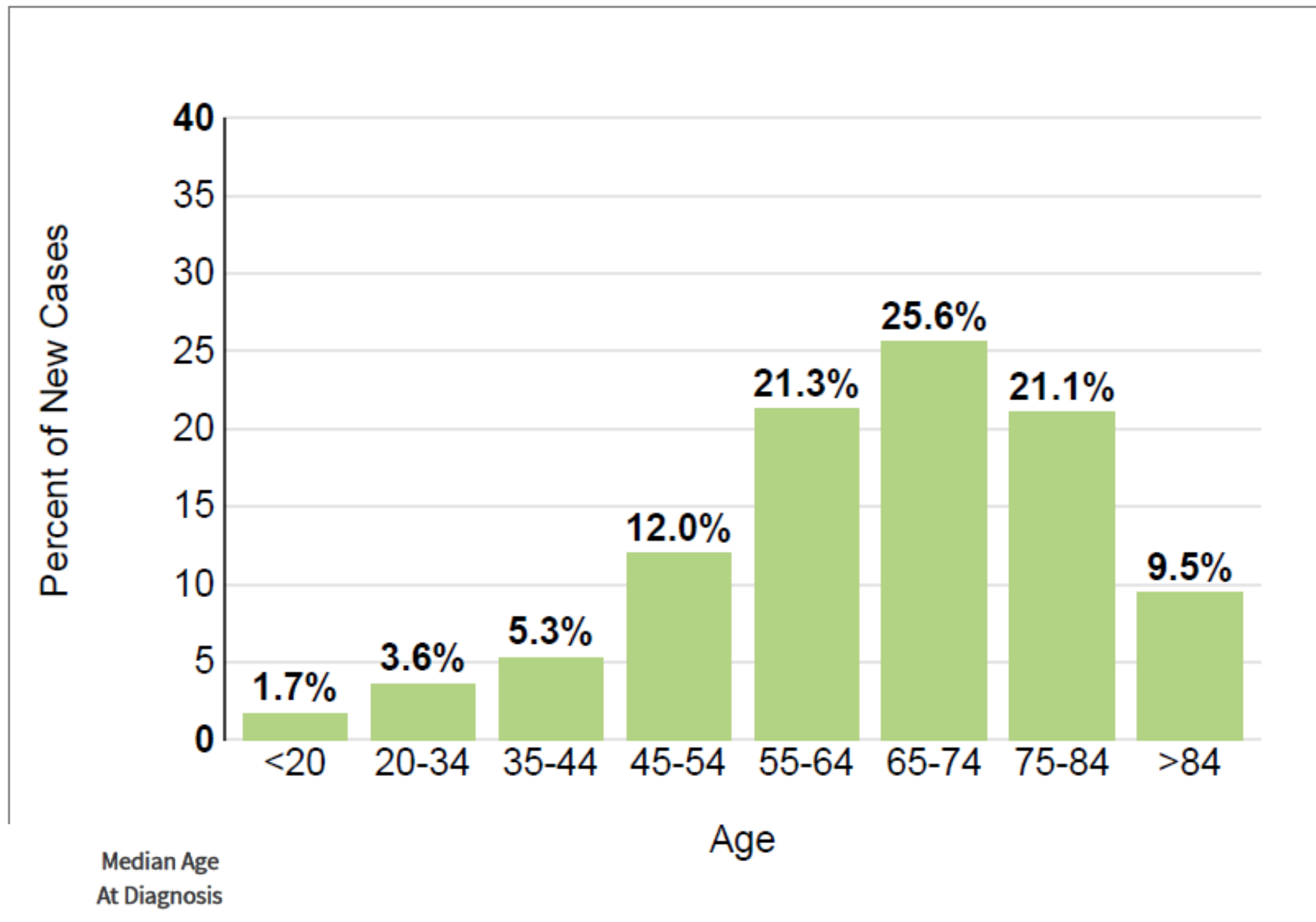
LA TRISTE TOP TEN

Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1. Breast Cancer (Female)	266,120	40,920
2. Lung and Bronchus Cancer	234,030	154,050
3. Prostate Cancer	164,690	29,430
4. Colorectal Cancer	140,250	50,630
5. Melanoma of the Skin	91,270	9,320
6. Bladder Cancer	81,190	17,240
7. Non-Hodgkin Lymphoma	74,680	19,910
8. Kidney and Renal Pelvis Cancer	65,340	14,970
9. Uterine Cancer	63,230	11,350
10. Leukemia	60,300	24,370

Non-Hodgkin lymphoma represents 4.3% of all new cancer cases in the U.S.



Percent of New Cases by Age Group: Non-Hodgkin Lymphoma



Median Age
At Diagnosis

67

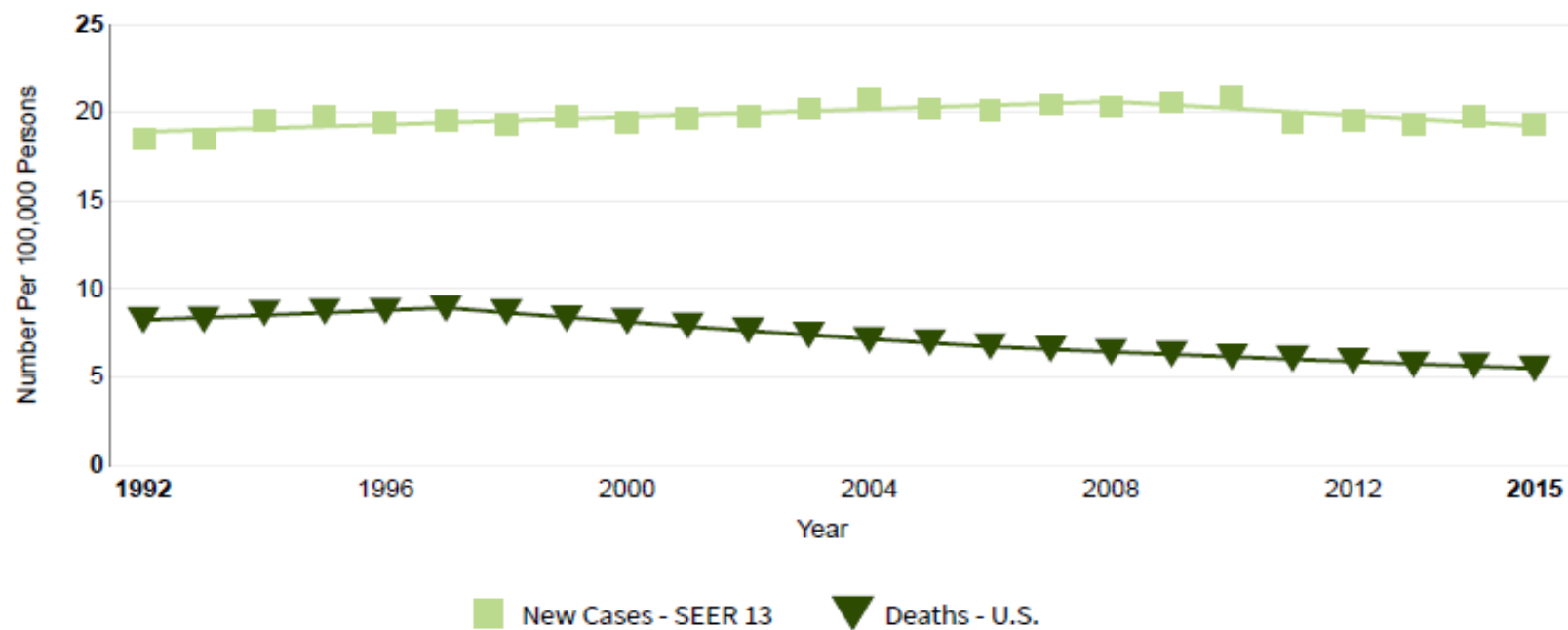


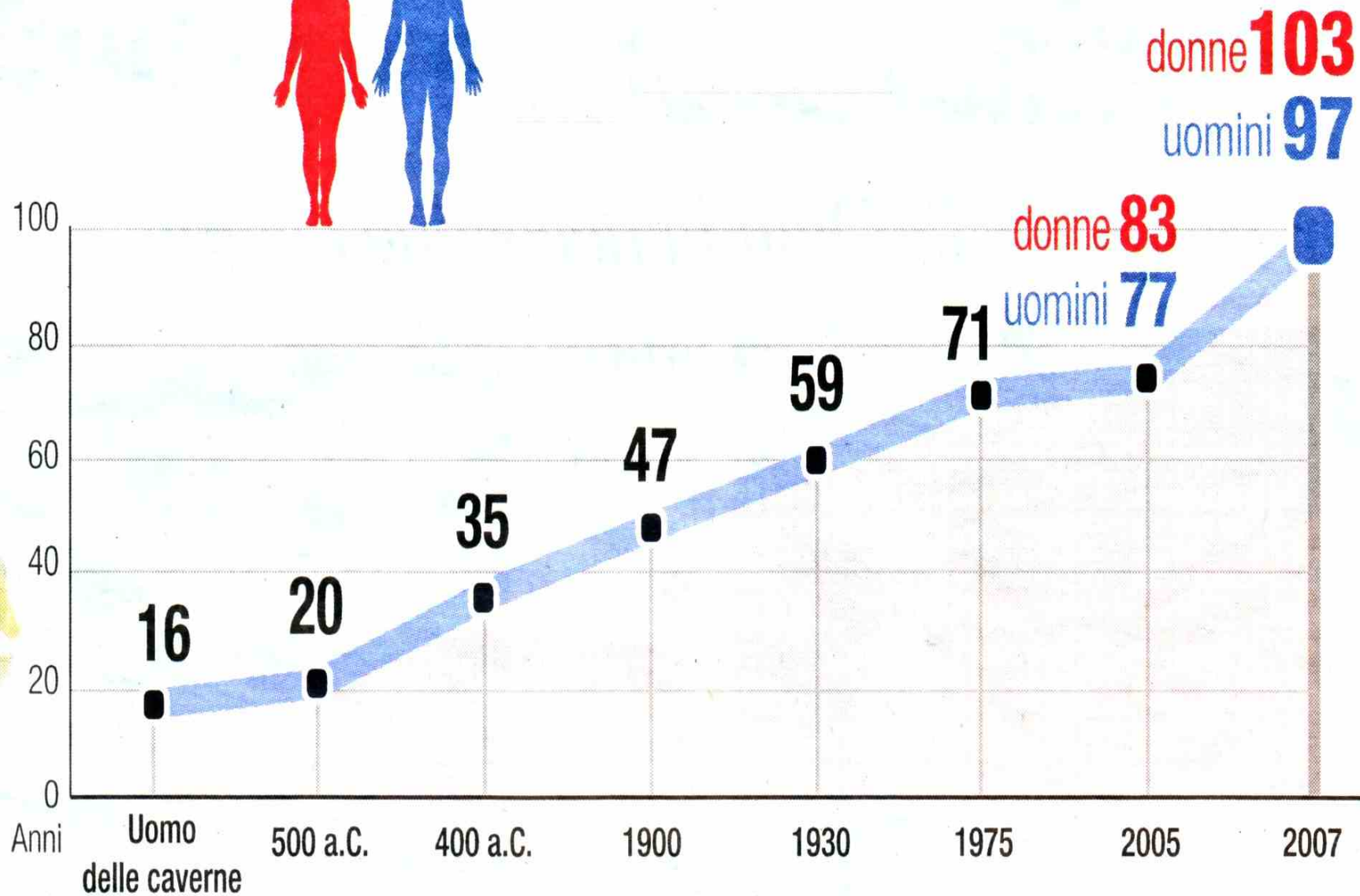
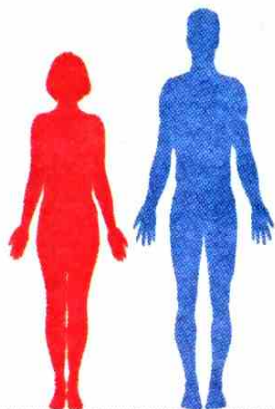
NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

Percent Surviving
5 Years

71.4%

2008-2014





COME E' CAMBIATA L'ITALIA.....

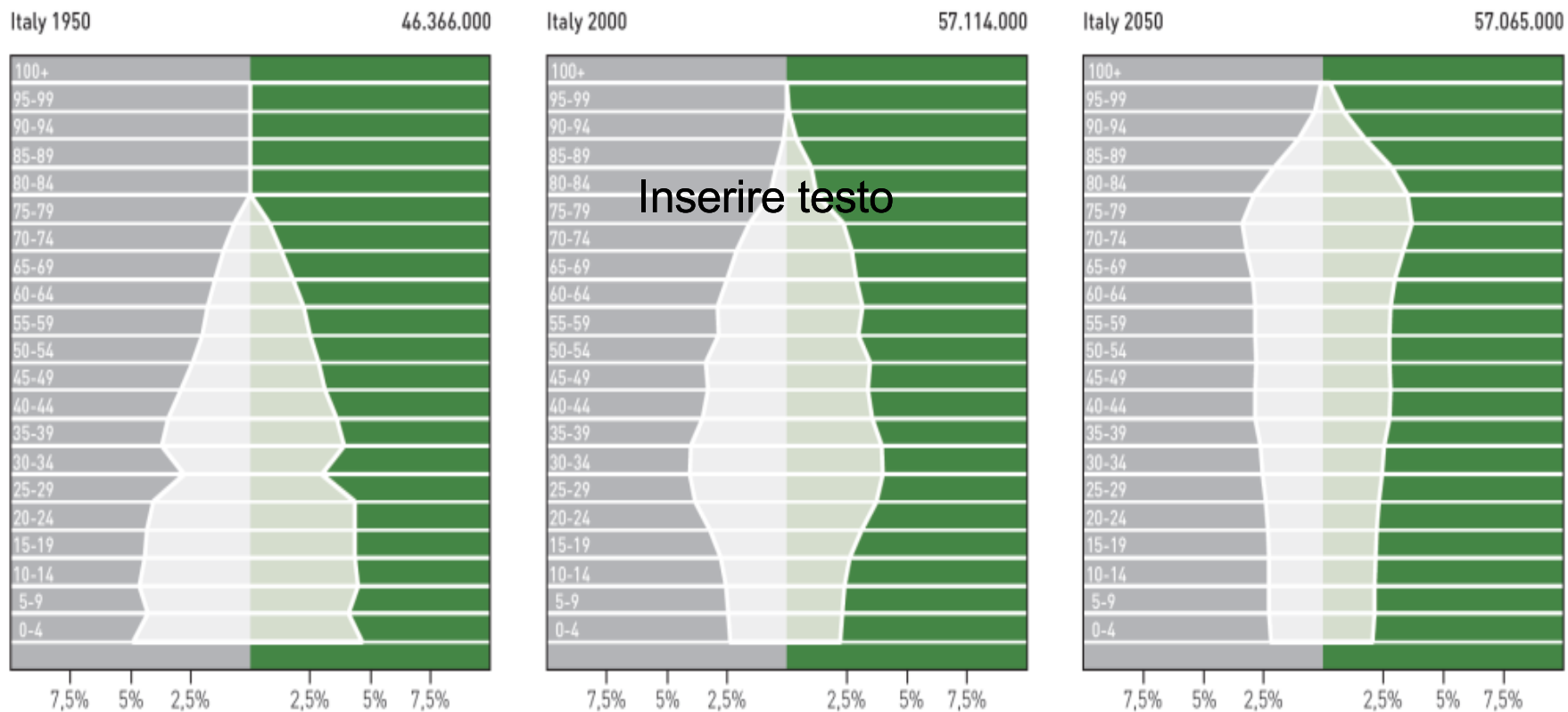


FIGURA 4. Struttura per età della popolazione italiana (<http://populationpyramid.net/it>).

DATI AIRTUM SUI LINFOMI IN ITALIA

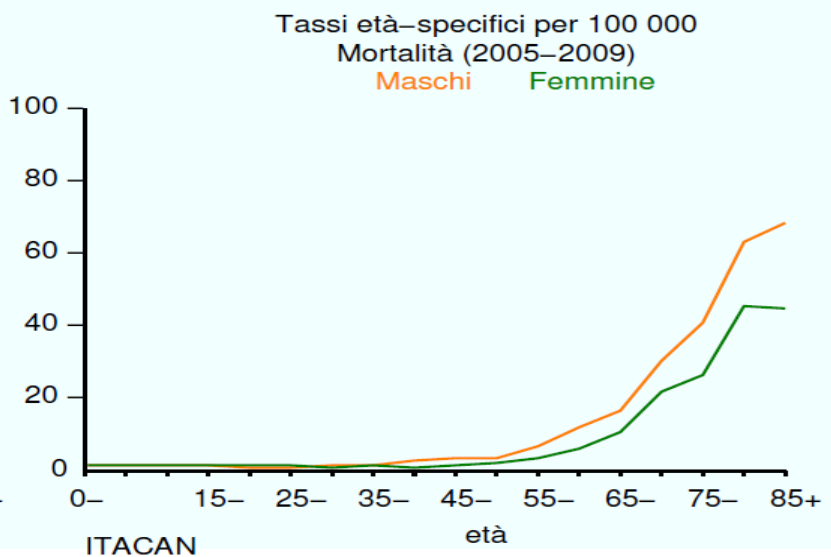
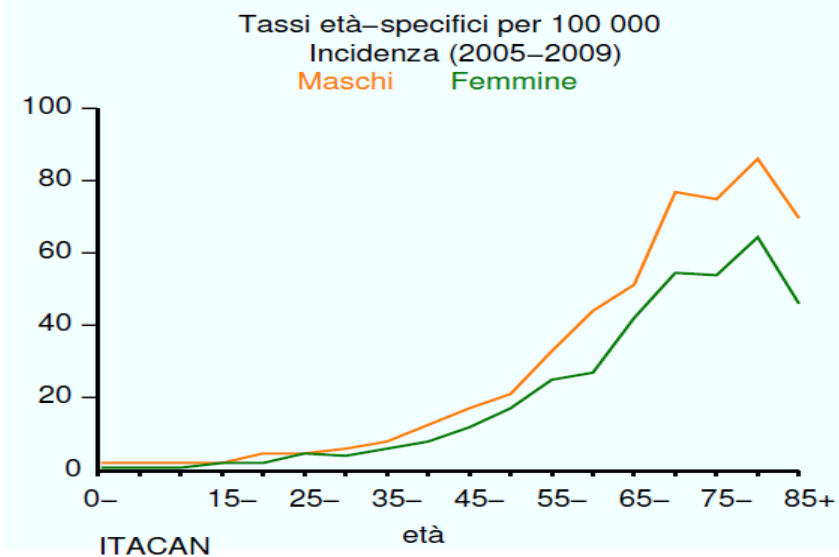
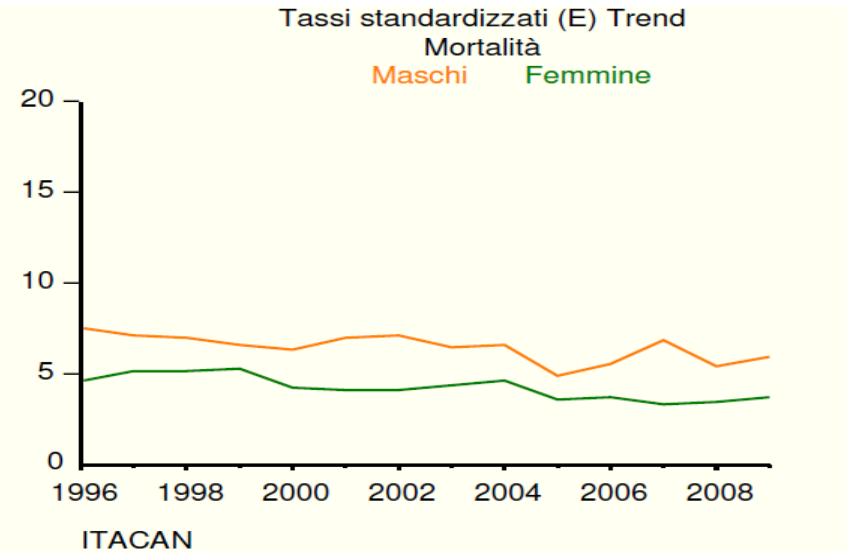
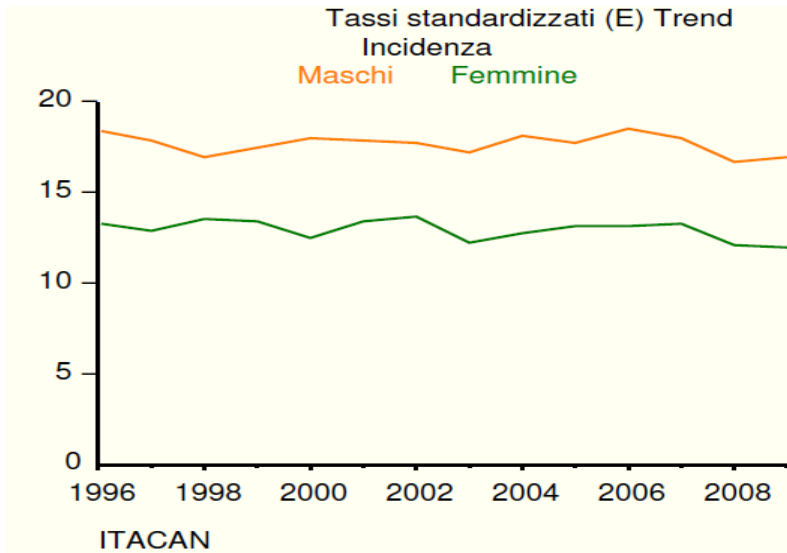
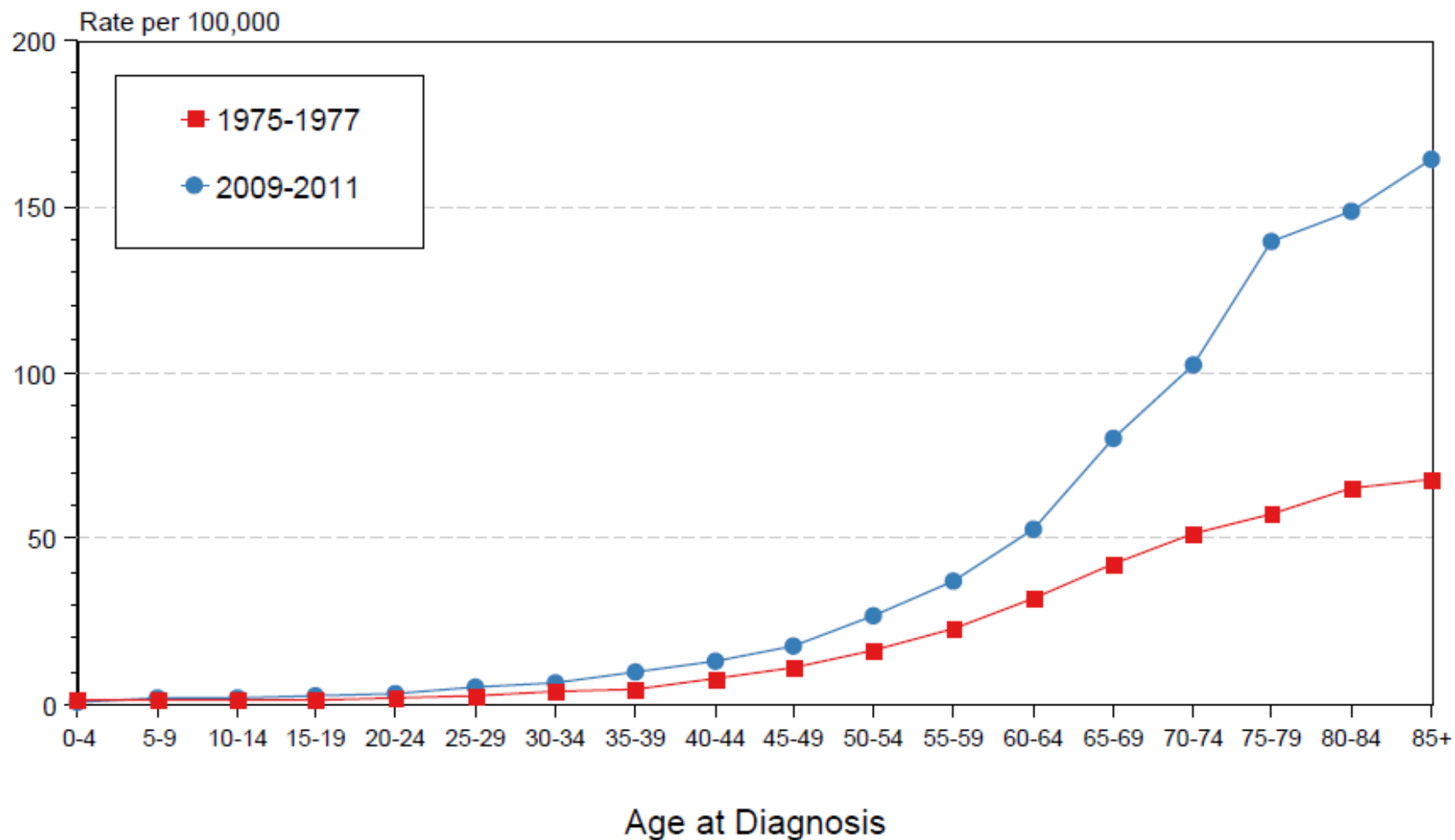


Figure 19.4

Non-Hodgkin Lymphoma SEER Incidence by Age 1975-1977 vs 2009-2011 All Races, Males



Source: SEER 9 areas. Rates are age-adjusted as appropriate to the 2000 US Std Population (19 age groups - Census P25-1103)

UN PO' DI STORIA

[CANCER RESEARCH 33, 3024–3028, November 1973]

Chemotherapy of Malignant Lymphoma with Adriamycin¹

Jeffrey A. Gottlieb,² Jordan U. Gutterman, Kenneth B. McCredie, Victorio Rodriguez, and Emil Frei, III³

Department of Developmental Therapeutics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas 77025

with four patients still responding. In a third regimen, nine patients with minimal or no previous chemotherapy received adriamycin combined with cyclophosphamide, vincristine, and prednisone. All nine responded; seven complete and two partial remissions were observed for a median duration of more than 8 months, with six patients still in complete remission. For the 16 patients with complete remissions on all three regimens, the median duration of response is now more than 11 months. In the patients with non-Hodgkin's lymphoma, the response rate was similar in the different histological subtypes. Major side effects included nausea, alopecia, and myelosuppression, with the last side effect most pronounced in the combination with arabinosylcytosine. Our studies suggest that adriamycin is a new, effective agent in the treatment of patients with advanced malignant lymphoma. The response rate with the combination of adriamycin, cyclophosphamide, vincristine, and prednisone is particularly encouraging in non-Hodgkin's lymphoma, and this regimen is currently being further pursued in a larger multiinstitutional study.

Chemotherapy regimens in aggressive NHL

Generation	Regimen	RC	OS	Months
I	CHOP	47	32	6
	C-MOPP	41	35	6
	BACOP	48	36	6
II	m-BACOD	72	48	7
	COP-BLAM	73	55	6
	pro-MACE-MOPP	74	48	6
	LNH 84	75	48	6
III	COP-BLAM III	84	65	8
	MACOP-B	84	75	3
	ProMACEcytaBOM	79	60	5
	F-MACHOP	78	66	6



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

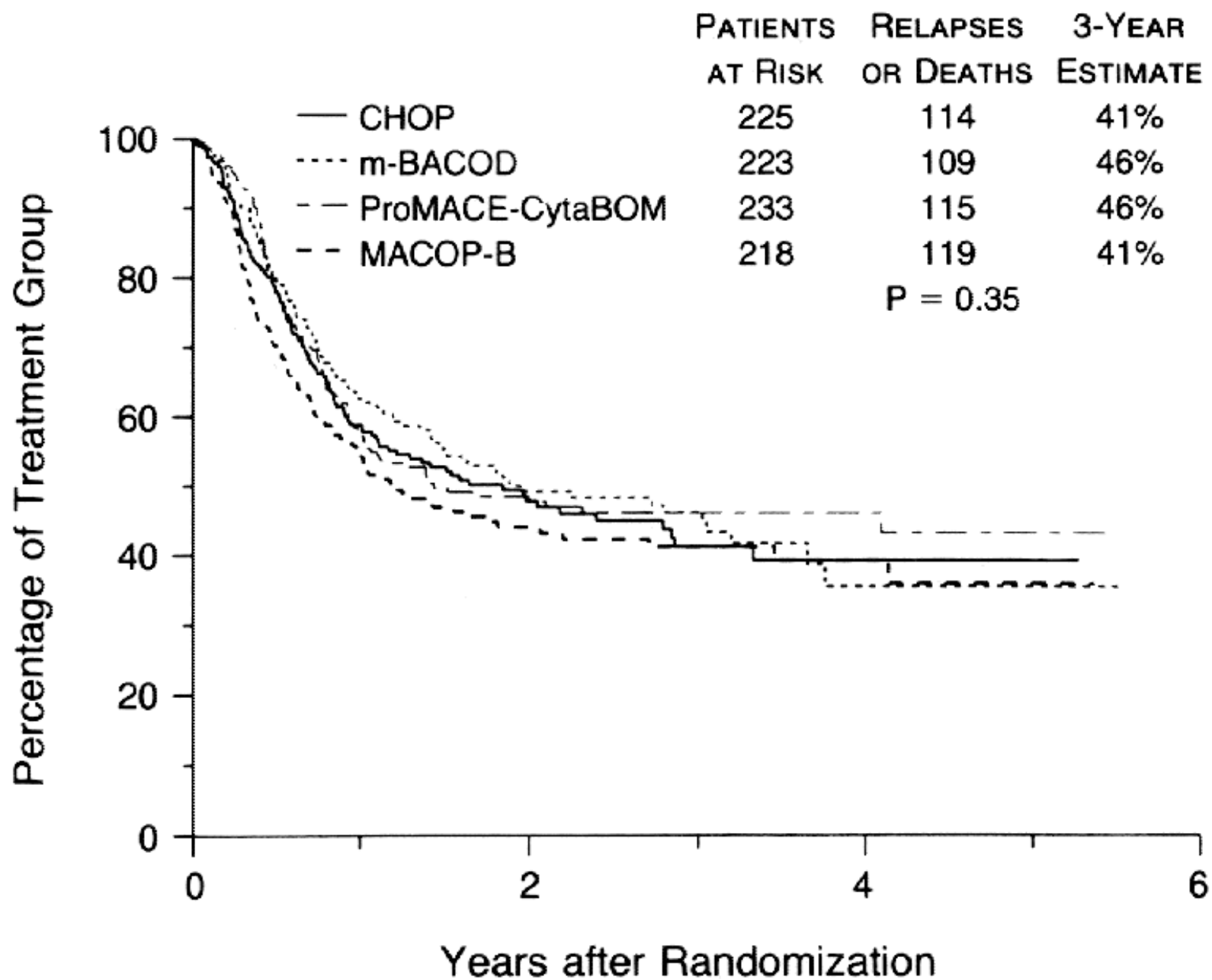
Volume 328:1002-
1006

April 8, 1993

Number 14

Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma

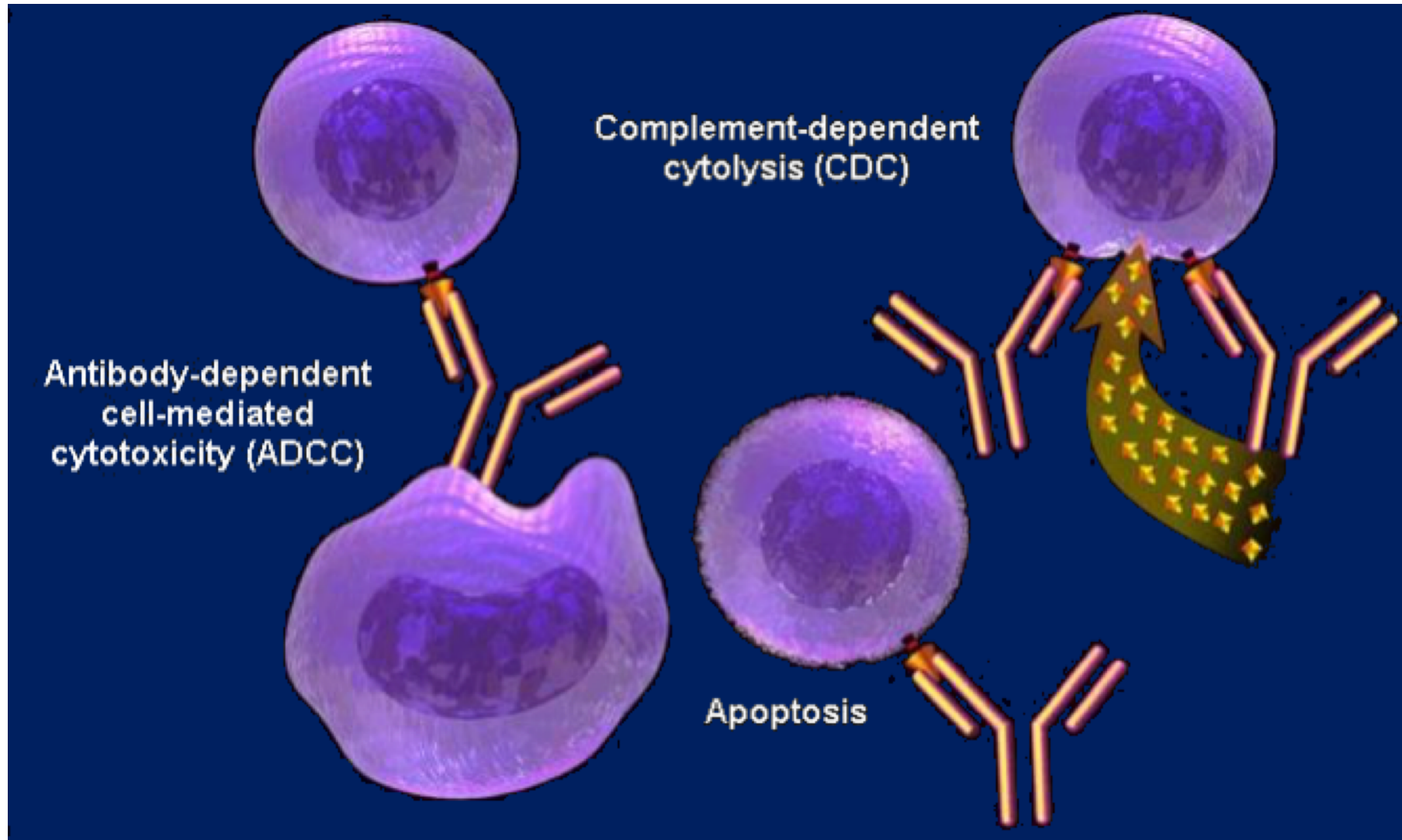
*Richard I. Fisher, Ellen R. Gaynor, Steve Dahlberg, Martin M. Oken,
Thomas M. Grogan, Evonne M. Mize, John H. Glick, Charles A. Coltman,
and Thomas P. Miller*



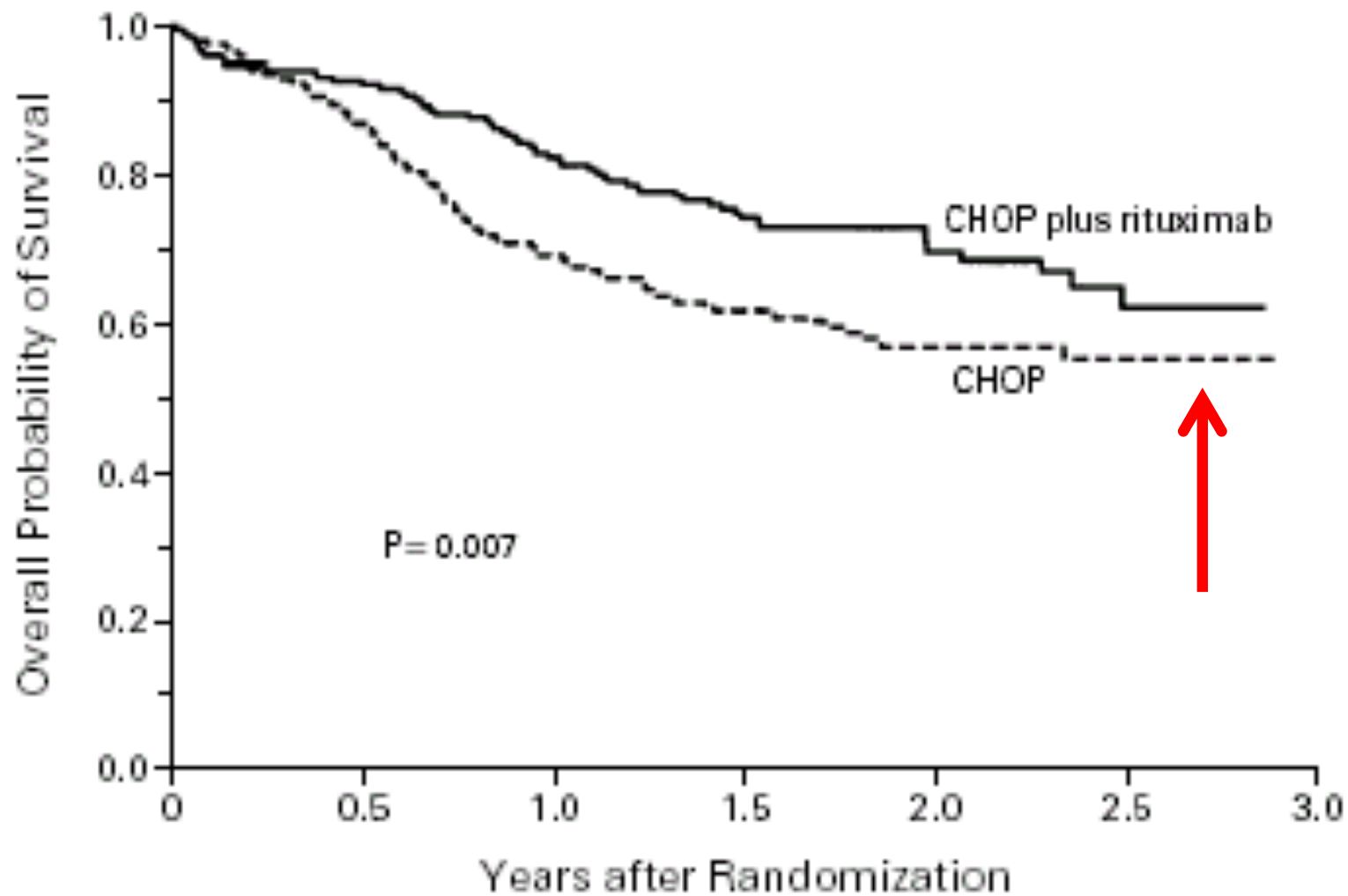


"Un timoniere di valore
continua a navigare anche con
la vela a brandelli."
Lucio Anneo Seneca

Monoclonal Antibodies Provide a Targeted Approach to the Treatment of NHL



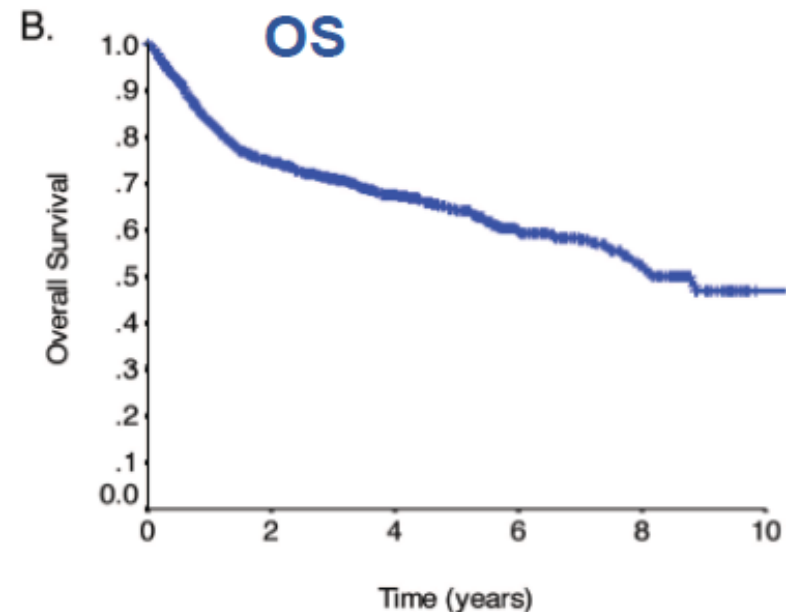
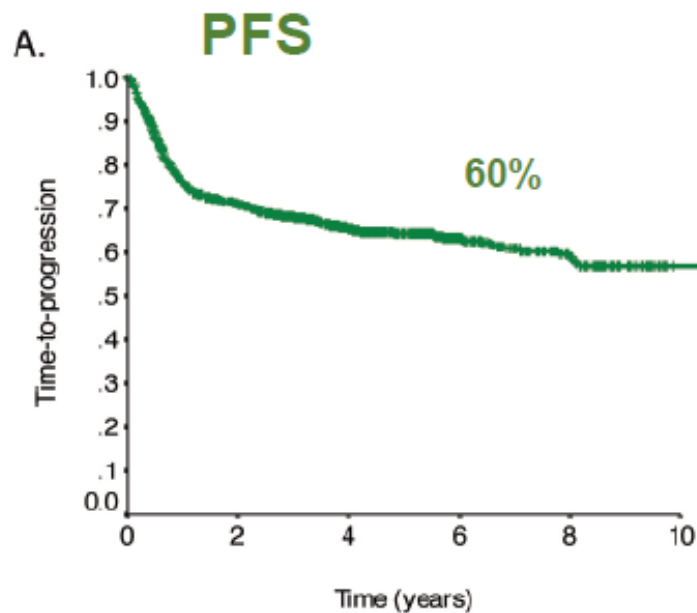
Coiffier et al, NEJM 2002



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



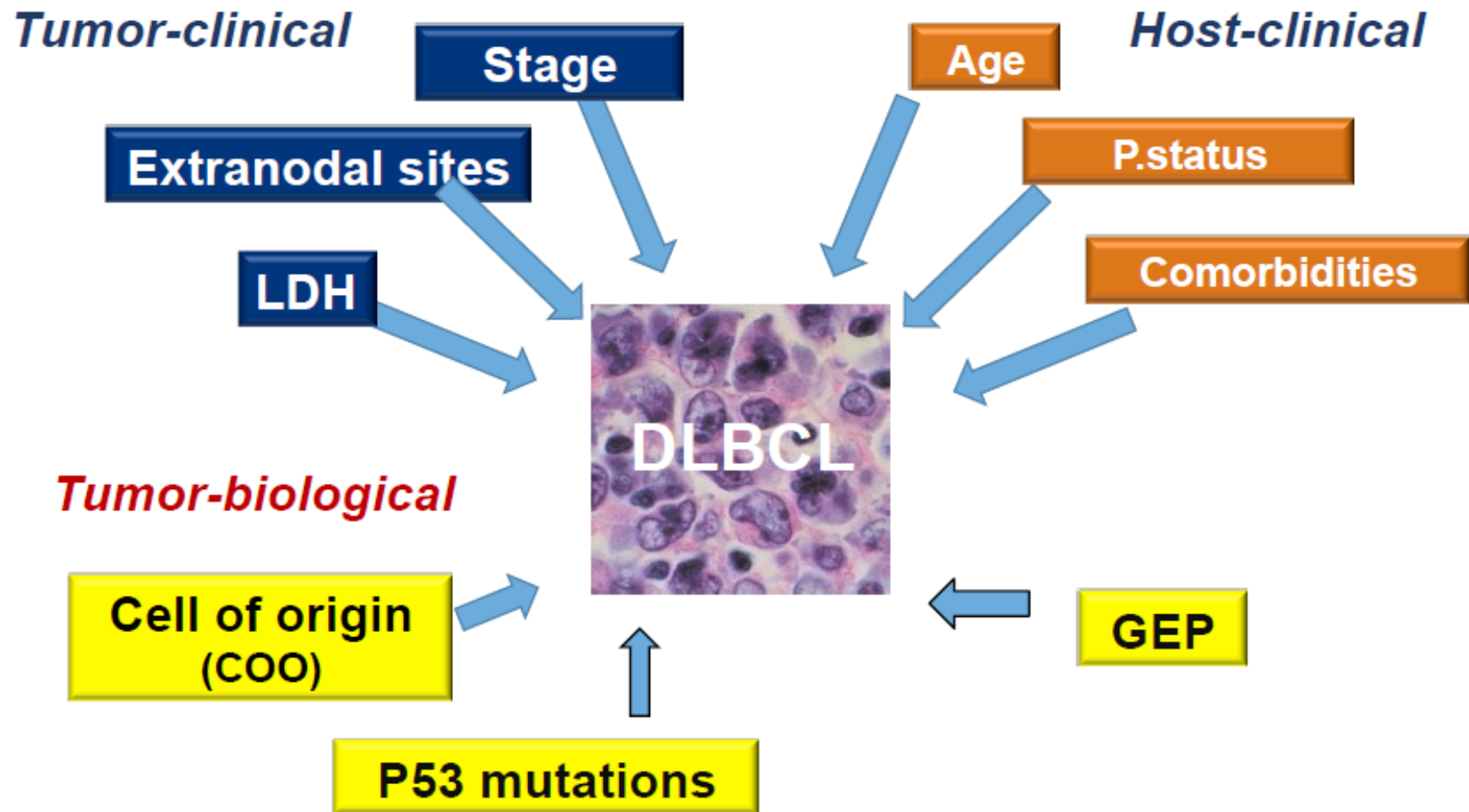
Patients with DLBCL treated with R-CHOP-21 at BCCA (n=1476)



Main role of front line therapy in DLBCL and low activity of salvage therapy

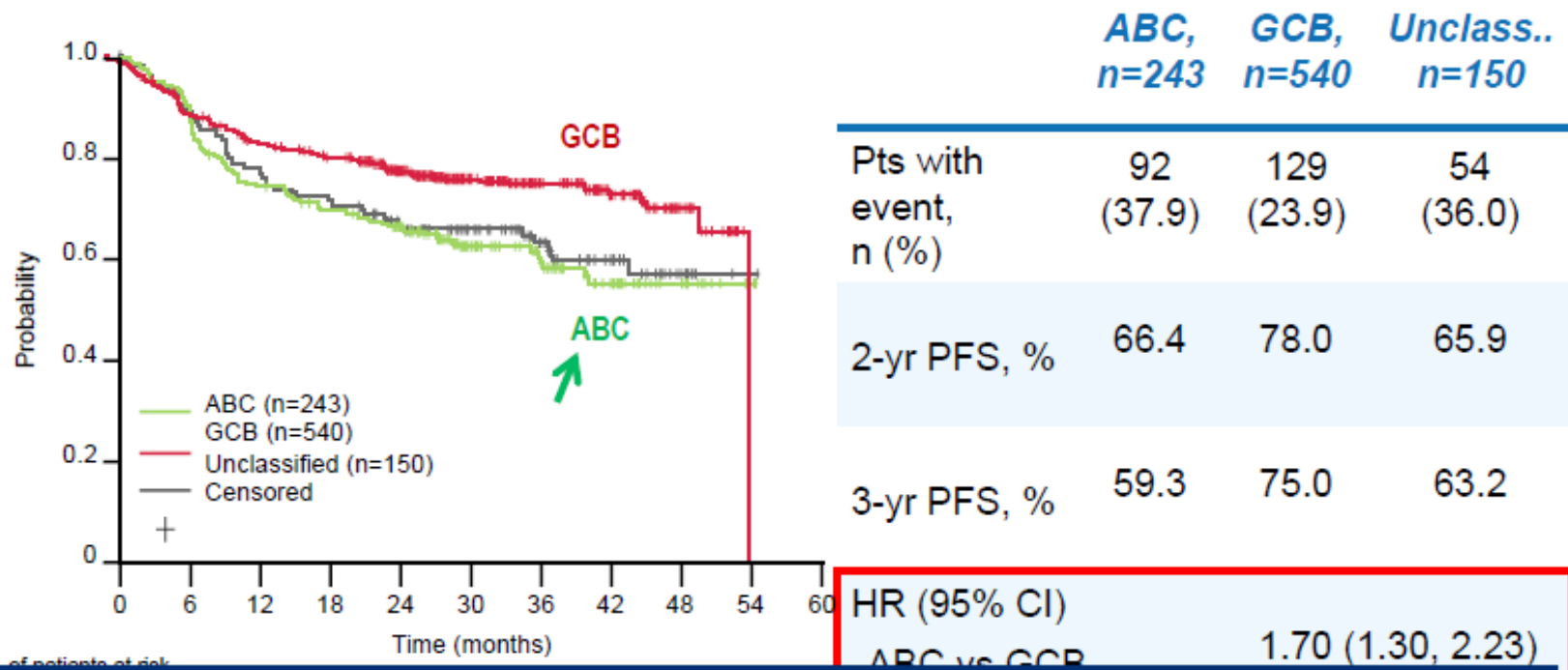
BC Cancer Agency Database Sehn Hematology 2012

Biological factors affecting response in DLBCL



Goya study: investigator-assessed PFS by cell of origin*

Kaplan-Meier plot of investigator-assessed PFS by COO (Nanostring test)



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

Treatment of B-Diffuse large cell Lymphoma



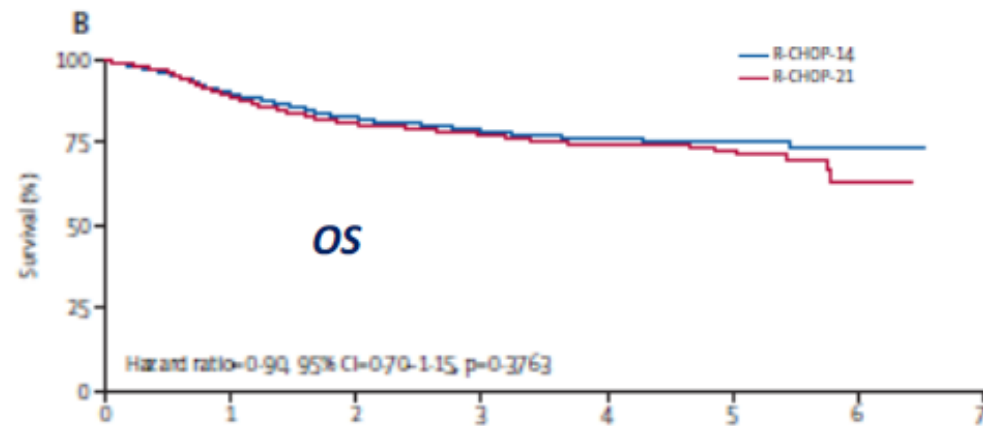
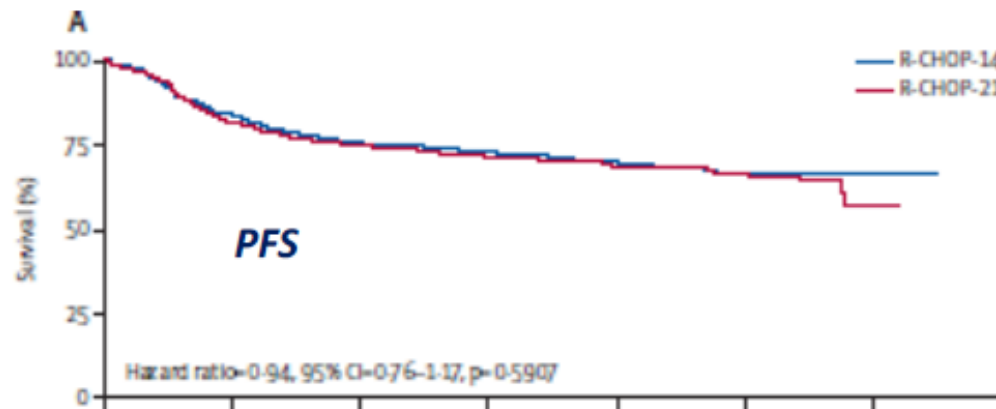
**CAN WE DO
ANY BETTER?**

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles



Articles

David Cunningham*, Eliza A Hawkes*, Andrew Jack, Wendi Qian, Paul Smith, Paul Mouncey, Christopher Pocock, Kirit M Ardeshna, John A Radford, Andrew McMillan, John Davies, Deborah Turner, Anton Kruger, Peter Johnson, Joanna Gambell, David Linch



R-HDT-ASCT or conventional therapy (R-Chemo) in younger patients with poor-risk IPI (2-3) DLBCL

	FOLLOW UP	PFS		OS	
		HDT	conventional	HDT	conventional
Stiff et al.*	2 yrs.	72%	62%	76%	72%
Chiappella al.	3 yrs.	71%	58%	83%	80%
Schmitz et al.	4 yrs.	67%	72%	75%	85%
Le Gouill et al.	3 yrs.	37%	56%	82%	85%
Cortelazzo	2 yrs	73%	68%	80%	78%

* PFS and OS for pts. treated with R-CHOP ± HDT

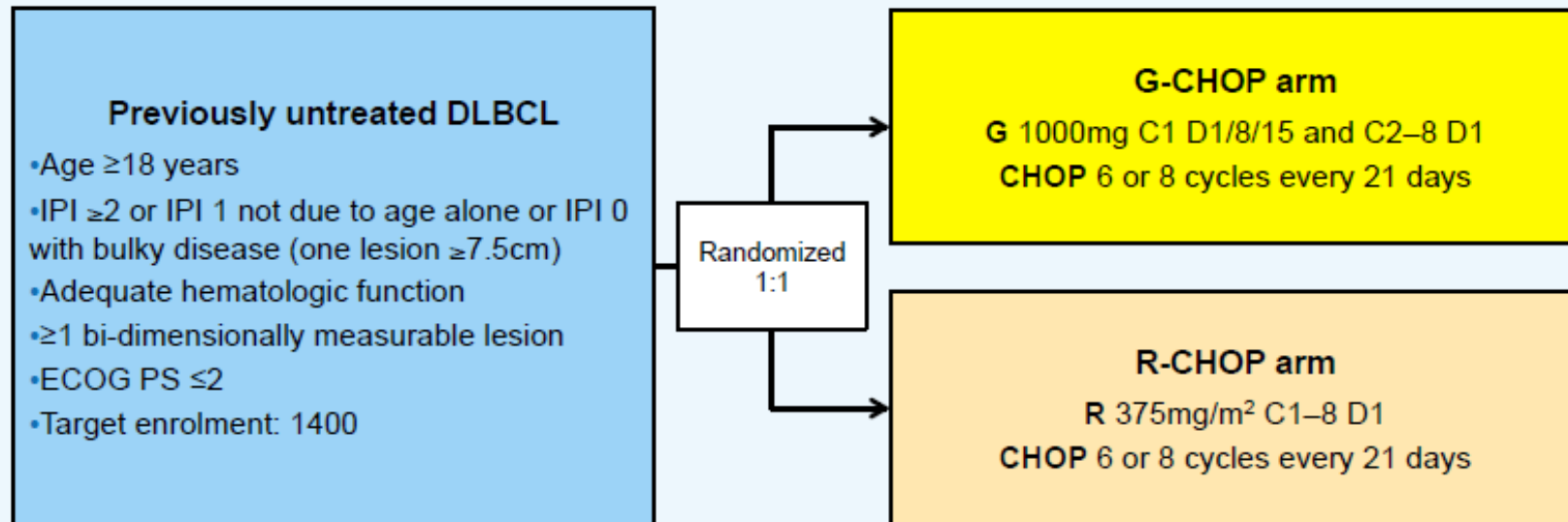


Goya study design

International, open-label, randomized Phase III study in 1L DLBCL pts

- *Scientific support from the Fondazione Italiana Linfomi*

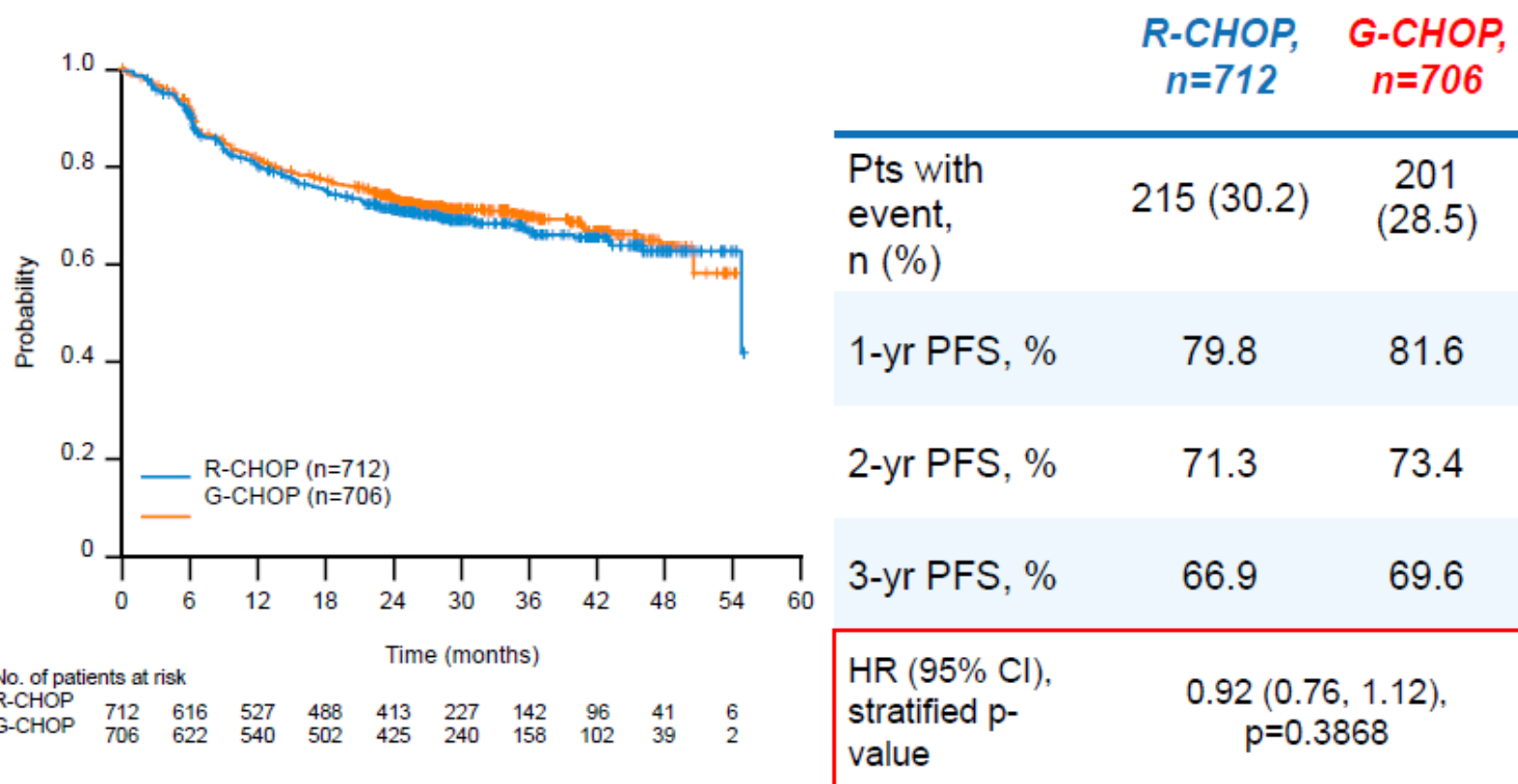
Pts enrolled: 1416



- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Investigator-assessed PFS (primary endpoint)*

KM plot of INV-assessed PFS
by treatment arm



No. of patients at risk

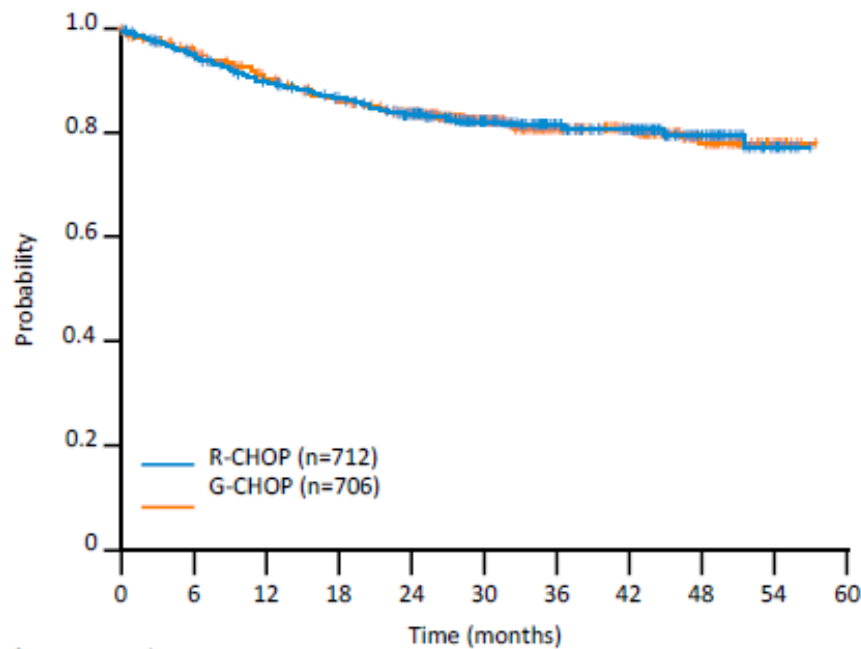
	0	6	12	18	24	30	36	42	48	54
R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

*ITT population

Median follow-up: 29 months

Overall survival

Kaplan-Meier plot of OS by treatment arm

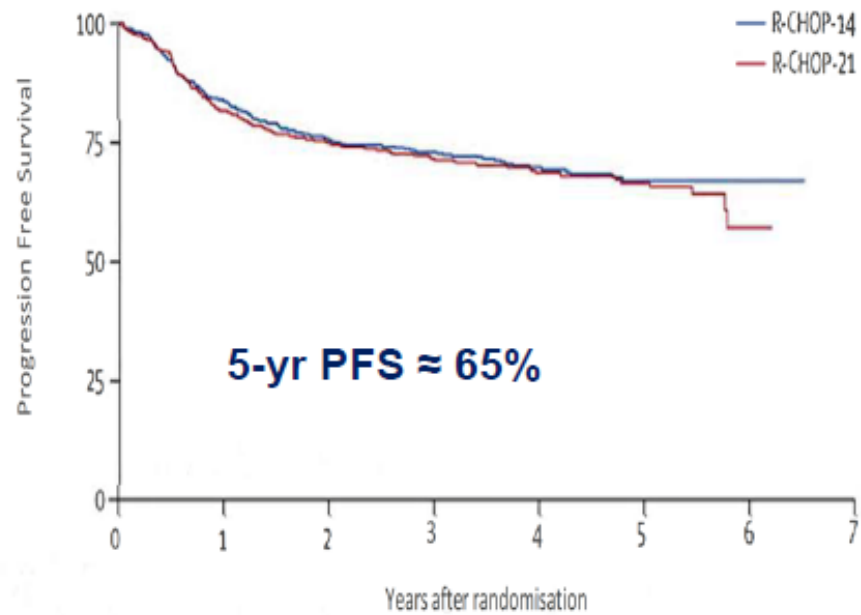


No. of patients at risk		Time (months)										
		0	6	12	18	24	30	36	42	48	54	60
R-CHOP	712	663	617	586	540	319	190	138	71	9		
G-CHOP	706	659	616	582	552	316	201	138	67	8		

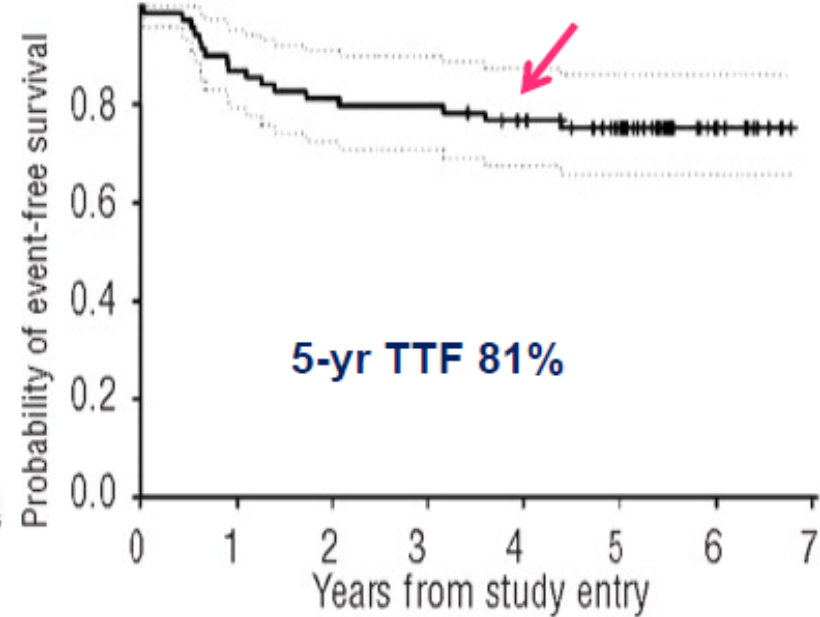
	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	126 (17.7)	126 (17.8)
1-yr OS, %	89.9	90.7
2-yr OS, %	83.7	83.9
3-yr OS, %	81.4	81.2
HR (95% CI), p-value*	1.00 (0.78, 1.28), p=0.9982	

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Multicenter Phase 3 **R-CHOP (14 vs 21)**



Multicenter Phase 2 **DA-EPOCH-R**



Cunningham et al. Lancet. 2013;381: 1817-1826 *Wilson et al. Haematologica. 2012;97:758-765*



ASH

58th Annual Meeting & Exposition
San Diego, CA • December 3-6, 2016



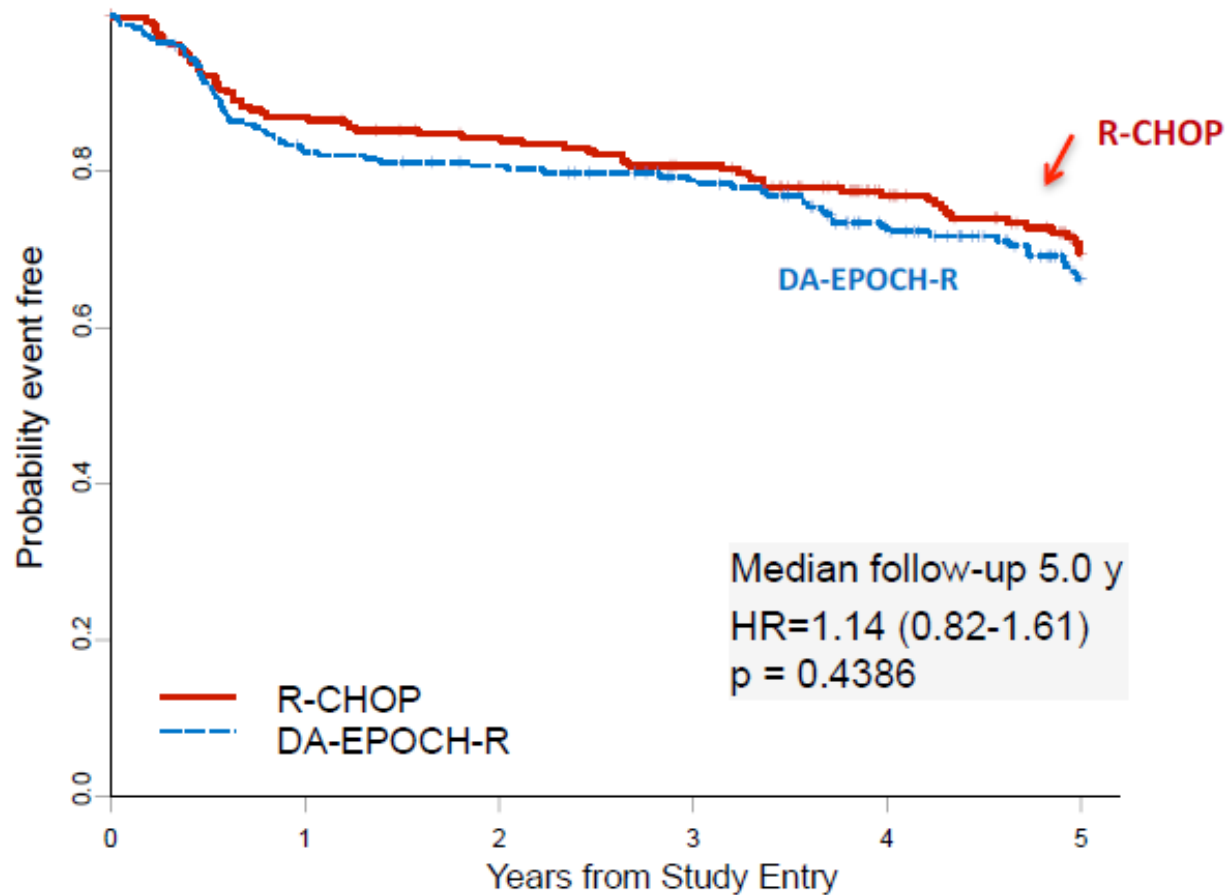
Phase III Randomized Study of R-CHOP 21 vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/ Alliance 50303

Wyndham H. Wilson, Sin-Ho Jung, Brandelyn N. Pitcher, Eric D. Hsi, Jonathan Friedberg, Bruce Cheson, **Nancy L. Bartlett**, Scott Smith, Nina Wagner-Johnston, Brad S. Kahl, Louis M. Staudt, Kristie A. Blum, Jeremy Abramson, Oliver W. Press, Richard I. Fisher, Kristy L. Richards, Heiko Schoder, Julie E. Chang, Andrew D. Zelenetz, John P. Leonard

Abstract 469, American Society of Hematology, Dec 4, 2016



50303 Event Free Survival

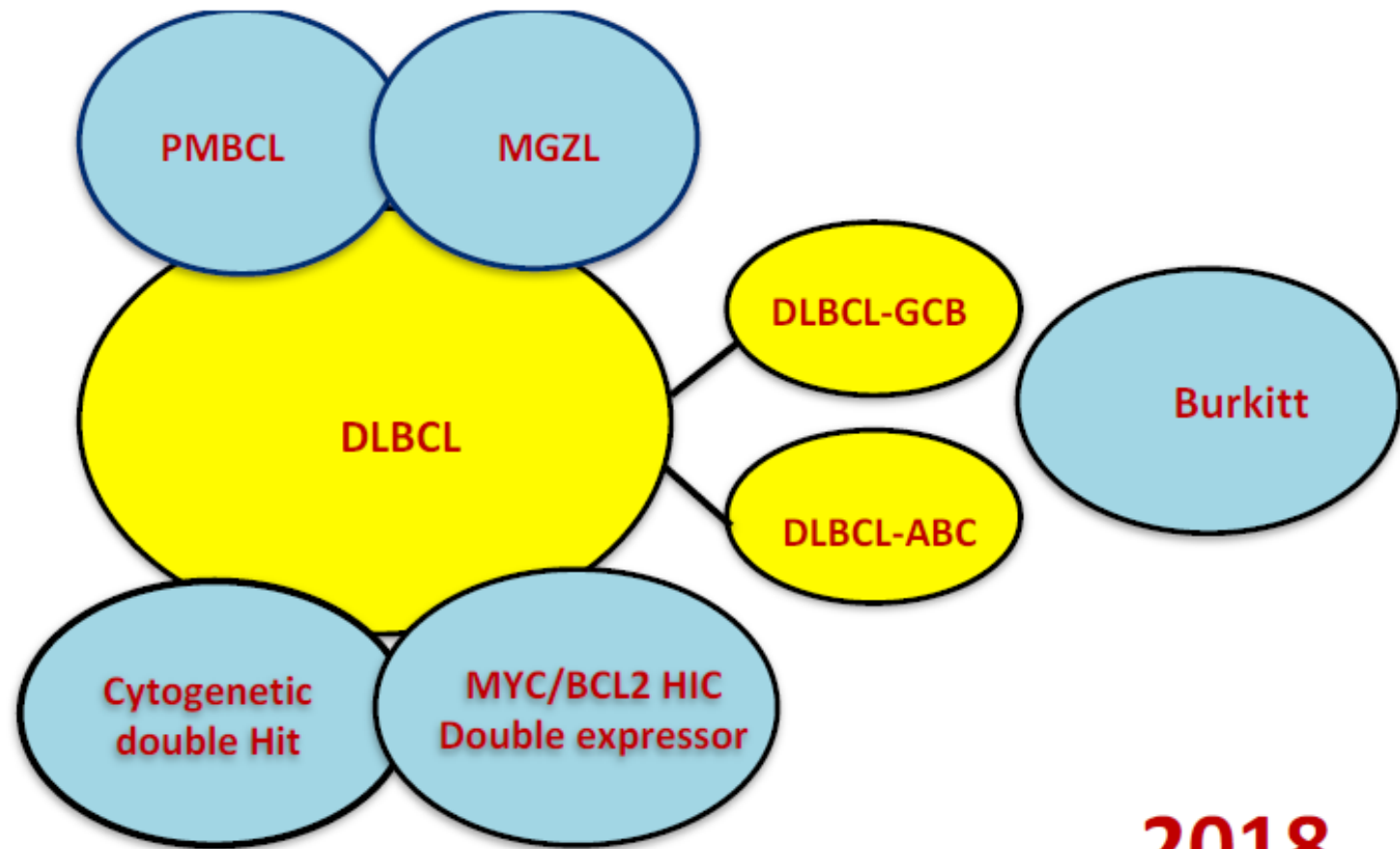


Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES




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

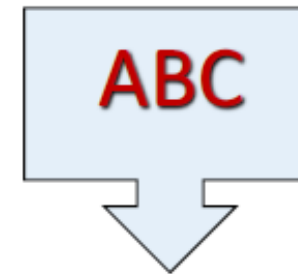
Steven H. Swerdlow,¹ Elias Campo,² Stefano A. Pileri,³ Nancy Lee Harris,⁴ Harald Stein,⁵ Reiner Siebert,⁶ Ranjana Advani,⁷ Michele Ghilmini,⁸ Gilles A. Salles,⁹ Andrew D. Zelenetz,¹⁰ and Elaine S. Jaffe¹¹



2018

Towards molecular driven therapy: R-CHOP + X Novel drugs

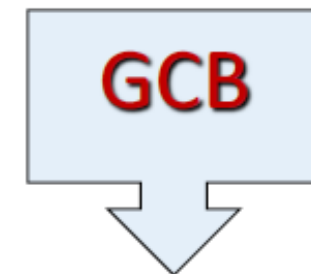
New Agent	Mechanism
 Lenalidomide	Immunomodulator
 Bortezomib	Proteasome inhibitor
Everolimus	mTOR inhibitor
Panobinostat	HDACs inhibitor
 Ibrutinib	BTK inhibitor
Tamatinib	Inhibitors of Syk in B-cell signaling pathway
Enzastaurin	PKC β -selective inhibitors
ABT 199	Pro-apoptotic ABT-263 Bcl-2 family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



Proteasome
inhibitors

BTK inh.

Immunomod.



Histone
modifiers

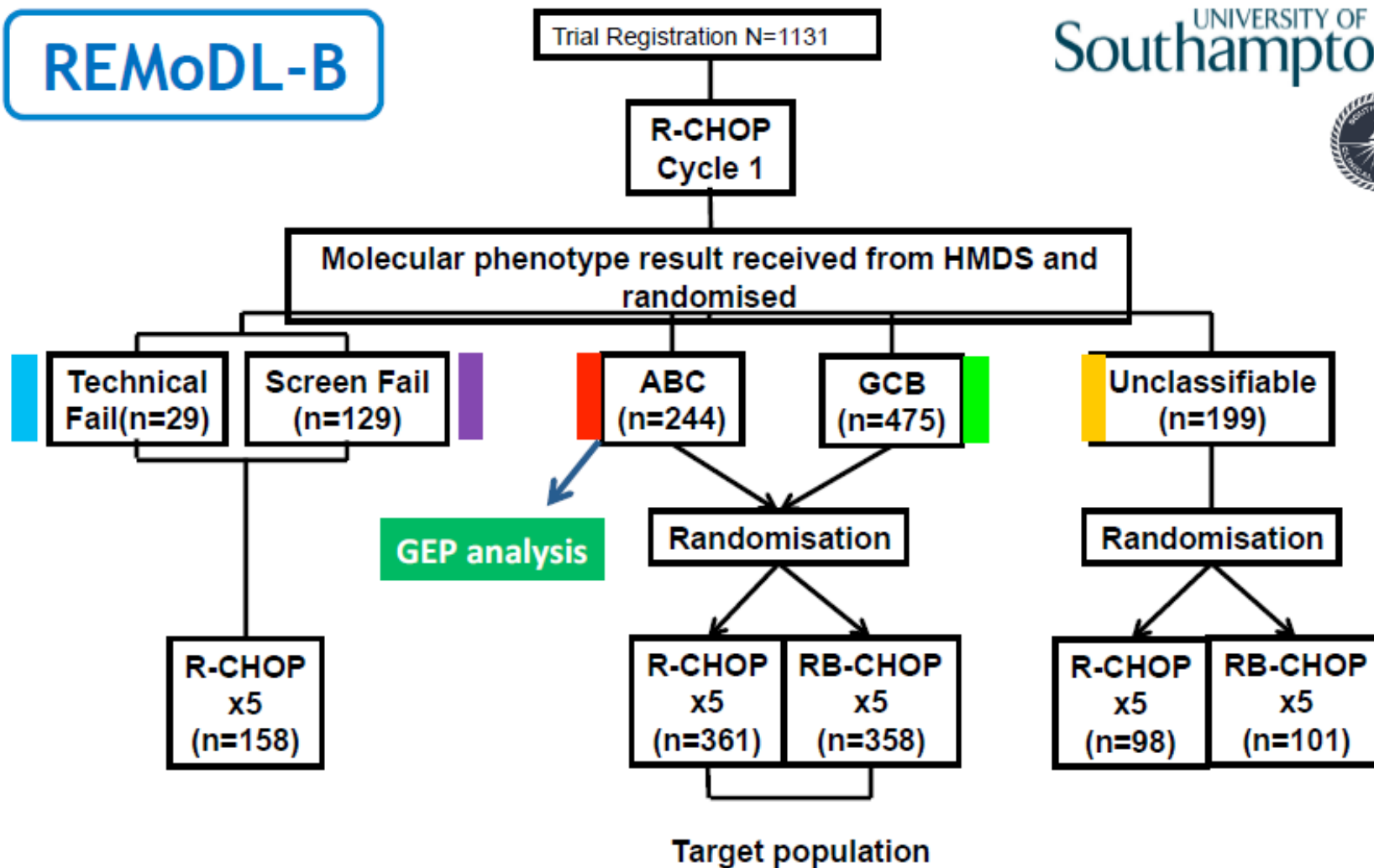
BCL2 inh.

PTEN/PI3K

REMoDL-B

Trial Registration N=1131

UNIVERSITY OF
Southampton



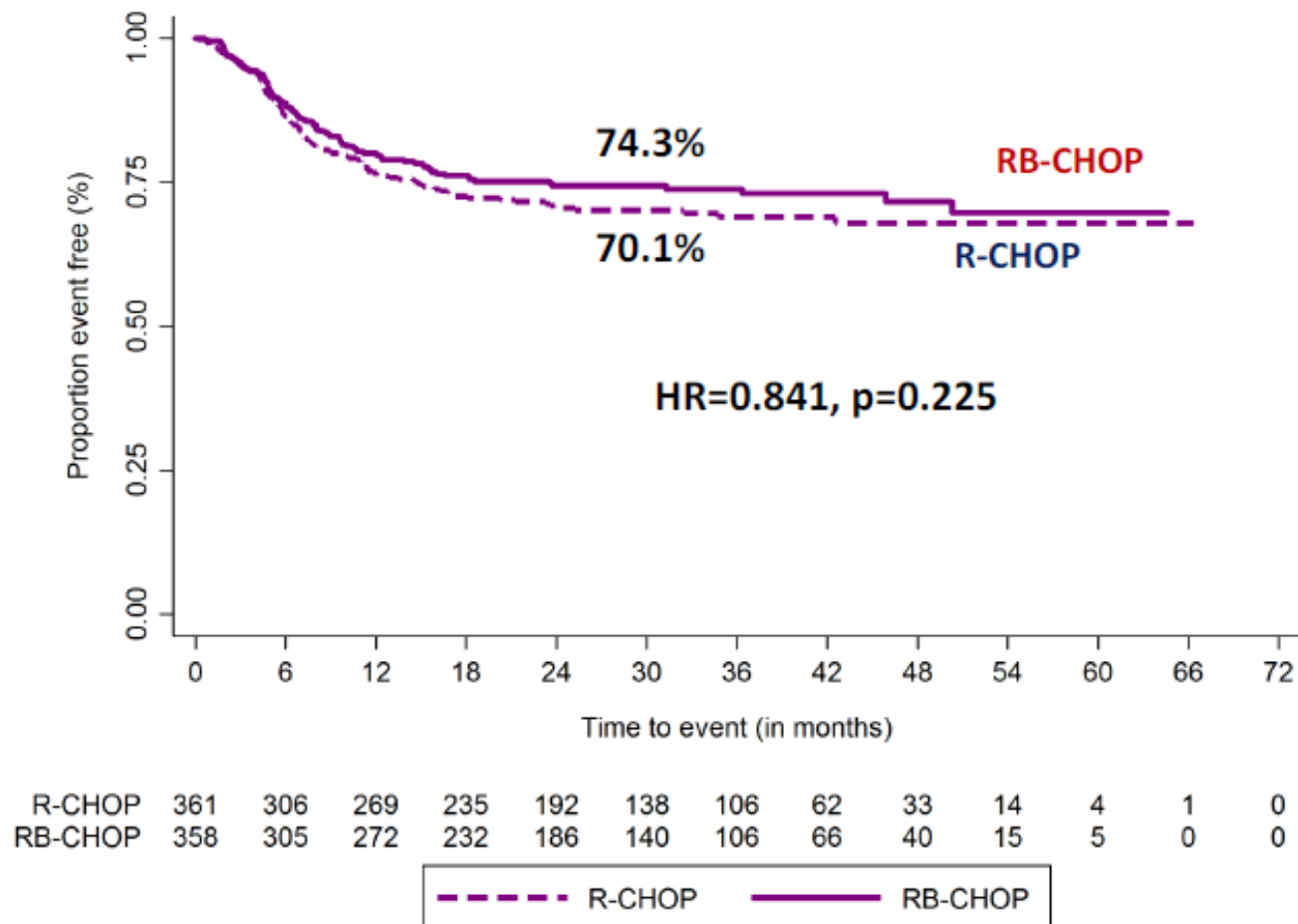
Recruitment period: June 2011-May 2015

Bortezomib: 318 pts. treated at 1.3 mg/m² IV

141 pts treated at 1.6 mg/m² sub cut

Progression-free survival: primary endpoint

ITT population: GCB + ABC patients N=719



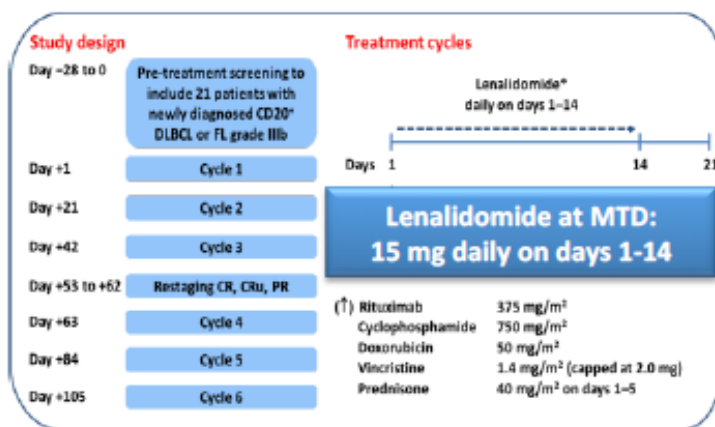
Median follow-up of surviving patients: 28.4 months

REMoDL-B

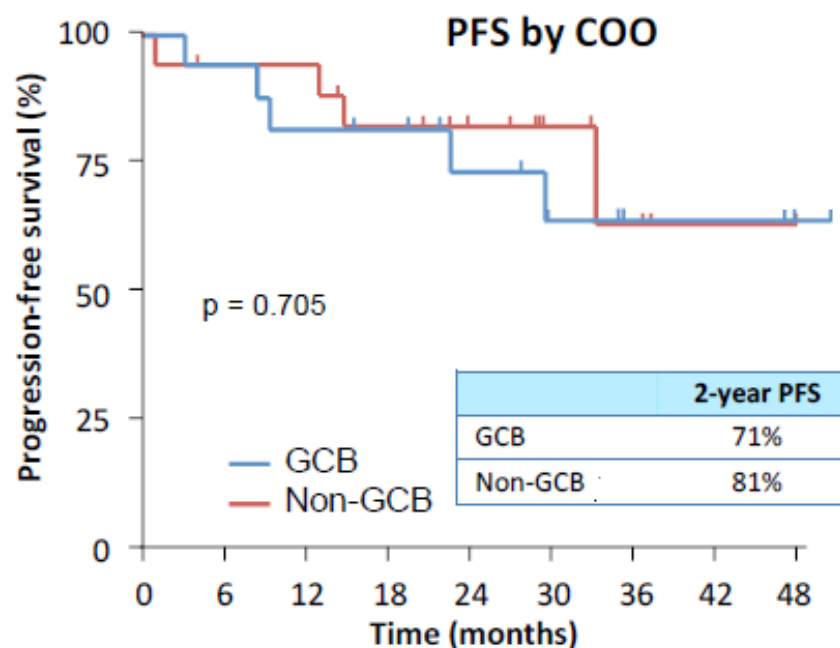
Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial



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 Castellina, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi



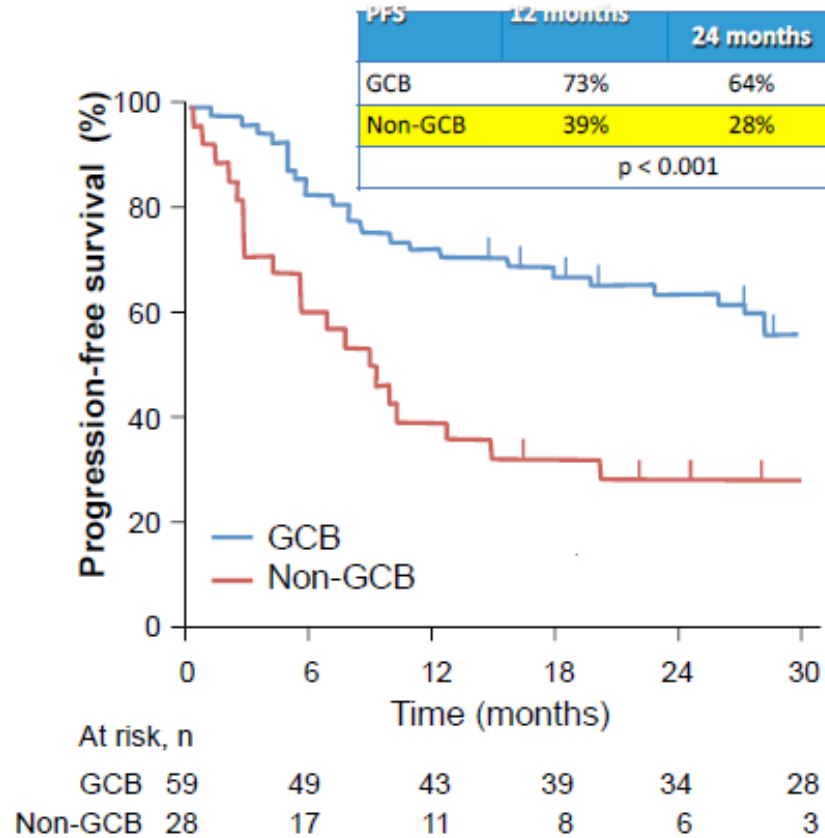
CNS prophylaxis according to Italian Society of Hematology guidelines
 Pegfilgrastim or G-CSF as neutropenia prophylaxis
 Low Molecular Weight Heparin as DVT prophylaxis



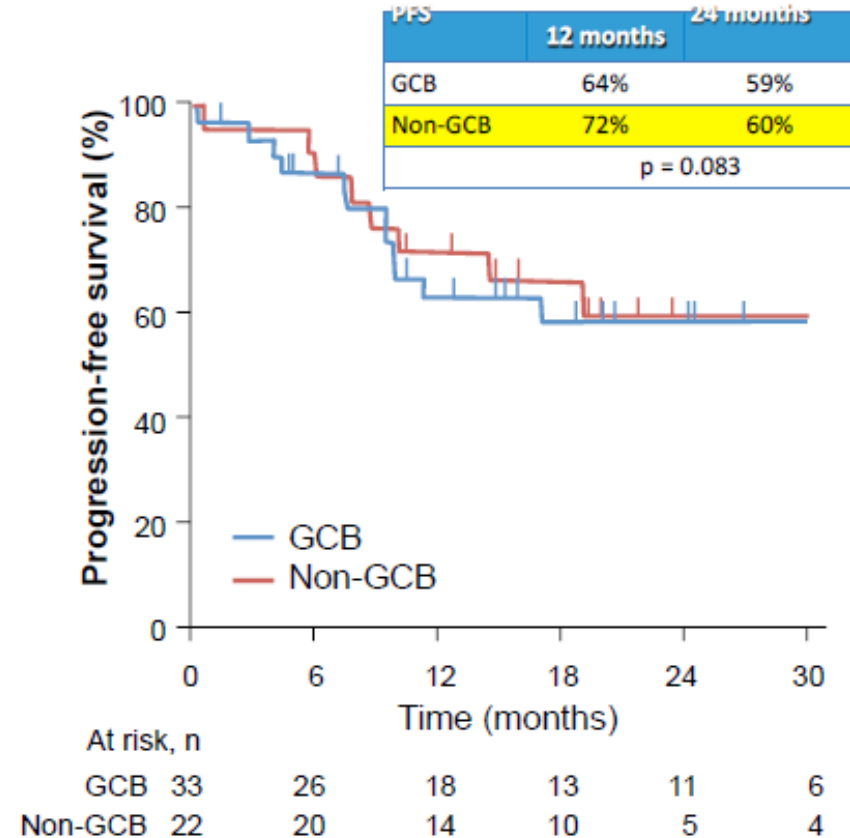


PFS in GCB and non-GCB DLBCL for patients treated with R-CHOP and R2-CHOP

Historical R-CHOP PFS¹

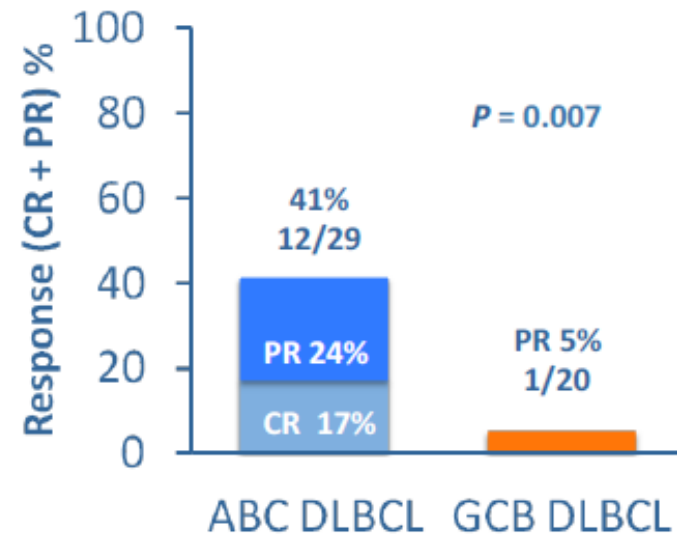
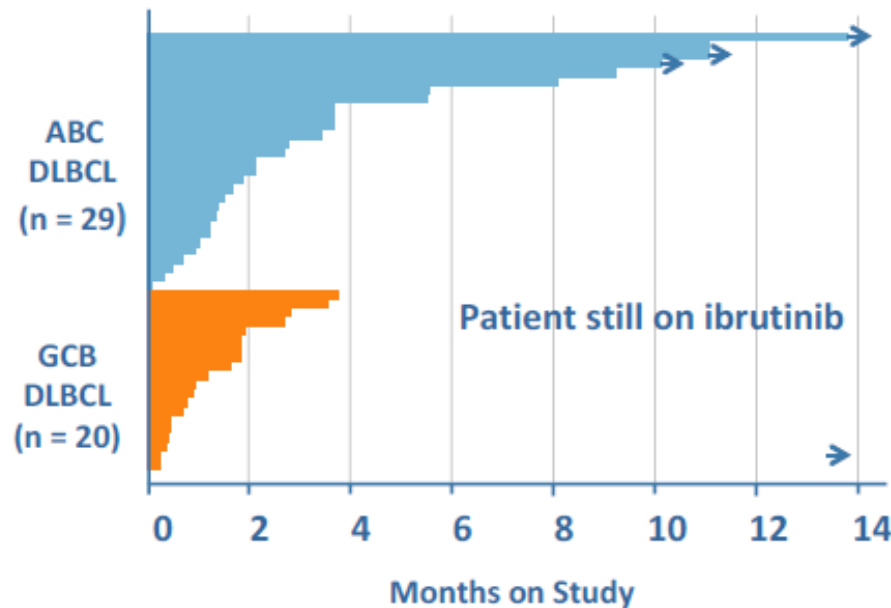


R2-CHOP PFS¹



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

Ibrutinib single agent: response in ABC and GCB refractory DLBCL



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

Wilson et al, ASH 2012

R-CHOP + X NOVEL DRUGS: R-CHOP + IBRUTINIB

PCI-32765 DBL3001 PHASE III RANDOMIZED TRIAL



Non GC
DLBCL

IHC



R
a
n
d
o
m



Treatment A: Placebo + R-CHOP

6 or 8 cycles



Treatment B: Ibrutinib + R-CHOP

Eligible patients:

- Subject with DLBCL in NON-CGB determined by central IHC

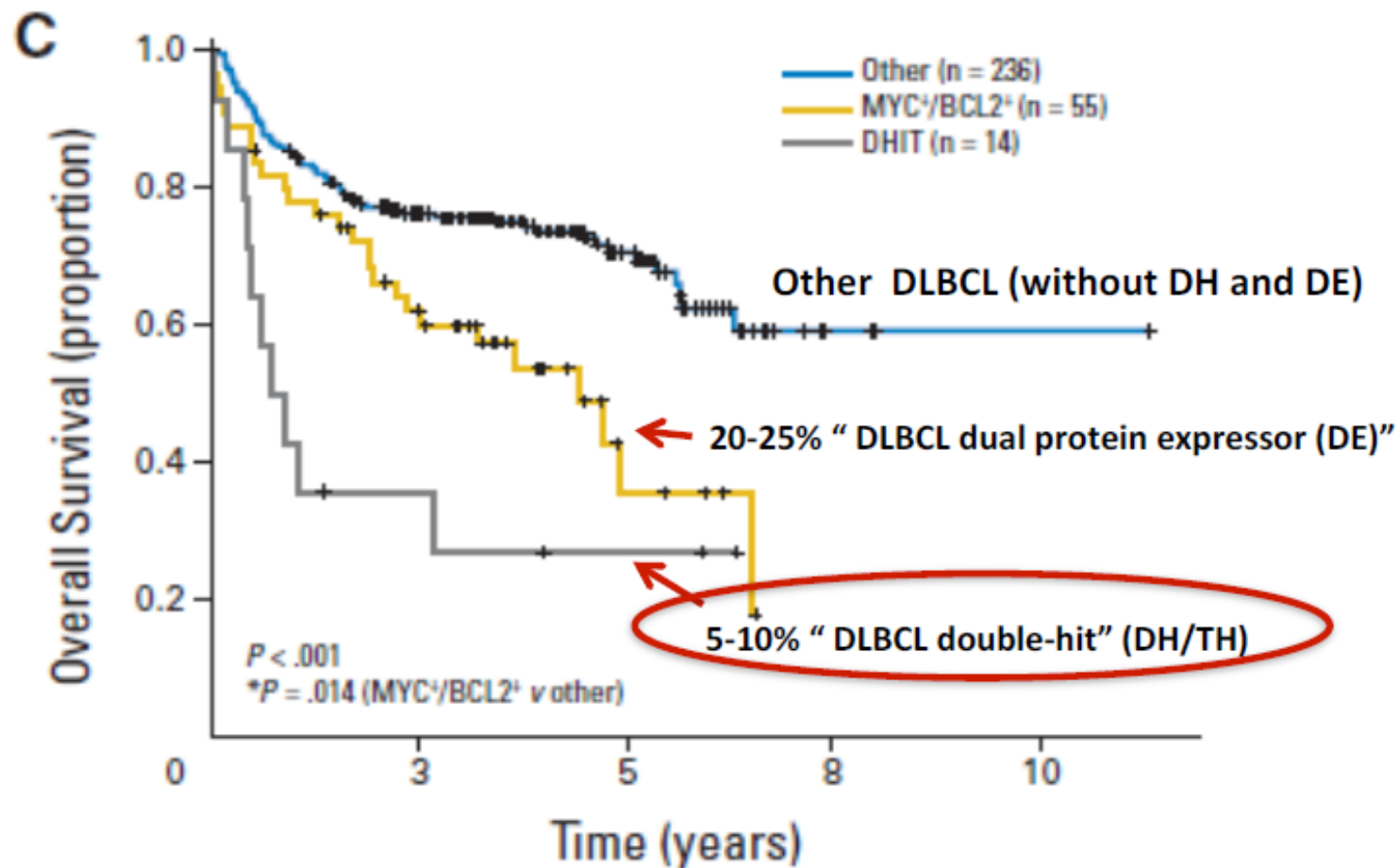
Stratification factors:

- R-IPI score low risk (1) versus intermediate (2-3) versus high risk (4-5)
- Region (US/Western Countries vs Rest of the World)
- Number of treatment cycles (6 versus 8 cycles)

MYC or double HIT DLBCL

- Typical morphology large cell; BCL6 +/-,CD10 +/-;BCL2+
- **Ki67= 70-90%**
- IG MYC,BCL2+/BCL6+ (DH-THT)
- DH present in 5-10% of DLBCL
- **Most frequent in GCB type**
- Median age: range 51-65; extremely rare in <18 years
- **More often widely disseminated**
- Cannot be predicted by histology, proliferation rate or clinical features
- **Intermediate-High or High risk IPI: frequent**
- Pleural effusion: common
- **Extranodal involvement: often, especially BM and CNS**
- **High risk CNS involvement**

Overall survival of patients with DLBCL (DH) or DLBCL (DE) treated with R-CHOP in the 2018

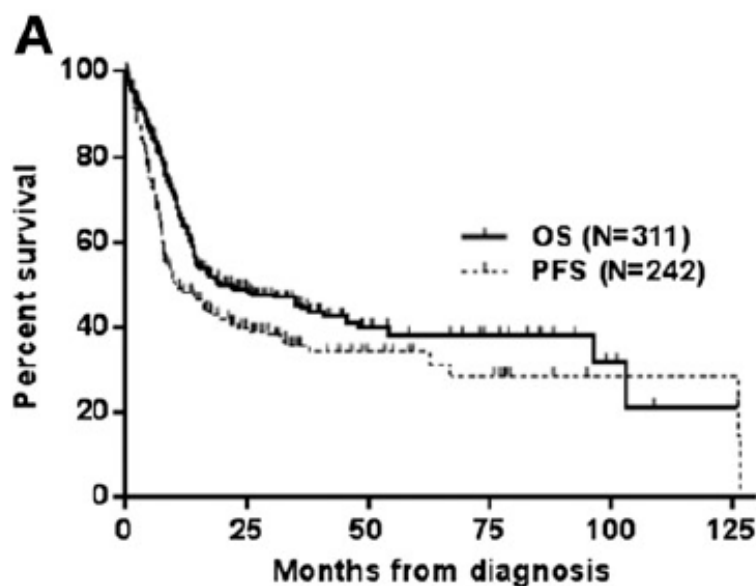




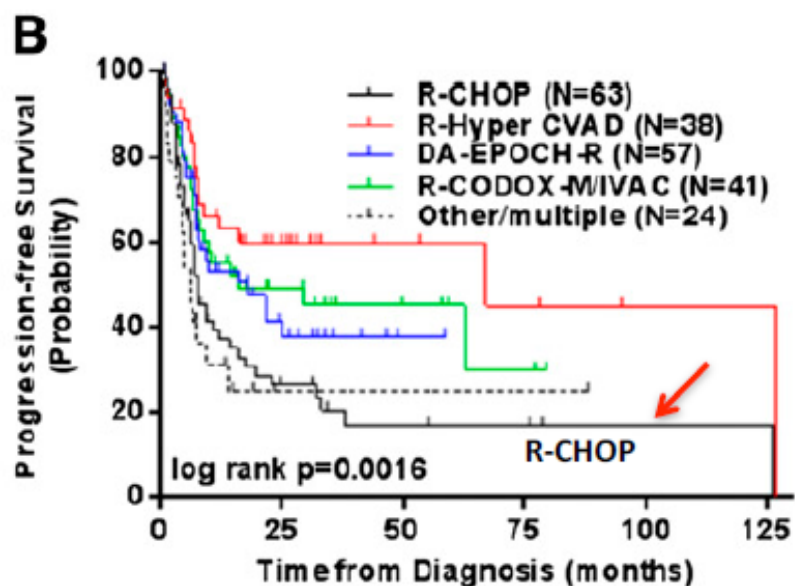
Double Hit Lymphoma (DHL)

- 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)



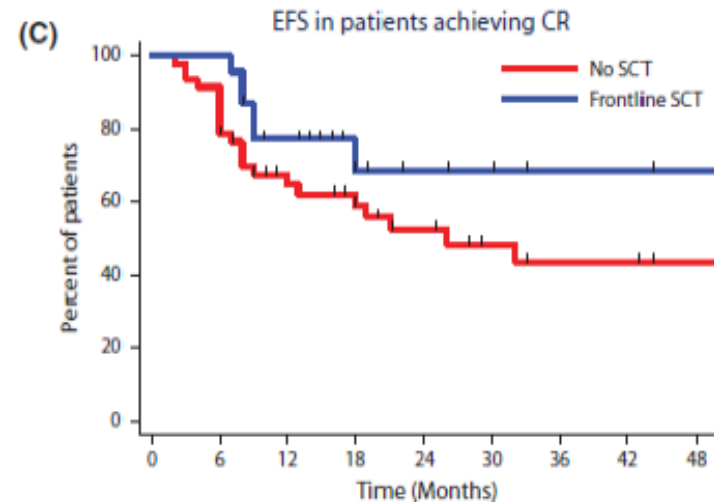
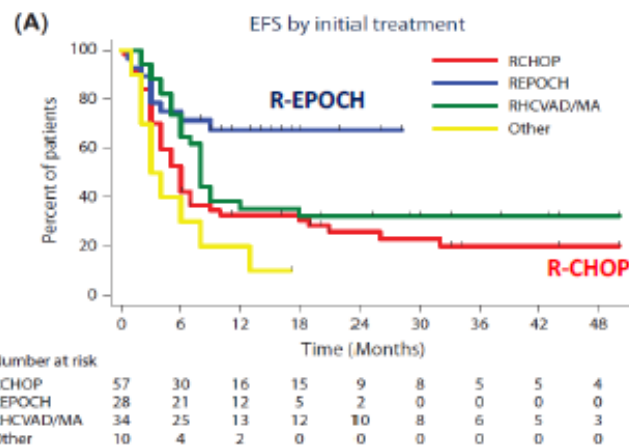
Educational ASH 2014



Petrich M, Gandhi M et al Blood 2014

D-Hit DLBCL: MDACC experience

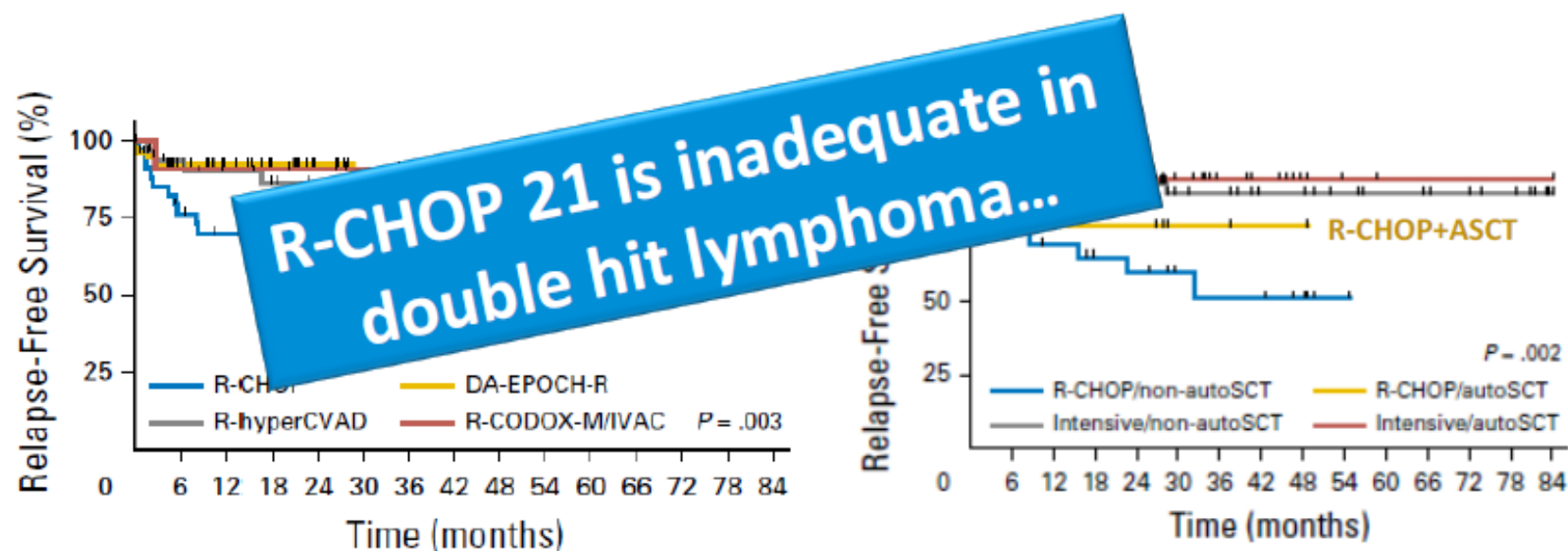
Characteristic	RCHOP n = 54	R-EPOCH n = 28	RHCVAD/MA n = 34	Other n = 10	All n = 129
CR after initial therapy (%)	23 (40)	19 (68)	23 (68)	6 (60)	71 (55)
Frontline SCT (%)					
Any (auto+allo)	2 (4)	14 (50)	8 (24)	2 (20)	26 (20)
Allo	1 (2)	0	1 (3)	0	2 (2)



Okii et al Br. J. Hematol. 2014

Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission

Daniel J. Landsburg, Marissa K. Falkiewicz, Joseph Maly, Kristie A. Blum, Christina Howlett, Tatyana Feldman, Anthony R. Mato, Brian T. Hill, Shaoying Li, L. Jeffrey Medeiros, Pallawi Torke, Francisco Hernandez-Ilizaliturri, Nishitha M. Reddy, Arun Singavi, Timothy S. Fenske, Julio C. Chavez, Jason B. Kaplan, Amir Behdad, Adam M. Petrich, Martin A. Bast, Julie M. Vose, Adam J. Olszewski, Cristiana Costa, Frederick Lansigan, James N. Gerson, Stefan K. Barta, Oscar Calzada, Jonathon B. Cohen, Jennifer K. Lue, Jennifer E. Amengual, Xavier Rivera, Daniel O. Persky, David J. Peace, Sunita Nathan, and Ryan D. Cassaday



Landsburg D et al. J.Clin. Oncol 2017

Conclusioni

- La prognosi dei DLBCL nel corso degli ultimi 20 anni è migliorata MA....
- Nuove combinazioni con anticorpi monoclonali di seconda generazione non hanno prodotto vantaggi in EFSMA
- La conoscenza biologica del DLBCL e di suoi sottotipi ha aperto la strada a nuove combinazioni terapeutiche MA....

Conclusioni (2)

- L'associazione con Lenalidomide al CHOP-R sembra la più promettente nel poter migliorare la prognosi dei DLBCL ABC... MA.....
- Nei DLBCL DH e DE la terapia deve essere intensificata

E.....

Sperando di non aver detto troppe
banalità.....



Vi ringrazio per l'attenzione