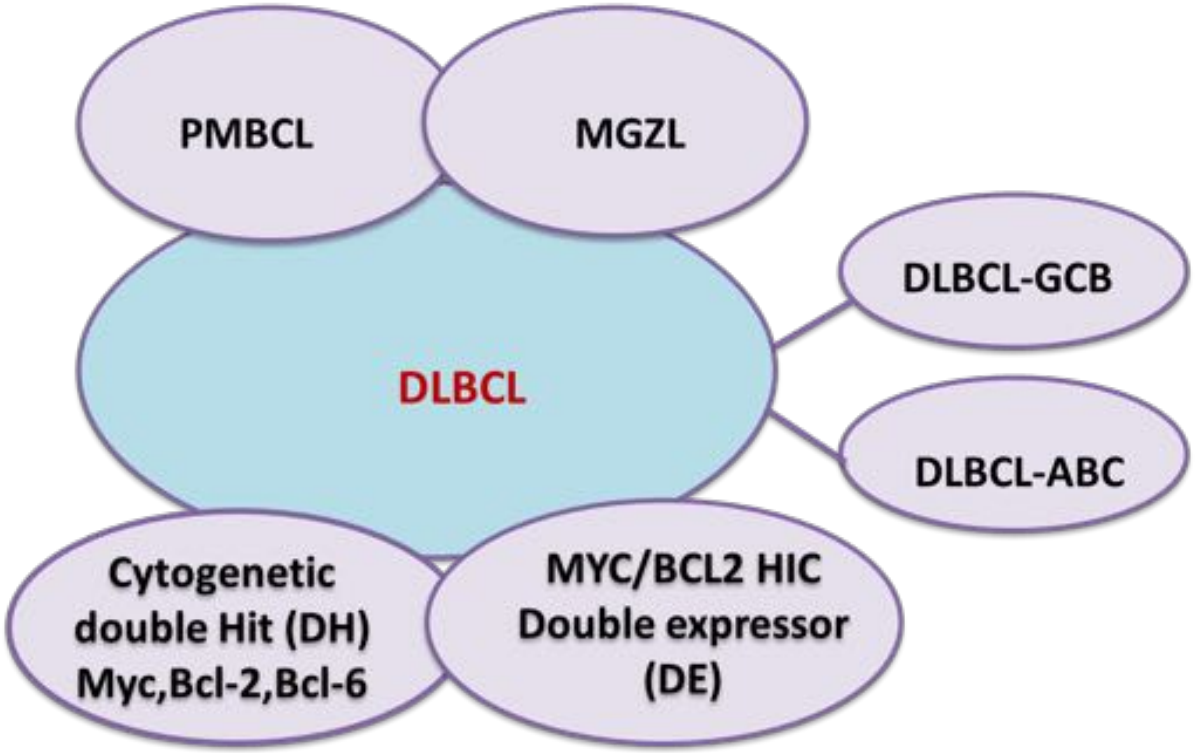
É possibile una terapia molecular driven nei linfomi diffusi a grandi cellule

Maurizio Martelli
Dipartimento di Medicina Traslazionale e di Precisione
Sezione di Ematologia
"Sapienza" – Università di Roma

Outline of discussion

- **DLBCL is an heterogeneous disease**
- What is the outcome with standard R-CHOP in DLBCL?
- Is time of a molecular driven therapy in DLBCL ?
- When we can consider an alternative therapy to R-CHOP ?

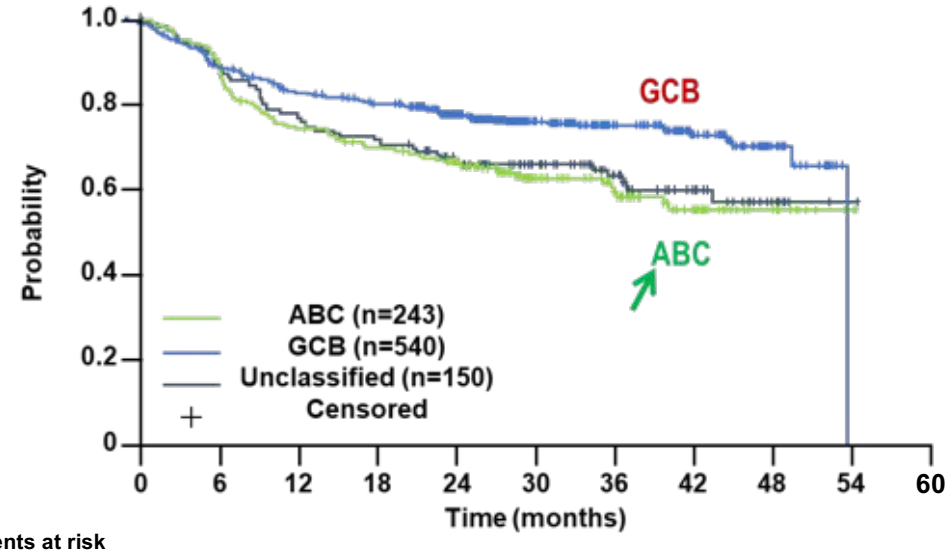
The 2016 revision of the World Health Organization classification of lymphoid neoplasm



Steven H. Swerdlow, Blood 2016 127:2375-2390

Goya study: Investigator-assessed PFS by cell of origin (COO)

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

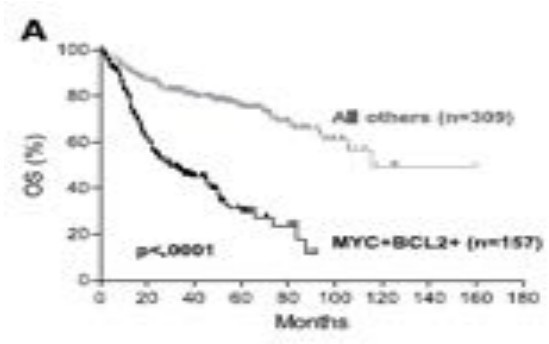


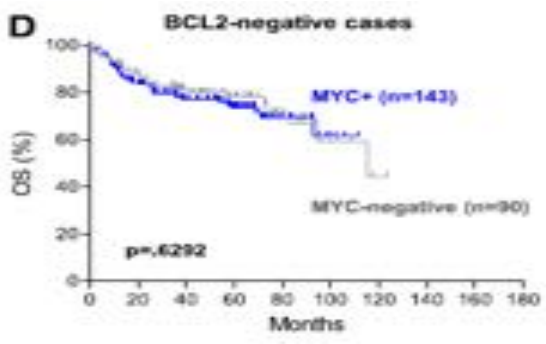
No. of patients at risk										
ABC	243	209	174	161	144	78	52	32	13	2
GCB	540	480	417	398	344	207	139	96	41	3
Unclassified	150	128	111	103	86	64	42	25	9	1

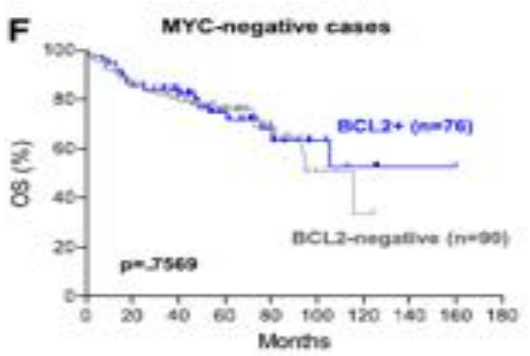
	ABC, n=243	*GCB, n=540*	*Unclass.. n=150*
Pts with event, n (%)	92 (37.9)	129 (23.9)	54 (36.0)
2-yr PFS, %	66.4	78.0	65.9
3-yr PFS, %	59.3	75.0	63.2
HR (95% CI)			
ABC vs GCB			1.70 (1.30, 2.23)
Unclassified vs GCB			1.57 (1.14, 2.16)

Vitolo et al J.Clin Oncol 2017

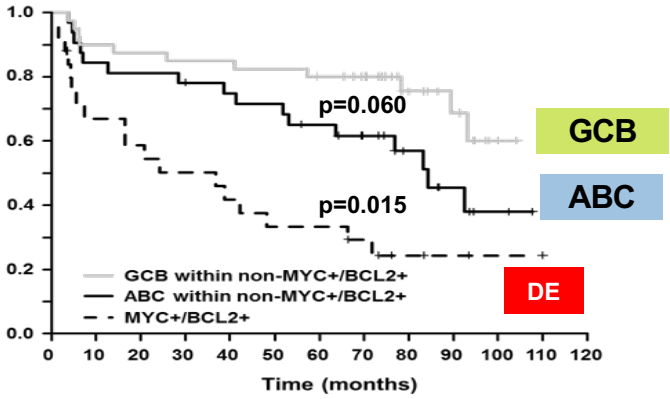
MYC/BCL2 DE status is a risk factor independent from COO



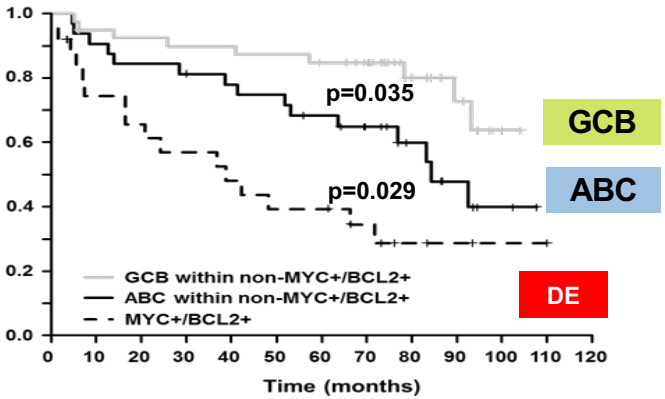




EFS



PFS



OS

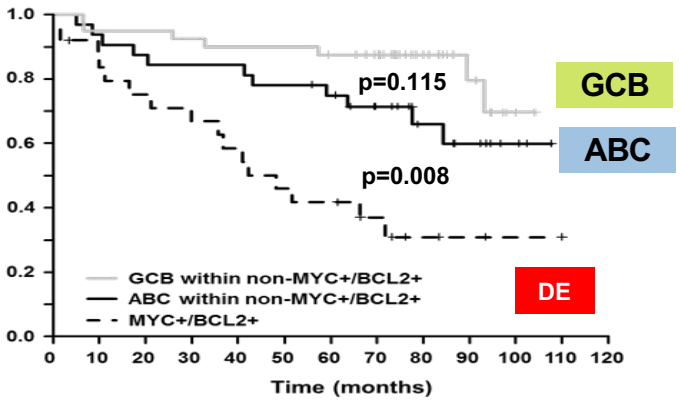
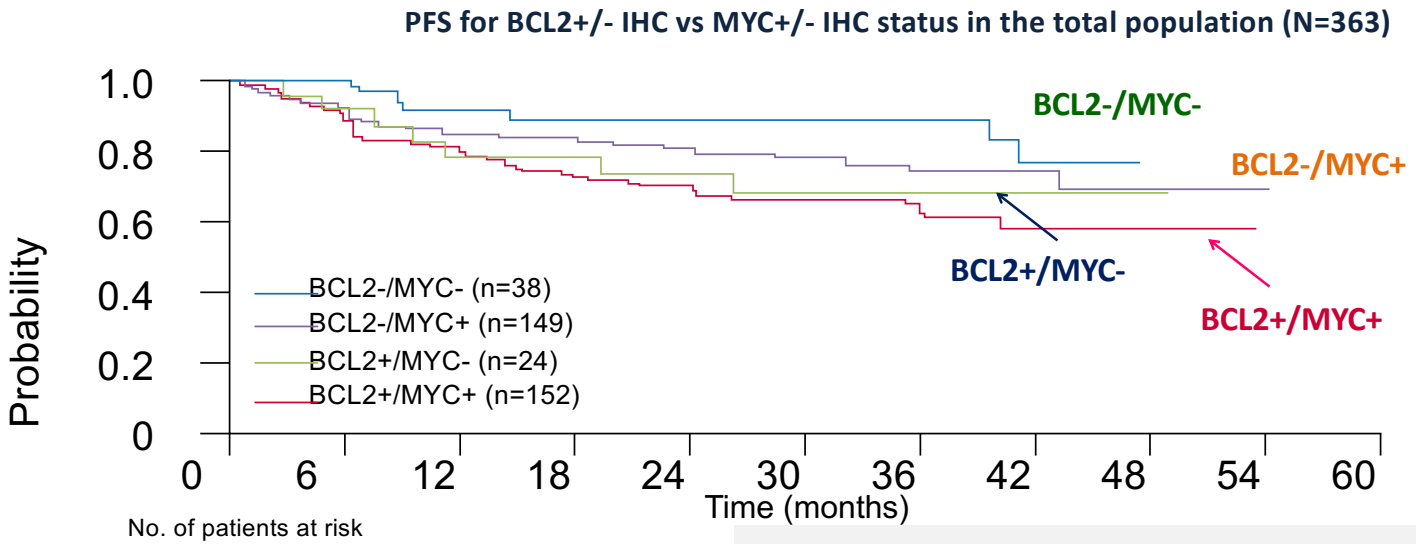


Fig. A,D,F*: Hu et al. Blood 2013* - Fig. EFS, PFS,OS: *Staiger A et al . J.Clin Oncol 2017*

FONDAZIONE ITALIANA LINFOMI

Prognostic impact of BCL2 and MYC expression in the Goya study



No. of patients at risk

BCL2-/MYC- (n=38)	38	36	32	31	28
BCL2-/MYC+ (n=149)	149	132	122	117	104
BCL2+/MYC- (n=24)	24	22	17	17	16
BCL2+/MYC+ (n=152)	152	133	117	106	95

	BCL2-/MYC-, n=38	BCL2-/MYC+, n=149	BCL2+/MYC- n=24	BCL2+/MYC+, n=152
3-yr PFS, % (95% CI)	88.6 (72.5, 95.6)	73.9 (64.1, 81.4)	68.1 (44.2, 83.4)	63.1 (53.8, 71.0)

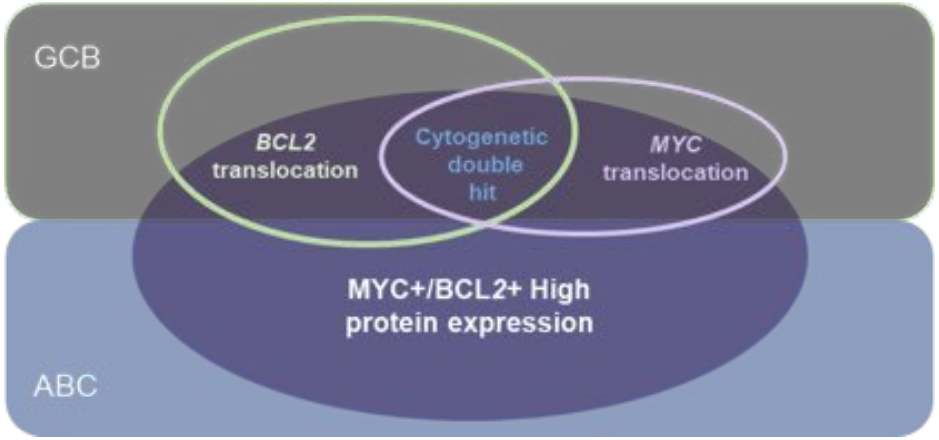
- **Poor prognosis of DE appears to be driven by expression of BCL2**
- **MYC+ IHC does not further discriminate prognostic impact in BCL2+ IHC pts**

Vitolo U, et al. Presented at ICML 2017. Hematol Oncol;35:131-3.

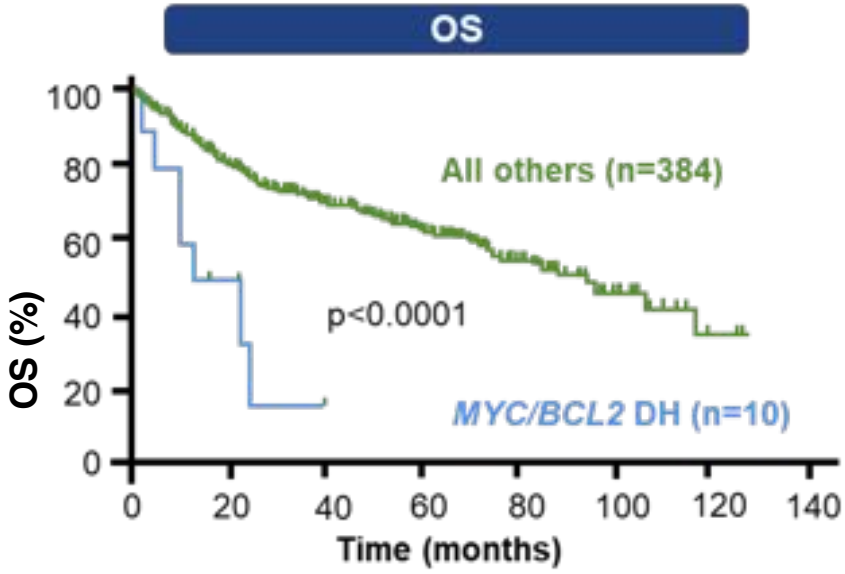
Patients with double-hit lymphomas respond poorly to chemotherapy and have very poor survival outcomes

- In the WHO revised classification of lymphoid neoplasms, genomic translocations in *MYC*, *BCL* and/or *BCL6* oncogenes were added to HGBL[1]
  - HGBL occurs in <10% cases of DLBCL[2]

Relationship among cell of origin in DLBCL in terms of MYC/BCL2 protein expression and genetic translocations[3]



Patients diagnosed with *de novo* DLBCL with *MYC/BCL* rearrangement (n=10)[4]



Patients with double-hit lymphomas respond poorly to chemotherapy and have very poor survival outcomes

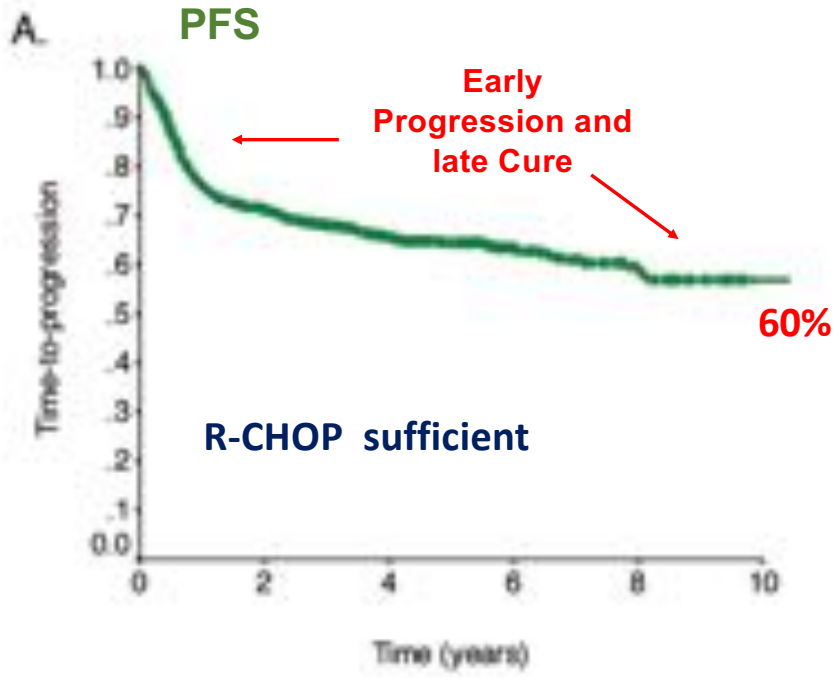
Swerdlow SH, et al. Blood 2016; 127:2375–2390.
Friedberg JW. Blood 2017; 130: 590–596

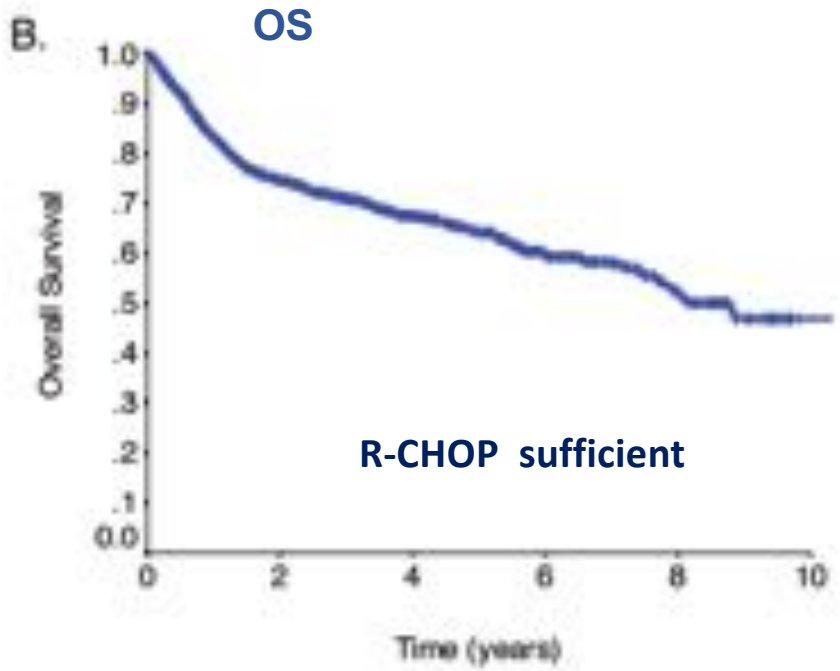
Outline of discussion

- DLBCL is an heterogeneous disease
- **What is the outcome with standard R-CHOP in DLBCL?**
- Is time of a molecular driven therapy in DLBCL ?
- When we can consider an alternative therapy to R-CHOP ?

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

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



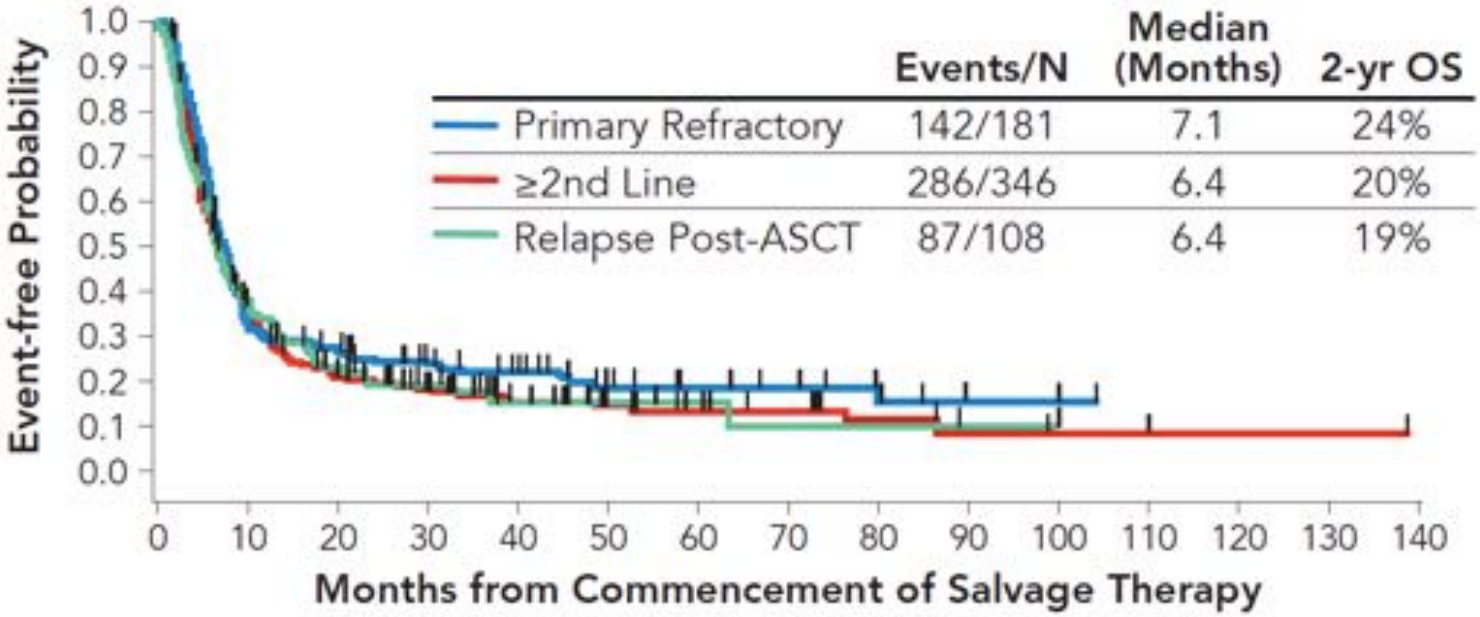


BC Cancer Agency Database, Sehn, Hematology 2012

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]



Median OS
6.3 months

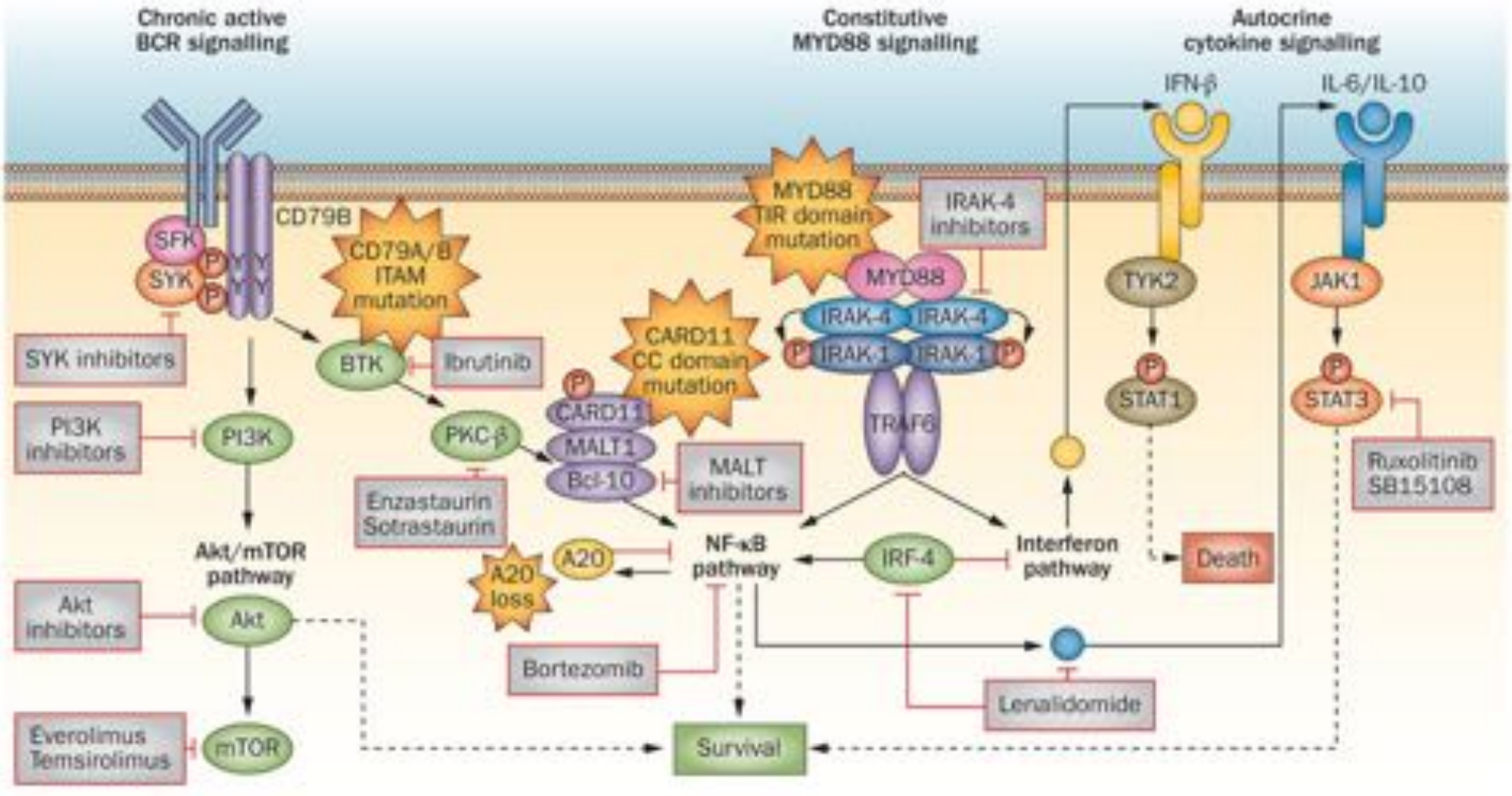
Main role of front line therapy in DLBCL and low activity of salvage therapy

Crump M. et al. Blood. 2017;130:1800–8.

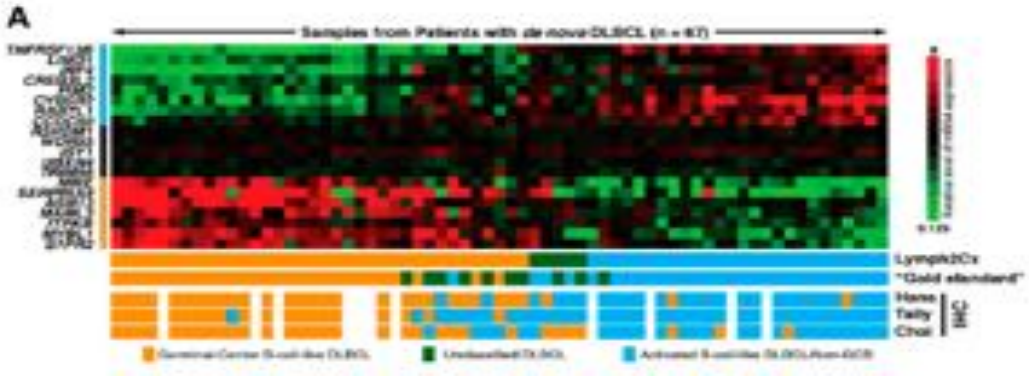
Outline of discussion

- DLBCL is an heterogeneous disease
- What is the outcome with standard R-CHOP in DLBCL?
- **Is time of a molecular driven therapy in DLBCL ?**
- When we can consider an alternative therapy to R-CHOP ?

Pathways with therapeutic potential in ABC DLBCL

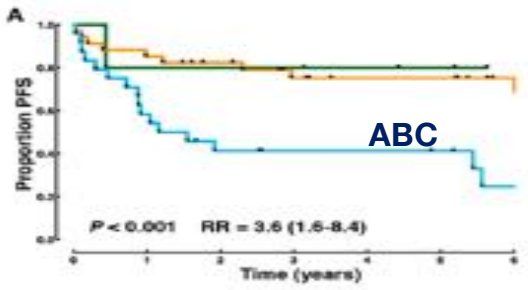


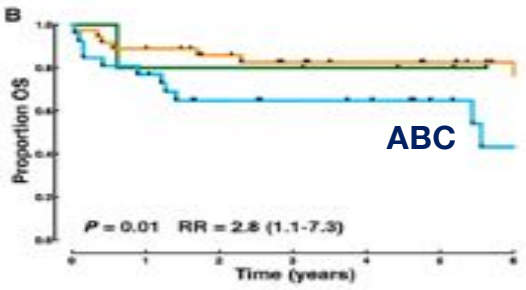
DLBCL: COO profile subgroups



Nanostring test

Lymph 2Cx assay
20 gene assay





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	-	+++

Scott D et al Blood 2014

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

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

What X?

- **Bortezomib: Bor-RCHOP (Phase 2/3)**
- **Ibrutinib: IR-CHOP (Phase 3)**
- **Lenalidomide: R2-CHOP (Phase 3)**
- **Venetoclax: Ven+ R-CHOP (Phase 2)**

PYRAMID: Non-GCB DLBCL

Study design

Prospective randomized, open-label, Phase II study

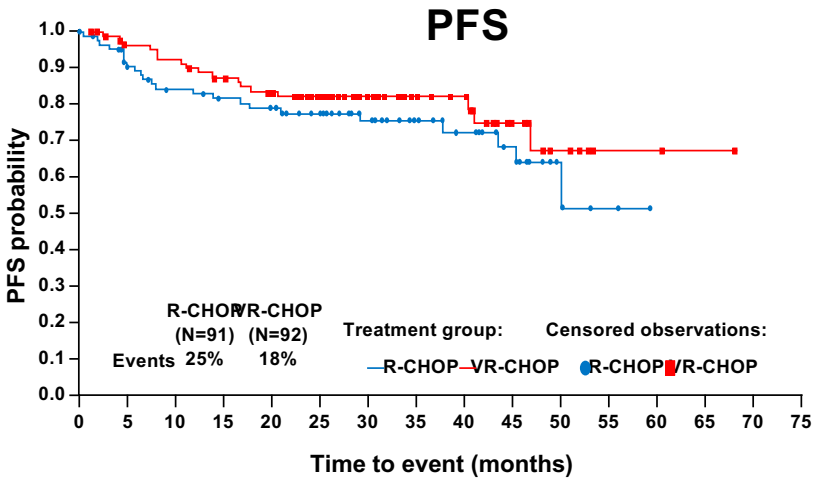
Treatment-naïve, non-GCB DLBCL by Hans IHC with measurable disease, ECOG PS 0–2 (N=183)

→ **Bortezomib 1.3 mg/m² i.v. Days 1, 4 + R-CHOP* 21 days x 6 cycles (n = 92)**

→ **R-CHOP* 21 days x 6 cycles (n = 91)**

Limits:

- Patient selection in the PYRAMID trial may have played a role → R-CHOP alone produced better outcomes than expected
- IHC based on Hans algorithm



- **2-year PFS: 78% R-CHOP vs 82% VR-CHOP**
  - **HR (95% CI): 0.73 (0.43–1.24); p=0.611**

Leonard JP, et al. Blood 2015;126:811a.
(Updated data presented in oral presentation at ASH 2016)

Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial

Patients with DLBCL in need of full course of R-CHOP

Con-sent

R-CHOP #1

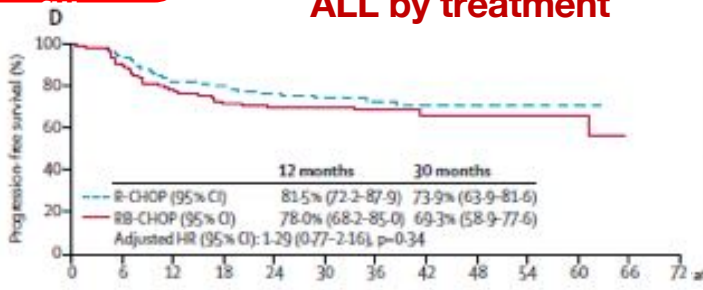
Biopsy sent to HMDS for molecular

Rando-misation Stratified for molecular phenotype and IPI

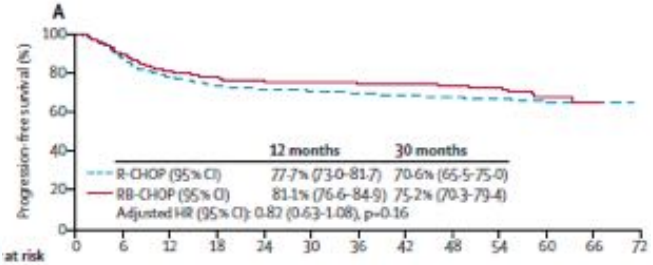
5 x R-CHOP

5 x R-CHOP + bortezomib 1.3 mg/m^2 days 1+8

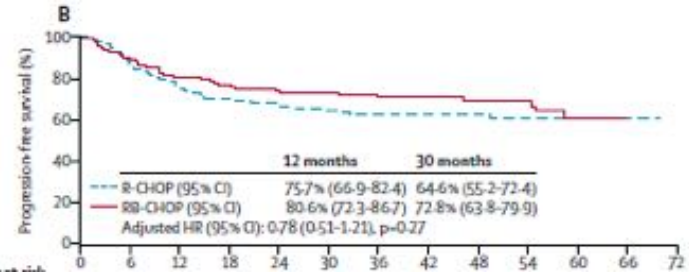
ALL by treatment



ABC: N=244



GCB: N=475



Davies A. et al Lancet Oncology 2019

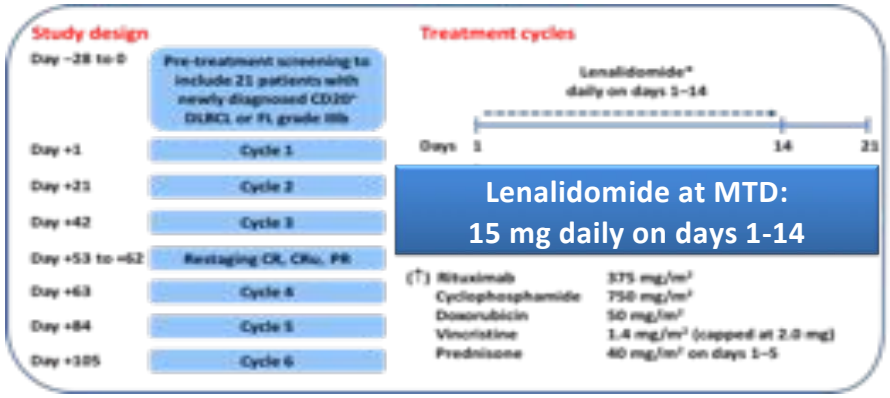
FONDAZIONE ITALIANA LINFOMI

Lancet Oncol 2014

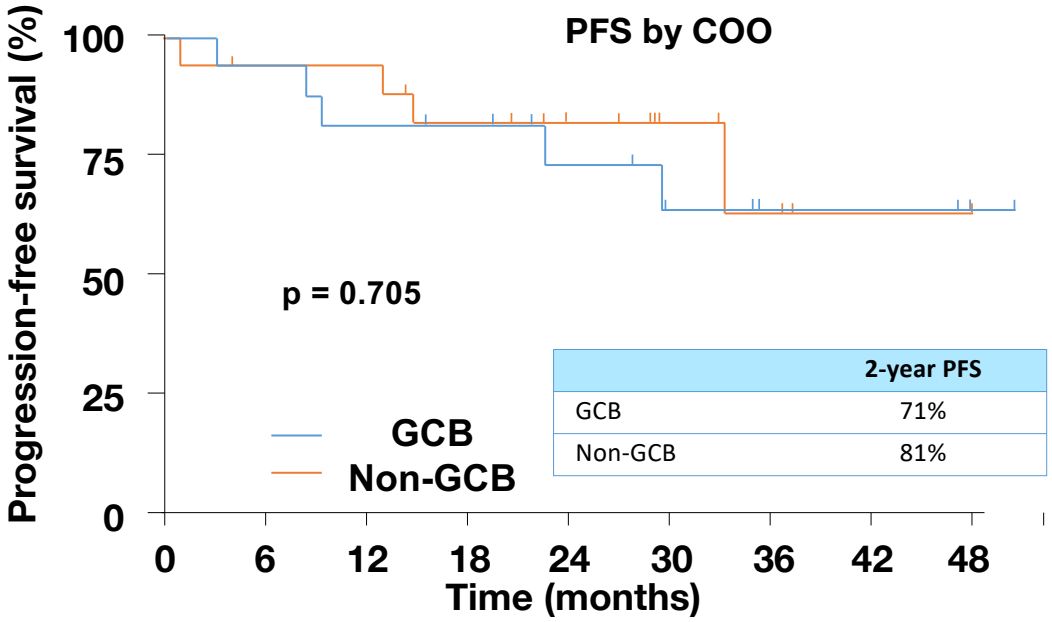
Articles

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

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, 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

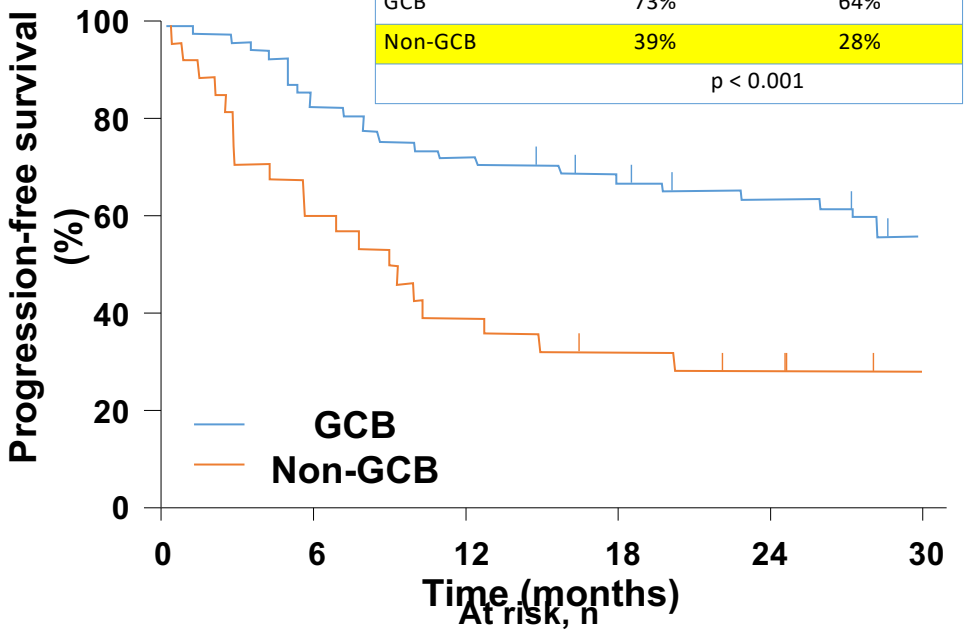


	2-year PFS
GCB	71%
Non-GCB	81%

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	

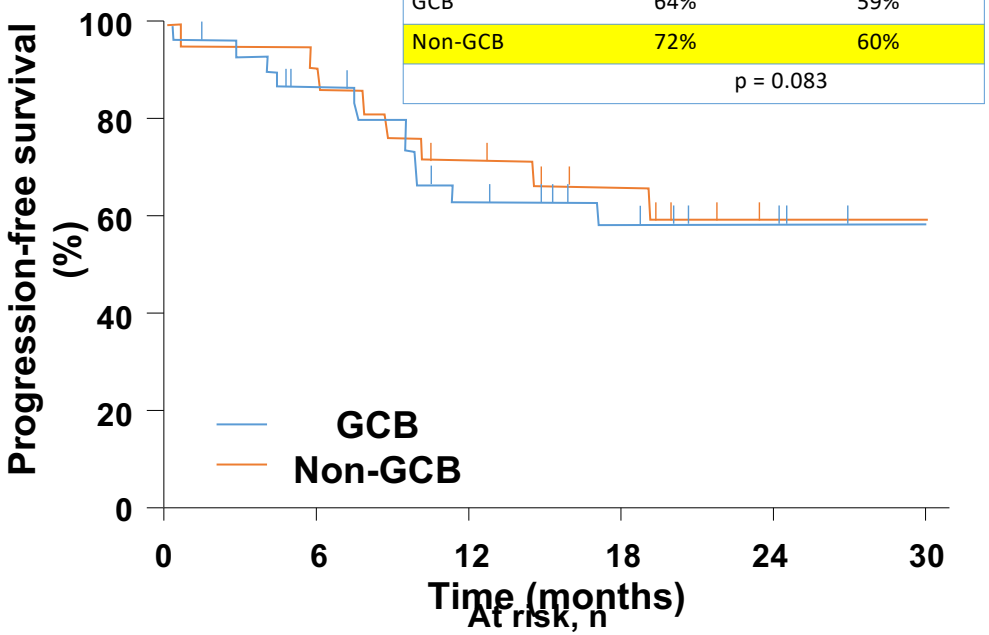


At risk, n

GCB	59	48	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	



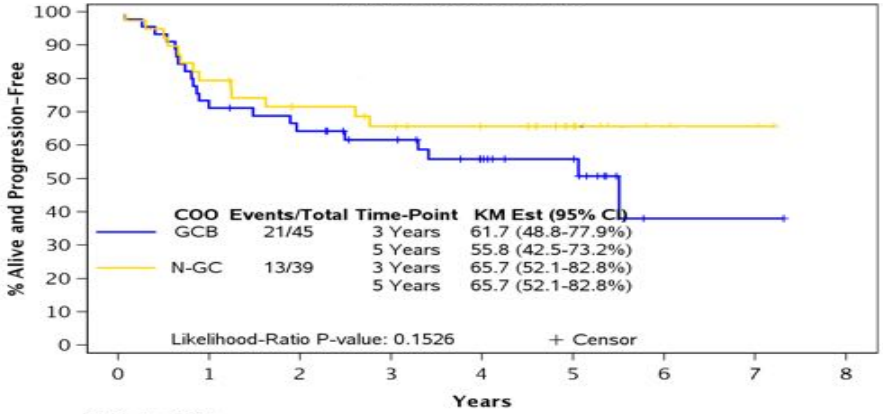
At risk, n

GCB	33	28	18	13	11	6
Non-GCB	22	20	14	10	5	4

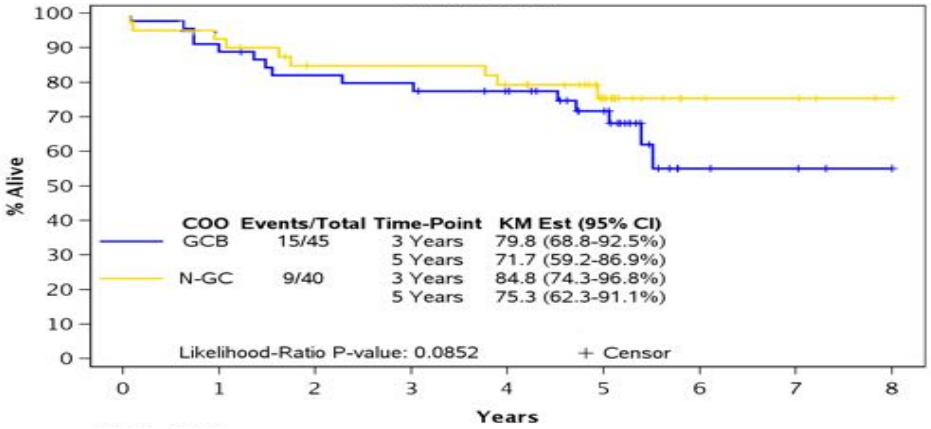
Nowakowski GS, et al. J Clin Oncol. 2015; 33:251-7.

Results: long-term outcome, subgroup analysis by COO

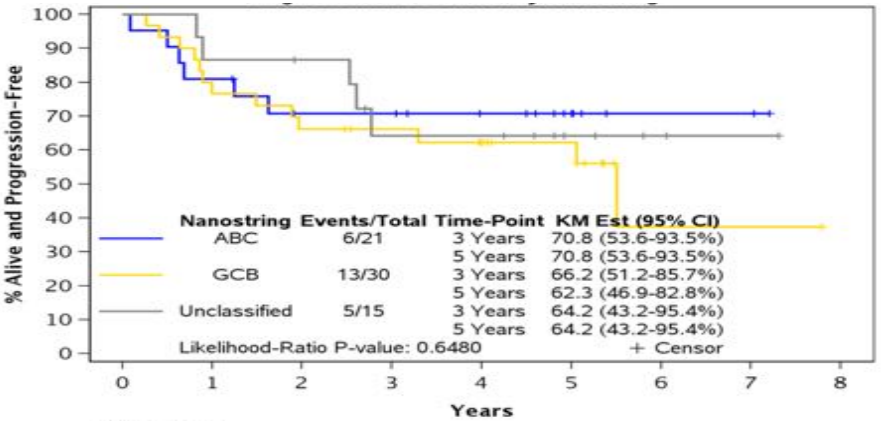
PFS by COO (IHC)



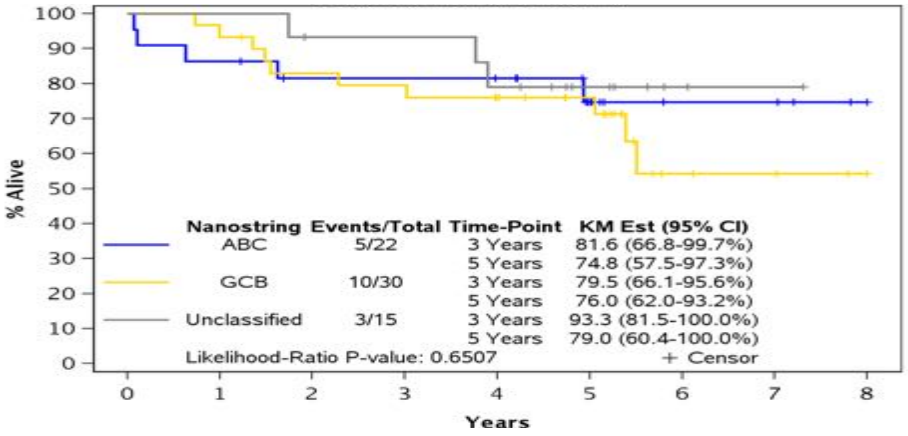
OS by COO (IHC)



PFS by COO (Nanostring)



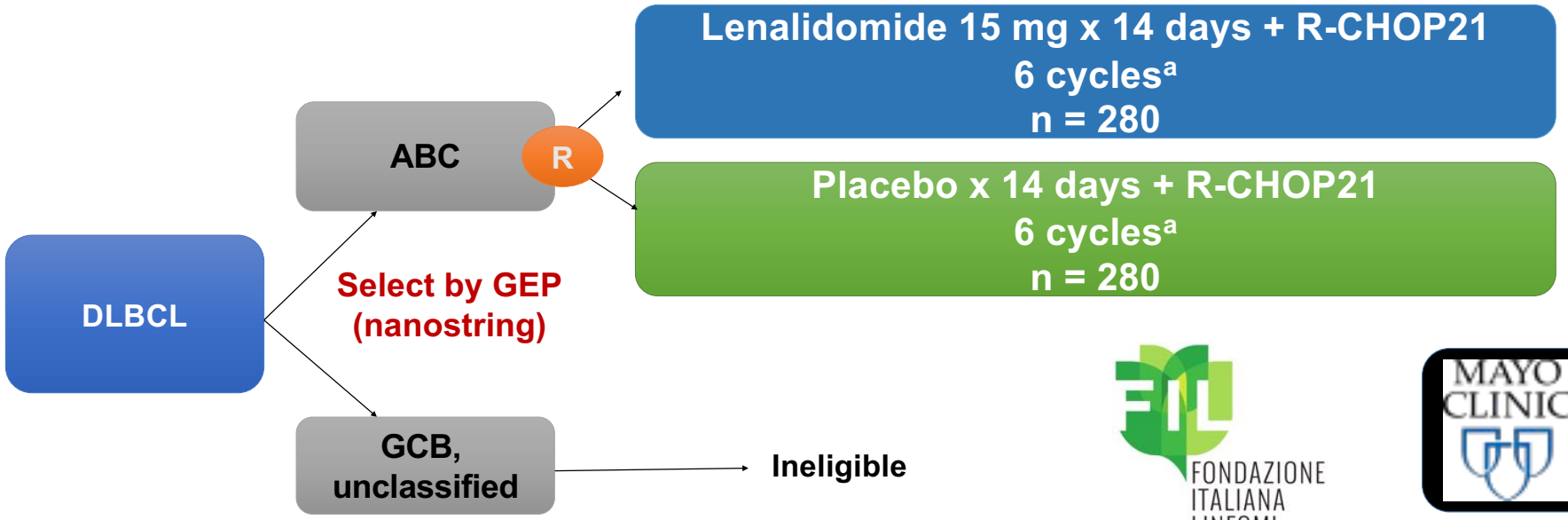
OS by COO (Nanostring)



Castellino A et al ASCO 2018

ROBUST Phase III Study Design

. Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.



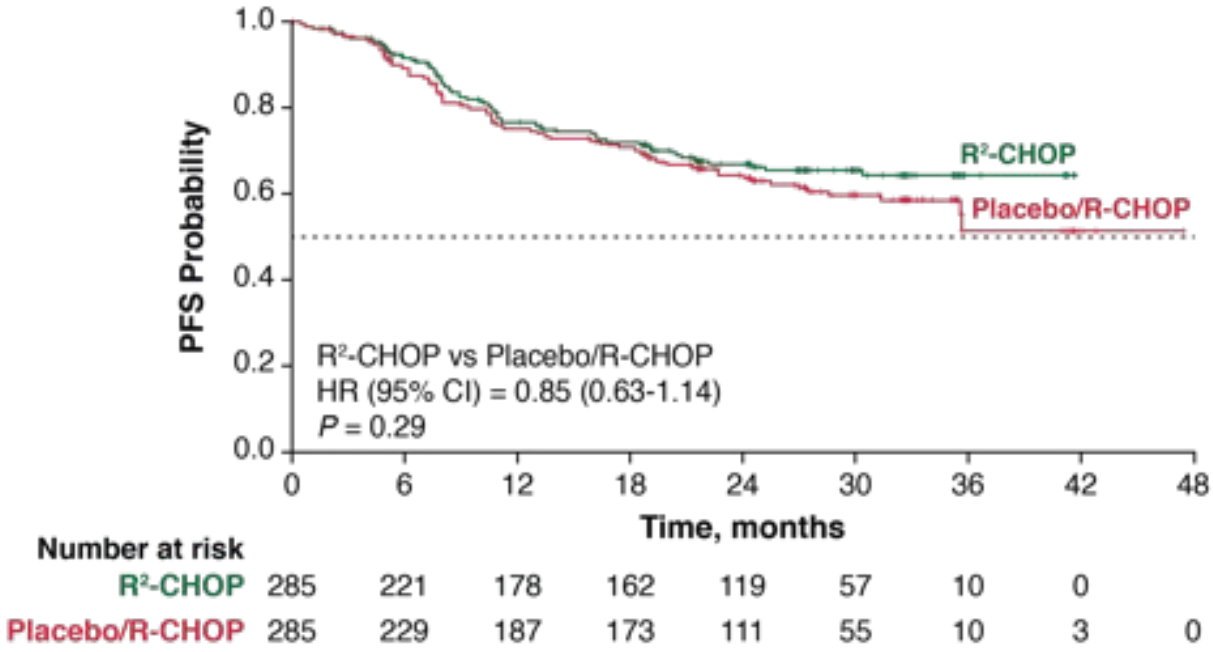
FONDAZIONE ITALIANA LINFOMI

MAYO CLINIC

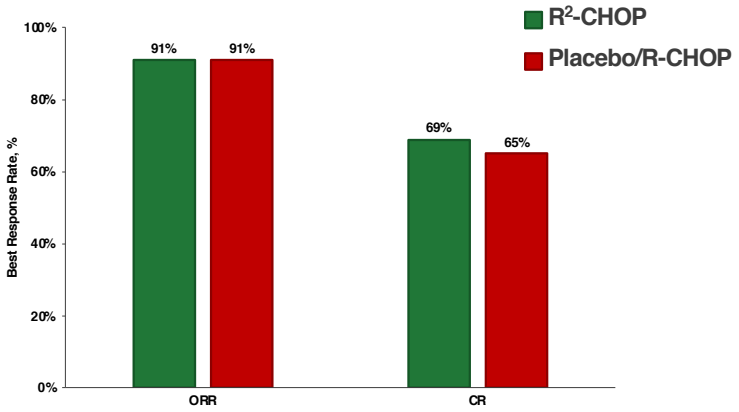
ROBUST

- 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

Primary Endpoint: Progression-Free Survival (ITT, IRAC)



PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%

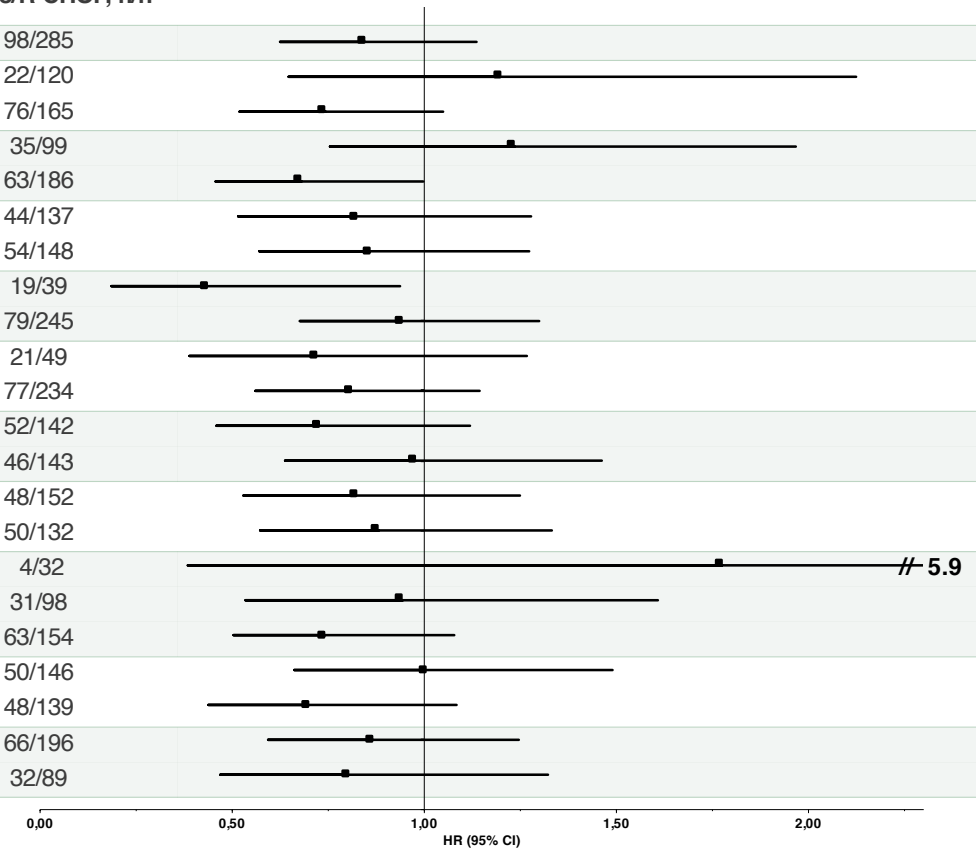


- At a median follow-up of 27.1 mo (range, 0-47), the primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

Vitolo et al ICML 2019

Subgroup Analysis of PFS (ITT)

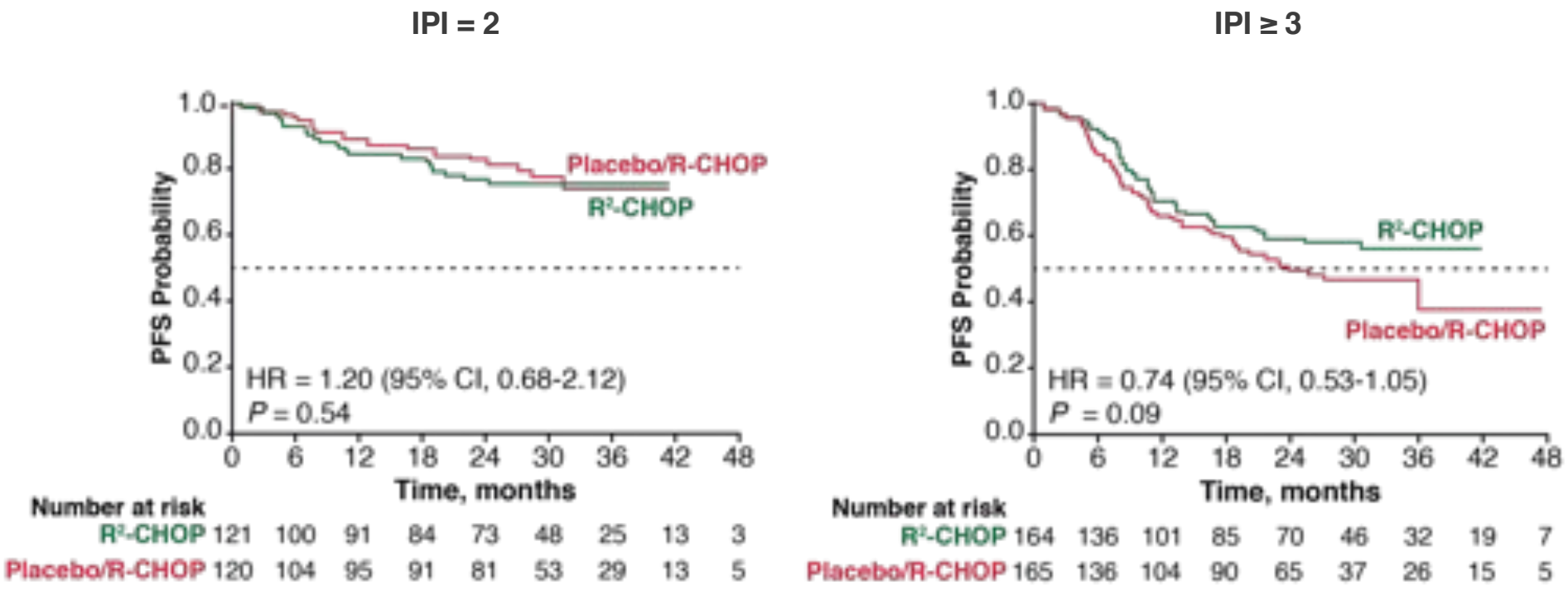
		R^2-CHOP, n/n	Placebo/R-CHOP, n/n
Overall		81/285	98/285
Baseline IPI*	2	25/121	22/120
	≥ 3	56/164	76/165
Presence of bulky disease*	Bulky (≥ 7 cm)	36/97	35/99
	Non-bulky (< 7 cm)	45/188	63/186
Age*	< 65 y	35/138	44/137
	≥ 65 y	46/147	54/148
Baseline CrCl	30 to < 60	10/41	19/39
	≥ 60	71/244	79/245
Total lenalidomide/placebo planned dose	< 75%	27/82	21/49
	≥ 75%	53/200	77/234
Sex	Female	33/121	52/142
	Male	48/164	46/143
Prephase steroid	No	40/156	48/152
	Yes	41/129	50/132
DLBCL stage at diagnosis	II	8/37	4/32
	III	24/80	31/98
	IV	49/168	63/154
Time from diagnosis to treatment	≤ 31 days	48/146	50/146
	> 31 days	33/129	48/139
Asian	No	52/184	66/196
	Yes	29/101	32/89



Data cut-off 15Mar2019. *Stratification factors.

Vitolo et al ICML 2019

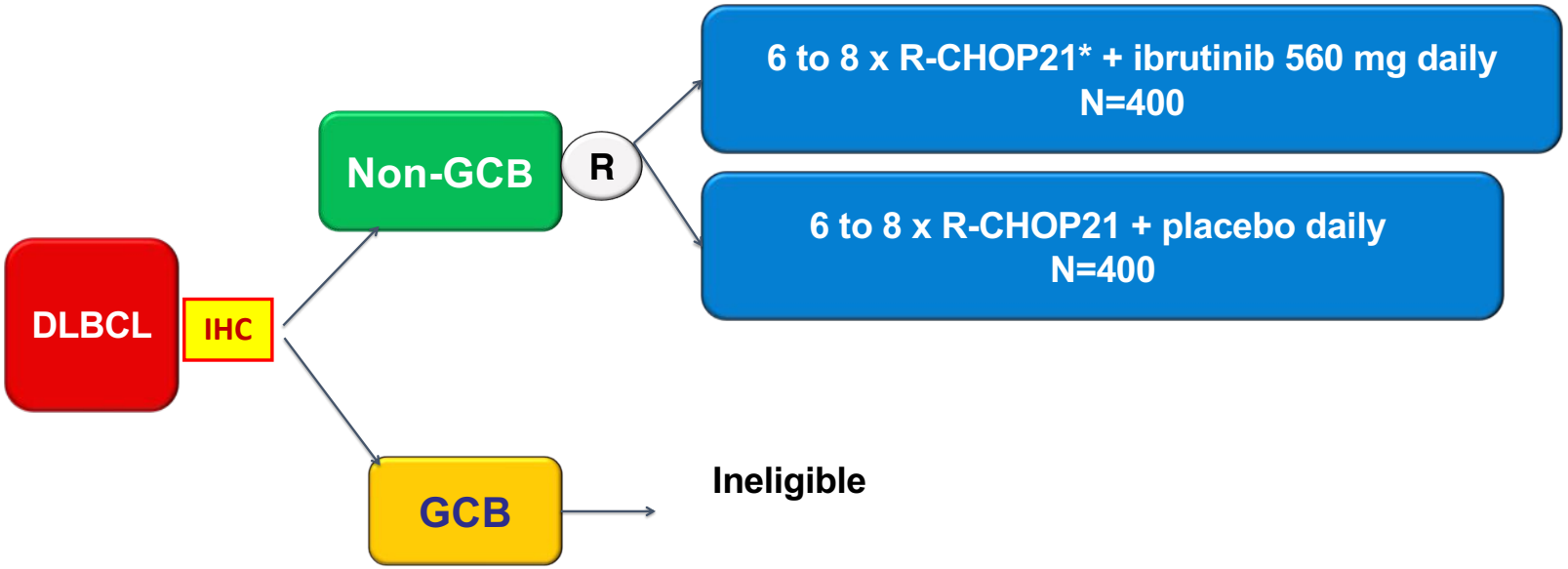
PFS Based on International Prognostic Index Score (ITT)



- Positive trend for PFS favoring R²-CHOP was observed in patients with IPI score ≥ 3

Vitolo et al ICML 2019

Study Design: Double-Blind, Placebo-Controlled



- Newly diagnosed DLBCL of non-GCB type
- Stage II to IV
- IPI ≥ 2; ECOG PS ≤ 2; Age >18
- Primary Endpoint = EFS
- N = 838

Primary end point

- EFS in ITT for non- GCB and ABCsubgroup

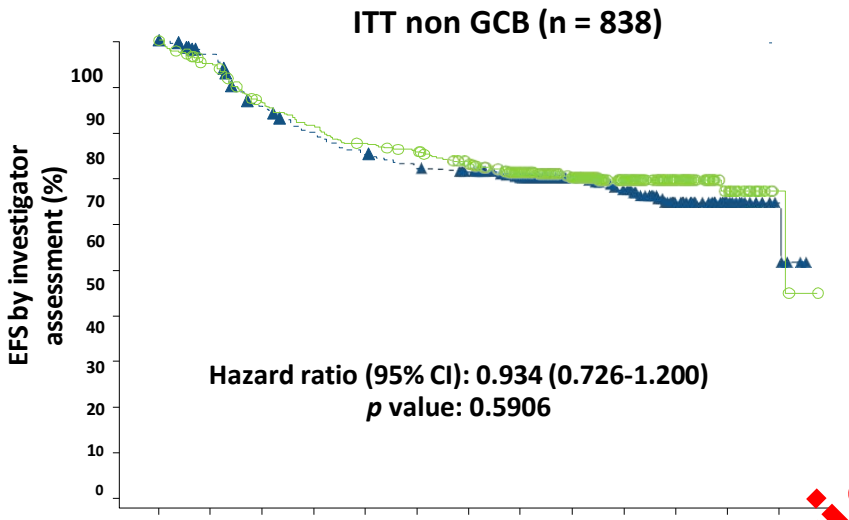
Secondary end points

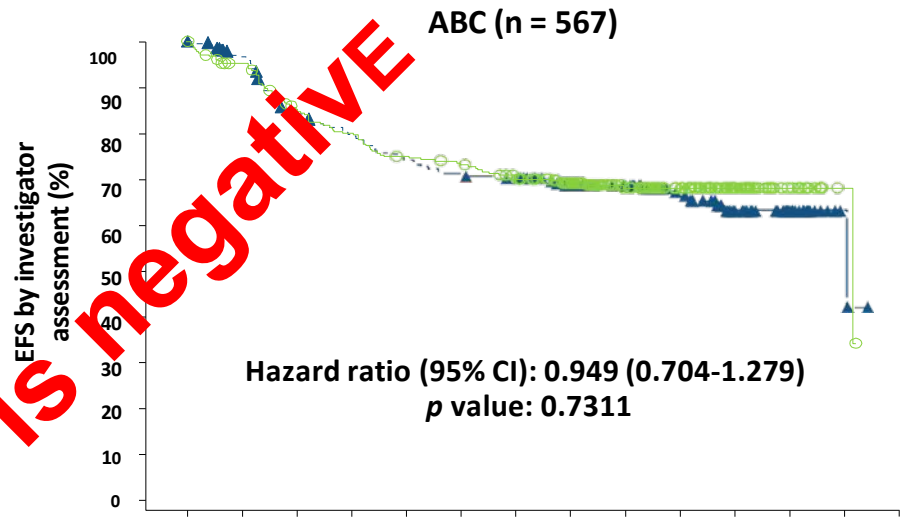
- PFS, CR rate, OS, safety

Younes et al J.Clin .Oncol .2019

Primary End Point:

EFS in the ITT and ABC Population



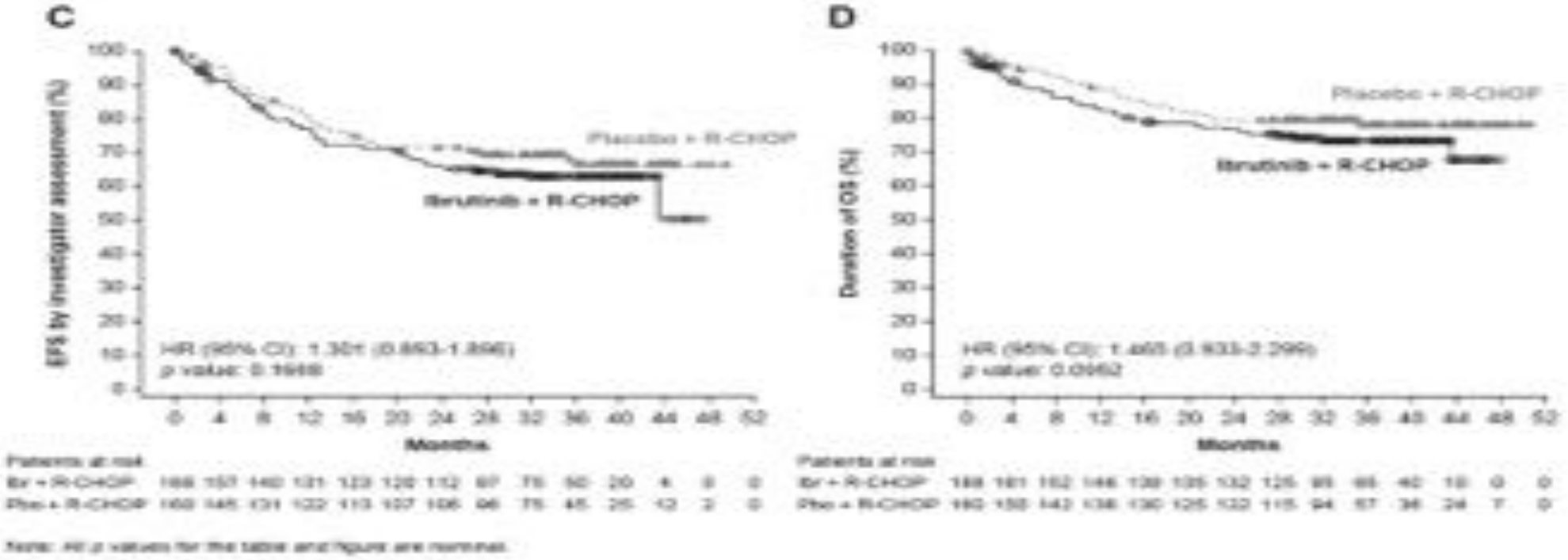


Overall trial is negative

- Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population
- CNS progression was observed in 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

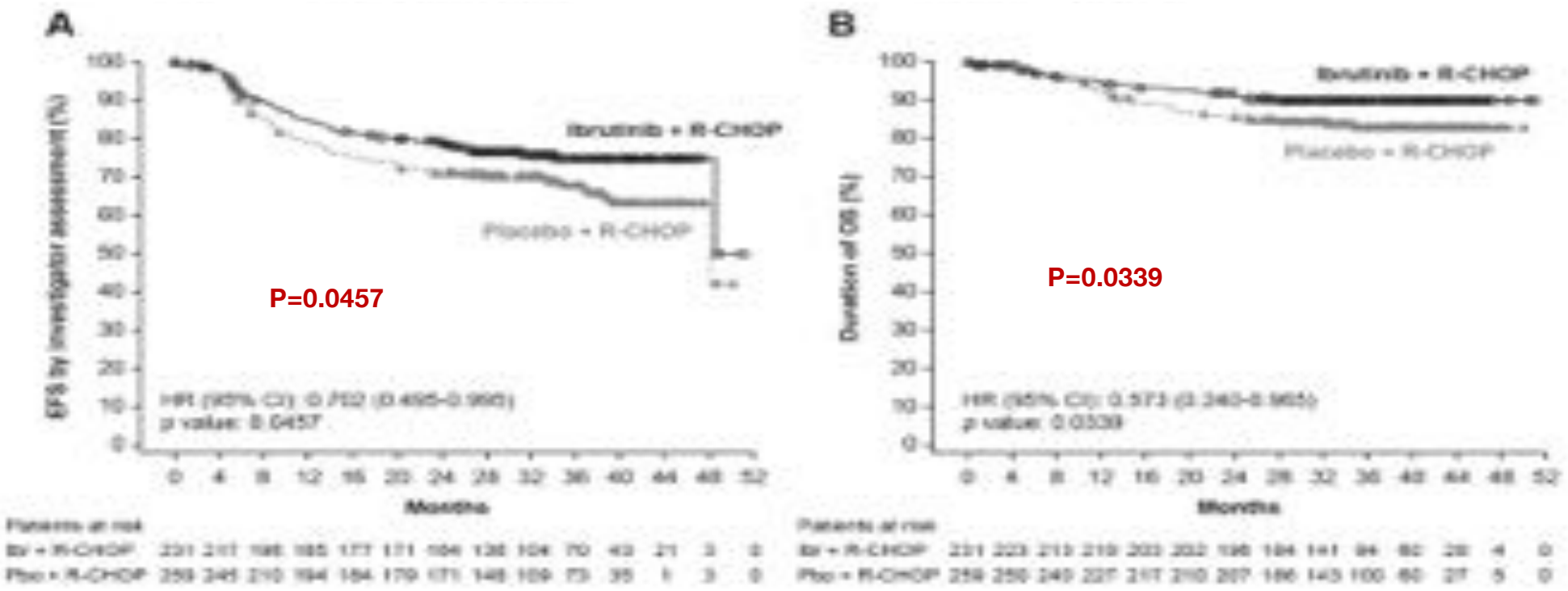
Younes et al J.Clin .Oncol. 2019

EFS and OS in patients > 60 years (348 pts)



Ibr+RCHOP arm (73.7%) received ≥ 6 cycles compared with lacebo + RCHOP arm (88.8%)
SAEs (67.4% vs 40.6%)

EFS and OS in patients < 60 years (470 pts)



Ibr+RCHOP arm (92.9%) received ≥ 6 cycles compared with the pbo + RCHOP arm (93.0%)
SAEs (41.5% vs 29.8%)

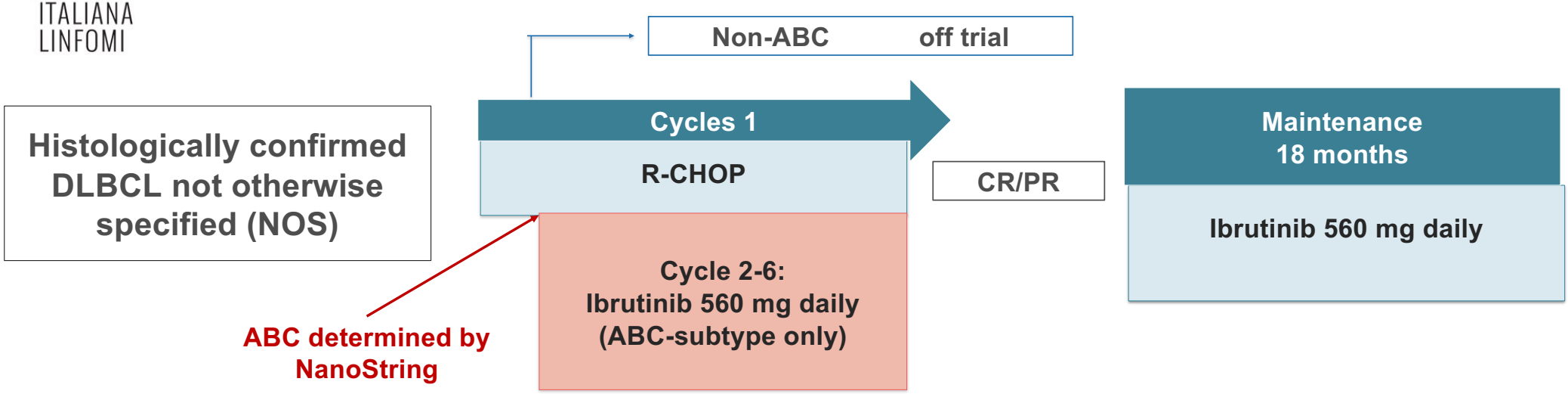
Younes et al J.Clin .Oncol. 2019

Phase II multicentric single arm study to evaluate the efficacy and safety of ibrutinib in combination to rituximab-CHOP followed by ibrutinib maintenance in younger DLBCL(IPI ≥2).

FONDAZIONE ITALIANA LINFOMI

Patients accrual 2019-2021

- Previously untreated disease
- Age < 65 years
- IPI score ≥ 2
- ABC nanostring



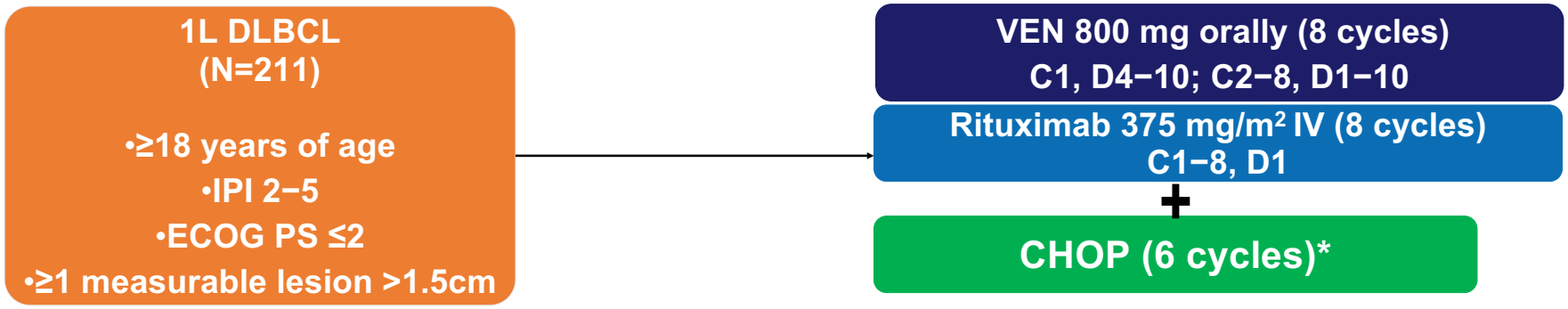
Primary End-points

- The 2-years PFS of R-CHOP21 in combination with ibrutinib followed by maintenance in untreated with ABC-DLBCL, at IPI ≥2.
- The safety of R-CHOP21 in combination with Ibrutinib and during Ibrutinib maintenance.

PI: Maurizio Martelli

CAVALLI Phase II: R-CHOP + VEN

Study design



- **Primary endpoint:** PET-CR rate at end of treatment by modified Lugano criteria 2014[1] (6–8 wks after last R dose; IRC-assessed)
- Secondary endpoints: OR rate, CR rate as determined by CT scan, DOR, PFS (investigator-assessed), OS, PK, safety
- Historical control: R-CHOP GOYA IPI 2–5[2]
  - The R-CHOP control arm from GOYA[2] reflects the most recent SOC for DLBCL and was selected as the historical comparator arm for exploratory analyses
  - Efficacy analyses of CAVALLI vs GOYA were conducted using double-robust covariate adjusted analyses

Morschhauser ASH 2018 oral session

PET-CR rate by IRC in CAVALLI vs GOYA

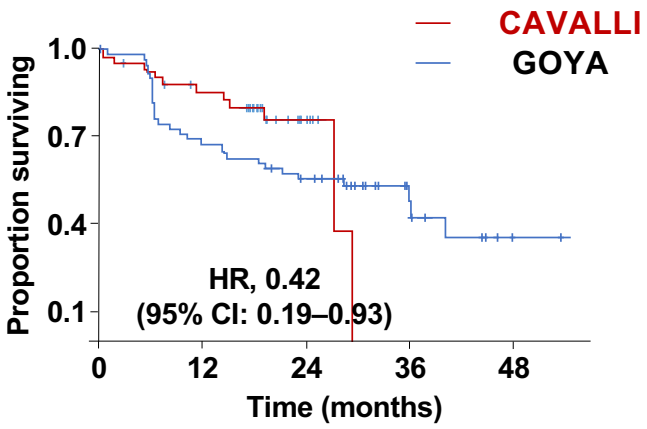
Pts Tot=208	PET-CR rate				Delta CR, % (95% CI)
	CAVALLI		GOYA		
	%	N	%	N	
All	69	208	63	564	6 (0–13)
BCL-2 IHC+	65	105	60	151	5 (0–14)
DE	67	81	61	124	6 (0–18)
BCL-2 FISH+	70	40	48	59	23 (7–39)
DH	71	7	25	8	46 (37–56)

Morschhauser ASH 2018 oral session

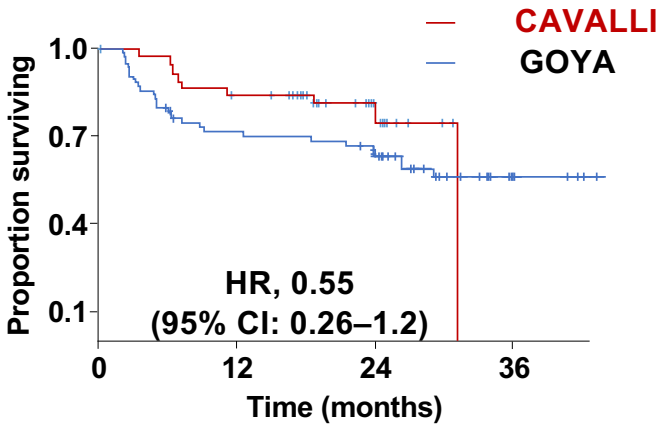
PFS benefit observed in BCL-2+ pts in COO subgroups

(investigator-assessed; covariate adjusted*)

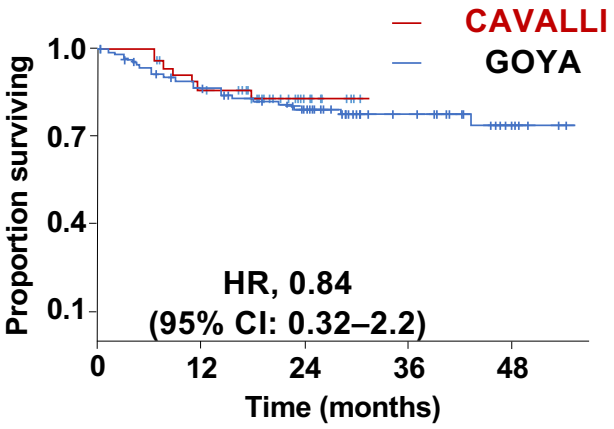
BCL-2 IHC+/ABC†



BCL-2 IHC+/GCB



BCL-2 IHC–/GCB



*Covariates: age, sex, ECOG PS, BMI, IPI (high vs non-high), bulky disease (>7.5cm), disease stage (IV vs I−III), LDH

These data support further exploration of VENETOCLAX combination with R-CHOP in BCL-2+ DLBCL

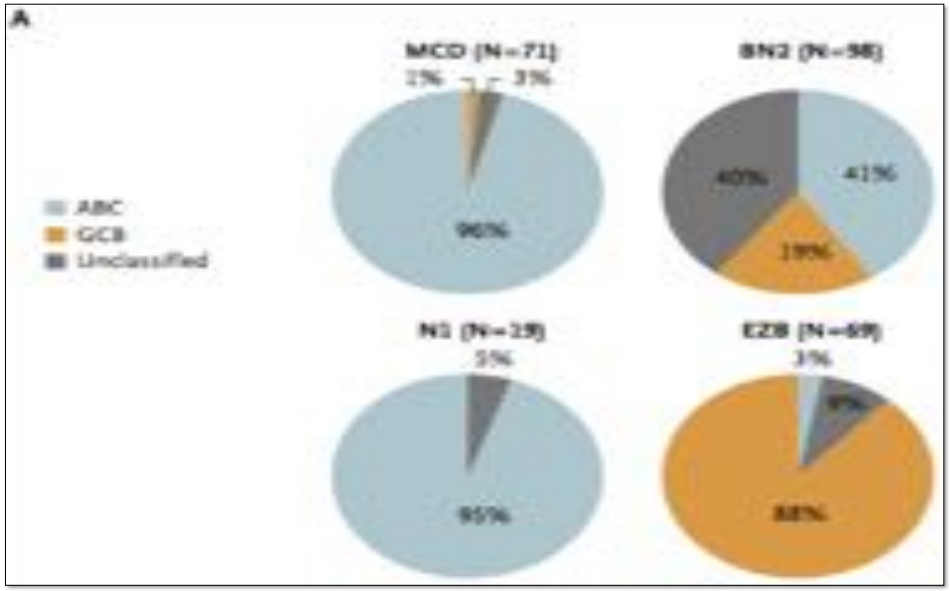
Morschhauser ASH 2018 oral session

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

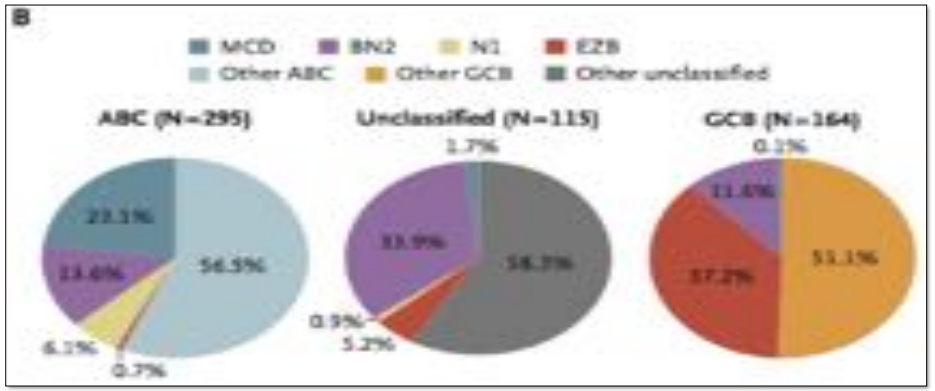
Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

R. Schmitz, G.W. Wright, D.W. Huang, C.A. Johnson, J.D. Phelan, J.Q. Wang, S. Roulland, M. Kasbekar, R.M. Young, A.L. Shaffer, D.J. Hodson, W. Xiao, X. Yu, Y. Yang, H. Zhao, W. Xu, X. Liu, B. Zhou, W. Du, W.C. Chan, E.S. Jaffe, R.D. Gascoyne, J.M. Connors, E. Campo, A. Lopez-Guillermo, A. Rosenwald, G. Ott, J. Delabie, L.M. Rimsza, K. Tay Kuang Wei, A.D. Zelenetz, J.P. Leonard, N.L. Bartlett, B. Tran, J. Shetty, Y. Zhao, D.R. Soppet, S. Pittaluga, W.H. Wilson, and L.M. Staudt



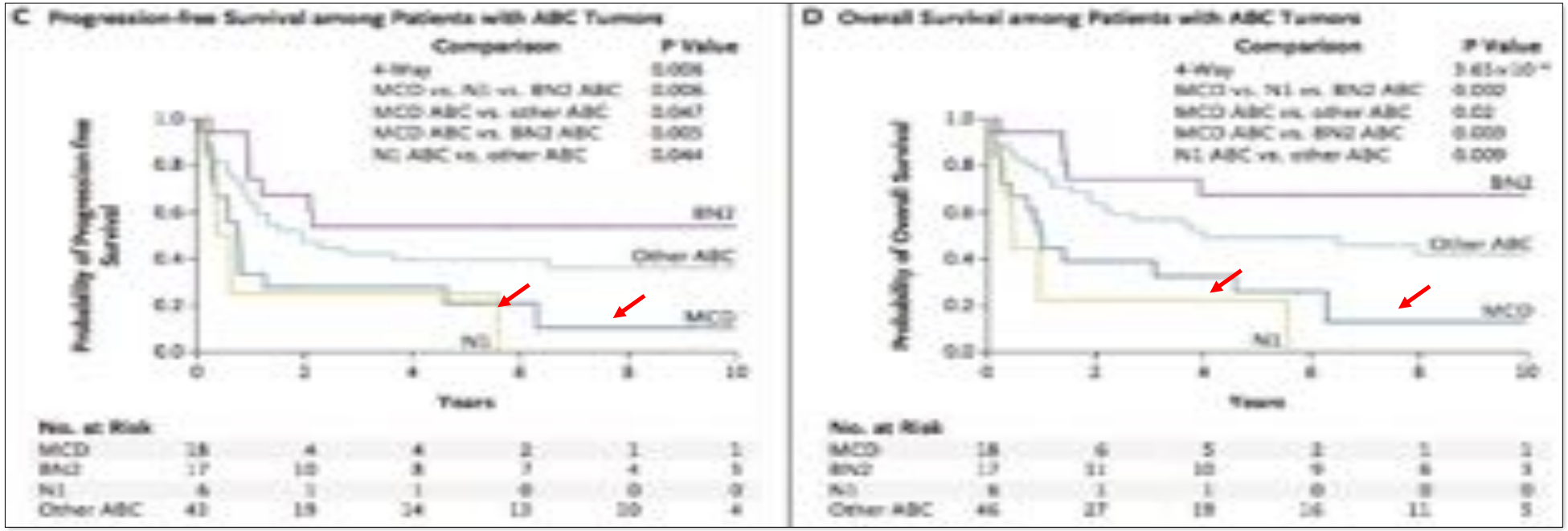
- **4 nuove categorie di DLBCL sulla base delle alterazioni genetiche associate:**
  - **MCD caratterizzato dalla presenza di *MYD88*^{L265P} e mutaz di *CD79***
  - **BN2 caratterizzato da fusioni di *BCL6* con diversi partner genici e mut di *NOTCH2***
  - **N1 caratterizzato da mut di *NOTCH1***
  - **EZB caratterizzato da mut di *EZH2* e traslocaz di *BCL2***

- **MCD and BN2 DLBCL si basano sulla segnalazione cronicamente attiva del BCR**



Schimtz et al, N.Engl J Med 2018

Improving R-CHOP in high risk genomic DLBCL in 2019-2024…… precision therapy



DLBCL COO-ABC subtype
MCD and N1
poor prognosis group

MCD→ BTK inhibitors
BN2→ BTK inhibitors
N1→ immune checkpoint inhibitors

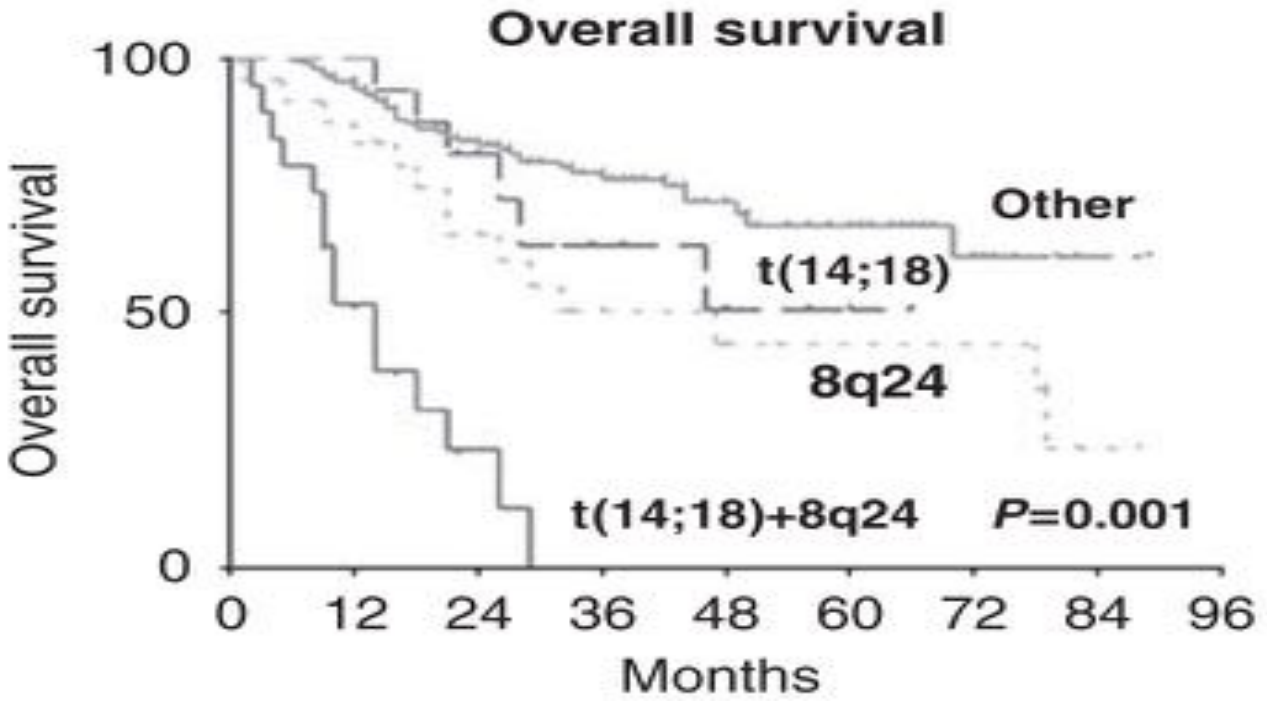
Precision therapy

Schimtz et al, N.Engl J Med 2018

Outline of discussion

- Heterogeneity of the disease
- What outcomes can we expect with R-CHOP in DLBCL?
- Is time of a molecular oriented therapy in DLBCL ?
- **When we can consider an alternative therapy to R-CHOP ?**

DLBCLs with *MYC* and *BCL2* translocations are characterized by inferior survival



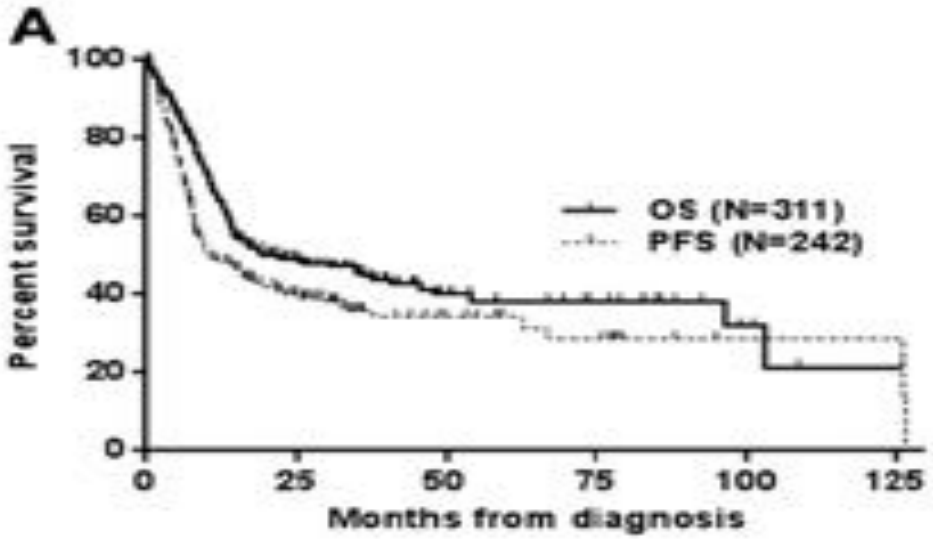
Niitsu et al., Leukemia 2009

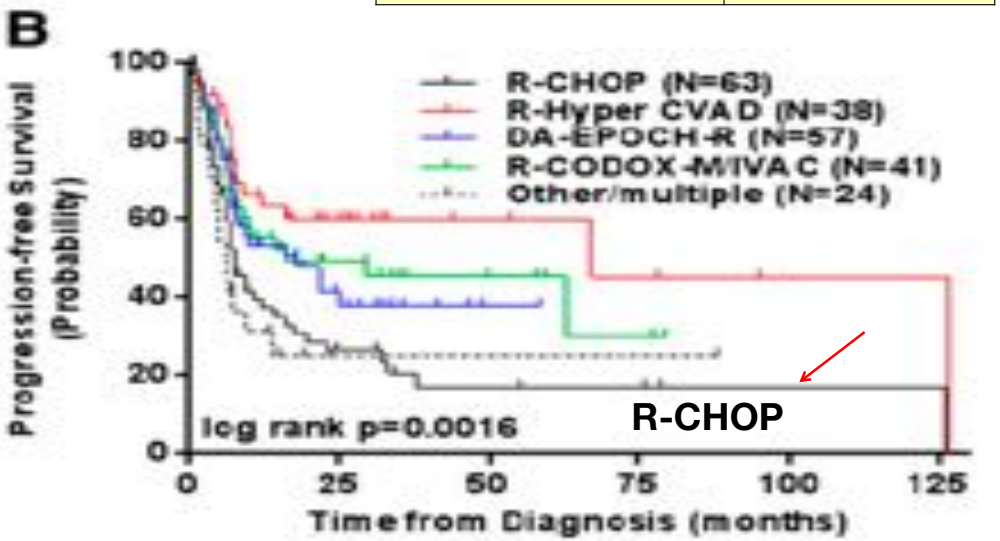
blood 2014 124: 2354-2361

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)



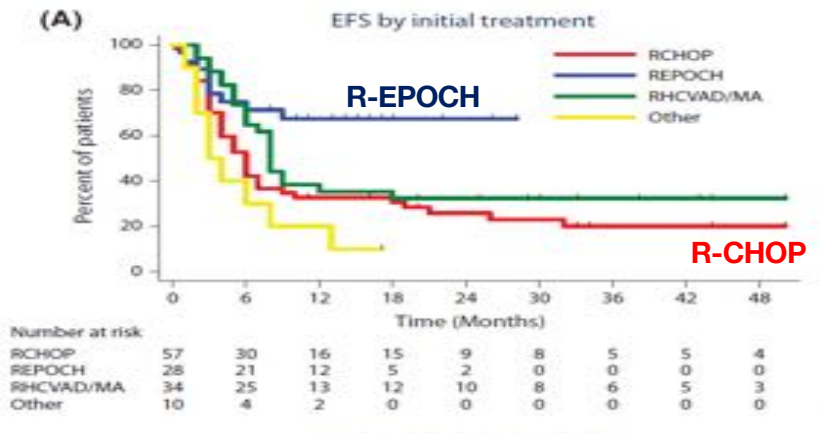


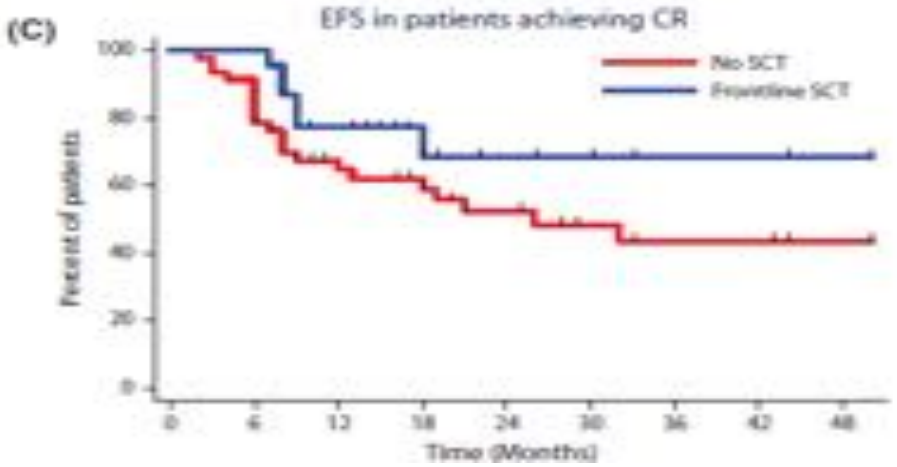
Educational ASH 2014

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)



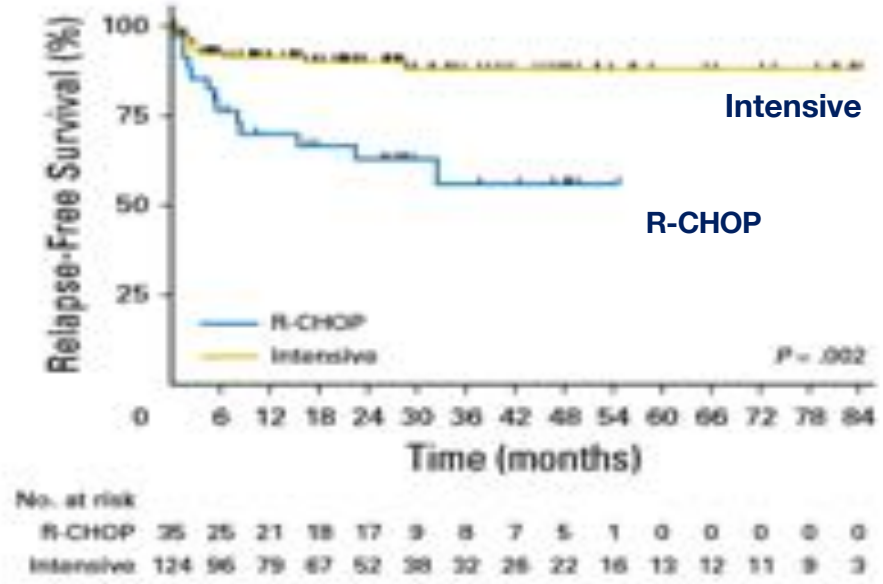


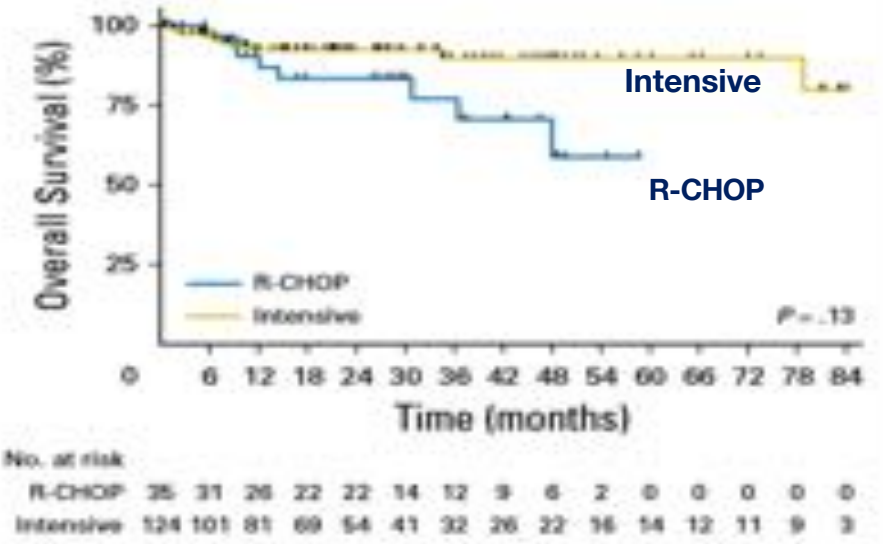
Oki et al Br. J. Hematol. 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

	R-CHOP n 35	R-DaEPOCH n 81	RhyperCVAD n 32	R-CODOXM/IVAC n 11	p
3y-EFS	56%	88%	87%	91%	0.003
3y-OS	77%	87%	90%	100%	0.36





Landsburg et al, JCO 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

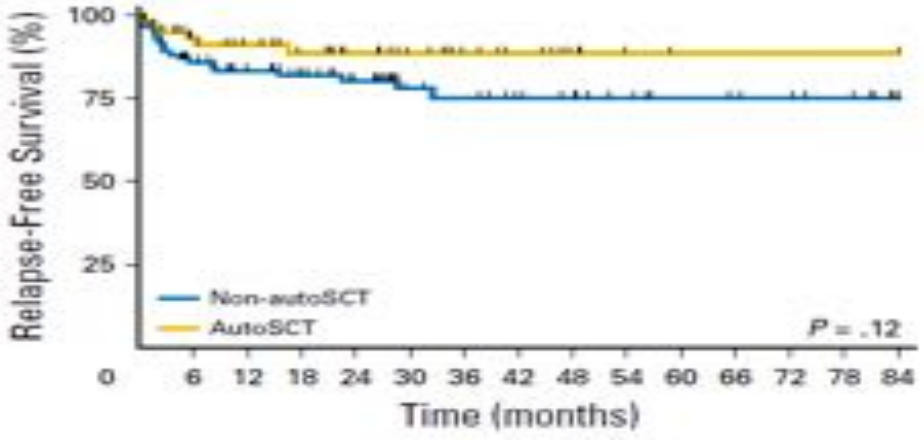
Daniel J. Landsburg, Marissa K. Falkiewicz, Joseph Maly, Kristie A. Blum, Christina Howlett, Tatyana Feldman, Anthony R. Mato, Brian T. Hill, Shaoying Li, L. Jeffrey Medeiros, Pallawi Torka, Francisco Hernandez-Ilizaliturri, Nishitha M. Reddy, Arun Singavi, Timothy S. Fenske, Julio C. Chavez, Jason B. 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

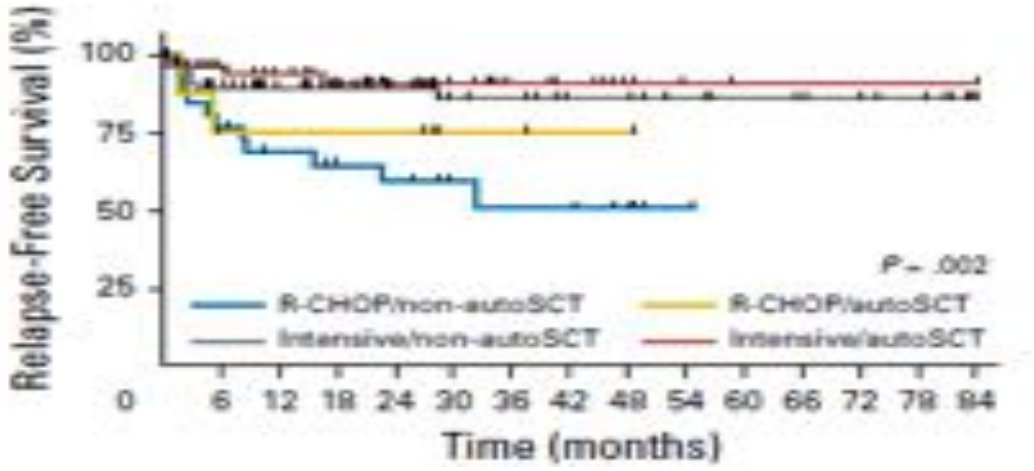
Tot. patients : 159

Auto ASCT : 62

non Auto ASCT: 97

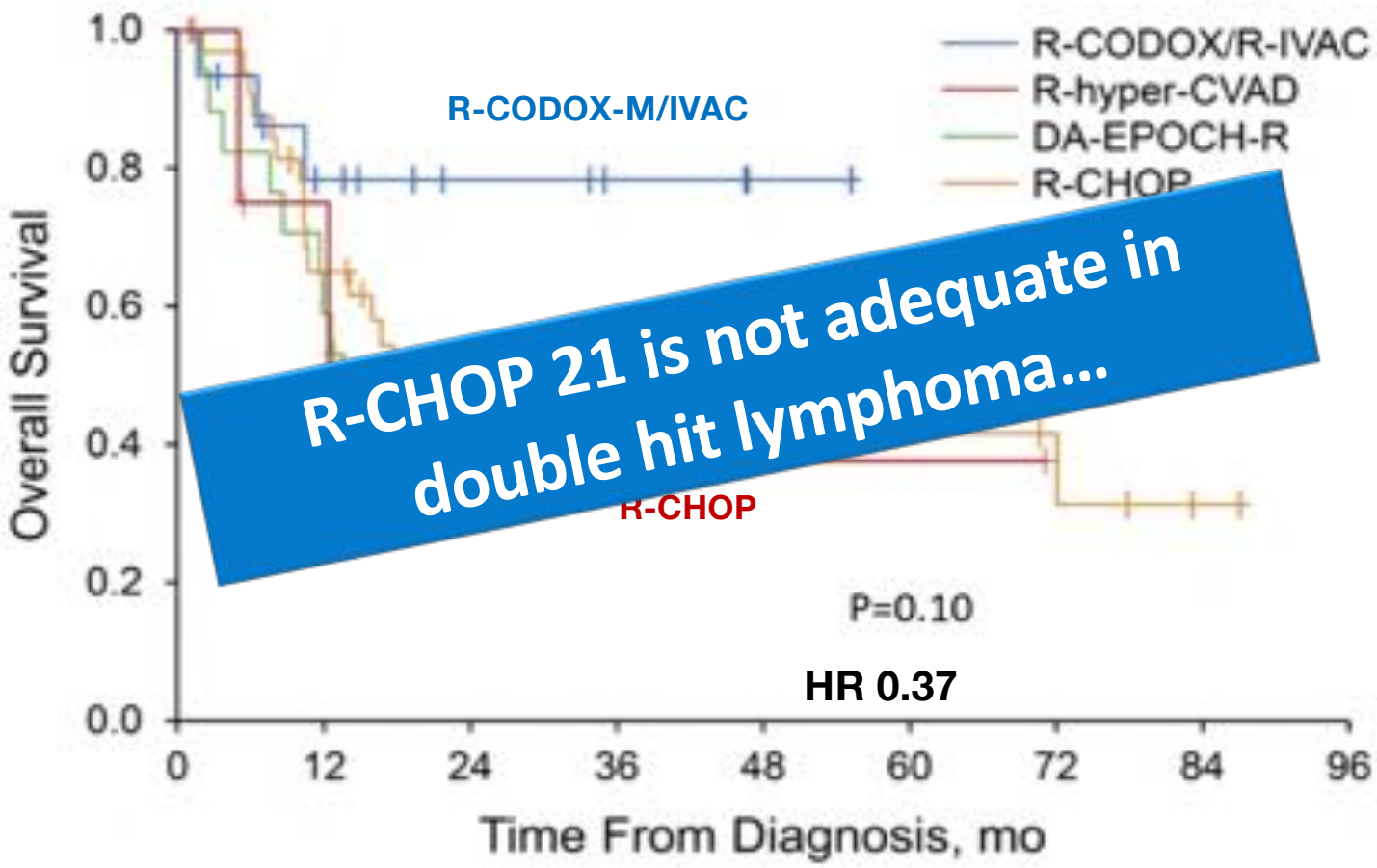
A





Landsburg D et al . J.Clin. Oncol 2017

DHL and THL : retrospective CALGB study front- line treatment



R-CHOP 21 is not adequate in double hit lymphoma…

100 patients with DHL

>60 years, in 53% pts

R-CHOP 36%
R-EPOCH 17%
R-CODOX-M/IVAC 17%
R-hyper-CVAD 6%

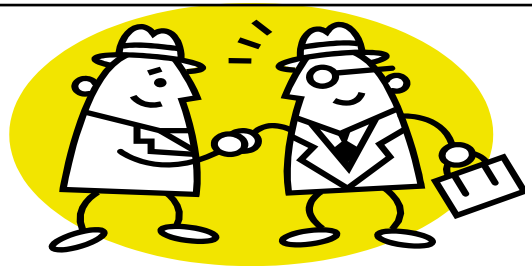
McPhail et al. Hematologica 2018

Take home messages (1)

- ***R-CHOP*** is still the standard of care in DLBCL and ***about 60%*** of patients with DLBCL may be cured in the clinical practice .
- ***R-CHOP*** is not adeguated therapy for ***DLBCL-DH***
- A more accurate ***recognition of unfavourable DLBCL*** subsets is now recommended to better tailor the treatment
- **COO** is predictive of the outcome with ***ABC s***ubtype having a ***worst prognosis*** in terms of survival

Take home messages (2)

- **ABC subtype** can be targeted by ***Bortezomib, Lenalidomide and Ibrutinib*** might be helpful in young patients but the final data of the randomized trial do not show any improvement of cure in the combination arm **(R-CHOP+X)**
- DLBCL with ***BCL2 overexpression*** have a worse prognosis that may be overcome by the addition of ***Venetoclax*** to R-CHOP awaiting for large randomized trials
- New genetic subtype of DLBCL with distinct genotypic, epigenetics and clinical characteristcs providing a future potential nosology for a precision-medicine strategies in DLBCL



SAPIENZA
UNIVERSITÀ DI ROMA

Alice Di Rocco
Luigi Petrucci
Clara Minotti

Robin Foà

FONDAZIONE ITALIANA LINFOMI

All FIL Centers

Grazie per l'attenzione .....