Report dei gruppi di lavoro "10 anni di Highlights" Linfomi

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Disclosures – Maurizio Martelli

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

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008

Gubbio, 18-19 Settembre 2009

Stresa 17-18 Settembre 2010

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Matera 15 -16 Settembre 2012

Firenze 20-21 Settembre 2013

Firenze 19-20 Settembre 2014

Firenze 18-19 Settembre 2015

Vitolo Zinzani Martelli

22-23 SETTEMBRE 2017
GRAND HOTEL BAGLIONI
FIRENZE

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008

Gubbio, 18-19 Settembre 2009

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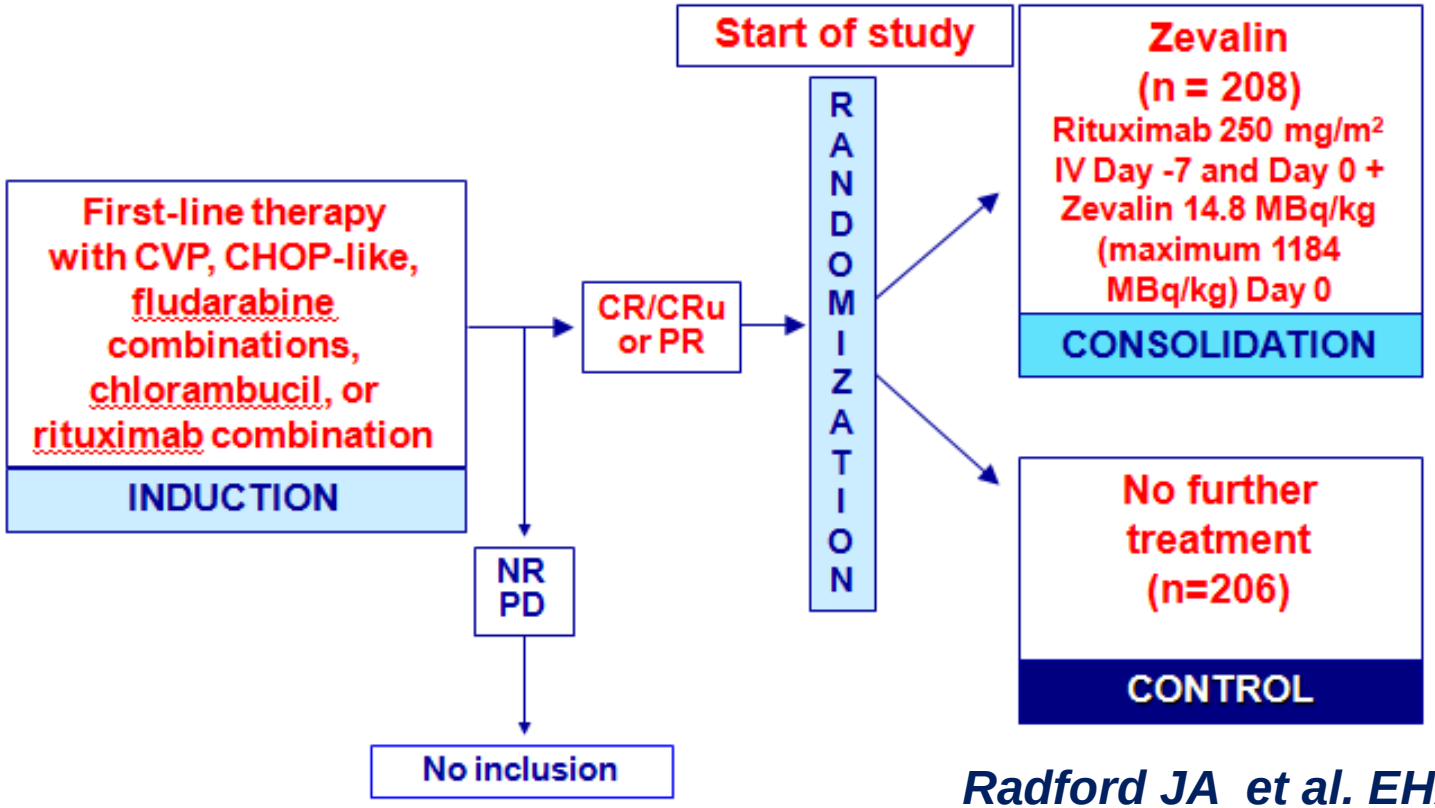
Firenze 19-20 Settembre 2014

Firenze 18-19 Settembre 2015

Results from the randomized phase 3 First-line Indolent Trial (FIT) of consolidation of first remission with 90Y-Ibritumomab Tiuxetan in advanced follicular non-Hodgkin's lymphoma (FL).

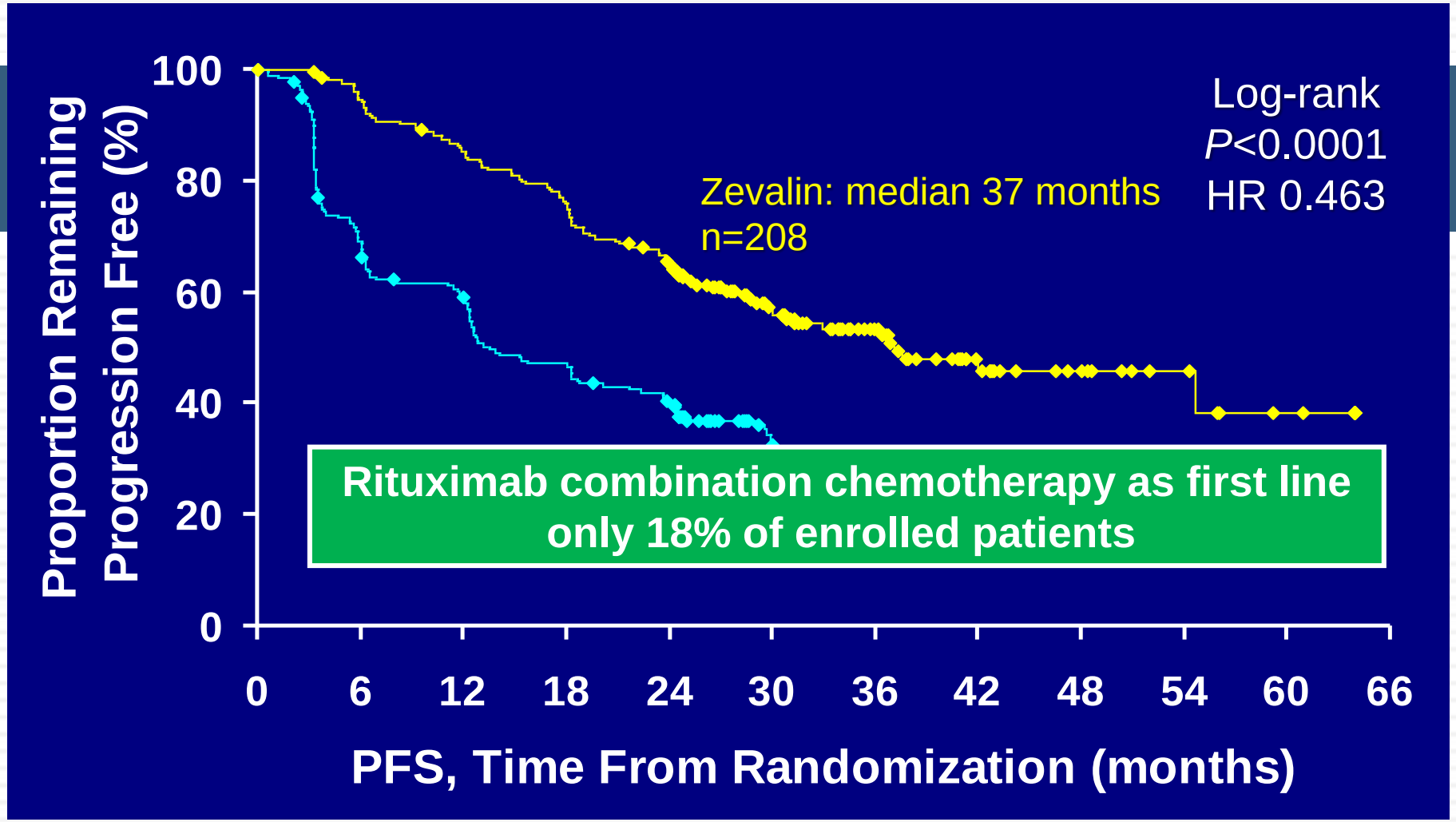
Radford JA, Morschhauser F, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, Kunz M, Hagenbeek A.

FIT Study Schema



Radford JA et al. EHA 2008

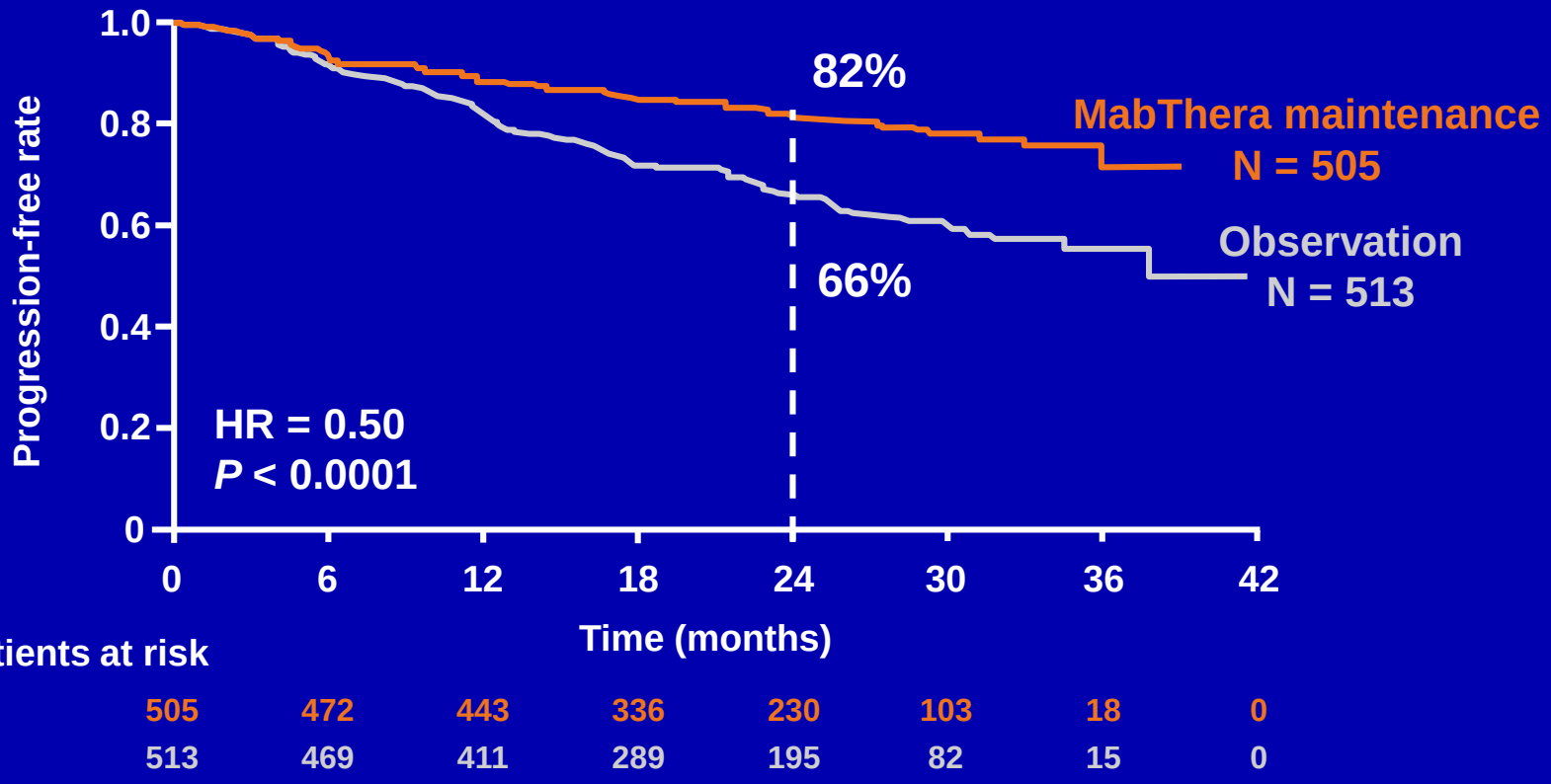
FIT Primary Endpoint: Median PFS in All Patients (median observation period: 3.5 years)



Radford JA et al. EHA 2008

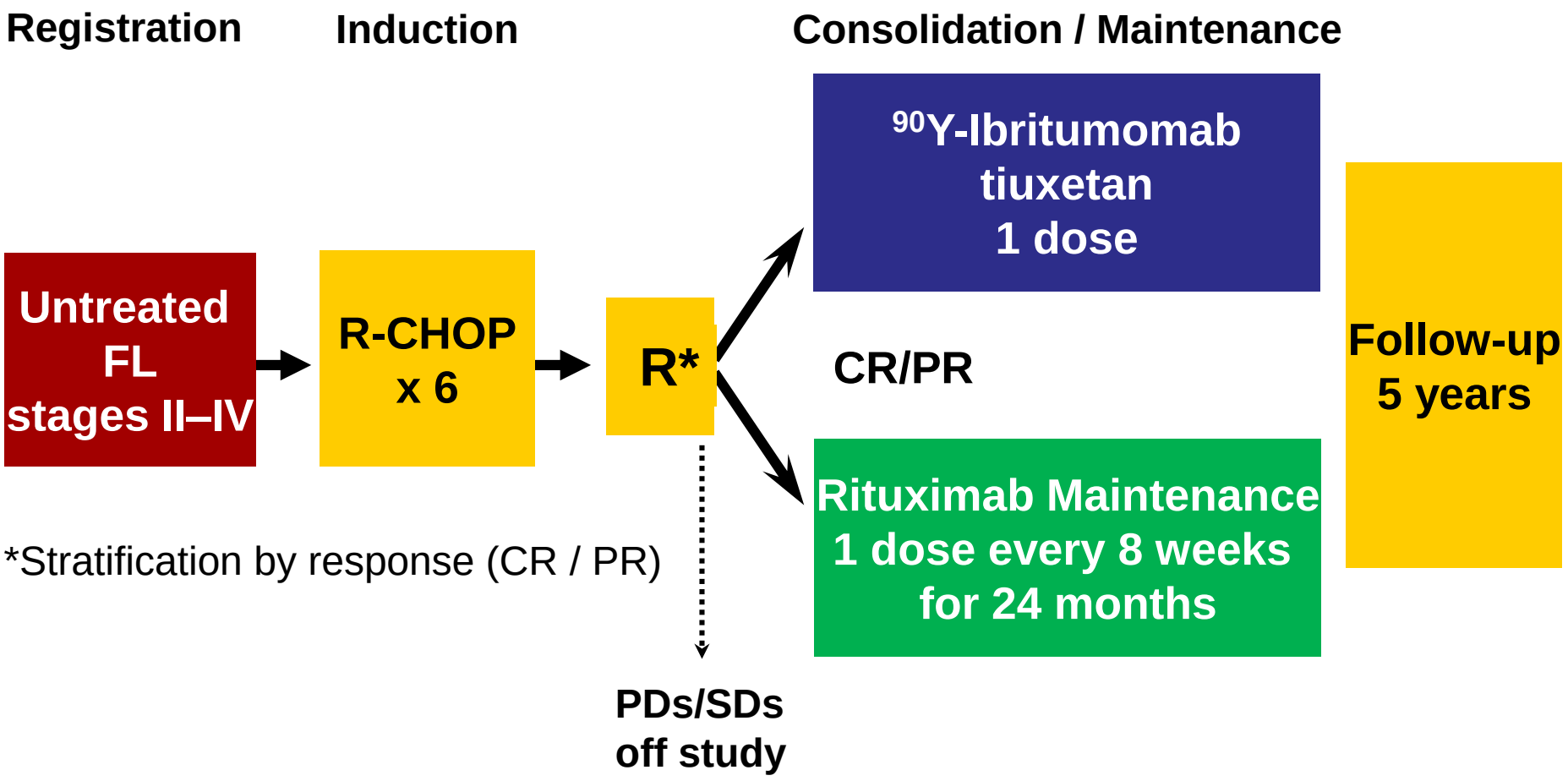
PRIMA study: primary endpoint (PFS) met at the planned interim analysis

- MabThera maintenance significantly reduced the risk of lymphoma progression by 50% (stratified by response and induction regimen, HR = 0.50, 95% CI 0.39; 0.64)



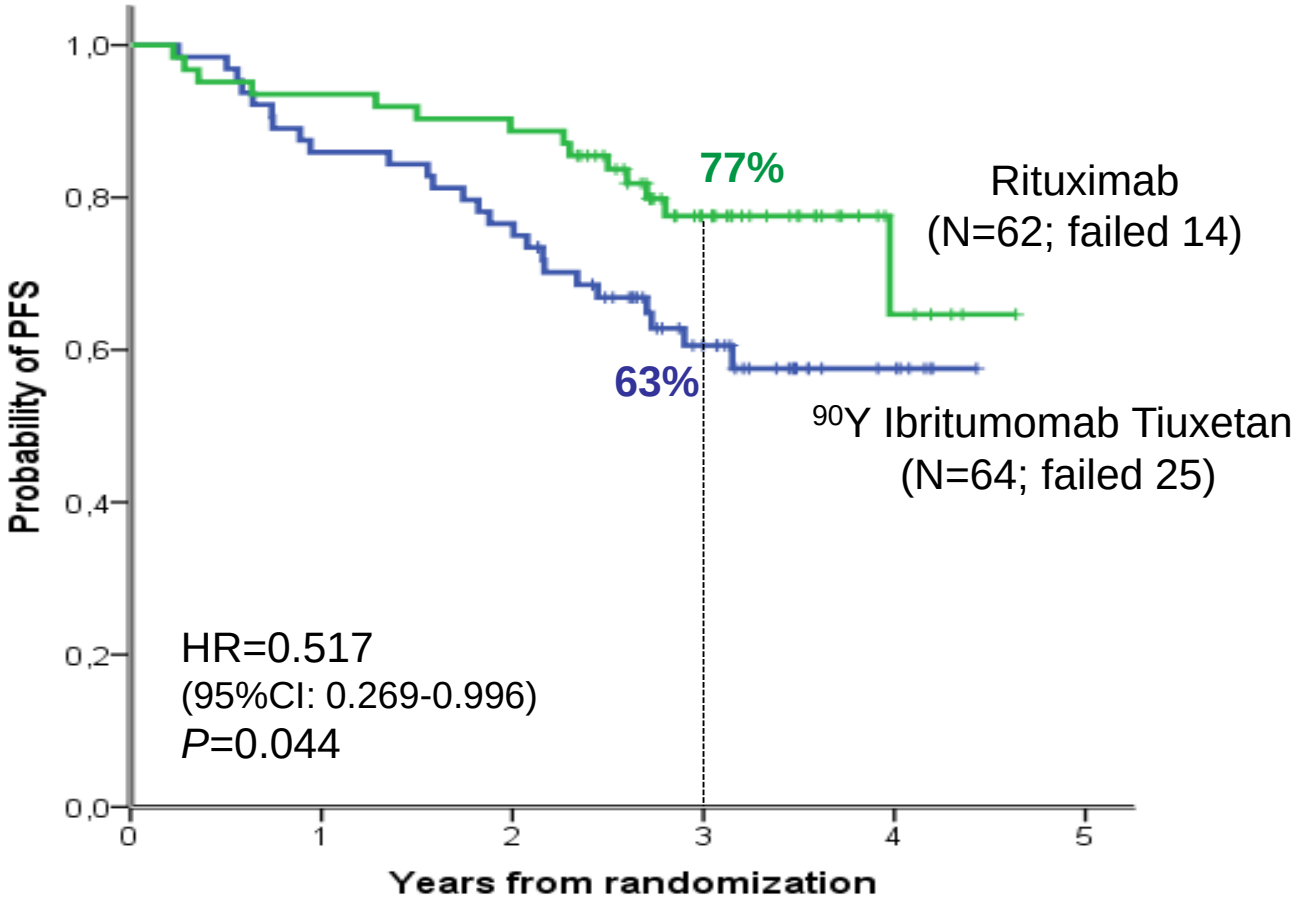
Salles GA, et al. Lancet 2011; 377: 42-51

ZAR : study design



A. López-Guillermo 55th ASH Annual Meeting New Orleans,

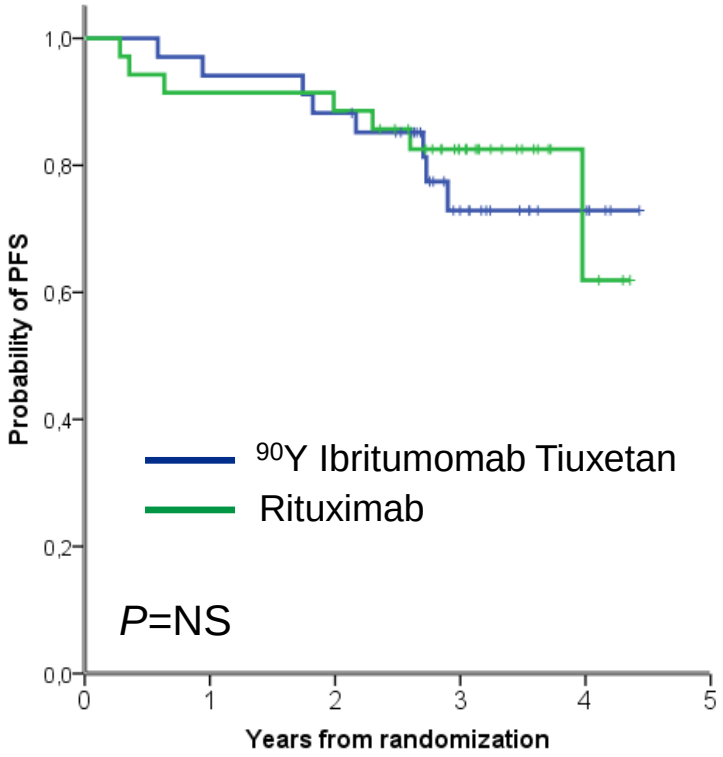
Primary endpoint: Progression-free survival (PFS)



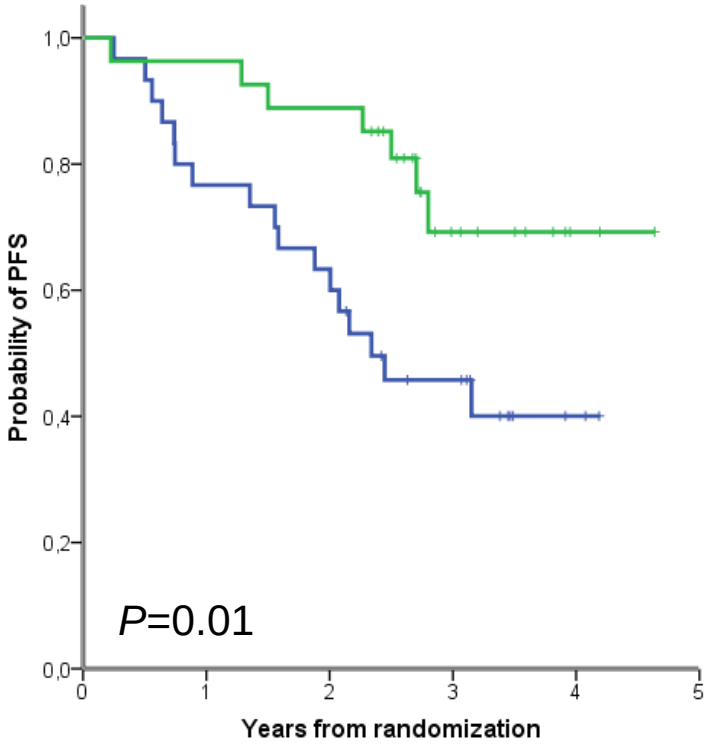
A. López-Guillermo 55th ASH Annual Meeting New Orleans,

Progression-free survival (PFS) by arm

Patients in CR after R-CHOP



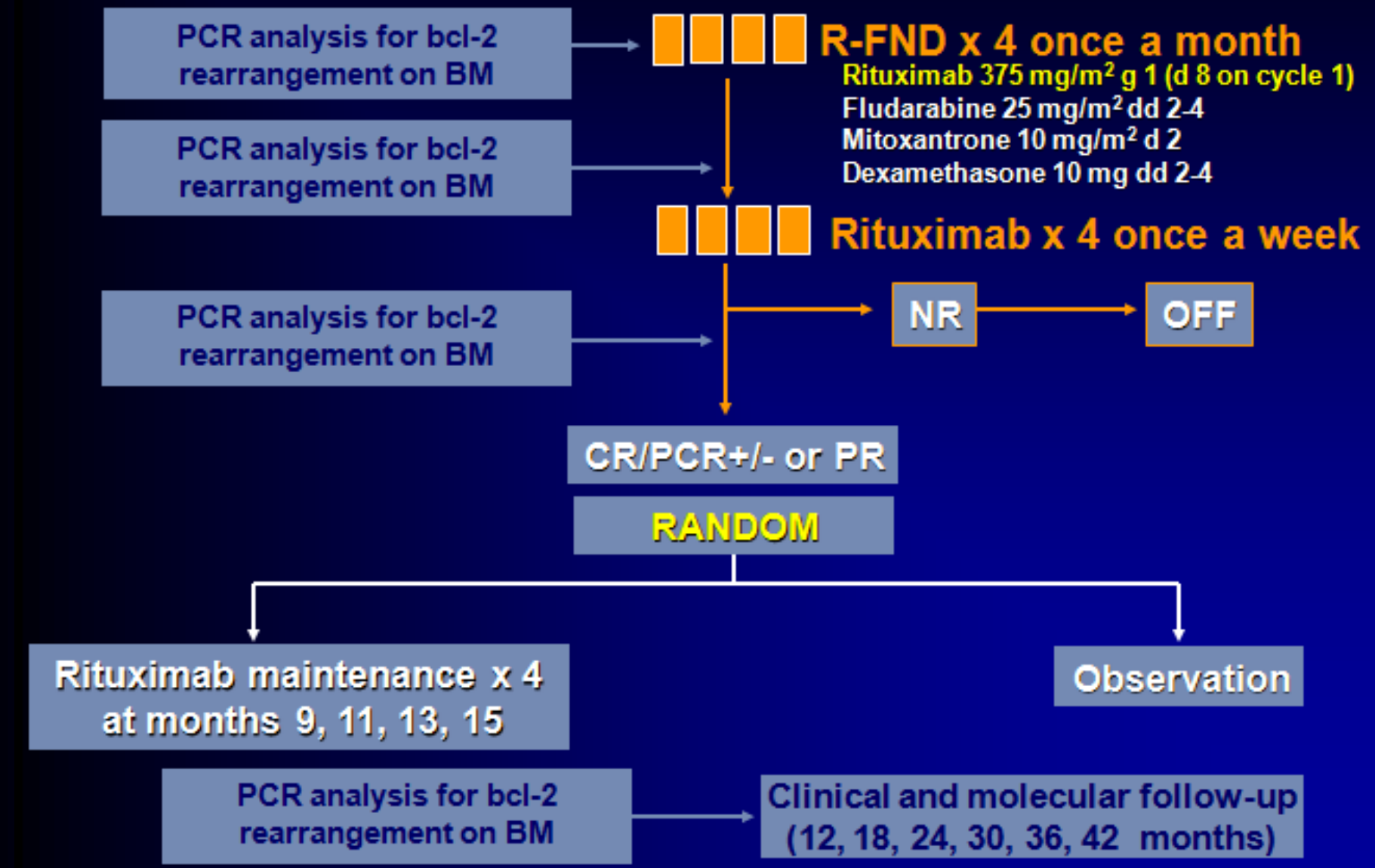
Patients in PR after R-CHOP



A. López-Guillermo 55th ASH Annual Meeting New Orleans,

Brief chemoimmunotherapy Rituximab-FND ± Rituximab maintenance is effective and safe in newly diagnosed Follicular Lymphoma elderly patients: an Intergruppo Italiano Linfomi (IIL) randomized trial.

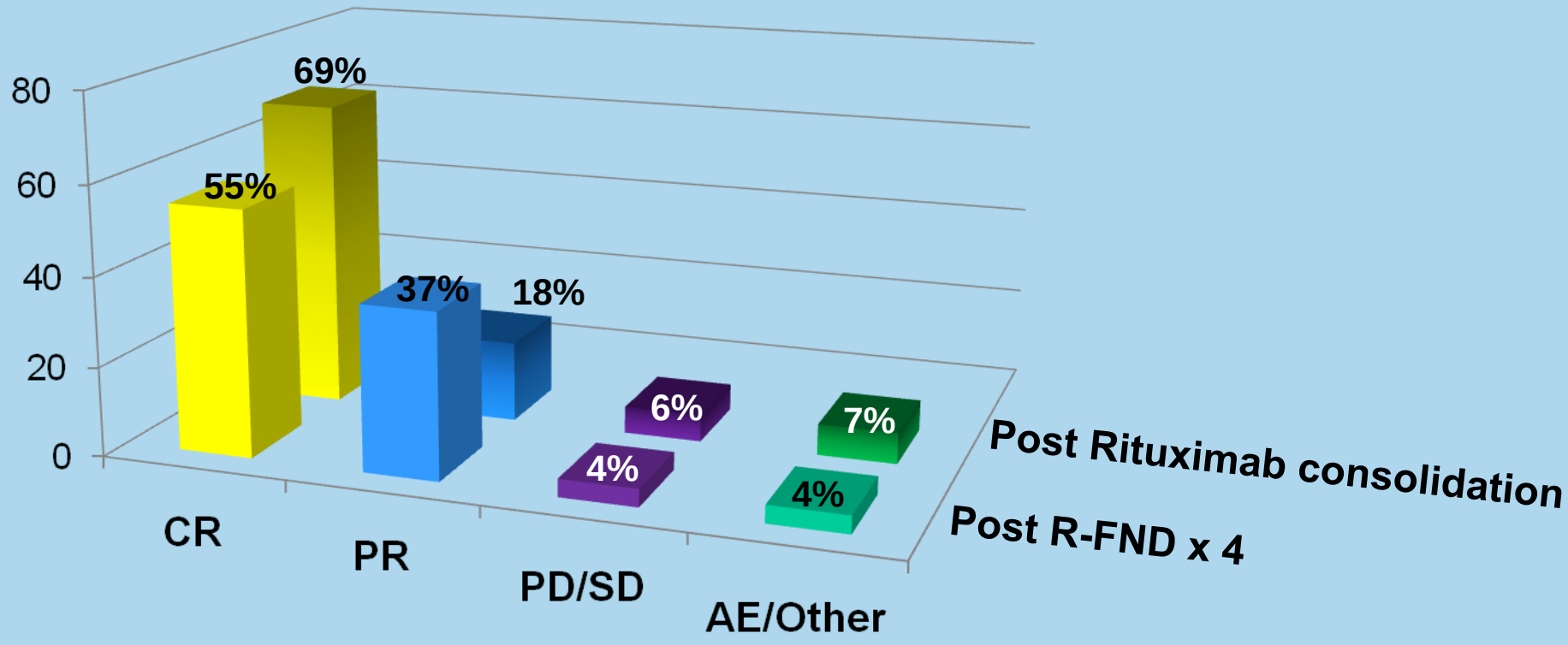
U. Vitolo, et al.



Study ML17638 – IIL FL04

Clinical response to treatment

OVERALL RESPONSE RATE: 86%

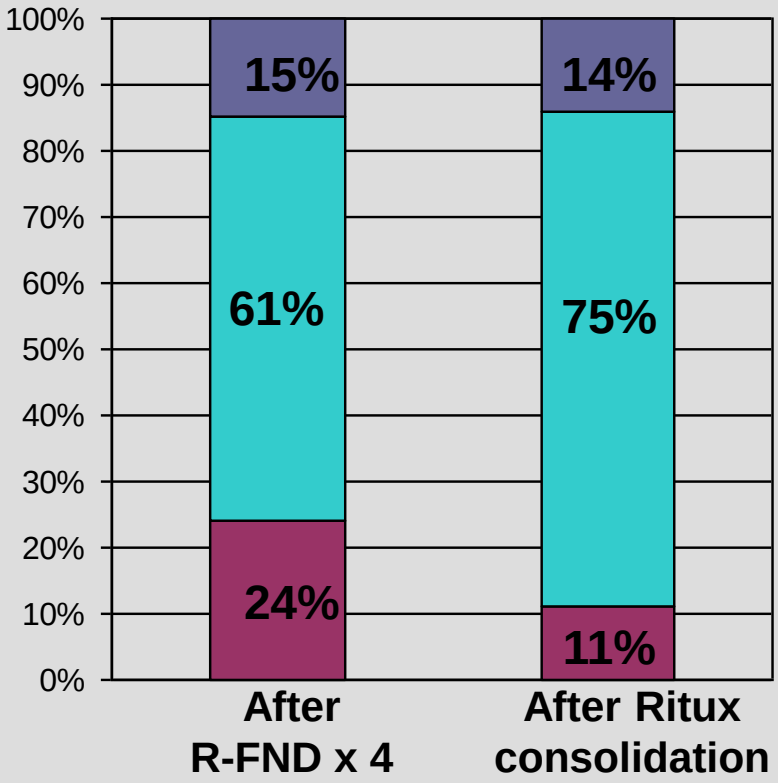


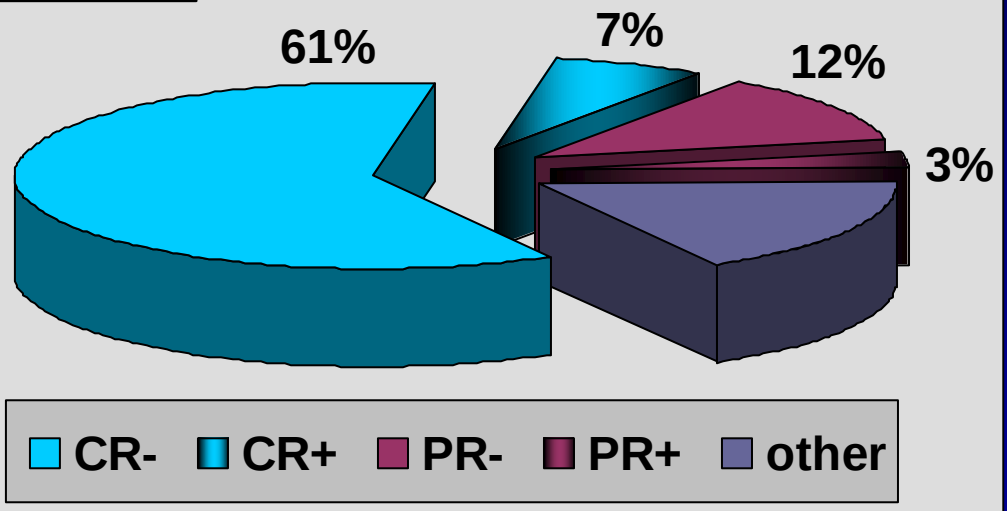
37/90 (41%) PRs after R-FND were converted to CR with R consolidation

Study ML17638 – IIL FL04

bcl2/IgH status on BM at each step of the treatment

114 patients bcl2+ at diagnosis

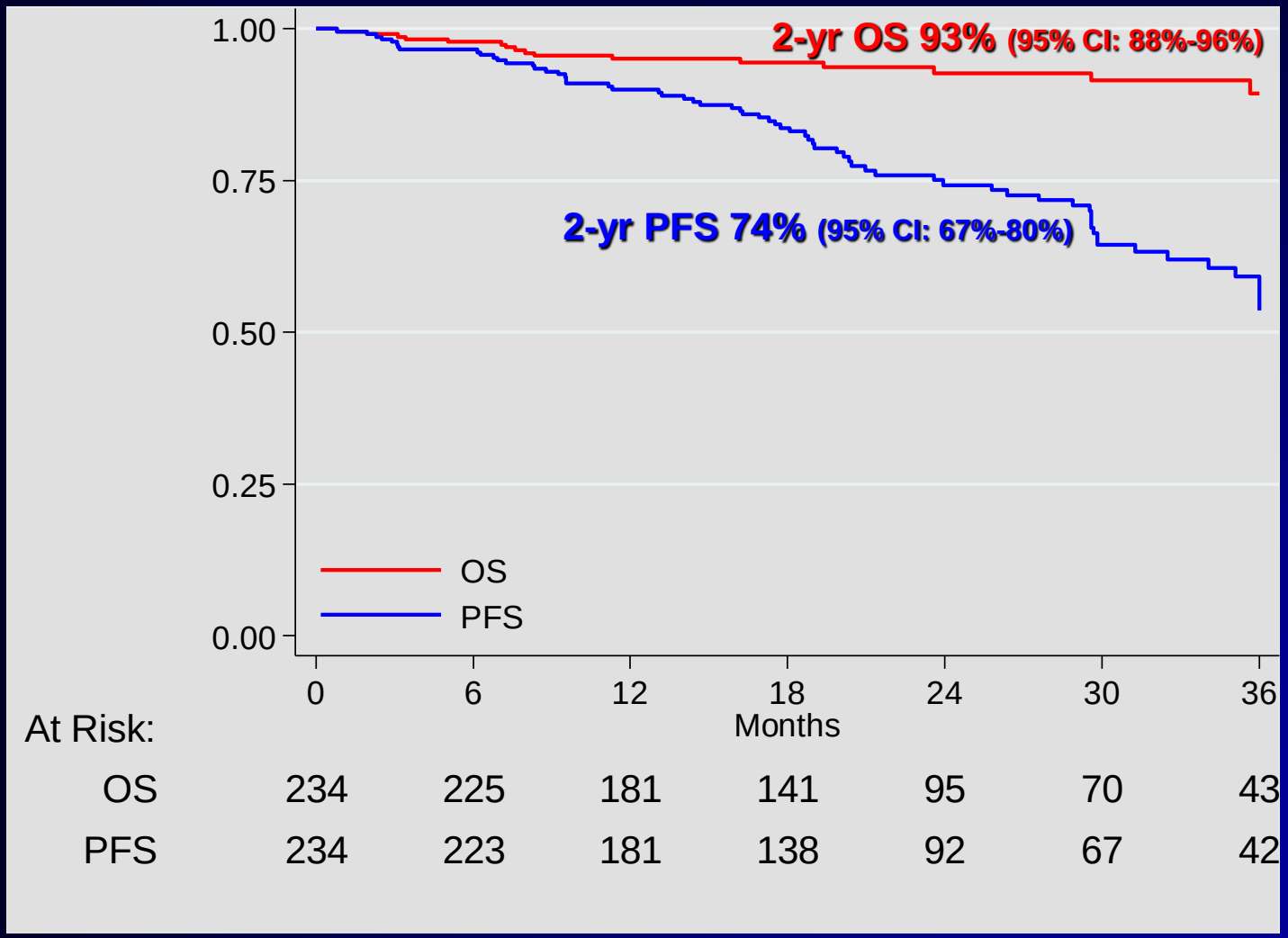




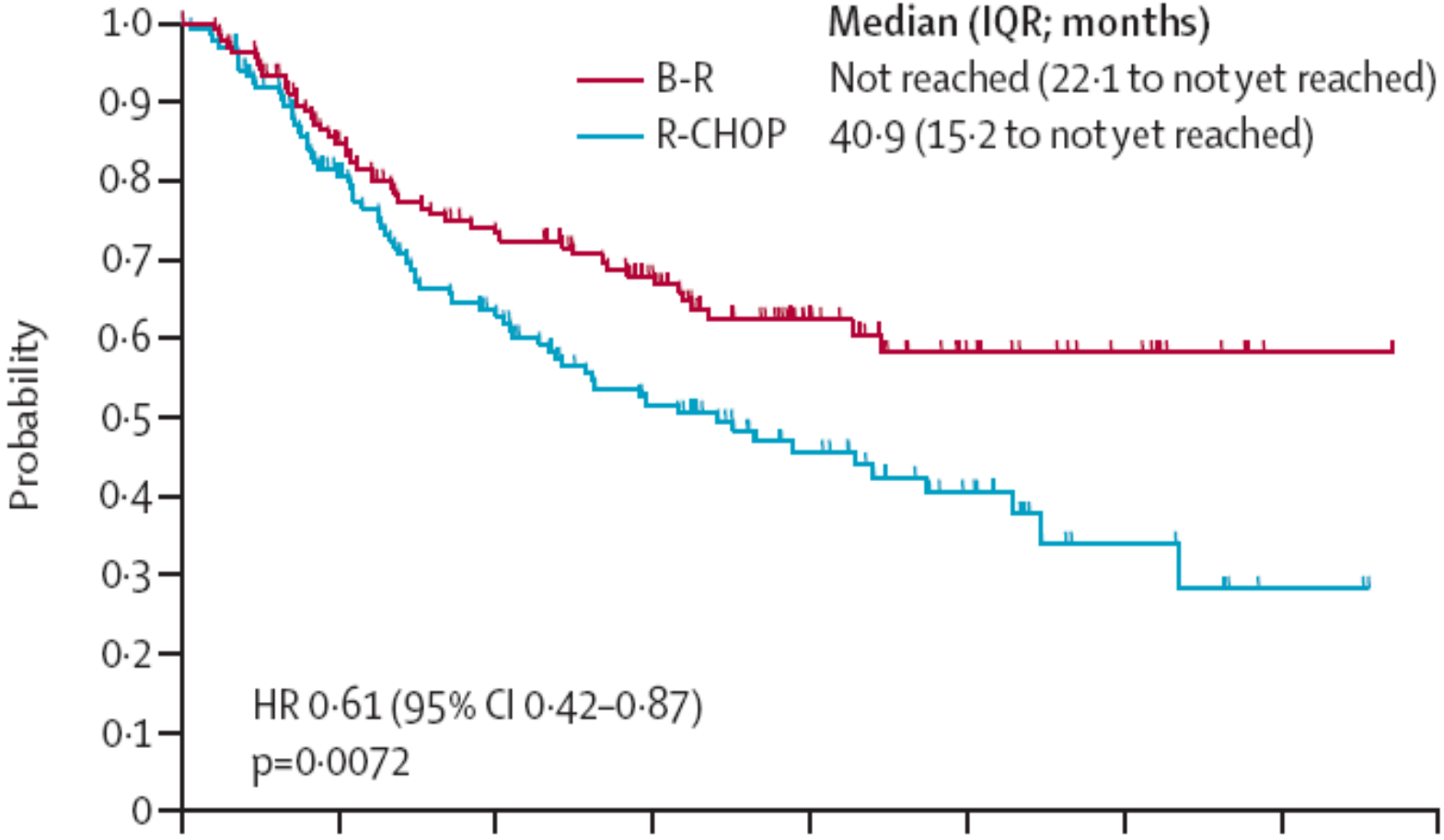
Qualitative PCR analysis

Study ML17638 – IIL FL04

Median follow-up: 19 months



R-Bendamustine versus R-CHOP
Progression free survival follicular lymphoma



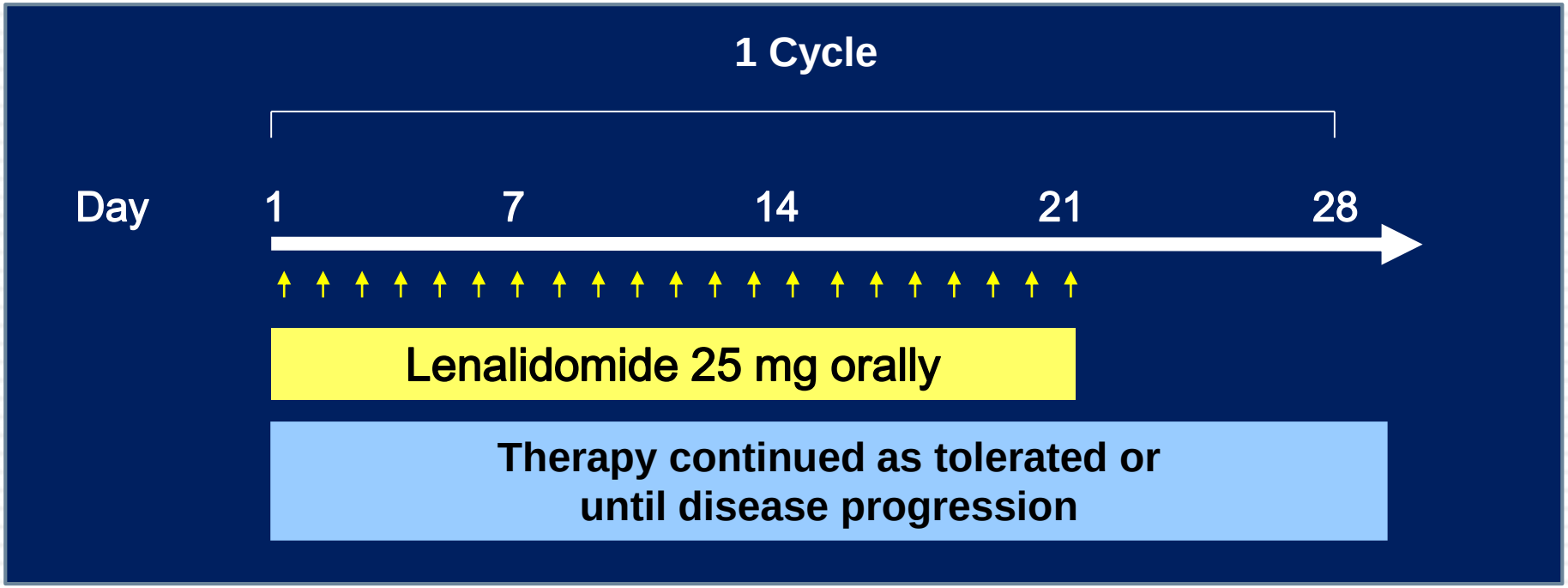
NB: only grade 1-2 follicular lymphoma

Rummel et al.: Lancet , 2013

Results from an international study investigating the efficacy and safety of Lenalidomide in relapsed or refractory aggressive Non-Hodgkin's Lymphoma.

Haioun C, Reeder CB, Polikoff J, Chowhan NM, Esseessee I, Greenberg R, Ervin-Haynes A, Pietronigro D, Zeldis JB, Witzig TE, Czuczman MS.

Study Schema



Response to Lenalidomide: 83 patients

Objective Response	% (n)
Overall Response	29% (24)
CR/CRu	6% (5)
PR	23% (19)
SD	19% (16)

Response to Lenalidomide vs NHL histology

Histology	Objective Response % (n/N)
Mantle cell	36% (8/22)
Mantle cell post-Velcade	50% (3/6)
Diffuse large B-cell	22% (11/49)
Follicular lymphoma, Gr 3	33% (2/6)
Transformed lymphoma	50% (3/6)

MCL: Lenalidomide

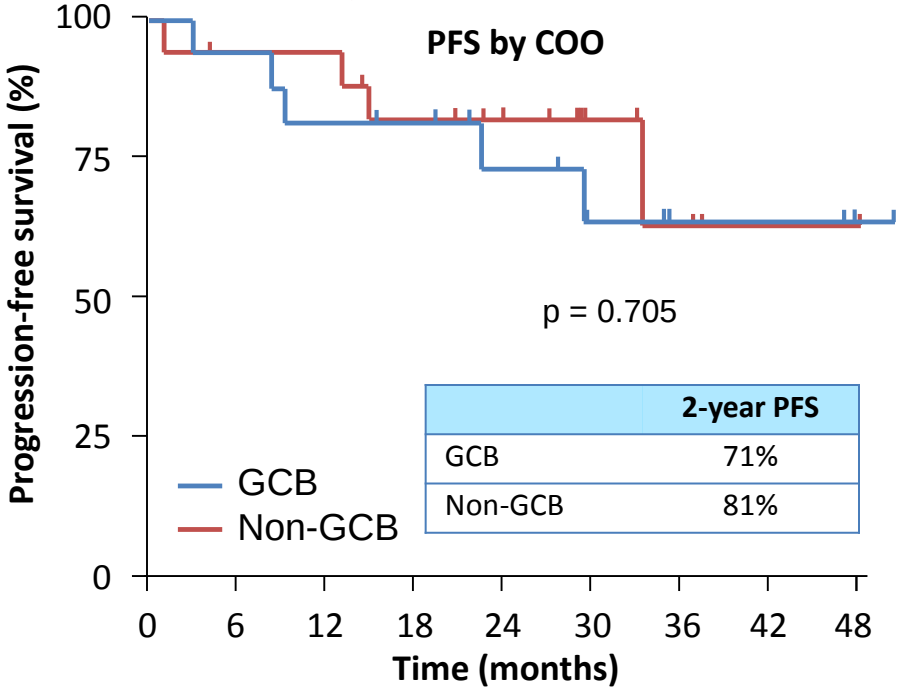
Trial	NHL-002[1] (MCL subset)	NHL-003[2] (MCL subset)	FIL – MCL[3] study Salvage therapy	Wang et al.,[4,5]
Phase	**Phase 2**	**Phase 2**	**Phase 2**	**Phase 1/2**
Treatment	**lenalidomide**	**Lenalidomide**	**lenalidomide plus dexamethasone***	**lenalidomide plus rituximab****
Lenalidomide Dose	25mg d1-21/ 28d cycle	25mg d1-21/ 28d cycle	25mg d1-21/ 28d cycle	20mg d1-21/28d cycle
Efficacy data				
Response rates	**ORR = 53%** **CR/CRu = 20%**	**ORR = 42%** **CR/CRu = 21%**	**ORR = 52%** **CR/CRu = 24%**	**ORR = 57%** **CR/CRu = 36%**
median PFS	**5.6mo**	**5.7mo**	**12mo**	**11.1mo**
median DOR	**13.7mo**	**NR**	**18mo20mo**	**18.9mo**
median OS	**ND**	**ND**		**24.3mo**

*: 40mg d1-8-15-22 / 28d cycle; **: 375 mg/m^2 once weekly for 4 weeks during cycle 1
CR: complete response; DOR: median duration of response; MCL: Mantle cell lymphoma; ND: not determined; NR: not reached; NHL: Non-Hodgkin lymphoma; ORR: overall response rate; PFS: median progression-free survival

1: Habermann et al (2009) *Brit J Haematol* 145: 344-9; 2 Zinzani et al (2013) *Ann Oncol* 24: 2892-7; 3: Zaja et al (2012) *Haematologica* 97: 416-22; 4: Wang et al., *Lancet Oncol.* (2012) 13: 716-23; 5: Wang et al., Oral presentation at ICML, (2011) *Ann Oncol* 22(suppl 4): iv119

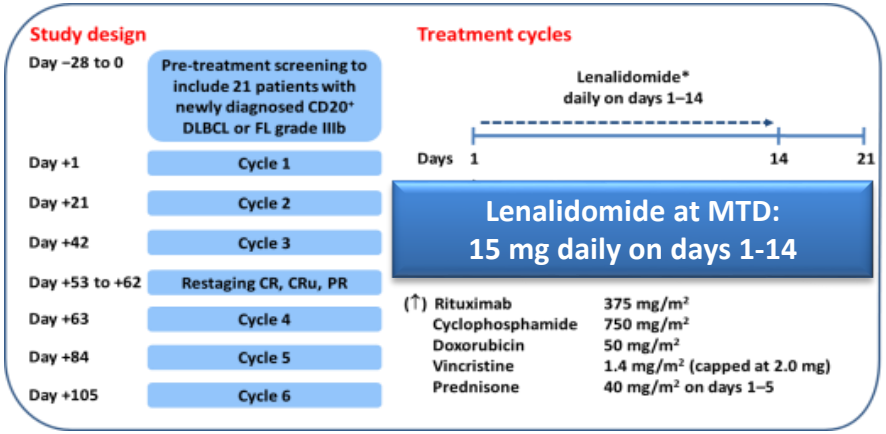
Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

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



At risk, n

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

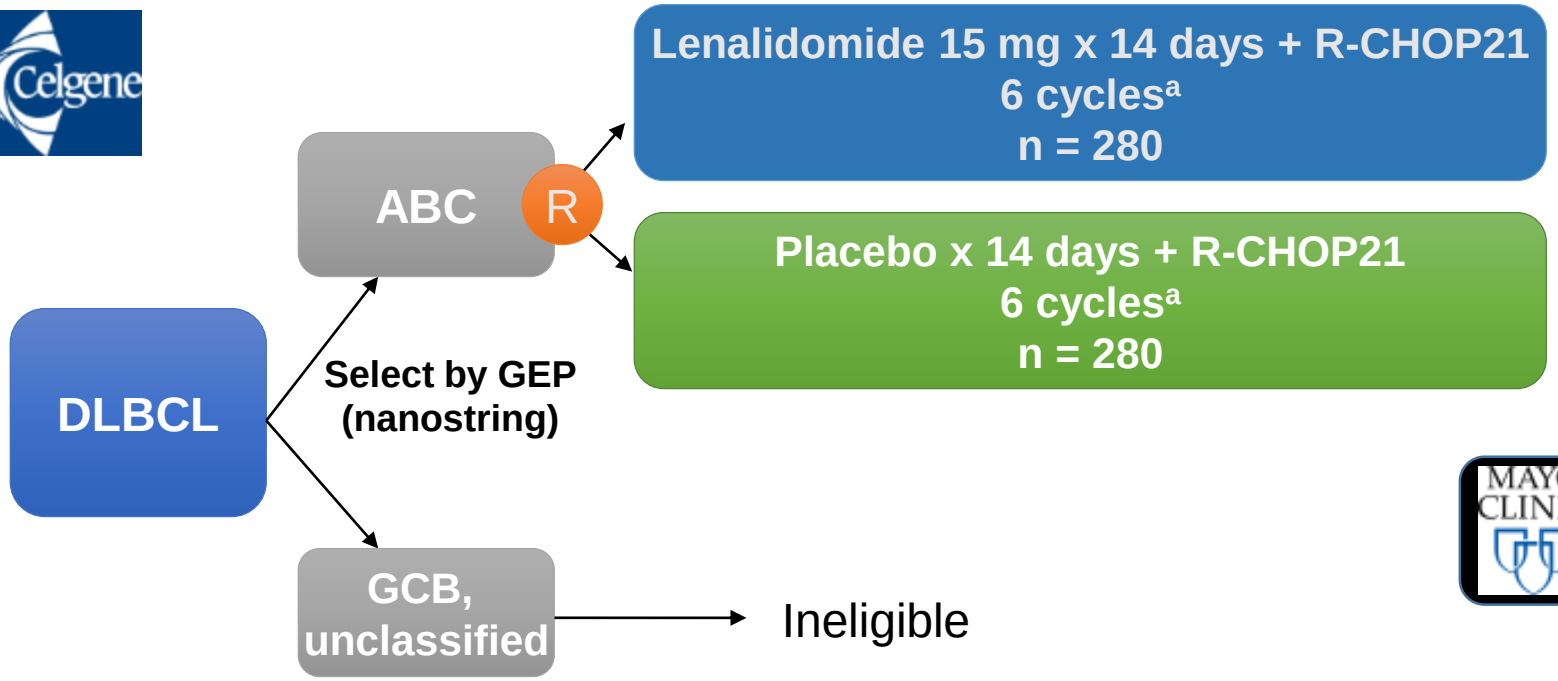


CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

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

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

Randomized phase II trial on primary chemotherapy (CHT) with high-dose methotrexate (Mtx) alone or associated with high-dose cytarabine (AraC) for patients with primary CNS lymphoma (PCNSL).

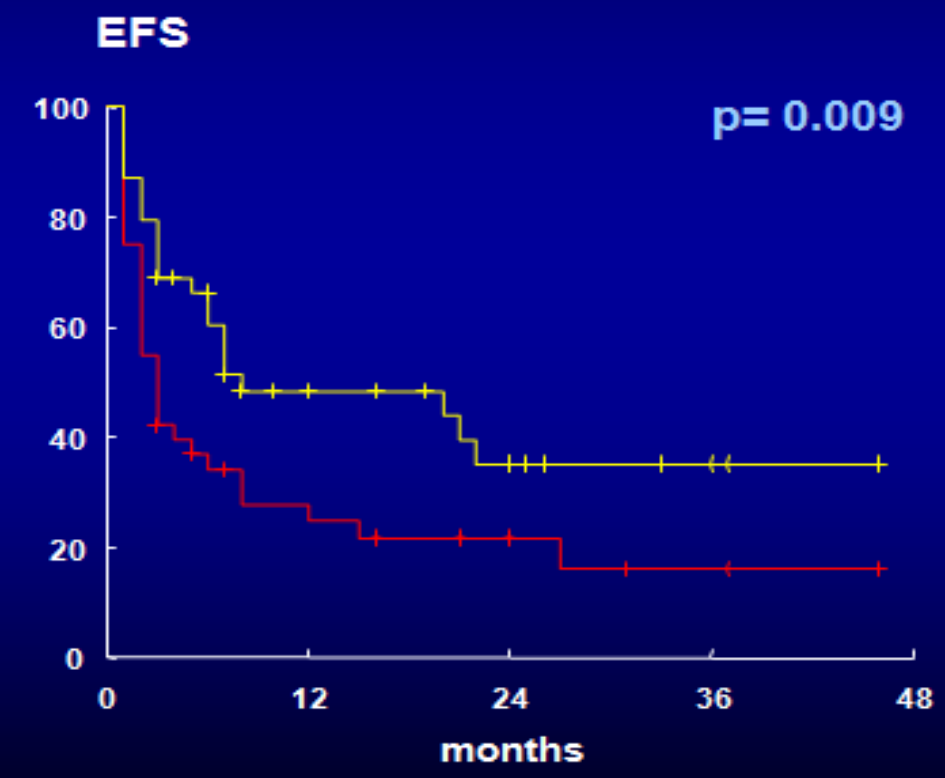
Ferreri AJM, Foppoli M, Martelli M, Pangalis G, Frezzato M, Cabras G, Fabbri A, Corazzelli G, Ilariucci F, Rossi G, Soffietti R, Stelitano C, Vallisa D, Zaja F, Zoppegno L, Aondio G, Annibali O, Balzarotti M, Brandes A, Fajardo J, Gómez H, Guarini A, Pinotti G, Rigacci L, Uhlmann C, Ponzoni M, Reni M, Zucca E, and Cavalli F.

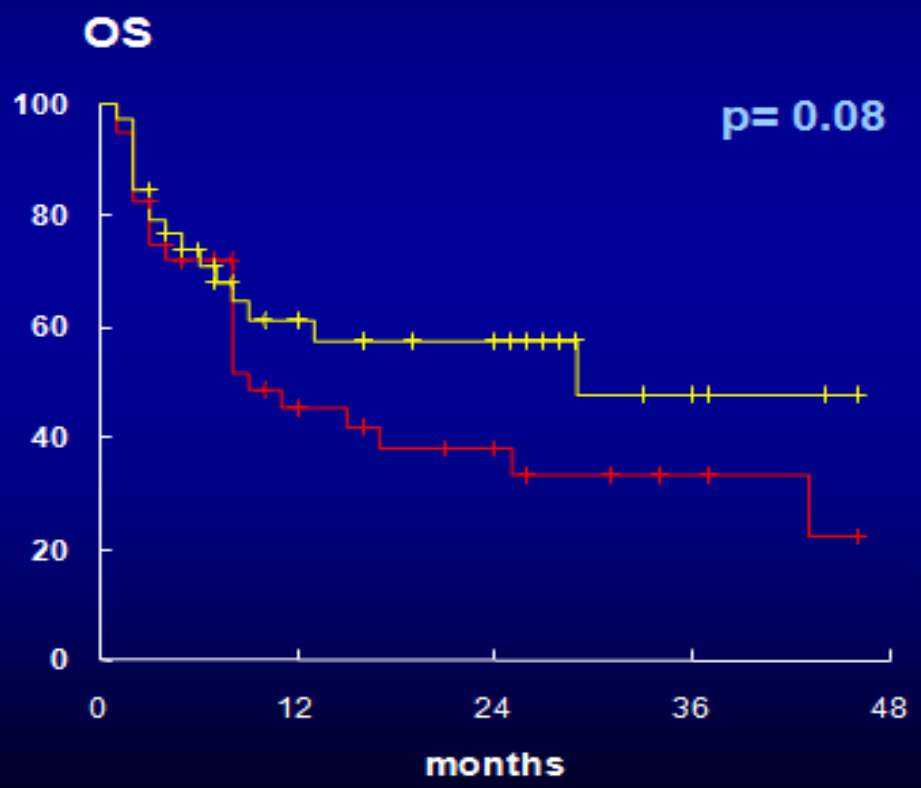
Study IELSG 20

Median f-up: 16 months

MTX + araC (n= 39)

MTX (n= 40)

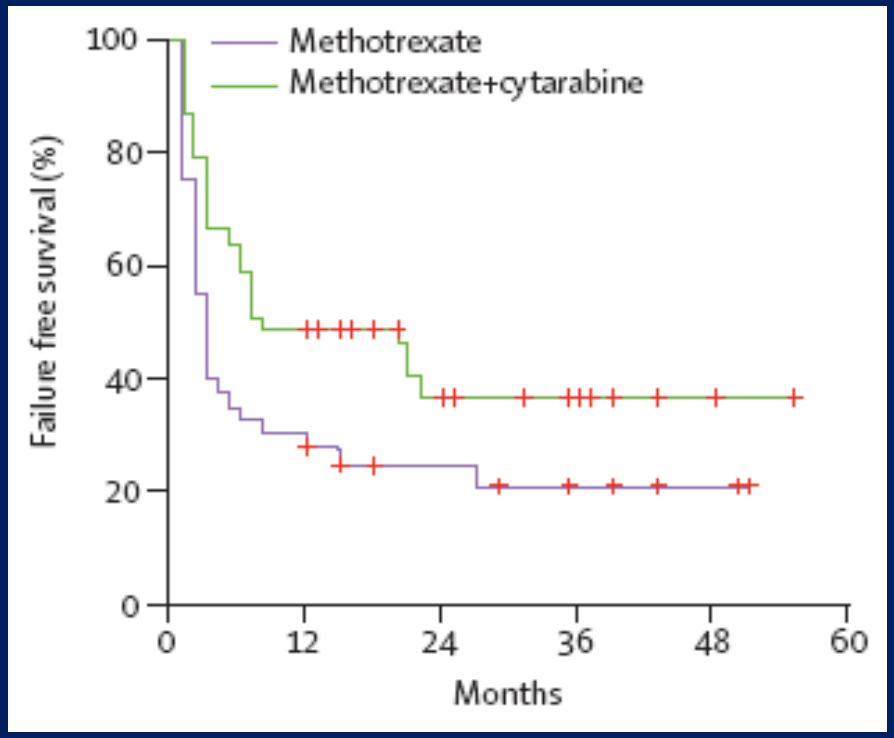


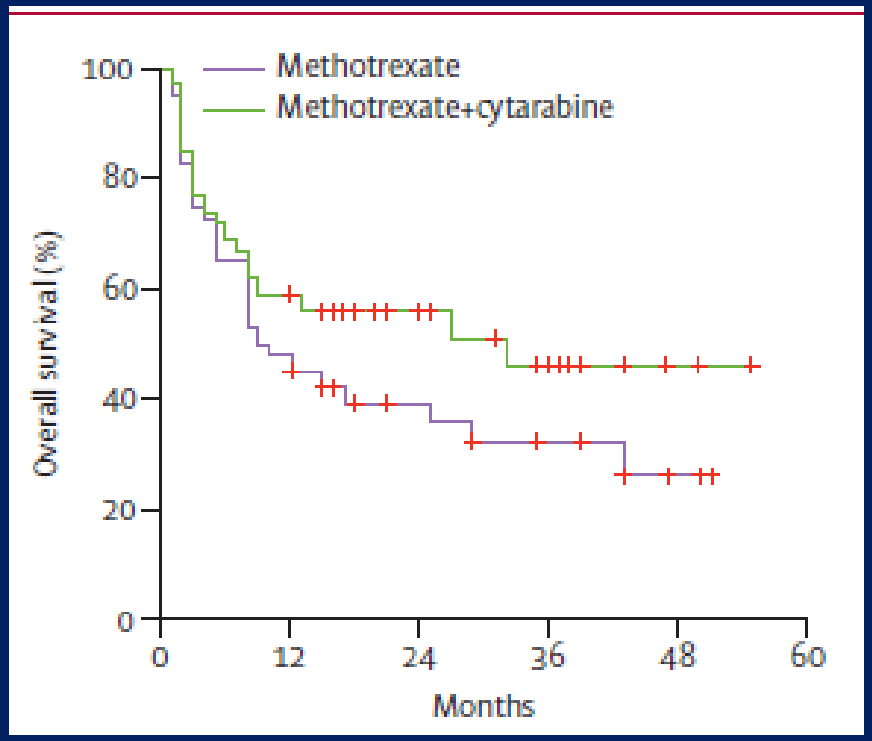


High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

Andrés J M Ferreri, Michele Reni, Marco Foppoli, Maurizio Martelli, Gerasimus A Pangalis, Maurizio Frezzato, Maria Giuseppina Cabras, Alberto Fabbri, Gaetano Corazzelli, Fiorella Ilariucci, Giuseppe Rossi, Riccardo Soffietti, Caterina Stelitano, Daniele Vallisa, Francesco Zaja, Lucía Zoppegno, Gian Marco Aondio, Giuseppe Avvisati, Monica Balzarotti, Alba A Brandes, José Fajardo, Henry Gomez, Attilio Guarini, Graziella Pinotti, Luigi Rigacci, Catrina Uhlmann, Piero Picozzi, Paolo Vezzulli, Maurilio Ponzoni, Emanuele Zucca, Federico Caligaris-Cappio, Franco Cavalli, on behalf of the International Extranodal Lymphoma Study Group

Lancet 2009; 374: 1512–20





Median follow-up: 30 months

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008	*Gubbio, 18-19 Settembre 2009*
Stresa 17-18 Settembre 2010	*Gubbio, 23-24 Settembre 2011*
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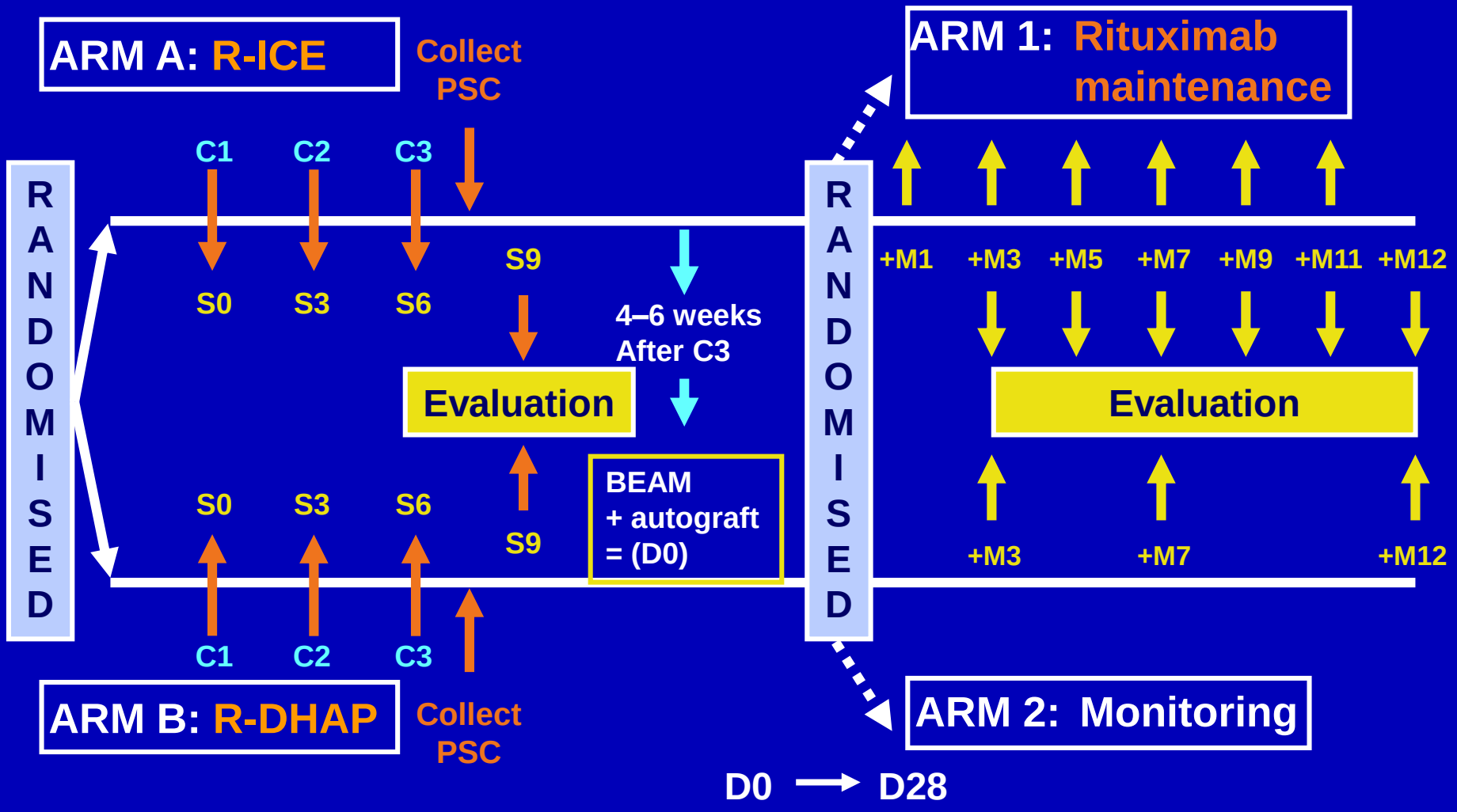
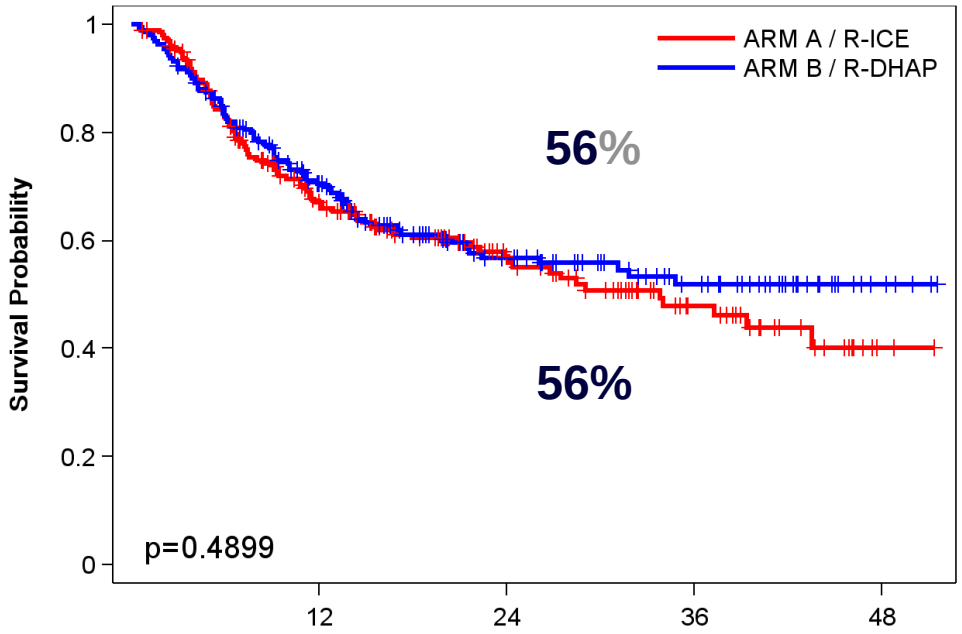
Firenze 19-20 Settembre 2014	*Firenze 18-19 Settembre 2015*

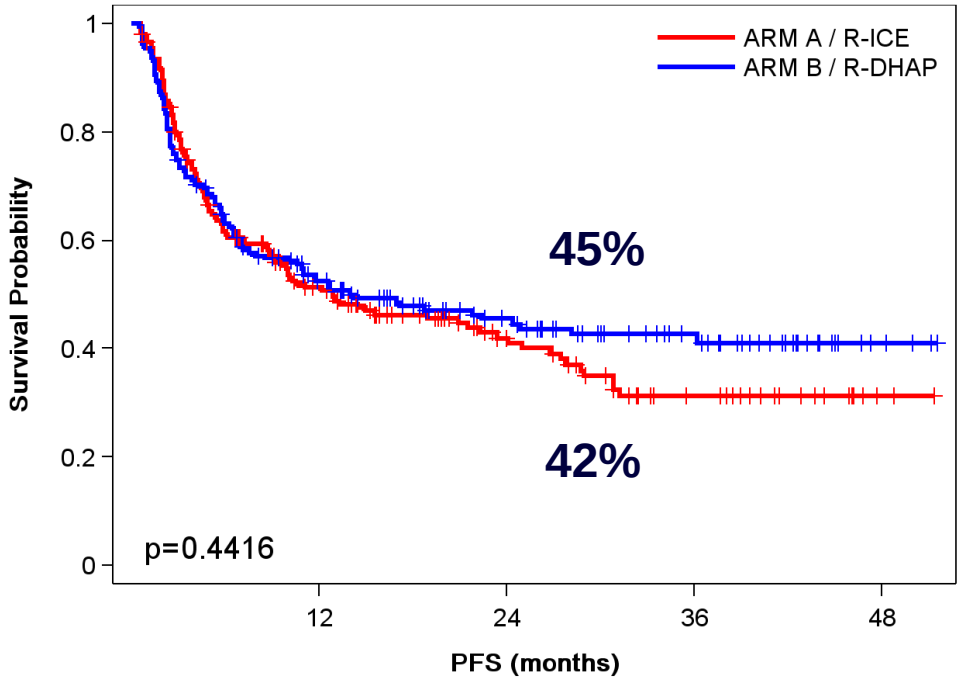
RR/ DLBCL: CORAL trial (GELA and others): R-ICE vs R-DHAP



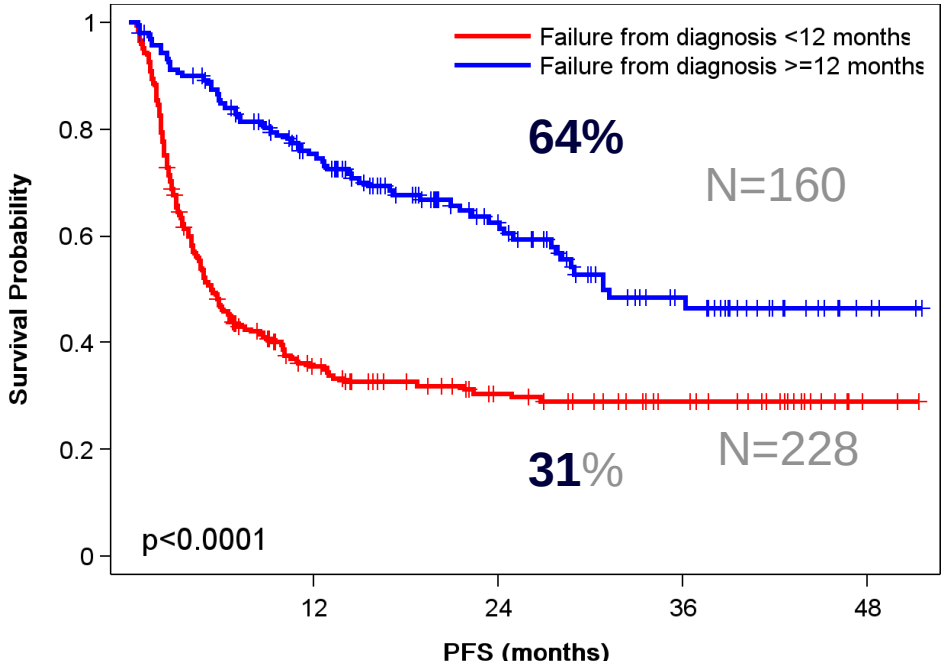
By Courtesy of Christian Gisselbrecht



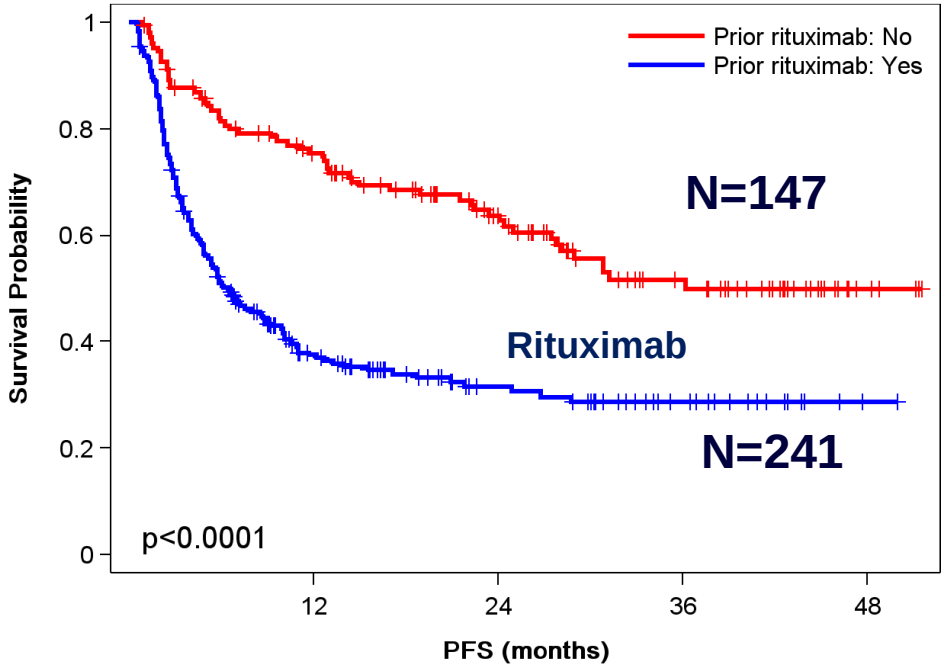
OVERALL SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)



PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)



PROGRESSION-FREE SURVIVAL ACCORDING TO FAILURE FROM DIAGNOSIS (INDUCTION ITT)



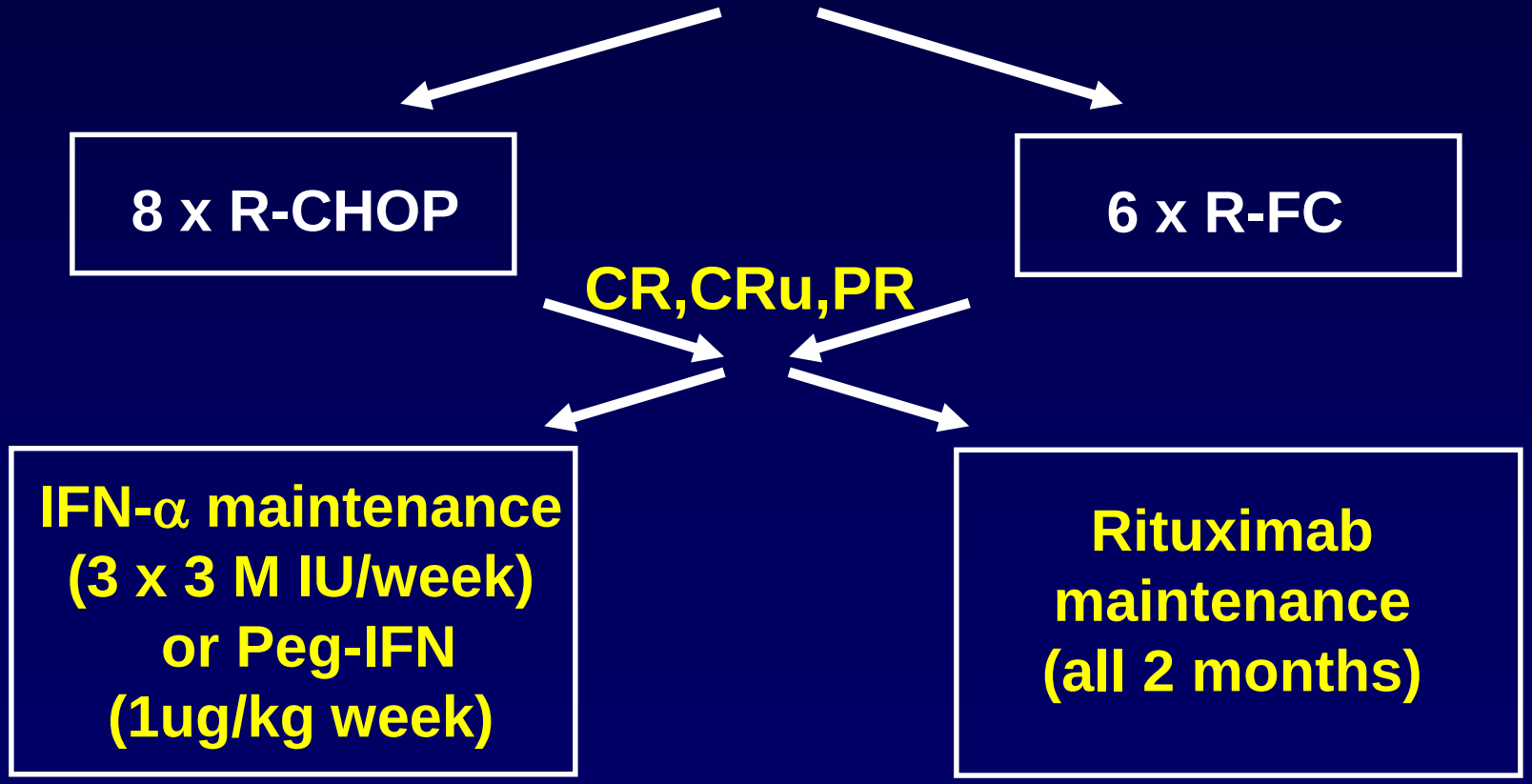
PROGRESSION-FREE SURVIVAL ACCORDING TO PRIOR RITUXIMAB (INDUCTION ITT)

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008	*Gubbio, 18-19 Settembre 2009*
Stresa 17-18 Settembre 2010	*Gubbio, 23-24 Settembre 2011*
Matera 15 -16 Settembre 2012	*Firenze 20-21 Settembre 2013*
Firenze 19-20 Settembre 2014	*Firenze 18-19 Settembre 2015*

First RCT for MCL Elderly

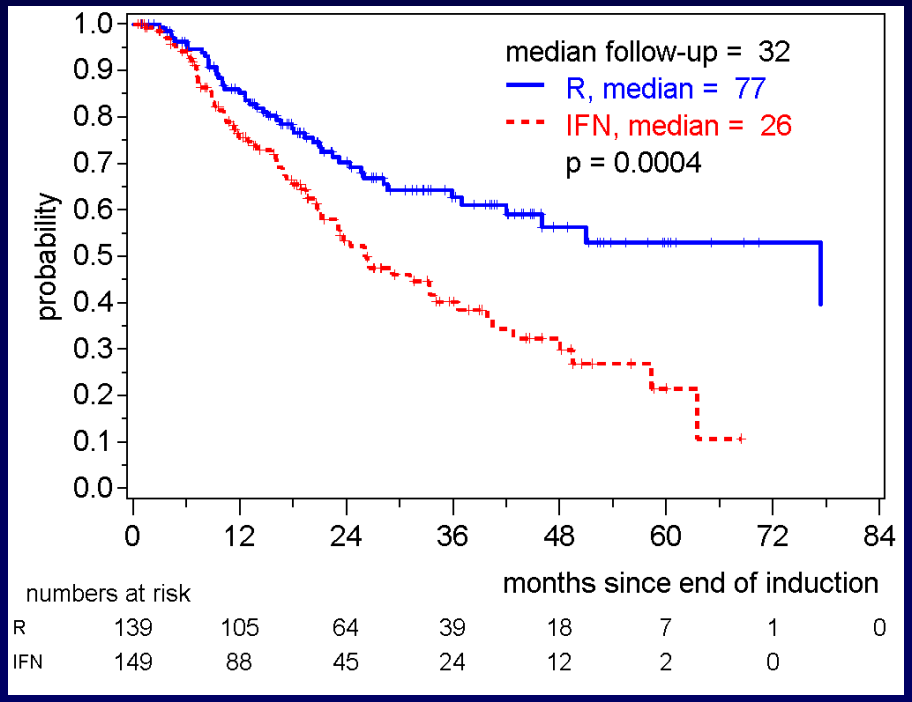
8 countries, n = 560 (Jan 2004-Oct 2010)

Newly diagnosed, >60-65 yr; performance 0-2, Stages II-IV, central PA review

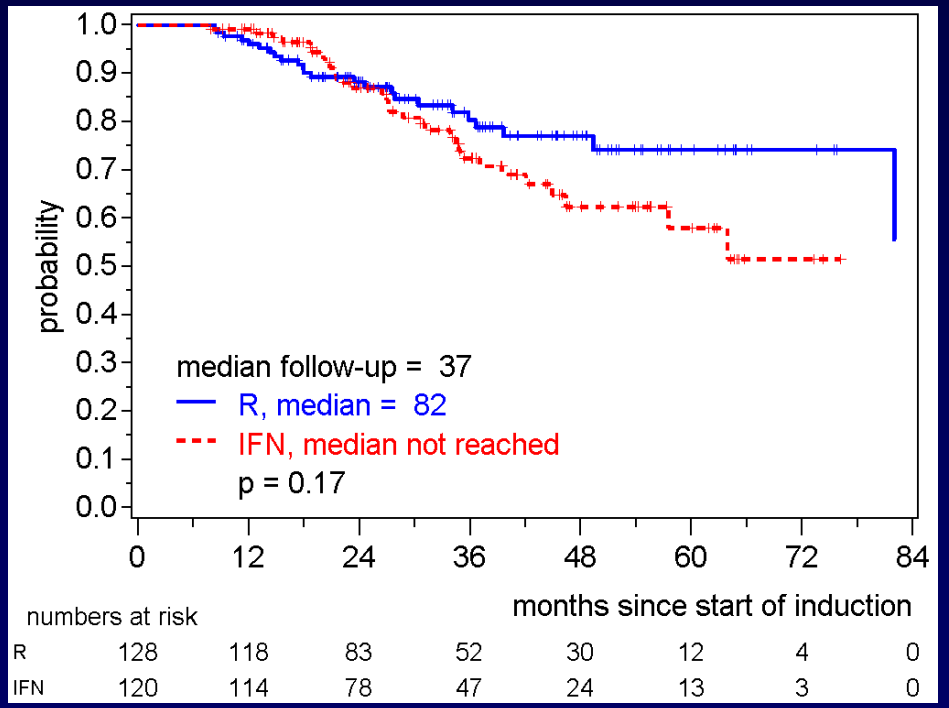


MCL Elderly study
Remission duration maintenance

Remission duration maintenance



Overall survival maintenance



The NEW ENGLAND JOURNAL of MEDICINE

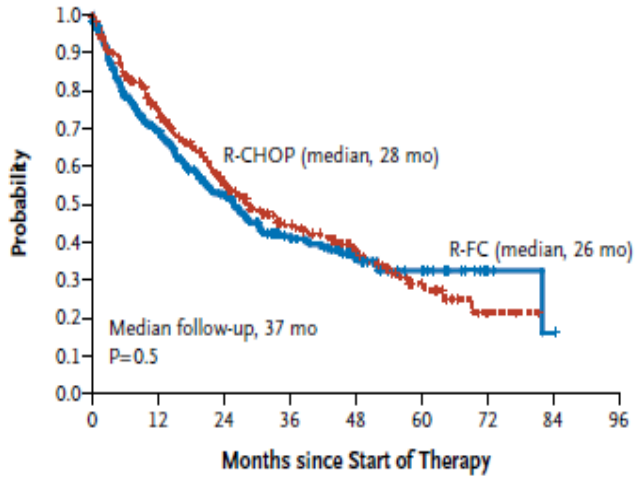
ORIGINAL ARTICLE

Treatment of Older Patients with Mantle-Cell Lymphoma

H.C. Kluin-Nelemans, E. Hoster, O. Hermine, J. Walewski, M. Trneny, C.H. Geisler, S. Stilgenbauer, C. Thieblemont, U. Vehling-Kaiser, J.K. Doorduijn, B. Coiffier, R. Forstpointner, H. Tilly, L. Kanz, P. Feugier, M. Szymczyk, M. Hallek, S. Kremers, G. Lepeu, L. Sanhes, J.M. Zijlstra, R. Bouabdallah, P.J. Lugtenburg, M. Macro, M. Pfreundschuh, V. Procházka, F. Di Raimondo, V. Ribrag, M. Uppenkamp, M. André, W. Klapper, W. Hiddemann, M. Unterhalt, and M.H. Dreyling

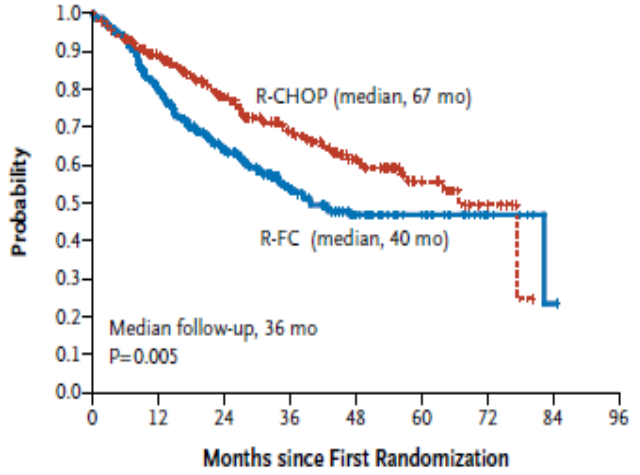
NEJM 2012;367:520-31

A Time to Treatment Failure



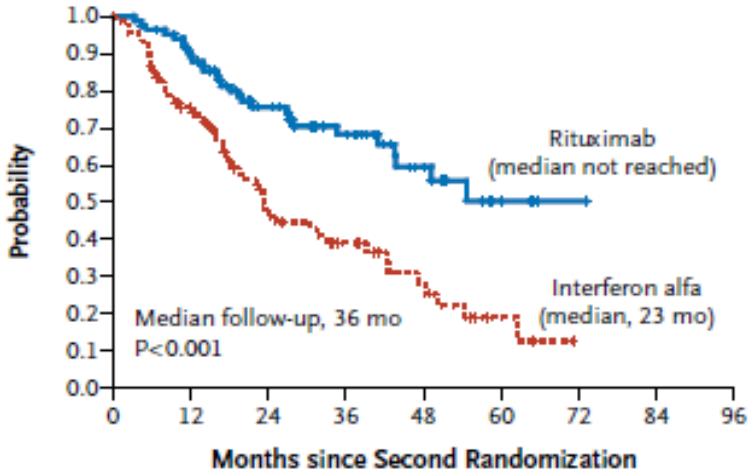
No. at Risk									
R-FC	276	164	104	61	36	18	3	1	0
R-CHOP	274	179	107	64	36	16	2	0	

B Overall Survival



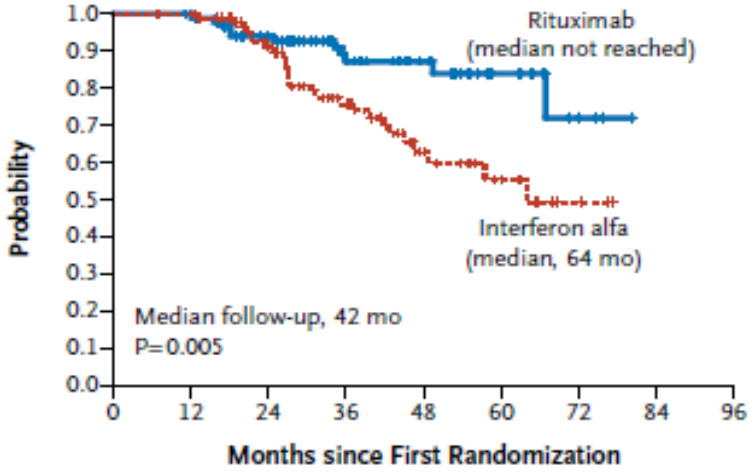
No. at Risk									
R-FC	280	196	123	74	46	25	7	1	0
R-CHOP	280	214	150	95	55	26	8	0	

B Remission Duration, Patients Assigned to R-CHOP



No. at Risk								
Rituximab	87	72	48	32	17	4	1	0
Interferon alfa	97	63	29	18	10	3	0	

D Overall Survival, Patients Assigned to R-CHOP



No. at Risk								
Rituximab	87	86	71	46	30	13	3	0
Interferon alfa	97	92	65	43	22	11	3	0

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008	*Gubbio, 18-19 Settembre 2009*
Stresa 17-18 Settembre 2010	*Gubbio, 23-24 Settembre 2011*
Matera 15 -16 Settembre 2012	*Firenze 20-21 Settembre 2013*
Firenze 19-20 Settembre 2014	*Firenze 18-19 Settembre 2015*

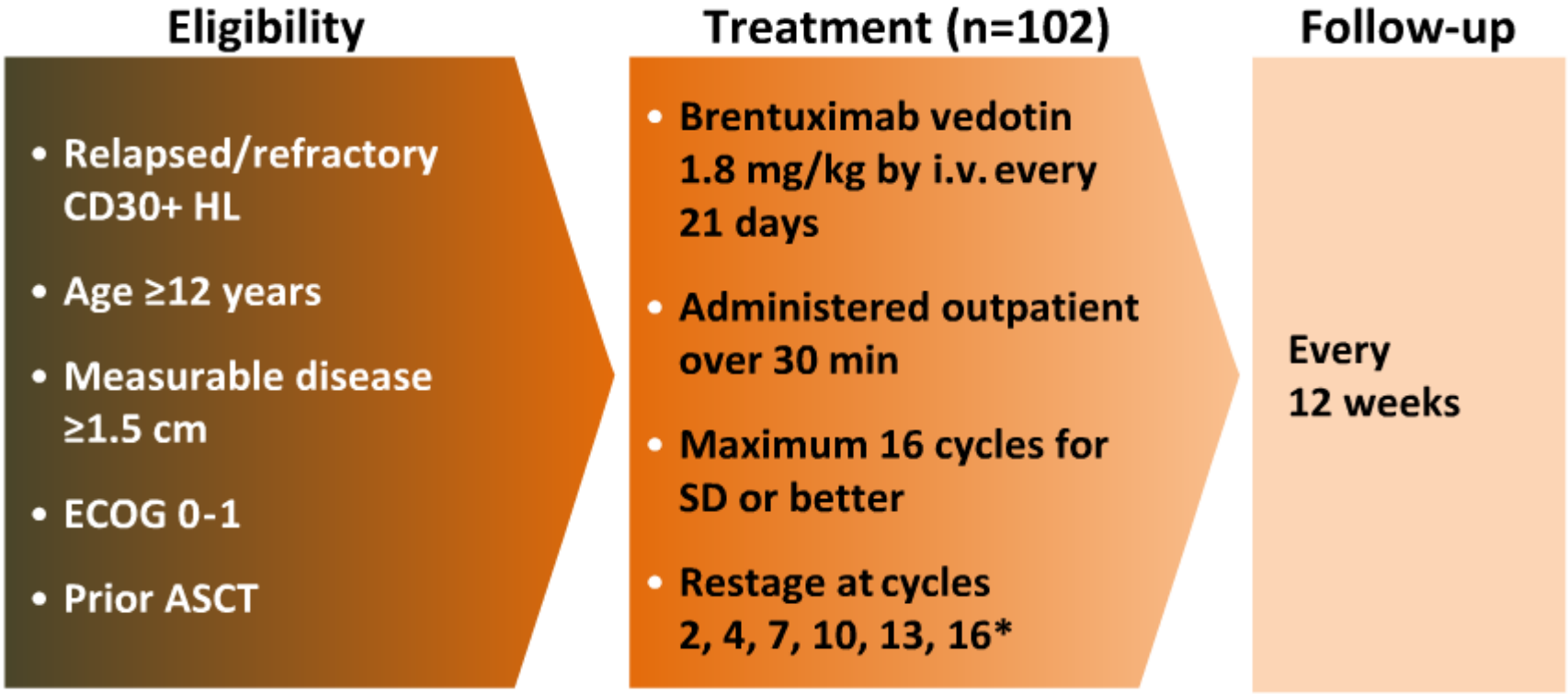
Long term follow up results of an ongoing PIVOTAL study of Brentuximab vedotin in patients with relapsed or refractory Hodgkin Lymphoma (HL)

S.Smith

Smith et al EHA 2012 abs 1109 oral session

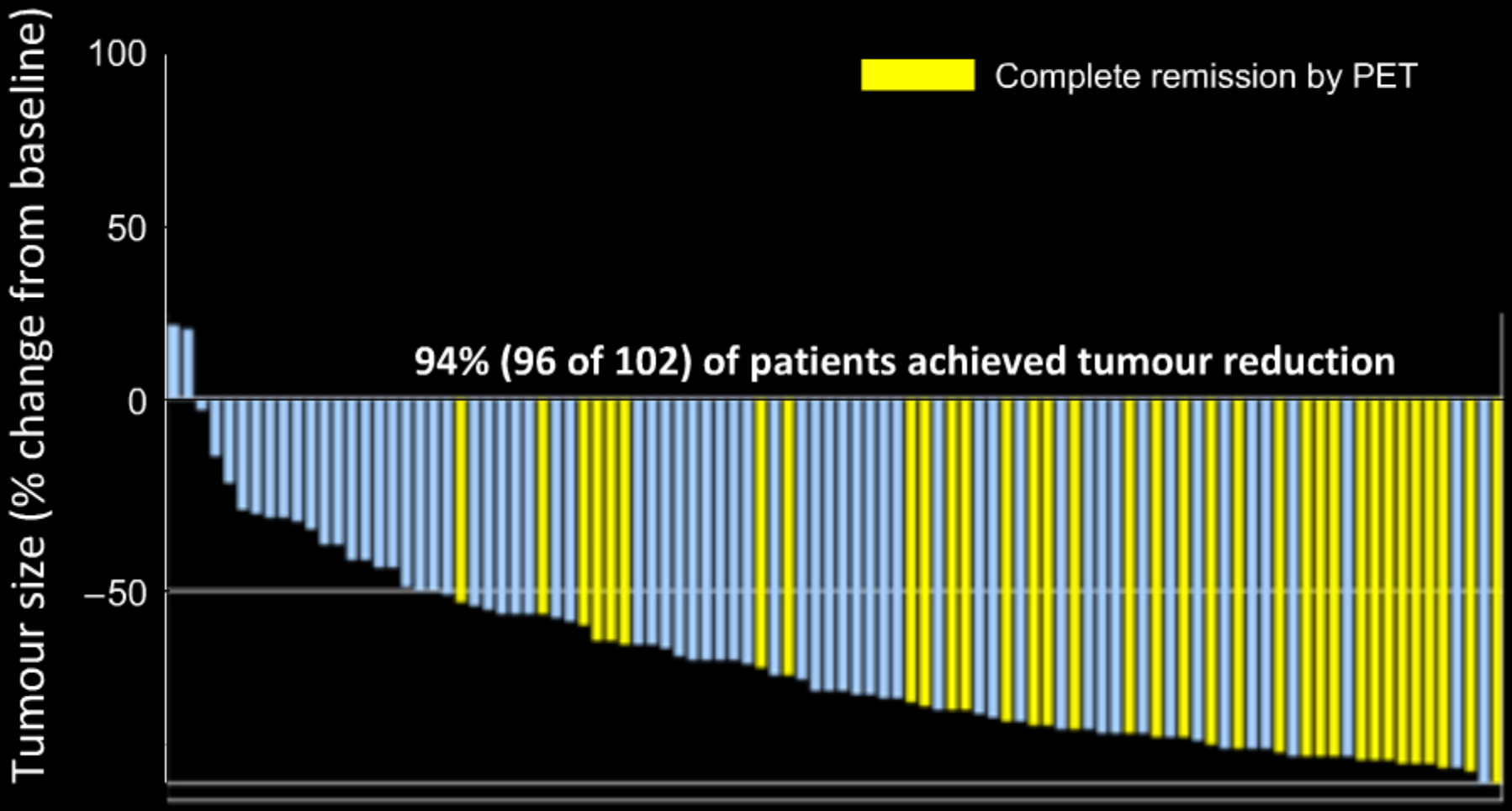
Brentuximab vedotin: pivotal Phase II trial

- 102 patients with relapsed/refractory HL post-autologous stem cell transplantation (ASCT)



*restaged according to Revised Response Criteria for malignant lymphomas (Cheson et *al*. (2007).

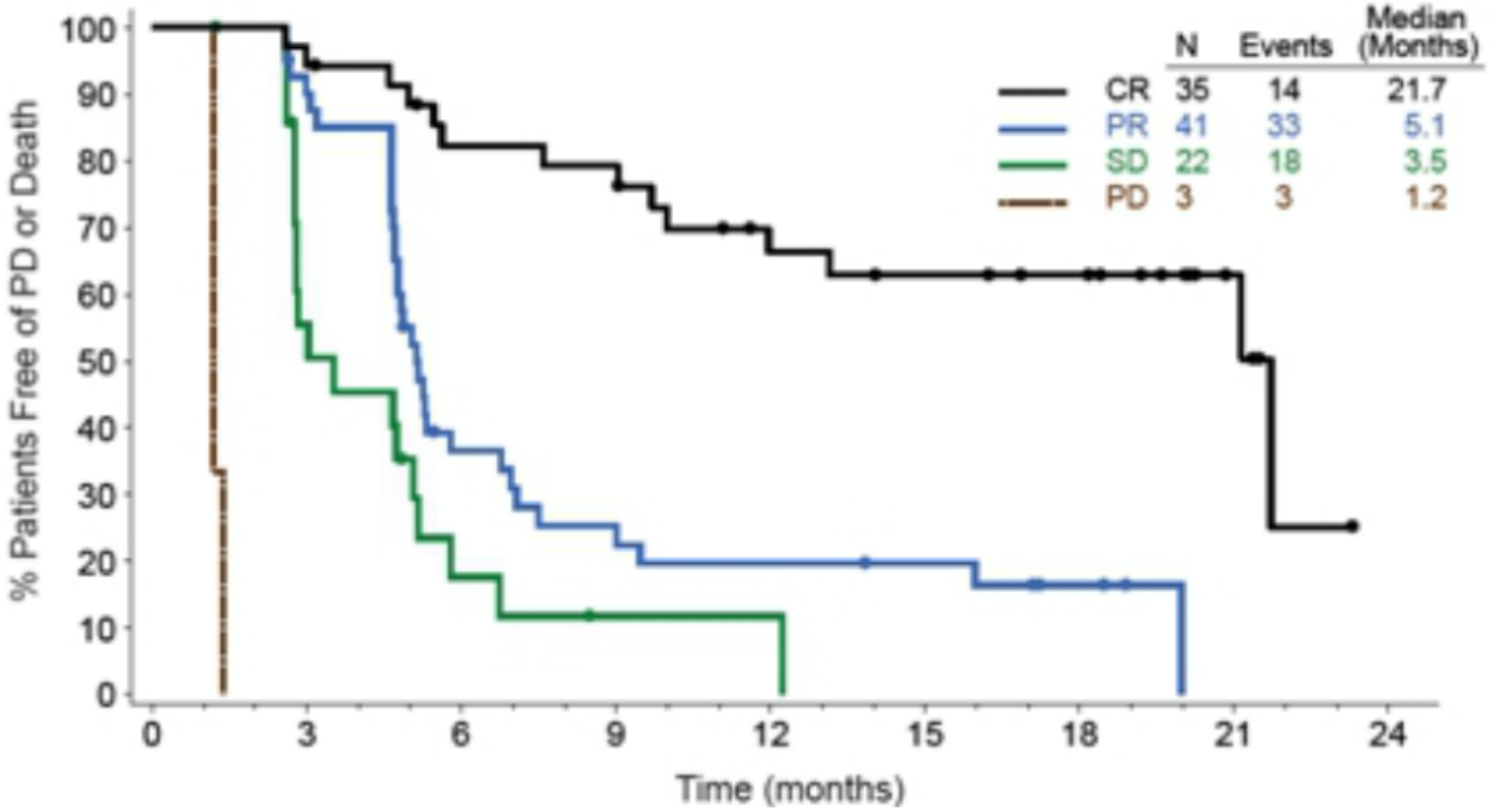
Brentuximab vedotin: pivotal Phase II trial maximum tumour reduction per IRF



Smith et al EHA 2012 abs 1109 oral session

Brentuximab vedotin: pivotal Phase II trial PFS results by best response

- Phase II pivotal study of brentuximab vedotin in 102 patients with relapsed/refractory HL post ASCT: PFS by best response



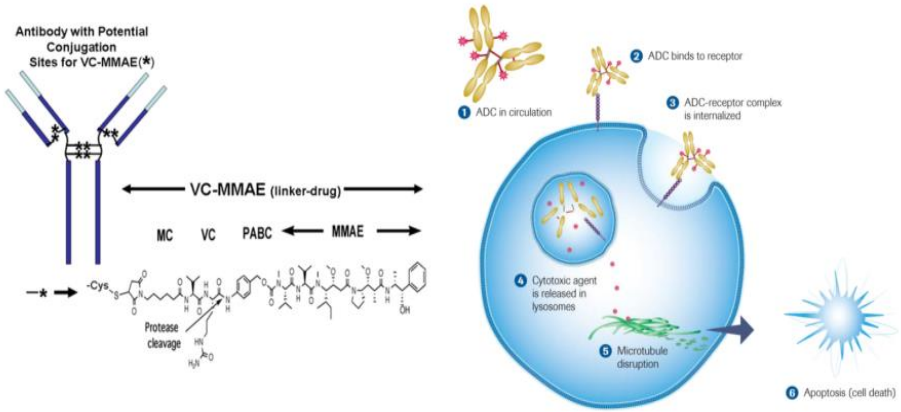
Smith et al EHA 2012 abs 1109 oral session

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008	*Gubbio, 18-19 Settembre 2009*
Stresa 17-18 Settembre 2010	*Gubbio, 23-24 Settembre 2011*
Matera 15 -16 Settembre 2012	*Firenze 20-21 Settembre 2013*
Firenze 19-20 Settembre 2014	*Firenze 18-19 Settembre 2015*

Polatuzomab Vedotin

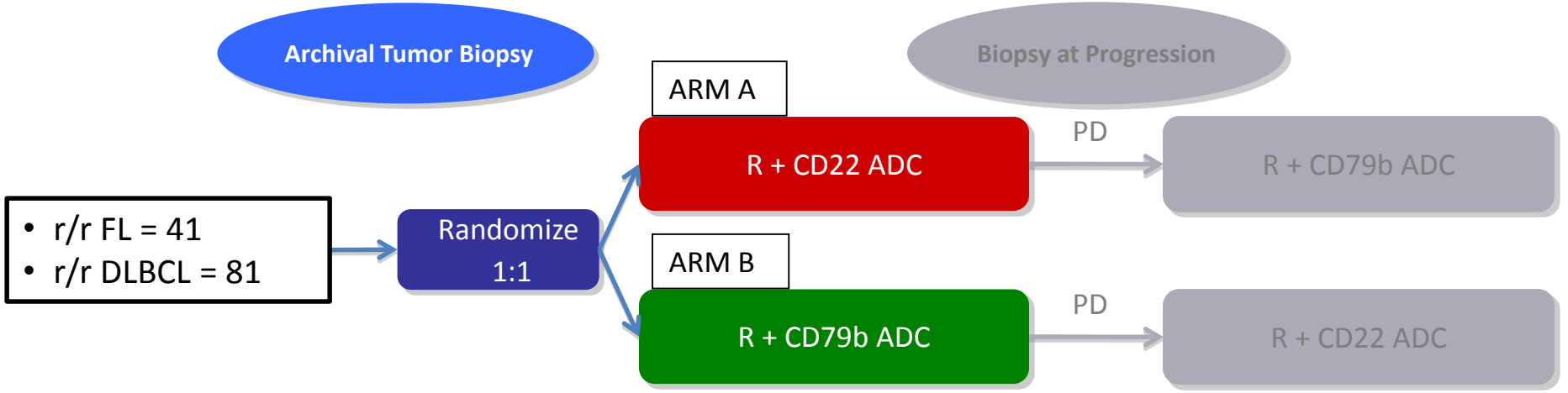
Preliminary Results of a Phase II Randomized Study (ROMULUS) of Polatuzumab Vedotin or Polatuzumab Vedotin Plus Rituximab in Patients with Relapsed/Refractory NHL

Morschhauser F, et Al.



- ADC consisting of the microtubule inhibitor MMAE conjugated to anti-CD22 and CD79b monoclonal Ab via a protease-cleavable peptide linker
- CD22 and CD79b are expressed by most B-cell hematologic malignancies
- Both ADCs have shown clinical activity in Phase I studies

TRIAL DESIGN



Rituximab (R) (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles up to one year

Polatuzomab Vedotin

RESPONSE ANALYSIS

	DLBCL		FL	
	R+CD22 ADC (N=42)	R+CD79b ADC (N=39)	R+CD22 ADC (N=21)	R+CD79b ADC (N=20)
Objective response, n (%)	**24 (57%)**	**22 (56%)**	**13 (62%)**	**14 (70%)**
Complete Response	10 (24%)	6 (15%)	2 (10%)	8 (40%)
Partial Response	14 (33%)	16 (41%)	11 (52%)	6 (30%)
Stable disease, n (%)	3 (7%)	4 (10%)	6 (29%)	6 (30%)
Progressive disease, n (%)	7 (21%)	11 (30%)	1 (5%)	0
Unable to evaluate, n (%)	8 (19%)	2 (5%)	1 (5%)	0
Median Duration of Response, mo. (95% CI)	6.0 (2.9-12.2)	NR (2.6-NR)	5.8 (2.6-10.1)	NR (5.7-NR)

TOXICITIES

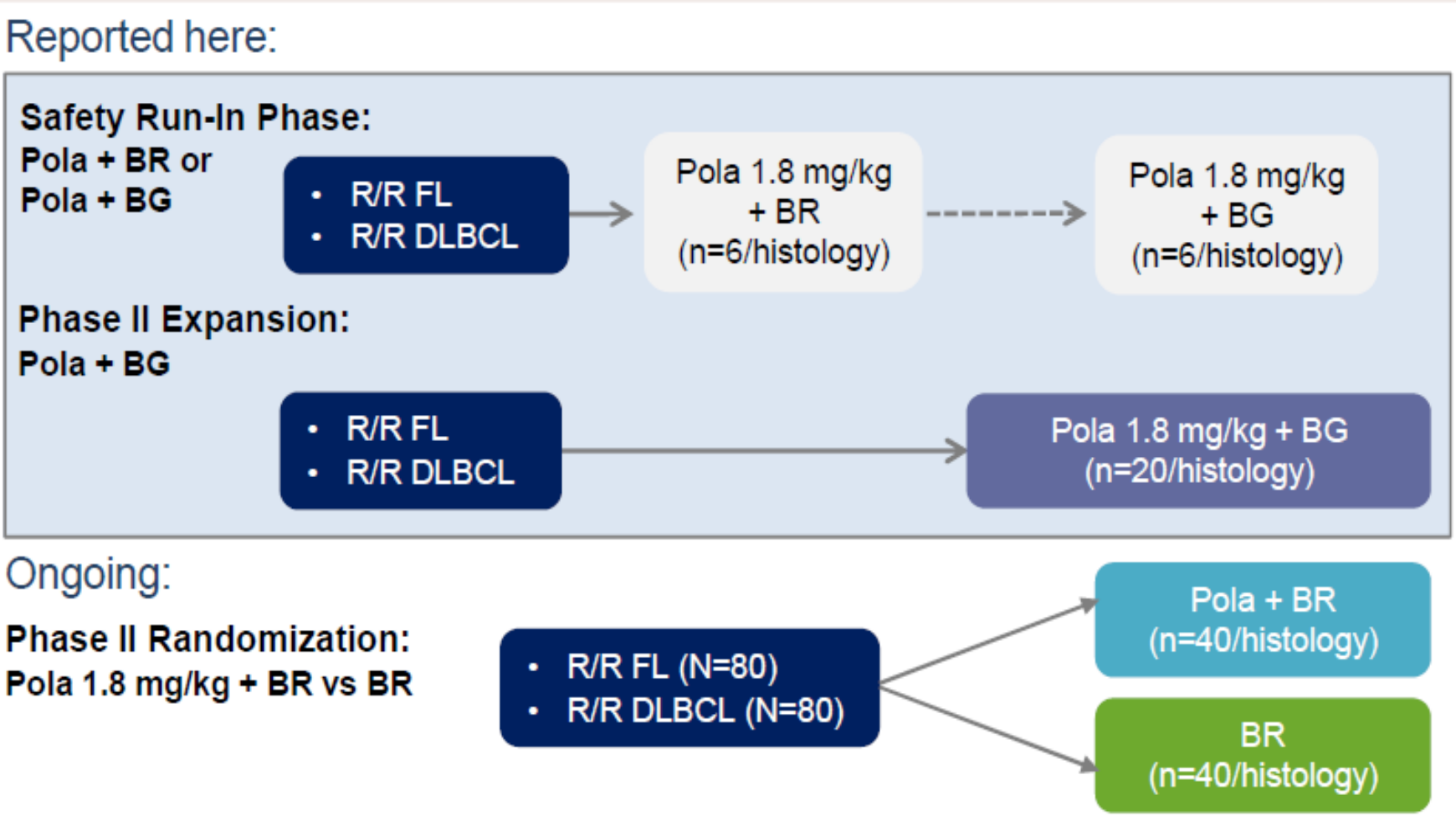
Neutropenia and peripheral neuropathy (above all sensitive) are principal toxicities

Neutropenia was most common g 3-4 treatment emergent adverse event

- Primarily laboratory abnormality with few clinically significant sequelae
- Febrile neutropenia reported in 4% of all patients
- Only one patient discontinued study treatment for neutropenia

Peripheral neuropathy was the most common AE leading to study treatment discontinuation

Figure 2: Study Design



Tx: Pola 1.8 mg/kg IV with BR or BG every 28 days for FL pts and every 21 days for DLBCL pts for a total of 6 cycles. Response assessed after 3 cycles, end of tx, and every 6 months during follow-up

M. Matasar et al, ICML LUGAN0 2017 Poster: 284

Results

Table 5: Investigator-Assessed Response by PET/CT[a]

	FL		DLBCL	
	Pola + BR (n=6)	Pola + BG (n=26)	Pola + BR (n=6)	Pola + BG (n=27)
Best Objective Response				
ORR, n (%)	6 (100)	23 (89)	3 (50)	16 (60)
CR	4 (67)	17 (65)	2 (33)	11 (41)
PR	2 (33)	6 (23)	1 (17)	5 (19)
SD	0	0	0	2 (7)
PD	0	1 (4)	2(33)	6 (22)
UE	0	2 (8)	1 (17)	3 (11)
Objective Response at End of Tx				
ORR, n (%)	5 (83)	21 (81)	3 (50)	10 (37)
CR	4 (67)	17 (65)	2 (33)	9 (33)
PR	1 (17)	4 (15)	1 (17)	1 (4)
Median duration of response, mo (range)[b]	16.1 (3.8–16.3)	NR (15.2–20.6)	NR (0.03–14.5)	NR (0.03–15.7)
Median PFS, mo (range)[b]	18.4 (7.2–18.9)	NR (1.4–17.1)	NR (1.5–22.7)	5.4 (0.03–17.6)

[a]Modified Lugano 2014 response criteria: for CR, repeat bone marrow biopsy required to confirm clearance of bone marrow if involved at screening. [b]Kaplan-Meier method; range data are at clinical data cut-off. NR, not reached; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UE, unable to evaluate.

M. Matasar et al, ICML LUGAN0 2017 Poster: 284

Sabrina Study

SUBCUTANEOUS RITUXIMAB AND CHEMOTHERAPY ACHIEVES SIMILAR OVERALL RESPONSE RATES TO INTRAVENOUS RITUXIMAB IN FIRST-LINE FOLLICULAR LYMPHOMA: EFFICACY AND SAFETY RESULTS OF THE PHASE III SABRINA STUDY.

A Davies, et Al.

Two-stage phase III study of RSC 1400mg or RIV 375mg/m2 plus chemotherapy (≤8 cycles CHOP, or 8 cycles CVP every 3 weeks during induction (first cycle RIV on both arms) followed by RSC or RIV maintenance every 8 weeks in pts with FL.

Primary objective:

- efficacy data, ORR (CR + PR) at the end of induction treatment;
- safety analyses

In each arm, approximately 64% pts received CHOP and 36% received CVP chemotherapy

	ORR	CR
Rituximab sc (205)	**83.4 %**	**32.7 %**
Rituximab iv (205)	**84.4 %**	**31.7 %**

Sabrina Study

Median follow-up 14.4 months, similar rates of AEs:
184/197 [93%] Rituximab SC vs 194/210 [92%] Rituximab IV

Serious Aes: 57 pts (29%) Rituximab SC and 55 pts (26%) Rituximab IV

Common haematological Aes: neutropenia and anaemia (both ≤5% of pts in each group)

	Rituximab SC	Rituximab IV
Infections	20/197 (10%)	16/210 (8%)
Febrile neutropenia	11/197 (6%)	9/210 (4%)
Administration-related reactions	93/197 (47%)	70/210 (33%)

Difference was mainly due to grade 1 injection site erythema (10% *vs 0%)* *which was anticipated* following the change in route of administration.

CONCLUSIONS:

RSC demonstrated comparable ORR and CR rates with RIV. The safety profile of RSC and RIV was similar and there were no new safety concerns with the SC formulation. Availability of RSC administration over approximately 5 minutes is expected to have a positive impact on pt convenience and health care resource savings without compromising the anti-lymphoma activity of rituximab.

Borgo San Luigi Monteriggioni, 27-28 Ottobre 2008	*Gubbio, 18-19 Settembre 2009*
Stresa 17-18 Settembre 2010	*Gubbio, 23-24 Settembre 2011*
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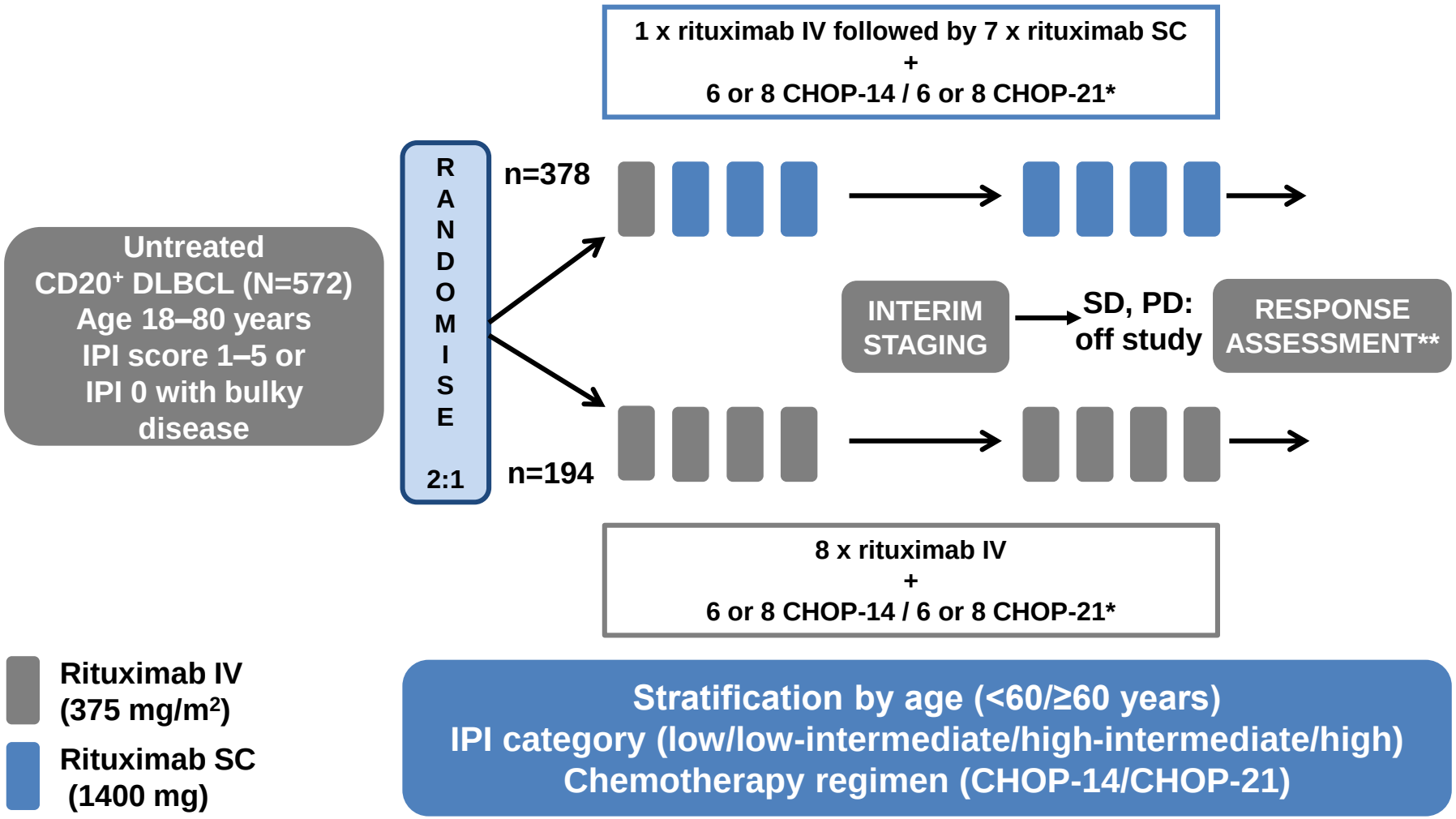
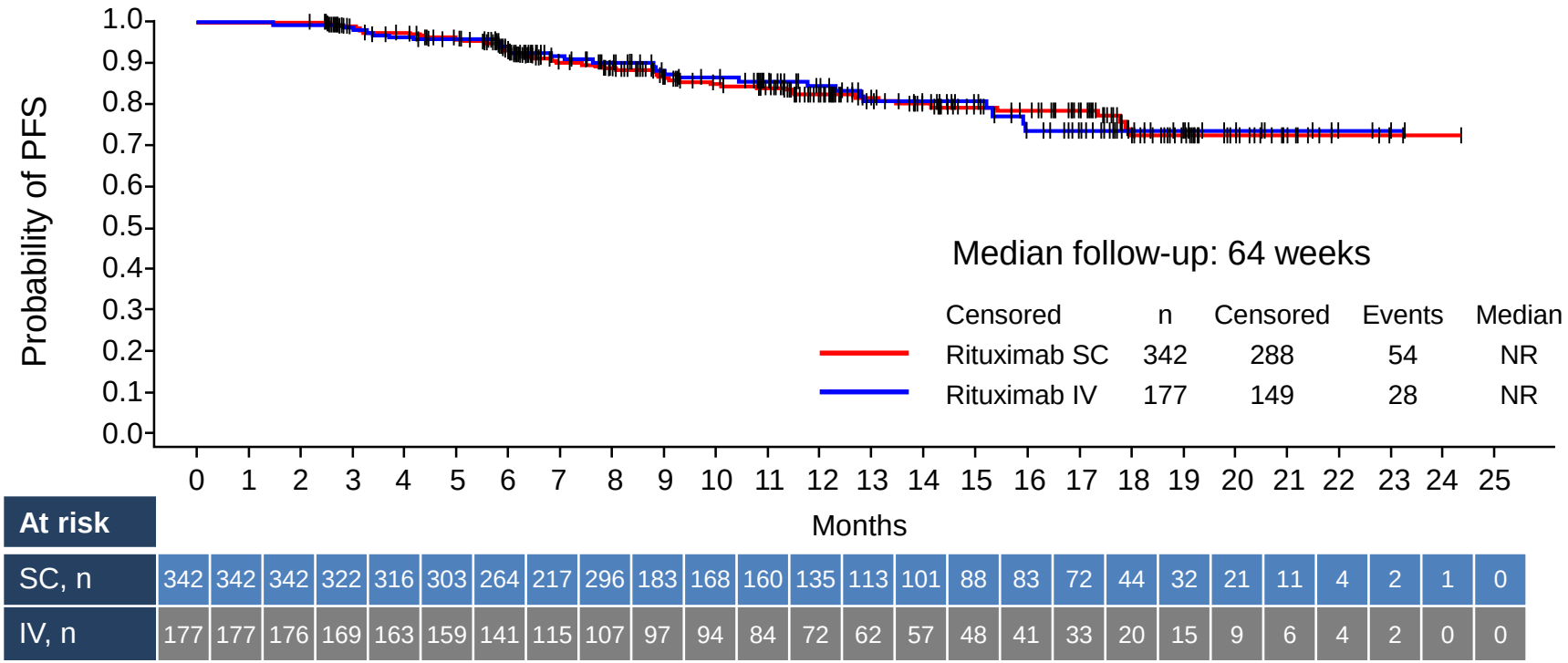
Firenze 19-20 Settembre 2014	*Firenze 18-19 Settembre 2015*

Subcutaneous versus intravenous rituximab in combination with CHOP for previously untreated diffuse large B-cell lymphoma: efficacy and safety results from the Phase IIIb MabEase study



*Selected by investigators
**Cheson 1999 criteria
IPI, International Prognostic Index; PD, progressive disease; SD, stable disease

Progression-free survival (ITT)



At risk																									
SC, n	342	342	342	322	316	303	264	217	296	183	168	160	135	113	101	88	83	72	44	32	21	11	4	2	1	0
IV, n	177	177	176	169	163	159	141	115	107	97	94	84	72	62	57	48	41	33	20	15	9	6	4	2	0	0

- The KM PFS curves were almost identical for rituximab SC (1400 mg) and IV (375 mg/m^2)

PFS was comparable between treatment arms

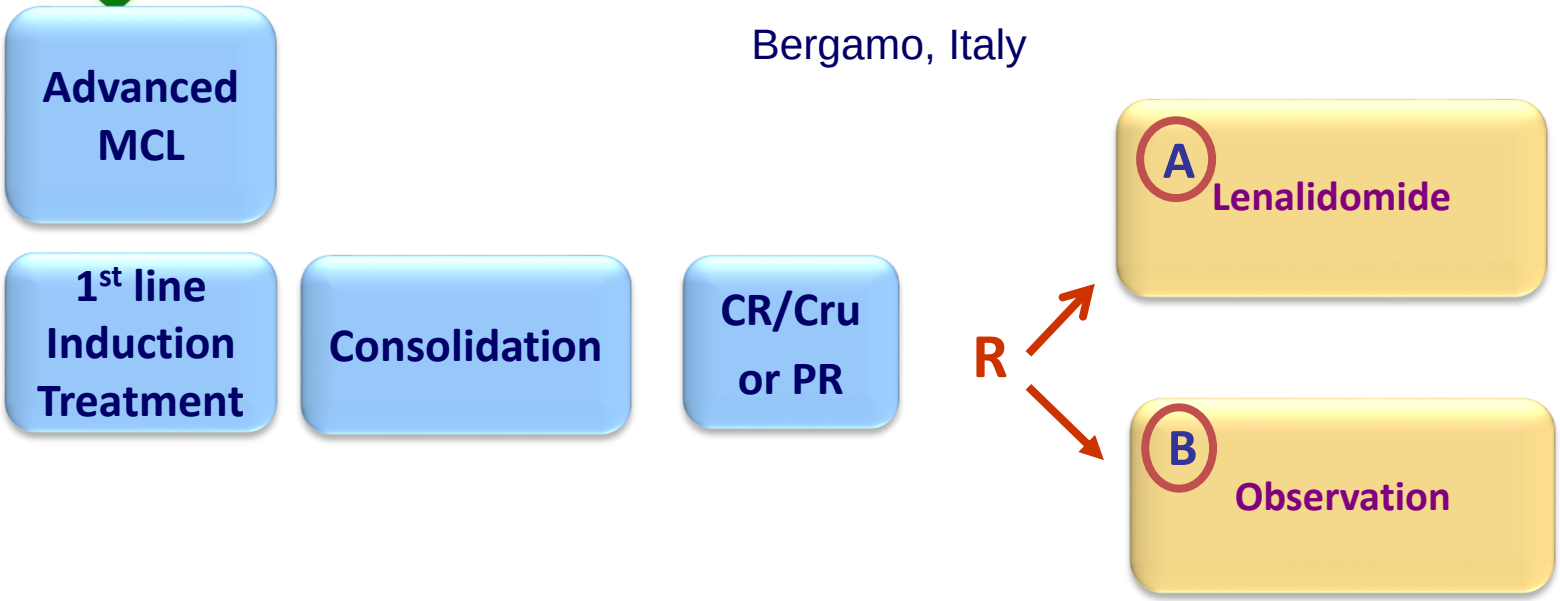
KM, Kaplan-Meier; NR, not reached; PFS, progression-free survival

A phase III multicenter, randomized study with Lenalidomide (Revlimid®) maintenance versus observation after intensified induction regimen containing rituximab followed by high dose chemotherapy and Autologous Stem Cell Transplantation as first line treatment in adult patients with advanced Mantle Cell Lymphoma

Sergio Cortelazzo, MD on behalf of FIL

Unit of Oncology-Hematology, Humanitas

Bergamo, Italy



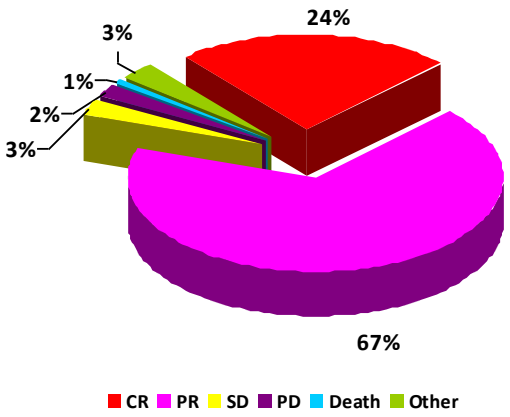
Randomization within 120 days after the end of consolidation

Arm A: Lenalidomide, once daily on days 1-21, every 28-days

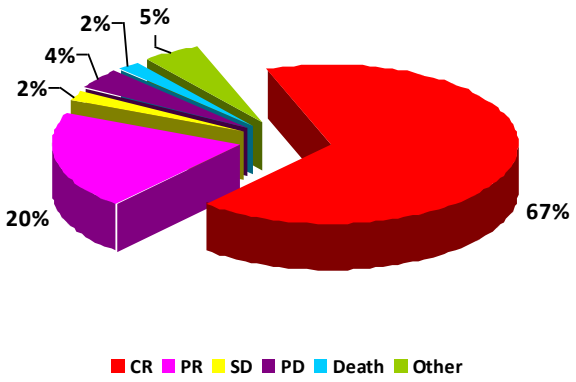
Arm B: Observation with no any active drugs for MCL

Response

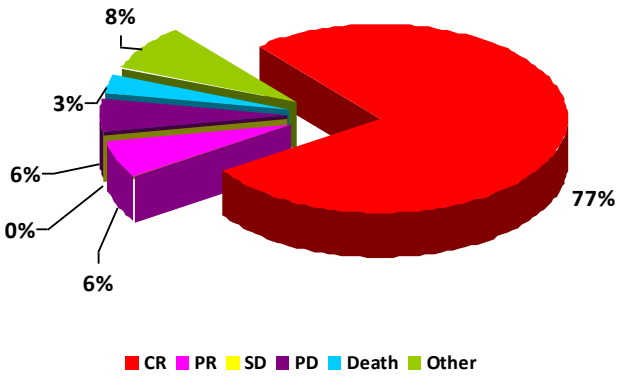
Restaging 1 – after Induction+hd-CTX



Restaging 2 – after hd-Ara-C



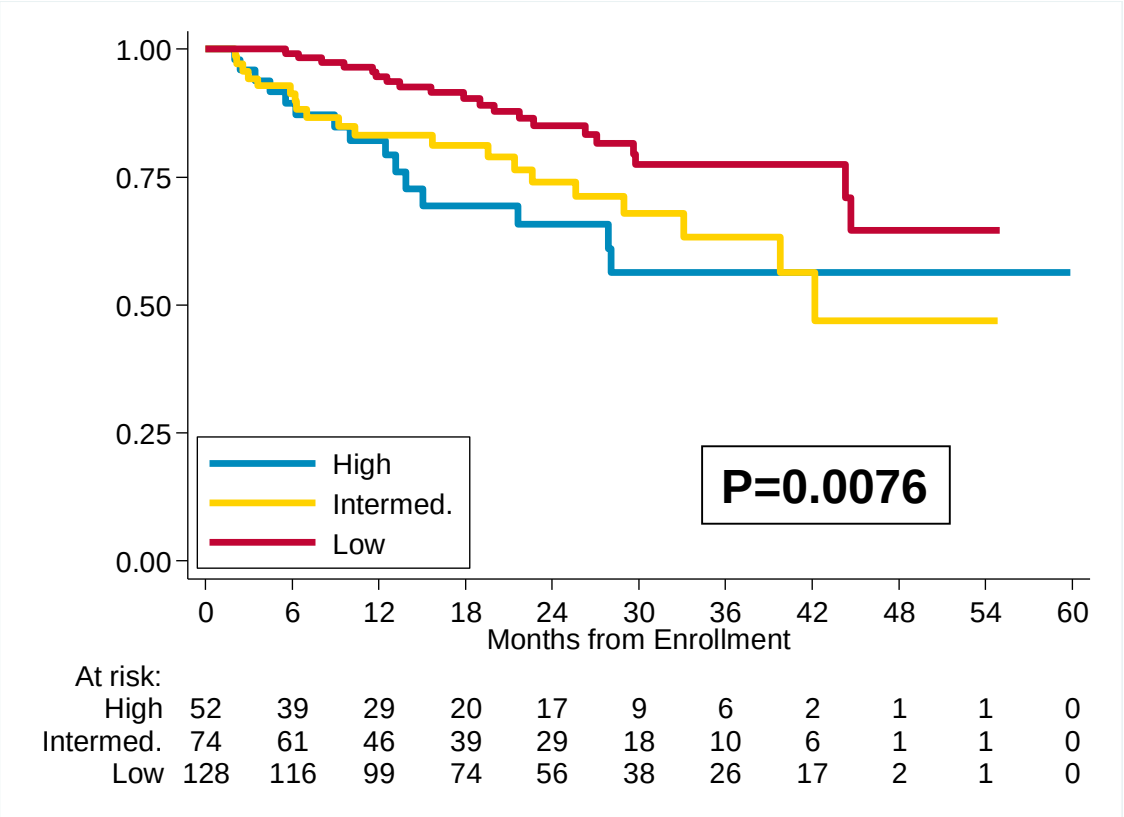
Restaging 3 – afer ASCT

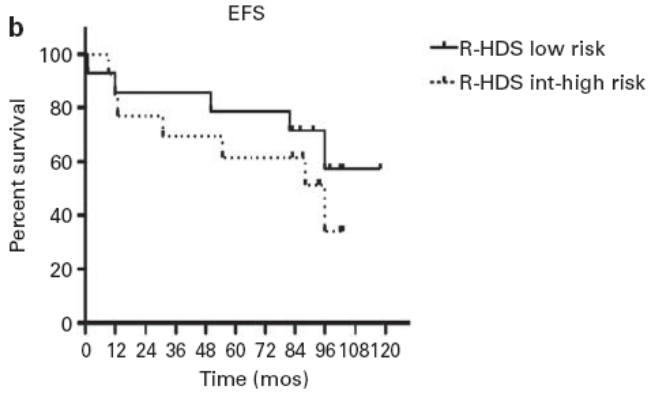


Final Response (including Intermediate+Final Response)	R-HDC+ASCT n = 228
CR/CRu	178(78%)
PR	18 (8%)
SD	3 (1%)
NR/PG	15 (7%)
Deaths during treatment*	7 (3%)
Interruption not due to PD or death	7(3%)

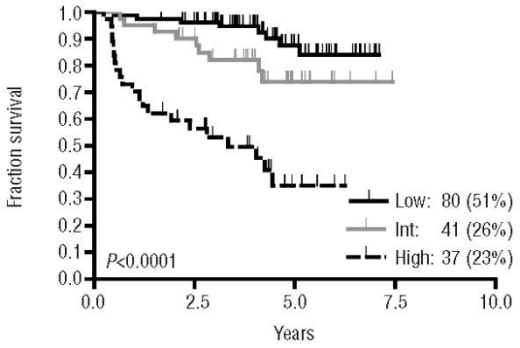
** One not related to treatment: road accident*

2-year PFS for MIPI low, intermediate and high





M Magni et al., Bone Marrow Transplant, 2009



CG Gaisler, Haematologica, 2010

Nivolumab in Relapsed or Refractory Lymphoid Malignancies and Classical Hodgkin Lymphoma: Updated Results of a Phase 1 Study

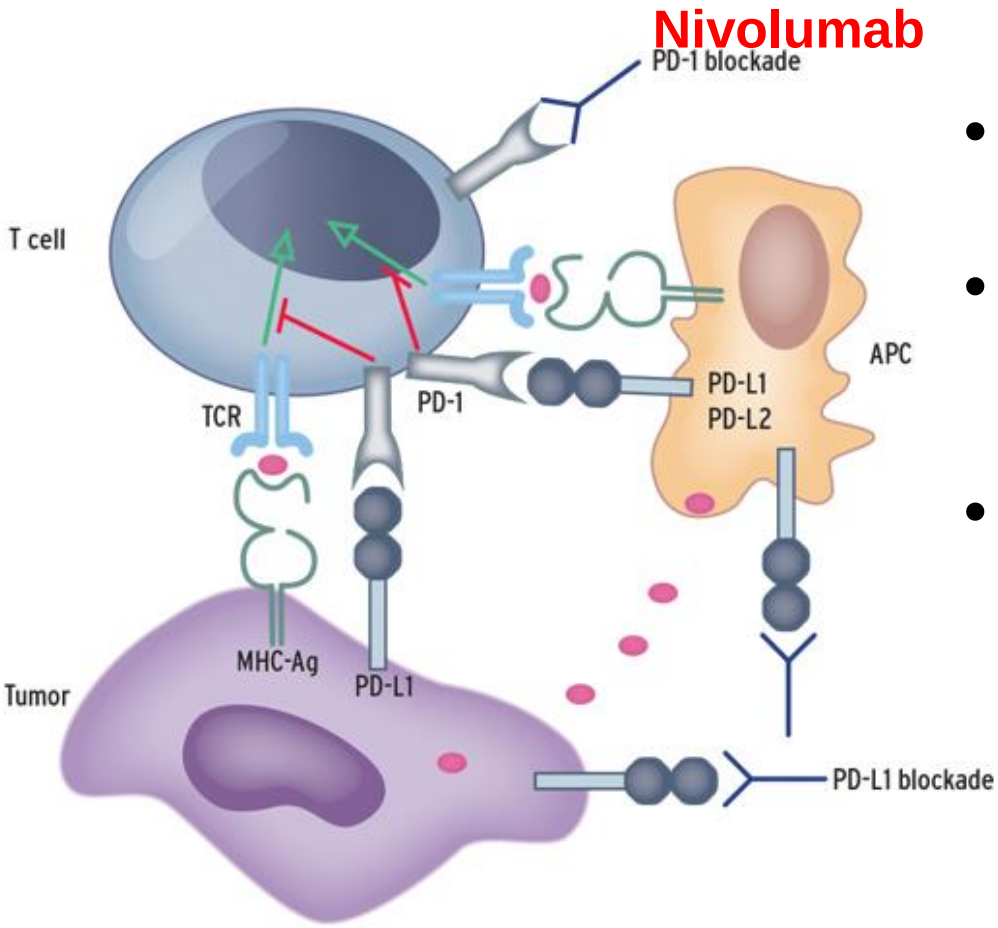
Philippe Armand[1], John Timmerman[2], Alexander M. Lesokhin[3], Ahmad Halwani[4], Michael M. Millenson[5], Stephen J. Schuster[6], Martin Gutierrez[7], Emma C. Scott[8], Deepika Cattry[3], Gordon J. Freeman[1], Bjoern Chapuy[1], Azra H. Ligon[9], Scott J. Rodig[9], Lili Zhu[10], Joseph F. Grosso[10], Jason Simon[10], Margaret A. Shipp[1], Adam D. Cohen[6], Daniel Lebovic[11], Madhav Dhodapkar[12], David Avigan[13], Stephen M. Ansell[14], Ivan Borrello[15]

EHA 20TH CONGRESS

JUNE 2015

VIENNA, AUSTRIA

PD-1 Pathway and Immune Surveillance



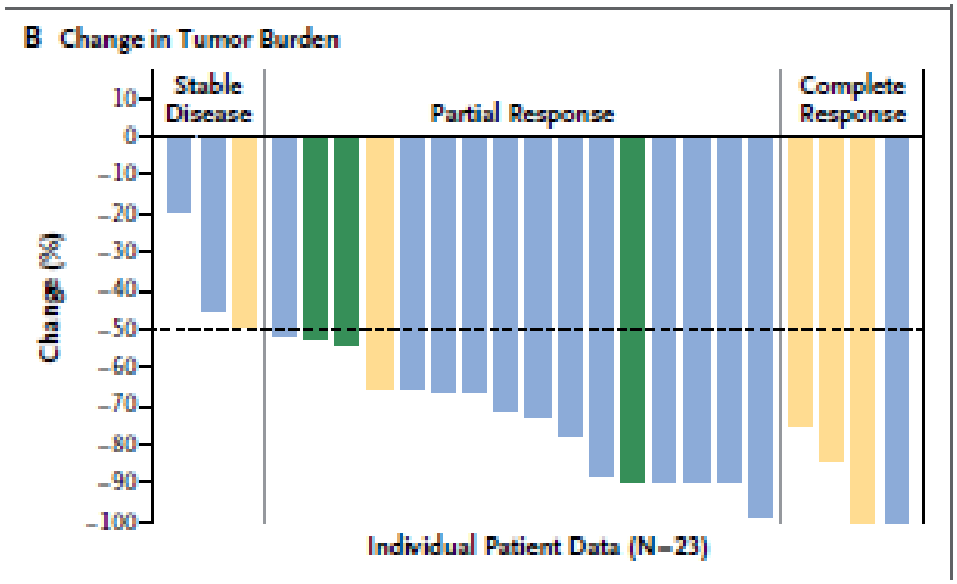
- PD-1 is expressed on the surface of activated T cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

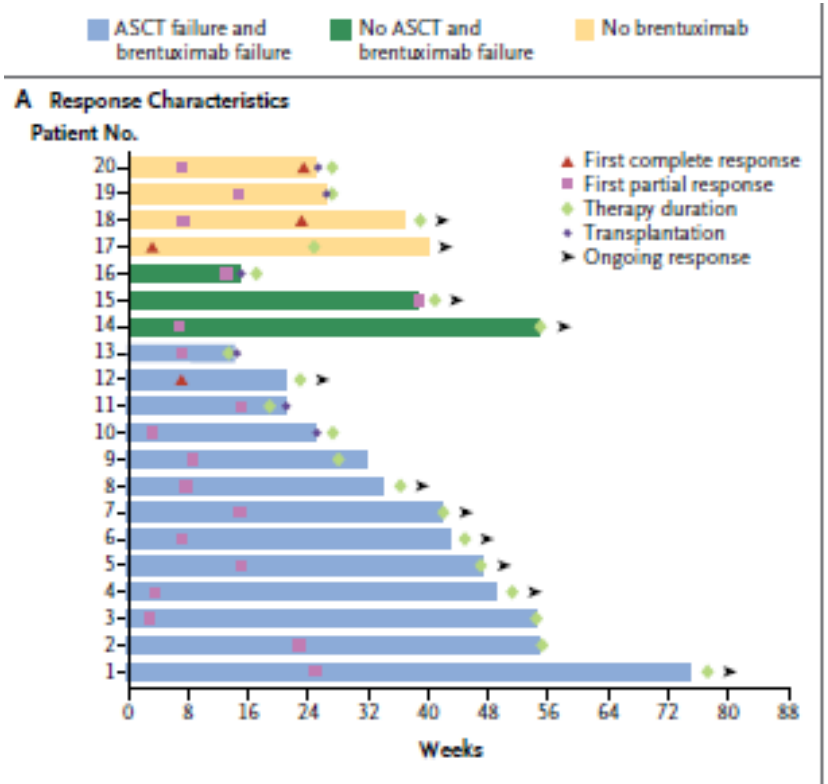
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.





Phase II Study of BEGEV [Bendamustine, Gemcitabine, Vinorelbine] as Induction Regimen Prior to ASCT in R/R HL

R. Mazza, A. Pulsoni, G. Rossi, C. Carlo-Stella, A. Anastasia, M. Bonfichi, C. Rusconi, F. Salvi, S. Luminari, A. Re, M. Gotti, A.M. Liberati, N. Di Renzo, L. Giordano, A. Santoro
on behalf of Fondazione Italiana Linfomi (FIL)

Day	Medication	Dose	Route
1	Gemcitabine	800 mg/sqm	IV
	Vinorelbine	20 mg/sqm	IV
2	Bendamustine	90 mg/sqm	IV
3	Bendamustine	90 mg/sqm	IV
4	Gemcitabine	800 mg/sqm	IV

Four cycles every 21 days

ClinicalTrials.gov Identifier: NCT01884441

Overall Response and by Disease Status

	n	%
Patients	59	100
CR	43	73
PR	6	10
SD	1	2
PD	8	13
Drop out	1	2

Disease Status at Study Entry	CR + PR	SD	PD	P
Relapse	30 (94%)	1 (3%)	1 (3%)	0.033*
Refractory	19 (70%)	-	8 (30%)	

* CR-PR *vs* SD-PD

Firenze, 22-23 settembre 2017

Novità dall'EHA

LINFOMI :
Report dei gruppi di lavoro

Maurizio Martelli
Dip. Biotecnologie Cellulari ed Ematologia
Sapienza Università di Roma

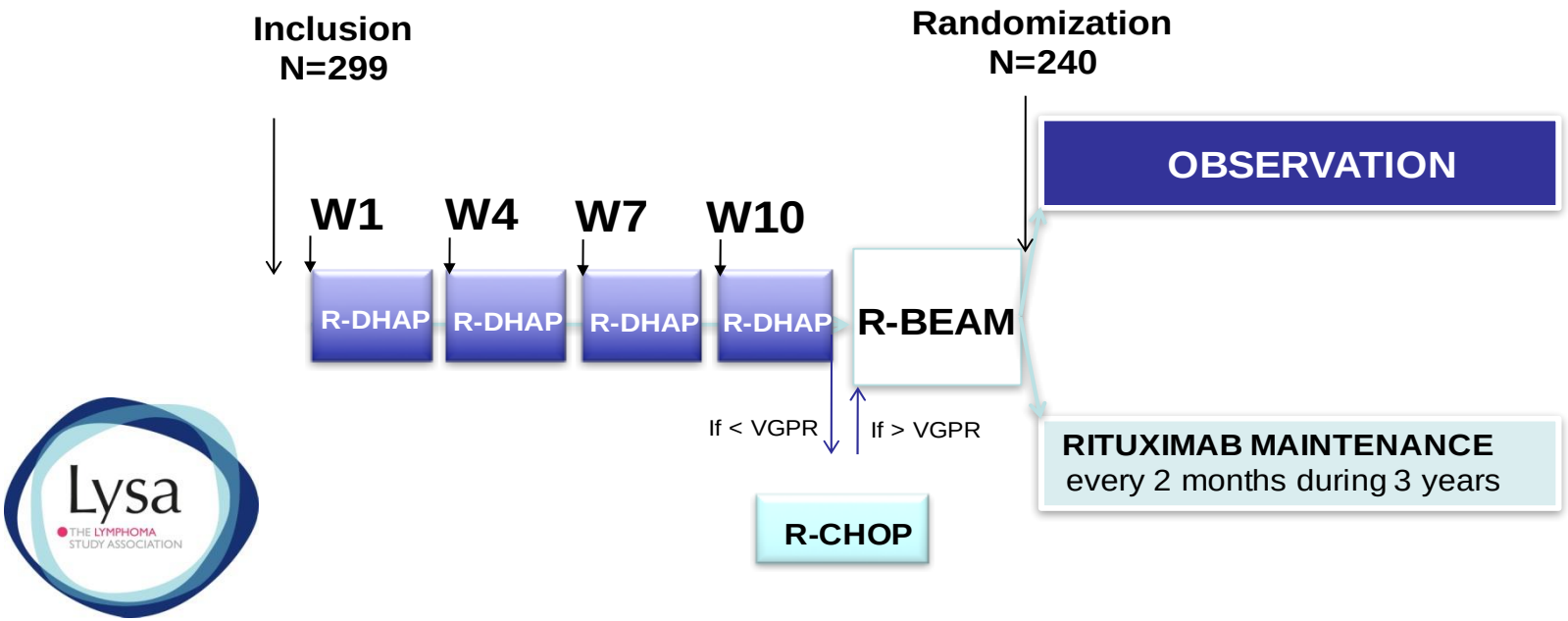
Gruppo di lavoro

	NOME	COGNOME	
1	Maria Licia	Barone	Ospedale A. Tortora Salerno
2	Giacomo	Cecere	"Ospedale S.g. Moscati" Statte
3	Flavio	Falcinelli	Perugia
4	Gianfranco	Giglio	Campobasso
5	Ursula	La Rocca	Roma
6	Giuseppe	Lo Scocco	
7	Giorgio	Martinelli	Perugia
8	Giuseppe	Musardo	Fospedale di Faenza
9	Lucia	Pantani	Ospedale Seragnoli Bologna
10	Tommasina	Perrone	Bari
11	Omar	Racchi	Ospedale Villa Scassi, Genova
12	Paolo	Radossi	Castelfranco Veneto
13	Alessandra	Scardocci	Policlinico Campus Biomedico Roma
14	Simona	Tomassetti	Ospedale Infermi Rimini
15	Annalisa	Tondo	Firenze
16	Filippo	Ballerini	Genova

Report del gruppo

- ✓ Non-Hodgkin Lymphoma
  - ✓ MCL
  - ✓ DLBCL
  - ✓ Follicular
  - ✓ Indolent NH
- ✓ Hodgkin
  - ✓ First line
  - ✓ Relapse

Rituximab maintenance after autologous stem cell transplantation prolongs survival in patients with mantle cell lymphoma (final result of the LyMa trial)



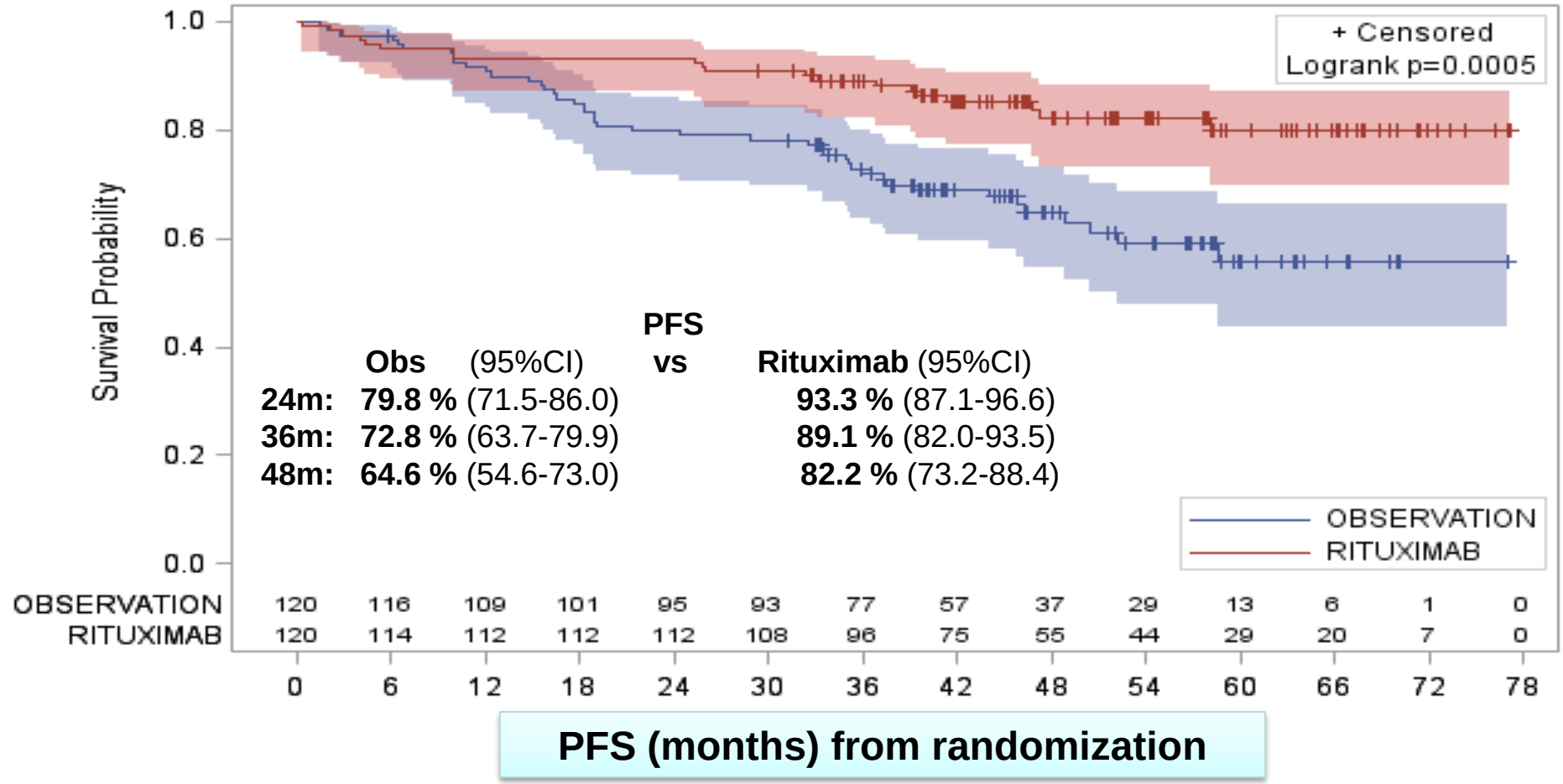
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

Le Gouill S et al, S105.

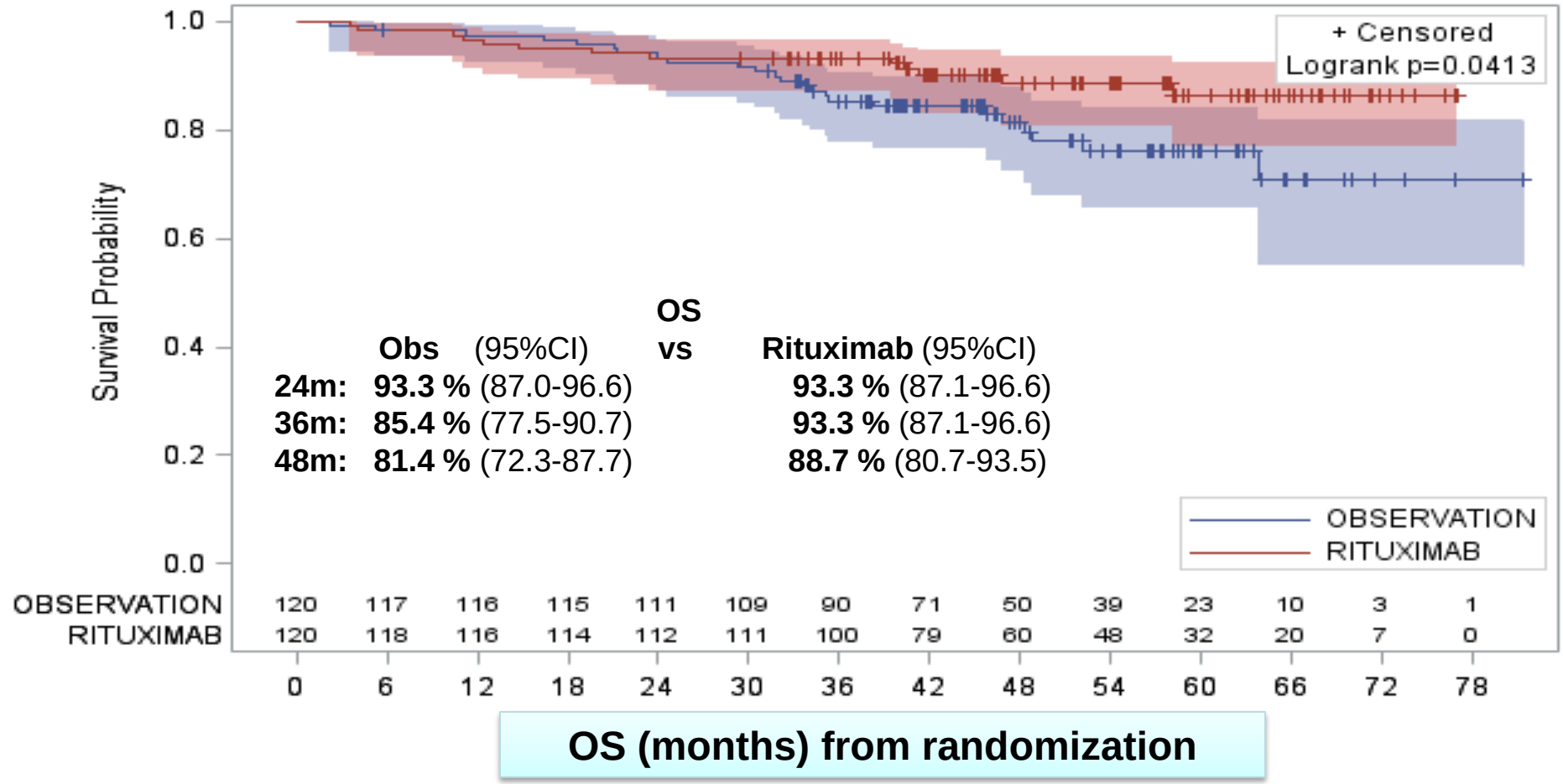
PFS from Randomization

mFU: 50.2m (46.4-54.2)



OS from Randomization

mFU: 50.2m (46.4-54.2)



Gruppo di lavoro

- Il disegno dello studio LyMa (R-DHAP/R-BEAM) può essere considerato la terapia standard del paziente giovane con MCL?

- Rituximab di mantenimento (375 mg/m^2 ogni 2 mesi per 3 anni) deve essere consigliato nei pazienti in RC dopo ASCT ?

Pola-R-CHP: Polatuzumab Vedotin Combined with Rituximab, Cyclophosphamide, Doxorubicin, Prednisone for Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

Hervé Tilly[1], Jeff Sharman[2,11], Nancy Bartlett[3], Franck Morschhauser[4], Corinne Haioun[5], Javier Munoz[6], Andy Chen[7], Thierry Lamy[8], Lijia Wang[9], Elicia Penuel[9], Jamie Hirata[9], Calvin Lee[9], Gilles Salles[10]

[1]Centre Henri Becquerel, University of Rouen, Rouen, France; [2]Willamette Valley Cancer Institute, Springfield, OR; [3]Washington University School of Medicine, Siteman Cancer Center, St Louis, MO; [4]University Hospital of Lille, Lille, France; [5]Henri Mondor University Hospital, Creteil, France; [6]Banner MD Anderson Cancer Center, Gilbert, AZ; [7]Oregon Health and Science University, Portland, OR; [8]Hematology Department, INSERM U917 / University Hospital of Rennes, Rennes, France; [9]Genentech, Inc., South San Francisco, CA; [10]Lyon University Hospital, Pierre Bénite, France; [11]US Oncology Research, The Woodlands, TX

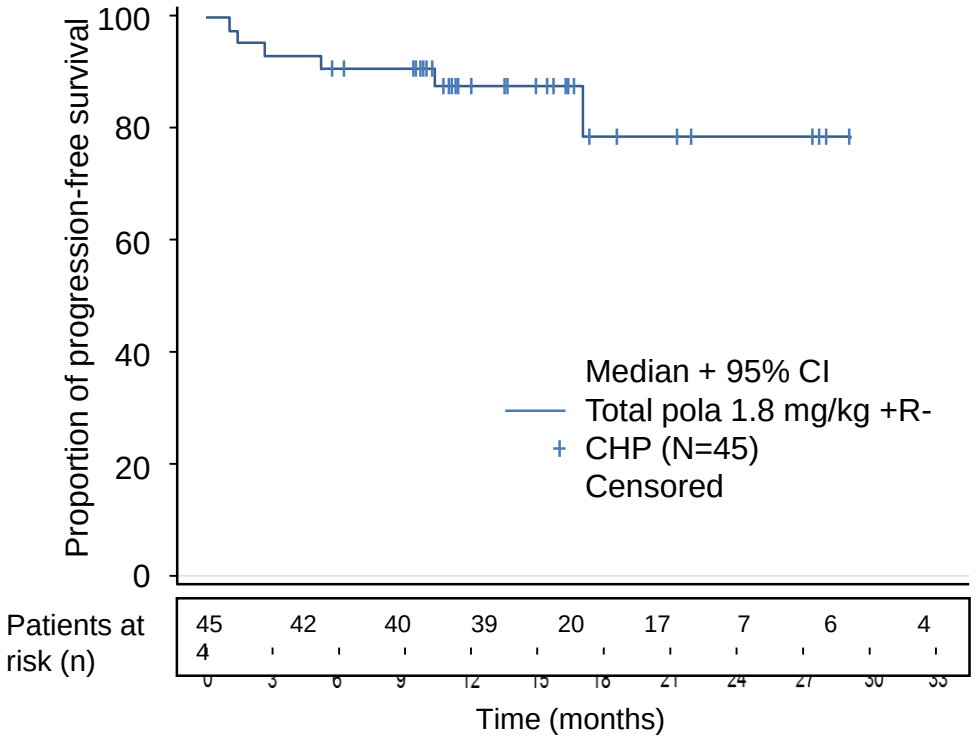
PET Response at End of Treatment by IPI

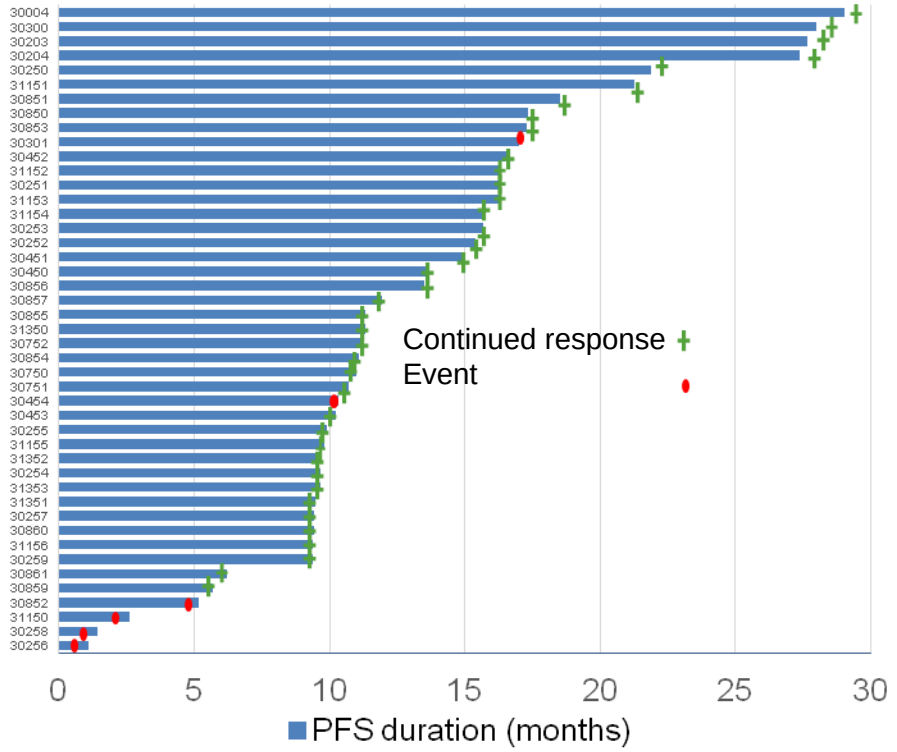
	Pola-R-CHP (N = 45) n, (%)	
	IPI 0–2 n = 10	IPI 3–5 n = 35
Overall response rate	**10 (100)**	**31 (89)**
Complete response	**10 (100)**	**25 (71)**
Partial response	-	**6 (17)**
Unevaluable	-	1 (3)
Progressive disease	-	3 (9)

IPI, International Prognostic Index; PET, positron emission tomography
PET as assessed by investigator. Cheson BD et al. J Clin Oncol 2007;25:579–86.

Progression-Free Survival

- Median study duration = 14.9 months





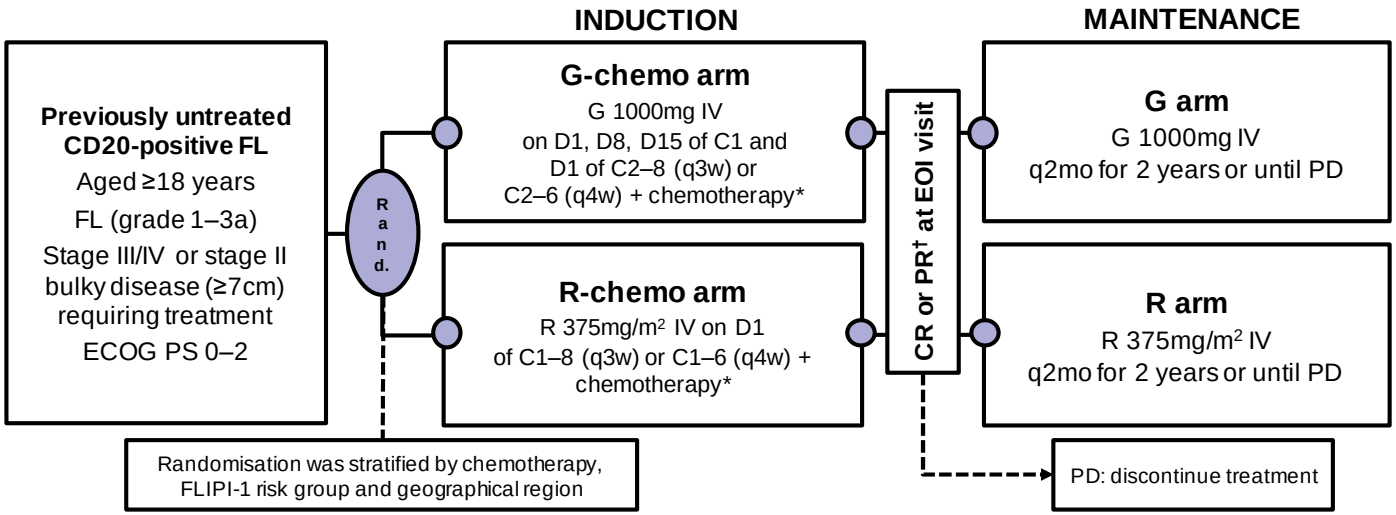
Data Cut-Off: April 14, 2017

Gruppo di lavoro

- Il regime Pola R-CHOP è una terapia efficace e sicura nel paziente con DLBCL ad alto rischio IPI ?.
- Necessario studio di fase III
- Allo stato attuale R-CHOP + X (farmaco biologico) deve essere considerato l'approccio di prima linea più indicato nei DLBCL

Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma (FL) in the randomised Phase III GALLIUM study: analysis by chemotherapy regimen

International, open-label, randomised Phase III study in 1L pts (NCT01332968)



Primary endpoint

- PFS (INV-assessed)

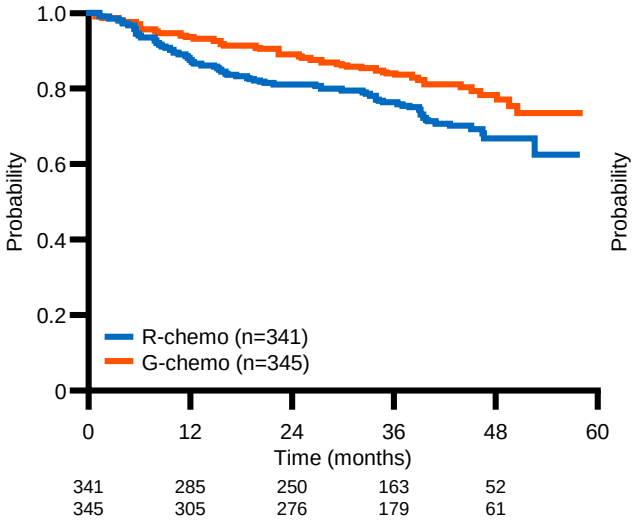
Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

*CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; chemo regimen chosen by site prior to initiation and received by all FL pts at site;
†patients with SD at EOI entered observation for up to 2 years or until PD if earlier

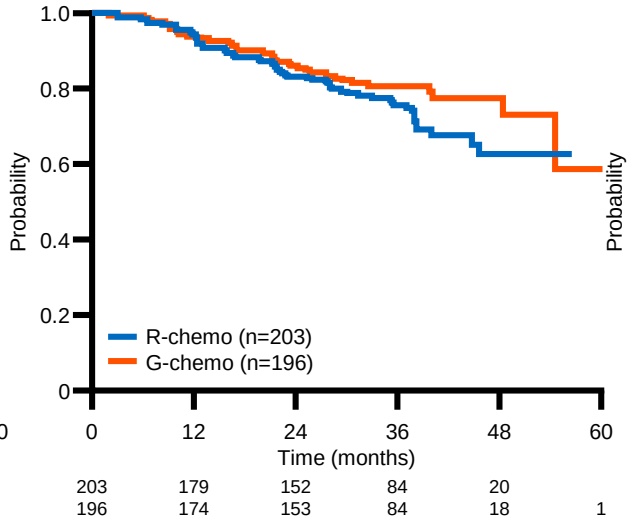
INV-assessed PFS by chemo*

Benda



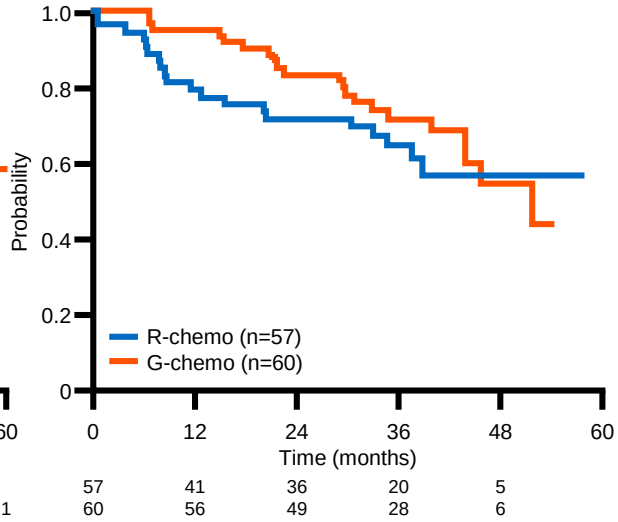
HR (95% CI)†	0.63 (0.46, 0.88)
3-yr PFS	84.1% G-B vs 76.4% R-B

CHOP



HR (95% CI)†	0.72 (0.48, 1.10)
3-yr PFS	80.6% G-CHOP vs 75.6% R-CHOP

CVP



HR (95% CI)†	0.79 (0.42, 1.47)
3-yr PFS	71.3% G-CVP vs 64.2% R-CVP

- By chemo analysis not powered to demonstrate statistically significant differences between treatment arms

*ITT population; †analysis stratified by FLIPI (as well as chemotherapy regimen)

AEs by chemo*

n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Any AE	331 (97.9)	338 (100)	201 (99.0)	191 (99.0)	56 (100)	61 (100)
Grade 3–5 AE	228 (67.5)	233 (68.9)	**151 (74.4)**	**171 (88.6)**	30 (53.6)	42 (68.9)
SAE	**160 (47.3)**	**176 (52.1)**	67 (33.0)	76 (39.4)	19 (33.9)	26 (42.6)
Grade 5 (fatal) AE†	**16 (4.7)**	**20 (5.9)**	4 (2.0)	3 (1.6)	1 (1.8)	1 (1.6)
AE leading to treatment discontinuation	48 (14.2)	52 (15.4)	31 (15.3)	32 (16.6)	9 (16.1)	11 (18.0)

- Grade 3–5 AEs most frequent with CHOP (neutropenia, leukopenia, febrile neutropenia, IRRs); SAEs and fatal AEs most frequent with benda
- Frequency of grade 5 AEs similar to R-CHOP arms in SABRINA (5.7%, i.v.; 3.6%, s.c.)

*Safety population, i.e. all randomised FL pts who received at least one dose of study drug; †includes 6 pts with fatal AEs that occurred after start of new anti-cancer therapy (G-benda, 4; R-benda, 2)

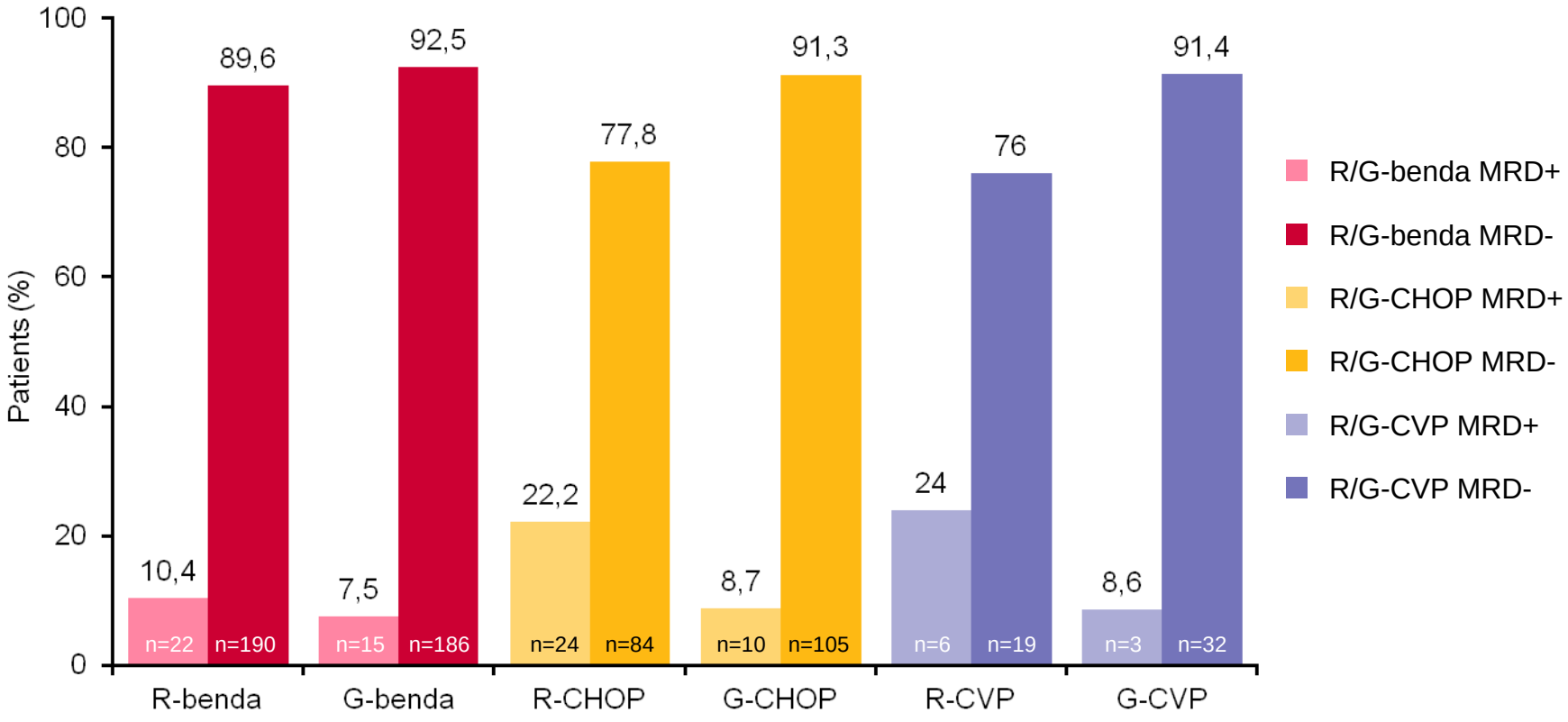
Gruppo di lavoro

- Nel prossimo futuro G-Chemo sarà la terapia standard del paziente con FL ?

- G-Chemo solo in casi selezionati : alto rischio FLIPI ? giovani?

- Dopo i risultati dello studio Gallium G/R Benda rimane una opzione terapeutica nella prima linea dei pazienti con FL

MRD response at end of induction



Prognostic value of PET-CT after first-line immunochemotherapy for follicular lymphoma in the Phase III GALLIUM Study

Based on early data[1–4] we hypothesised that

- Patients achieving PET negativity have a significant PFS and OS advantage
- If obinutuzumab-chemo is more effective than rituximab-chemo a higher percentage of patients should achieve PET negativity

Baseline and EOI PET imaging

Mandatory for first 170 pts where PET scanner available, and optional for remaining patients

EOI response assessments

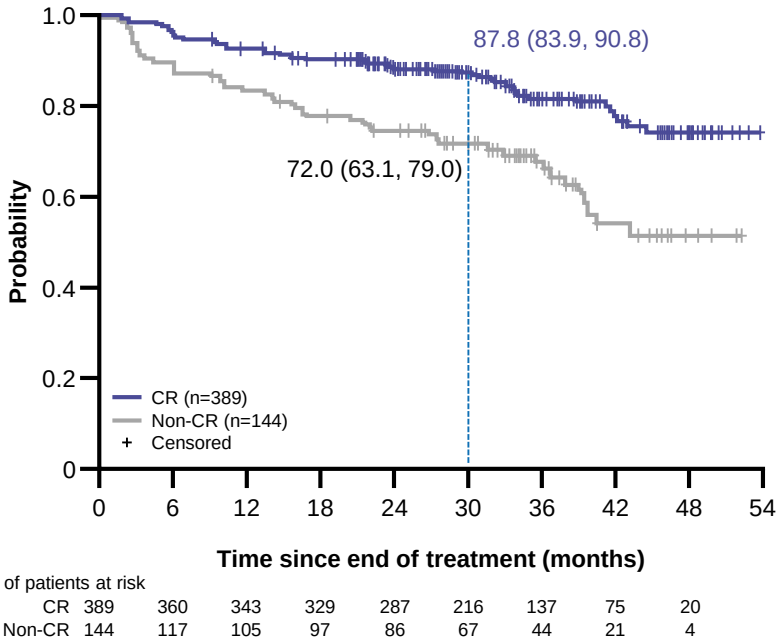
By investigator and IRC* with and without PET according to IHP 2007[5,6]

By IRC using 5PS[7] and Lugano 2014 criteria[8]

Landmark (from EOI) PFS analysis: by PET criteria

PFS for non-CR/CMR vs CR/CMR status according to IRC*

IHP 2007 criteria (N=533)[1]

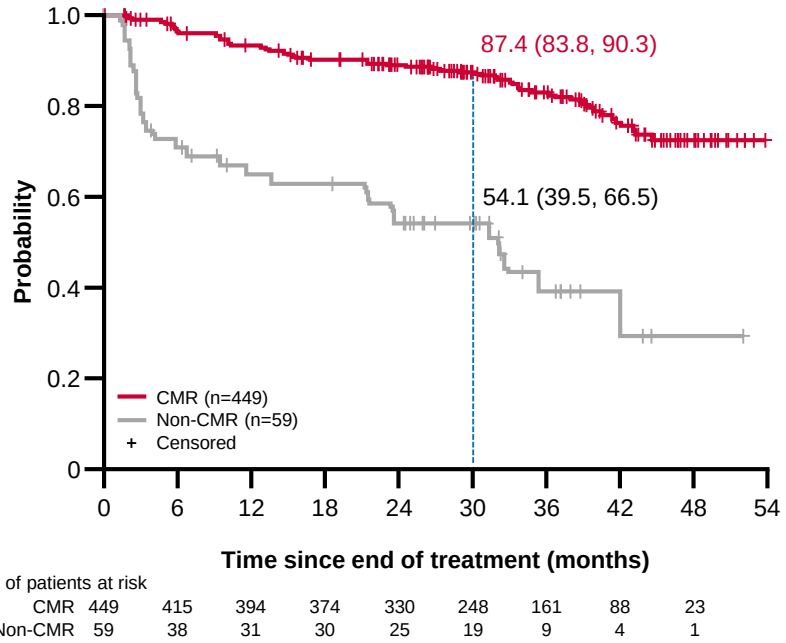


No. of patients at risk

CR	389	360	343	329	287	216	137	75	20
Non-CR	144	117	105	97	86	67	44	21	4

HR 0.37 (95% CI 0.25, 0.56); p<0.0001

Lugano 2014 criteria (N=508)[2,3]



No. of patients at risk

CMR	449	415	394	374	330	248	161	88	23
Non-CMR	59	38	31	30	25	19	9	4	1

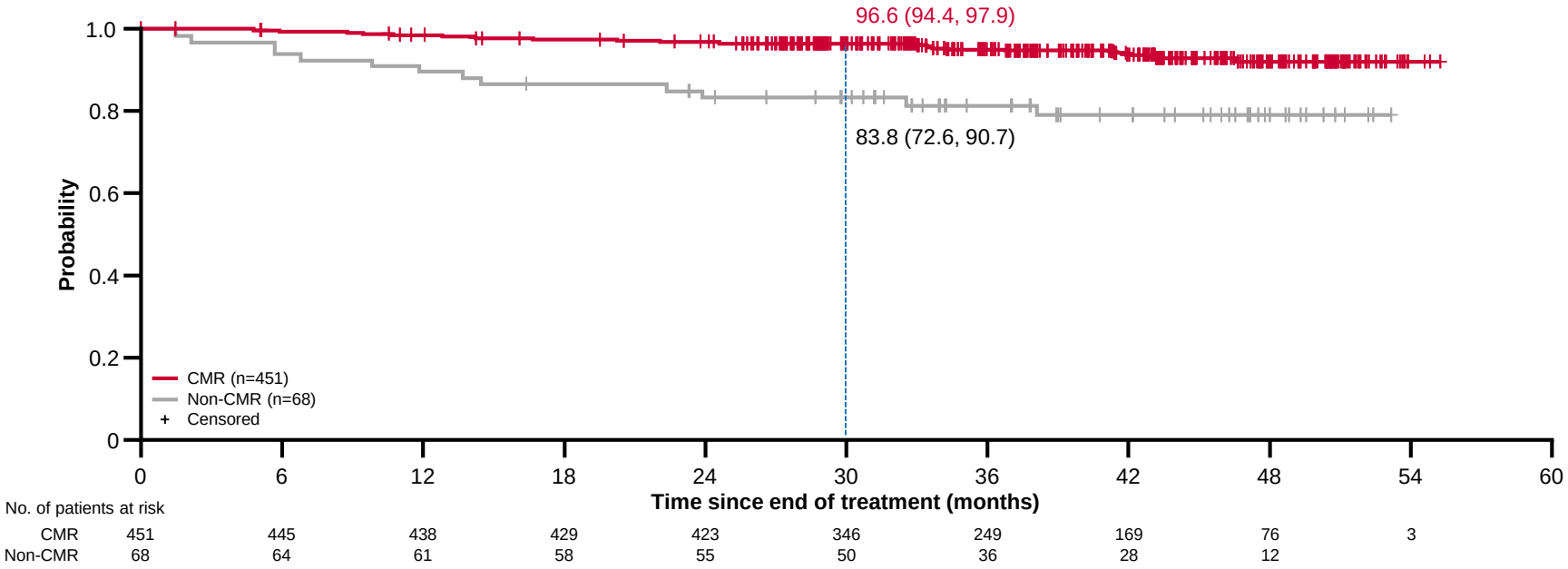
HR 0.21 (95% CI 0.13, 0.34); p<0.0001

*Patients who died or progressed (CT-based PD assessment or started next anti-lymphoma treatment) before or at EOI were excluded

1. Cheson BD, et al. JCO 2007;25:579–86
2. Barrington SF, et al. JCO 2014;32:3048–58
3. Cheson BD, et al. JCO 2014;32:3059–68

Landmark (from EOI) OS analysis

OS for non-CMR vs CMR status using Lugano 2014 criteria (N=519)*

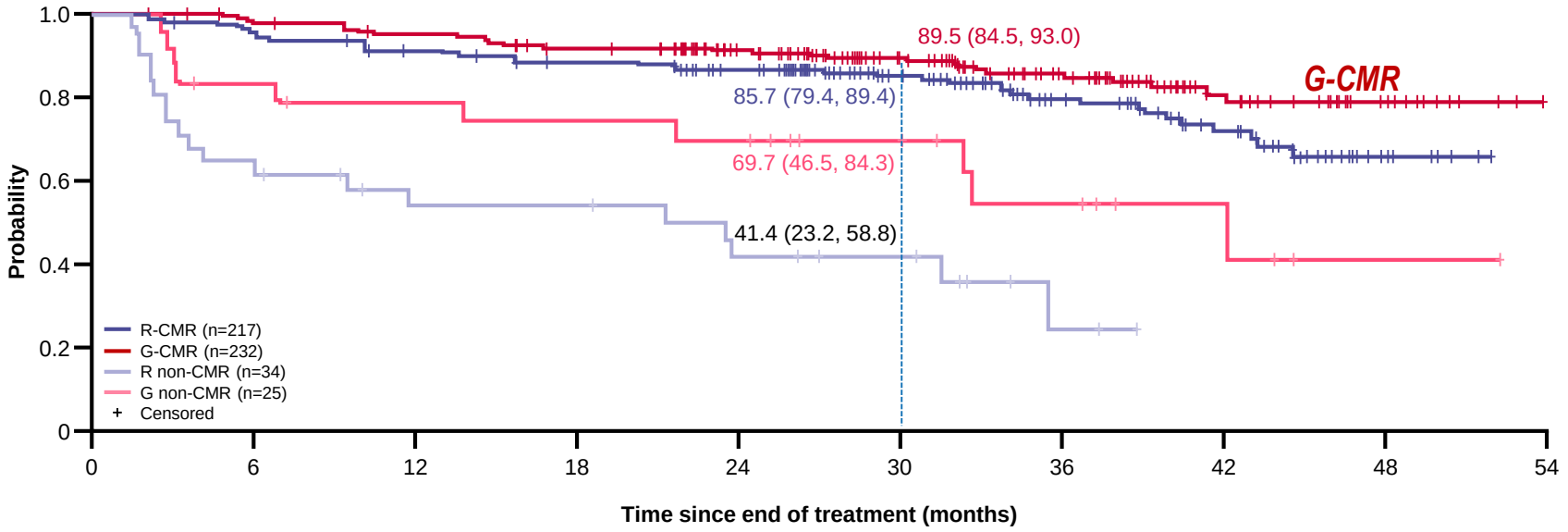


HR 0.22 (95% CI 0.11, 0.45); p<0.0001

*Patients who died or started a new anti-lymphoma treatment before EOI were excluded

Landmark (from EOI) PFS analysis: by antibody arm

PFS for non-CMR vs CMR status using Lugano 2014 criteria (N=508)



	R-CMR, n=217	*G-CMR, n=232*	*R non-CMR, n=34*	*G non-CMR, n=25*
2.5-year PFS from EOI, % (95% CI)	85.7 (79.4, 89.4)	89.5 (84.5, 93.0)	41.4 (23.2, 58.8)	69.7 (46.5, 84.3)
HR (95% CI)		**0.7 (0.4, 1.0); p=0.06**		**0.5 (0.2, 1.2); p=0.10**

Gruppo di lavoro

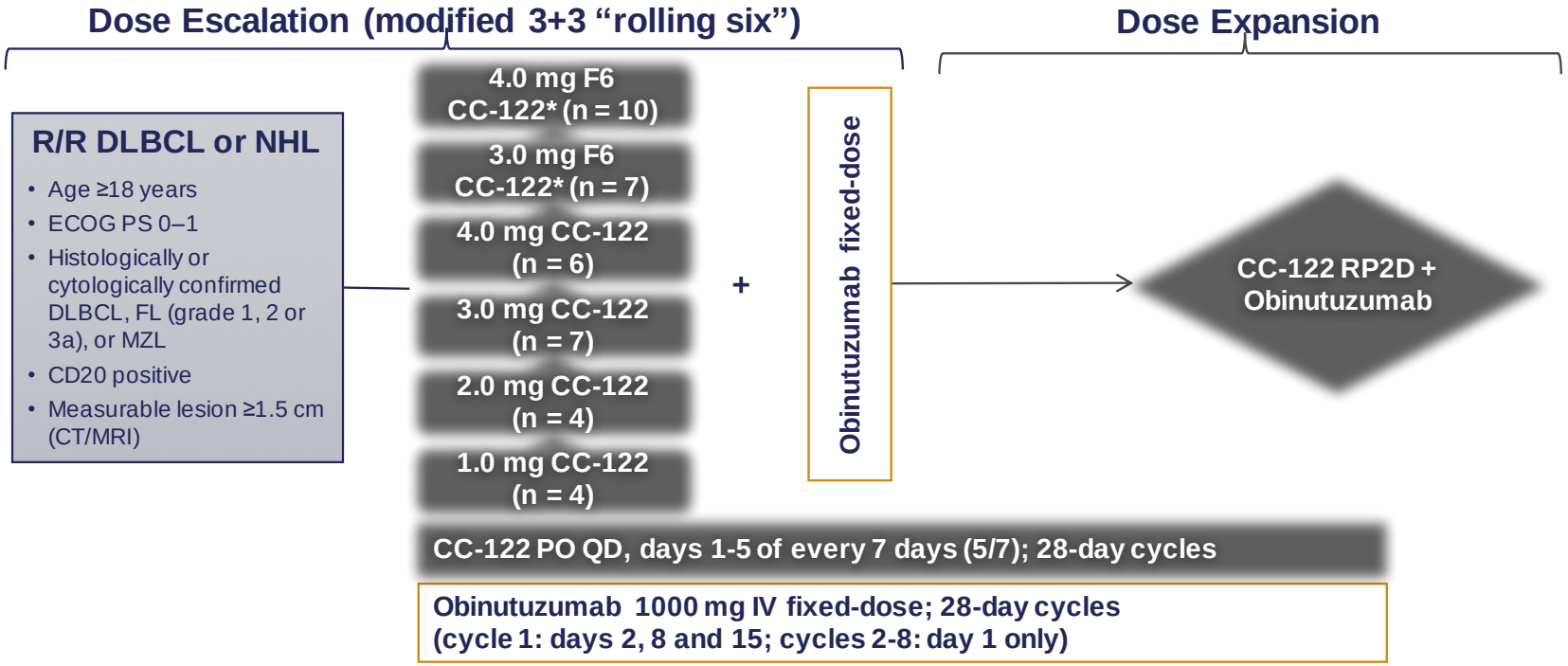
- La PET al termine della terapia (PET finale) deve essere considerata la migliore modalità di valutazione della risposta nei pazienti con FL?

- La migliore risposta metabolica (CMR) ottenuta con G-Chemo deve essere considerata un motivo aggiuntivo per la scelta di un regime G-Chemo

- La risposta alla PET finale può essere considerata come un surrogato della PFS e della OS e quindi considerata come un obiettivo primario nel disegno di uno studio prospettico dei FL?

CC-122 In Combination With Obinutuzumab (GA101): Phase IB Study in Relapsed or Refractory Patients With DLBCL, FL, or MZL

- Multicenter, open-label, phase IB dose-escalation and expansion study of CC-122 + obinutuzumab in patients with R/R DLBCL and NHL (FL and MZL; EUDRACT 2014-003333-26; NCT02417285)



F6, formulated capsule; RP2D, recommended phase II dose.
*An alternate dosing schedule with a formulated CC-122 capsule was examined in the 5th and 6th cohorts to assess safety.

Primary endpoints: examine safety and tolerability of CC-122 when co-administered with obinutuzumab; identify NTD, MTD, and RP2D of CC-122 when co-administered with obinutuzumab.

Michot JM et al, S467.

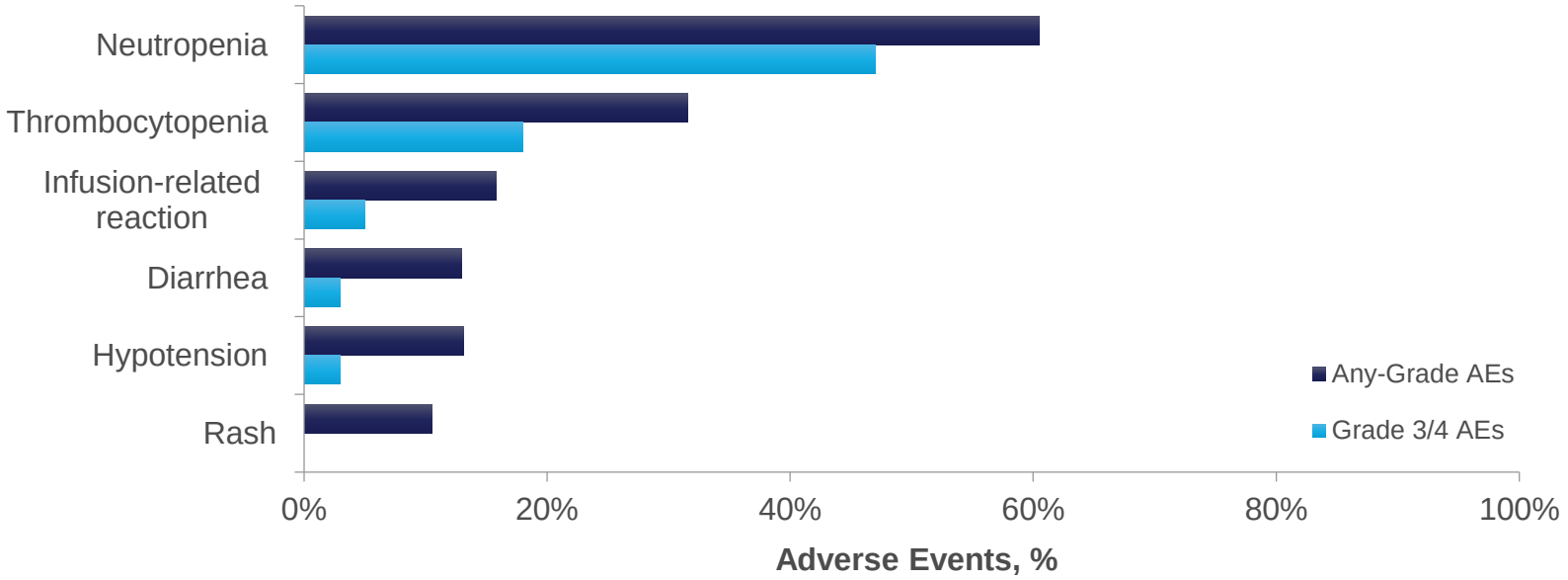
CC-122-NHL-001: EFFICACY BY NHL TYPE

Outcomes by Histology, n (%)	All Patients* (N = 38)	DLBCL (n = 19)	FL/MZL (n = 19)
ORR	25 (66)	9 (47)	16 (84)
CR	12 (32)	3 (16)	9 (47)
PR	13 (34)	6 (32)	7 (37)
SD	4 (11)	3 (16)	1 (5)
PD	6 (16)	4 (21)	2 (11)
Not evaluable/missing	3 (8)	3 (16)	0

- ORR was 66% overall, including 12 patients (32%) with a CR
- Median time to best response was 57 days (95% CI, 56-114)
- 23 of 30 (77%, including 40% CR) patients responded to CC-122 doses ≥ 3.0 mg + obinutuzumab
- To date, patients receiving CC-122 at a dose of 3.0 mg and higher have shown the best and more durable responses to CC-122 + obinutuzumab (n = 30)

Data cut-off 15May2017.
*Includes 19 DLBCL, 18 FL, and 1 MZL patients.

CC-122-NHL-001: SAFETY WITH CC-122 + OBINUTUZUMAB (N = 38)



- Most common grade 3/4 AEs (>10%) were hematologic AEs
  - 2 patients (5%) had grade 4 febrile neutropenia
  - 2 patients have discontinued treatment due to AEs
- 2 patients had a DLT
  - 1 patient had grade 4 neutropenia (3.0 mg CC-122 + obinutuzumab)
  - 1 patient had grade 5 tumor flare reaction (4.0 mg F6 CC-122 + obinutuzumab)

Data cut-off 15May2017. DLT, dose-limiting toxicity.

Gruppo di lavoro

- La chemio- immuno terapia in combinazione con nuovi farmaci biologici rappresenta il futuro della terapia di prima linea nei pazienti con linfoma a cellule B

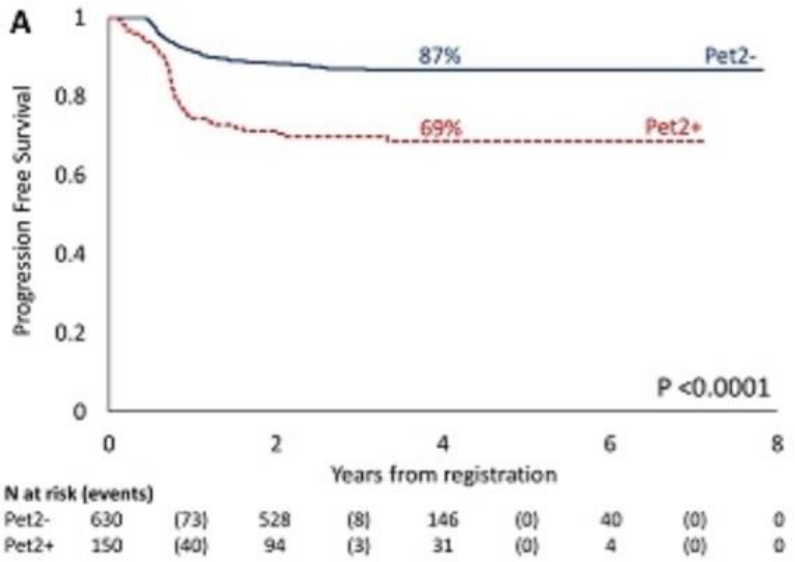
- Il monitoraggio della sicurezza e della tossicità di un nuovo farmaco biologico deve essere considerato l obiettivo principale negli studi di fase I-II

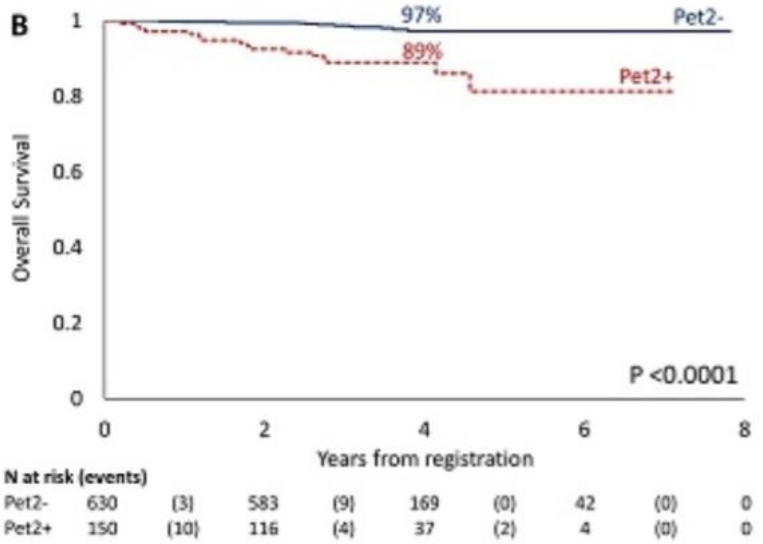
- Regimi di chemo-free rappresentano una futura opzione terapeutica per I pazienti con FL e DLBCL recidivi/ refrattari

Report del gruppo

- ✓ Non-Hodgkin Lymphoma
  - ✓ MCL
  - ✓ DLBCL
  - ✓ Follicular
  - ✓ Indolent NH
- ✓ Hodgkin
  - ✓ First line
  - ✓ Relapse

Early chemotherapy intensification with escalated BEACOPP in advanced-stage Hodgkin lymphoma with a positive interim PET-CT after 2 ABVD cycles: long-term results of the GITIL/FIL HD0607 trial





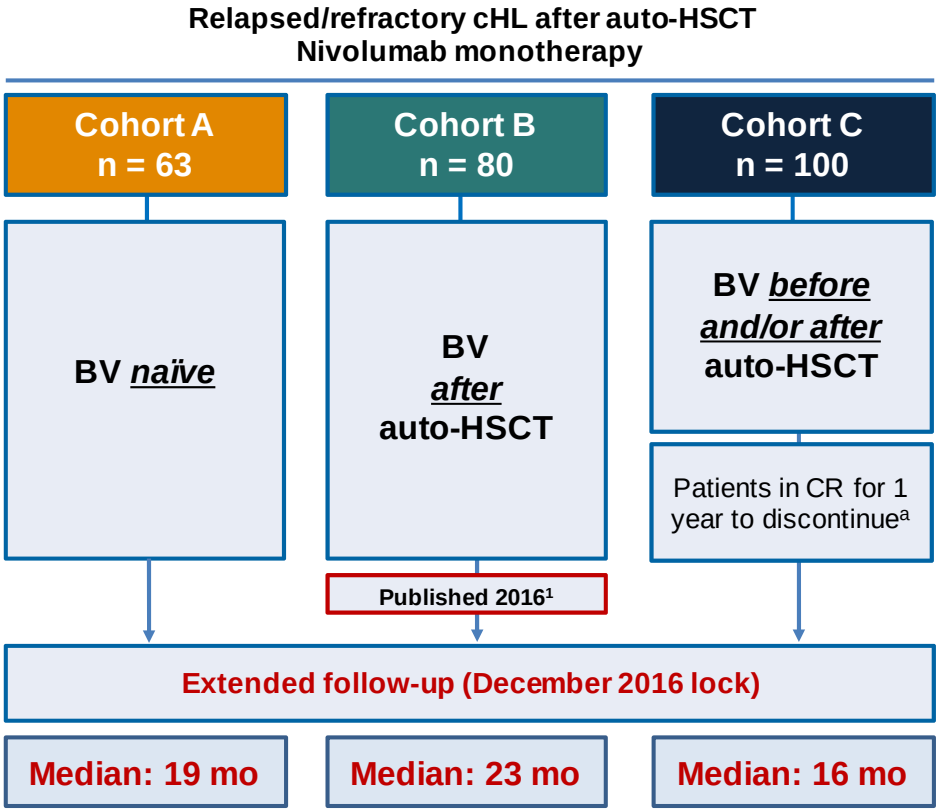
Gallamini A et al, S413.

Gruppo di lavoro

- Nei pazienti HD con PET 2 positiva dopo ABVD dobbiamo cambiare terapia

- BEACOPP è la terapia di salvataggio convenzionale nel paziente con HD PET-2 positivo trattato con ABVD?

Nivolumab for Relapsed/Refractory Classical Hodgkin Lymphoma After Autologous Transplant: Full Results After Extended Follow-Up of the Multicohort Multicenter Phase 2 CheckMate 205 Trial



Nivolumab 3 mg/kg IV Q2W
Treatment until disease progression or unacceptable toxicity[a]

Patients could elect to discontinue nivolumab and proceed to allogeneic (allo)-HSCT

Primary endpoint
- ORR by IRC

Additional endpoints
- CR/PR rate
- Duration of CR/PR
- PFS by IRC
- OS
- Safety

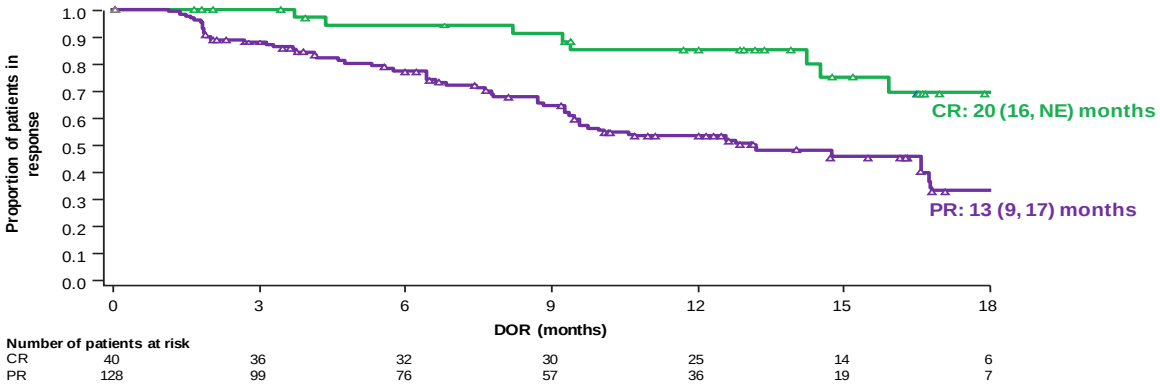
Best Overall Response After Extended Follow-Up

	BV naïve (Cohort A) n = 63	BV after auto-HSCT (Cohort B) n = 80	BV before and/or after auto-HSCT (Cohort C) n = 100	Overall N = 243
Objective response per IRC,[a] % (95% CI)	**65**	**68**	**73**	**69**
Best overall response per IRC, %				
Complete remission[b]	29	13	12	16
Partial remission	37	55	61	53
Stable disease	24	21	15	19
Progressive disease	11	8	10	9
Unable to determine	0	4	2	2

- Per investigator assessment, 33% of patients achieved CR and 39% achieved PR
- In post-hoc analyses, responses were similar irrespective of BV treatment sequence

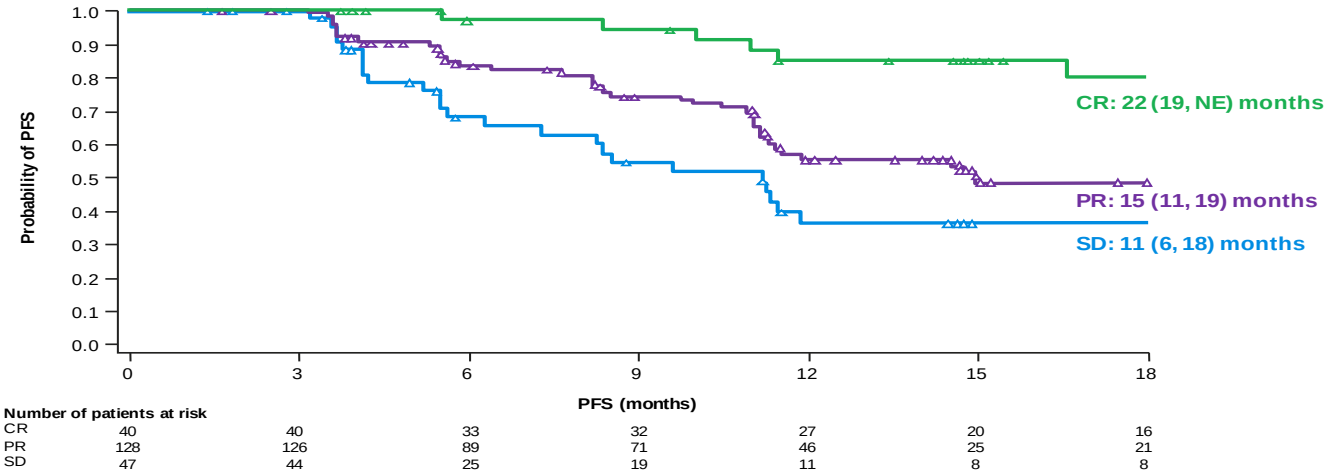
[a]Defined according to 2007 International Working Group criteria. [b]All CRs were confirmed by FDG-PET scan

DOR and PFS by Best Overall Response



DOR (per IRC) by cohort	Cohort A n = 41/63	Cohort B n = 54/80	Cohort C n = 73/100	Overall n = 168/243
Median DOR in all responders, months	20 (13, 20)	16 (8, 20)	15 (9, 17)	17 (13, 20)
Median DOR in CR patients, months	20 (NE, NE)	20 (4, NE)	15 (8, NE)	20 (16, NE)
Median DOR in PR patients, months	17 (9, NE)	11 (7, 18)	13 (9, 17)	13 (9, 17)

All values are medians (95% CI). n = responders/patients. NE = not evaluable



- Median (95% CI) PFS for overall patients (N = 243) was 15 (11, 19) months

All values are medians (95% CI). SD = stable disease

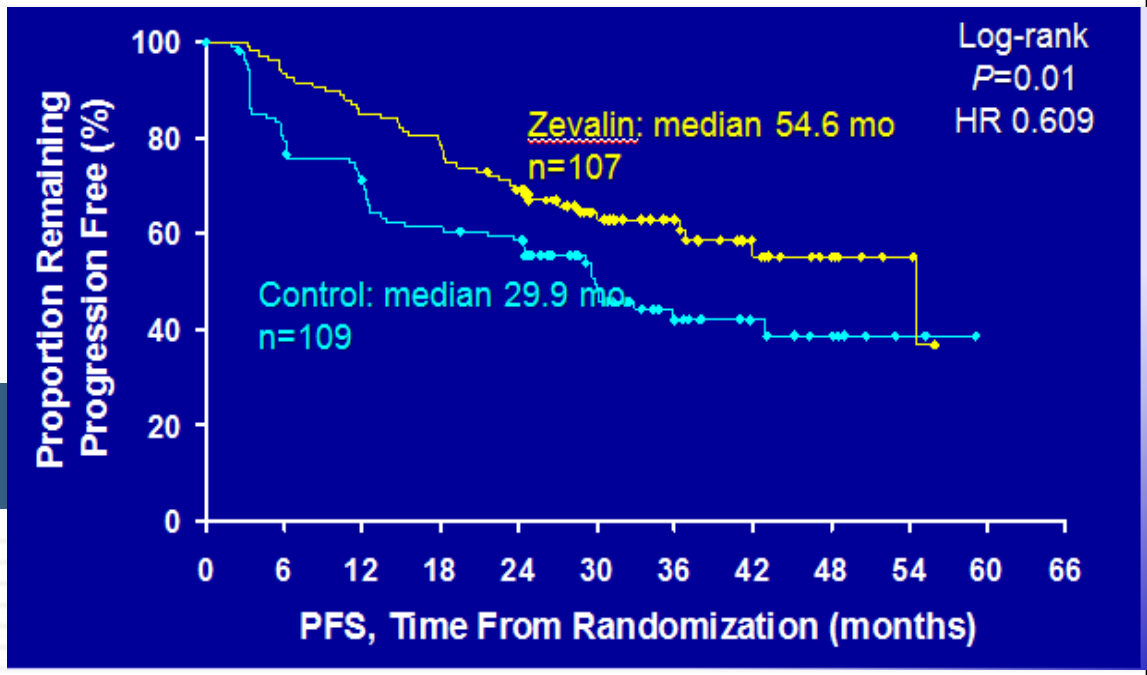
Gruppo di lavoro

- Nivolumab deve essere considerato come una terapia ponte al trapianto (allo/auto) nei pazienti con HD recidivati/ refrattario ?

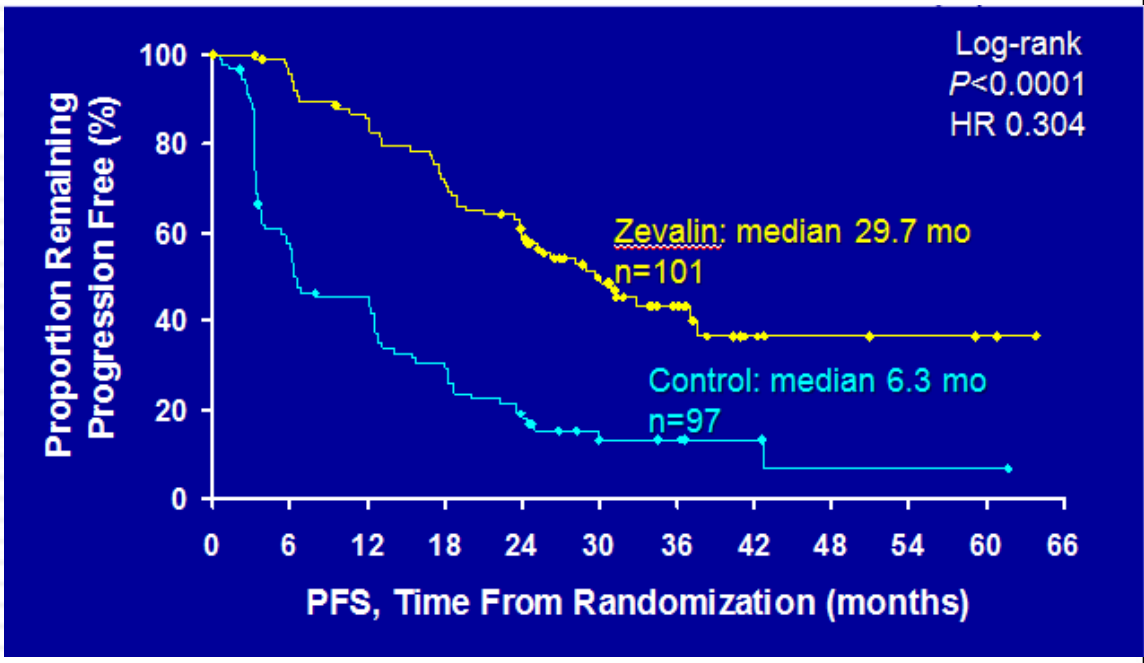
- Quale è il timing per considerare la migliore risposta a Nivolumab ?

Grazie per la cortese attenzione

FIT:
PFS in patients with CR/CRu after First-line Therapy



FIT:
PFS in patients with PR after First-line Therapy



Gruppo di lavoro

- The LyMa design (R-DHAP/R-BEAM) should be considred the standard first line therapy in young MCL?

- Rituximab maintenance (375mg/m2 every 2 months for 3 years) should be recommended to transplanted MCL patients?

-

Gruppo di lavoro

- *Is Pola R-CHOP regimen a promising first-line chemotherapy in a high risk DLBCL patients.*

- *Is R-CHOP + X (biological drugs)*

Gruppo di lavoro

- In the next future G-chemo will be the conventional therapy for FL ?

- G-Chemo only for high risk FL ? Younger FL?

- After theresults of Gallium study G/R Benda remains the preferred regimen for FL

Gruppo di lavoro

- Higher PET-CR rate with G-chemo vs R-chemo (IHP 2007 criteria).

- Is PET the gold standard imaging modality for response assessment ?

- PET should be considered a potential surrogate for PFS and OS and a platform for response-adapted therapy ?

Gruppo di lavoro

- The combination of novel drugs in addition to chemotherapy represents a promising therapeutic option in first line treatment
- The monitoring of safety is important during treatment with novel drugs
- Chemo-free regimens represent an option in both FL and DLBCL relapsed/refractory patients