NHL: State of the Art 2016
The Good News and the Bad News!

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Dicloure$

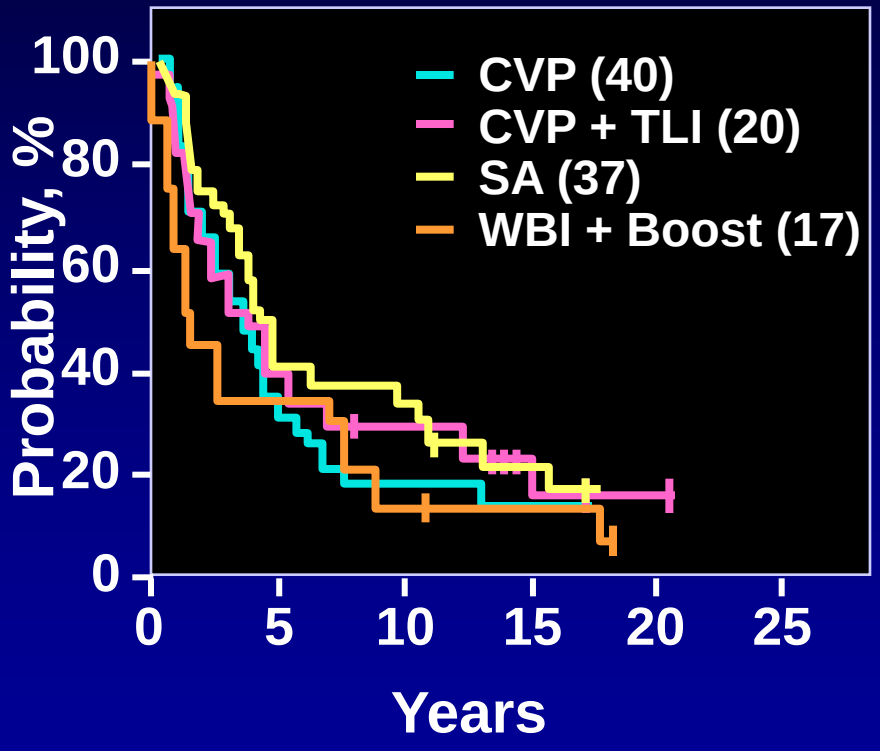
- Consulting & advisory roles: Roche/Genentech, Celgene, Gilead, Pharmacyclics, Astra-Zeneca, Astellas, Abbvie
- Research funding: Teva, Medimmune, Acerta, Gilead, Pharmacyclics, Celgene, Abbvie
- * All research funding to institution

Objectives

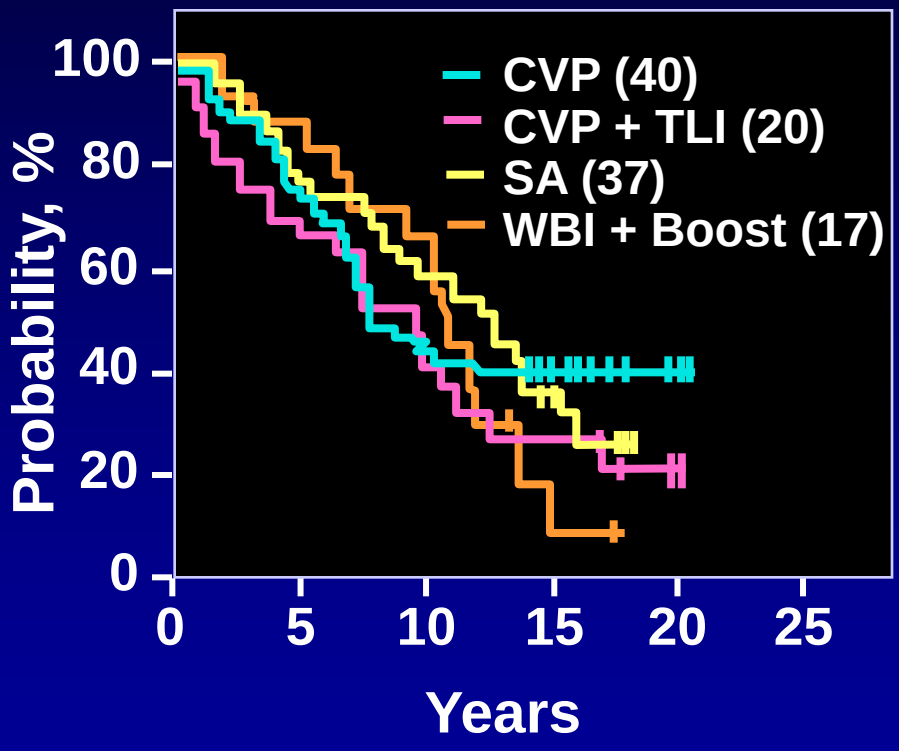
- Where we were
- Where we are
- Where we need to go

Treatment for Stage IV Indolent NHLs

Freedom From Progression

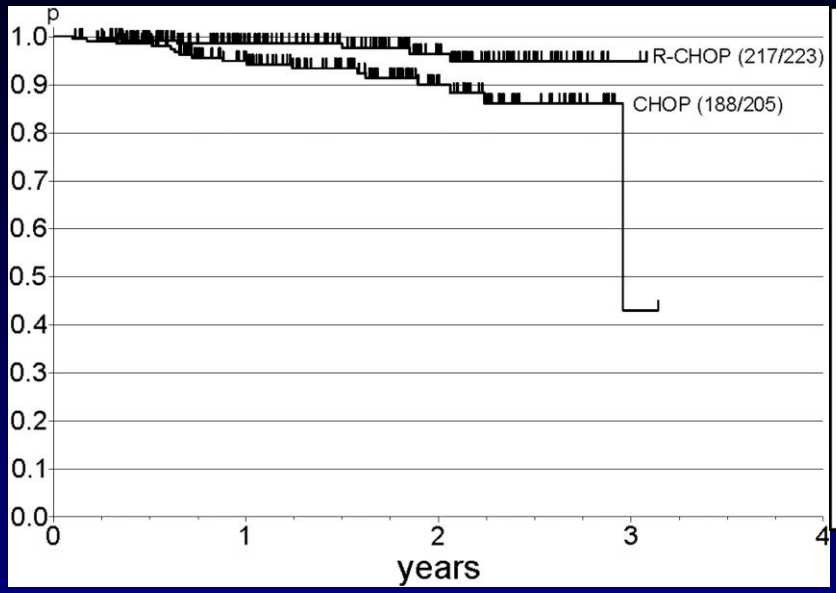


Survival

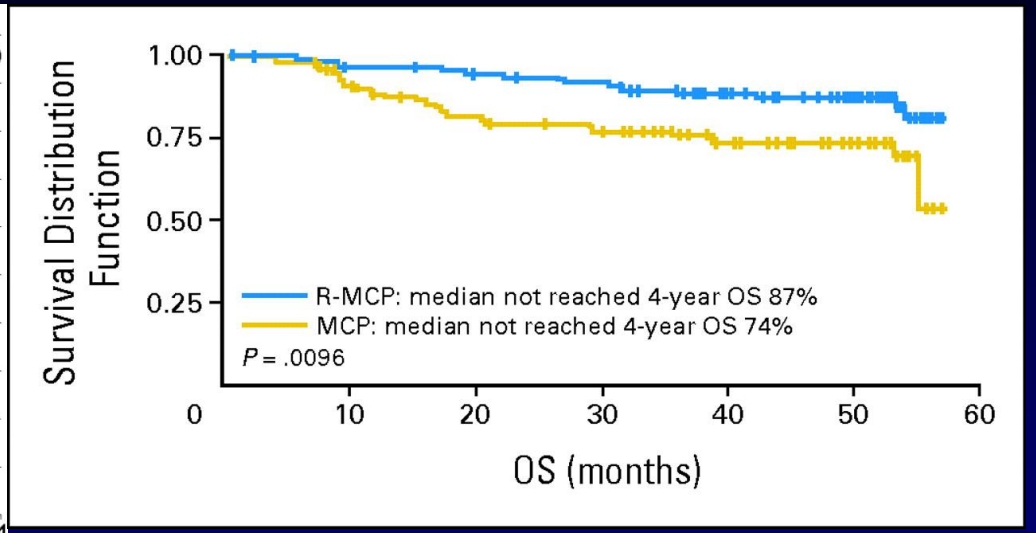


Rosenberg. *J Clin Oncol*. 1985;3:299-310.

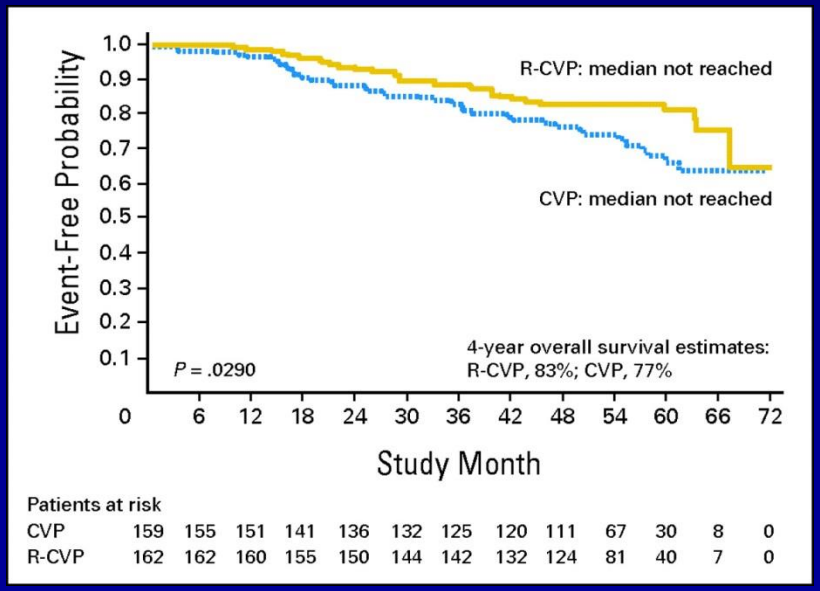
Rituximab in Front-line Follicular NHL



Hiddemann et al. Blood 2005;106:3725-3732

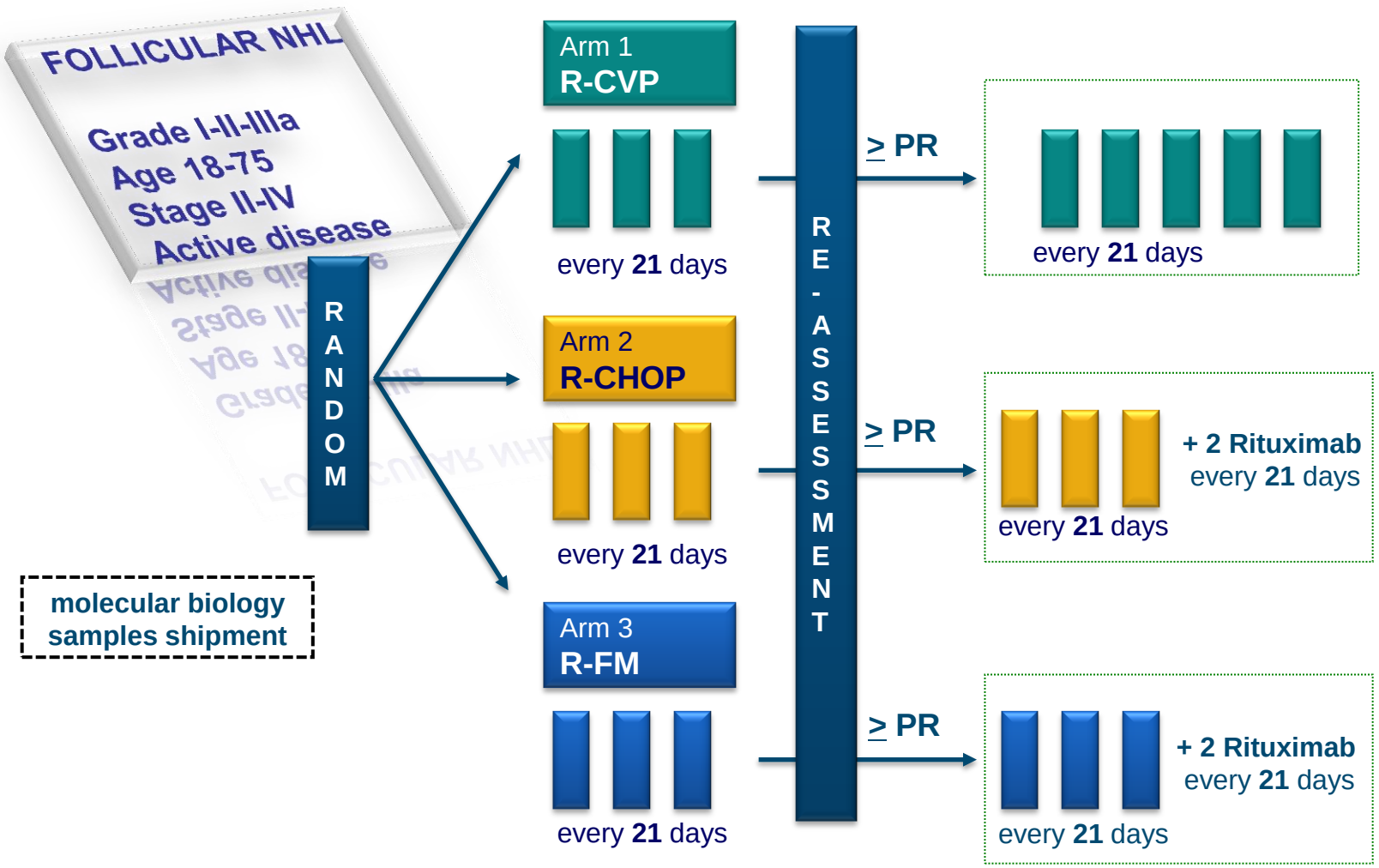


Herold et al. JCO 2007;25:1986-1992



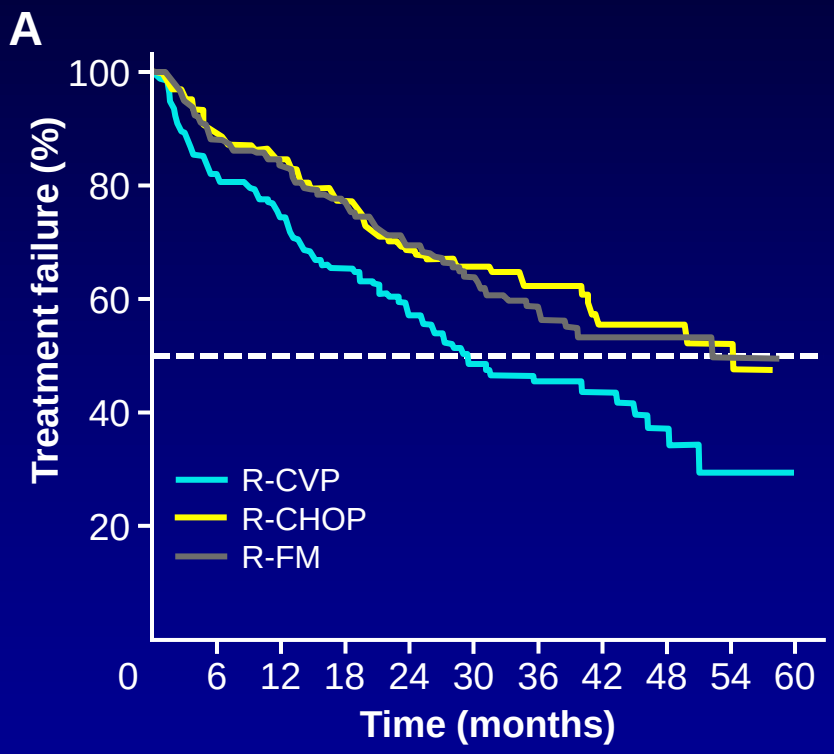
Marcus et al. JCO 2008;26:4579-4586

FOLL05



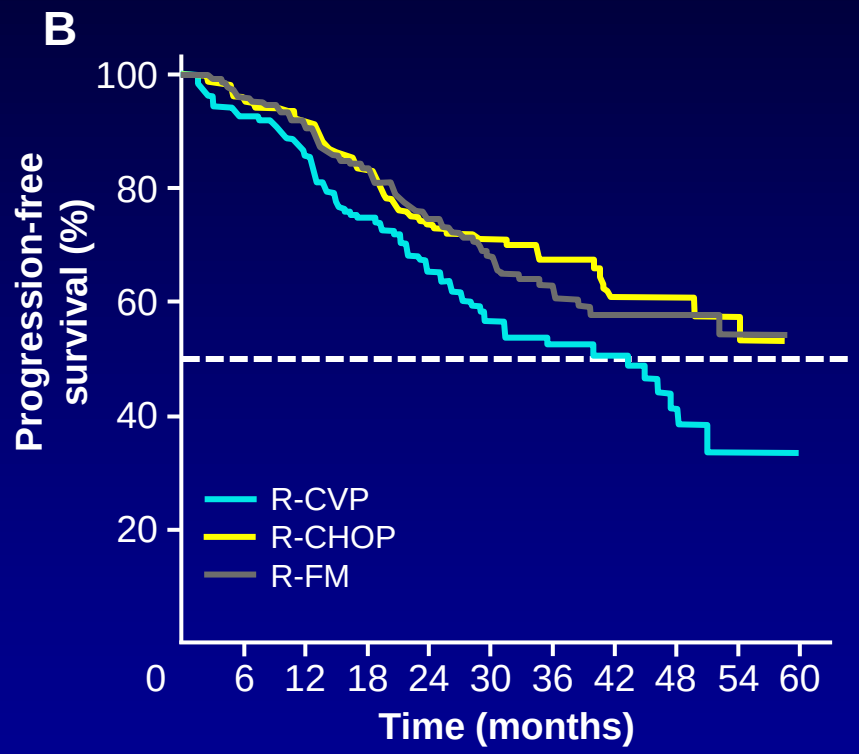
Federico et al. *J Clin Oncol*. 2013; 21:1506-1513.

Time to treatment failure and progression-free survival in FOLLO5 Study



No. at risk

R-CVP	168	136	119	95	74	51	36	23	13	5	1
R-CHOP	165	147	137	120	83	66	47	32	19	12	5
R-FM	171	150	139	120	95	68	50	32	20	12	4

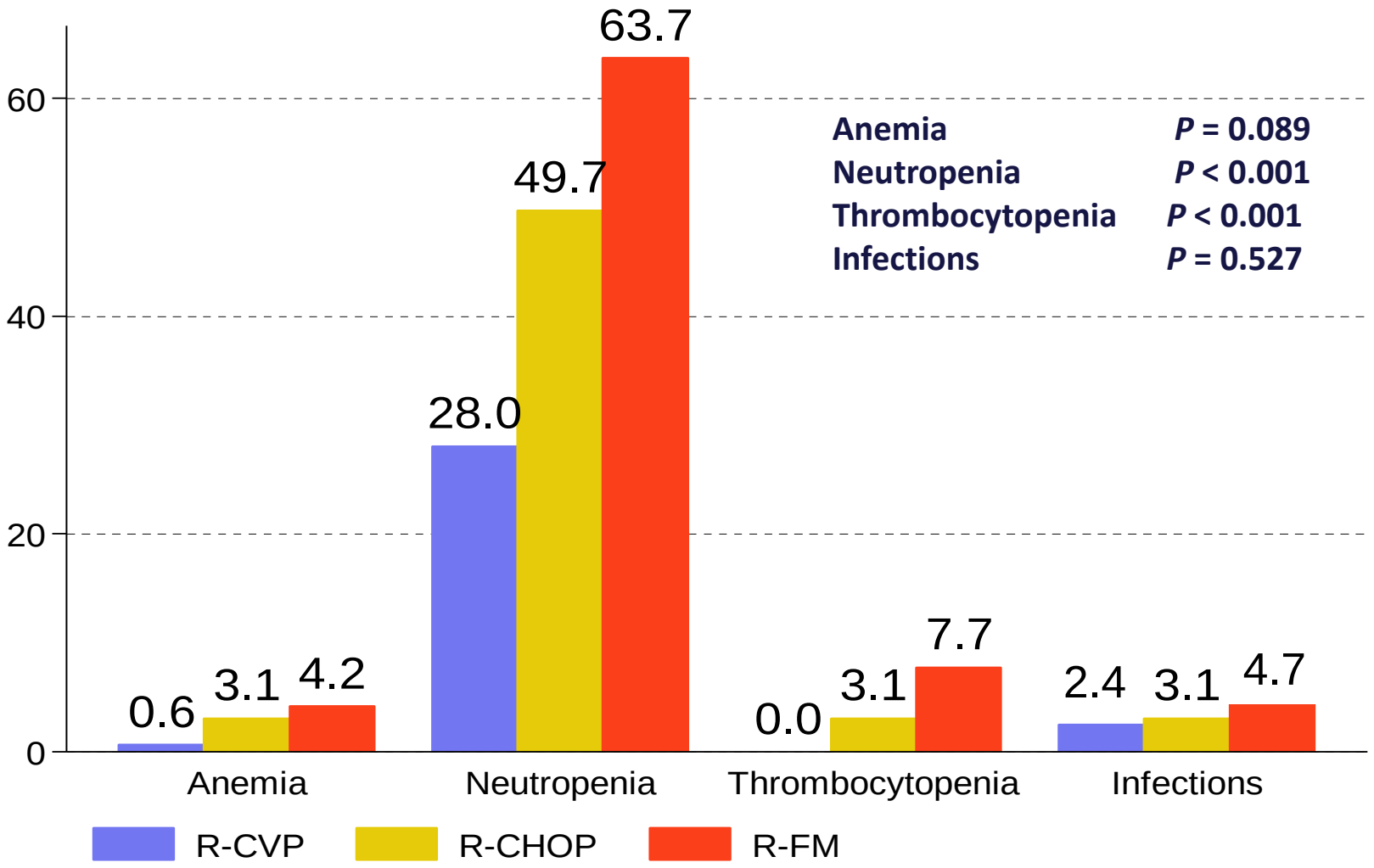


No. at risk

R-CVP	168	154	136	108	85	60	41	27	14	6	1
R-CHOP	165	157	147	128	89	70	51	36	22	14	6
R-FM	171	163	151	130	101	73	55	36	23	14	5

Federico M et al. JCO 2013;31:1506-1513

FOLL05: Grade 3-4 Toxicities by Arm (%)



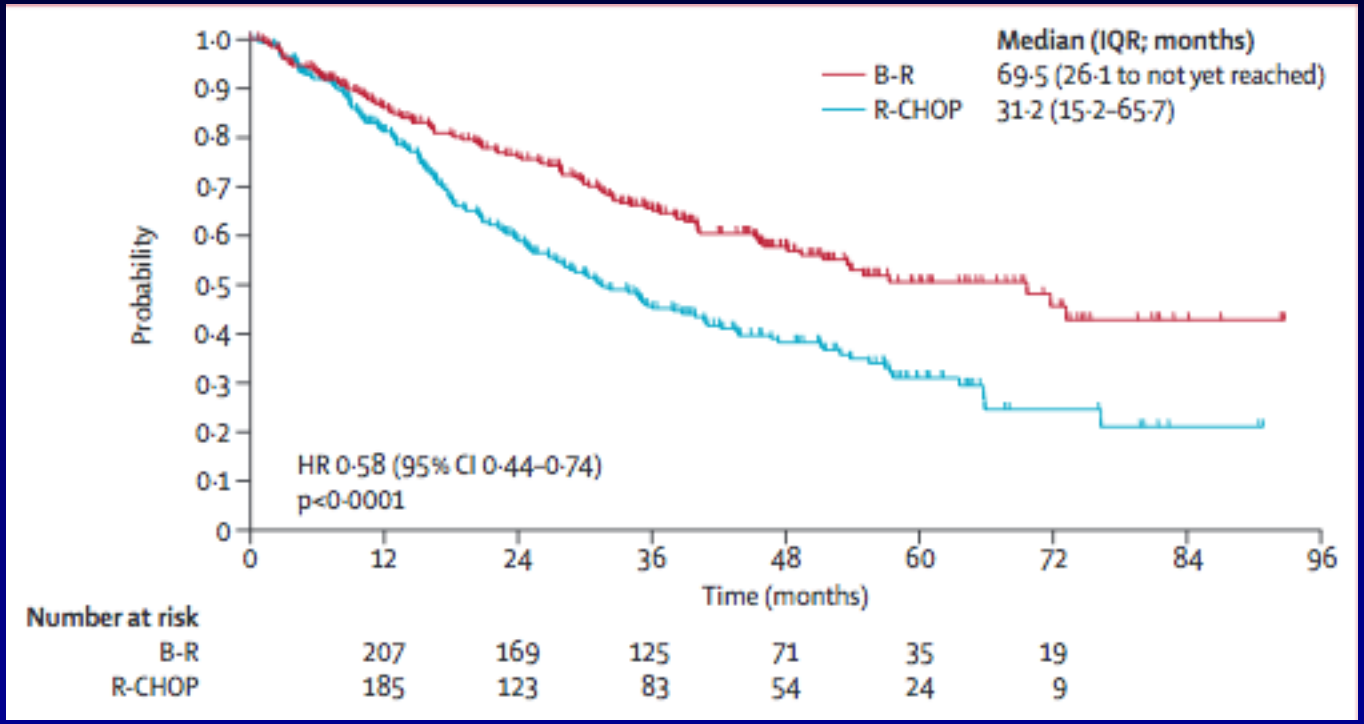
Federico et al. *J Clin Oncol*. 2013; 21:1506-1513.

Results — Response rates

	B-R (n=261)	CHOP-R (n=253)	*P* value
ORR	92,7 %	91,3 %	
CR	39,8 %	30,0 %	= 0.021
SD	2,7 %	3,6 %	
PD	3,5 %	2,8 %	

Rummel et al, Lancet 381:1203, 2013

BR vs R-CHOP in Untreated FL



Rummel et al, Lancet 381:1203, 2013

BRIGHT: Response Rates

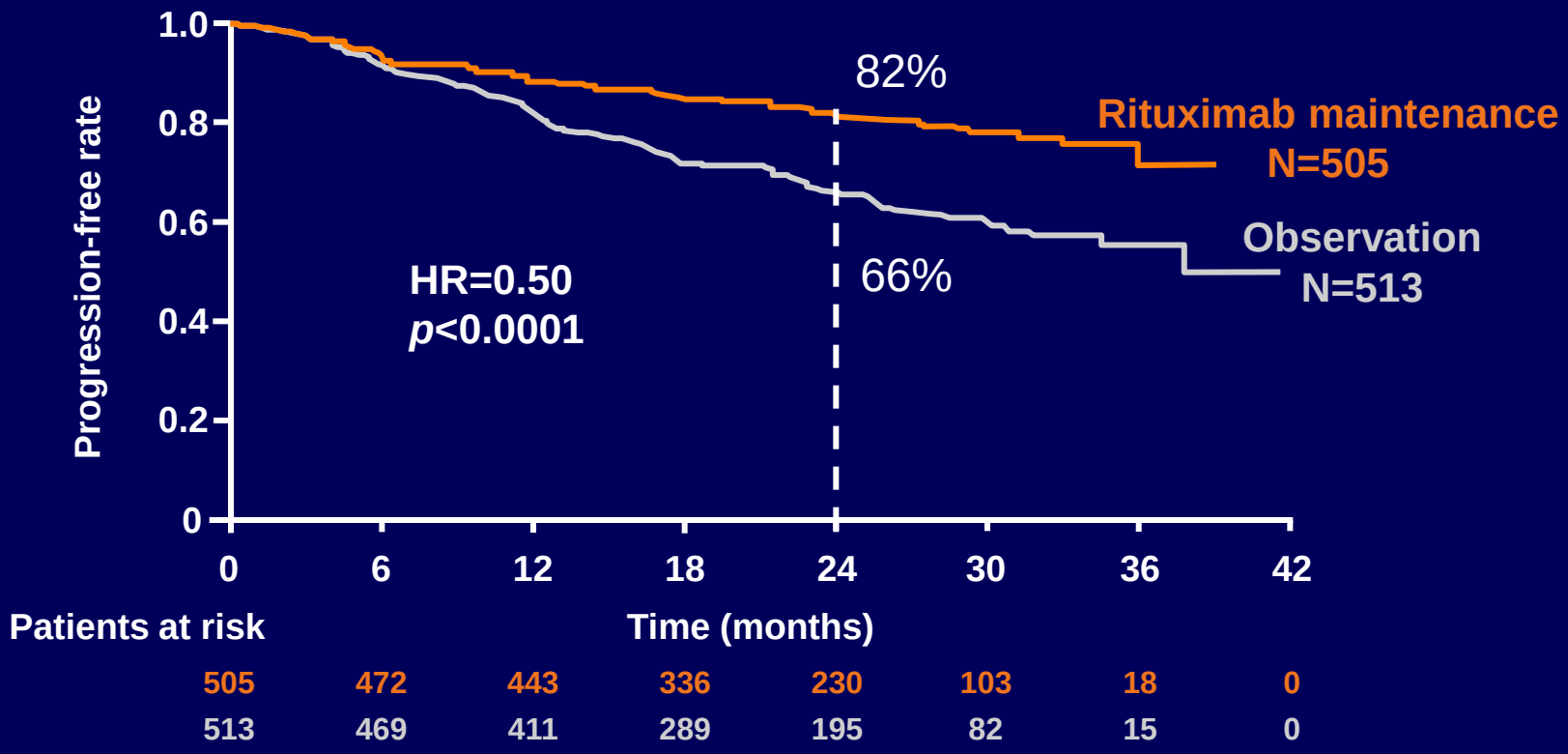
IRC Assessment of Response by Histology, n/N (%)	CR		CR + PR	
	BR	R-CHOP/R-CVP	BR	R-CHOP/R-CVP
iNHL	49/178 (28)	43/174 (25)	173/178 (97)	160/174 (92)
FL	45/148 (30)	37/149 (25)	147/148 (> 99)	140/149 (94)
MZL	5/25 (20)	4/17 (24)	23/25 (92)	12/17 (71)
LPL	0/5	1/6 (17)	3/5 (60)	6/6 (100)
MCL	17/34 (50)	9/33 (27)*	32/34 (94)	28/33 (85)*

*R-CHOP, n=22.

Flinn et al. *Blood*. 2014; 123:2944-2952.

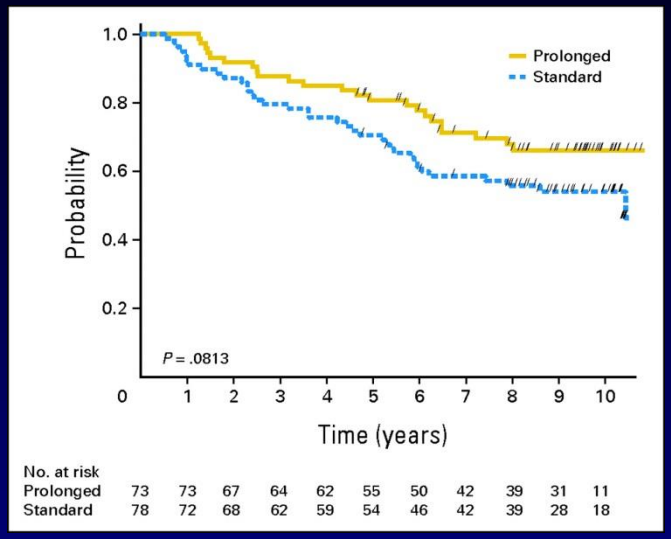
Primary endpoint (PFS) met at the planned interim analysis

- Rituximab 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)

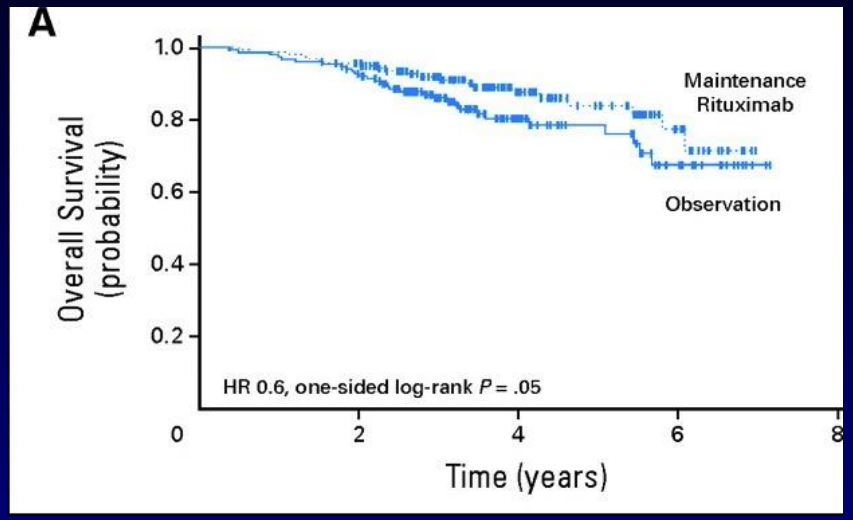


Salles et al, Lancet 377:42, 2011

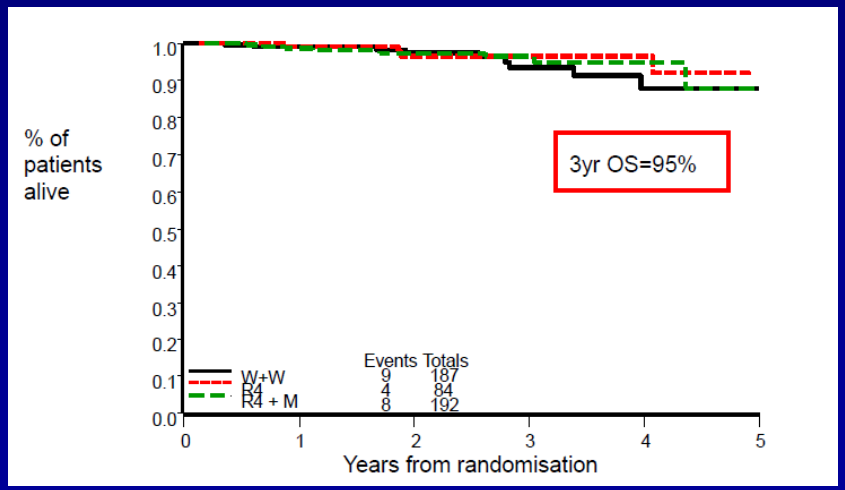
Overall Survival By Maintenance



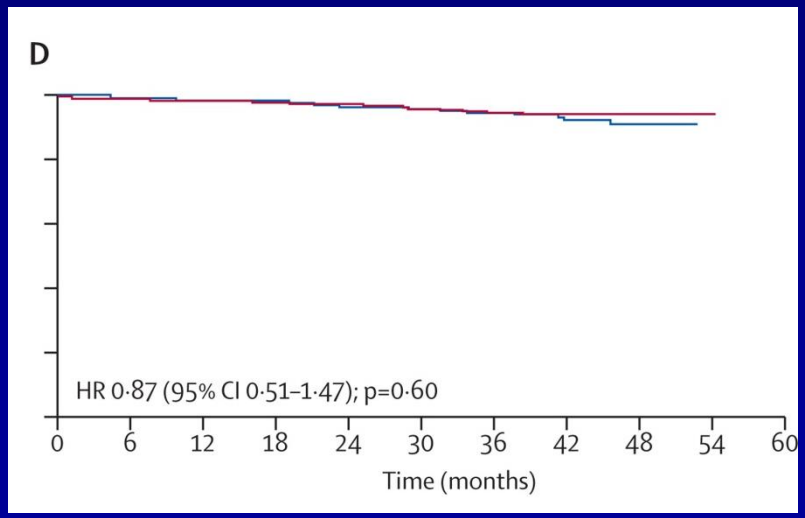
Martinelli G et al. JCO 2010;28:4480-4484



Hochster, H. et al. J Clin Oncol; 27:1607-1614 2009



Ardeshna KM et al. *Proc ASH* 2010; Abstract 6



Salles et al, Lancet 377:42, 2011

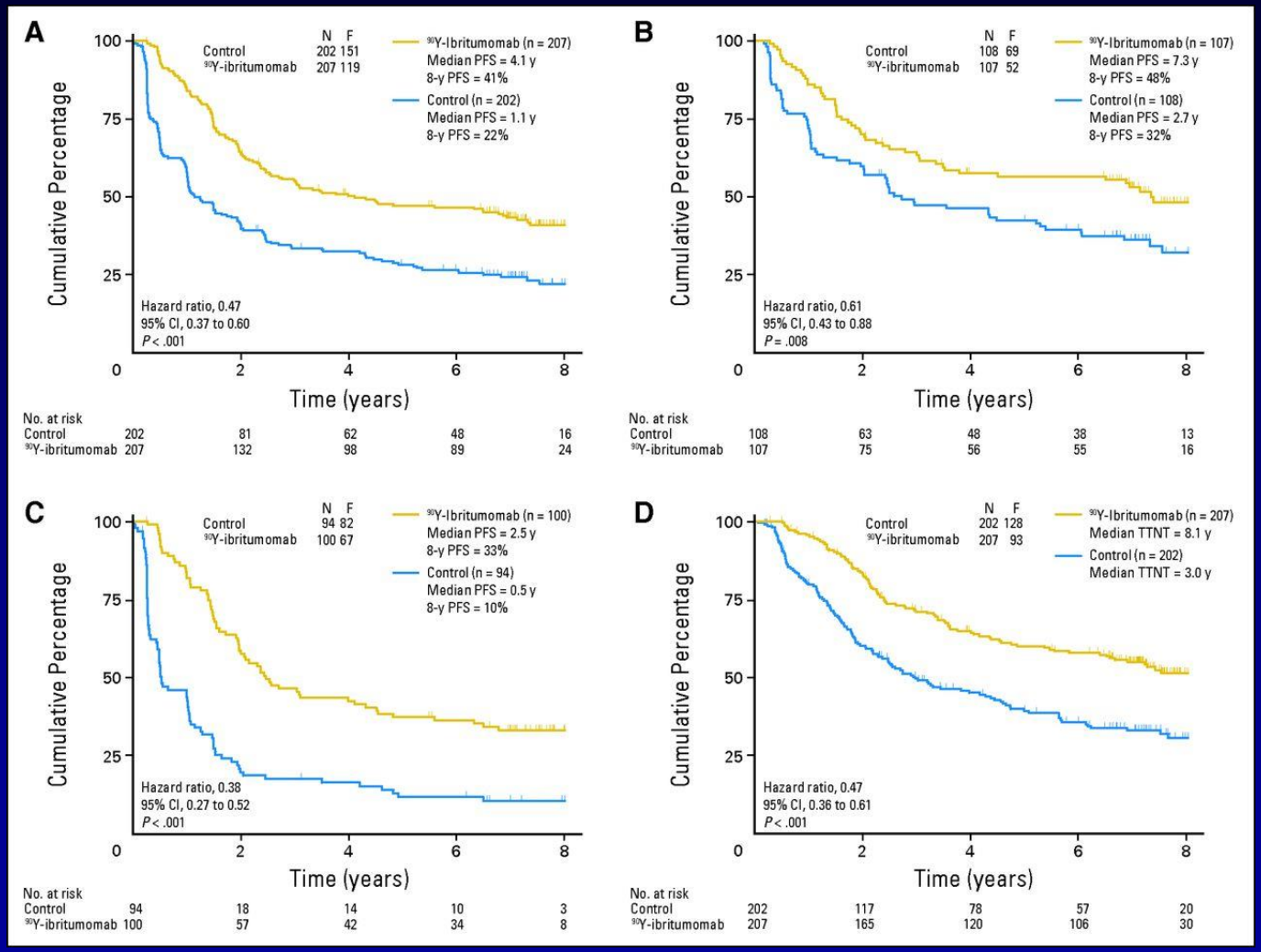
PFS FIT Trial

Overall

CR/CRu

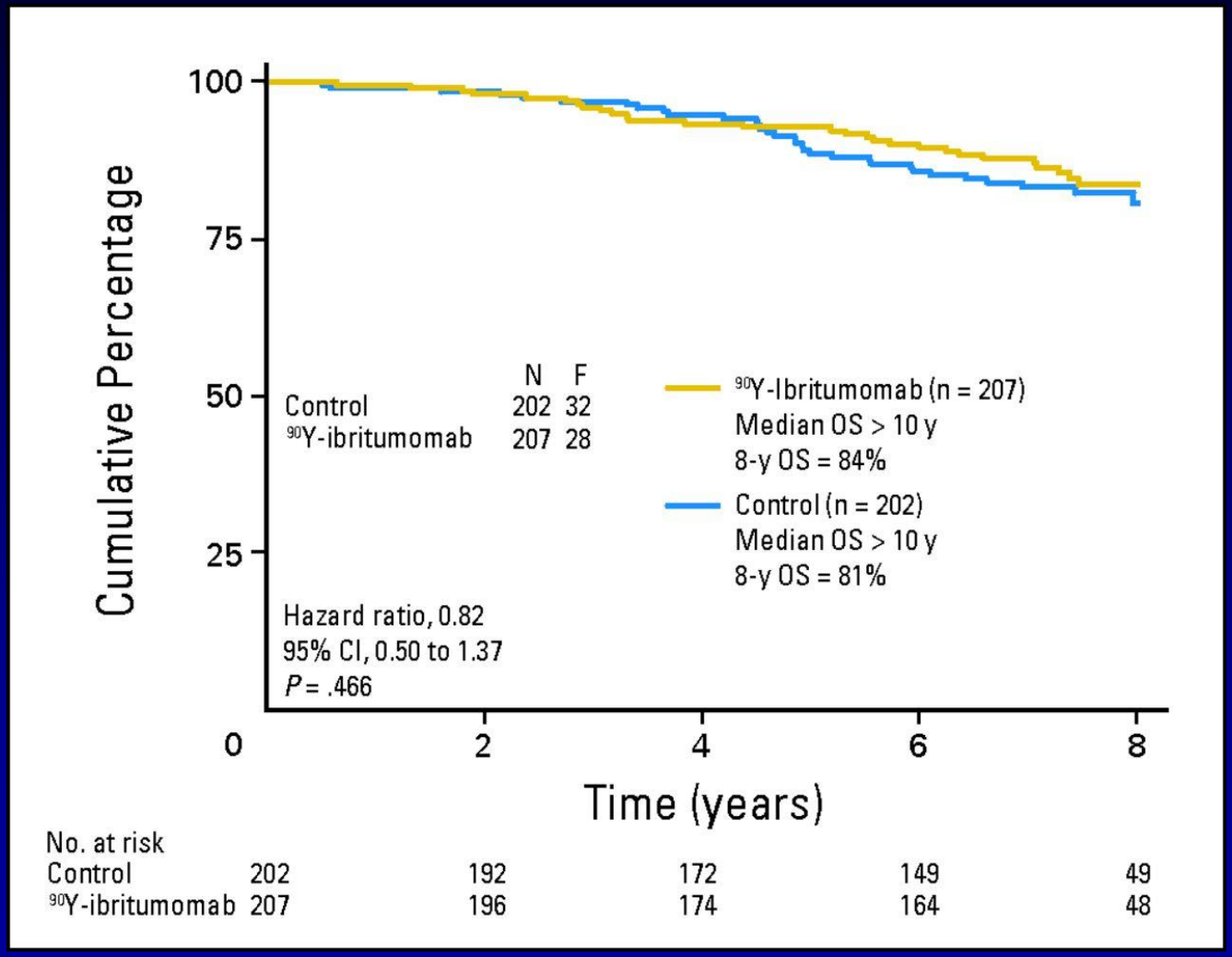
PFS

TTNT



Morschhauser F et al. JCO 2013;31:1977-1983

FIT Trial: Overall Survival



Morschhauser F et al. JCO 2013;31:1977-1983

Review Article

Montoto et al, Haematologica 98: 1014, 2013

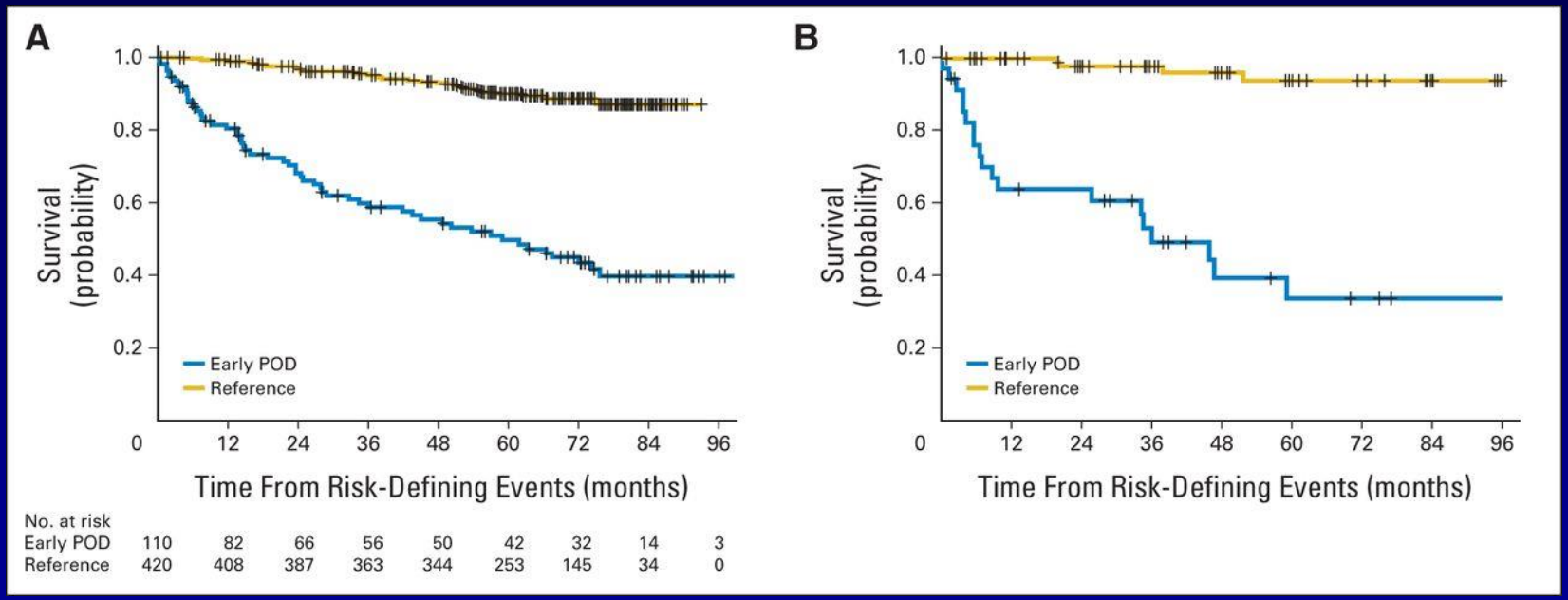
Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party

Silvia Montoto,[1] Paolo Corradini,[2] Martin Dreyling,[3] Michele Ghielmini,[4] Eva Kimby,[5] Armando López-Guillermo,[6] Stephen Mackinnon,[7] Robert E. Marcus,[8] Gilles Salles,[9] Harry C Schouten,[10] Anna Sureda,[11] and Peter Dreger[12]

[1]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; [2]Hematology and Bone Marrow Transplant Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [3]Internal Medicine III, University of Munich, Munich, Germany; [4]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [5]Division of Hematology, Department of Medicine at Huddinge, Karolinska Institutet, Stockholm, Sweden; [6]Department of Hematology, Hospital Clínic, Barcelona, Spain; [7]Department of Haematology, UCL Medical School, London, UK; [8]Haematological Medicine, King's College Hospital, London, UK; [9]Hematologie, Hospices Civils de Lyon and Université Claude Bernard Lyon-1, Pierre Bénite, France; [10]Department of Internal Medicine, Section of Hematology, University Medical Center Maastricht, Maastricht, The Netherlands; [11]Haematology Department, Addenbrookes Hospital, Cambridge, UK; and Internal Medicine V, University of Heidelberg, Heidelberg, Germany

Consensus n.	Statement n.	Agreed statement
1	1	HDT-ASCR is *not* an appropriate treatment option to consolidate first remission in patients with FL responding to immuno-chemotherapy, outside the setting of clinical trials.
2	5	In patients in first relapse with chemo-sensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission.
	9	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with a short response duration (<3 years) after immuno-chemotherapy.
	10	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with high-risk FLIPI at relapse.
	11*	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients previously treated with rituximab.*
3	12	Remission consolidation with HDT-ASCR is an appropriate treatment option in patients in second or subsequent relapses with chemo-sensitive disease.
4	13	Allogeneic transplantation should be considered in patients with relapse after HDT-ASCR.
	18	*Reduced-intensity*/ non-myeloablative conditioning regimens are generally more appropriate in patients receiving an allogeneic transplant.
5	19	In FL, the available biological and genetic risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for HDT-ASCR and allogeneic transplantation are mainly guided by the clinical course.

OS from a risk-defining event after diagnosis in patients who received R-CHOP chemotherapy in the National LymphoCare Study group.



Carla Casulo et al. JCO 2015;33:2516-2522

CALGB50803: Best Response

	Overall N =55	FLIPI 0-1 N = 16	FLIPI 2 N = 35	FLIPI 3 N = 2	FLIPI unk N=2
ORR	**53 (96%)**	16 (100%)	33 (94%)	2 (100%)	2 (100%)
CR	**39 (71%)**	12 (75%)	24 (69%)	2 (100%)	1 (50%)
PR	**14 (25%)**	4 (25%)	9 (26%)	-	1 (50%)
SD	**2 (4%)**	0 (0%)	2 (6%)	-	-

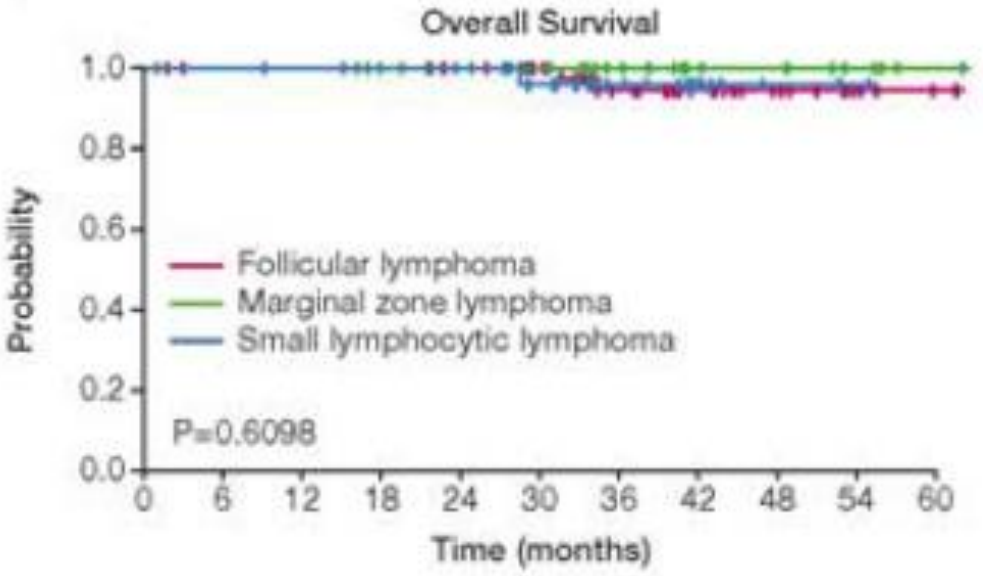
4 additional patients in PET- CR but not confirmed by BMBx. There was no significant association between CR rate and FLIPI score, presence of bulky disease, or grade.

Martin et al, Proc ASCO 2014, abstr 8521

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

R^2 in Untreated Indolent Lymphoma: Overall Survival

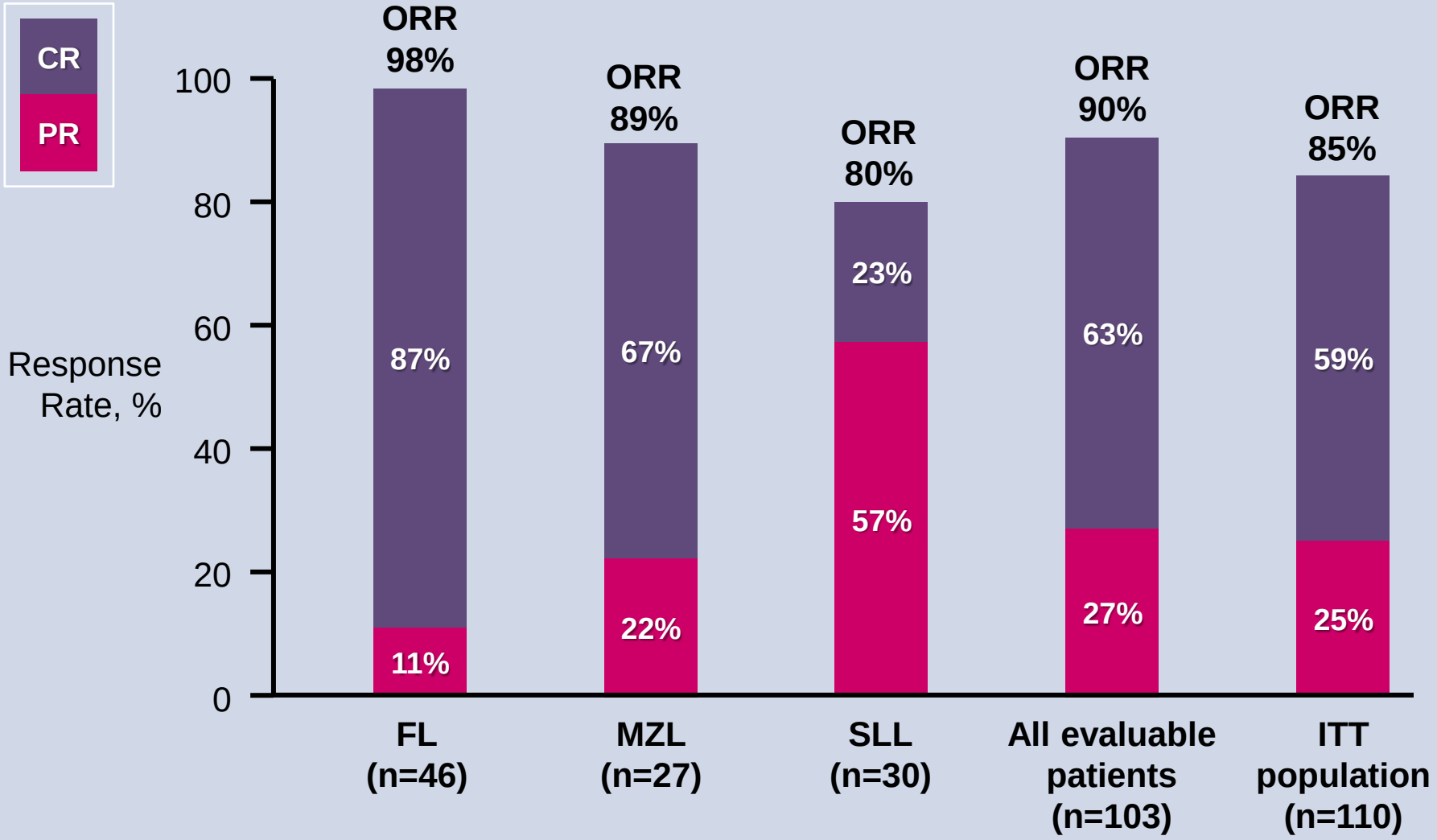
Estimated 3-year OS was 96.1%
(95% CI 91·9–100%)



Fowler et al. Lancet Oncol 15:1311, 2014

Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma

Response Rates



Fowler NH, et al. *Lancet Oncol.* 2014,15:1311-1318.

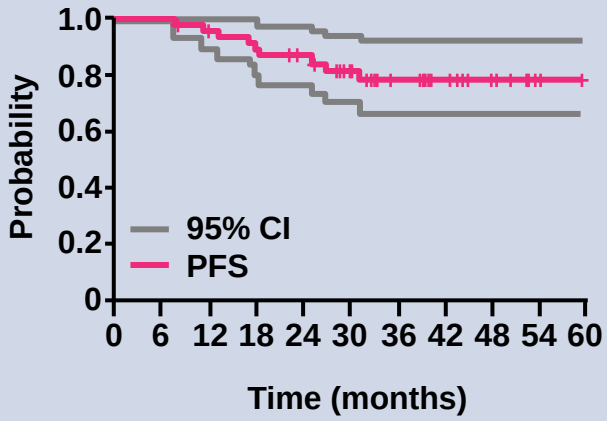
Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma

Efficacy

Median PFS for the entire cohort was 53.8 months (95% CI, 50.6–NA)

FL Median PFS: **not reached**

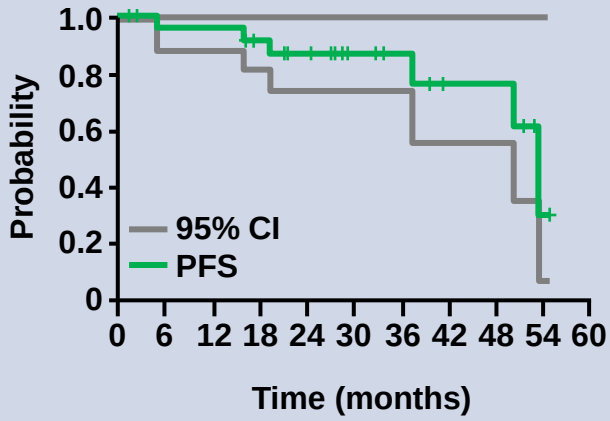
(median follow-up 40.6 months)



Patients at Risk

46 46 43 40 36 29 20 14 10 2 0

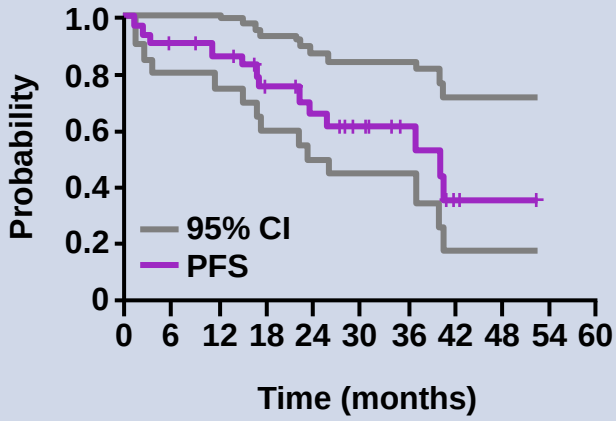
MZL Median PFS: **53.8 months**



Patients at Risk

27 23 23 19 16 10 8 5 5 1 0

SLL Median PFS: **40.4 months**



Patients at Risk

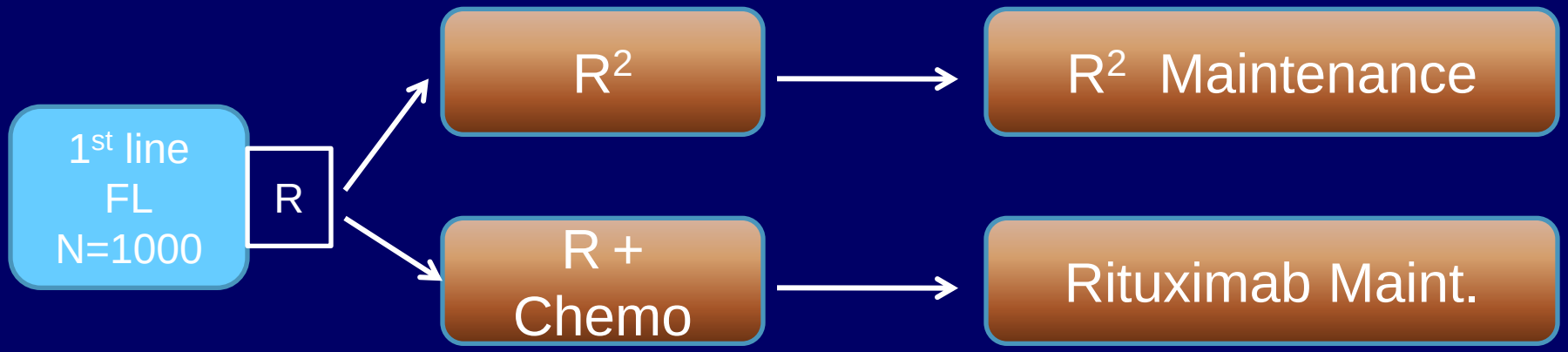
30 26 24 19 15 11 7 2 1 0 0

- As part of an exploratory analysis, pre- and post-treatment PET scans were obtained and available for 45 patients
- 44 (98%) were PET-positive prior to therapy
- **After treatment, 42 (93%) patients were PET-negative**

NA, not available.

Fowler NH, et al. *Lancet Oncol.* 2014,15:1311-1318.

RELEVANCE Study Design
(Rituximab and LEnalidomide versus Any ChEmotherapy)



- R+Chemo:
  - Investigator's choice of R-CHOP, R-CVP, BR
- Lenalidomide 20mg for 6 cycles, then 10mg if CR
- LYSA (PI: Morschhauser) + North America (PI: Fowler)

Bendamustine-R in Relapsed Indolent NHL: % Response Rate By Histology

Response Category	All Patients	Indolent Lymphoma	Mantle Cell Lymphoma
ORR	92	93	92
CR	41	41	42
CRu	14	13	17
PR	38	39	33
SD	8	7	8
PD	0	0	0

•**ORR, overall response rate (CR + CRu + PR); CR, complete response; CRu, complete response, unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease**

Robinson et al, JCO 26:4473, 2008

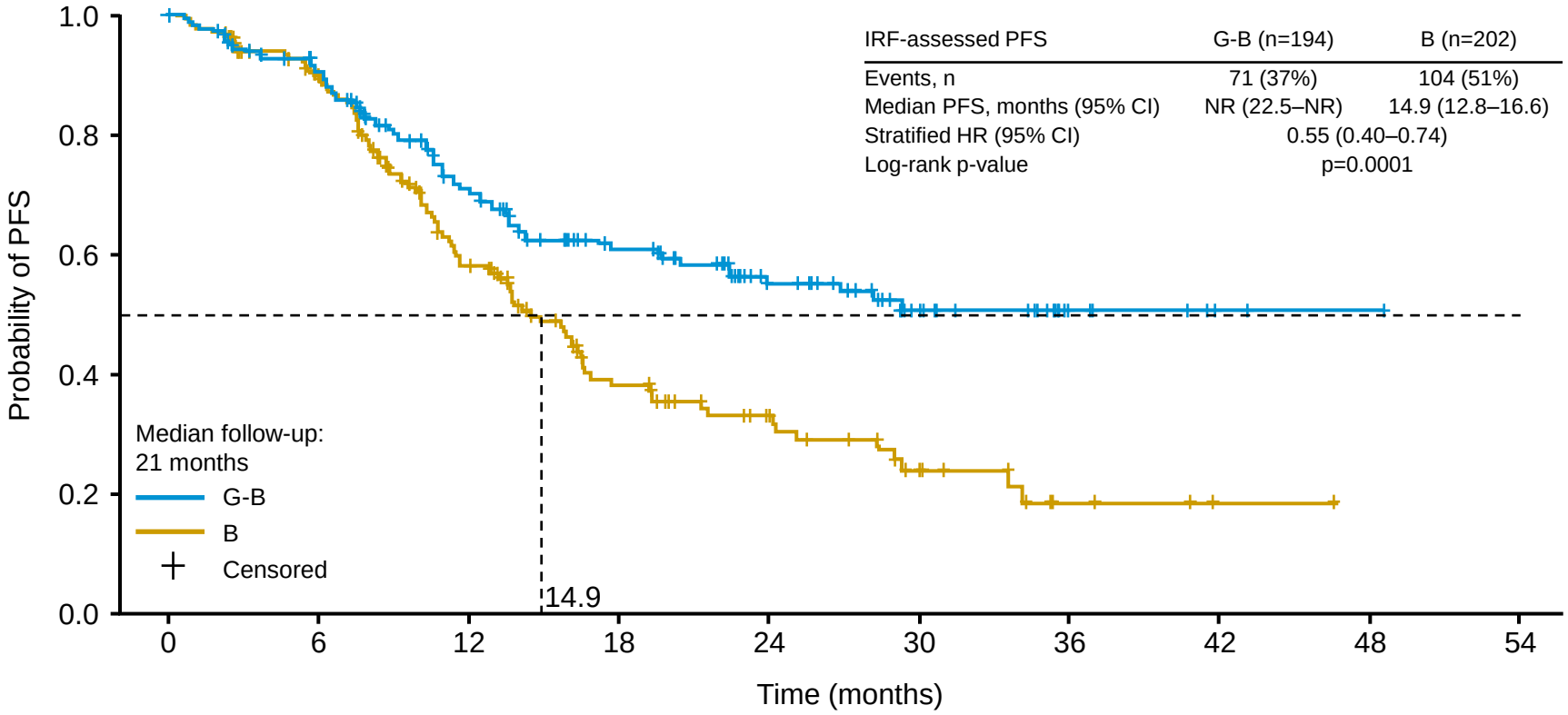
GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma

L.H. Sehn[1], N. Chua[2], J. Mayer[3], G. Dueck[4], M. Trneny[5], K. Bouabdallah[6], N. Fowler[7], V. Delwail[8], O. Press[9], G. Salles[10], J. Gribben[11], A. Lennard[12], P.J. Lugtenburg[13], N. Franklin[14], E. Wassner-Fritsch[15], G. Fingerle-Rowson[15], B.D. Cheson[16]

[1]British Columbia Cancer Agency and the University of British Columbia, Vancouver, Canada; [2]University of Alberta, Alberta, Canada; [3]University Hospital and Masaryk University, Brno, Czech Republic; [4]BC Cancer Agency, British Columbia, Canada; [5]Charles University, Prague, Czech Republic; [6]CHU Haut-Leveque, Pessac, France; [7]University of Texas, Houston, TX, USA; [8]University Hospital, INSERM, Poitiers, France; [9]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; [10]Hospices Civils de Lyon, Pierre Bénite, France; [11]Queen Mary University of London, London, United Kingdom; [12]Newcastle University, Newcastle upon Tyne, UK; [13]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [14]F. Hoffmann-La Roche Ltd, Welwyn Garden City, UK; [15]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Georgetown University Hospital, Washington DC, USA.

Lancet Oncol, in press

GADOLIN primary outcome: IRF-assessed PFS



IRF, independent radiology facility; HR, hazard ratio; CI, confidence interval; NR, not reached

CALGB 50401: Response and event-free survival

	L (N=45)	L + R (N=44)
Overall (ORR)	51.1% 95% CI (35.8-66.3)	72.7% 95% CI (52.2-85.0)
Complete (CR)	13.3%	36.4%
Partial (PR)	37.8%	36.4%
Median EFS	1.2 yrs	2.0 yrs
2 year EFS	27%	44%

Median F/U 1.7 years (0.1 – 4.1)

Unadjusted EFS HR of L vs L+R is 2.1 (p=0.010)

Adjusted (for FLIPI) EFS HR of L vs L+R is 1.9 (p=0.061)

Leonard et al, JCO 33:3635, 2015

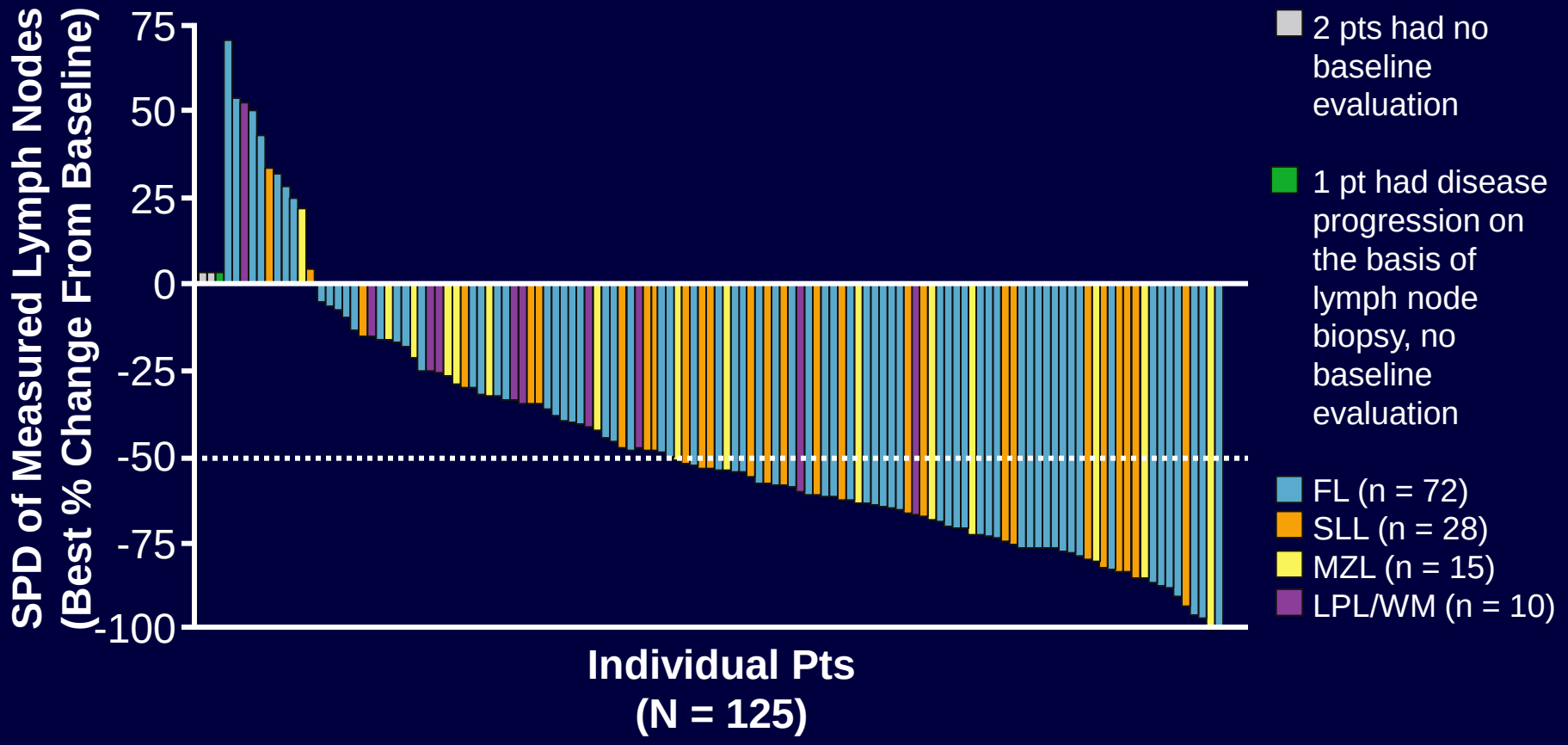
Idelalisib Monotherapy in Refractory iNHL (Phase II): Responses

Characteristic	Patients, n (%) (N = 125)
ORR, n (%)	71 (57)
CR	7 (6)
PR	63 (50)
Minor response*	1 (1)
SD	42 (34)
PD	10 (8)
Not evaluated	2 (2)
Time to response, mos (n = 71)	
Median (interquartile range)	1.9 (1.8-3.7)

*LPL/WM

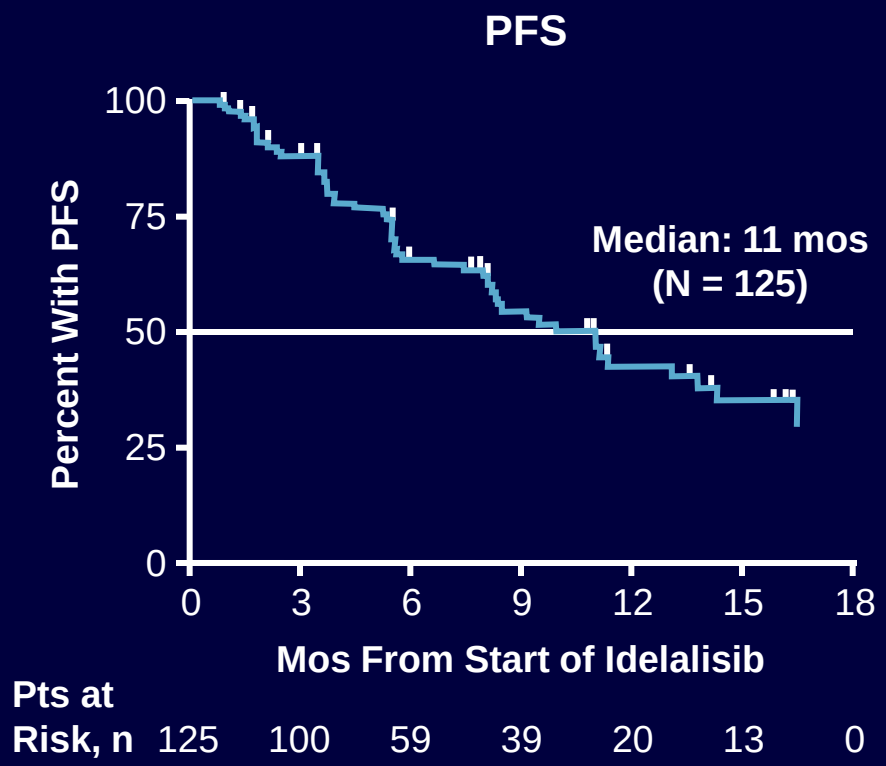
Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

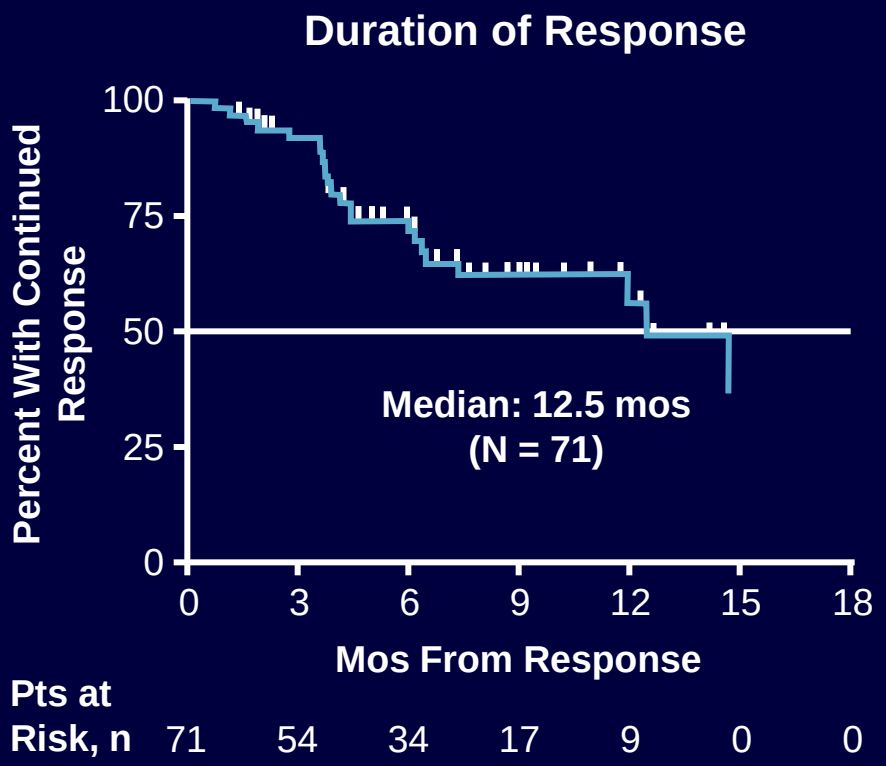
Idelalisib Monotherapy in Refractory iNHL (Phase II): LN Size Change from Baseline



Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

Phase II Study of Idelalisib Monotherapy in Refractory iNHL: PFS and DOR





Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

Idelalisib Monotherapy in Refractory iNHL (Phase II): Adverse Events

AE, n (%)	Any Grade	Grade ≥3
Diarrhea	54 (43)	16 (13)
Fatigue	37 (30)	2 (2)
Nausea	37 (30)	2 (2)

Transaminases, n (%)	Any Grade	Grade 3/4
ALT elevated	59 (47%)	16 (13%)
AST elevated	44 (35%)	10 (8%)

Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

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Gilead Cancer Drug Reviewed After Deaths in Combo Trials

by Doni Bloomfield
DoniBloomfield

March 11, 2016 – 6:39 PM CET *Updated on* March 11, 2016 – 11:50 PM CET

- FDA, European drug regulators are reviewing Gilead treatments
- Deaths, side effects reported after drug used in combination

U.S. and European regulators are reviewing Gilead Sciences Inc.'s cancer drug Zydelig after some patients died or suffered other side effects while taking it with other drugs in

Gilead Sciences Halts Drug Studies Over Side Effects, Death

By THE ASSOCIATED PRESS •
FOSTER CITY, Calif. — Mar 15, 2016, 5:37 PM ET

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3
SHARES

Biologic drugmaker Gilead Sciences Inc. has halted several patient studies of its cancer drug, Zydelig, because of increased risk of death and serious side effects.

The company told The Associated Press the "adverse events" were spotted during an ongoing review of late-stage testing in patients with chronic lymphocytic leukemia, a blood cancer, and patients with relapsed non-Hodgkin's lymphoma, a cancer of the infection-fighting lymphatic system.

Nathan Kaiser, a spokesman for the Foster City, California, company, wouldn't disclose details, including how many patients died or suffered serious side effects.

"We are conducting a comprehensive review of all ongoing studies and are consulting with regulatory authorities," Kaiser wrote in an email Tuesday.

CHOP vs COP for Diffuse Lymphoma

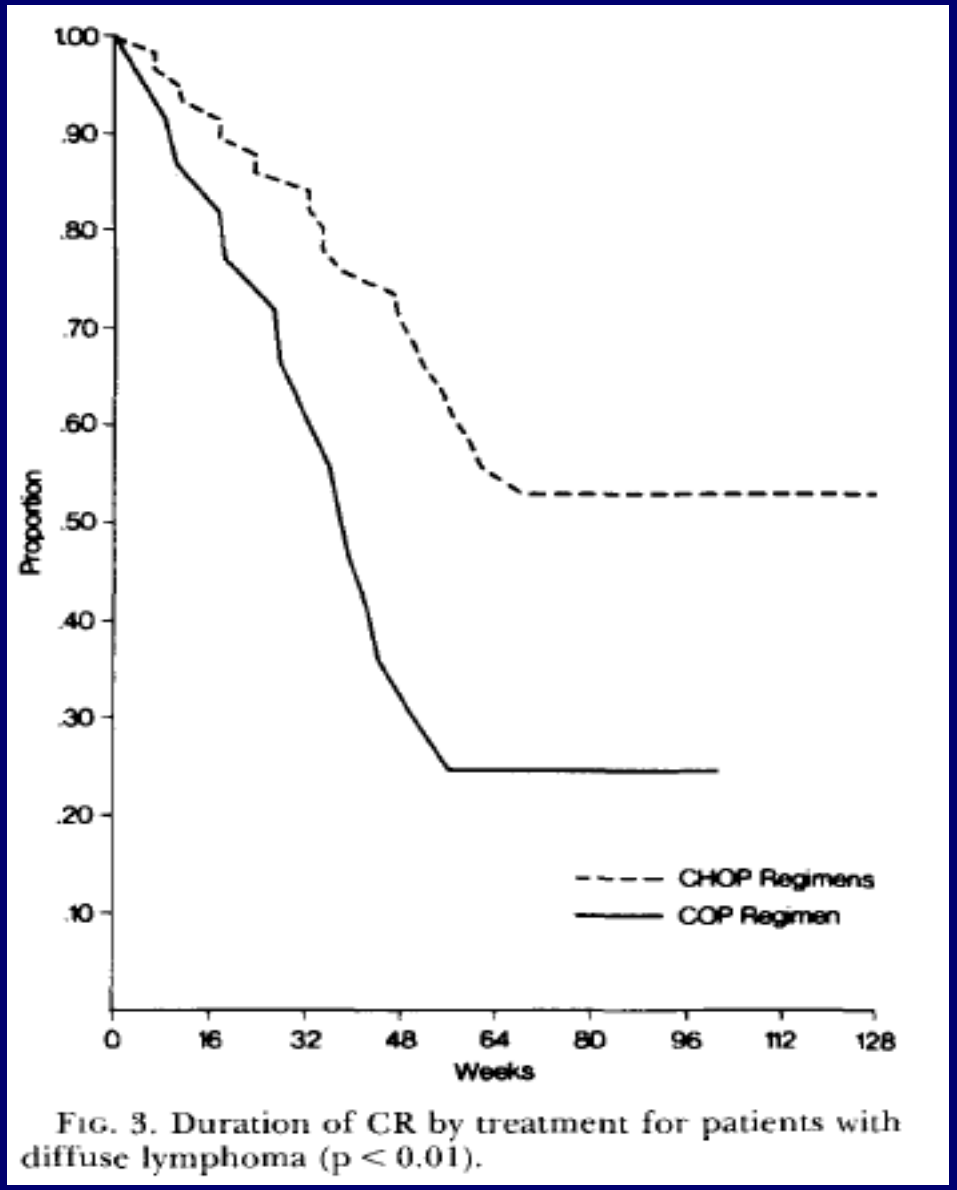


FIG. 3. Duration of CR by treatment for patients with diffuse lymphoma ($p < 0.01$).

Jones et al, Cancer 43:417, 1979

CHOP vs COP in Diffuse Lymphoma

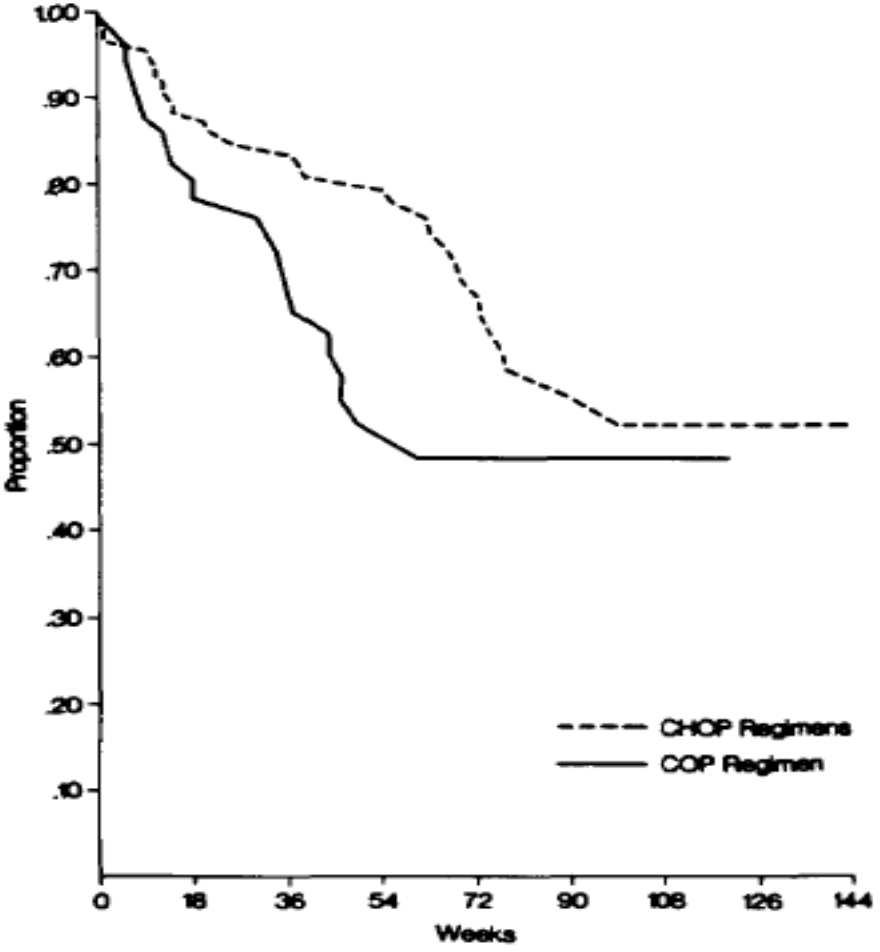
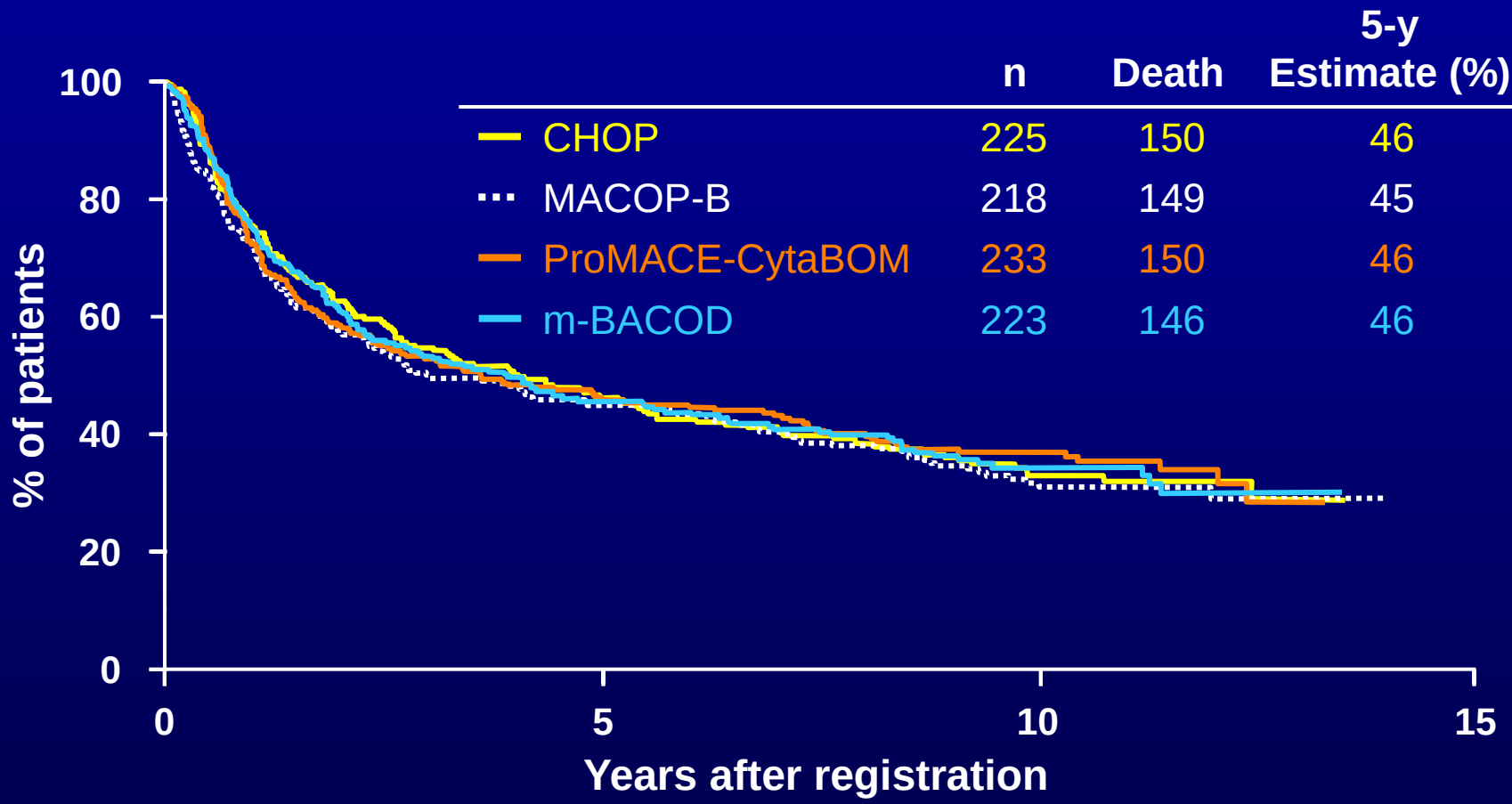


FIG. 5. Survival of patients with diffuse lymphoma according to initial treatment (p = 0.02).

Jones et al, Cancer 43:417, 1979

National High-Priority Lymphoma Study (S8516): OS



Update of Fisher et al. *N Engl J Med*. 1993;328:1002. Courtesy of R. Fisher, 2005.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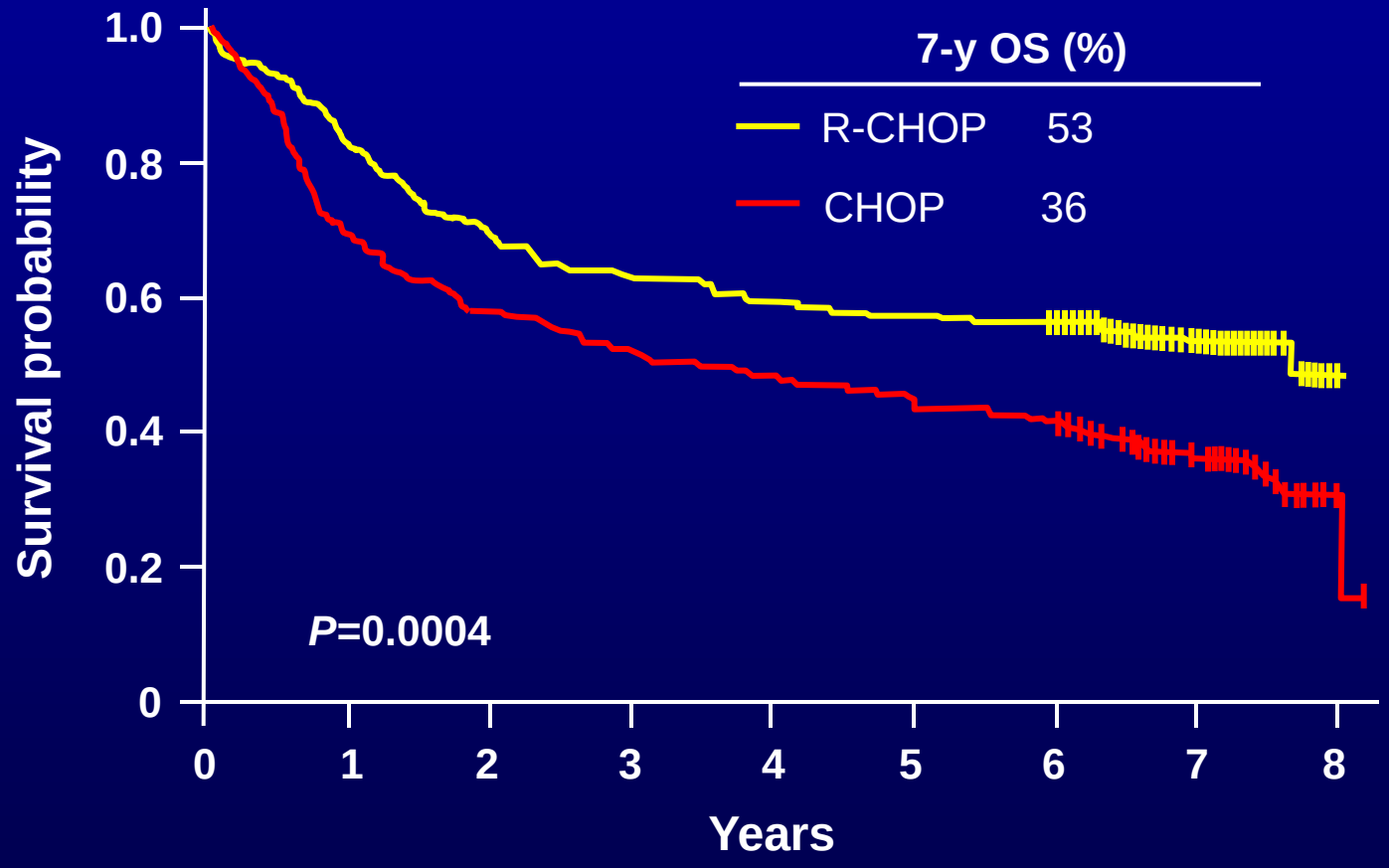
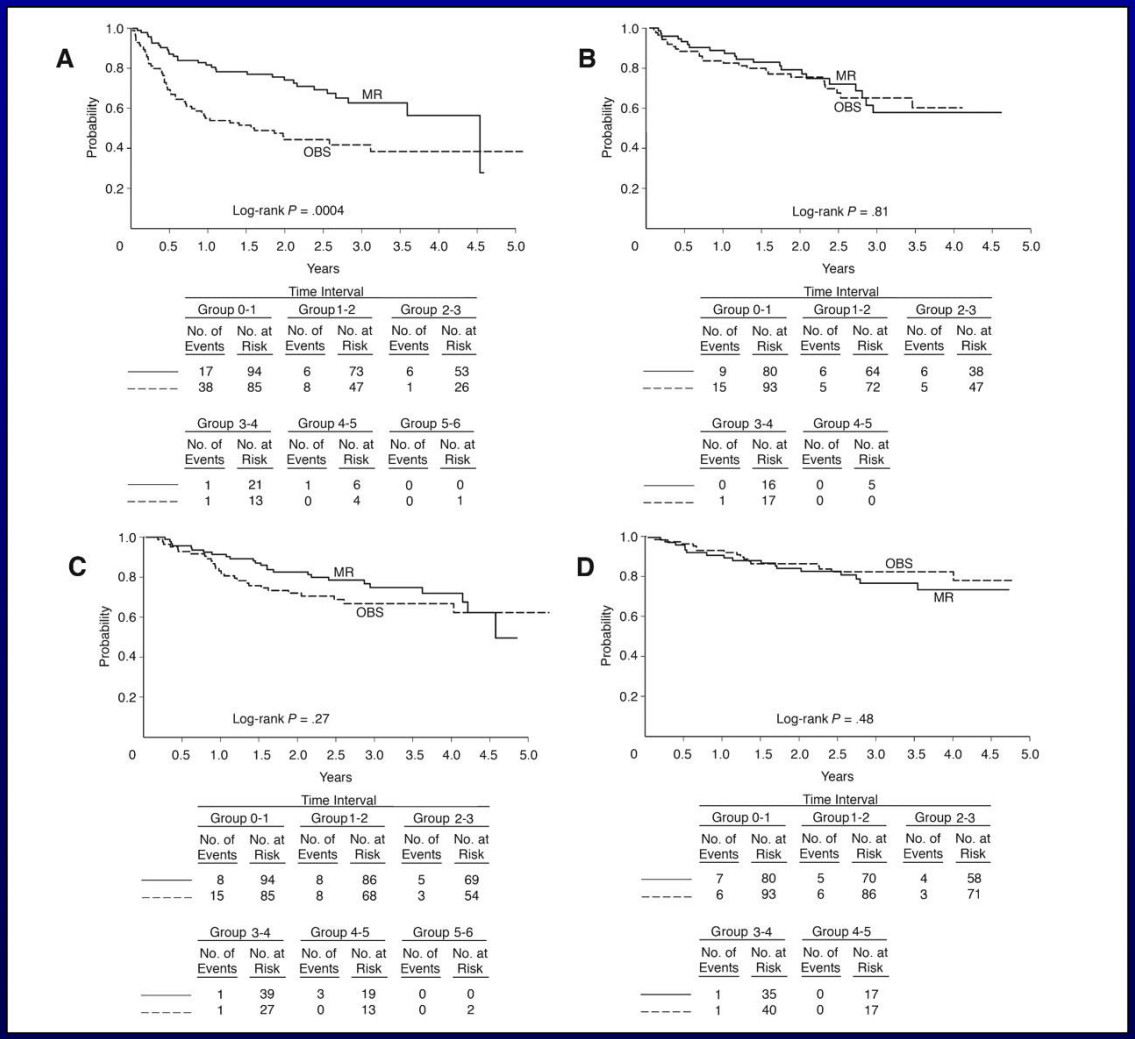
CHICKEN

7-Year Results of GELA Study of CHOP ± Rituximab in Older Patients With DLBCL: OS



Coiffier et al. ASCO, 2007. Abstract 8009.

FFS and OS by maintenance rituximab or observation by induction treatment.



Habermann T M et al. JCO 2006;24:3121-3127

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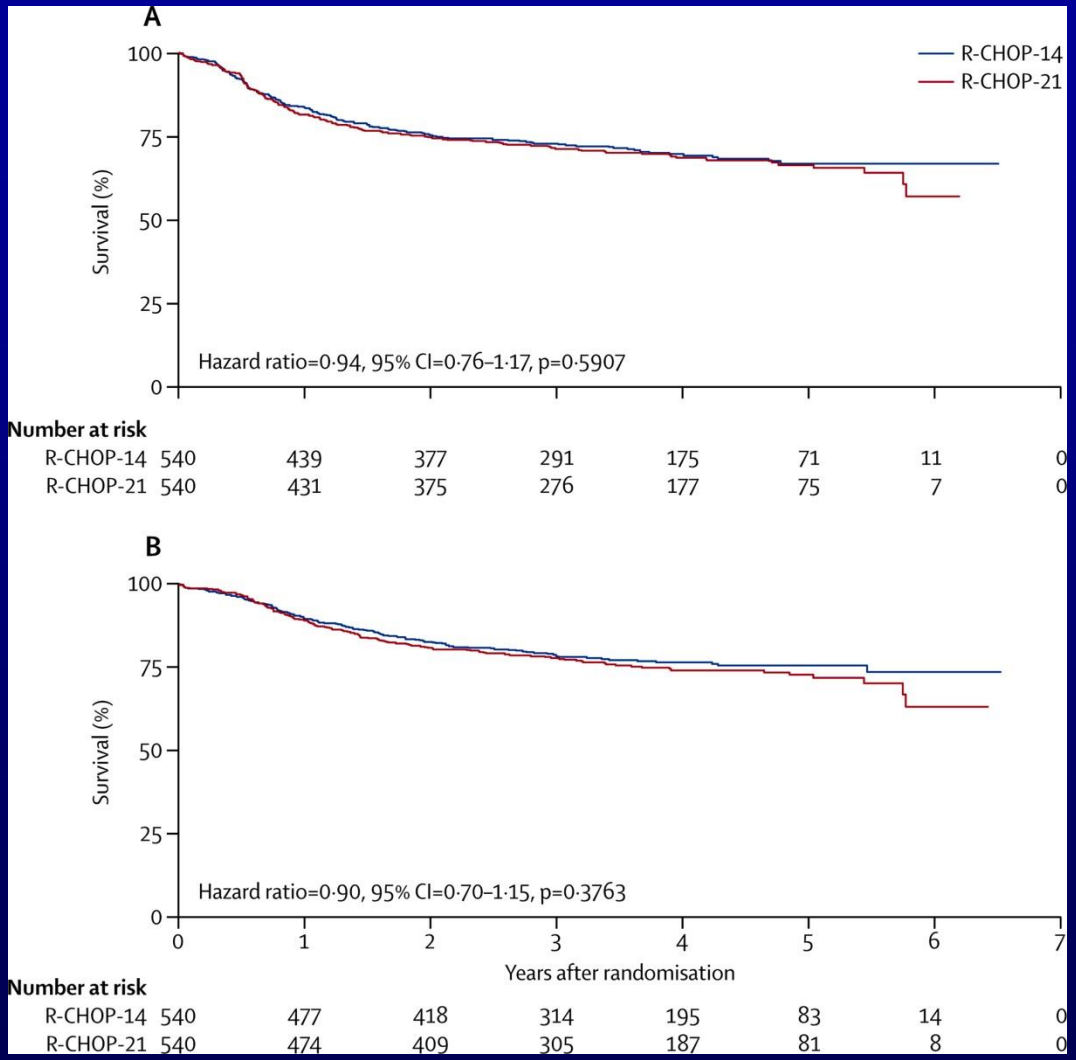
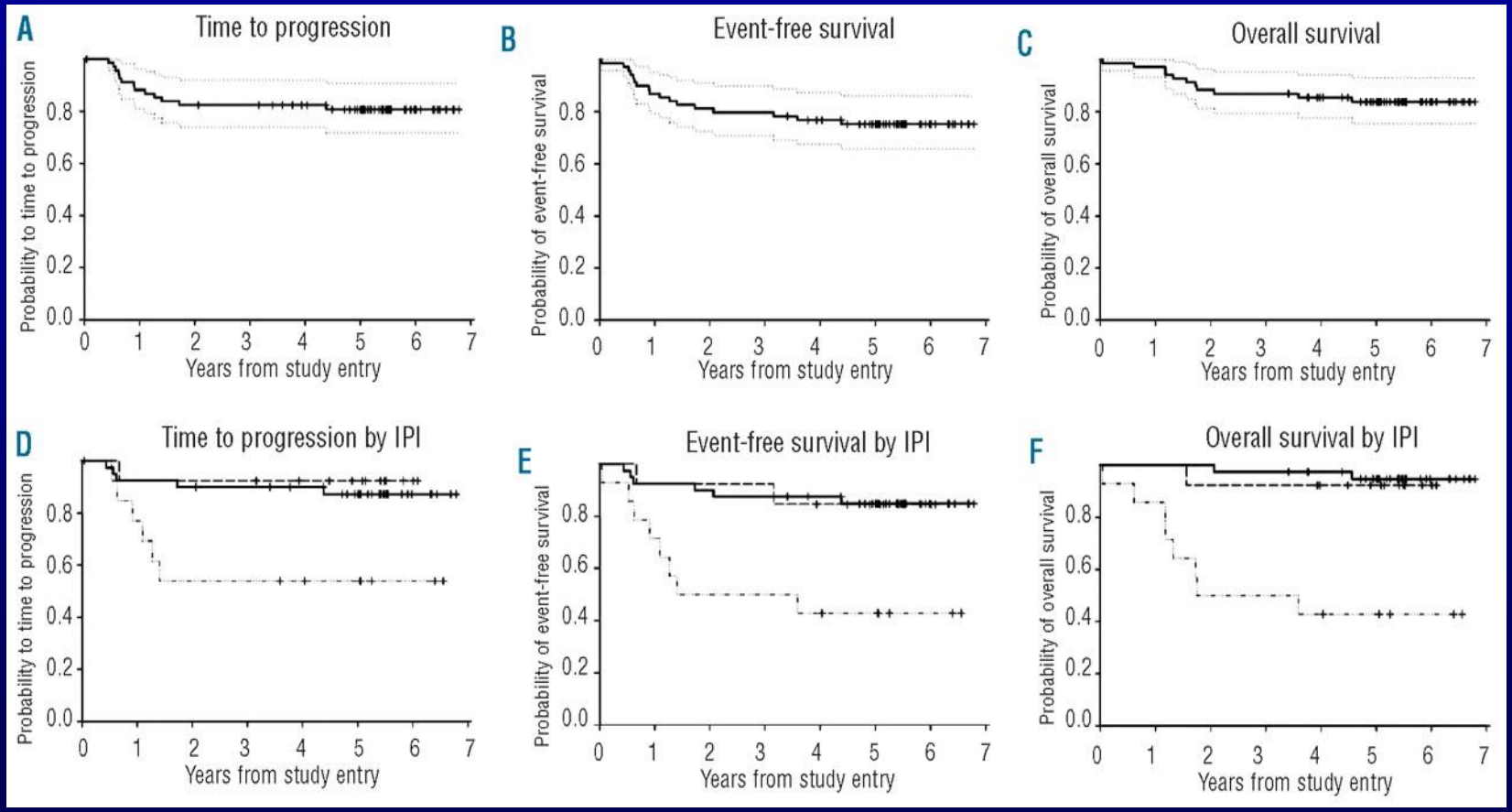
R-CHOP-21 vs R-CHOP 14 in DLBCL



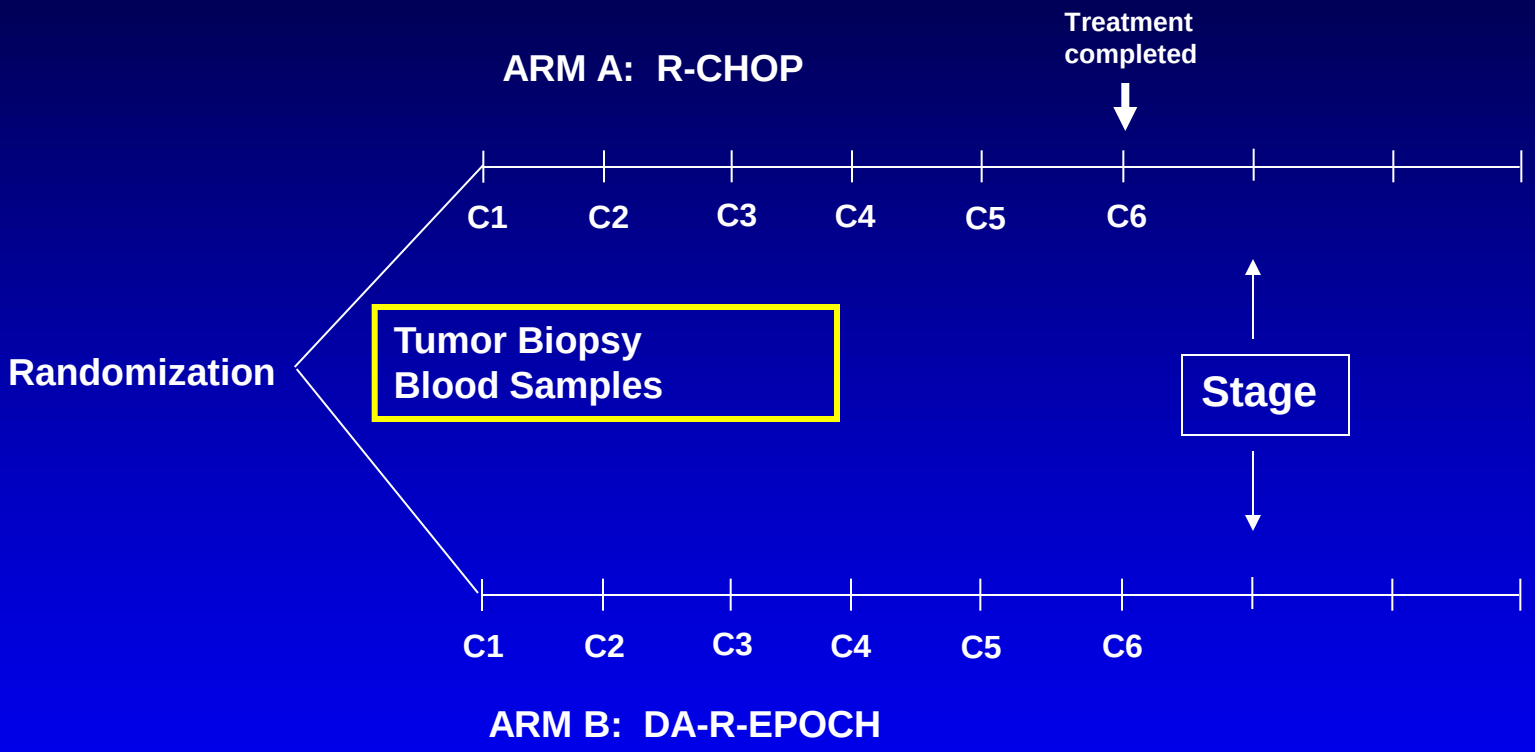
Cunningham et al, The Lancet 2013 381, 1817

CALGB50103: DA-R-EPOCH survival of all patients



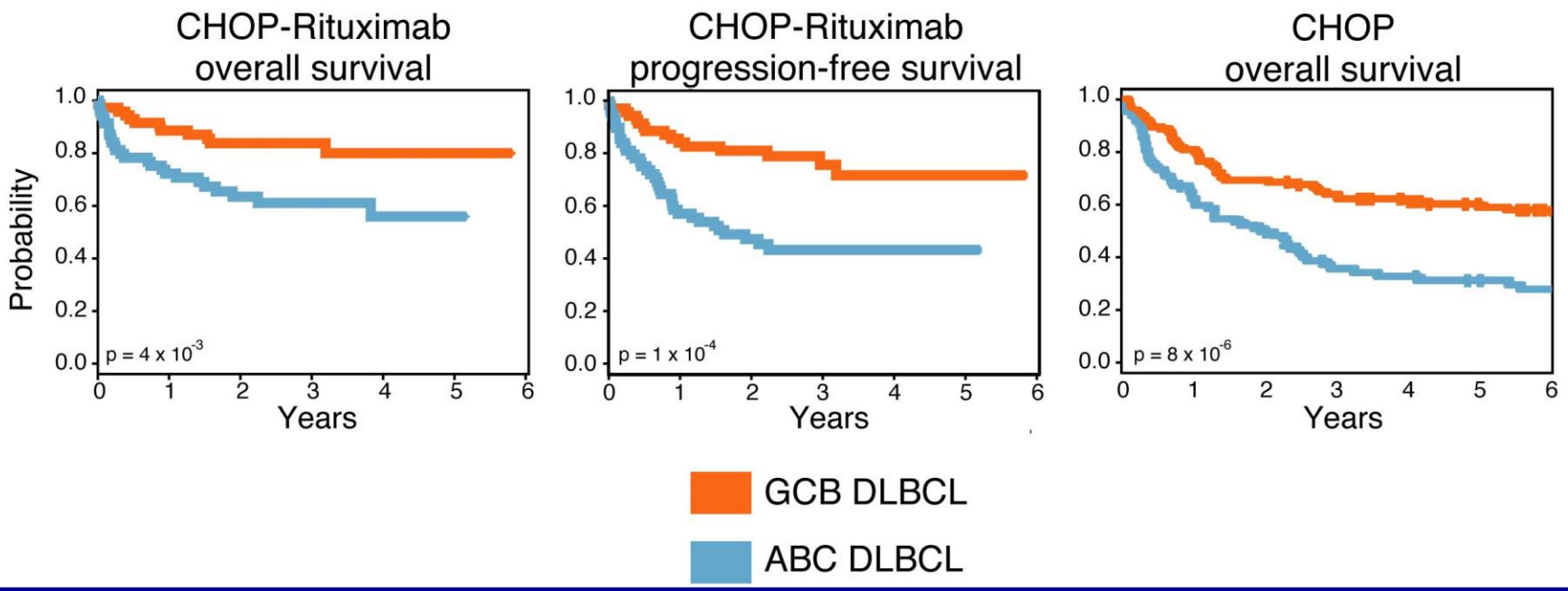
Wilson W H et al. Haematologica 2012;97:758-765

CALGB:50303 Phase III Randomized Study of R-CHOP v. DA-EPOCH-R with Microarray



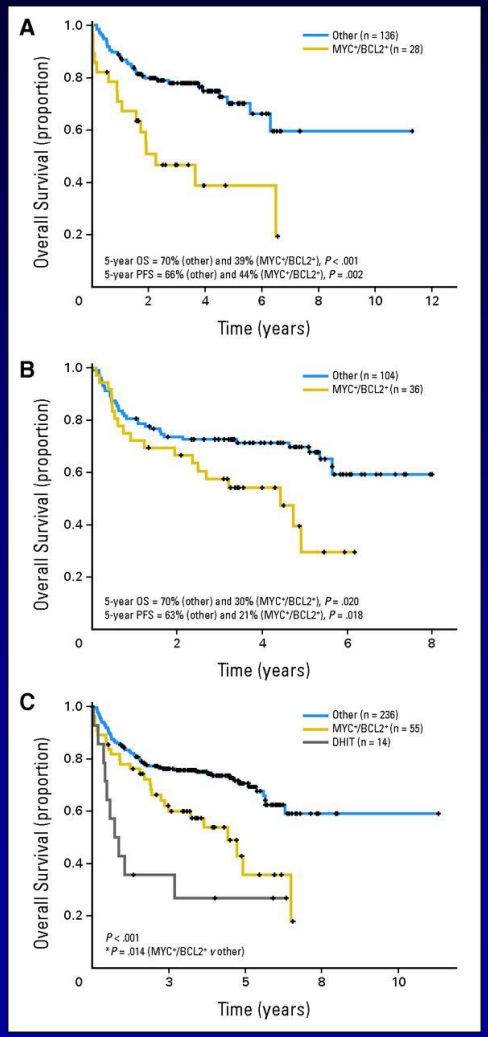
Blood Samples at Staging
Proteomics/Pharmacogenomics

The Distinction Between the GCB and ABC Subtypes of DLBCL Retains Prognostic Significance with CHOP-Rituximab Therapy



Lenz et al., N. Engl. J. Med. 2008
A study of the Lymphoma Leukemia Molecular Profiling Project (LLMPP)

OS and PFS of patients with DLBCL treated R-CHOP according to presence of concurrent expression of MYC and BCL2 proteins.



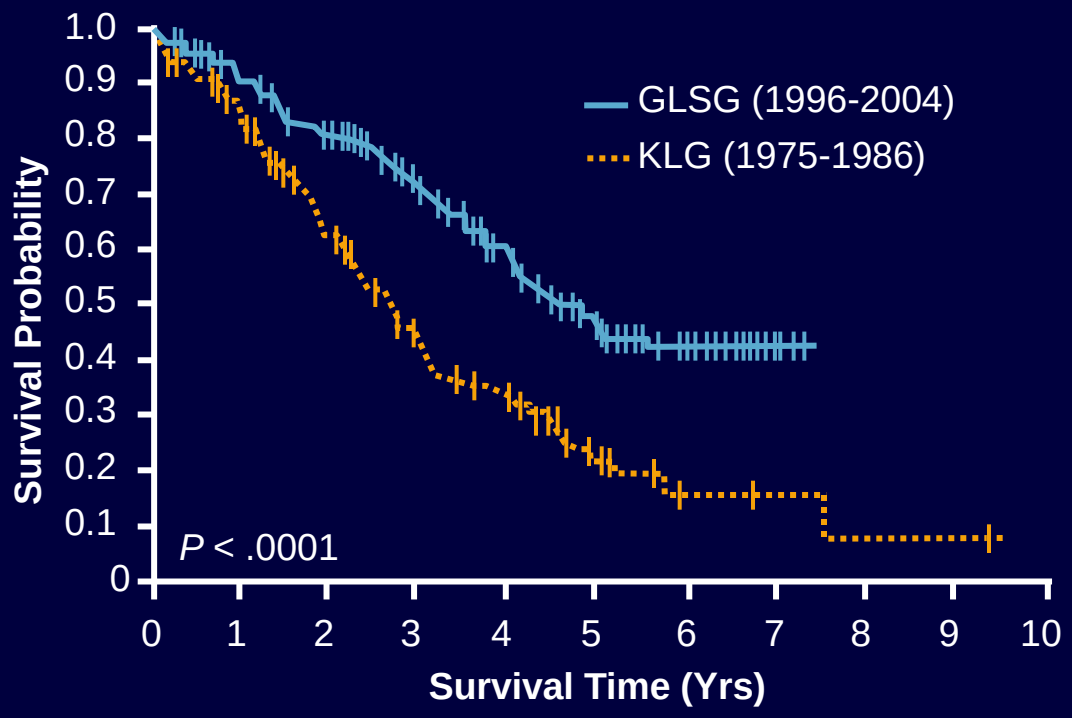
Johnson N A et al. JCO 2012;30:3452-3459

Challenges

- Integrate new drugs into front-line
  - ABC
  - Double/triple-hit
- Identify active agents for R/R patients

Improving Survival in MCL

- Median OS 1975-1986: ~ 3 yrs
- Median OS 1996-2004: ~ 5 yrs



Herrmann A, et al. J Clin Oncol. 2009;27:511-518.

Treatment Options for MCL

R-CHOP

Modified HyperCVAD

R-CHOP/RIT

R-Bendamustine

VR-CAP

Less intensive

vs

R-CHOP/ASCT

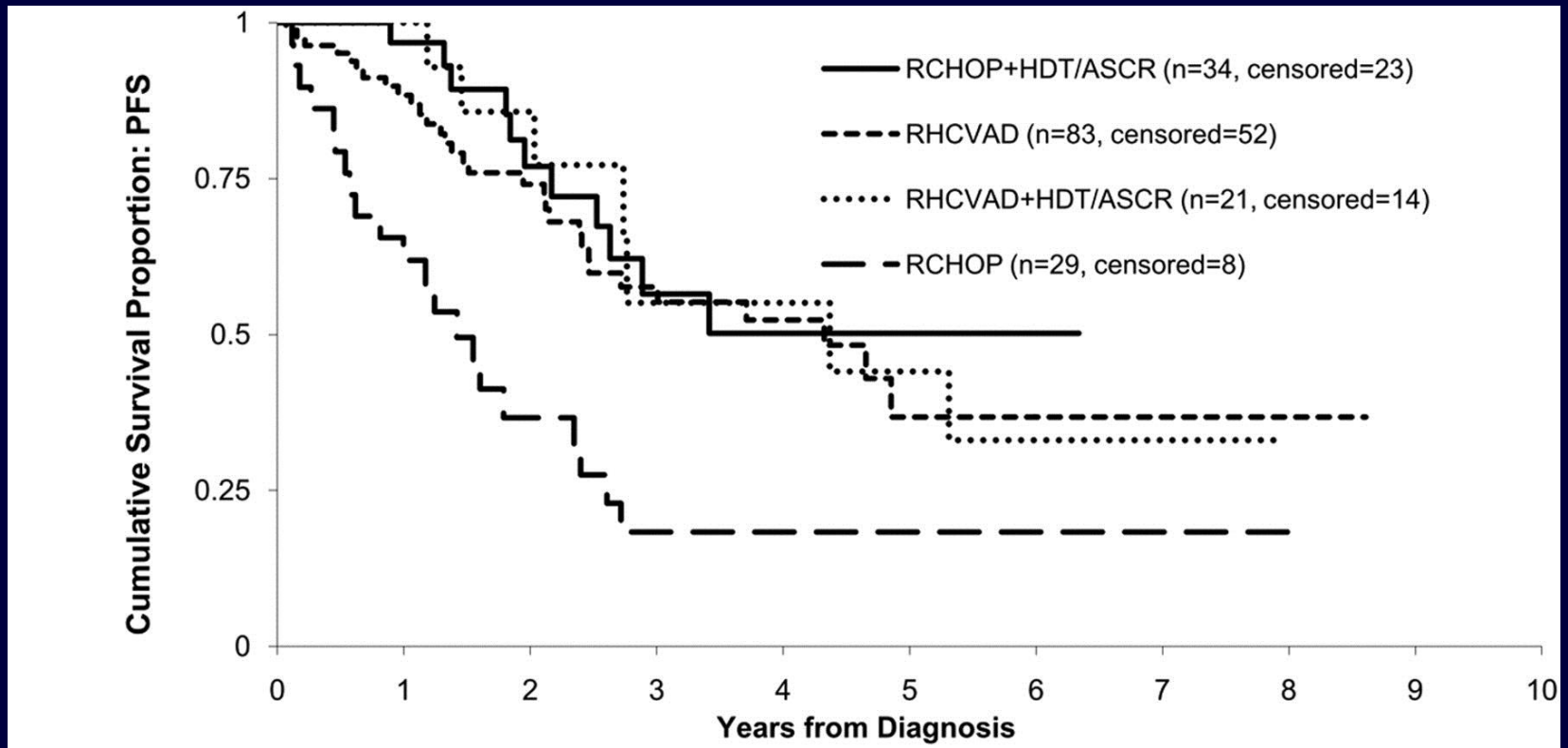
R-HyperCVAD/MTX/Ara-C

R-HyperCVAD/MTX/Ara-C/ASCT

NORDIC

More intensive

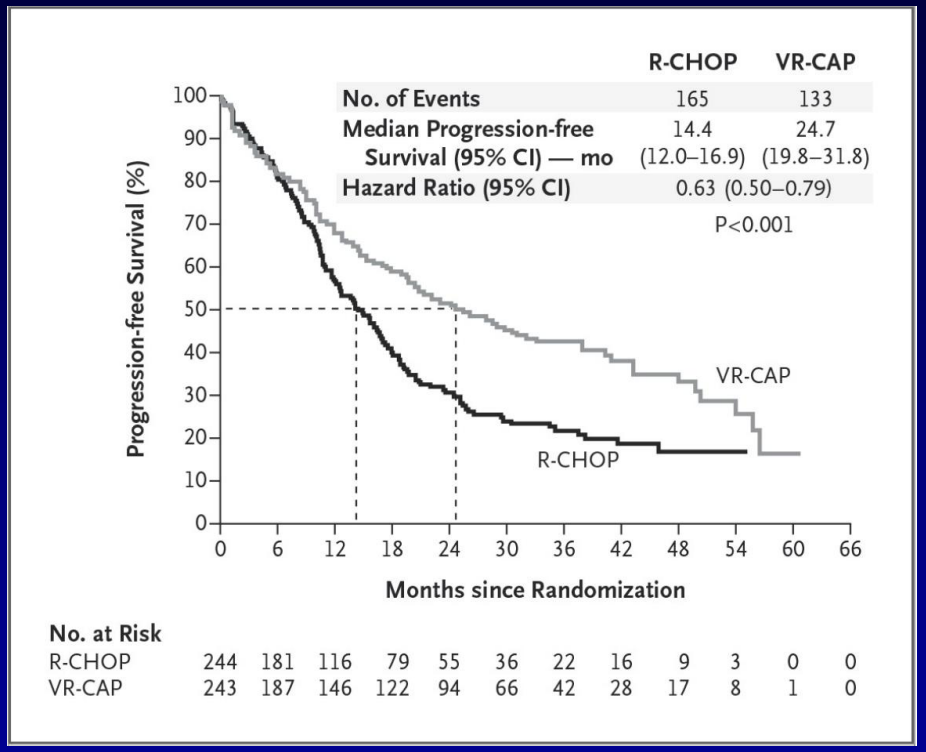
PFS of MCL From Diagnosis By Therapy

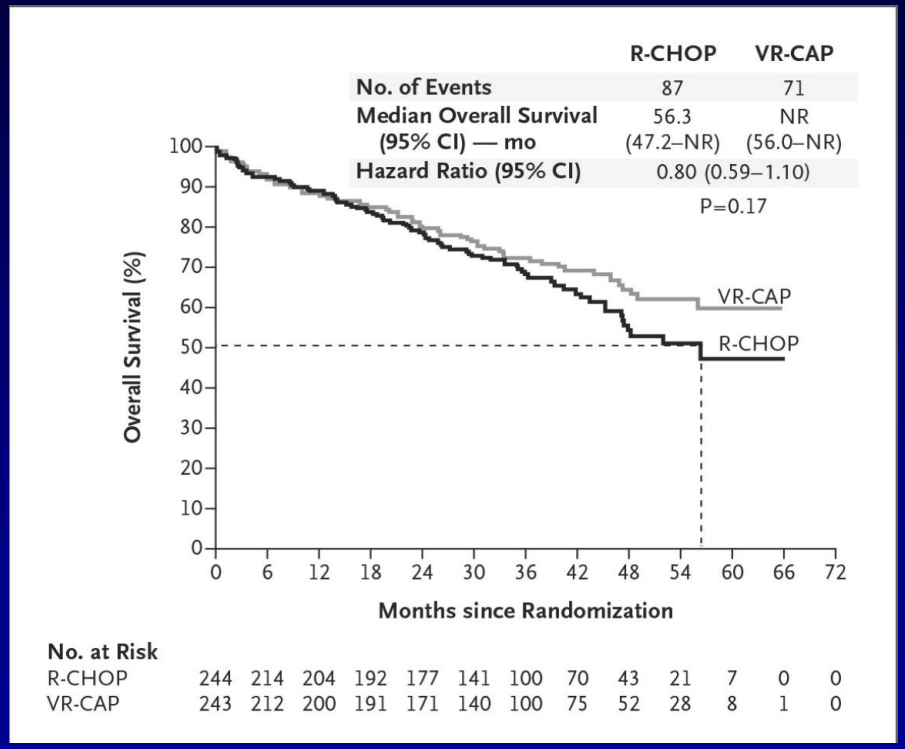


RCHOP	29	17	8	3	3	1	1	1	1
RCHOP+HDT/ASCR	34	28	18	9	3	2	1	0	0
RHCVAD	83	59	40	24	17	5	1	1	1
RHCVAD+HDT/ASCR	21	19	11	5	5	4	3	2	0

LaCasce et al. Blood 2012;119:2093-2099

VR-CAP in Untreated MCL





Robak et al, NEJM 372:944, 2015

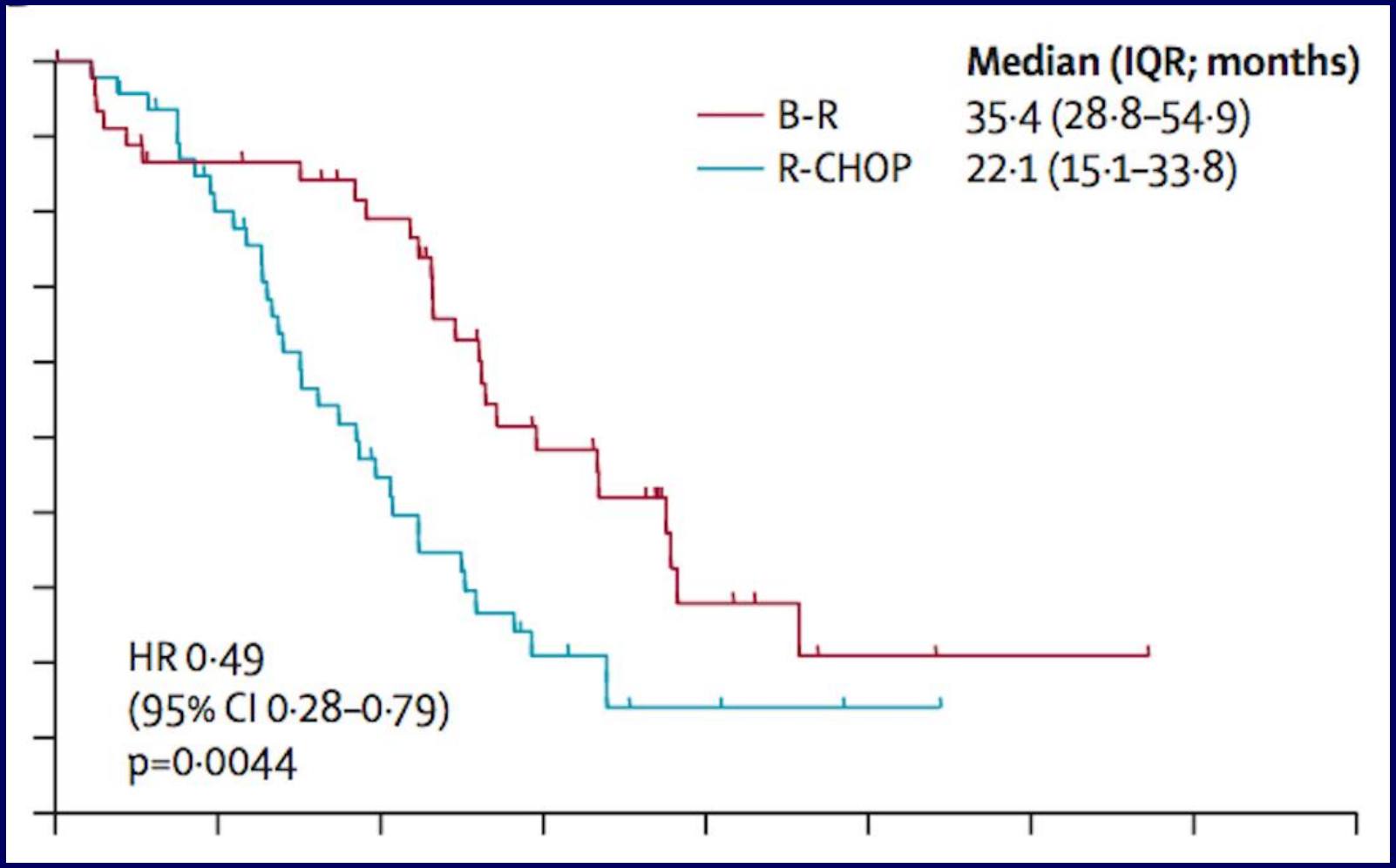
STiL: Secondary Endpoints

- B-R at least comparable to R-CHOP in all measurements

Measure	B-R	R-CHOP	*P* Value
CR, %	39.6	30.3	.026
TTNT, mos	NR	37.5	.001

Rummel MJ, et al. ASH 2009. Abstract 405.

BR vs R-CHOP in Untreated MCL



Rummel et al Lancet 381:1203, 2013

BR vs R-HyperCVAD in MCL

	RHCVAD	BR
Pts	16	35
ORR (%)	94.1	82.9
CR (%)	35	40
2 yr PFS (%)	81	81
2 yr OS (%)	87	87
Failure to collect SCs	5	1

Chen et al Hematol Oncol 33 (suppl 1):062, 2015 (updated)

R^2 in Untreated MCL: Objective Responses

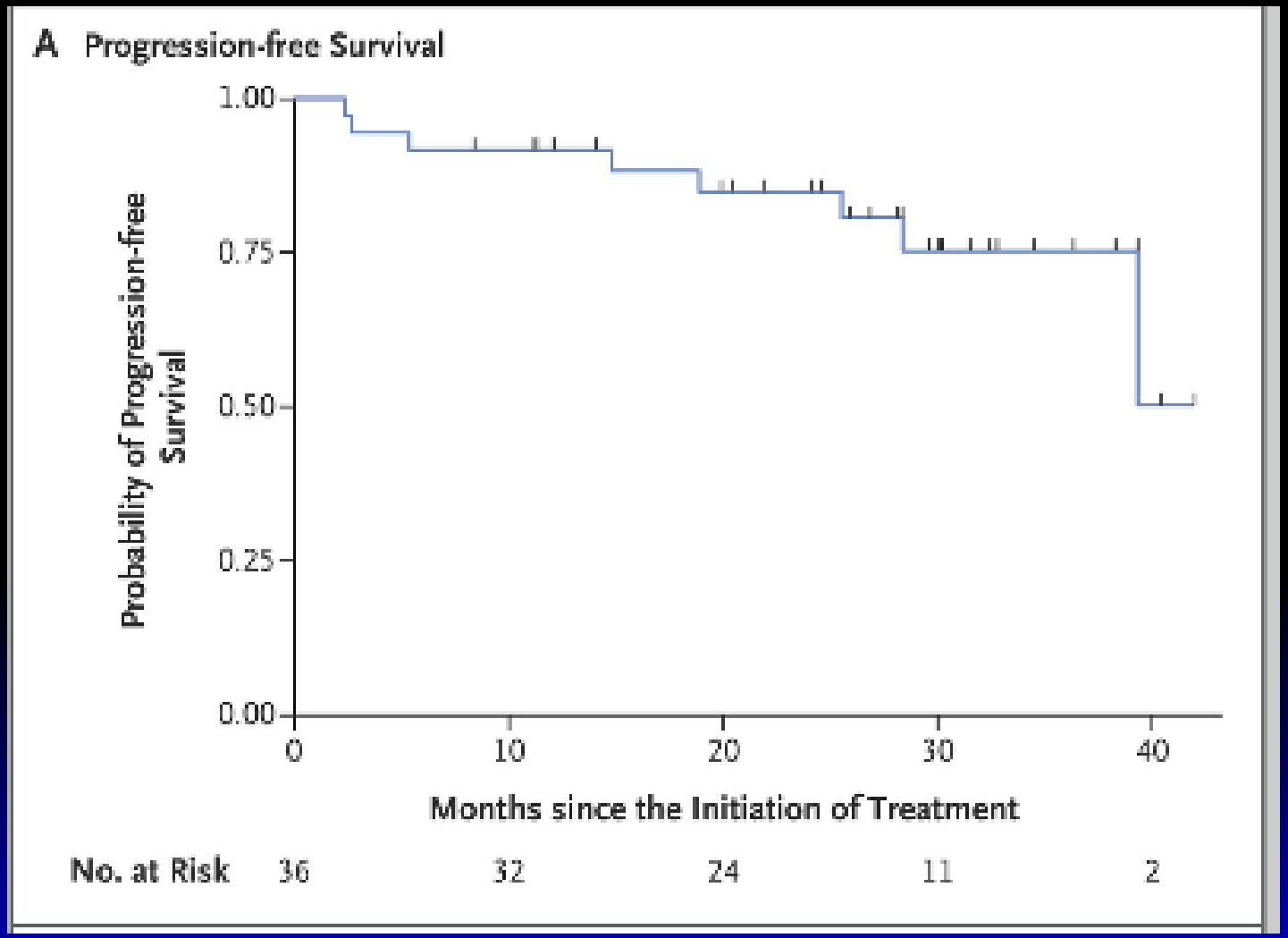
Response	No. of patients	ITT (n=38)	Evaluable (n=36)
Overall response	33	87%	92%
CR	23	61%	64%
PR	10	26%	28%
SD	1	3%	3%
PD	2	5%	6%
Inevaluable[#]	2		
Median follow-up	30 months (range 1-42)		
Median time to PR	3 months (range 3-13)		
Median time to CR	11 months (range 3-22)		

ITT: Intent-to-treat

[#]: Treatment was discontinued in 2 patients due to tumor flare without progression before tumor response evaluation.

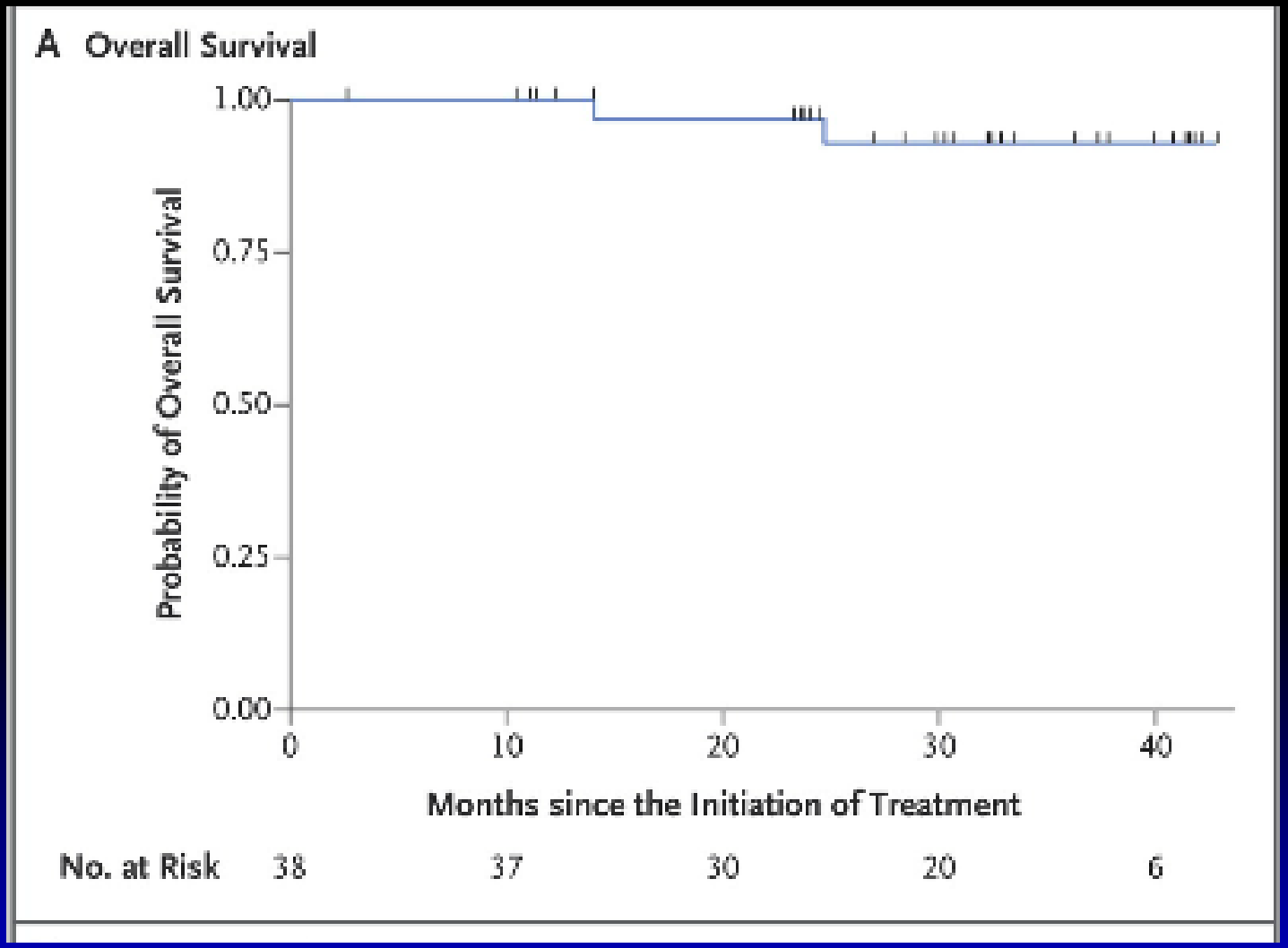
Ruan et al, NEJM 373:1835-1844, 2015

Efficacy: Progression-Free Survival



Ruan et al, NEJM 373:1835-1844, 2015

Efficacy: Overall Survival



Ruan et al, NEJM 373:1835-1844, 2015

Lenalidomide in Relapsed/Refractory MCL

Author (yr)	Pts	Dose/Schedule	ORR (%)	CR (%)	PFS (mo)
Wiernik (‘08) Habermann (‘09)	15	25 mg, d1-21	53	20	6
Witzig (‘11)	57	25 mg, d1-21	42	21	8.9

Bortezomib in MCL:PINNACLE Trial

Response/Subsets Analysis

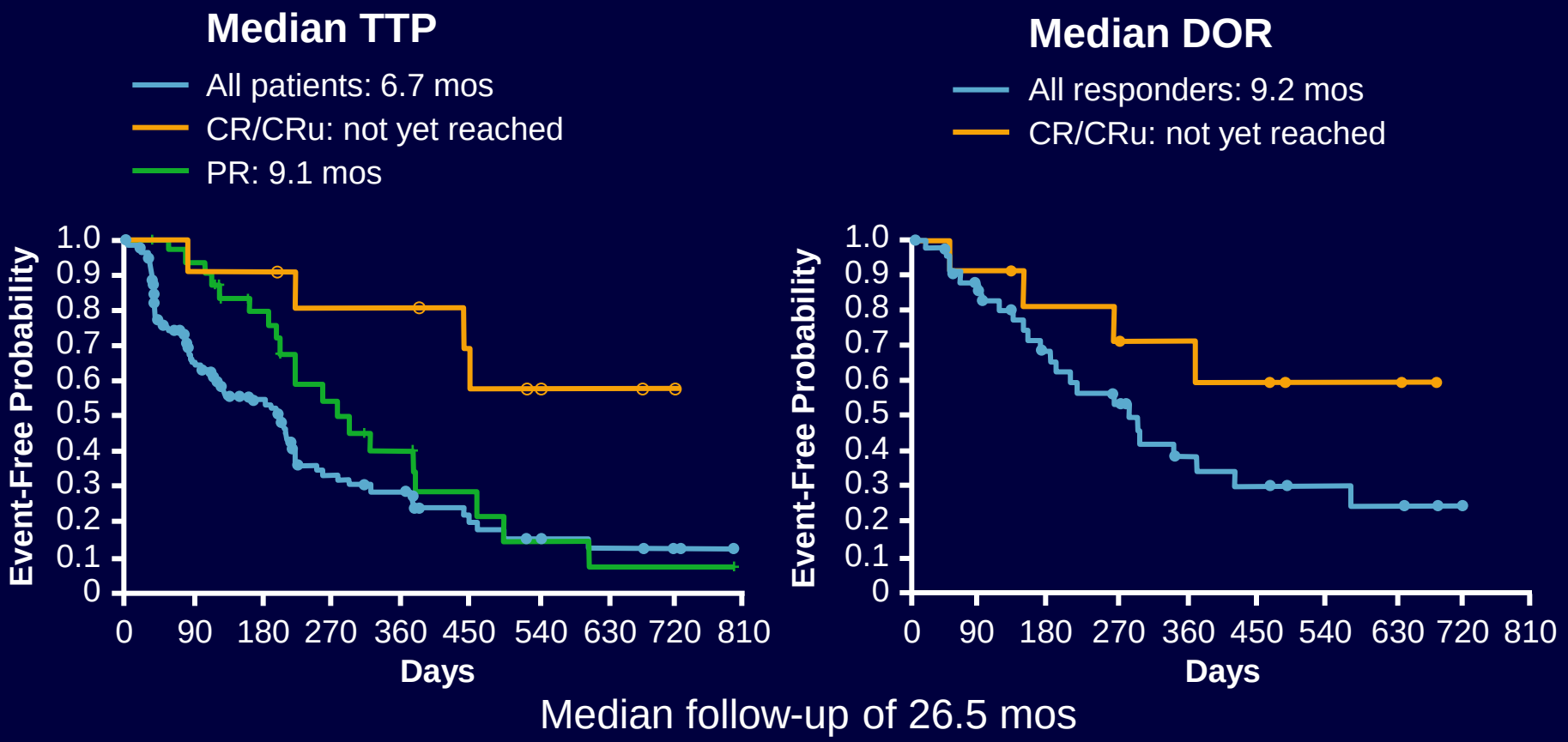
Parameter	Response: Evaluable (n = 141)	Refractory MCL* (n = 51)	Previous High-Intensity Therapy† (n = 52)
ORR, %	32	29	25
CR/CRu, %	8	6	10
Median DOR, mos	9.2	5.9	Not reached

*Refractory subgroup: no response or response with TTP < 6 mos to last prior line of therapy.
†High-intensity subgroup: ASCT or therapies containing high-dose cytarabine or ifosfamide/carboplatin etoposide.

Among patients who achieved CR/CRu: median DOR not reached at 26.4 mos

Goy A, et al. Ann Oncol. 2009;20:520-525.

PINNACLE Trial Update



Median follow-up of 26.5 mos

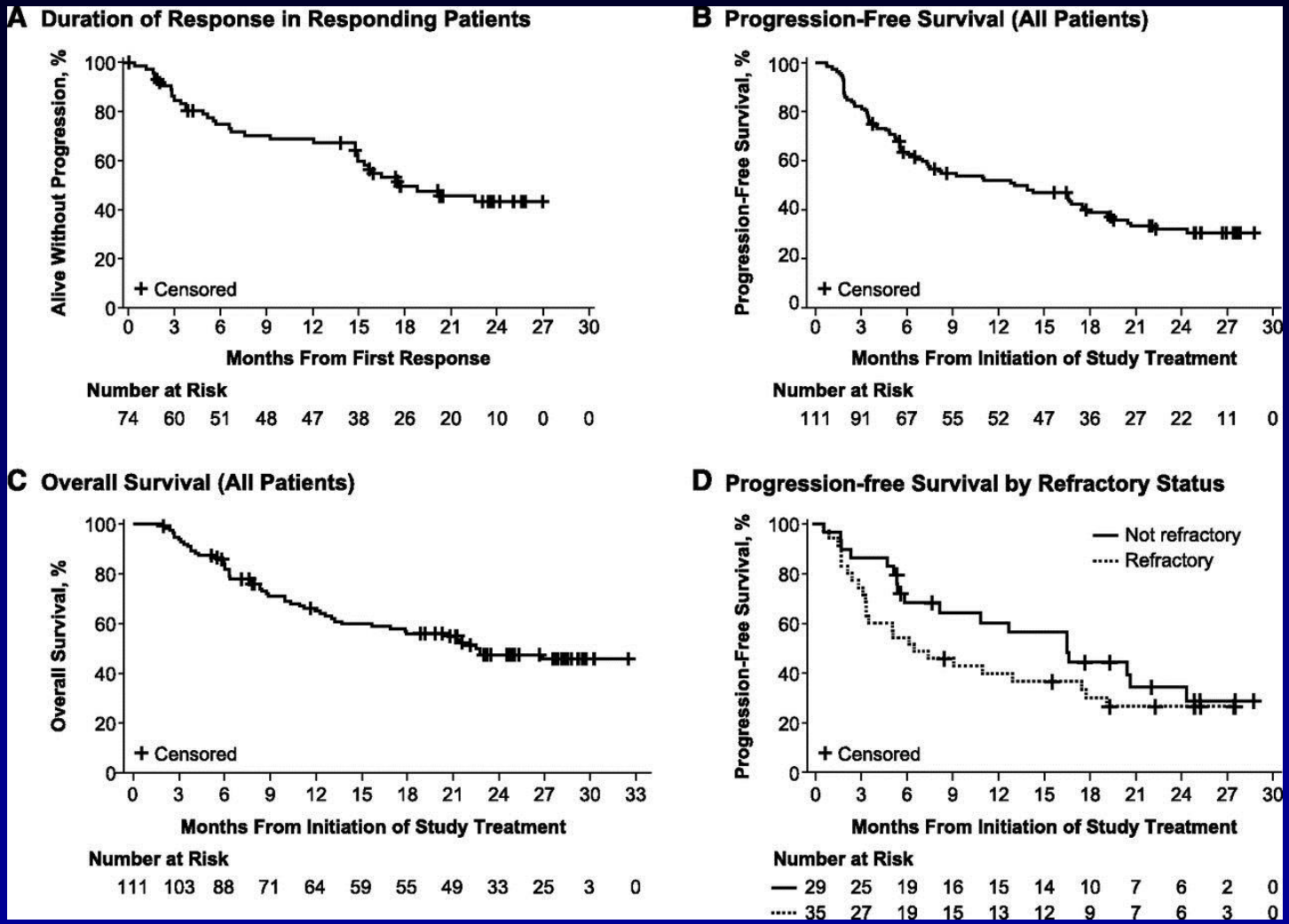
Goy A, et al. Ann Oncol. 2009;20:520-525. Reprinted with permission of Oxford University Press.

Ibrutinib in R/R MCL

- N=111
- Ibrutinib 560 mg po qd
- Median age 68 yrs; median 3 prior txs
- Median F/U 26.7 mo
- ORR 67%; 23% CR
- Median tx duration 8.3 mo; 22% > 2 yrs
- AEs – diarrhea, fatigue, nausea, dyspnea, bleeding

Wang et al. Blood 2015;126:739-745

Ibrutinib in MCL: time-to-event end points



Wang et al. Blood 2015;126:739-745

New Standards for Other NHL

- WM – ibrutinib
- CLL/SLL –
  - Front-line - BR, ibrutinib, clb/obinutuzumab
  - R/R – ibrutinib, venetoclax, idelalisib-R
- MZL – no clear standard; R, BR, R-CVP, idelalisib

Conclusions

- Major improvement in outcome of most B-NHL; rituximab, bendamustine, ibrutinib, other new agents
- Many patients do not respond, others relapse
- Need a better understanding of tumor biology
- Posttreatment strategies less effective
- Need to incorporate novel agents into induction regimens based on scientific rationale