MANTLE CELL LYMPHOMA

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Disclosures: S Rule

Research Support/P.I.	Janssen, Celgene
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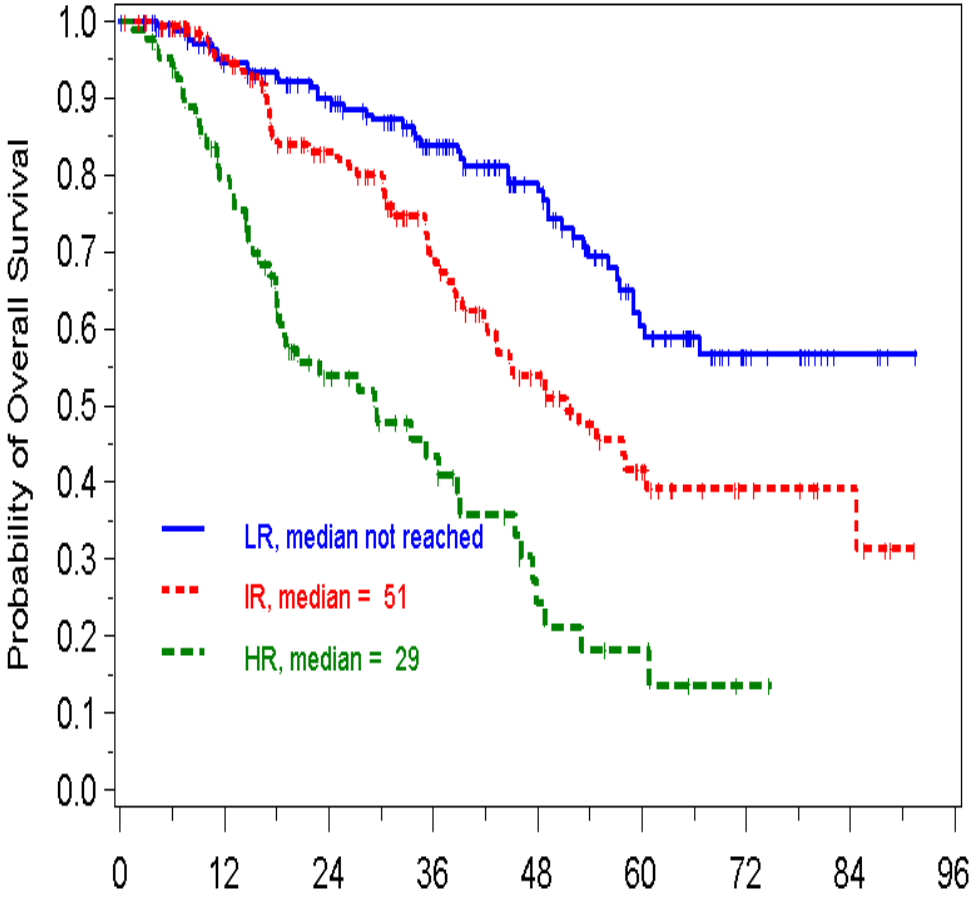
Outline

- Management of young patients
  - Role of cytarabine
  - Autografting / Allografting
- Management of older patients
  - CHOP v bendamustine based therapy
  - Bortezomib / Lenalidomide / Ibrutinib

Clinical risk factors: MIPI



numbers of patients at risk

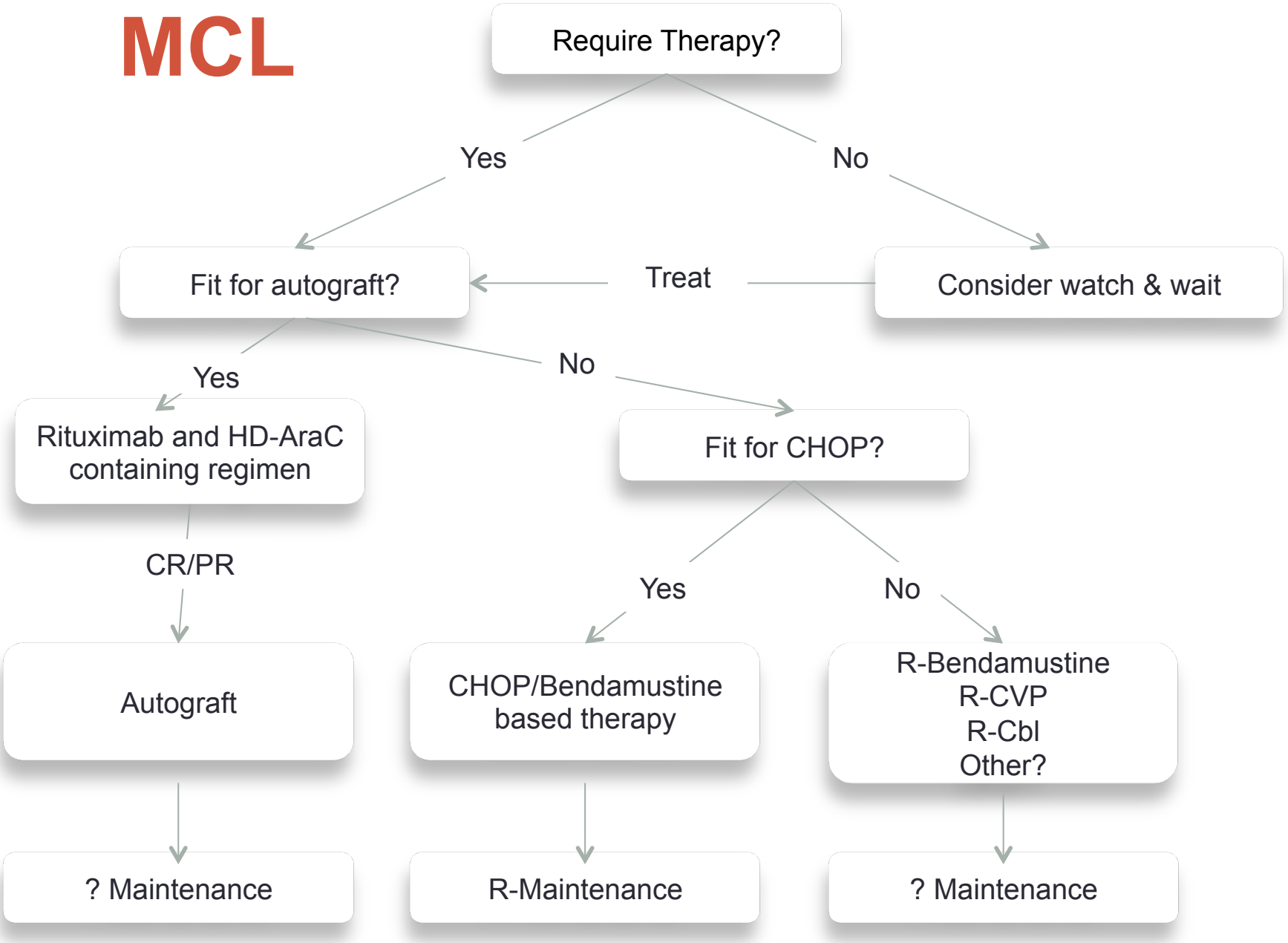
LR	180	153	131	99	69	39	15	4
IR	145	116	83	57	37	19	9	5
HR	84	58	29	19	8	5	1	0

(PALL: PS, age, LDH, leucocyte count)

Hoster, ASH 2006

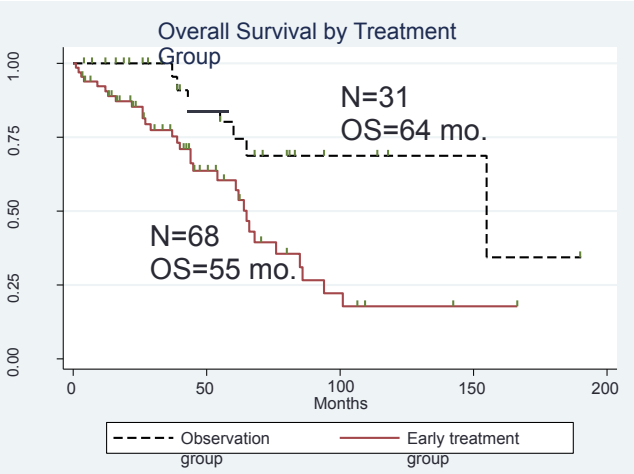
Treatment Algorithm 2017

MCL



Campo & Rule Blood 2015 Jan 1;125(1):48-55

Treatment may be safely deferred in some patients with MCL



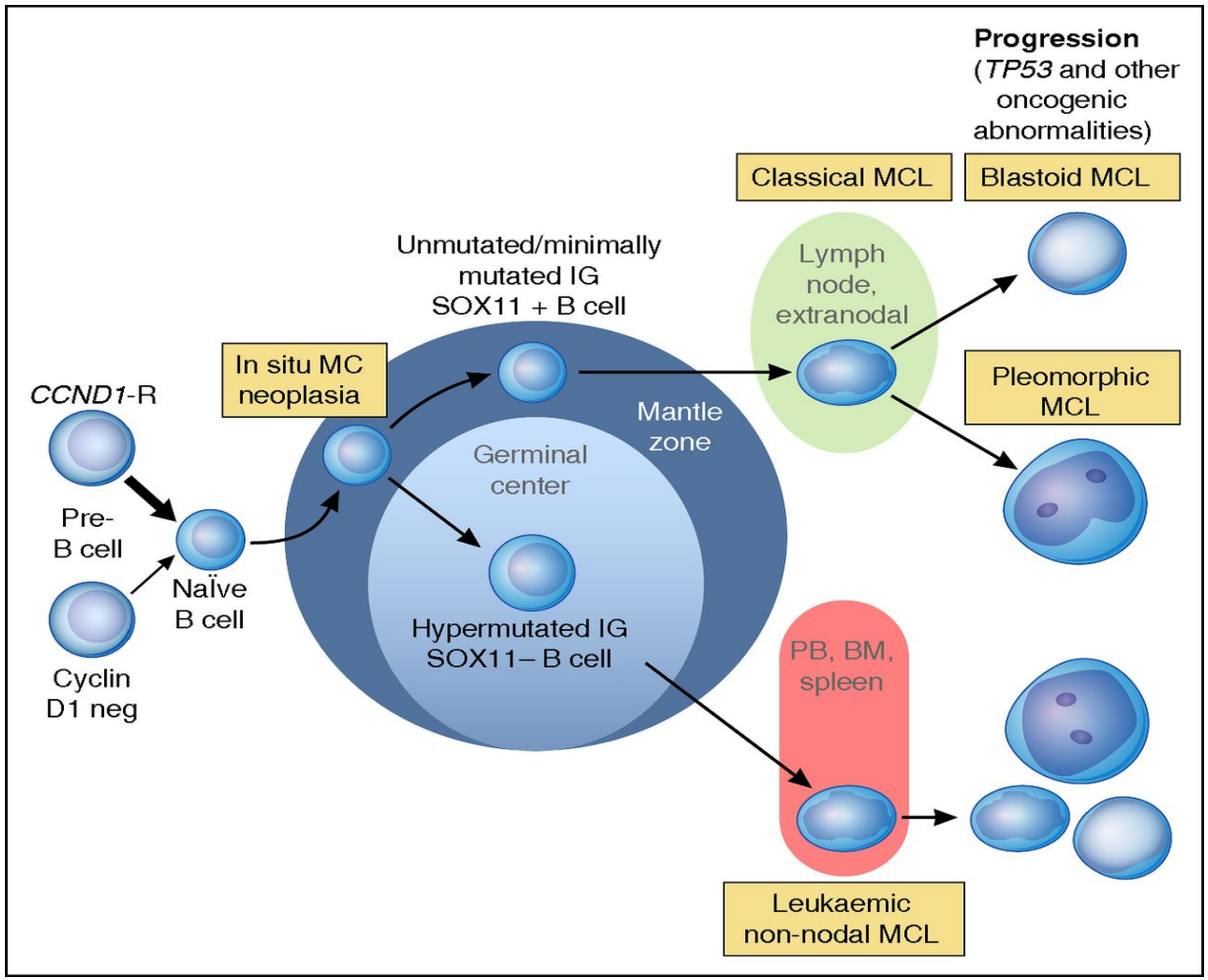
What characteristics are define these patients?

- **Not blastoid morphology[1]**
- **Normal LDH[2]**
- **Ki67 <30%[3]**
- **No B symptoms[4]**
- **Mutated IGHV[5]**
- **SOX11-**
- **Non-nodal[6]**
- **MIPI is NOT a defining characteristic**

Center	N	Defn. of deferred tx.	TTT	Impact on OS
Derriford[7]	16/52	3 mo.	11.1 mo.	No difference
FHCRC[8]	13/118	3 mo.	5 mo.	No difference
Nordic[2]	29/1389	NR	NR	79% vs. 61%
BCCA[3]	74/439	3 mo.	35.5 mo.	66 mo. vs. 50 mo.
NCDB[4]	492/8029	90 days	NR	HR 0.79

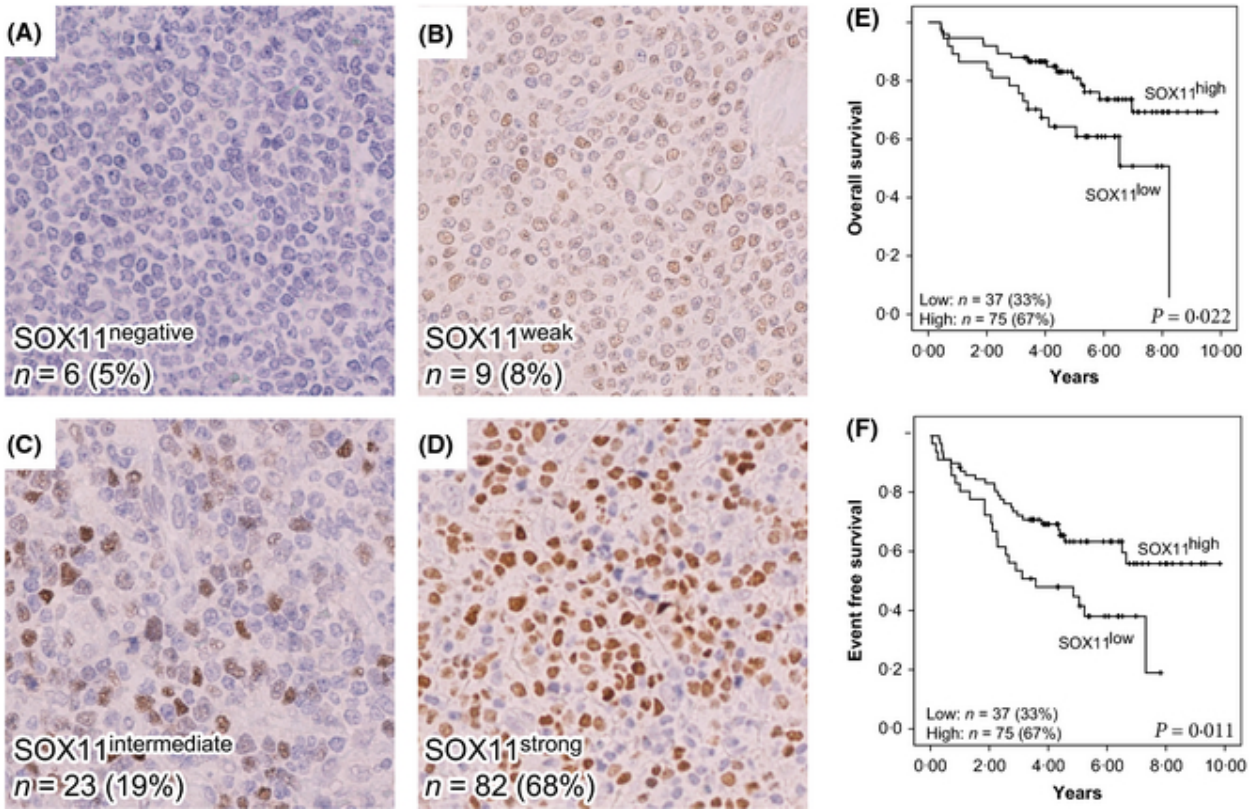
1-Martin JCO 2009, 2-Abrahamsson Blood 2014, 3-Abrisqueta ASH abstract 2015, 4-Cohen ASH abstract 2015, 5-Orchard Blood 2003, 6-Ondrejka Haematologica 2011, 7-Eve JCO 2009, 8-Budde JCO 2010

Pathogenesis of MCL

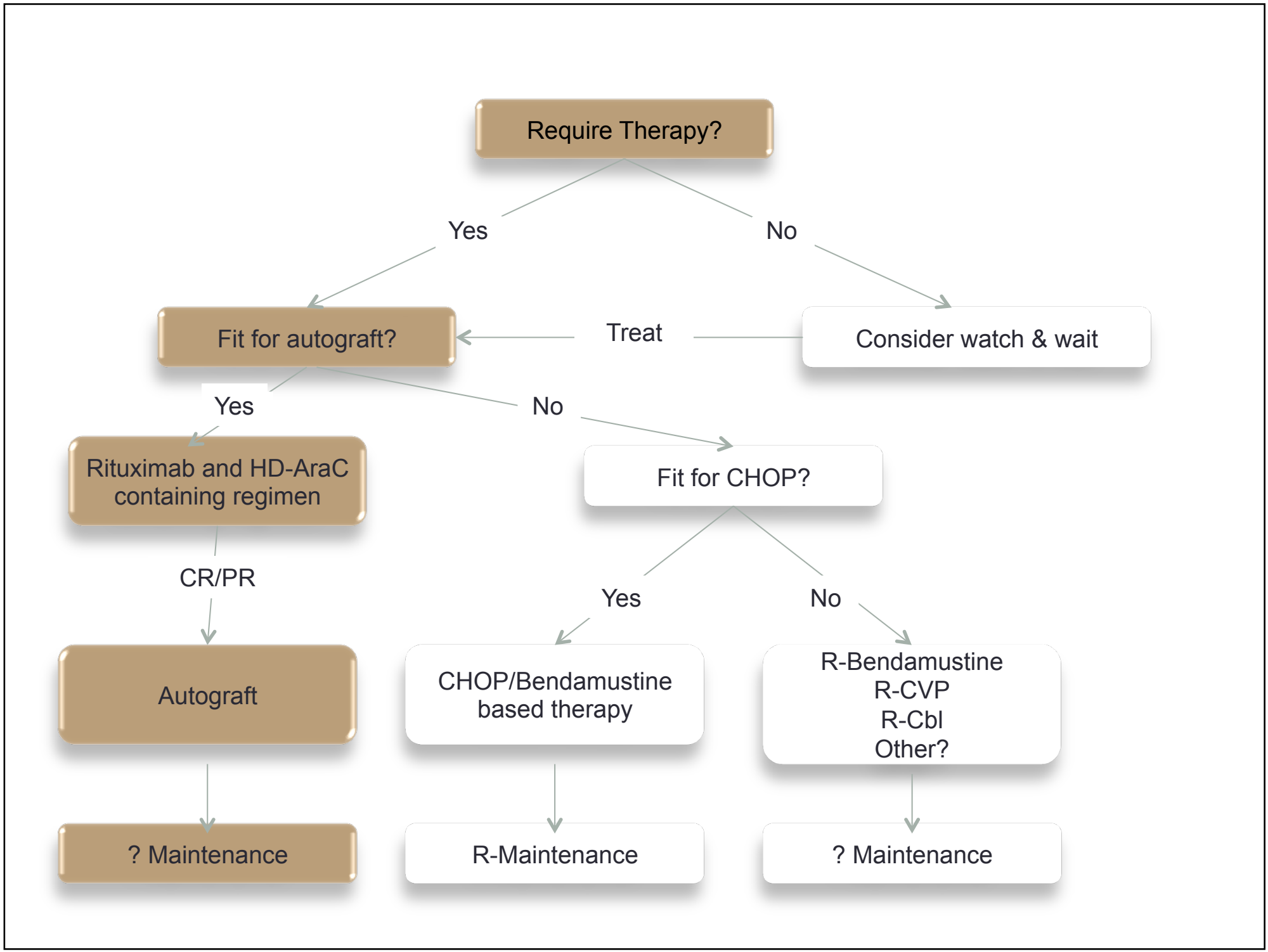


Courtesy of E Campo

SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma – a Nordic Lymphoma Group study



British Journal of Haematology
Volume 166, Issue 1, pages 98-108, 29 MAR 2014 DOI: 10.1111/bjh.12854
http://onlinelibrary.wiley.com/doi/10.1111/bjh.12854/full#bjh12854-fig-0001


Require Therapy?
Yes
No
Fit for autograft?
Treat
Consider watch & wait
Yes
No
Rituximab and HD-AraC containing regimen
Fit for CHOP?
CR/PR
Yes
No
Autograft
CHOP/Bendamustine based therapy
R-Bendamustine
R-CVP
R-Cbl
Other?
? Maintenance
R-Maintenance
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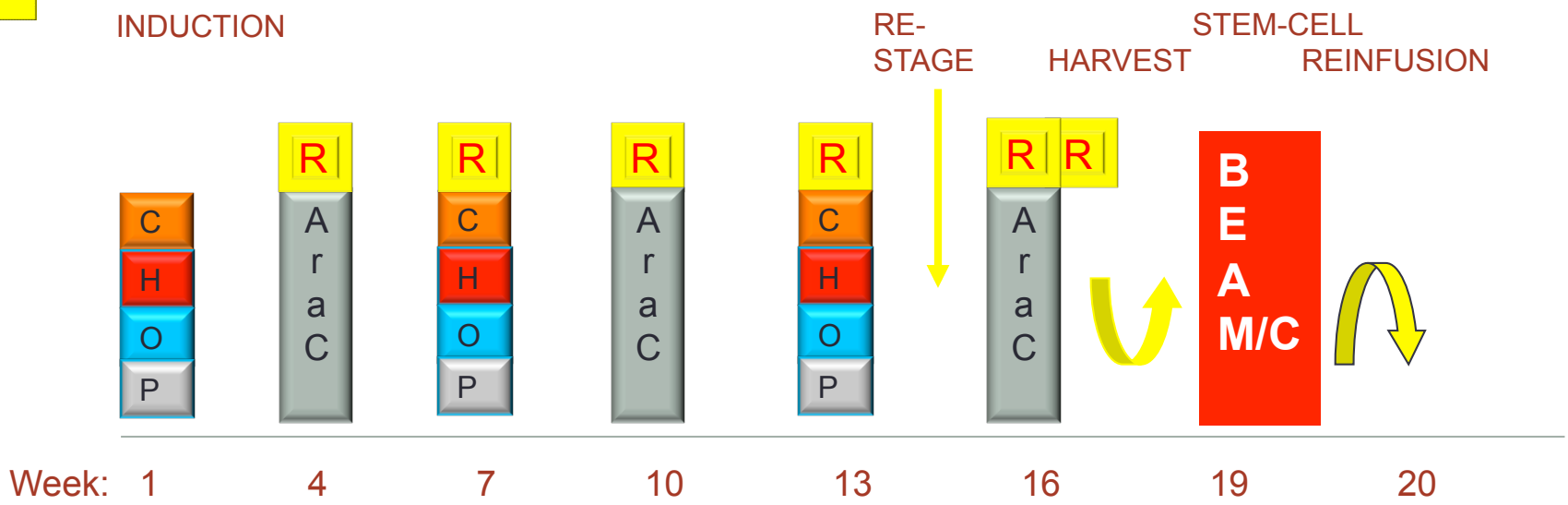
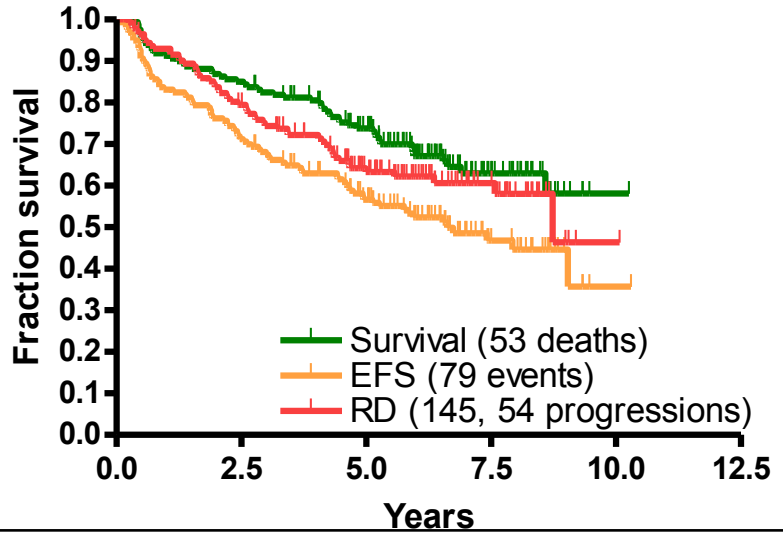
NORDIC MCL2 200-2006:



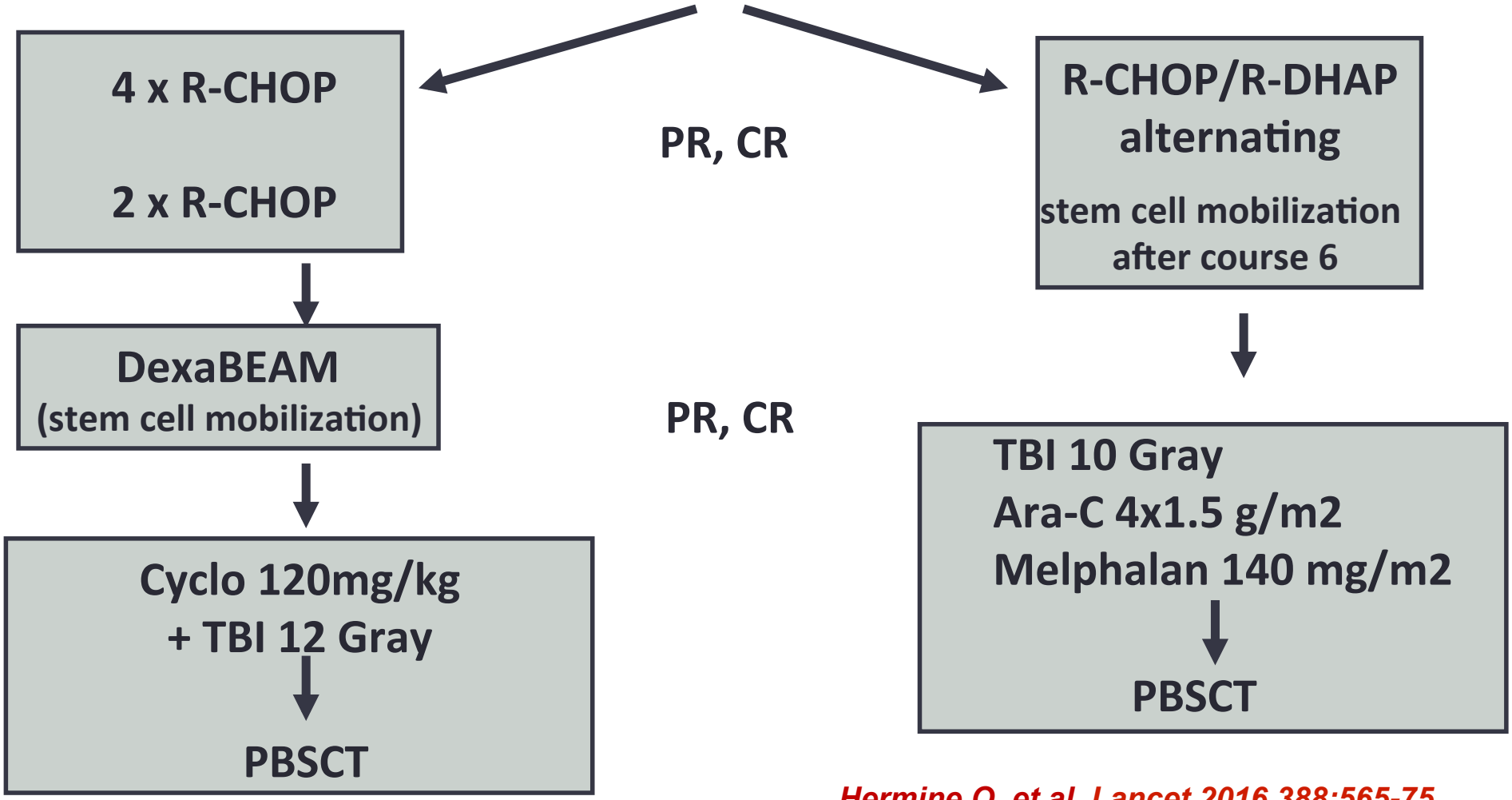
No. Eval.	CR/CRu	ORR
160	54%	96%

MCL2 Update 2010:
- Overall and Event-freeSurvival.
- Response Duration



Intensive schemes including ASCT

MCL Network younger Trial



Hermine O, et al. Lancet 2016 388;565-75

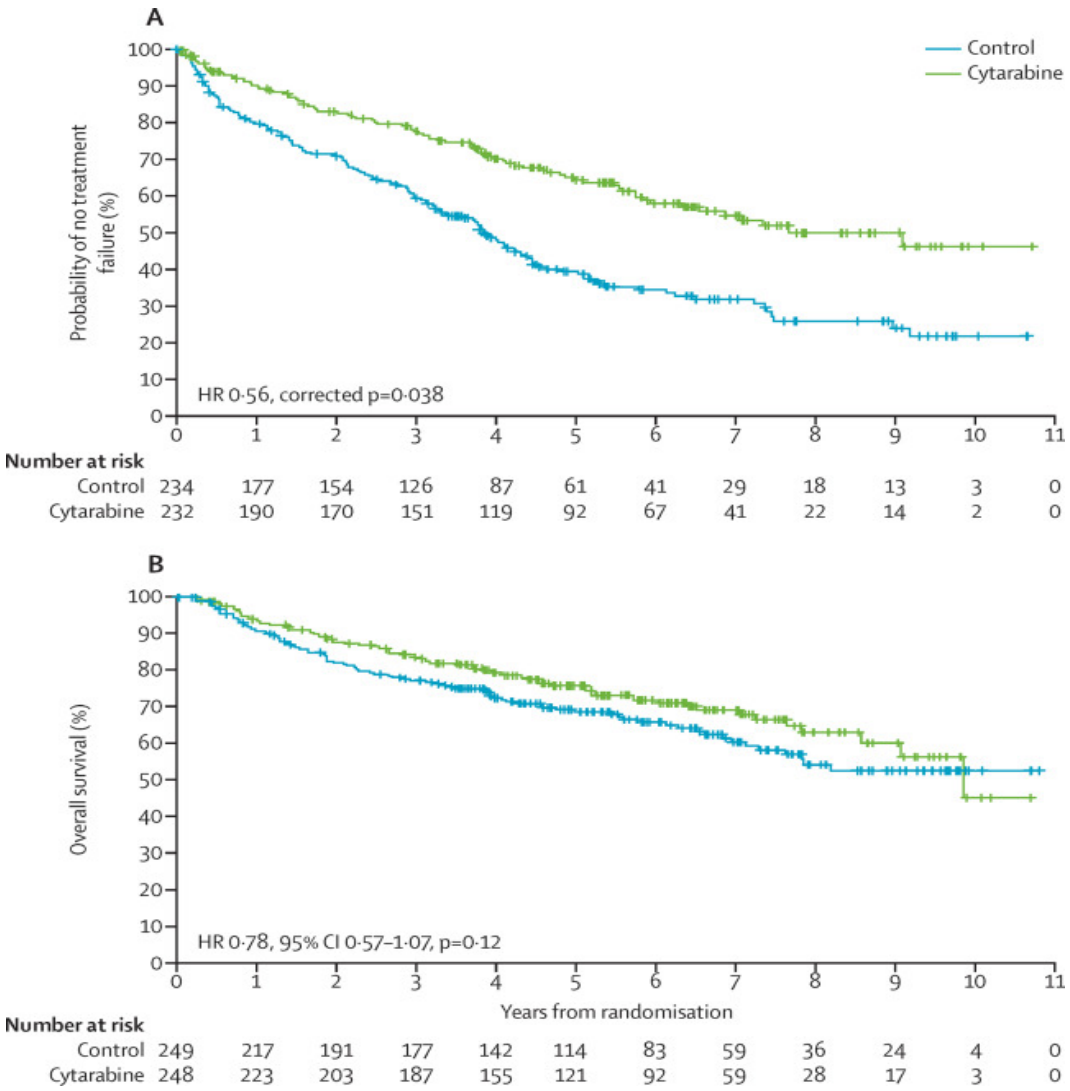


Figure 2. (A) Time to treatment failure in primary analysis and (B) overall survivalHR=hazard ratio.

Olivier Hermine et al. Lancet 2016;388:565-575

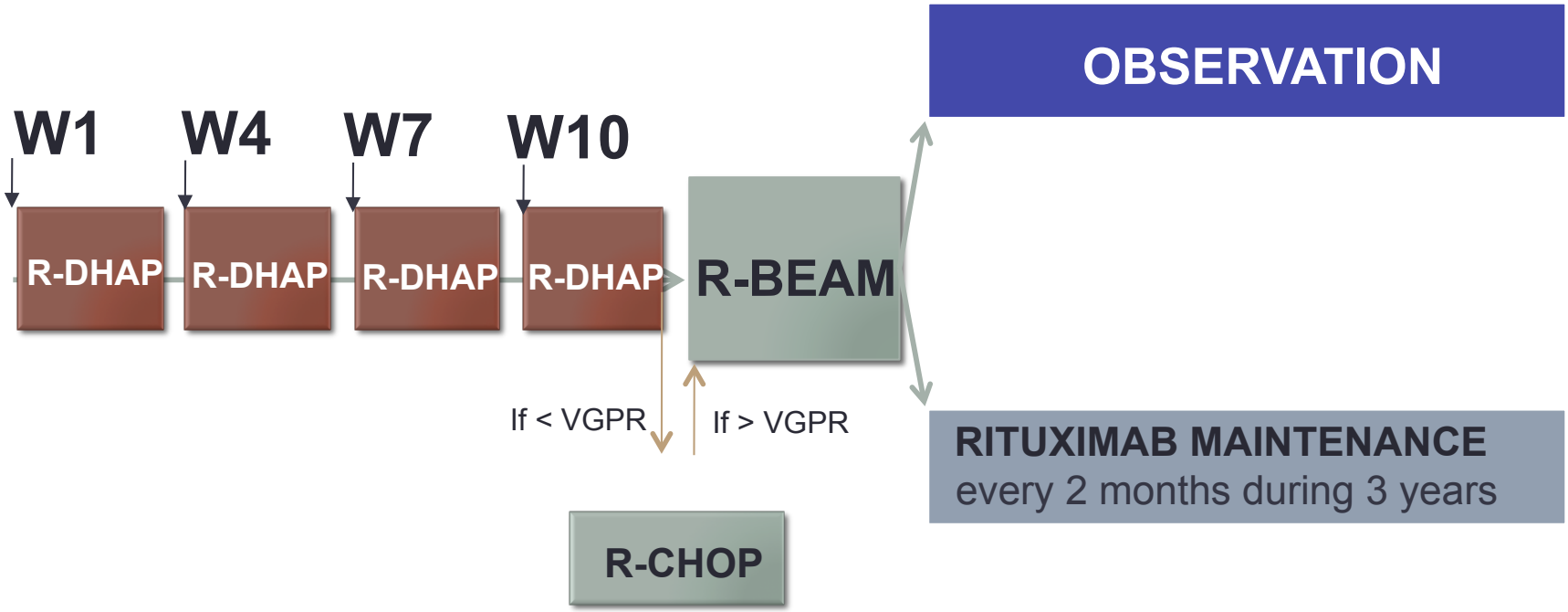
Rituximab maintenance after autologous stem cell transplantation prolongs survival in patients with mantle cell lymphoma (final result of the LyMa trial)

Steven Le Gouill, MD, PhD, Catherine Thieblemont, MD, PhD, Anne Moreau, MD, Lucie Oberic, MD, Krimo Bouabdallah, MD, Emmanuel Gyan, MD, PhD, Gandhi Damaj, MD, PhD, Vincent Ribrag, MD, PhD, Pierre Feugier, MD, PhD, Olivier Casasnovas, MD, Hacène Zerazhi, MD, Corinne Haioun, MD, PhD, Hervé Maisonneuve, MD, Eric Van Den Neste, MD, PhD, Olivier Tournilhac, MD, PhD, Katell Ledu, MD, Franck Morschhauser, MD, PhD, Bernard Christian, MD, Guillaume Cartron, MD, PhD, Luc Fornecker, MD, PhD, Danielle Canioni, MD, PhD, Marie-Christine Béné, MD, PhD, Gilles Salles, MD, PhD, Hervé Tilly, MD, PhD, Thierry Lamy, MD, PhD, Remi Gressin, MD, Olivier Hermine, MD, PhD, on behalf of the LYSA group

ClinicalTrials.gov, NCT00921414

Lysa
THE LYMPHOMA STUDY ASSOCIATION

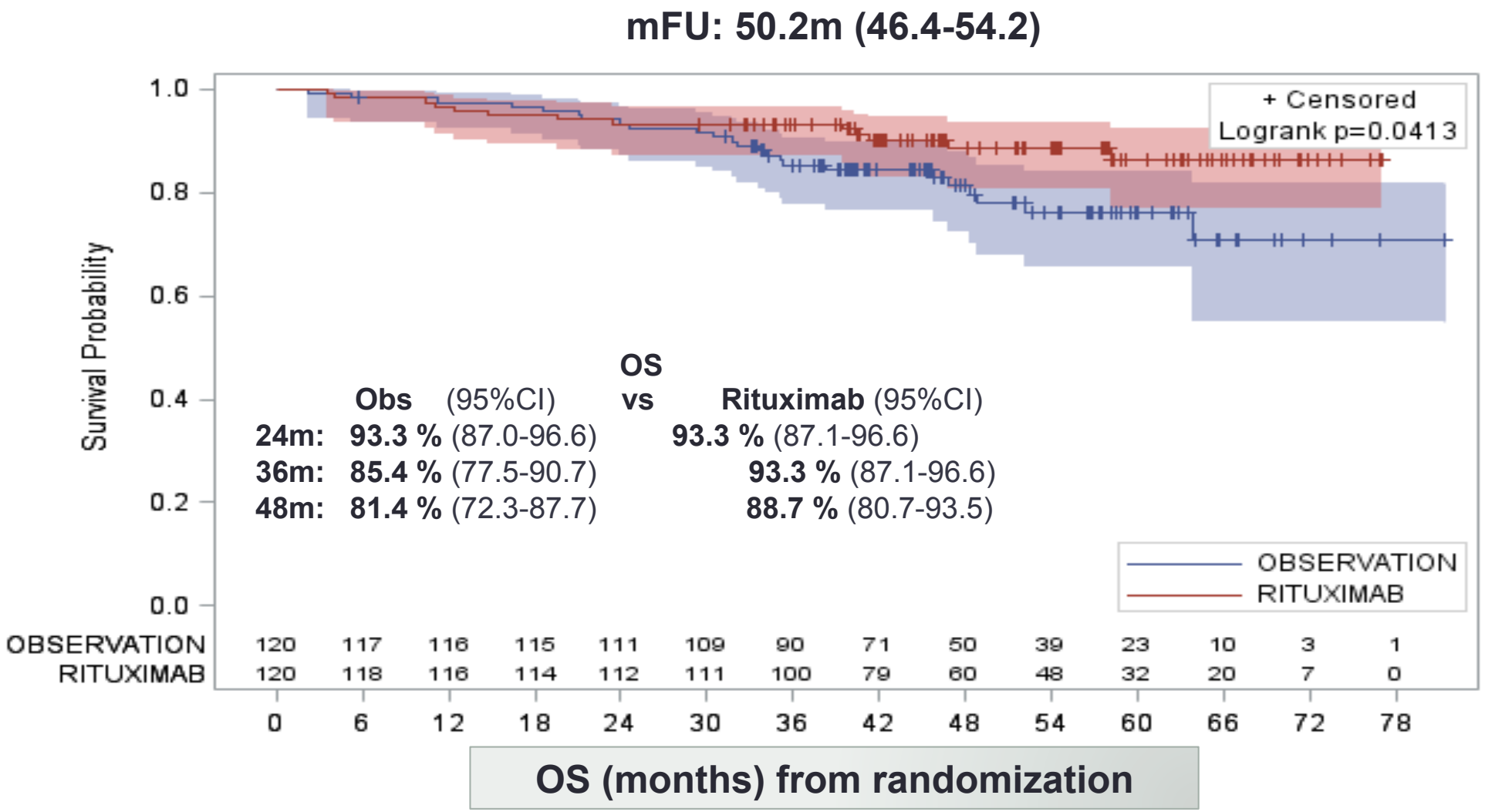
Abstract # 145 ASH 2016



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

OS from Randomization



Prognostic Value of Proliferation (Ki-67), Cytology, and Growth Pattern in Mantle Cell Lymphoma (MCL): Results from Randomized Trials of the *European MCL Network*

E. Hoster, A. Rosenwald, F. Berger, H. W. Bernd, S. Hartmann, C. Loddenkemper, T. Barth, N. Brousse, S. Pileri, G. Rymkiewicz, R. Kodet, S. Stilgenbauer, R. Forstpointner, C. Thieblemont, M. Hallek, B. Coiffier, U. Vehling-Kaiser, V. Ribrag, M. Unterhalt, W. Hiddemann, J. C. Kluin-Nelemans, O. Hermine, M. Dreyling, W. Klapper

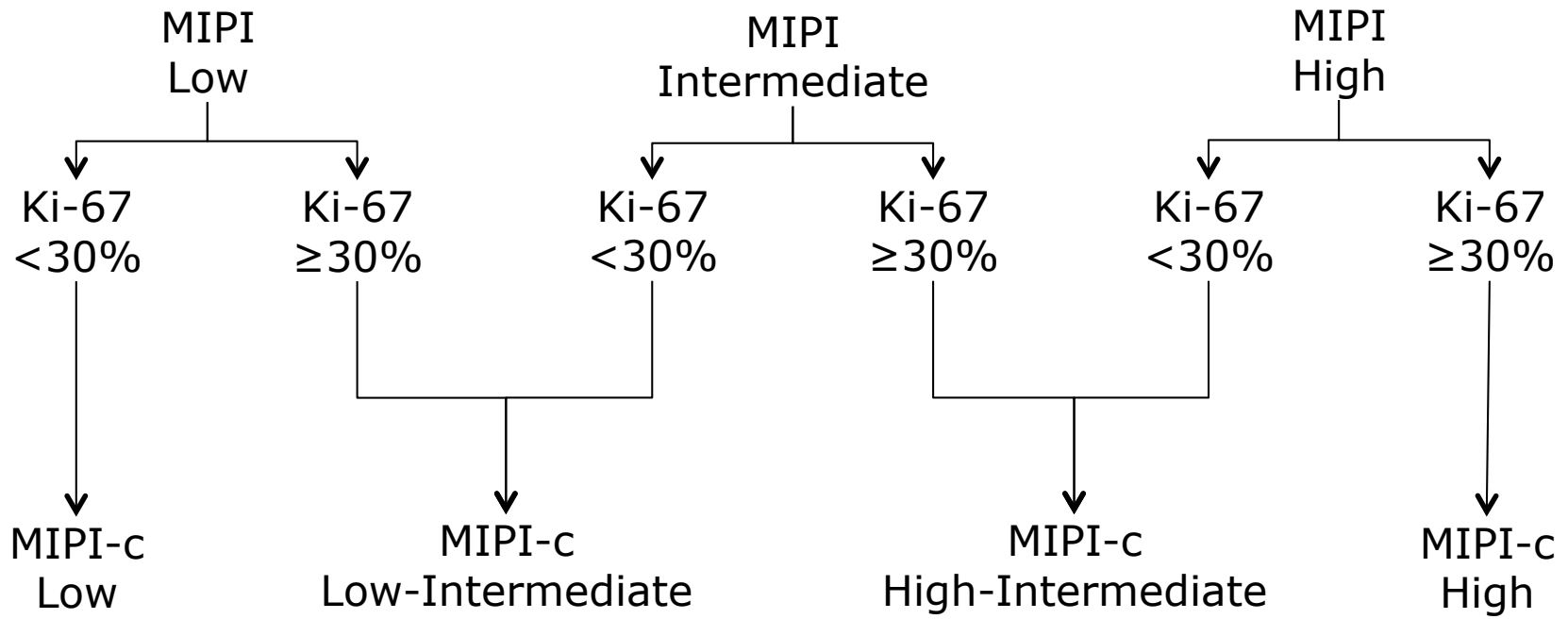
On Behalf of *European MCL Pathology Panel* and *European MCL Network*

Hoster et al, 2016 J Clin Oncol 34;1386-94

Alternative Combined MIPI: MIPI-c

Multivariable Cox Regression

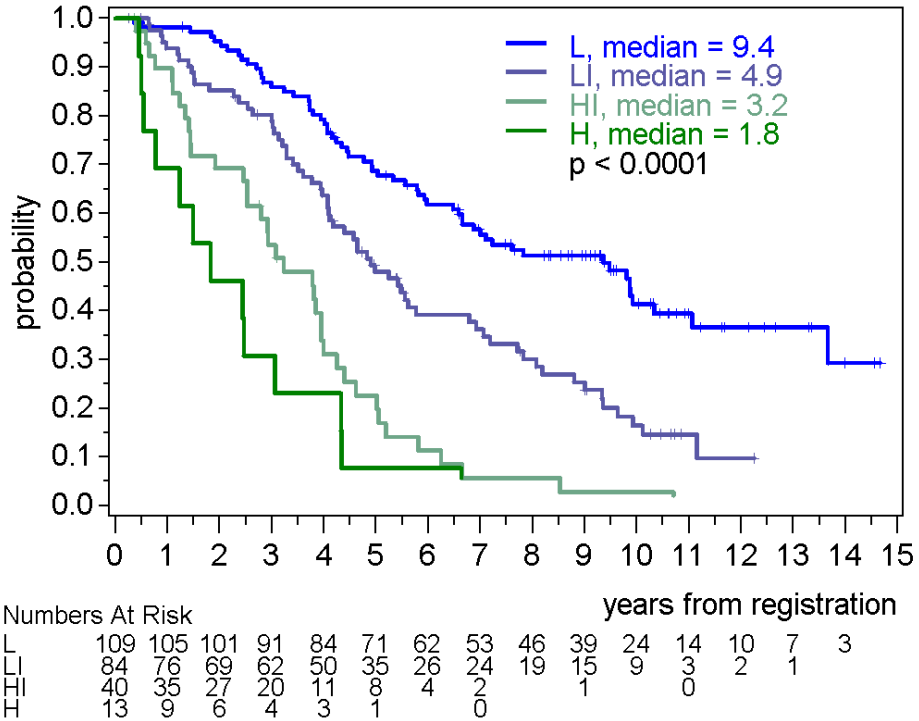
- MIPI and Ki-67 index consistently seen as the independent prognostic factors and should be combined for improved risk stratification



Hoster et al, 2016 J Clin Oncol 34;1386-94

OS According to MIPI-c

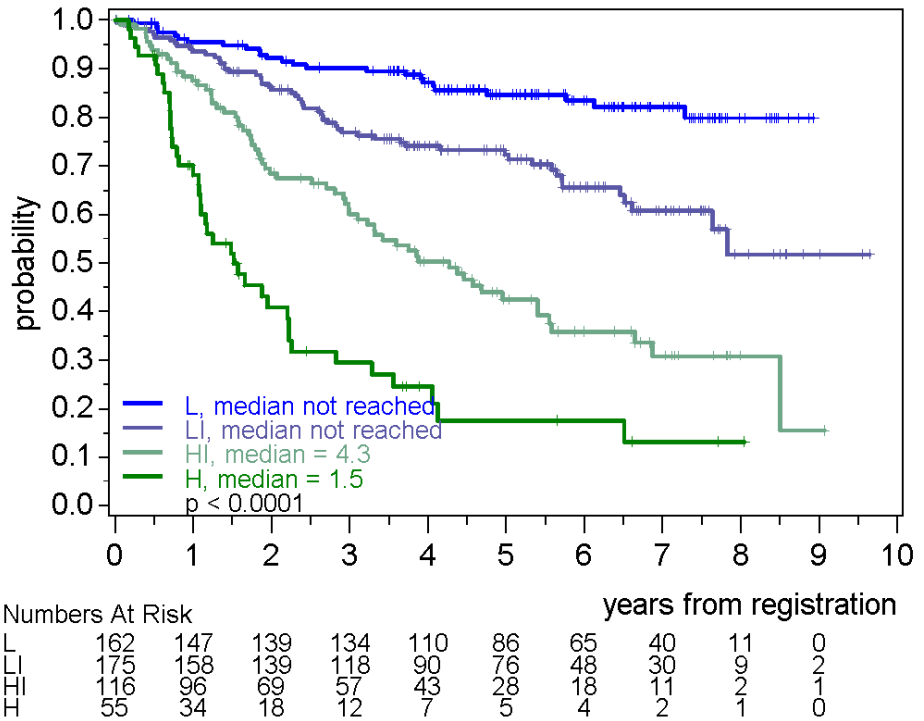
GLSG1996/2000



Numbers At Risk

L	109	105	101	91	84	71	62	53	46	39	24	14	10	7	3
LI	84	76	69	62	50	35	26	24	19	15	9	3	2	1	
HI	40	35	27	20	11	8	4	2		1		0			
H	13	9	6	4	3	1		0							

MCL Younger/MCL Elderly



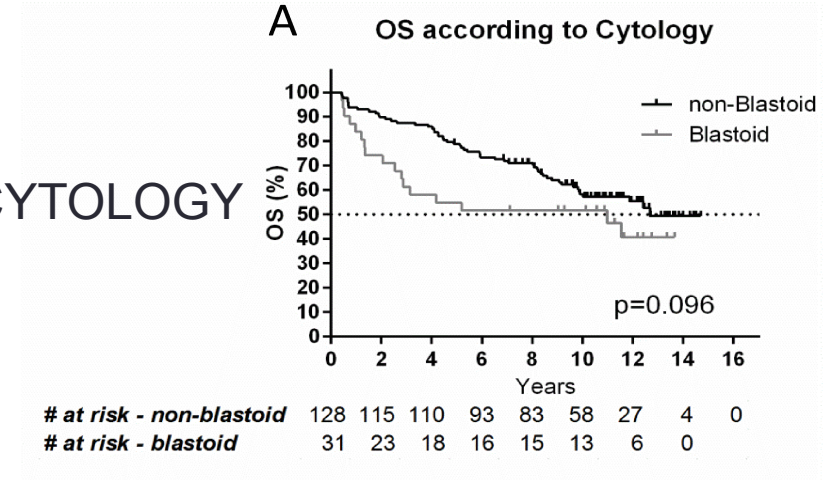
Numbers At Risk

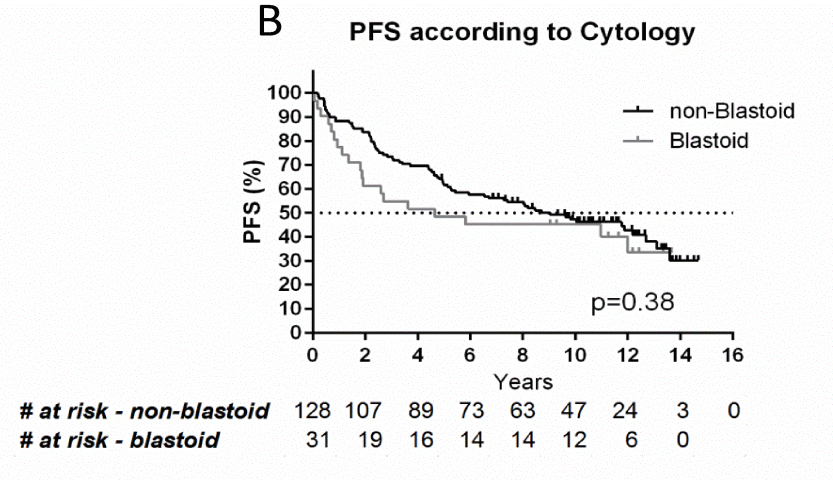
L	162	147	139	134	110	86	65	40	11	0
LI	175	158	139	118	90	76	48	30	9	2
HI	116	96	69	57	43	28	18	11	2	1
H	55	34	18	12	7	5	4	2	1	0

Hoster et al, 2016 J Clin Oncol 34;1386-94

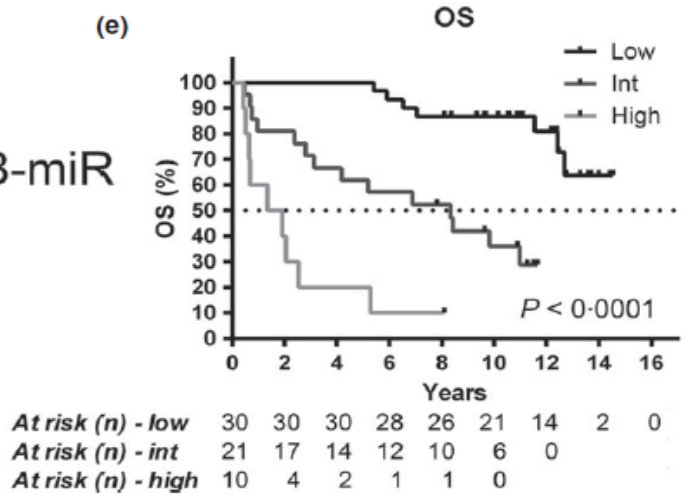
Nordic Protocol 15 Year Follow up

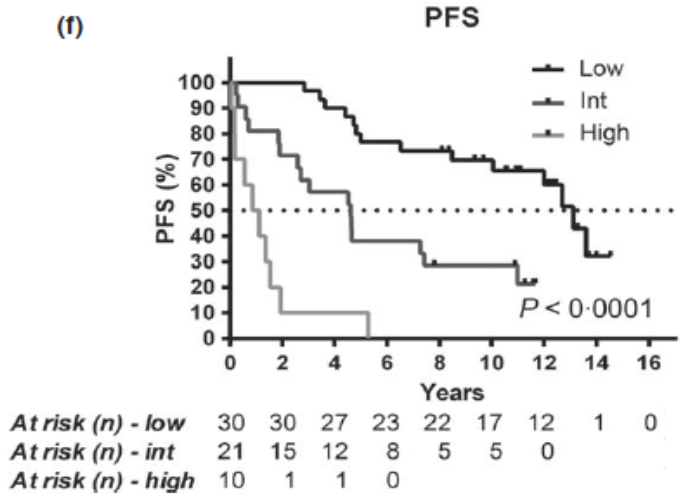
CYTOLOGY





MIPI-B-miR



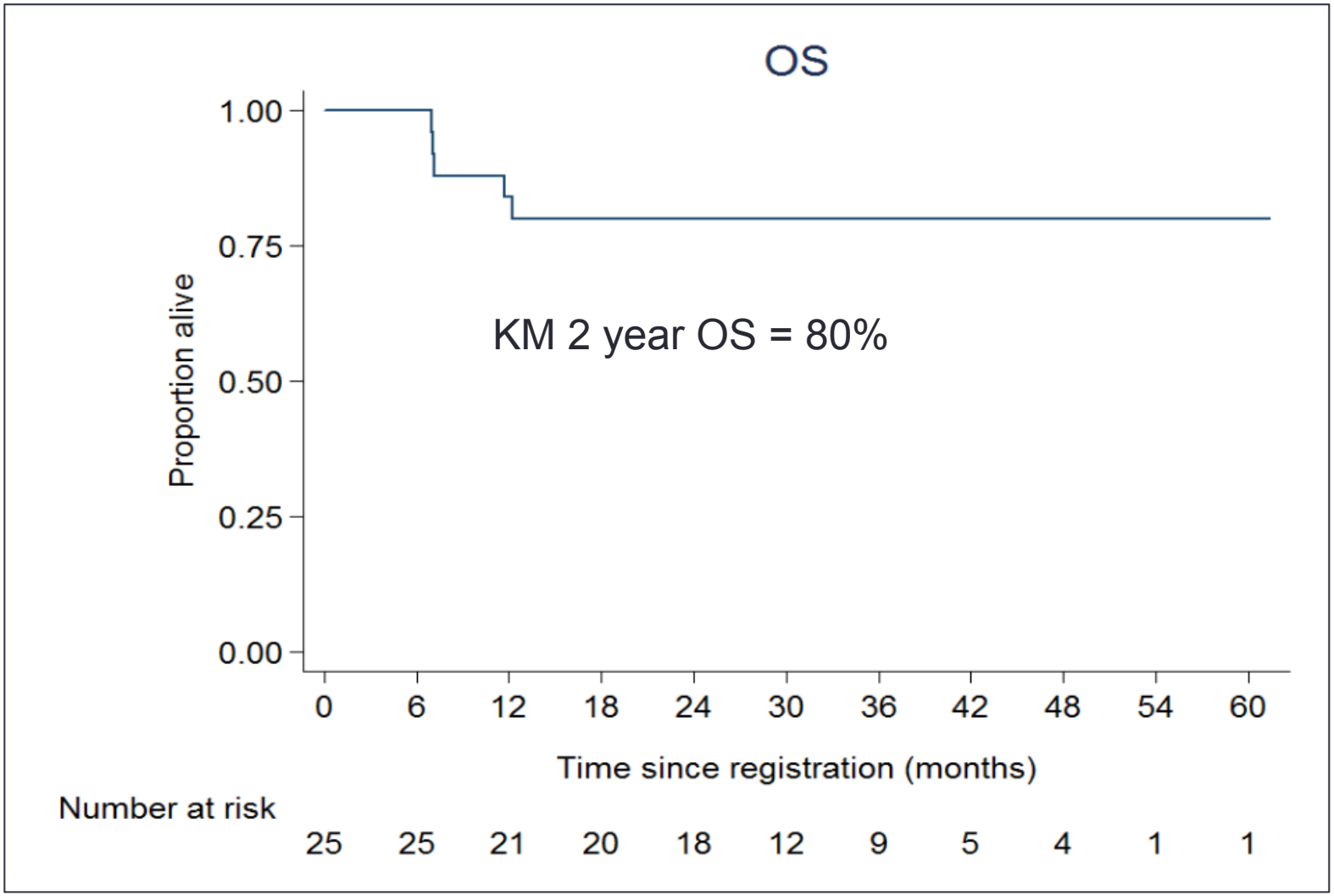


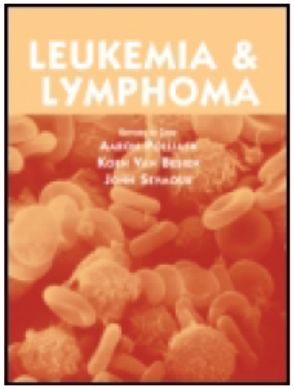
Eskelund Br J Haematol 2016

REDUCED INTENSITY CONDITIONING TRANSPLANTATION AS PART OF FIRST LINE THERAPY FOR MANTLE CELL LYMPHOMA: RESULTS FROM THE PHASE II MINI ALLO TRIAL (CRUK: C7627/A9080)

Peggs KS, Cook G, S Robinson, Russell N, Hunter A, Morley NJ, Sureda A, Smith P, Patrick P, Braganca N, Stevens L, Adedayo T, Kirkwood AA, Rule S

MCL MiniAllo: Overall Survival



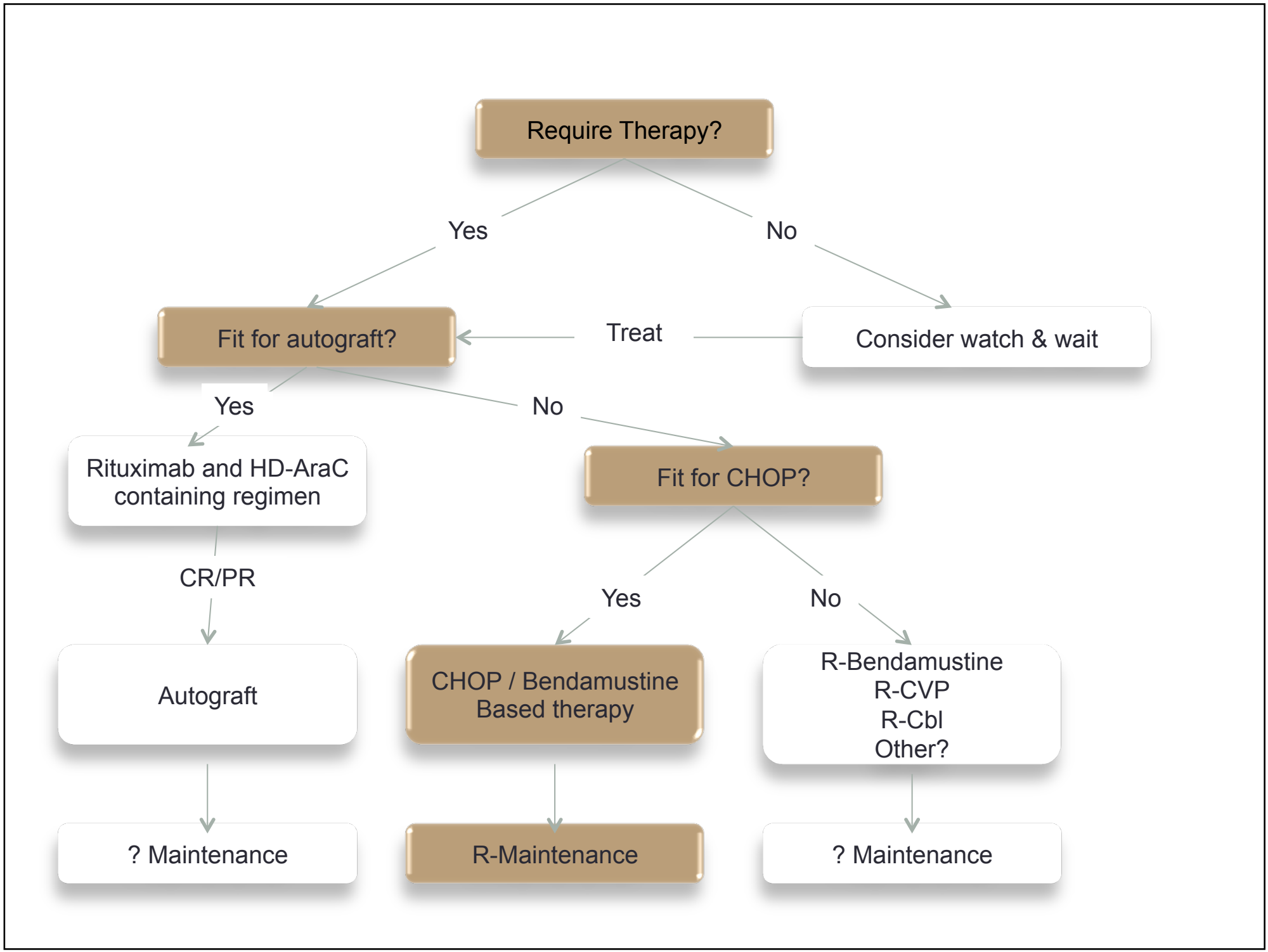


Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

The use of Bruton's tyrosine kinase inhibition as a bridging strategy to successful allogeneic stem cell transplant in relapsed mantle cell lymphoma

Michelle Furtado, Kathleen Clarke, Patrick Medd, Hannah Hunter & Simon Rule


Require Therapy?
Yes
No
Fit for autograft?
Treat
Consider watch & wait
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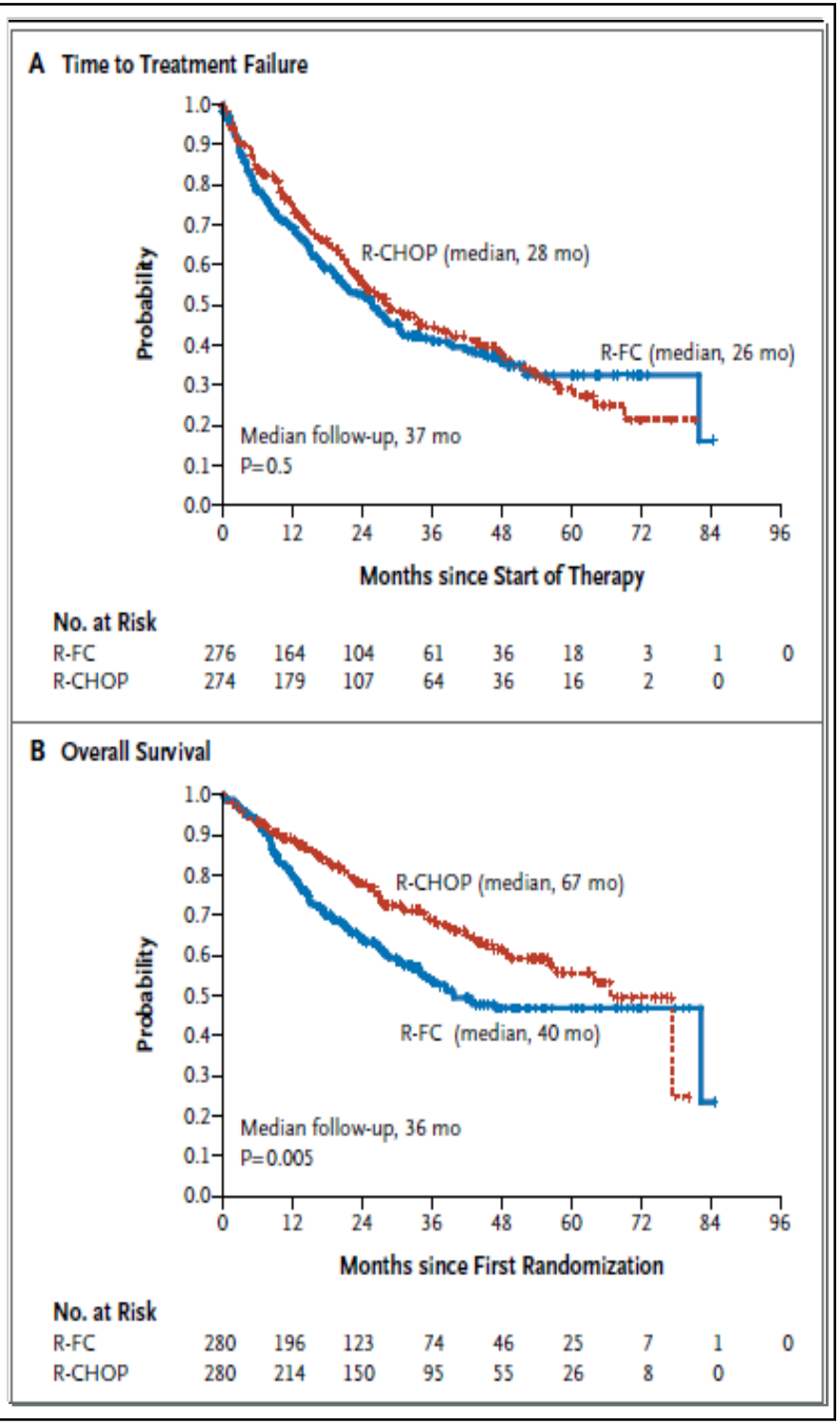
Rituximab and HD-AraC containing regimen
Fit for CHOP?
CR/PR
Yes
No
Autograft
CHOP / Bendamustine Based therapy
R-Bendamustine
R-CVP
R-Cbl
Other?
? Maintenance
R-Maintenance
? Maintenance

R-CHOP vs R-FC in elderly patients with MCL

	ORR (%)	CR (%)
R-CHOP	**86**	**34**
R-FC	**78**	**40**

P=0.06 P=0.10

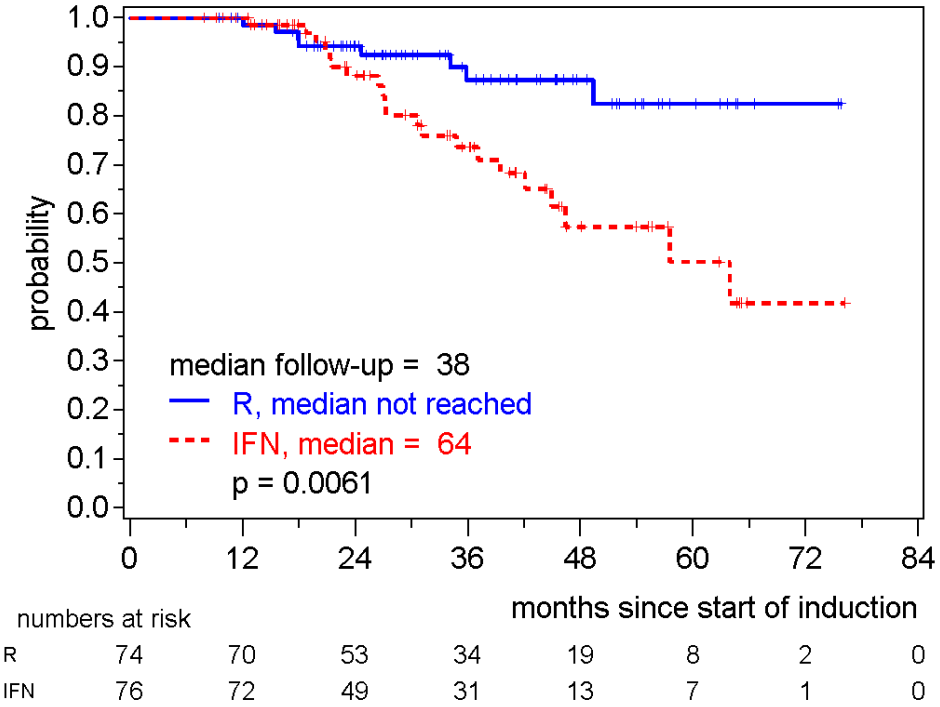
Cause of death	R-FC	R-CHOP
Died in CR/PR	10%	4%
Infections	7%	4%
Second cancer	3%	1%



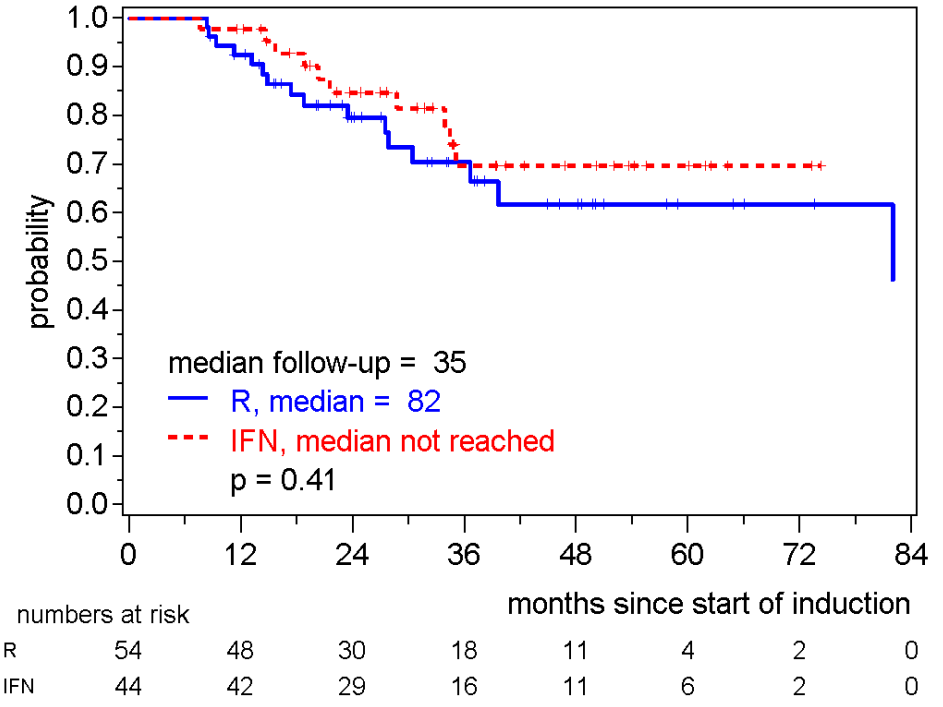
Kluin-Nelemans HC et al. NEJM 2012;367:520-31

MCL Elderly: overall survival related to induction regimen

After R-CHOP



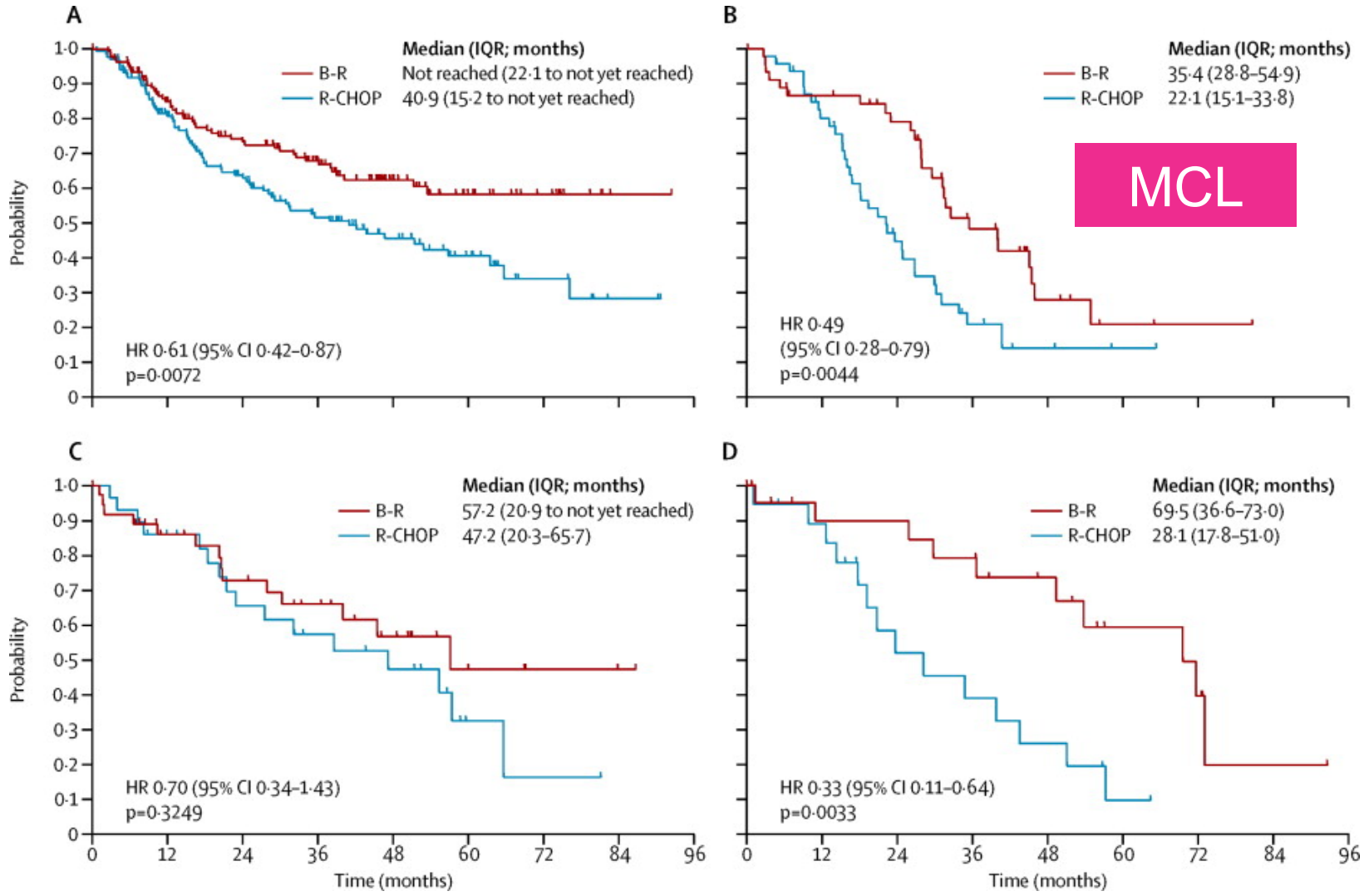
After R-FC



Kluin-Nelemans HC et al. NEJM 2012;367:520-31

R-Bendamustine

PFS



Rummel MJ et al, Lancet 2013

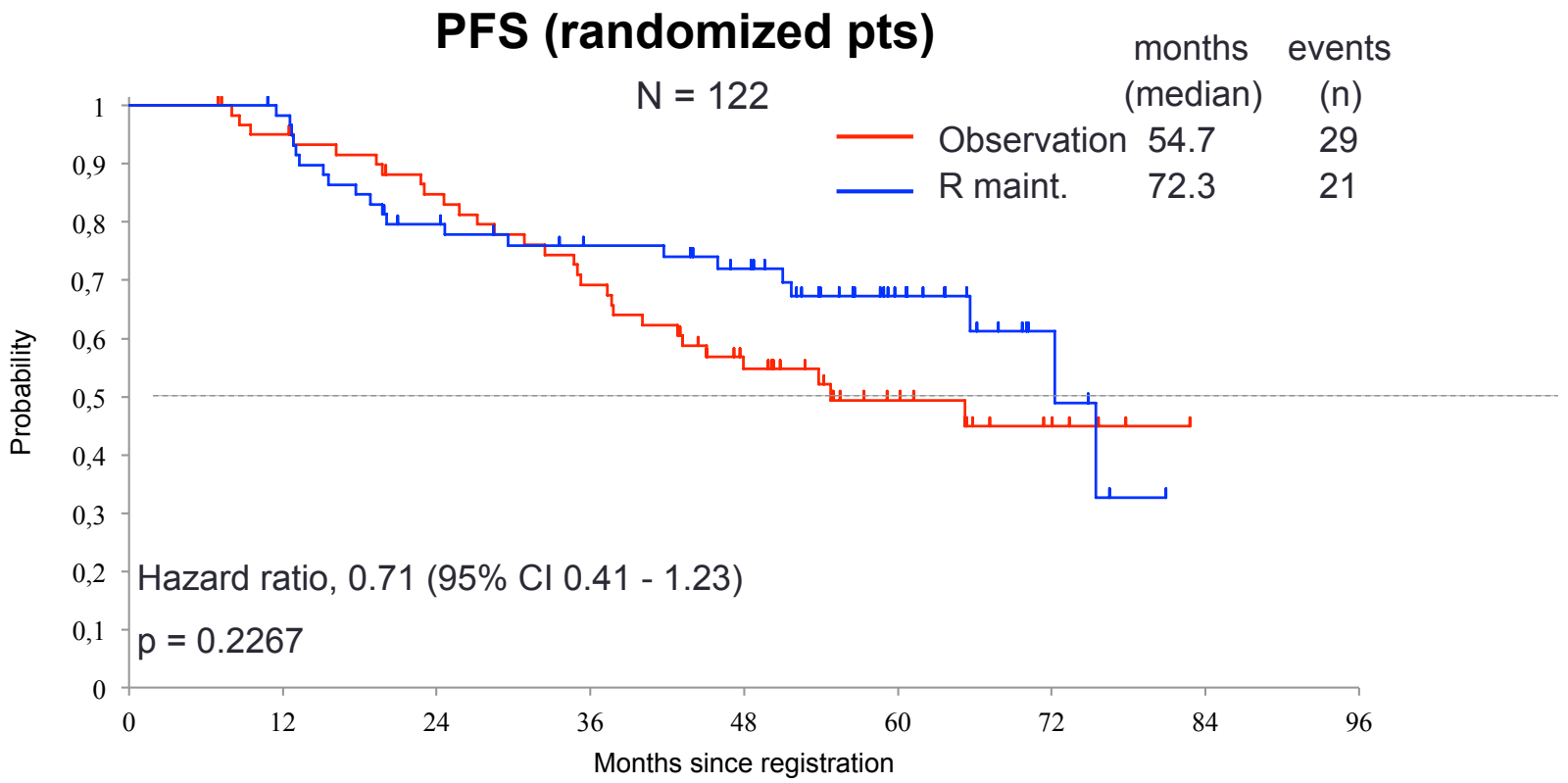
Two Years Rituximab Maintenance vs. Observation after 1st-line treatment with Bendamustine plus Rituximab in pts with Mantle Cell Lymphoma

Results of a prospective, randomized, multicentre phase 2 study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial)

Mathias Rummel, Wolfgang Knauf, Martin Goerner, Ulrike Soeling, Elisab. Lange, Bernd Hertenstein, Jochen Eggert, G. Schliesser, R. Weide, Kl. Blumenstengel, N. Detlefsen, Axel Hinke, Frank Kauff, Juergen Barth on behalf of **StiL Study group indolent Lymphomas**, Giessen, Germany

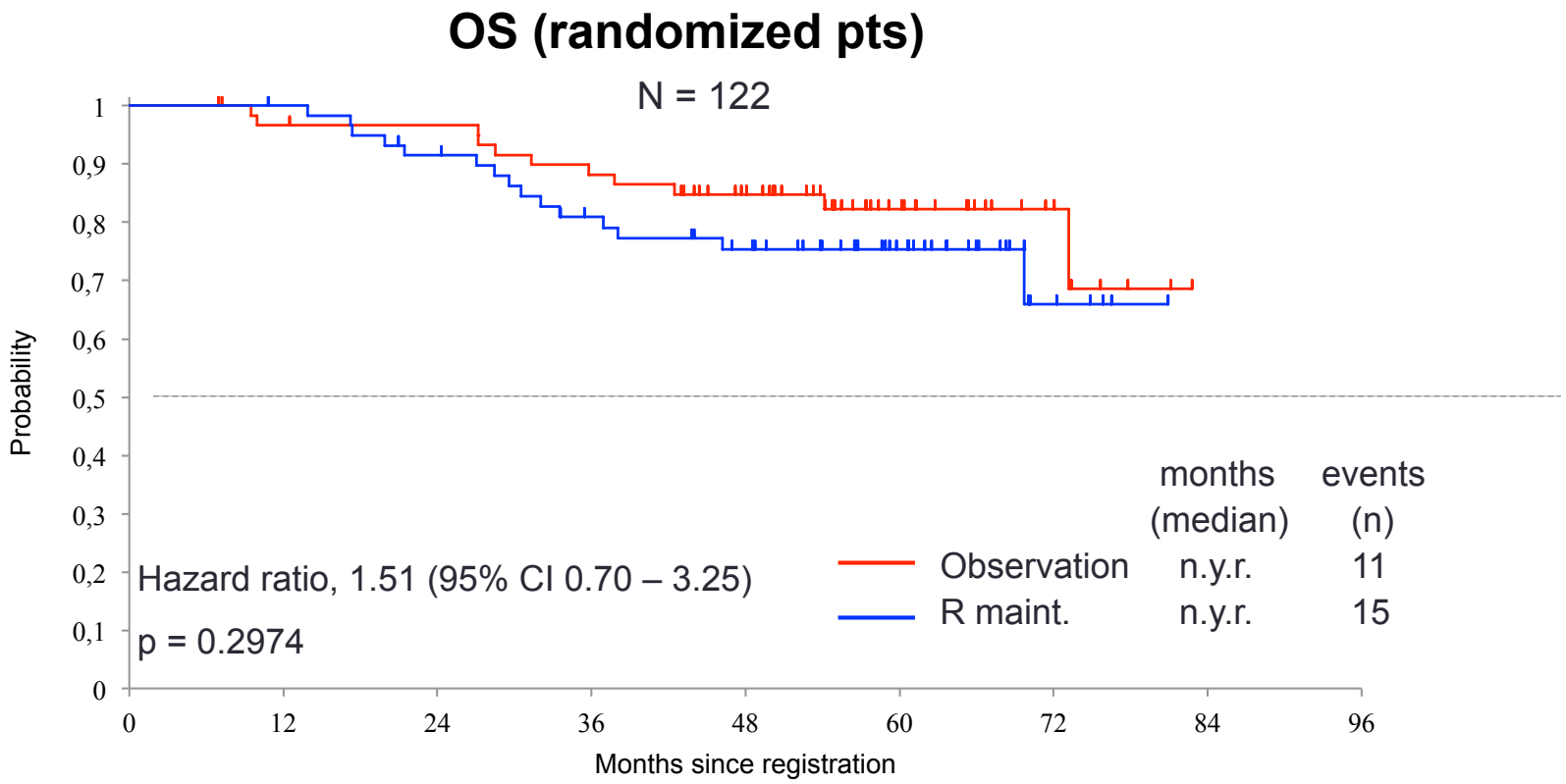
StiL
Studiengruppe indolente Lymphome

Progression free survival (58.6 months median follow-up)



Pts at risk							
Observ	62	57	49	40	26	13	5
R maint	60	58	45	39	24	18	5

Overall survival (58.6 months median follow-up)



Pts at risk							
Observ	62	58	57	52	43	21	8
R maint	60	59	53	44	38	23	5

Cross study comparison

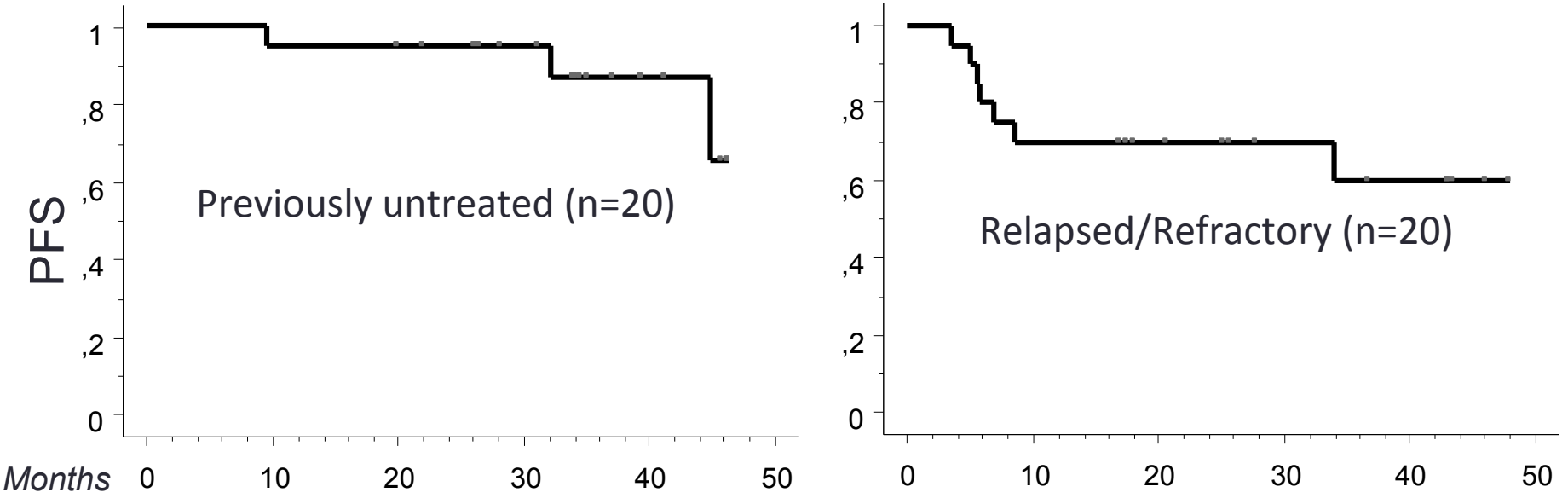
	StiL NHL 7-2008		Kluin-Nelemans et al	
	n = 122 (of 168)		n = 184 (of 280)	
Rate of randomized patients	73 %		66 %	
	B-R	**B-R + R**	**CHOP-R + INF**	**CHOP-R + R**
Remission duration				
median (months) since randomization	57	68	23	n.y.r
rate at 72 months (estimated)	49%	40%	12%	50%
OS				
median (months) since randomization	n.y.r.	n.y.r.	64	n.y.r.
rate at 72 months (estimated)	70%	66%	50%	71%

Rituximab, Bendamustine, Cytarabine (R-BAC)

Treatment	Day 1	2	3	4
Rituximab 375 mg/m²	↓			
Bendamustine 70 mg/m²		↓	↓	
Ara-C 800 mg/m²		↓	↓	↓

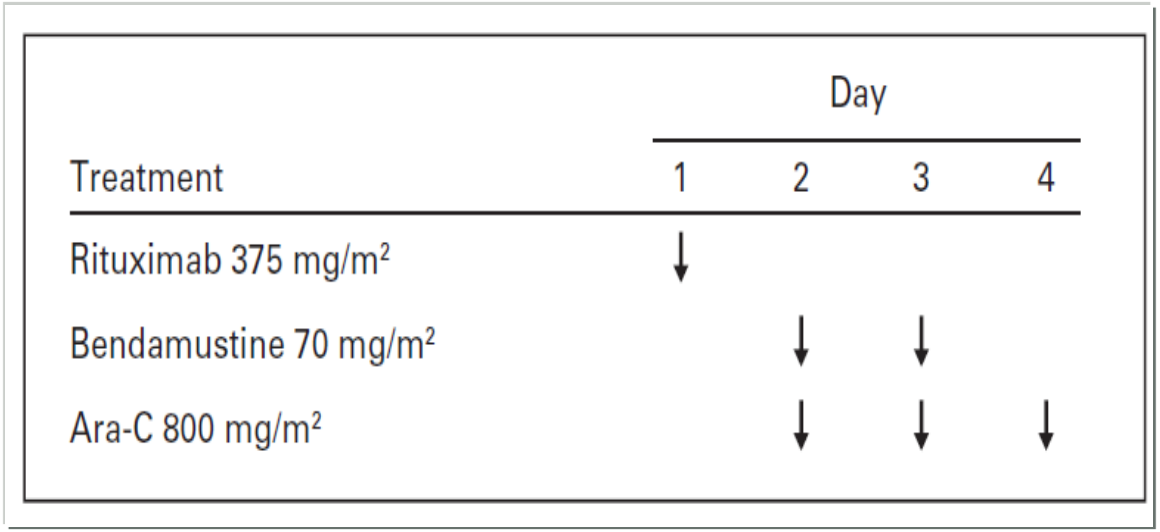
	ORR (%)	CR (%)
Untreated	100	95
R/R	80	70

Median F/U 35 months (17-49)



Updated (june 2013) from Visco et al, JCO 2013

Rituximab, Bendamustine, Cytarabine (R-BAC)



	ORR (%)	CR (%)
Untreated	100	95
R/R	80	70

	Overall			
	Cycles (N = 182)		Patients (N = 40)	
Grade 3 or 4 Event	No.	%	No.	%
Leukopenia	87	48	23	57
Neutropenia	56	31	16	40
Febrile neutropenia	7	4	5	12
Thrombocytopenia	138	76	35	87
Anemia	48	26	18	45

RBAC500 as induction therapy for elderly patients

- Rituximab 375 mg/m^2 on day 1; Bendamustine 70 mg/m^2 days 2 and 3; Cytarabine (dose reduced) 500 mg/m^2 days 2-4
- Included previously untreated patients aged >65 years or 60-65 unfit for ASCT with no history of indolent disease (non-nodal leukemic disease)
- Primary objectives: CR rate and safety

End of treatment PET/CT		
	N=57	**%**
ORR	52	91
CR	52	91
PD	2	4
NA	3	5

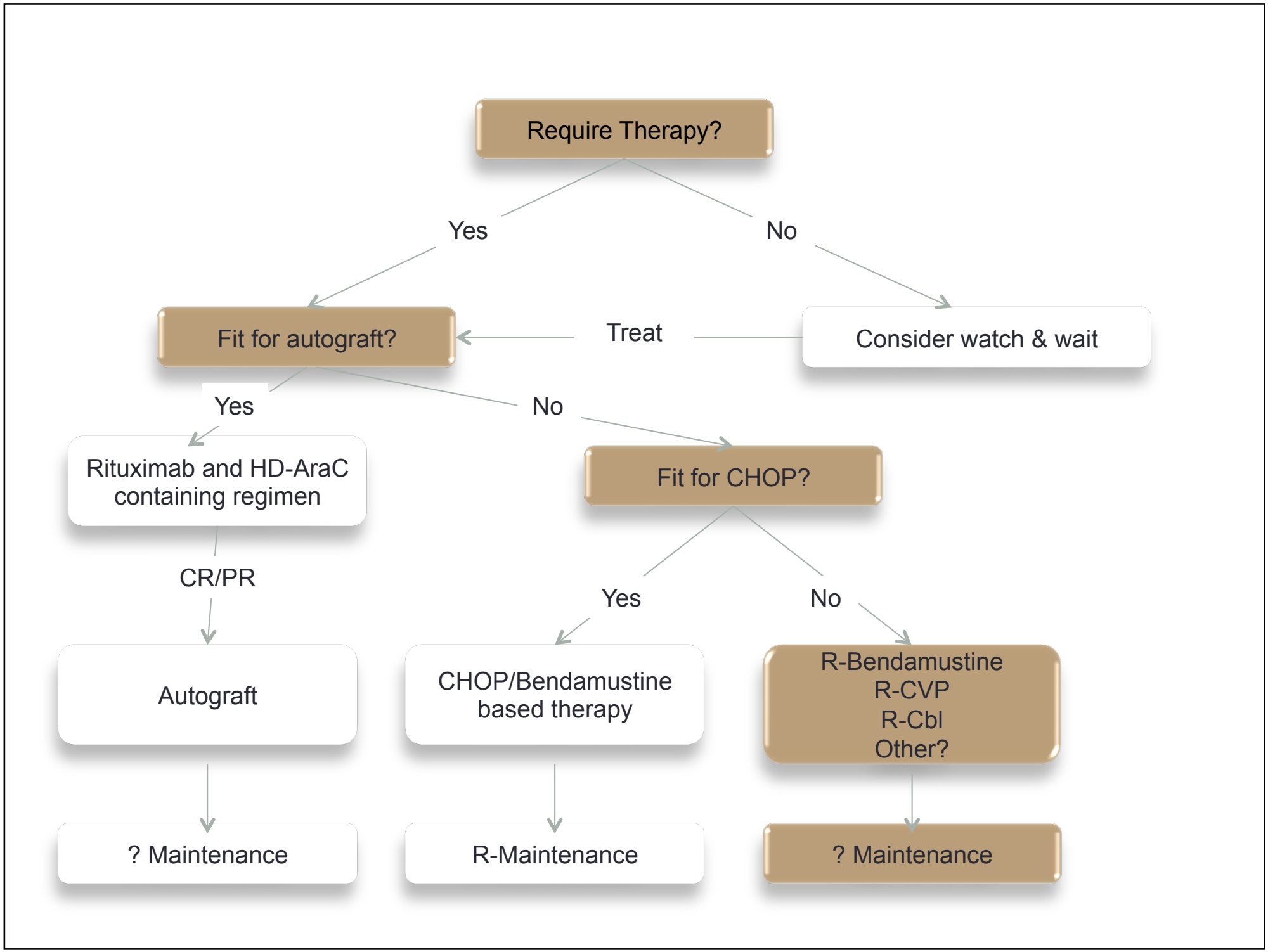
MRD by n-PCR (n=45, 79%)		
Timepoints	**n**	**MRD- BM/PB**
After cycle 2	45	54/62
End of therapy	45	55/79
+12 months	28	57/75

Visco et al., ASH 2016 (abstract 472, oral presentation)

RBAC500 as induction therapy for elderly patients

	Overall					R-BAC (JCO 2013)
Grade	0	1	2	3	4	4
Leukopenia		30%	26%	17%	27%	28%
Neutropenia		15%	36%	14%	35%	17%
Febrile neutropenia				5%	1%	4%
Thrombocytopenia		14%	34%	16%	36%	64%
Anemia	21%	24%	43%	12%	<1%	12%
Platelet transfusion	89 of 304 (29%)					62%

Visco et al., ASH 2016 (abstract 472, oral presentation)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Autograft
CHOP/Bendamustine based therapy
R-Bendamustine
R-CVP
R-Cbl
Other?
? Maintenance
R-Maintenance
? Maintenance

RELAPSE

Table of Various Treatment for R/R MCL

Treatment	Study or Literature Reference	N	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	PCYC-1104-CA	111	68%	21%	17.5	13.9	Not reached
Bortezomib	Fischer 2006 Goy 2009	155[a]	33%	8%	9.2	6.5	23.5
Lenalidomide	Goy 2012	134	28%	8%	16.6	4.0	19.0
Temsirolimus[b]	Hess 2009	54	22%	2%	7.1	4.8	12.8

CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival; PFS= progression-free survival.

[a] Of the 155 patients enrolled, 141 were assessable for response.

[b] Results are presented for temsirolimus 175/75 mg dose group.

Campo & Rule Blood 2015 Jan 1;125(1):48-55

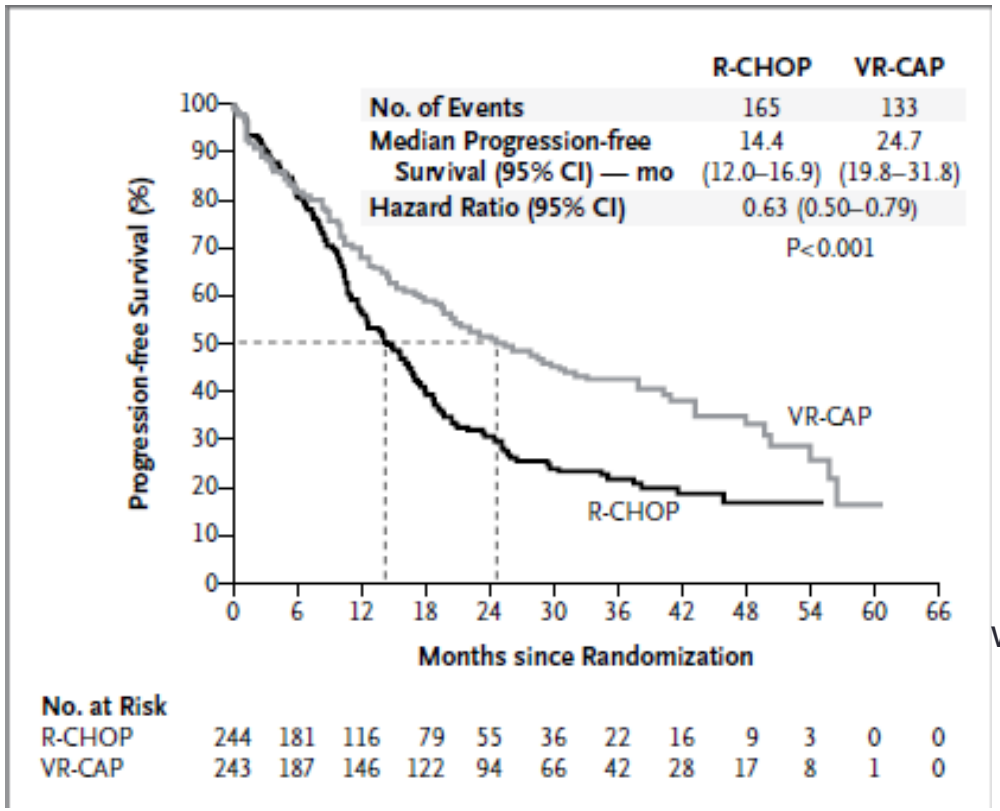
BORTEZOMIB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

Tadeusz Robak, M.D., Huiqiang Huang, M.D., Jie Jin, M.D., Jun Zhu, M.D., Ting Liu, M.D., Olga Samoilova, M.D., Halyna Pylypenko, M.D., Gregor Verhoef, M.D., Ph.D., Noppadol Siritanaratkul, M.D., Evgenii Osmanov, M.D., Ph.D., Julia Alexeeva, M.D., Ph.D., Juliana Pereira, Ph.D., Johannes Drach, M.D., Jiri Mayer, M.D., Xiaonan Hong, M.D., Rumiko Okamoto, M.D., Lixia Pei, Ph.D., Brendan Rooney, Ph.D., Helgi van de Velde, M.D., Ph.D., and Franco Cavalli, M.D., for the LYM-3002 Investigators*



	ORR (%)	CR (%)
R-CHOP	89	42
VR-CAP	92	53

No difference in OS.
VR-CAP was more effective than R-CHOP in patients with newly diagnosed MCL but at the cost of increased hemo-toxicity.

Robak T et al, NEJM 2015

LENALIDOMIDE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Jia Ruan, M.D., Ph.D., Peter Martin, M.D., Bijal Shah, M.D., Stephen J. Schuster, M.D., Sonali M. Smith, M.D., Richard R. Furman, M.D., Paul Christos, Dr.P.H., Amelyn Rodriguez, R.N., Jakub Svoboda, M.D., Jessica Lewis, P.A., Orel Katz, P.A., Morton Coleman, M.D., and John P. Leonard, M.D.

Table 2. Rates of Best Response at the Median Follow-up of 30 Months.

Response	Patients	Intention-to-Treat Population (N=38)	Patients Who Could Be Evaluated (N=36)
	no.	%	
Overall response	33	87	92
Complete response*	23	61	64
Partial response	10	26	28
Stable disease	1	3	3
Progressive disease†	2	5	6
Could not be evaluated‡	2	5	

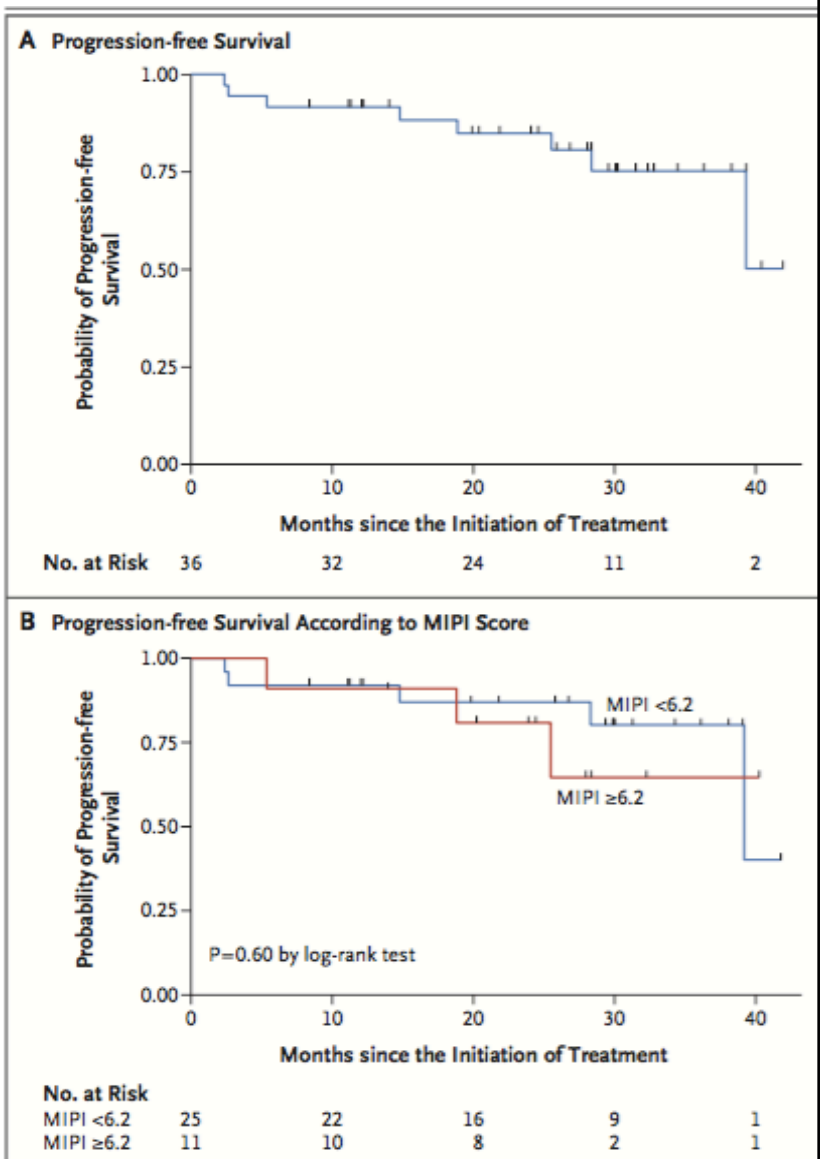
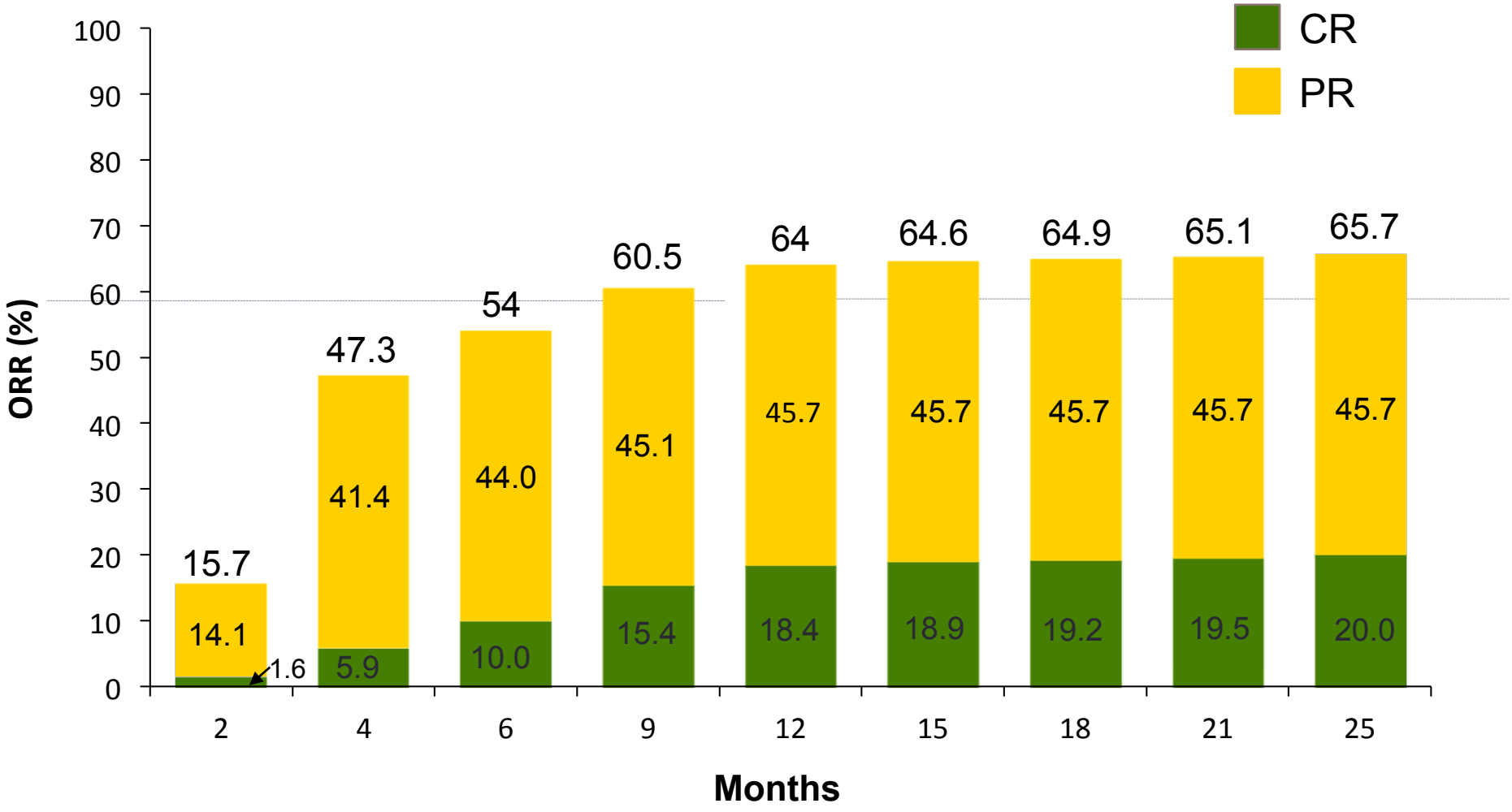


Figure 1. Progression-free Survival.

Panel A shows the probability of progression-free survival among the 36 patients who could be evaluated. Panel B shows the probability of progression-free survival according to the baseline score on the Mantle Cell Lymphoma International Prognostic Index (MIPI) — lower than 6.2 (indicating low-risk or intermediate-risk disease) versus 6.2 or higher (indicating high-risk disease).

IBRUTINIB

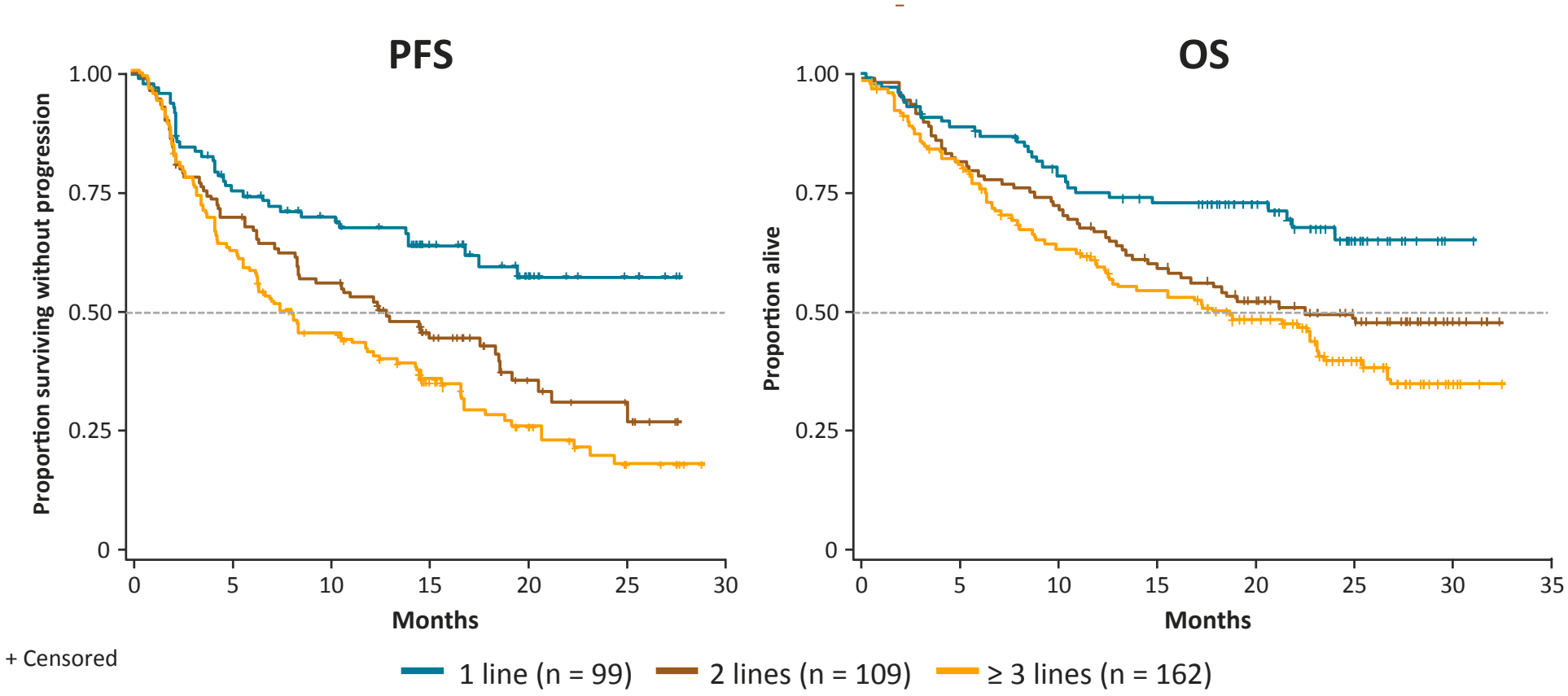
Pooled MCL Analysis: Improvement in Response Rates Over Time



PR, partial response.

N = 370

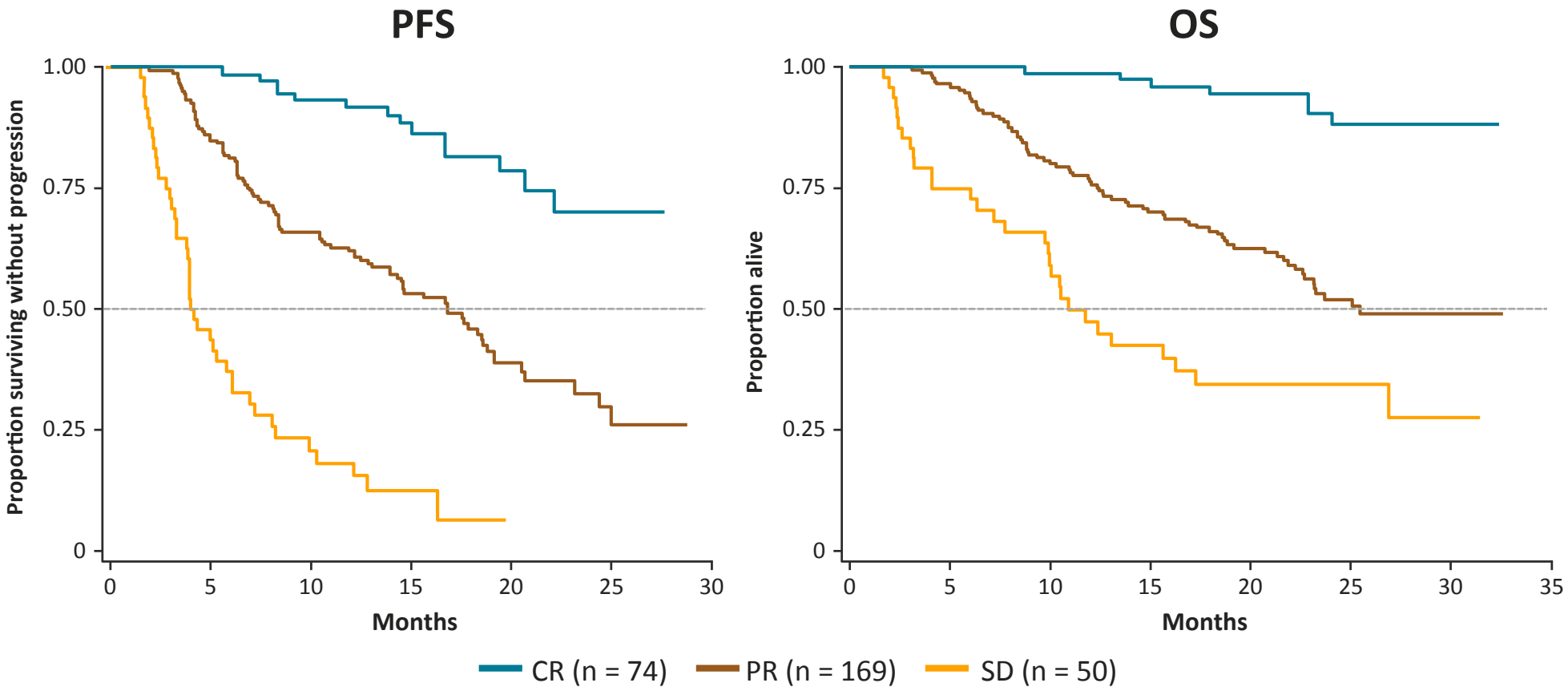
Pooled MCL Analysis: PFS and OS by Prior Lines of Therapy (1, 2, ≥ 3)



- Patients who had received only 1 prior line of therapy had the longest PFS and OS; 2-year PFS and OS were 57% and 68%, respectively

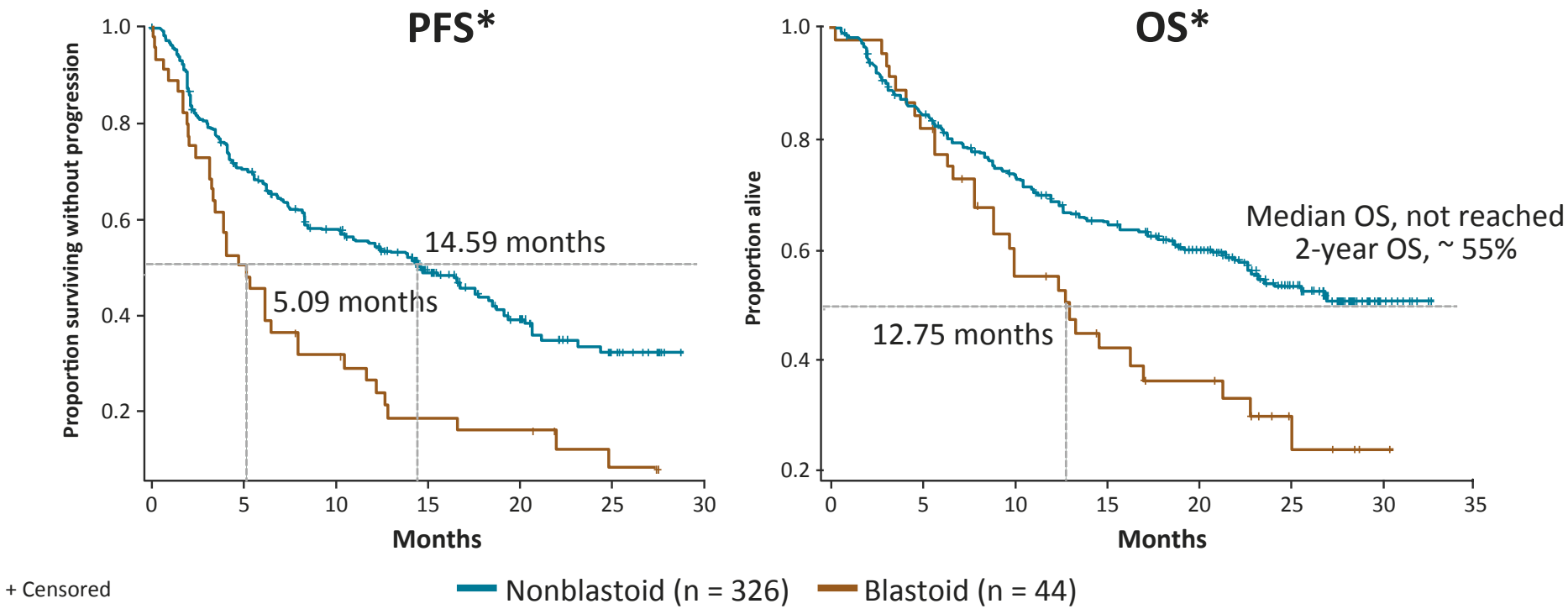
Rule et al ASH 2015 oral presentation

Pooled MCL Analysis: PFS and OS by Response



- Patients who achieved a CR had the longest PFS and OS; 92% of patients who achieved a CR were alive at 2 years

Pooled MCL Analysis: PFS and OS by Blastoid Histology



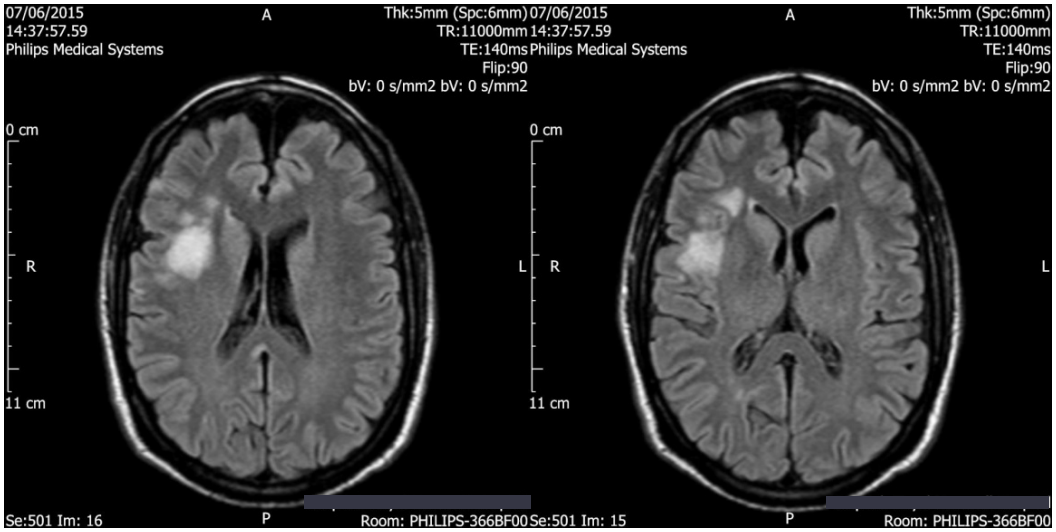
CI, confidence interval.
*Statistically significant.

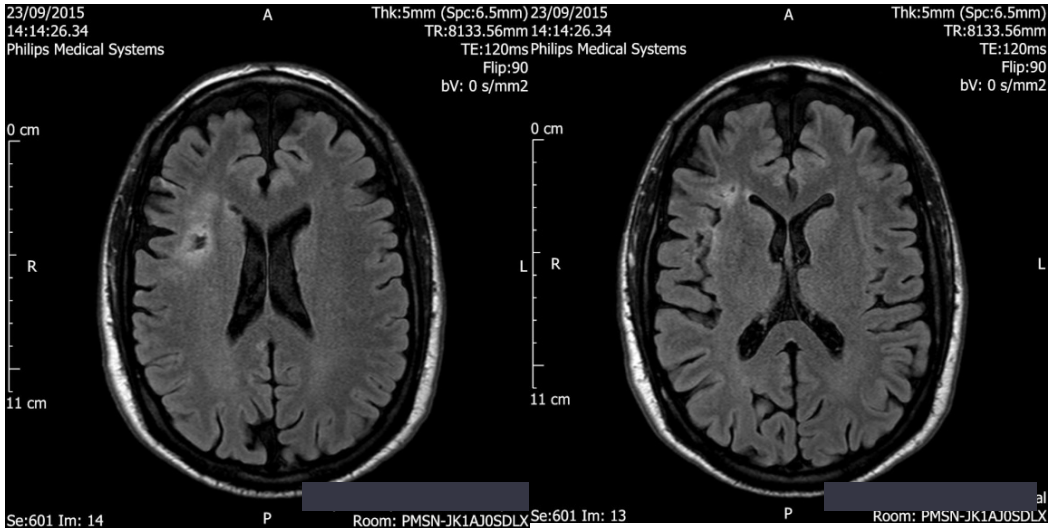
Comparison of the 4 drugs licensed for the use in MCL: data as single agents and in combination with rituximab

Treatment	No. Patients	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	111	68%	21%	17.5	13.9	Not reached
+ rituximab	50	87%	38%	NR	15 month PFS 69%	15 month OS 83%
Bortezomib	155	33%	8%	9.2	6.5	23.5
+ rituximab	19	58%	16%	NR	NR	NR
Lenalidomide	134	28%	8%	16.6	4	19
+ rituximab	44	57%	36%	19	11.1	24.3
Temsirolimus	54[a]	22%	2%	7.1	4.8	12.8
+ rituximab	69	59%	19%	10.6	9.7	29.5

CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival; PFS= progression-free survival; NR=not reported.

Ibrutinib for CNS mantle cell NHL





A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma

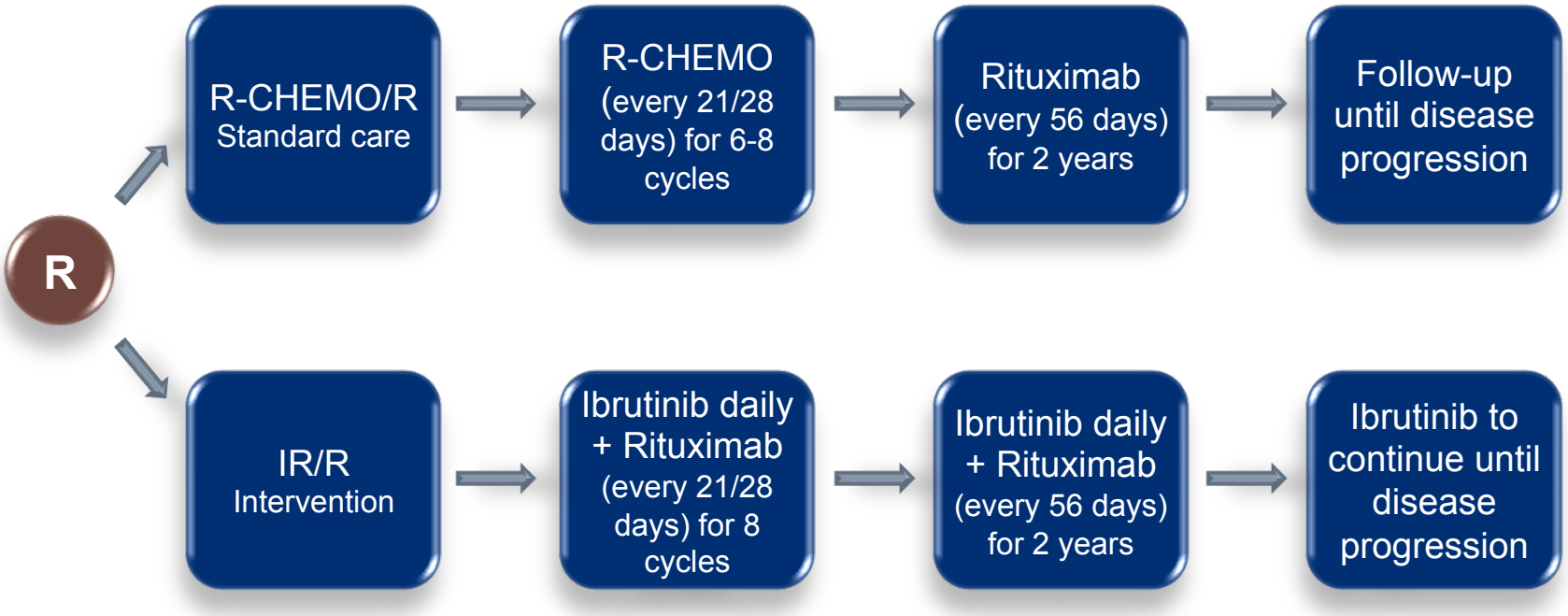
Kami Maddocks,[1] Beth Christian,[1] Samantha Jaglowski,[1] Joseph Flynn,[1] Jeffery A. Jones,[1] Pierluigi Porcu,[1] Lai Wei,[2] Cynthia Jenkins,[3] Gerard Lozanski,[4] John C. Byrd,[1] and Kristie A. Blum[1]

Table 3. Response by NHL subtype

Histology	No. evaluable patients*	CR (%)	PR (%)	OR (%)
MCL	17	13 (76)	3 (18)	16 (94)
DLCL	16	5† (31)	1† (6)	6 (37)
FL	10*	5 (50)	4 (40)	9 (90)
MZL	1	0	1 (100)	1 (100)
Transformed lymphoma	2	1 (50)	0	1 (50)
All patients	46*	24 (52)	9 (20)	33 (72)

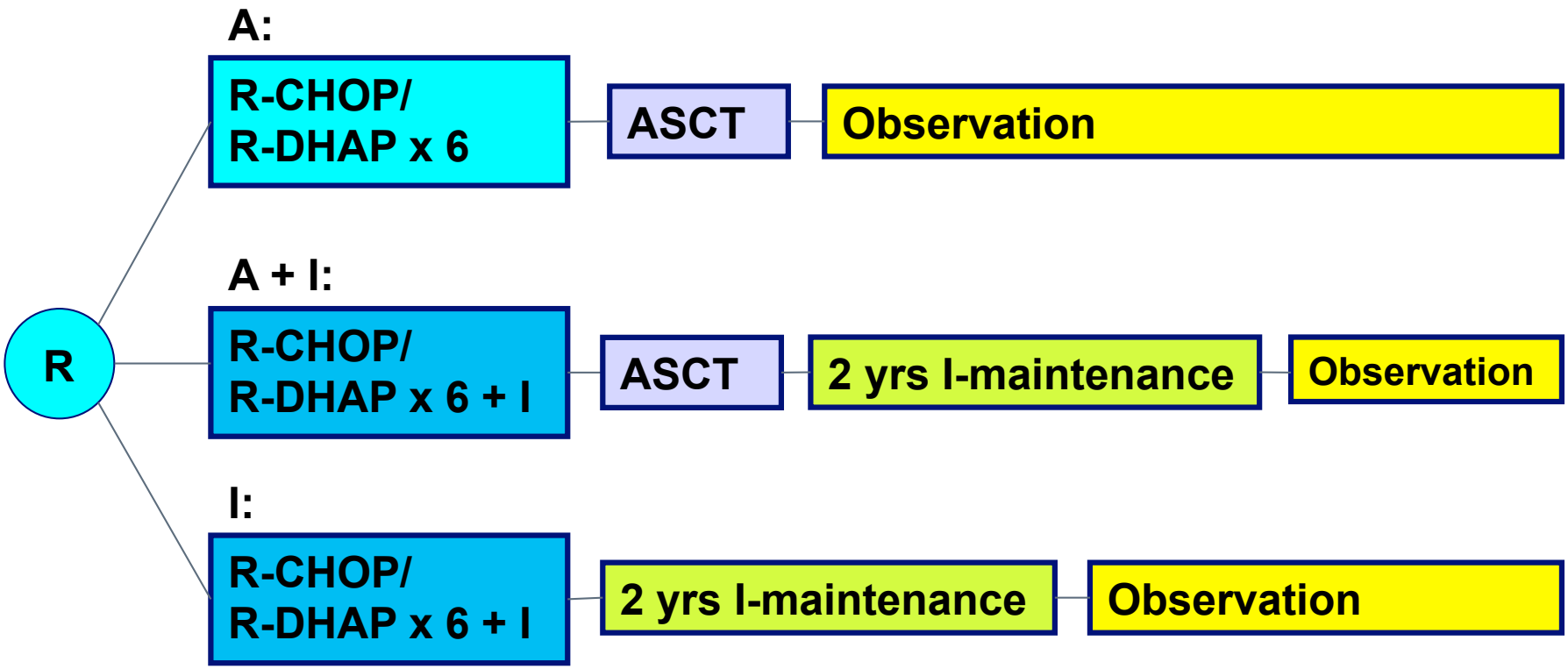
ENRICH – NCRI multicentre Randomised open label phase II/III trial of Rituximab & Ibrutinib *vs* Rituximab & CHemotherapy in Elderly mantle cell lymphoma

CANCER RESEARCH UK



Principal Investigator : S. Rule

Triangle



superiority/non-inferiority: time to treatment failure
HR: 0.60; 65% vs. 77% vs. 49% at 5 years

Courtesy of the European MCL Network

HOW TO TREAT POST IBRUTINIB?

ABSOLUTELY NO IDEA

ABSOLUTELY NO IDEA

But it almost certainly depends on when it is used

Next generation BTKi's

ONO 4059

ACP 196

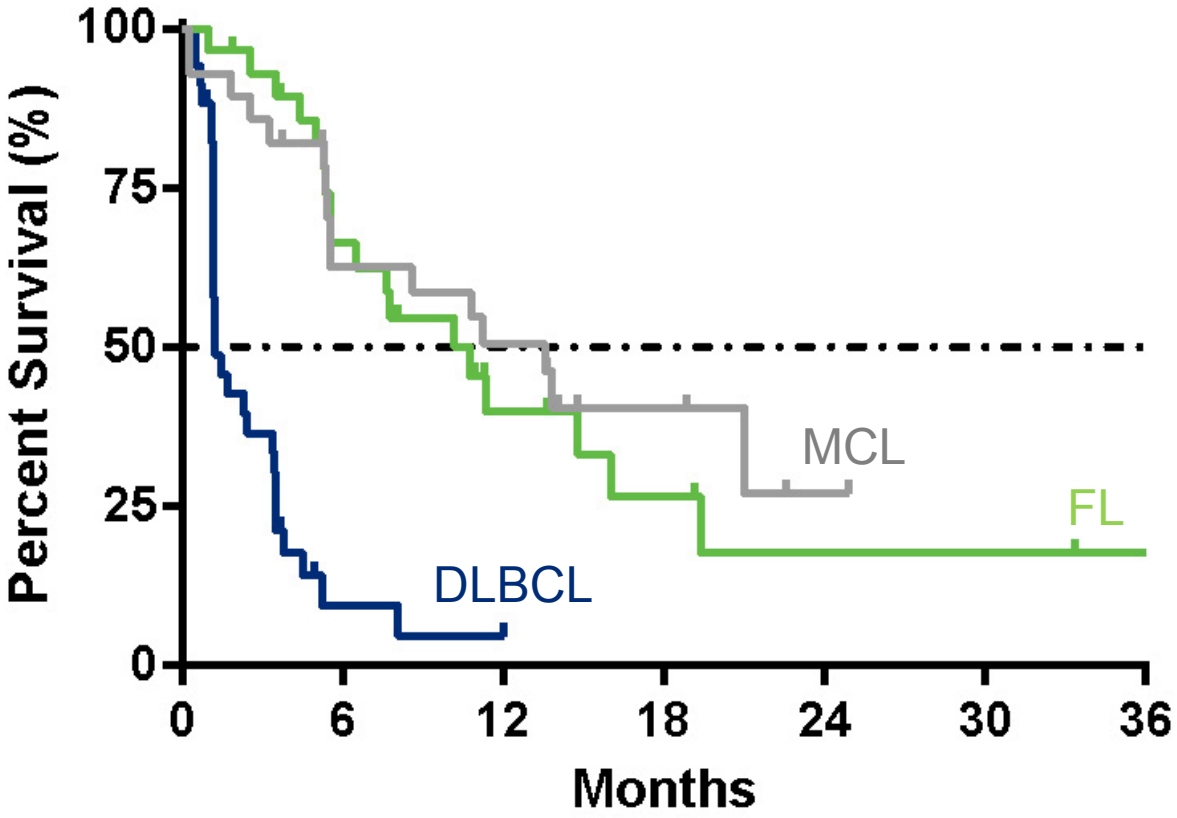
M 7583

A PHASE 1 STUDY OF VENETOCLAX (ABT-199 / GDC-0199) MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

John F. Gerecitano[1], Andrew W. Roberts[2,3], John F. Seymour[4], William G. Wierda[5], Brad S. Kahl[6], John M. Pagel[7], Soham Puvvada[8], Thomas J. Kipps[9], Mary Ann Anderson[2,3], Martin Dunbar[10], Ming Zhu[10], Lori Gressick[10], Lindsay Wagner[10], Su Young Kim[10], Sari Heitner Enschede[10], Rod Humerickhouse[10], Matthew S. Davids[11]

[1]Memorial Sloan-Kettering Cancer Center, USA; [2]Royal Melbourne Hospital, Australia; [3]Walter and Eliza Hall Institute of Medical Research, Australia; [4]Peter MacCallum Cancer Centre, Australia; [5]University of Texas MD Anderson Cancer Center, Houston, TX; [6]Washington University, USA; [7]Swedish Medical Center, USA; [8]University of Arizona, USA; [9]University of California San Diego, USA; [9]University of Texas, USA; [10]AbbVie, USA; [11]Dana-Farber Cancer Institute, USA

Progression-Free Survival by Histology Subtype

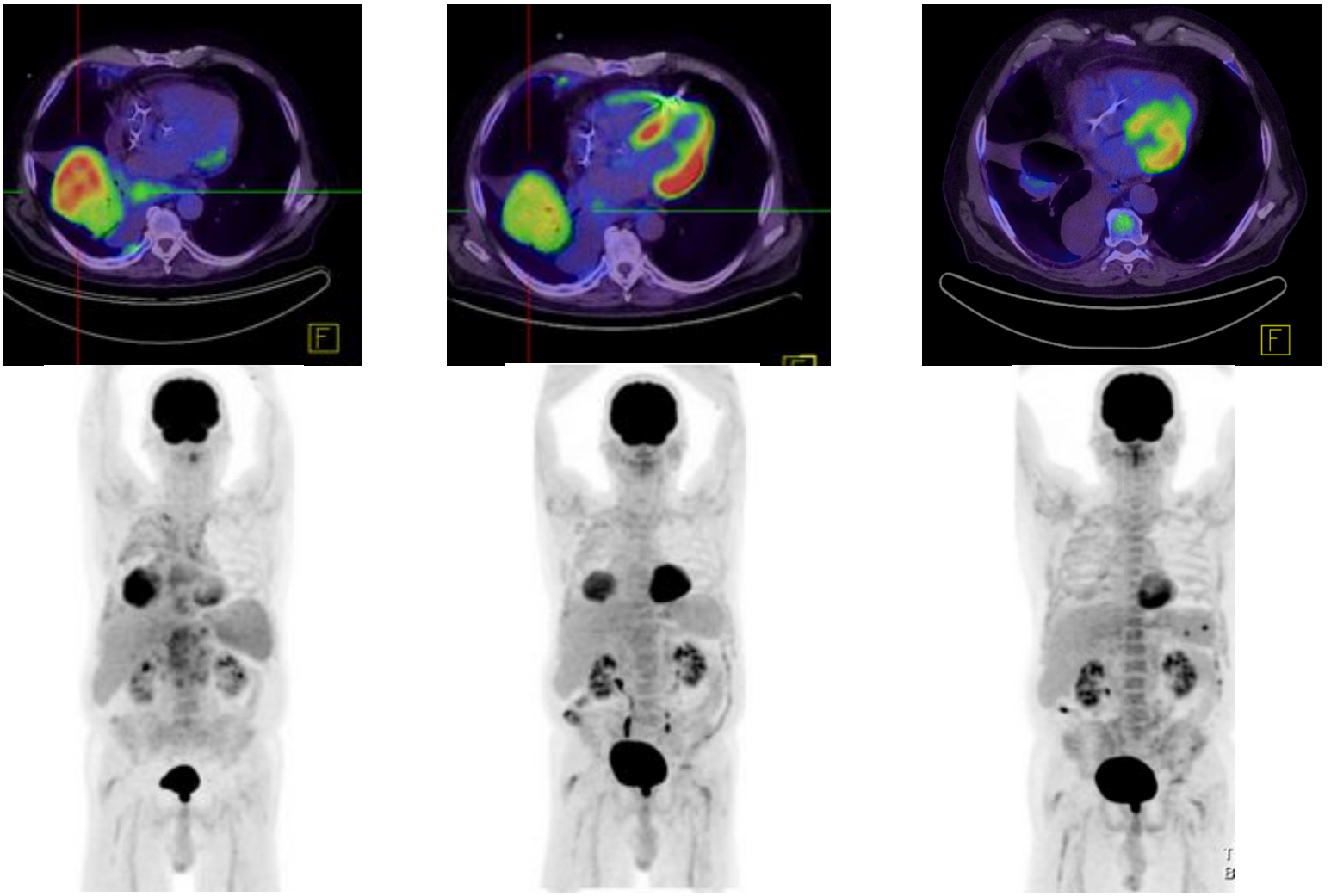


MCL:	28 16 12 4 1
FL:	29 17 7 4 2 1 1
DLBCL:	34 2

	Median PFS, Months (95% CI)
All, n=106	17 (14, 22)
MCL, n=28	14 (ND)
FL, n=29	11 (6, 19)
DLBCL, n=34	1 (1, 3)

As of September 15, 2015

AIM Patient #1: Response Kinetics (PET)



Baseline

1 month (Ibrutinib)

4 months (both drugs)

Summary

- Treat when clinically indicated
- Young patients
  - Cytarabine is the key drug
  - What you add to it is not clear
- Older patients
  - CHOP or Bendamustine based treatment appropriate
- New agents are rapidly moving into the front line
  - Likely to be part of the standard of care soon
- Clinical trials are how we improve outcomes