

Case #3—Emerging Options for a Patient with Follicular Lymphoma



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Disclosures for Mathias J. Rummel, MD, PhD

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Major Stockholder	N/A
Speakers' Bureau	N/A

Follicular Lymphoma International Prognostic Index (FLIPI)

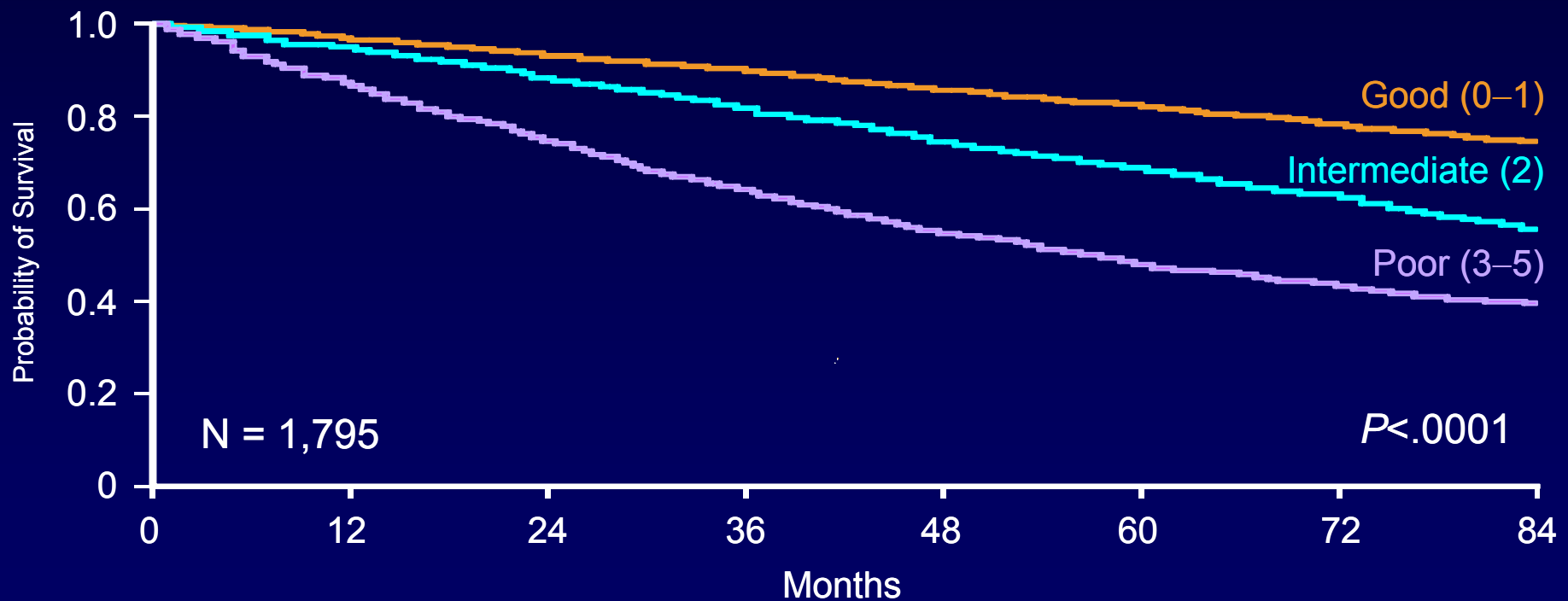
Parameter	Adverse Factor	RR	95% CI
Age	≥60	2.38	2.04-2.78
Stage	III or IV	2.00	1.56-2.58
Hbemoglobin	<12 g/dL	1.55	1.30-1.88
Serum LDH	>Norm	1.50	1.27-1.77
LK-Areale	>4	1.39	1.18-1.64

Cox regression analysis in 1795 patients

Relative Risk of Death According to Risk Group (FLIPI)

Risk Group	Number of Factors	Distr. of Patients	5-Year OS, %	10-Year OS, %	RR
Low	0-1	36	90.6	70.7	1.0
Intermed.	2	37	77.6	50.9	2.3
High	≥3	27	52.5	35.5	4.3

The Follicular Lymphoma International Prognostic Index (FLIPI): Overall Survival



Watch & Wait or Early Treatment?

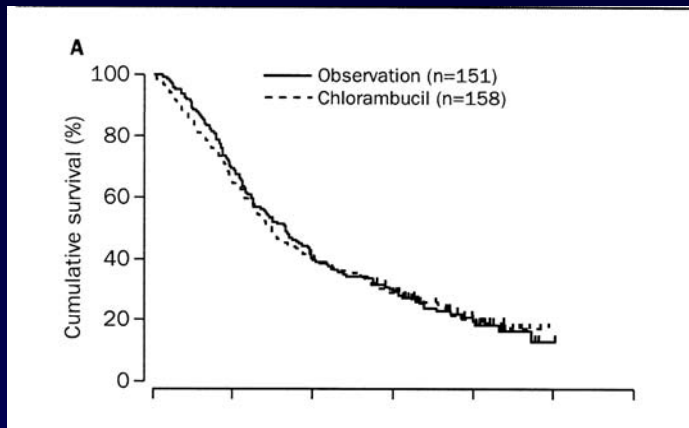
Is there a need for immediate treatment in asymptomatic patients with advanced indolent/follicular lymphomas or can a watch and wait strategy being considered?

Watch & Wait or Early Treatment?

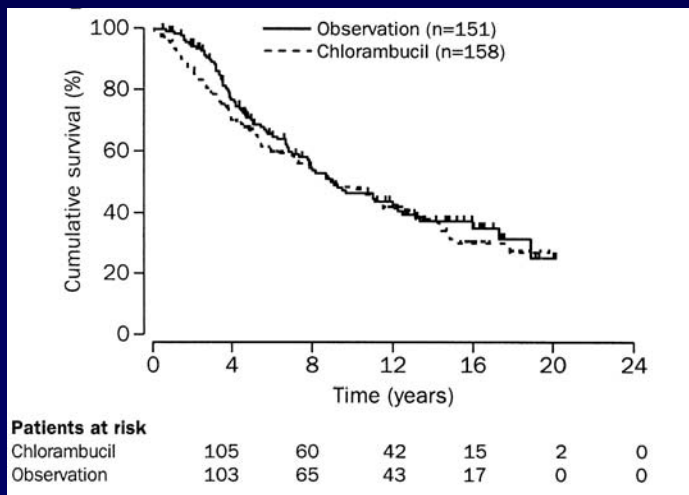
Watchful waiting versus chlorambucil 10 mg daily contin.
prospective randomized, n = 309, recruitment phase 1981-1990

Survival	Watch & Wait	Immediate Treatment
5 years	58%	57%
10 years	34%	35%
15 years	22%	21%
Median	6.7 years	5.9 years

Watch & Wait or Early Treatment?

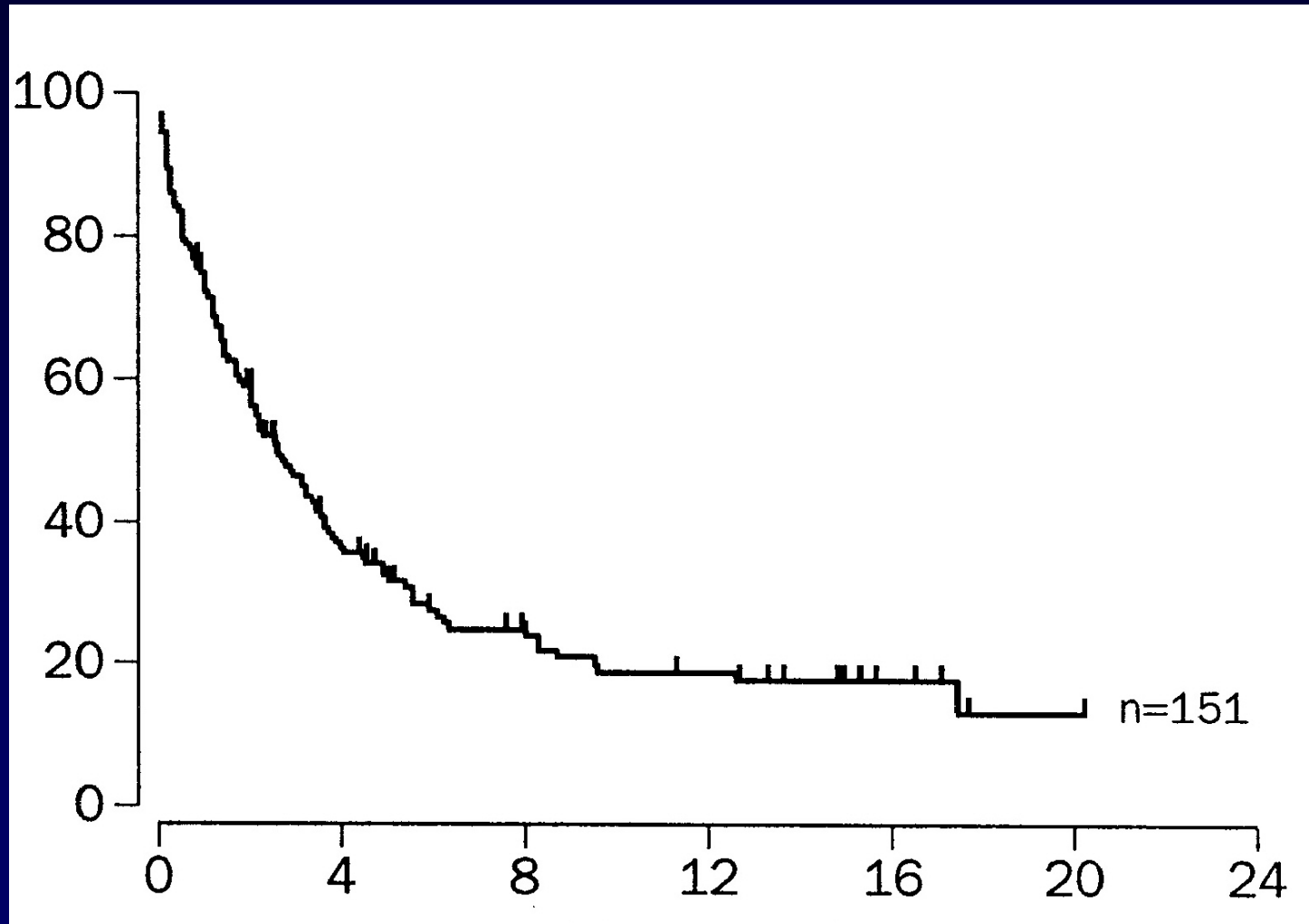


Overall survival



Disease-associated survival

Watch & Wait or Early Treatment?



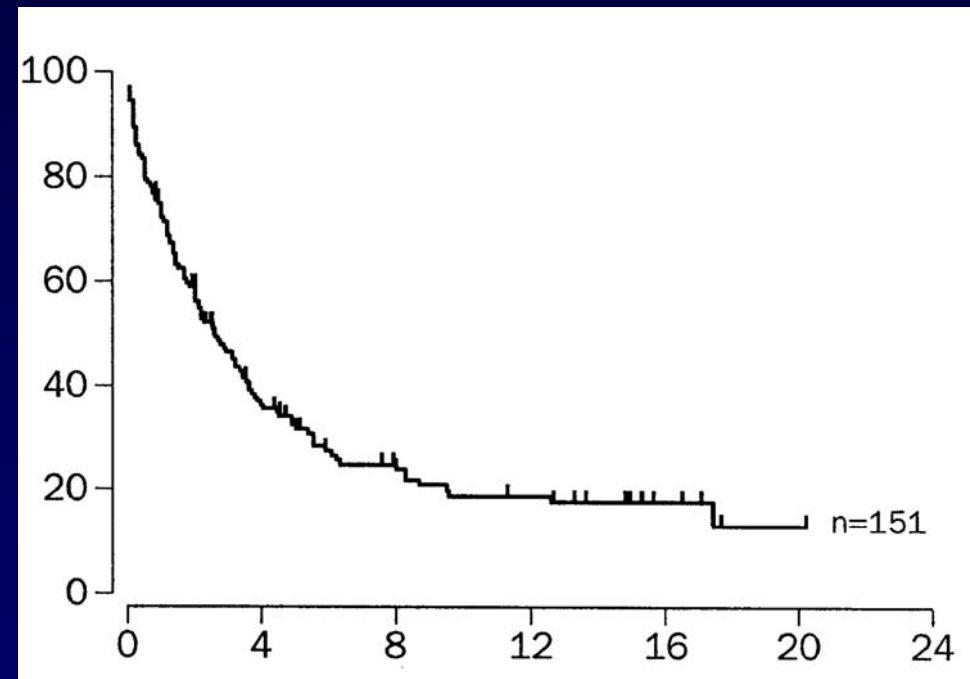
Watch & Wait or Early Treatment?

Watch & wait: Time to first treatment

Median time to first treatment: 2.6 years

Actuarial chance of not needing chemotherapy at 10 years was 19%

and 40% in patients older than 70 years



Treatment in Indolent Lymphomas

- There is still a role of watchful waiting in asymptomatic patients in absent of a curative treatment strategy in these indolent lymphoma entities
- Initial choice of chemotherapy does not affect survival and should, therefore, be at palliative intent
- Toxicity influences the treatment choice, unless no initial treatment differs the outcome

Indications For Treatment In Indolent Lymphomas

- Stages I, II, limited III (up to 5 involved lymph node regions): Curative intention?
- Disease associated symptoms (B-symptoms)
- Hematopoietic insufficiency: Anemia, granulocytopenia, thrombocytopenia
- Rapid tumor progression: Doubling of manifestations within 1 year
- Bulky disease (>6 cm diameter)
- Autoimmune phenomens, such as AIHA or ITP
- Hypogammaglobulinemia with recurrent infections
- Hyperviscosity syndrome by monoclonal paraproteinemia

Clinical Criteria for Starting Therapy in Patients with Follicular Lymphoma

Adapted GELF criteria (FL2000 and PRIMA studies): any one of these criteria

High tumor bulk defined by either:

- a tumor > 7 cm
- 3 nodes in 3 distinct areas each > 3 cm
- symptomatic splenic enlargement
- organ compression
- ascites or pleural effusion

Presence of systemic symptoms

ECOG performance status >1 *

Serum LDH or β 2-microglobulin above normal values

BNLI criteria:⁷³ any one of these criteria

Rapid generalized disease progression in the preceding 3 months

Life threatening organ involvement

Renal or macroscopic liver infiltration

Bone lesions

Presence of systemic symptoms or pruritus

Hemoglobin < 10 g/dL or WBC < $3.0 \times 10^9/L$ or platelet counts < $100 \times 10^9/L$; related to marrow involvement

Standard of Care in Patients with Indolent Lymphomas

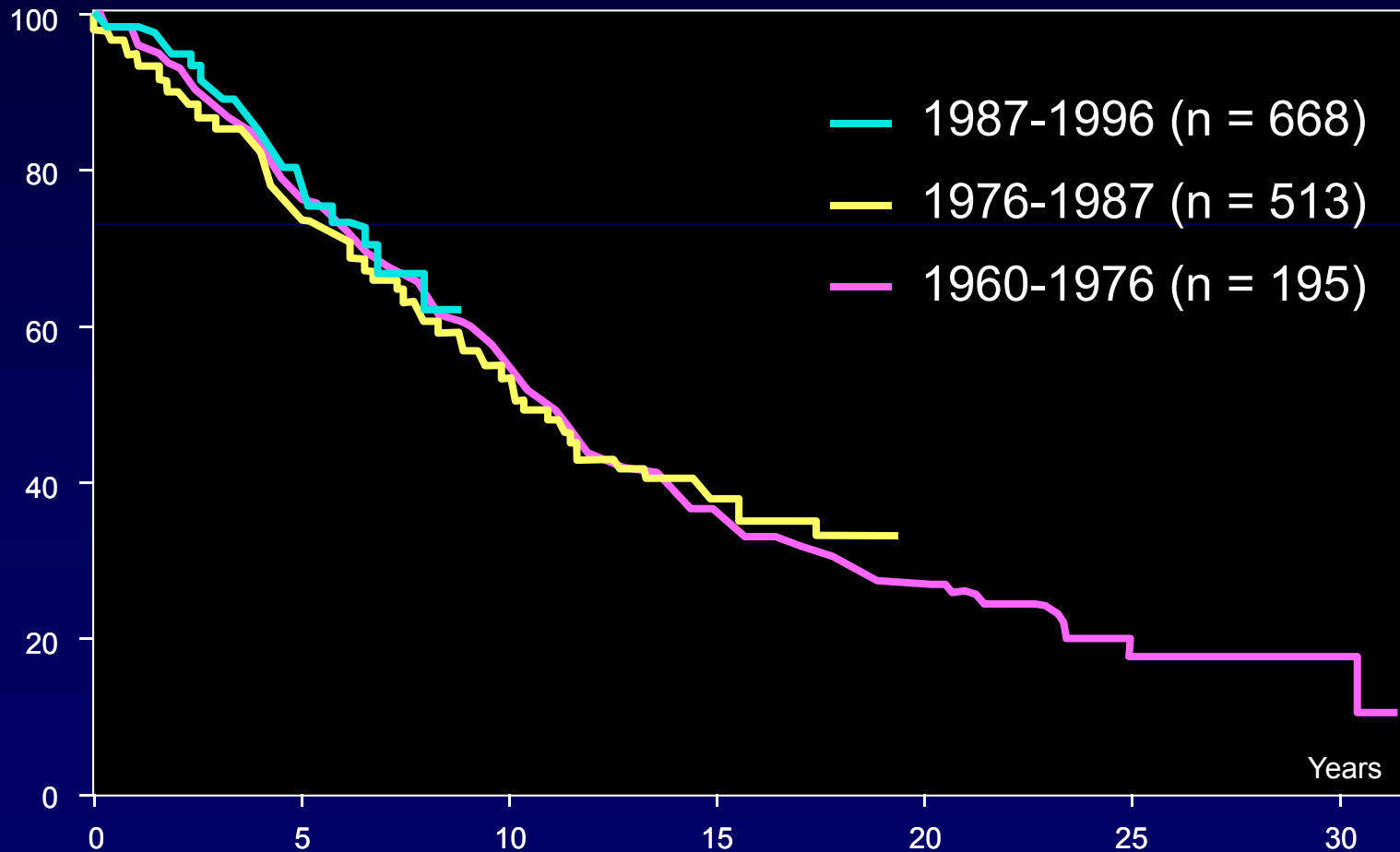
- **Combined immunochemotherapy is the standard of care**
- **R-chemotherapy plus R-maintenance appears as the optimal strategy for patients with relapsed disease**
- **Which chemotherapy in combination with rituximab?**
 - **Chlorambucil-based (MCP), F-based (FCM), CHOP-like, CVP**
 - **Role of bendamustine has been recently investigated (ASH 2009)**
- **R-maintenance after first-line R-containing regimens?**
 - **PRIMA study addresses this question**
 - **StiL NHL 7-2008 study proves duration of maintenance**
 - **SAKK study proves duration of maintenance after R**

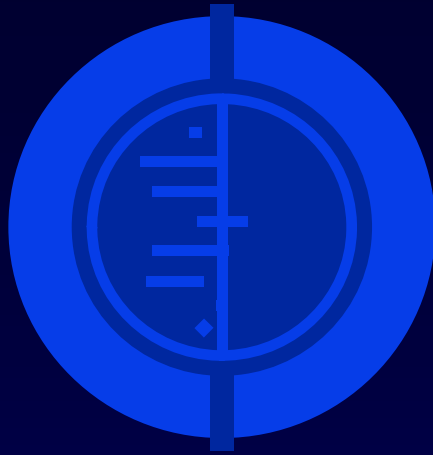
Indolent NHL—Chemotherapy in Stages III and IV

Therapy	Pat.- No	Response Rate (CR and PR)	5-Year DFS	5-Year OS	References
Cb	33	33	0	60	Portlock et al. 1987
CP	48	64	22	62	Ezdinli et al. 1985
CP	132	36	n.a.	49	Kimby et al. 1984
Mitox	21	100	50	85	Nissen et al. 1990
COP	35	91	n.a.	n.a.	Bagley et al. 1972
COP	84	57	18	60	Steward et al. 1988
COP	99	85	n.a.	n.a.	Hiddemann et al. 1994
COP	248	80	n.a.	n.a.	Hagenbeck et al. 1993
PmM	93	86	n.a.	n.a.	Hiddemann et al. 1994
COP-Bleo	77	71	29	50	Jones et al. 1983
CHOP	415	64 (nur CR)	n.a.	35	Dana et al. 1993
CHOP	127	60	n.a.	54	Kimby et al. 1994
CHOP-Bleo	75	72	38	57	Jones et al. 1983
CHOP-Bleo	22	81	62 (est.)	81	Peterson et al. 1990
CHOP-Bleo	96	77	28	65	Romaguera et al. 1991
CHOP-Bleo + CMED	108	72 (nur CR)	60	62	Velasquez et al. 1994
M-BACOD	18	56	22	46	Anderson et al. 1984 and Licht et al. 1990
m-BACOD	86	69 (nur CR)	31	62	Canellos et al. 1987
MACOP-B	125	84 (nur CR)	25	70	Klimo et al. 1987
CAP-BOP	59	49 (nur CR)	16	40	Anderson et al. 1993

Indolent Lymphomas

Overall Survival





Does combined immuno- chemotherapy with rituximab improve overall survival in patients with indolent non- hodgkin's lymphoma compared to chemotherapy alone?

A Meta-Analysis

Holger Schulz, Nicole Skoetz, Julia F. Bohlius,
Sven Trelle, Alexander Greb, Thilo Kober
and Andreas Engert

Cochrane Review

Cochrane Haematological Malignancies Group (CHMG)
Internal Medicine I, University of Cologne. www.CHMG.de

Schulz H, et al. *J Natl Cancer Inst.* 2007;99(9):706-714.

Combined Immunochemotherapy with Rituximab Improves Overall Survival in Patients with Follicular and Mantle Cell Lymphoma: Updated Meta-Analysis

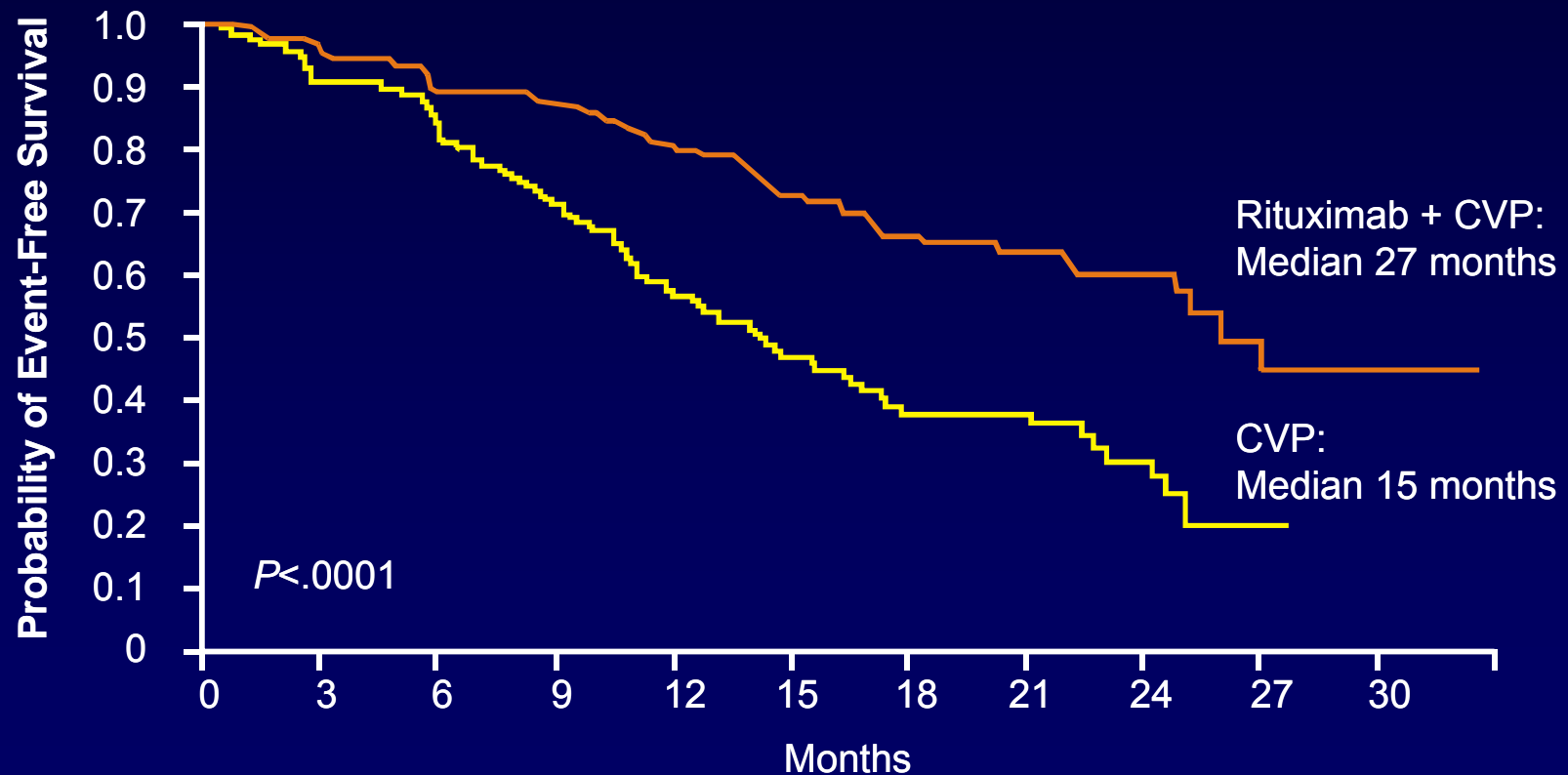
Holger Schulz, Andreas Engert et al. Cochrane Hematological Malignancies Group (CHMG)

- Six randomized, controlled trials comparing rituximab plus chemotherapy with chemotherapy alone in indolent and mantle cell lymphoma were identified
 - R-CHOP vs CHOP (x2)
 - R-CVP vs CVP
 - R-FCM vs FCM
 - R-MCP vs MCP
 - R-CNOP vs CNOP
- Survival meta-analysis performed on untreated patients (7 trials; n = 1943, 5 published, 2 abstract form)

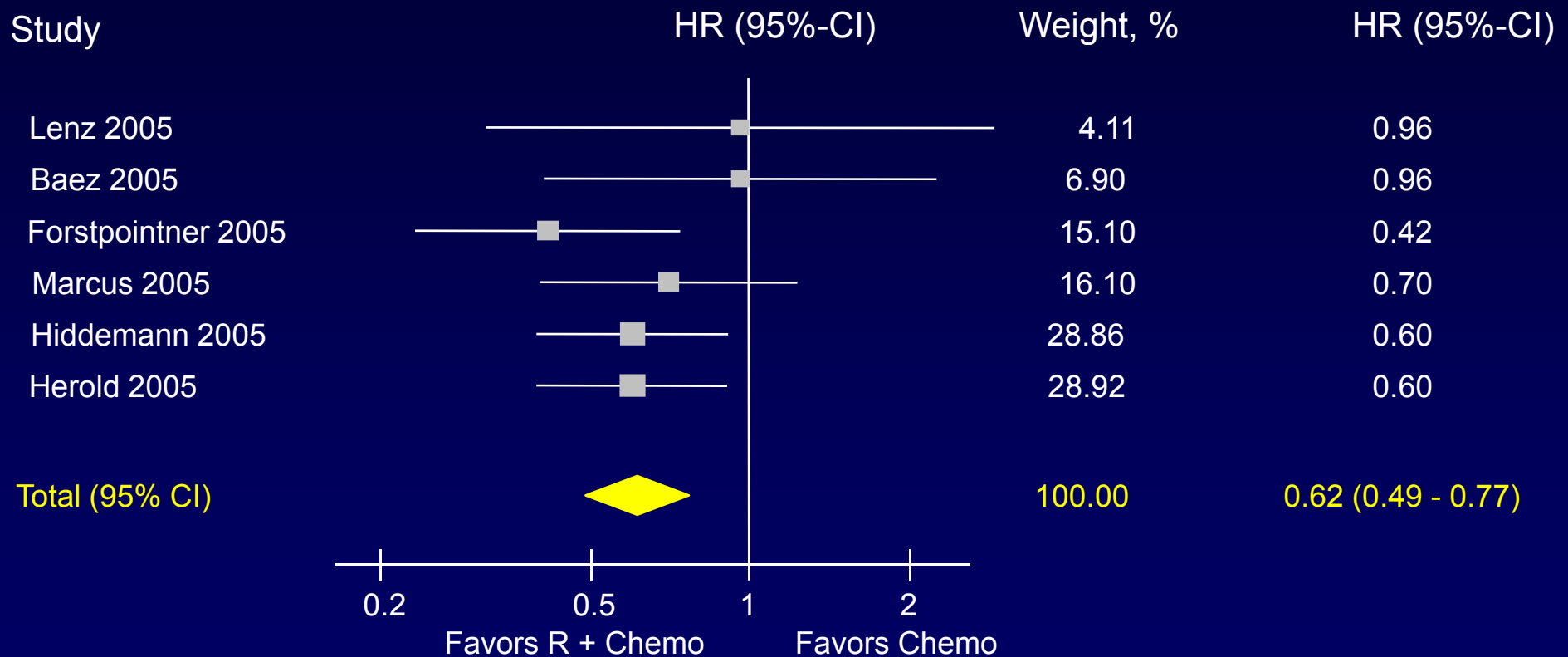
Rituximab plus Chemotherapy Combinations in First-Line Therapy of Follicular Lymphoma

Hiddemann et al	CHOP (n = 205)	R-CHOP (n = 223)	
Response rate	90%	96%	= .011
TTTF	31 months	Not reached	< .0001
OS at 4 yrs	77%	83%	= .029
Marcus et al	CVP (n = 159)	R-CVP (n = 162)	
Response rate	57%	81%	< .0001
TTTF	7 months	27 months	< .0001
OS at 4 yrs	81%	90%	= .039
Herold et al	MCP (n = 96)	R-MCP (n = 105)	
Response rate	75%	92%	< .001
EFS	19 months	Not reached	< .0001
OS at 4 yrs	74%	87%	= .009
Hochster et al	CVP (n = 130)	CVP + R (n = 117)	
EFS	17 months	50 months	= .0003
OS at 4 yrs	75%	91%	= .03

CVP vs CVP + Rituximab as First-Line Therapy in Indolent Lymphomas (EFS)



Overall Survival: Meta-Analysis Total Group



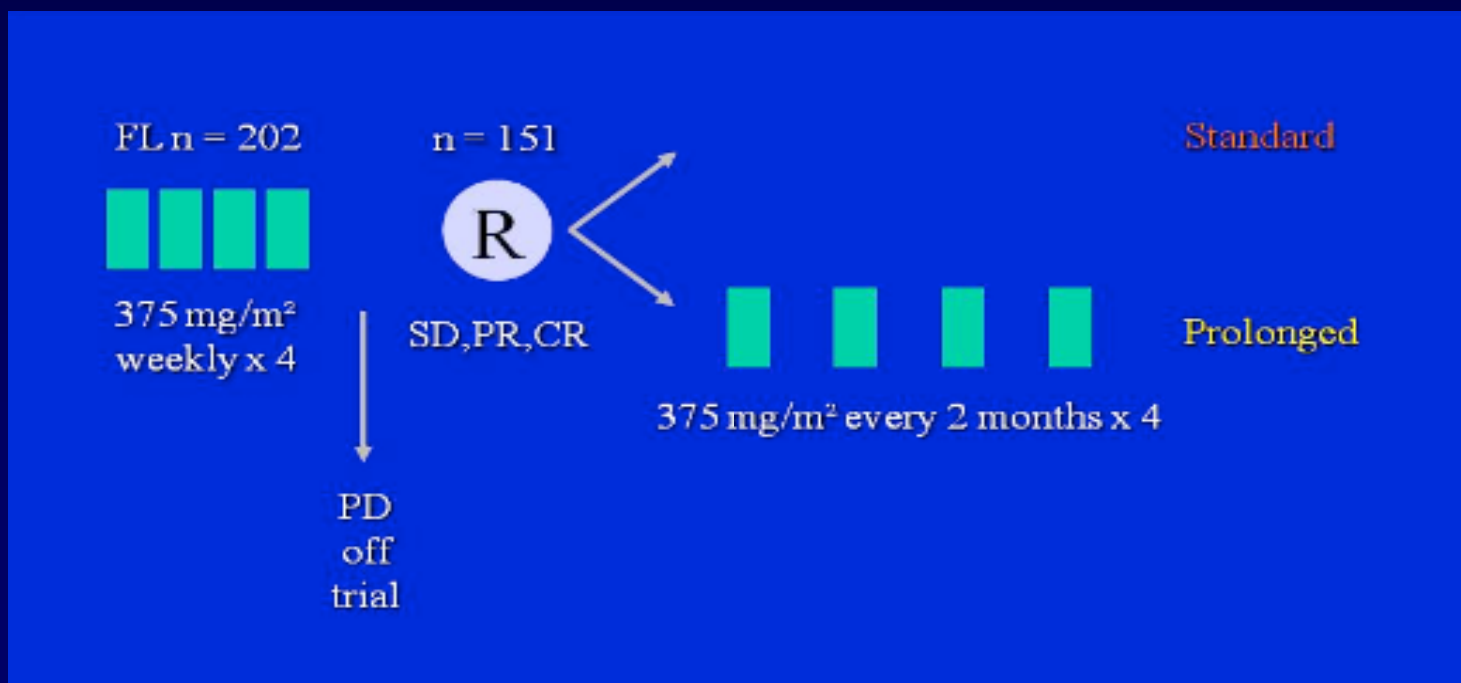
Total events: 100/760 143/718

Test for heterogeneity: ($P = .60$), $I^2 = 0\%$

Schulz H, et al. *J Natl Cancer Inst.* 2007;99(9):706-714.

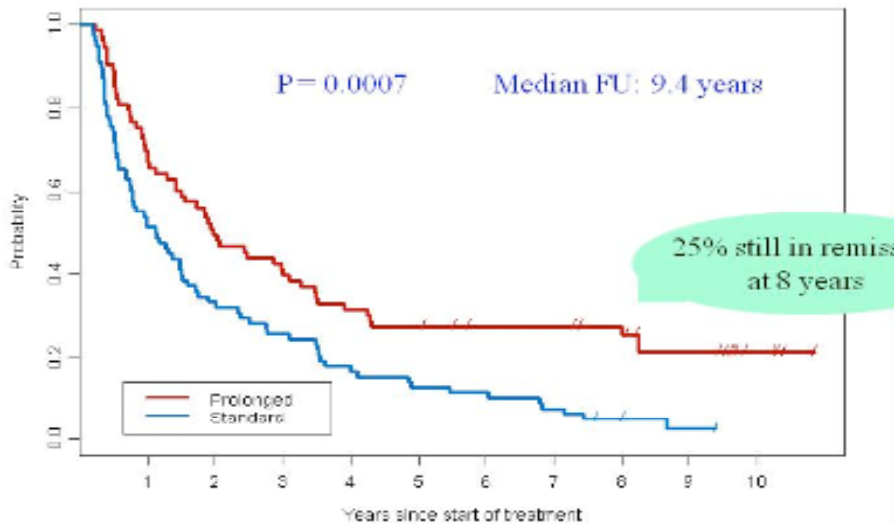
Prolonging Remission with Rituximab Maintenance Therapy

SAKK 35/98 Trial

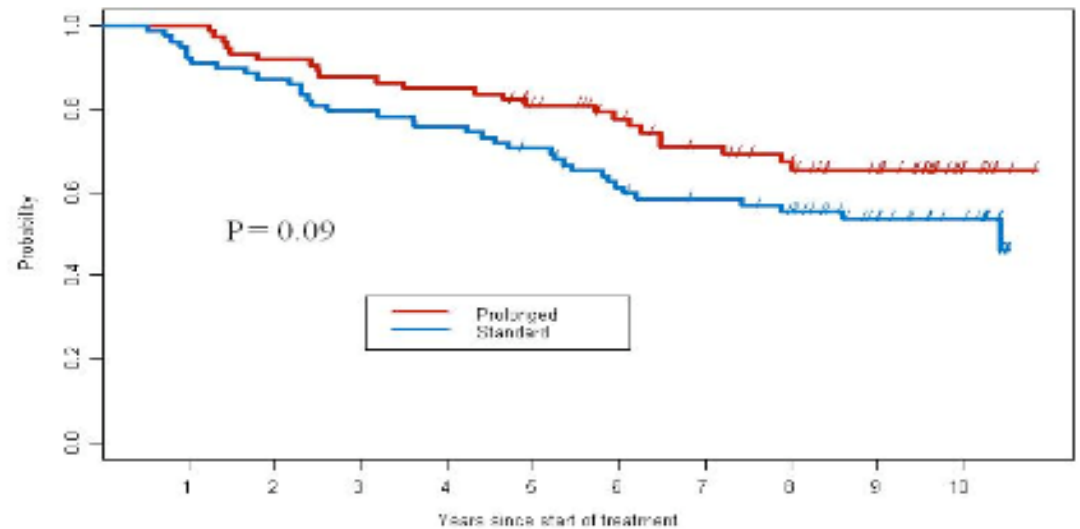


SAKK 35/98: Long-Term Follow-Up Standard vs Prolonged Rituximab

Event-free survival in randomized follicular lymphoma patients



Overall survival in randomized follicular lymphoma patients

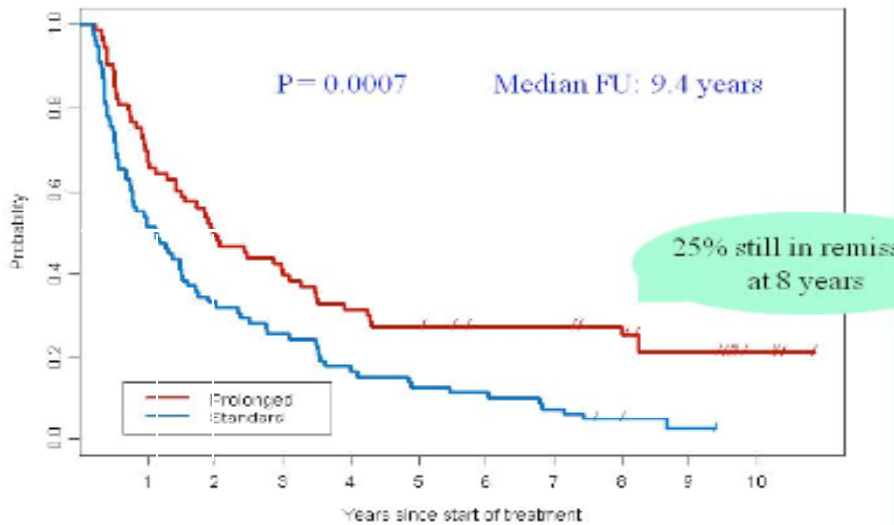


Ghielmini M, et al. *Blood*. 2004;103(12):4416-4423.

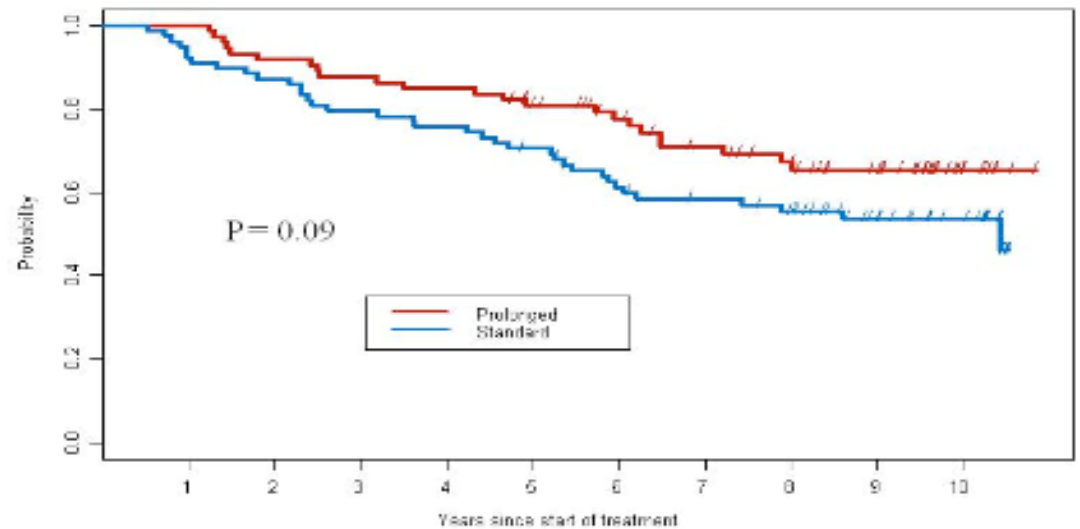
Ghielmini M, et al. *J Clin Oncol*. 2009;27(15S): Abstract 8512.

SAKK 35/98: Long-Term Follow-Up Standard vs Prolonged Rituximab

Event-free survival in randomized follicular lymphoma patients



Overall survival in randomized follicular lymphoma patients

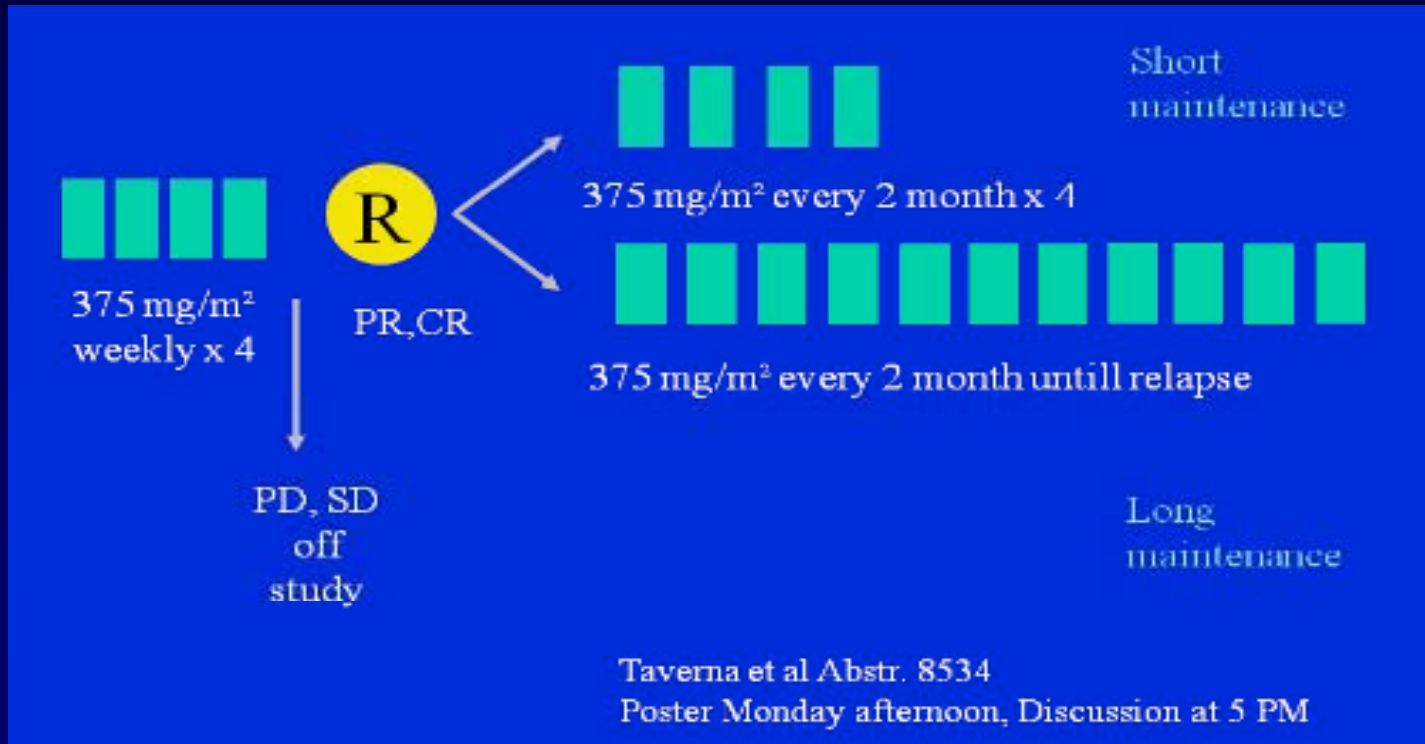


Ghielmini M, et al. *Blood*. 2004;103(12):4416-4423.

Ghielmini M, et al. *J Clin Oncol*. 2009;27(15S): Abstract 8512.

SAKK 35/03 Study

Follicular Lymphoma Untreated or in Relapse



Standard of Care in Patients with Indolent Lymphomas

- There is still a role for watch & wait in asymptomatic patients
- Combined immunochemotherapy is the standard of care
- R-chemotherapy plus R-maintenance appears as the optimal strategy for patients with relapsed disease
- **Which chemotherapy in combination with rituximab?**
 - Chlorambucil-based (MCP), F-based (FCM), CHOP-like, CVP
 - Role of bendamustine has been recently investigated (ASH 2009)
- R-maintenance after first-line R-containing regimens?
 - PRIMA study addresses this question
 - StiL NHL 7-2008 study proves duration of maintenance
 - SAKK study proves duration of maintenance after R

Challenging the Standard in Indolent Lymphoma

- Combined immunochemotherapy is the standard of care
- Which chemotherapy in combination with rituximab?
→ CHOP, CVP, F or FCM, MCP, R alone, or ... ?

Doctor's choice in the FIT trial
(induction before ibritumomab tiuxetan cons.)

First-Line Regimen	%
- Chlorambucil	10
- CVP / COP	27
- CHOP or CHOP-like	43
- Fludarabine-combination	5



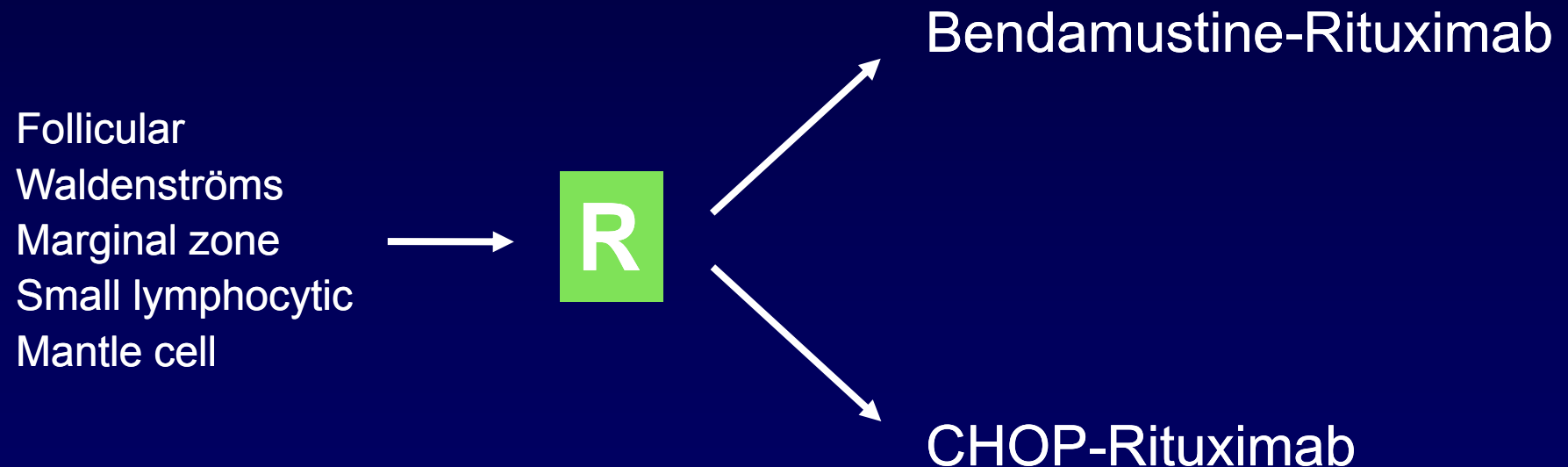
LymphoCare Study

(Friedberg JW, et al. *J Clin Oncol.* 2009;27(8):1202-1208.)

	%
CVP-R	23
CHOP-R	55
Fludarabine-R	15

Bendamustine-Rituximab (B-R) vs CHOP-R

StiL NHL 1-2003



Bendamustine 90 mg/m² day 1+2 + R day 1, max 6 cycles, q 4 weeks. CHOP-R, max 6 cycles, q 3 weeks.

Defined Indications for Treatment

- B-symptoms
- Hematopoietic failure
(Hb <11 g/dL, granulocytes < 1,500 / μ L, thrombocytes < 100,000 / μ L)
- Large tumor burden
(3 areas >5 cm or 1 area >7.5 cm)
- Rapid progression
(increase of tumor mass >50% within 6 months)
- Complications due to disease
(pain, infarction of spleen, hyperviscosity syndrome, etc)

Entities

549 patients randomized; 513 patients evaluable for response and toxicity

		B-R	CHOP-R	Age, median
Total	n	260	253	64
Follicular	54 %	139	140	60
Mantle cell	18 %	45	48	70
Marginal zone	13 %	37	30	66
Waldenströms	8 %	22	19	64
SLL	4 %	10	11	68
Unclassifiable	2 %	7	5	69

Patient Characteristics

	B-R (n = 260)	CHOP-R (n = 253)
Age (median)	64 yrs	63 yrs
>70 years	23 %	23 %
Stage IV	77 %	77 %
Bone marrow	68 %	67 %
B-Symptoms	38 %	29 %
LDH > 240 U/L	38 %	34 %
Bulky disease	27 %	29 %
IPI > 2	37 %	34 %
FLIPI 0-1	12 %	19 %
FLIPI 2	42 %	33 %
FLIPI ≥ 3	46 %	48 %

} n = 279

B-R vs CHOP-R: Hematotoxicity Grades 3+4

	B-R (n = 1450) % of Cycles	CHOP-R (n = 1408) % of Cycles	P Value
Leukocytopenia	12.1	38.2	<.0001
Neutropenia	10.7	46.5	<.0001
G-CSF administered	4.0	20.0	<.0001
Thrombocytopenia	0.7	1.2	
Anemia	1.4	1.9	

B-R vs CHOP-R: Toxicities (all CTC-grades)

	B-R (n = 260) No. of Patients	CHOP-R (n = 253) No. of Patients	P Value
Alopecia	-	+++	<.0001
Paresthesias	18	73	<.0001
Stomatitis	16	47	<.0001
Skin (erythema)	42	23	=.0122
Allergic reaction (skin)	40	15	=.0003
Infectious complications	96	127	=.0025
- Sepsis	1	8	=.0190

Results: Response rates

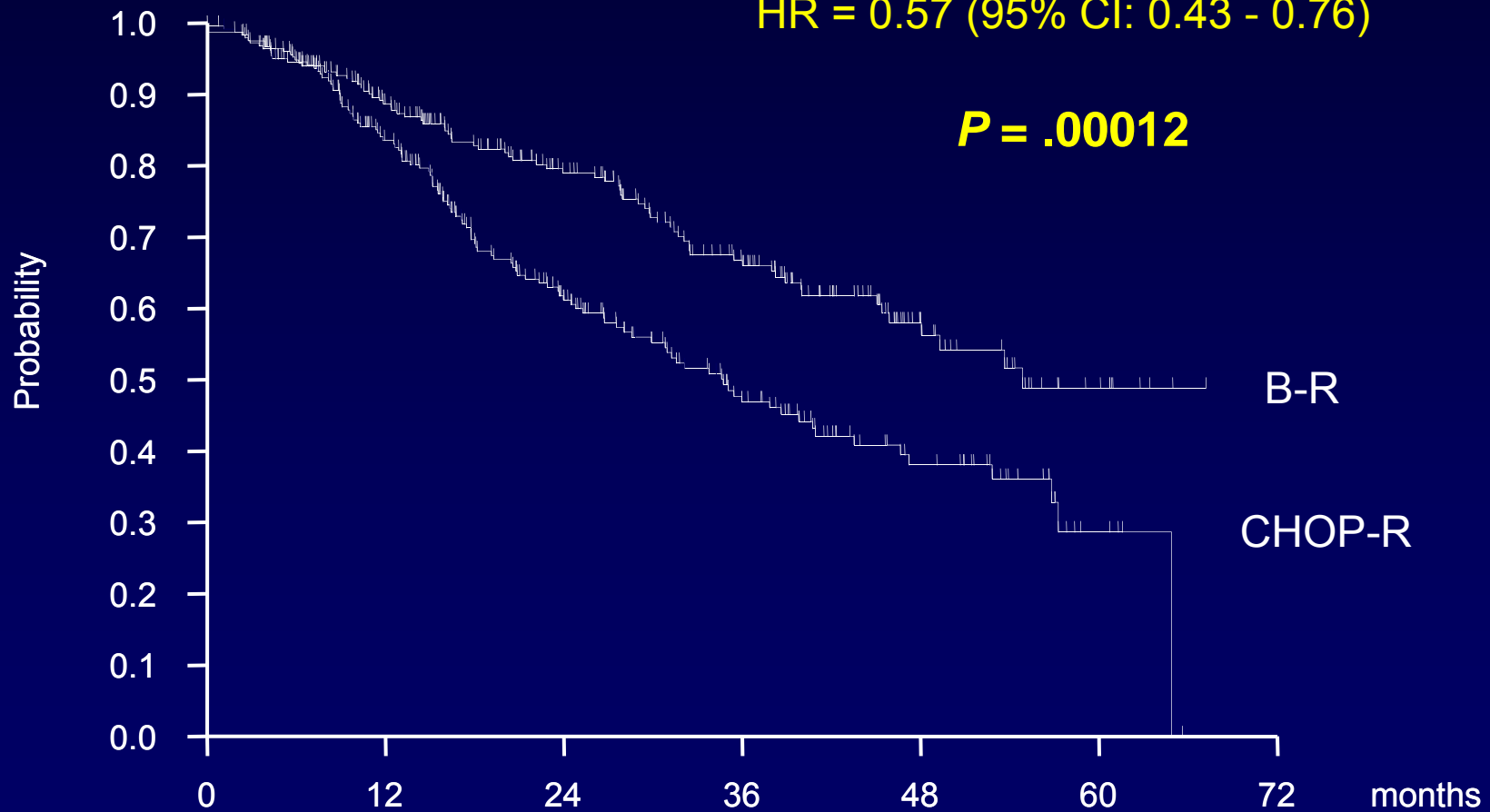
	B-R (n=260)	CHOP-R (n=253)	<i>P</i> value
ORR	92,7 %	91,3 %	
CR	39,6 %	30,0 %	= 0.0262
SD	2,7 %	3,6 %	
PD	3,5 %	2,8 %	

Progression-Free Survival

B-R: 54.9 months vs CHOP-R: 34.8 months (median)

HR = 0.57 (95% CI: 0.43 - 0.76)

$P = .00012$

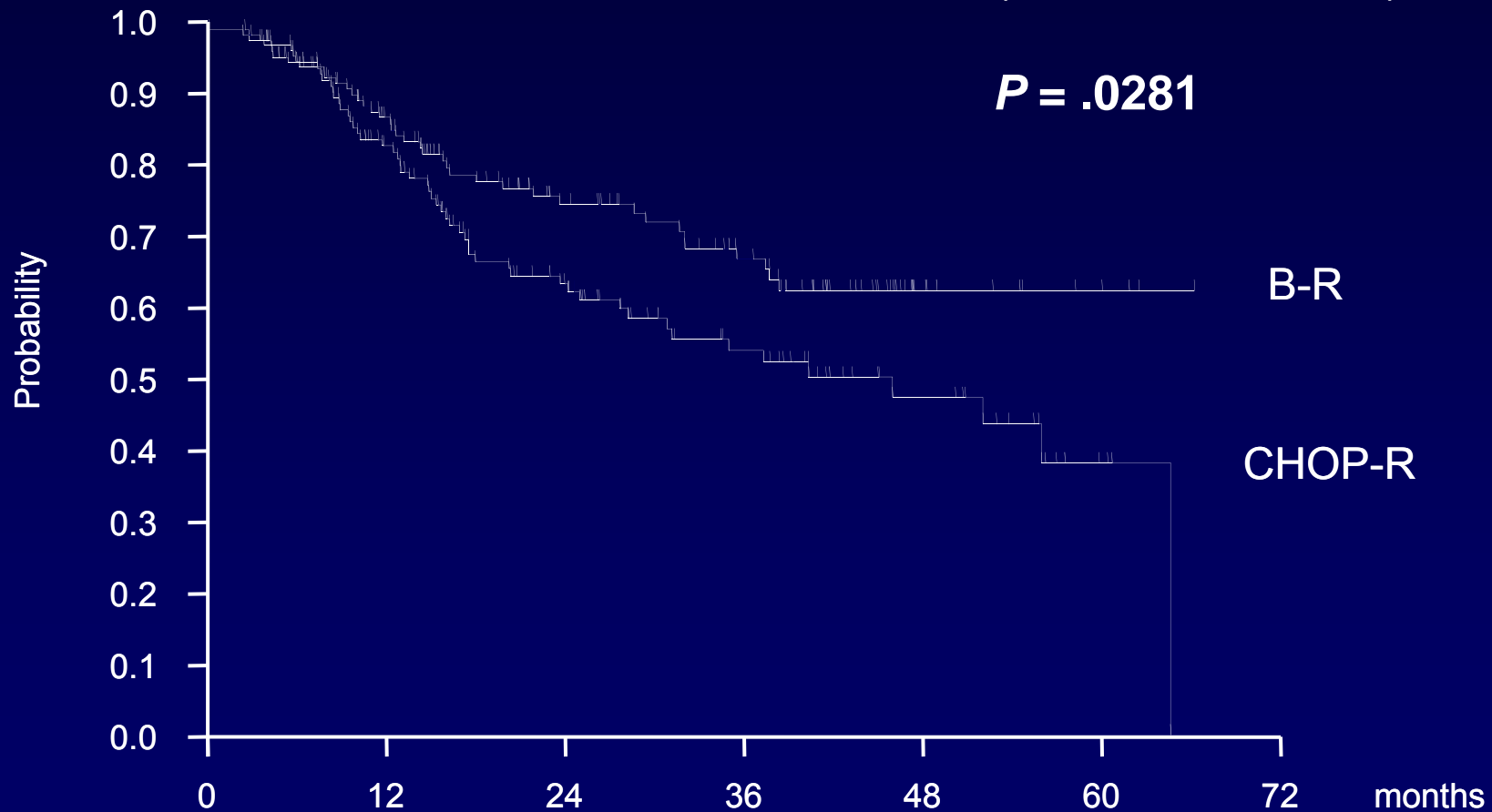


Median observation period 34 months

Progression-Free Survival—Follicular Lymphoma

B-R: not reached vs CHOP-R: 46,7 months (median)

HR = 0.63 (95% CI: 0.42 - 0.95)

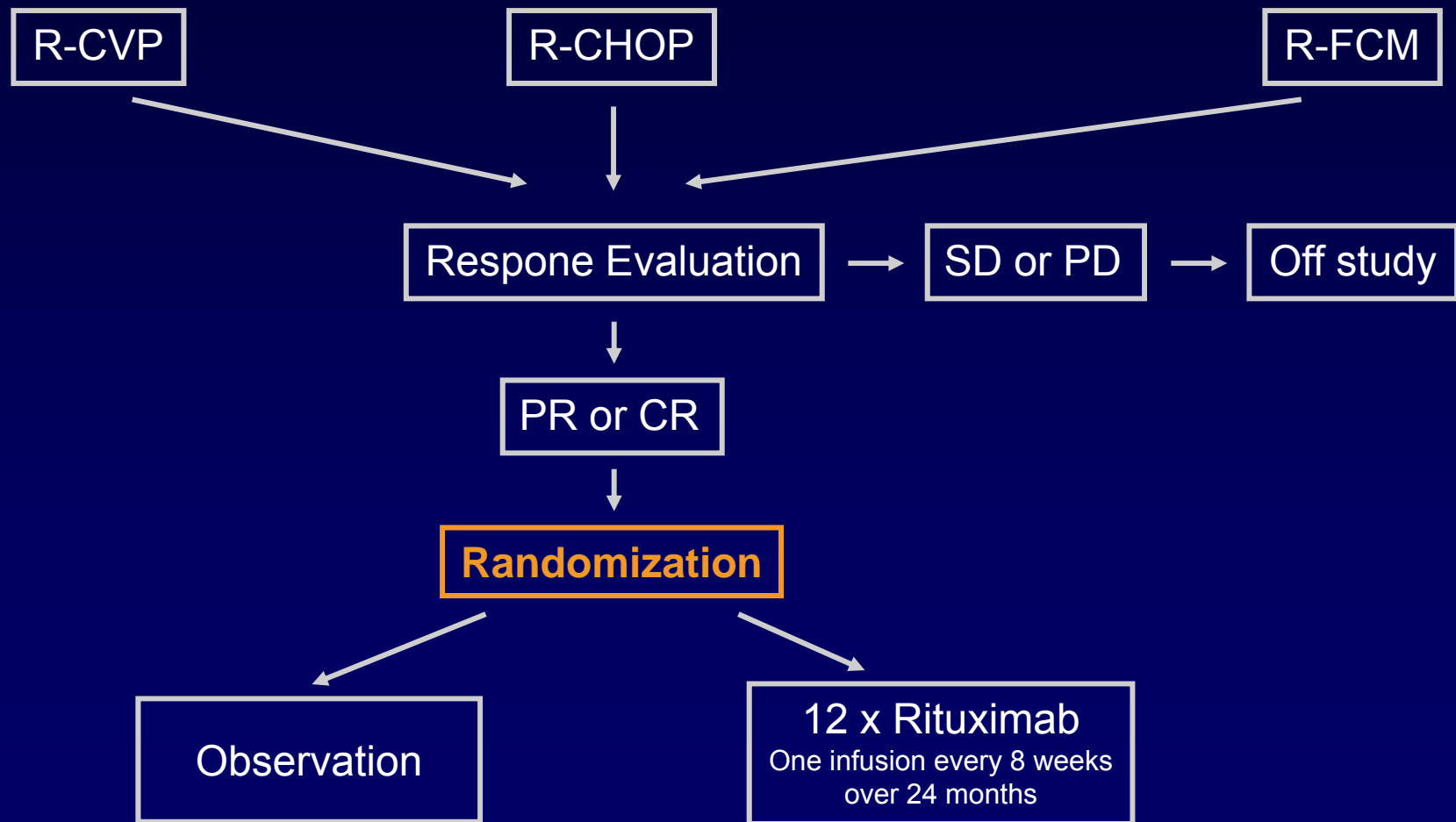


Bendamustine-R vs CHOP-R

Summary

- Randomized trial included 513 evaluable patients
- B-R significantly improved PFS and CR rates compared to CHOP-R in patients with FL, MCL and Waldenström`s macroglobulinemia
- B-R shows a better tolerability profile compared to CHOP-R with
 - No alopecia
 - Less hematotoxicity, G-CSF used, infections, and neuropathy

PRIMA Trial for Follicular Lymphoma (Primarily Rituximab and Maintenance)

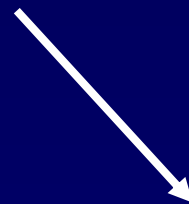
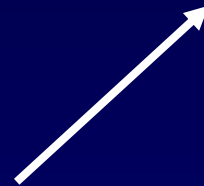


Bendamustine-Rituximab + 2 vs 4 Years Rituximab

StiL NHL 7-2008 - MAINTAIN

Randomized Phase III Study

Follicular Lymphoma

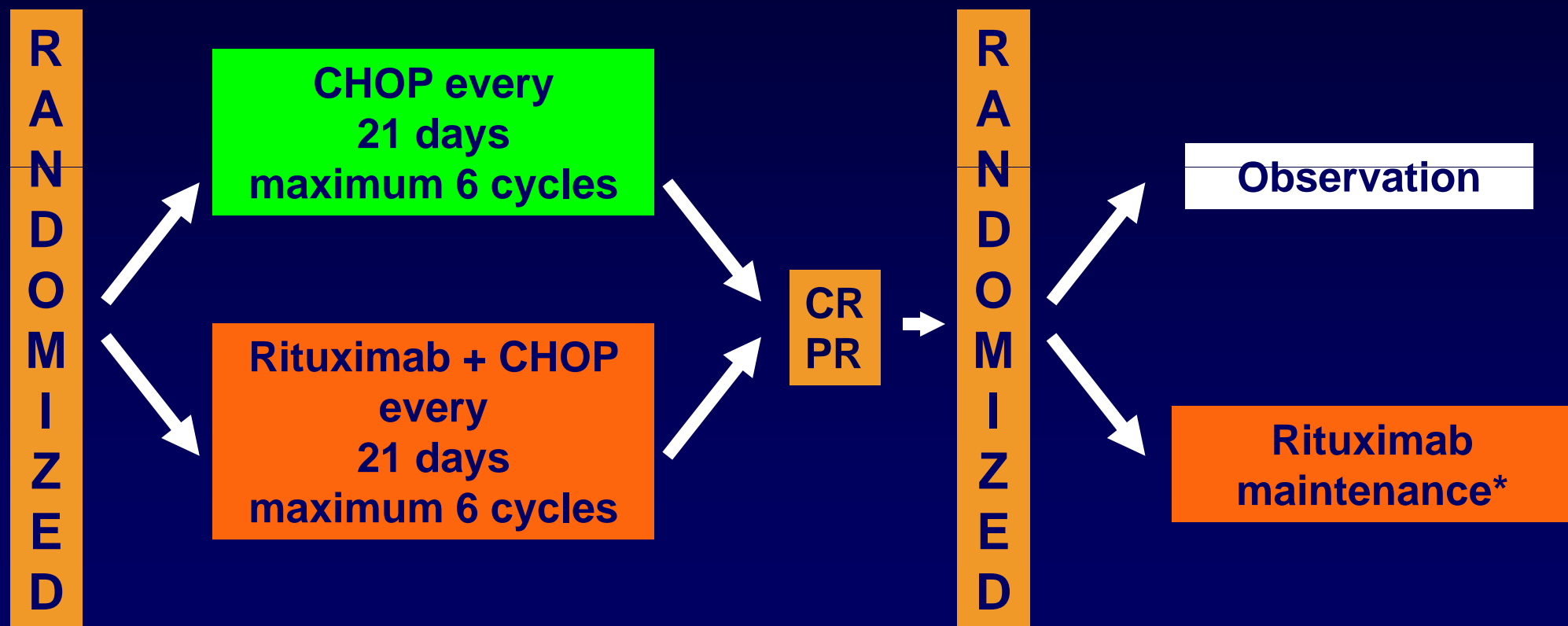


Bendamustine-Rituximab
+ 2 years Rituximab
q 2 months

Bendamustine-Rituximab
+ 4 years Rituximab
q 2 months



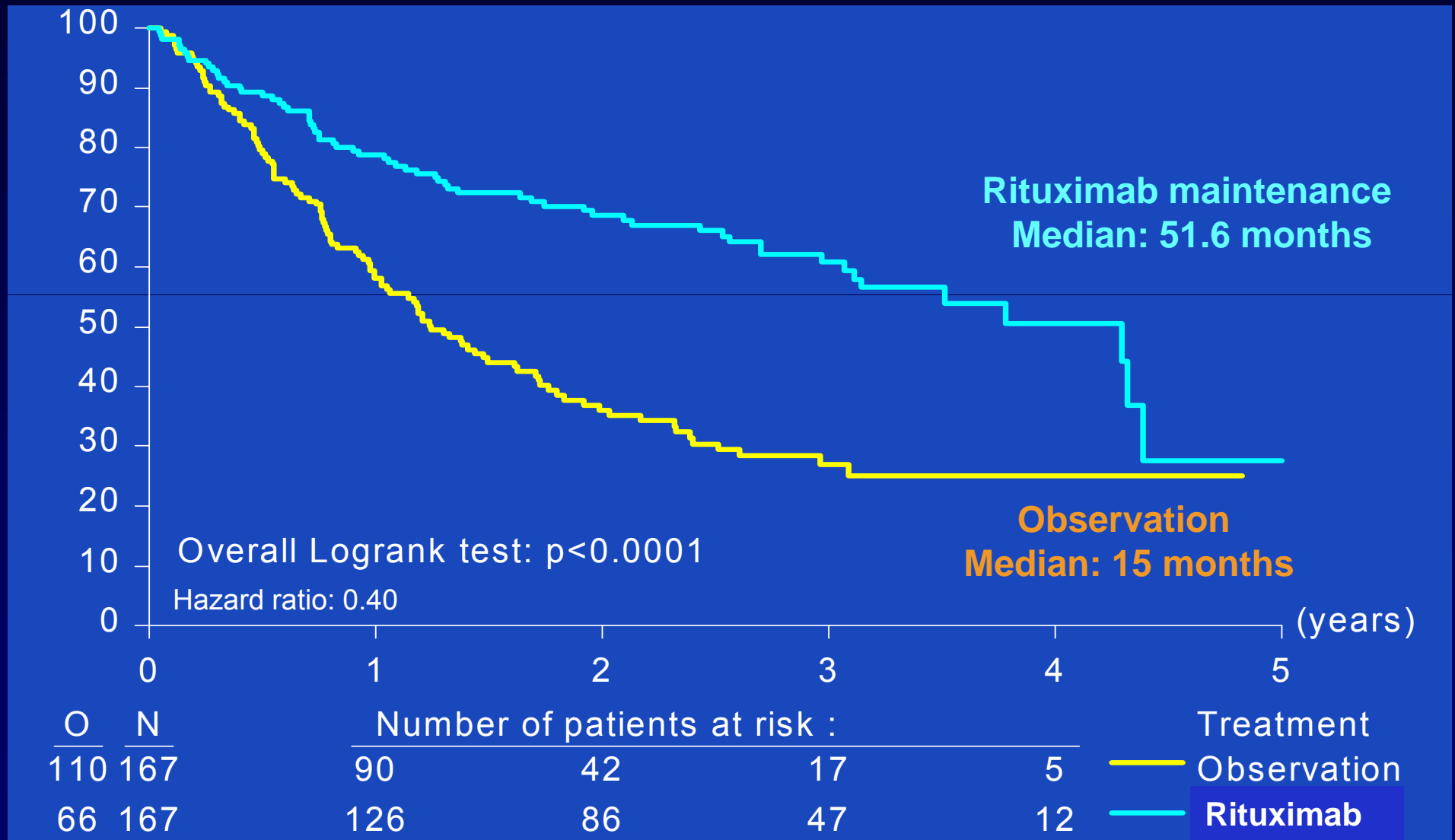
Intergroup Phase III Trial: Study Design



*375 mg/m² every 3 months
for 2 years or until relapse

Intergroup Phase III Trial

Progression-Free Survival from Second Randomization



EORTC 20981

Abstr. ASH 2005 (Maint 1 x R, q 3 mo, up to 2 yrs) Induction n = 465, Maint n = 334, med. follow up 33 months

	Observation	Maintenance Rituximab	
PFS* (months)	15.0	51.6	$P < .0001$
After CHOP	11.6	42	
After CHOP-R	23.1	52	$P = .004$
After CR	14.5	51.6	
After PR	15.6	45.4	
OS (3 years)	77.1%	85.1%	$P = .011^{**}$

* after 2nd randomization ** HR = 0.52

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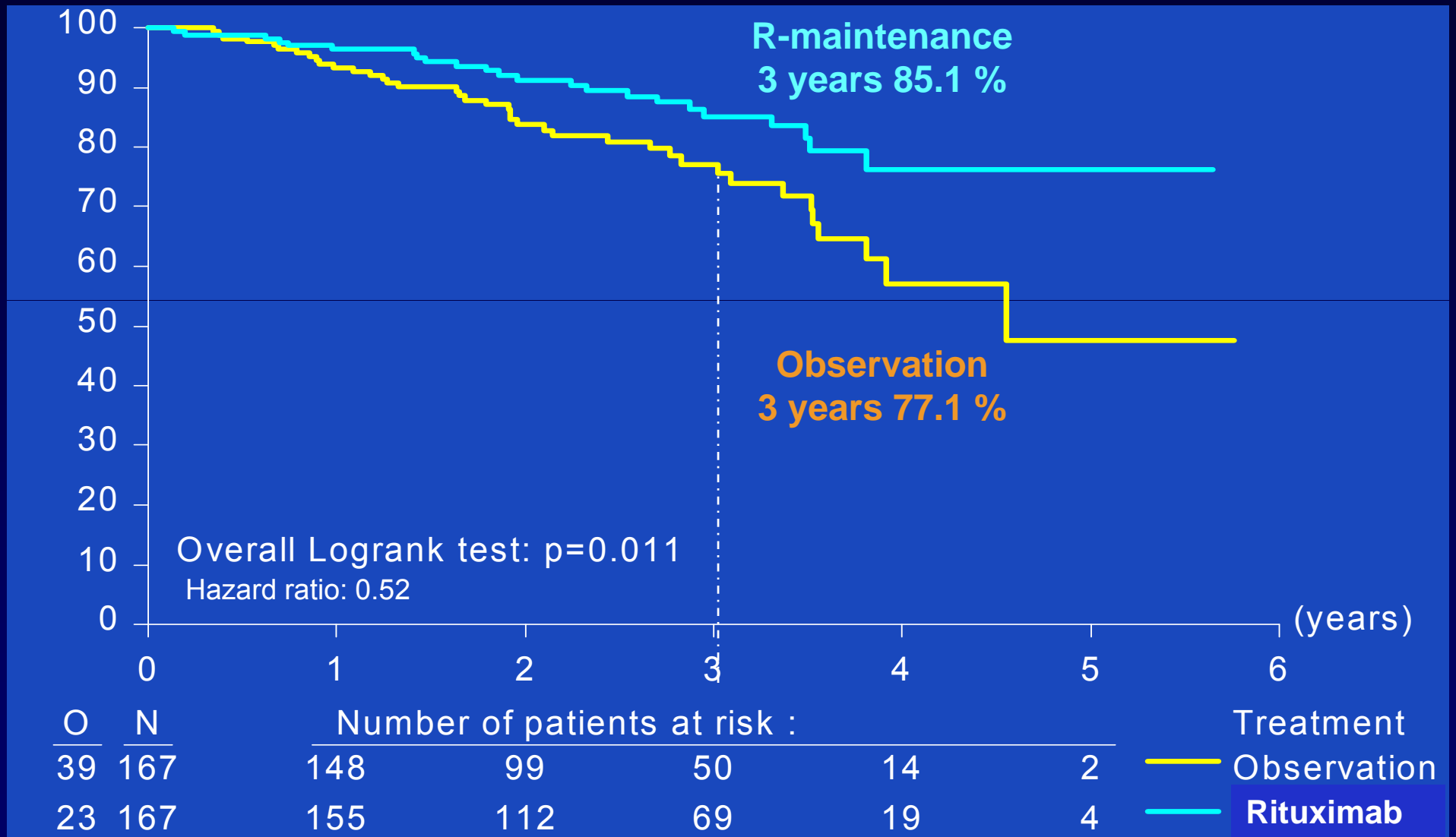
* after 2nd randomization ** HR = 0.52

Adverse Events - EORTC 20981

	Observation		Rituximab	
	Grade 3	Grade 4	Grade 3	Grade 4
Leukocytopenia	2.4%	1.8%	6.0%	0.6%
Granulocytopenia	3.6%	1.8%	6.6%	4.2%
Infections	1.8%	0.6%	7.2%	1.8%
Cardial	4.2%		4.2%	1.8%
Pulmonary			1.2%	1.2%
Skin	0.6%		2.4%	

Intergroup Phase III Trial

Overall Survival from Second Randomization



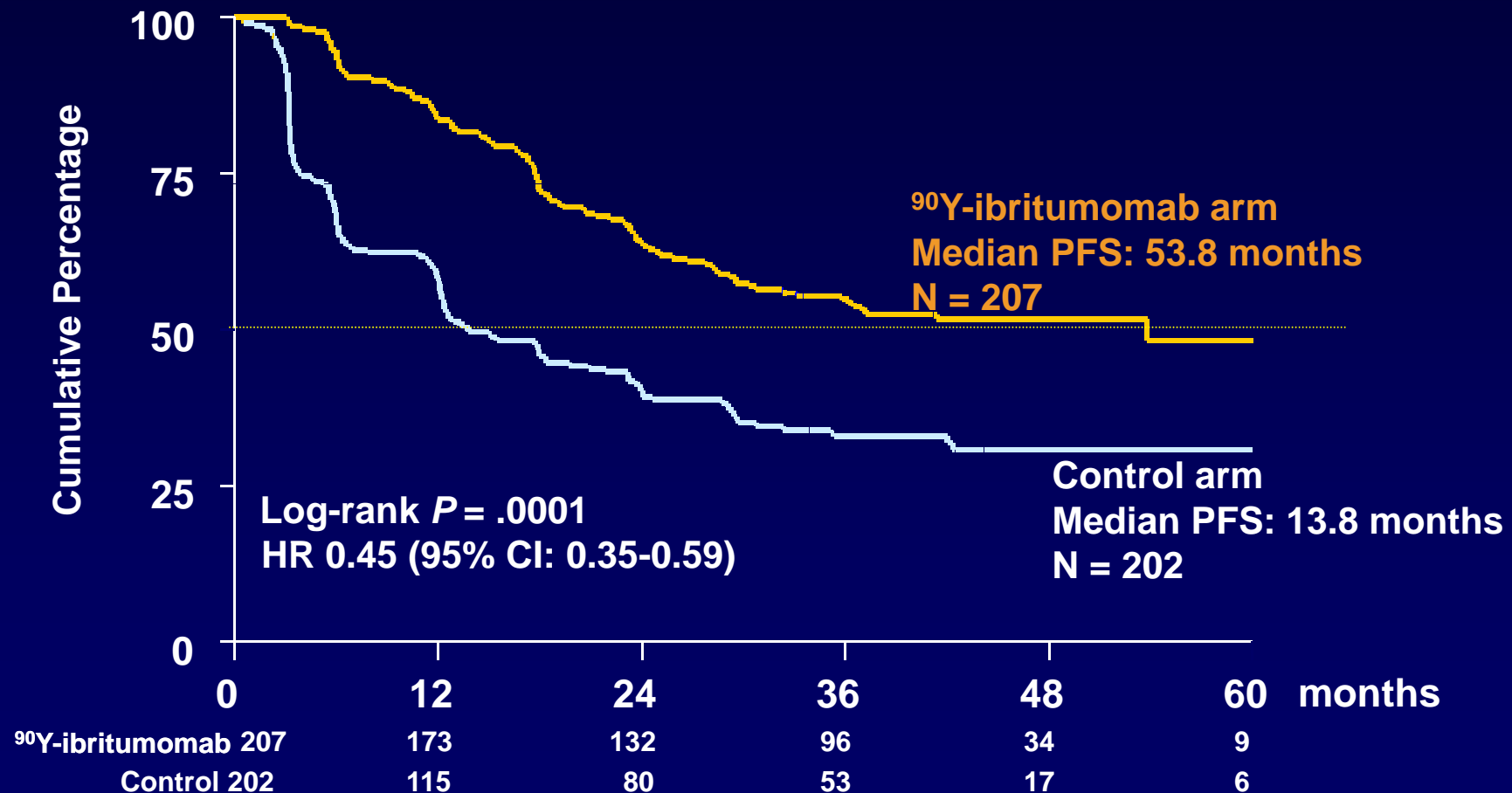
Extended Follow-up of the International Randomized Phase 3 First-Line Indolent Trial (FIT) Shows Durable Benefit of ⁹⁰Y-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced Stage Follicular Non-Hodgkin's Lymphoma

Franck Morschhauser,¹ Angelika Bischof-Delaloye,² Ama ZS Rohatiner,³ Gilles Andre Salles,⁴ Jens Kuhlmann,⁵ Willem JL Van Putten,⁶ John Radford,⁷ Pierre Soubeyran,⁸ Achiel Van Hoof,⁹ and Anton Hagenbeek¹⁰ for the FIT Investigators

¹Hôpital Huriez, Lille, France; ²Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ³St Bartholomew's Hospital, London, UK; ⁴Centre Hospitalier Lyon Sud, Pierre Bénite, France; ⁵Bayer Schering Pharma AG, Berlin, Germany; ⁶Erasmus MC, Rotterdam, the Netherlands; ⁷Christie Hospital, Manchester, UK; ⁸Université Victor Segalen, Bordeaux, France; ⁹General Hospital St-Jan, Brugge, Belgium; ¹⁰UMC Utrecht/HOVON, the Netherlands

Overall PFS for Treatment Groups

The 4-year overall PFS is
52% in the ⁹⁰Y-ibritumomab arm compared with 31% in the control arm



Effect of Treatment Arm on PFS by First-Line Treatment and Response to First-Line Treatment

PFS	Control			⁹⁰ Y-Ibritumomab			Hazard Ratio (95% CI)*
	No. of Patients	No. Failed	Median PFS, mo	No. of Patients	No. Failed	Median PFS, mo	
First-line treatment*							
CHOP	57	43	12.4	65	33	36.5	2.39 (1.52-3.78)
CVP/COP	53	40	7.9	53	30	29.6	2.25 (1.40-3.63)
CHOP-like	31	19	29.1	30	11	> 67	2.11 (1.00-4.44)
Fludarabine	11	6	28.7	11	6	41.4	1.11 (0.36-3.46)
Chlorambucil	19	15	11.9	20	10	37.2	2.76 (1.23-6.21)
Rituximab combination	31	13	> 44	28	9	> 45	1.39 (0.60-3.26)

*Note: FIT was not powered to detect significant differences in outcomes according to individual types of induction therapy

Morschhauser F, et al. *Blood*. 2008;112: Abstract 2002.

Effect of Treatment Arm on PFS by First-Line Treatment and Response to First-Line Treatment

PFS	Control			⁹⁰ Y-Ibritumomab			Hazard Ratio (95% CI)*
	No. of Patients	No. Failed	Median PFS, mo	No. of Patients	No. Failed	Median PFS, mo	
First-line treatment*							
CHOP	57	43	12.4	65	33	36.5	2.39 (1.52-3.78)
CVP/COP	53	40	7.9	53	30	29.6	2.25 (1.40-3.63)
CHOP-like	31	19	29.1	30	11	> 67	2.11 (1.00-4.44)
Fludarabine	11	6	28.7	11	6	41.4	1.11 (0.36-3.46)
Chlorambucil	19	15	11.9	20	10	37.2	2.76 (1.23-6.21)
Rituximab combination	31	13	> 44	28	9	> 45	1.39 (0.60-3.26)

*Note: FIT was not powered to detect significant differences in outcomes according to individual types of induction therapy

Morschhauser F, et al. *Blood*. 2008;112: Abstract 2002.

Standard of Care in Patients with Indolent Lymphomas

- There is still a role for watch & wait, despite new therapy modalities
- Combined immunochemotherapy is the standard of care
- R-chemotherapy plus R-maintenance appears as the optimal option for patients with relapsed disease
- A study of 513 randomized patients shows that bendamustine-R is superior to CHOP-R in regard of efficacy while being associated with less toxicity
- Bendamustine plus rituximab has the potential to become a treatment of first-choice in these disease entities
- R-maintenance after first-line R-containing regimens
 - PRIMA study was reported to be positive, results ASCO 2010
 - SAKK study proves duration of maintenance after R-monotherapy
 - StiL NHL 7-2008 study proves duration of maintenance R after B-R
- Role of lenalidomide, bortezomib and ofatumumab has to be defined