

Emerging Options For a Patient With Follicular Lymphoma



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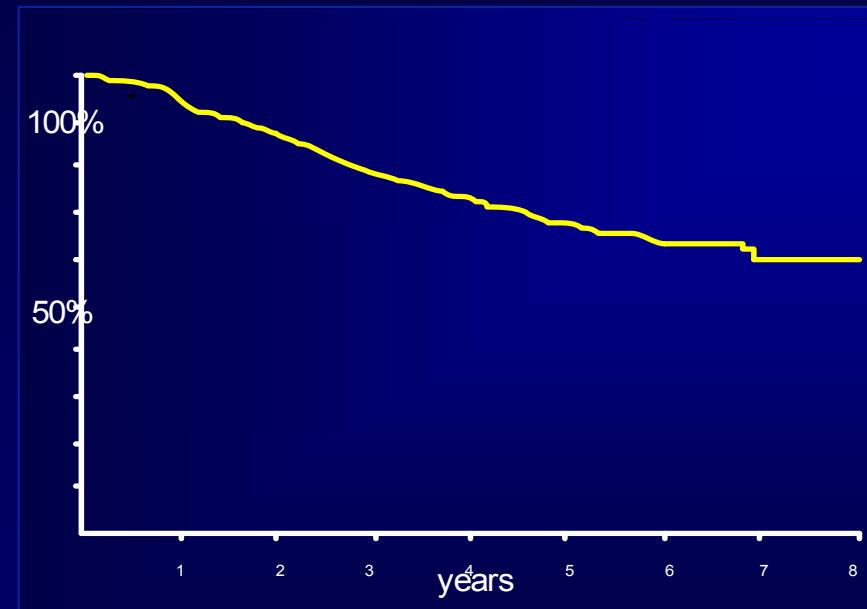
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Therapy for Follicular Lymphoma

- ⊙ Wait and see policy
- ⊙ Alkylating agents
- ⊙ Anthracycline-based chemotherapy
- ⊙ Purine analogues
- ⊙ Bendamustine
- ⊙ Unconjugated monoclonal antibodies
- ⊙ Radiolabelled monoclonal antibodies
- ⊙ Autologous stem cell transplantation
- ⊙ Allogeneic stem cell transplantation
- ⊙ Nonmyeloablative allogeneic SCT
- ⊙ (DNA vaccination, antisense, etc)

NHL Classification Project:

OS for 306 patients with follicular NHL:



Follicular Lymphoma International Prognostic Index (FLIPI)

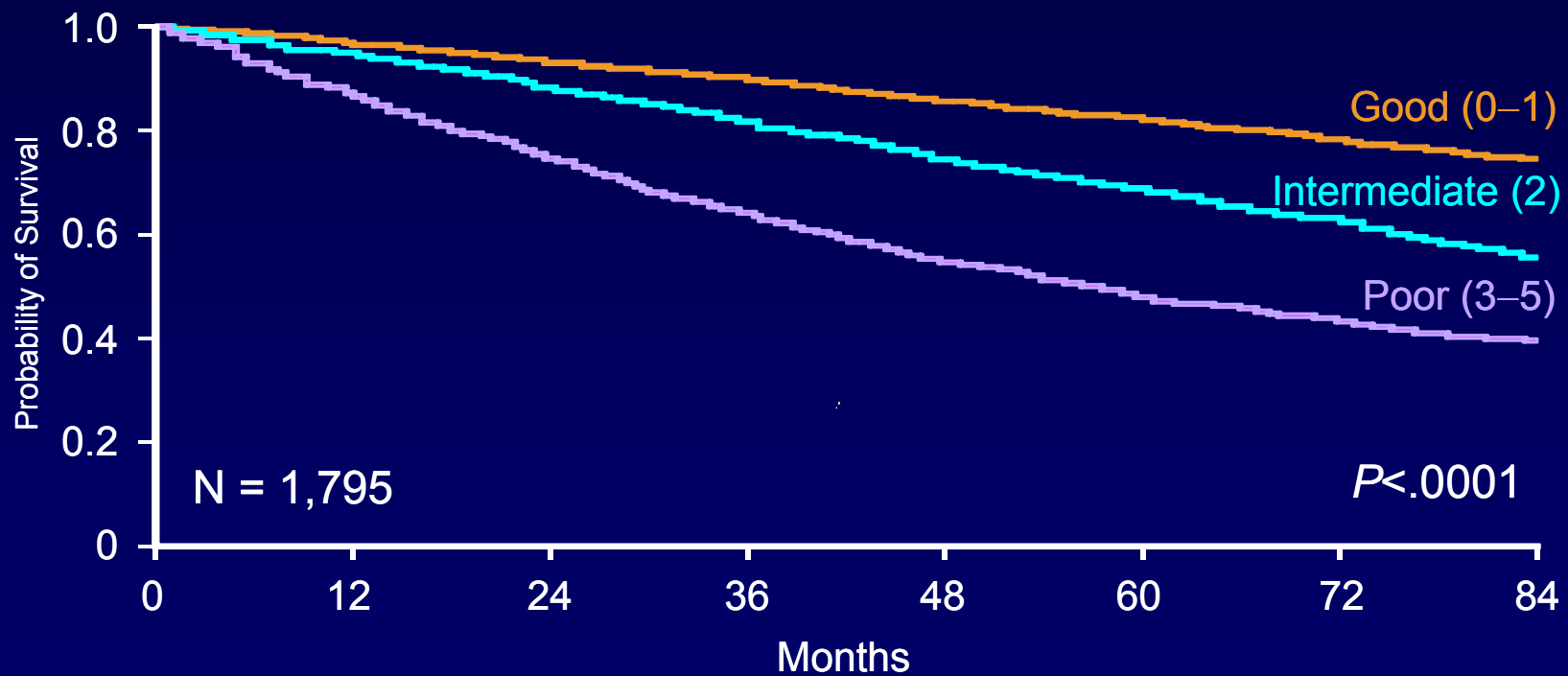
Parameter	Adverse Factor	RR	95% CI
Age	≥60	2.38	2.04-2.78
Stage	III or IV	2.00	1.56-2.58
Hemoglobin	<12 g/dL	1.55	1.30-1.88
Serum LDH	>Norm	1.50	1.27-1.77
LK-Areale	>4	1.39	1.18-1.64

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

FLIPI: Overall Survival



Watch & Wait or Early Treatment?

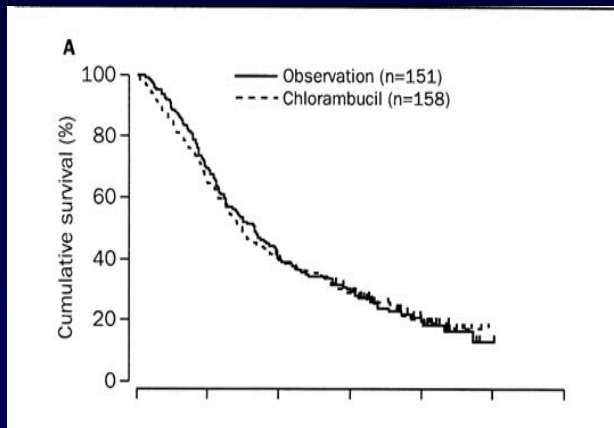
Is there a need for immediate treatment in asymptomatic patients with advanced indolent/follicular lymphomas or can a watch and wait strategy be considered?

Watch & Wait or Early Treatment?

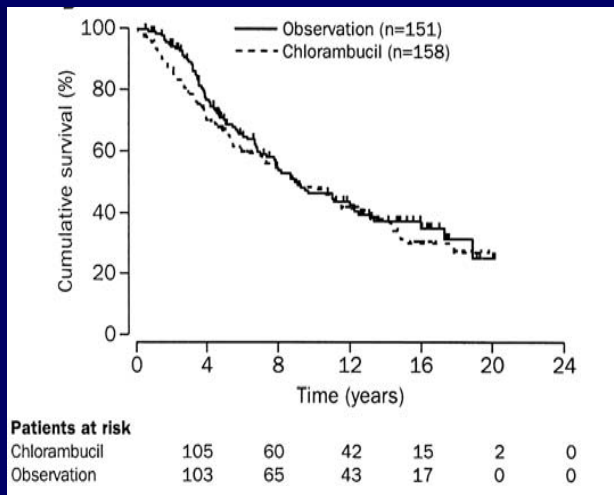
Watchful waiting versus chlorambucil 10 mg daily contin. prospective randomized, n = 309, recruitment phase 1981-1990

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?

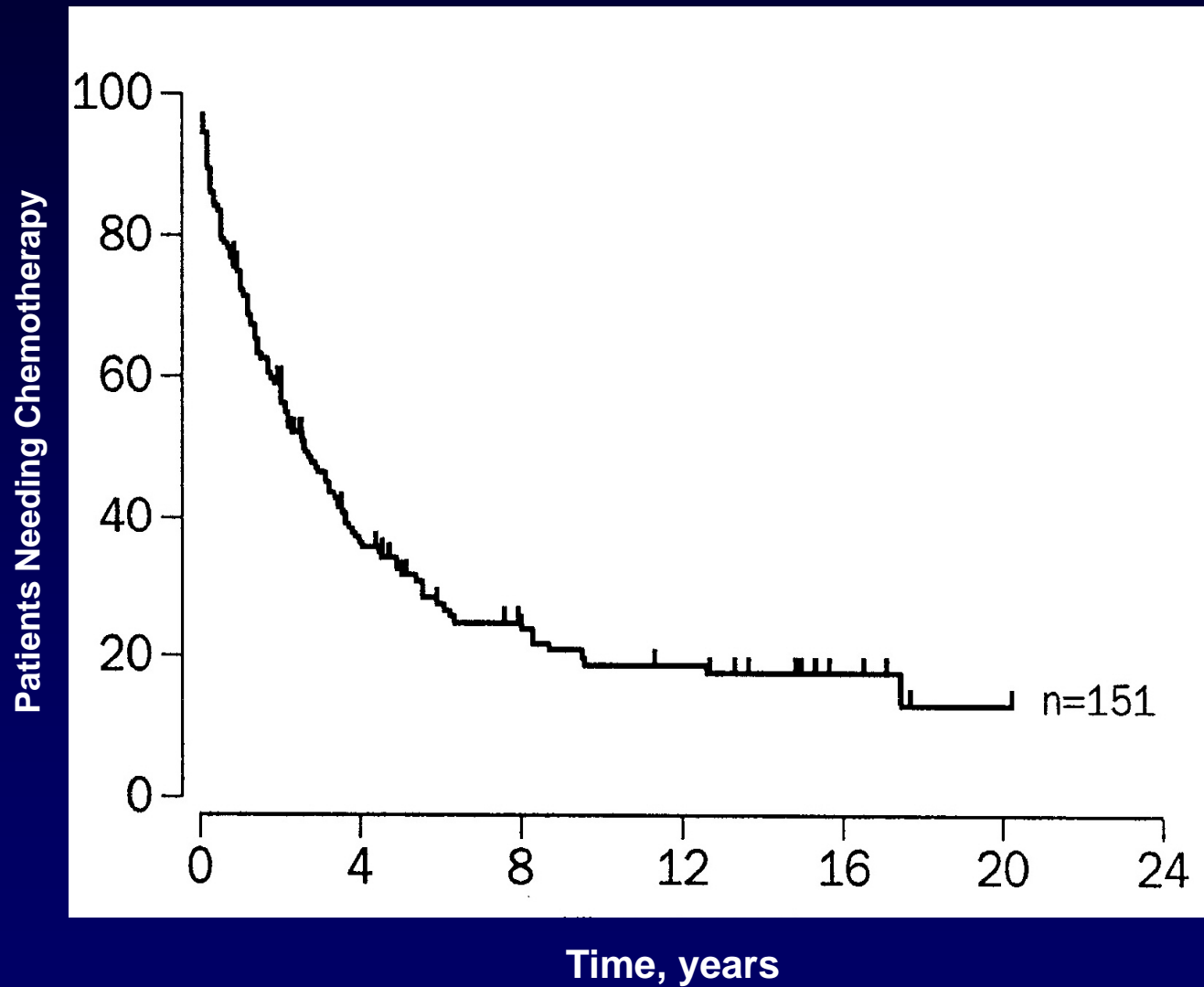


Overall survival



Disease-associated survival

Watch & Wait or Early Treatment?

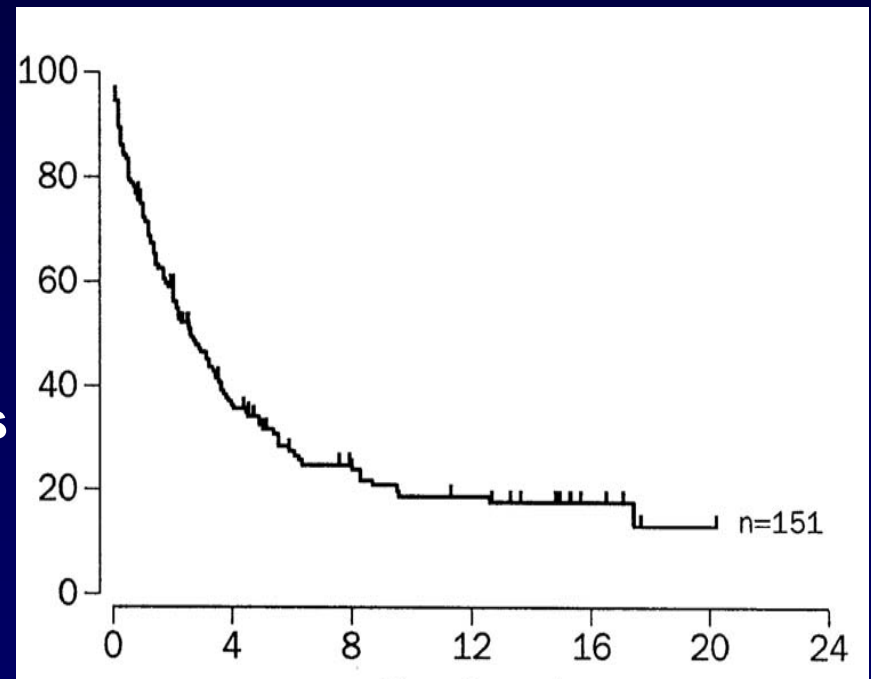


Ardeshtna KM, et al. *Lancet*. 2003;362(9383):516-522.

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

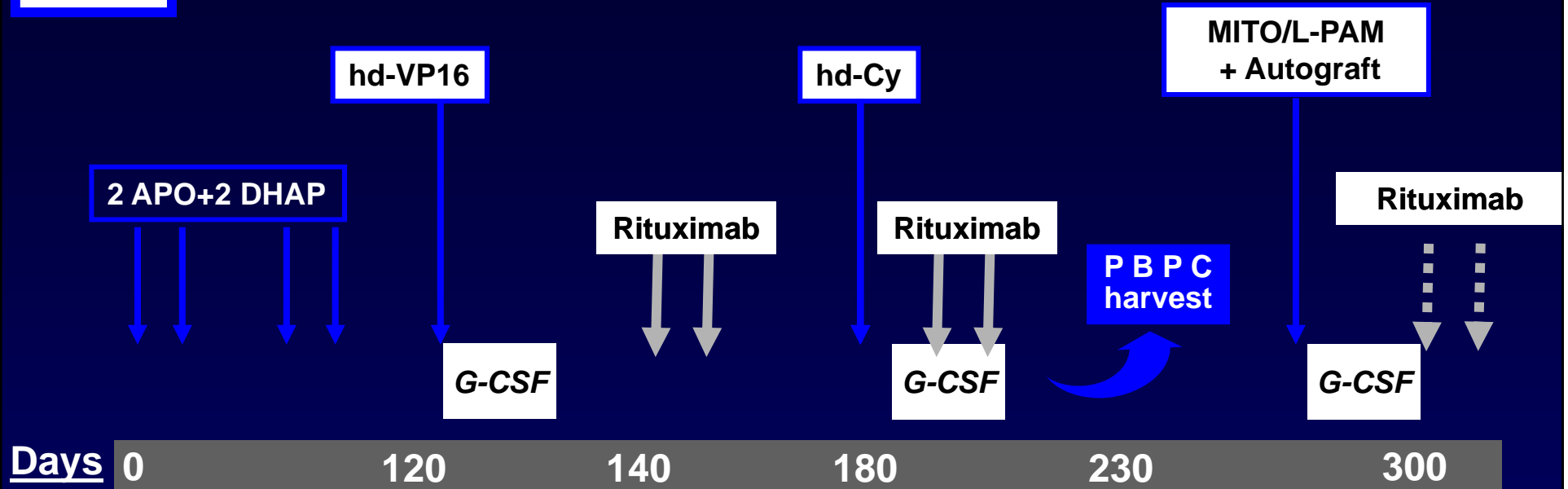


Indications for Treatment in Follicular Lymphomas

- ⊙ 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 phenomena, such as AIHA or ITP
- **No role for**
 - FLIPI
 - LDH or Beta-2-Microglobuline
 - age, stage or bone marrow involvement

Treatment Schedules

R-HDS



CHOP-R

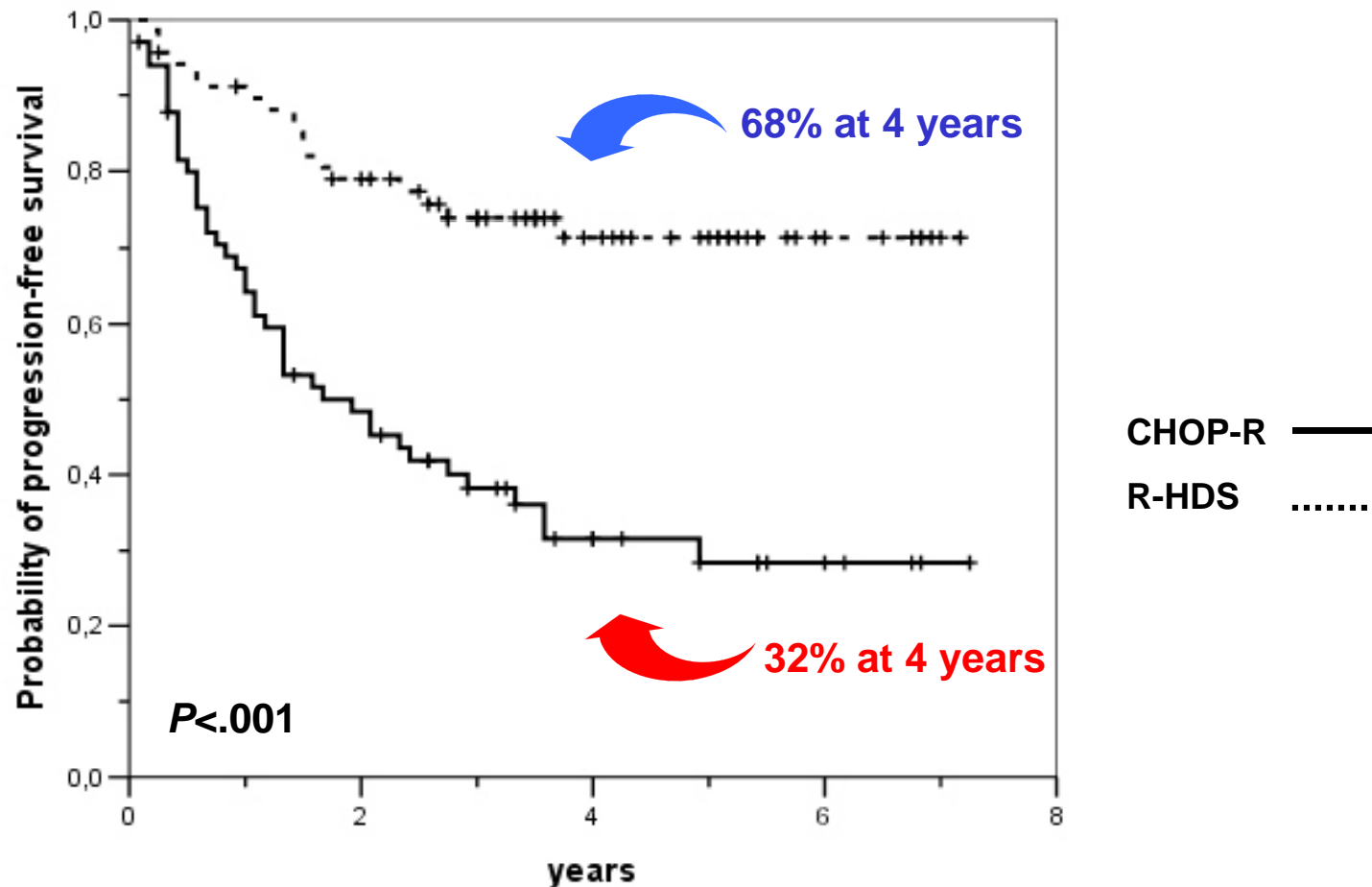
Ladetto M, et al. *Blood*. 2007;110: Abstract 20.

R-HDS vs CHOP-R Randomized Trial

Evaluable Patients: 134

PFS ACCORDING TO TREATMENT ARM

Median follow up: 51 months



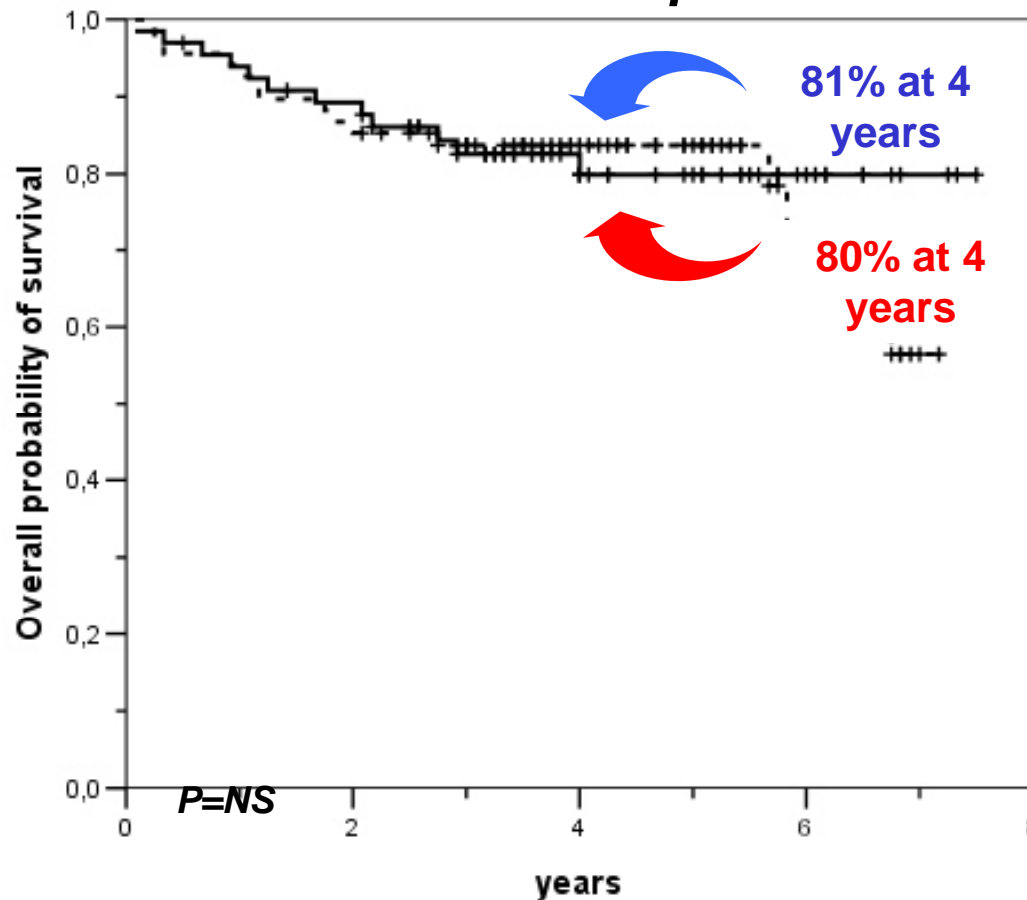
R-HDS vs CHOP-R Randomized Trial

Evaluable Patients: 134

OS ACCORDING TO TREATMENT ARM

R-HDS vs CHOP-R

Median follow up: 51 months



ASCT in Follicular Lymphomas

ASCT is an appropriate treatment choice for younger patients with chemosensitive recurrent follicular lymphoma

ASCT remains investigational in the initial treatment of follicular lymphoma

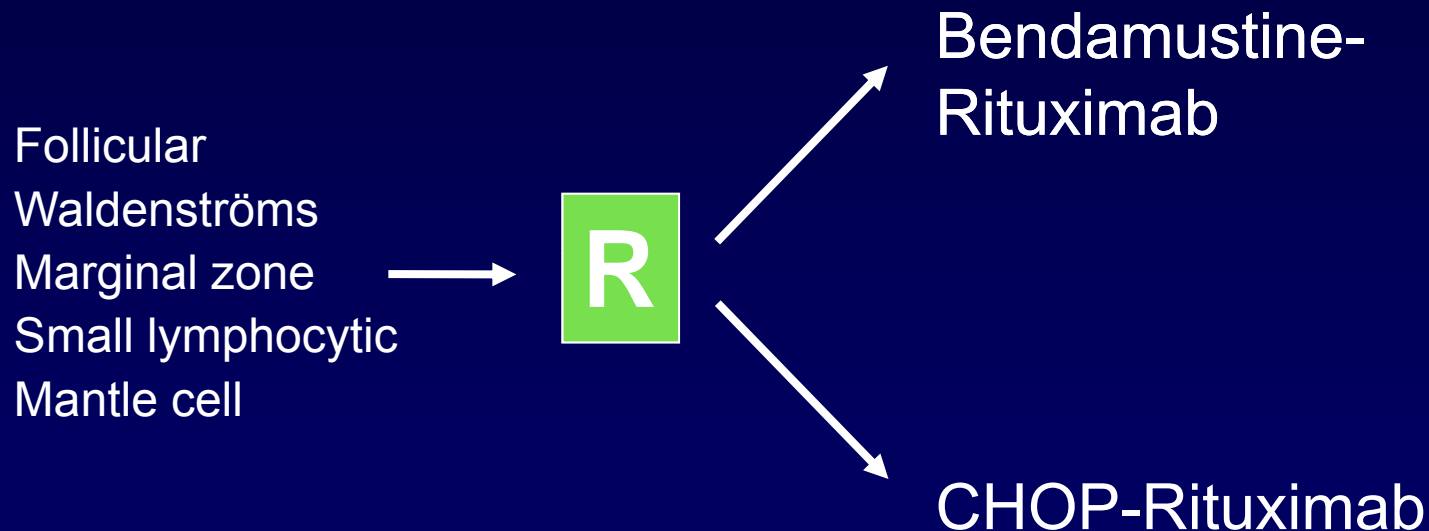
- **No demonstrated overall survival benefit**
- **Possible improvement in overall survival by adding rituximab in treatment strategies**
- **Increase of 2nd malignancies**

Standard of Care in Pts With Indolent Lymphomas

- There is still a role for watch & wait, despite new therapy modalities
- Wait for indication for treatment
- No relevant role for high-dose therapy plus autologous stem cell support
- Combined immuno-chemotherapy is the standard of care
- **Newer perspectives:**
 - Rituximab maintenance as consolidation of treatment success
 - Which chemotherapy should be best combined with rituximab
 - Bortezomib, lenalidomide, and ofatumumab are under investigation

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
Waldenström	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 years	63 years
> 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

549 patients randomized. 513 patients evaluable for response and toxicity

	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

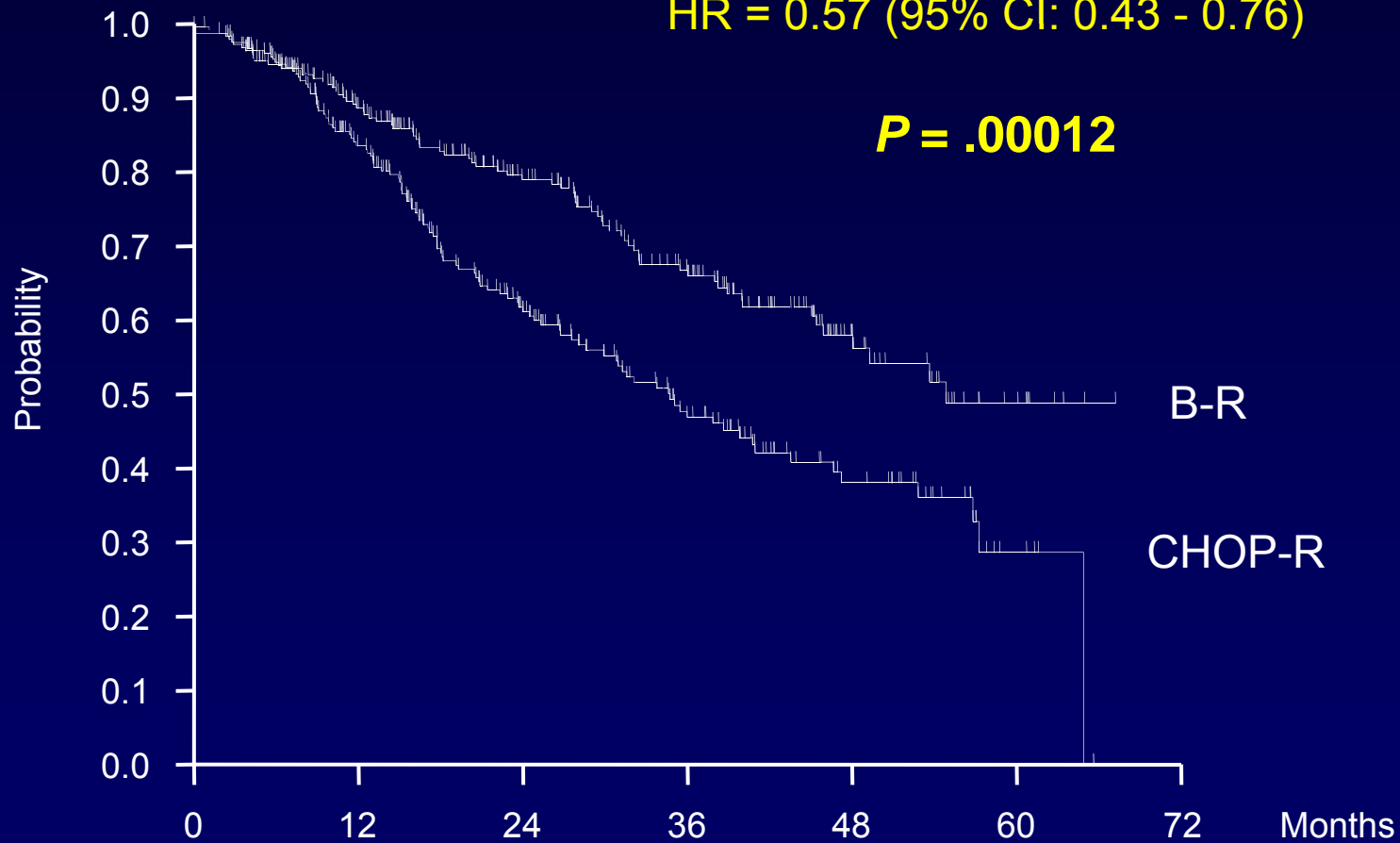
	B-R (n = 260)	CHOP-R (n = 253)	P Value
ORR	92.7%	91.3%	
CR	39.6%	30.0%	=.0262
SD	2.7%	3.6%	
PD	3.5%	2.8%	

Progression-Free Survival

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

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

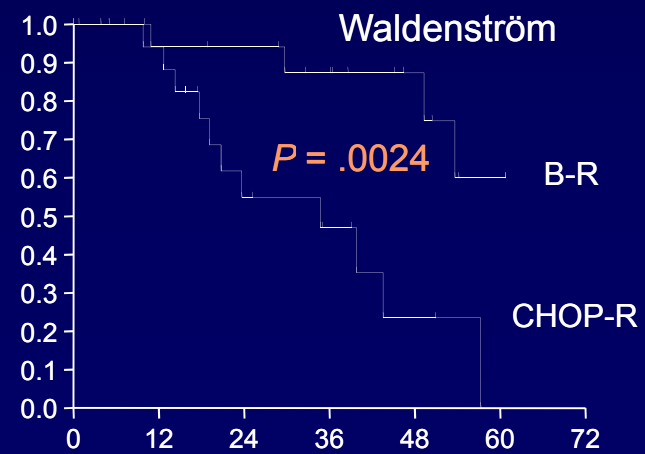
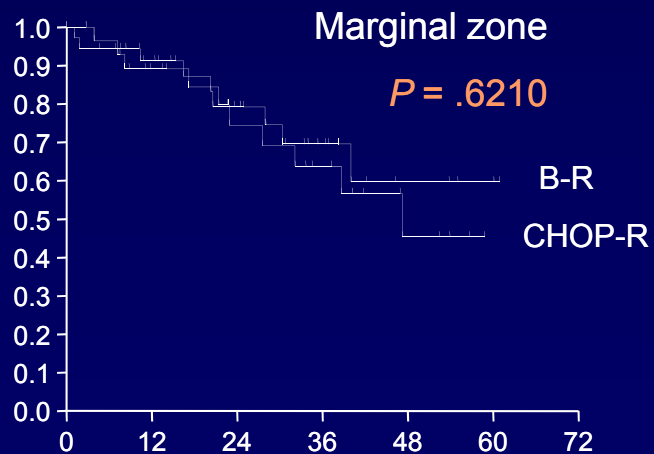
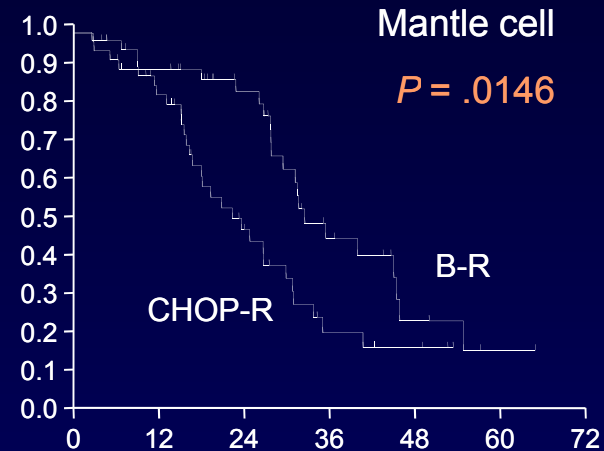
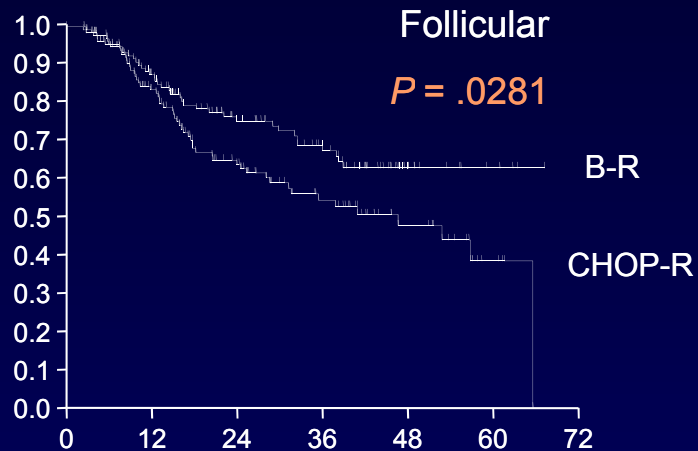
P = .00012



Median observation period 34 months

Rummel MJ, et al. *Blood*. 2009;114: Abstract 405.

Progression-Free Survival Subentities

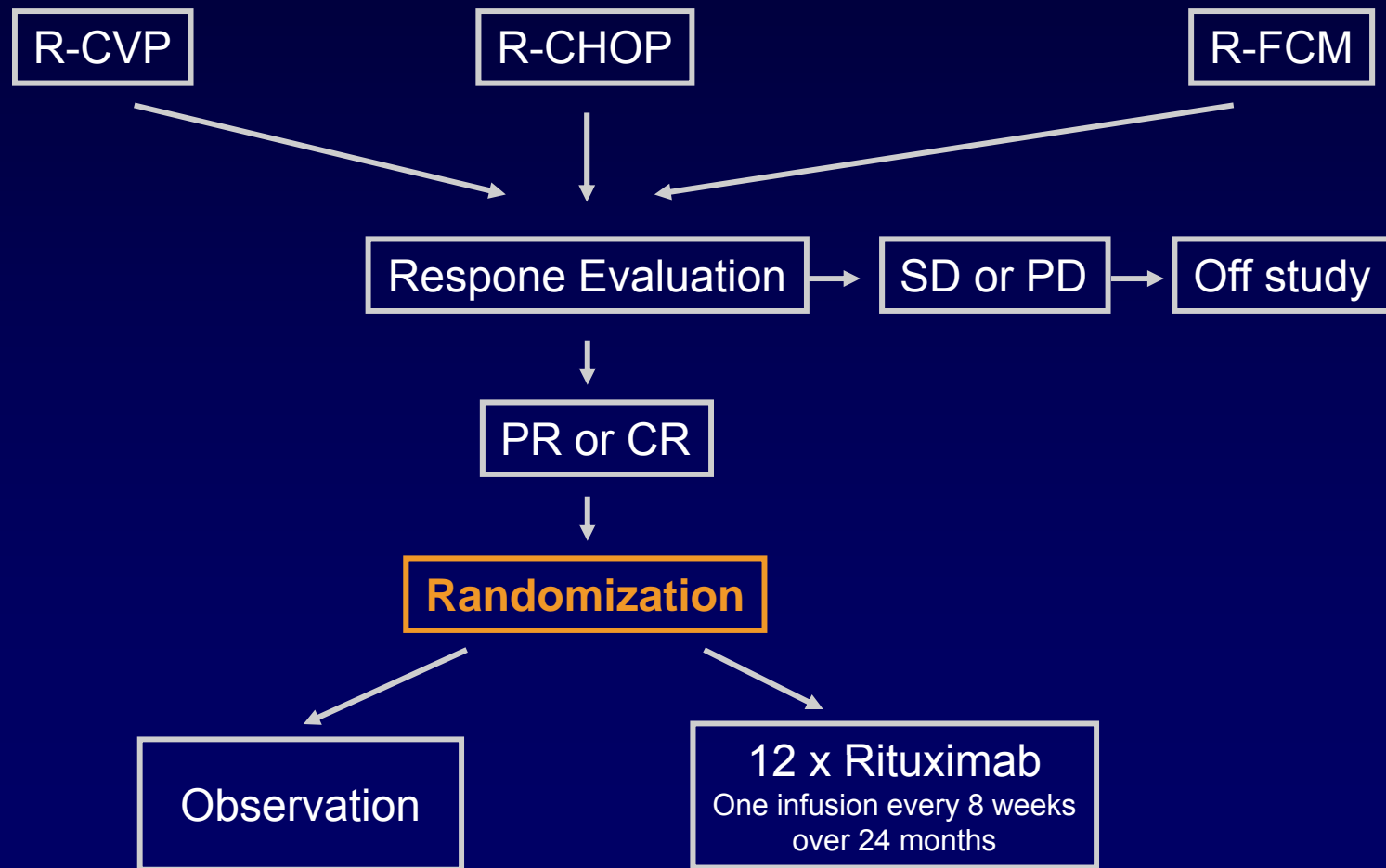


Bendamustine-R vs CHOP-R: Conclusion

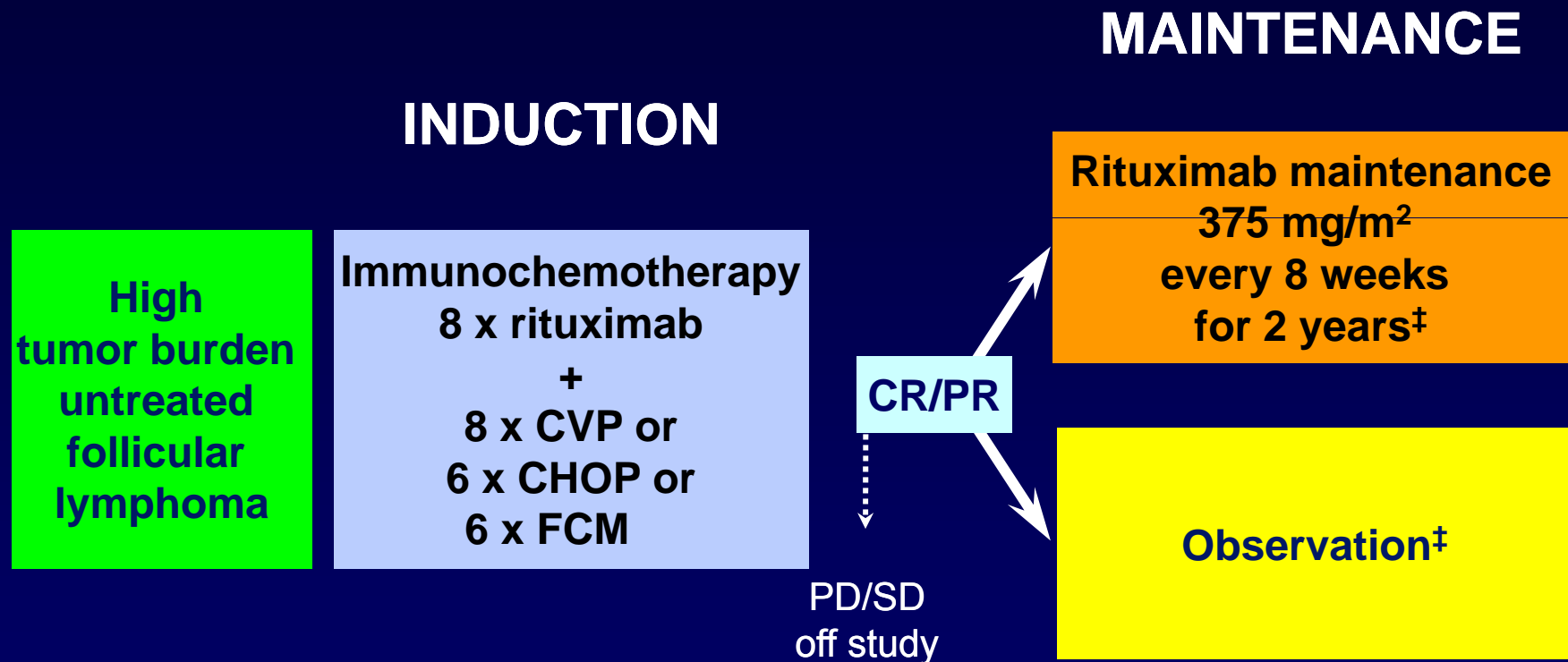
B-R is not only less toxic but also more effective than the most often used first-line treatment approach CHOP-R

Therefore, B-R should be considered as a new standard first-line treatment for patients with FL, indolent, and MCL

PRIMA Trial for Follicular Lymphoma (Primarily Rituximab and Maintenance)



PRIMA: Study Design

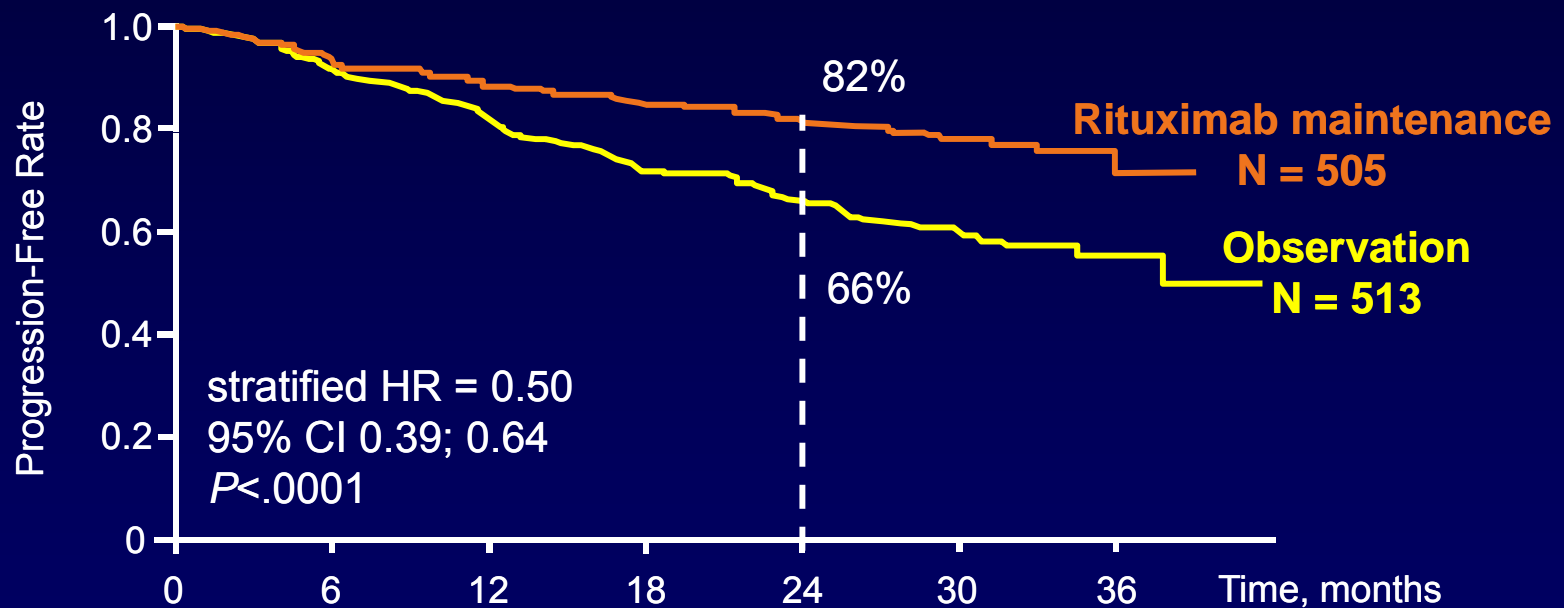


* Stratified by response after induction, regimen of chemo, and geographic region

‡ Frequency of clinical, biologic, and CT-scan assessments identical in both arms

PRIMA: Progression-Free Survival

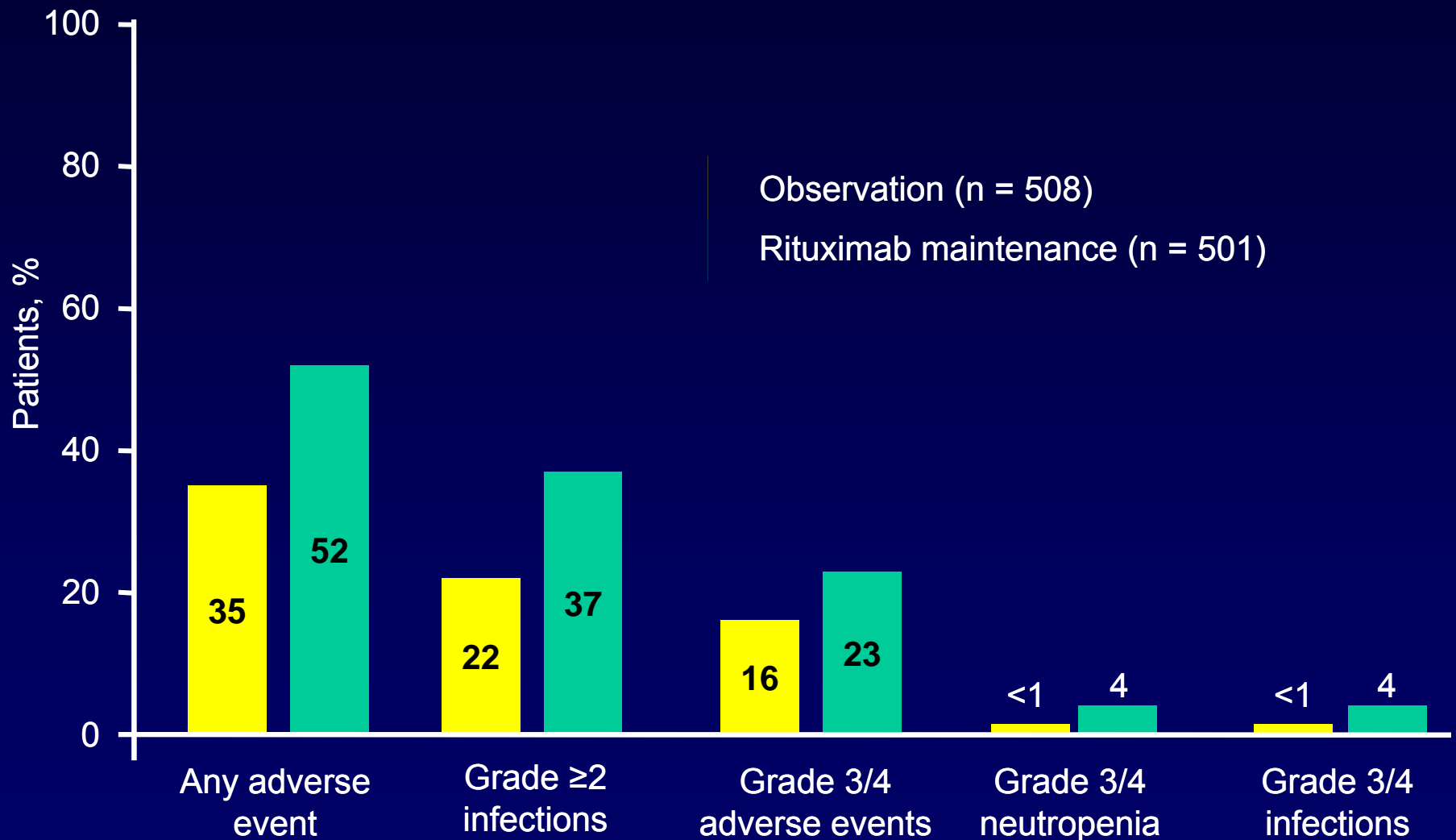
Rituximab maintenance significantly reduced the risk of progression by 50%



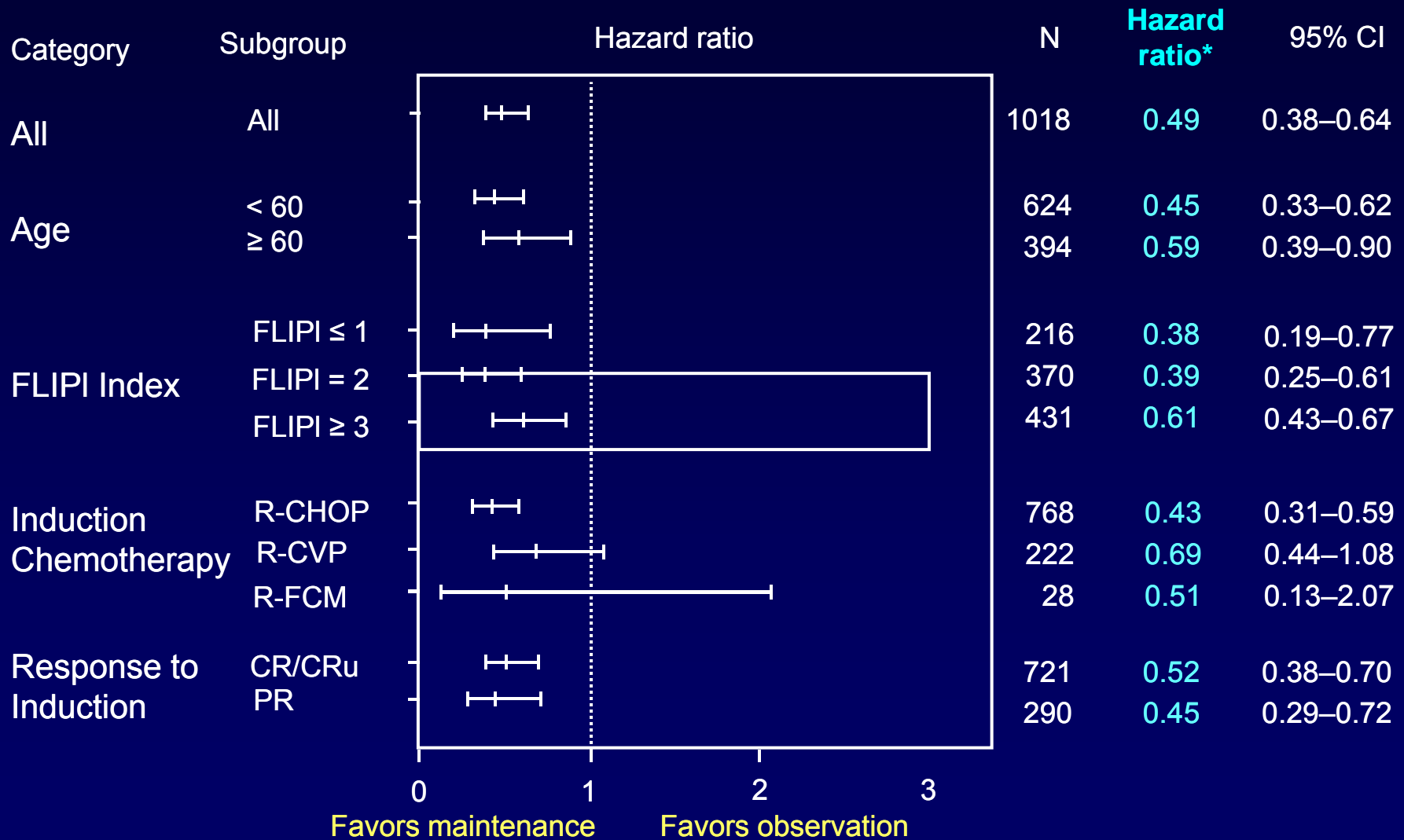
Patients at risk

505	472	443	336	230	103	18
513	469	411	289	195	82	15

PRIMA: Safety During Rituximab Maintenance



PRIMA: Benefits of R-Maintenance in All Subgroups



* Nonstratified analysis

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



Newer Perspectives In Follicular Lymphoma

Bortezomib

Lenalidomide

Ofatumumab

Phase III Trial of Bortezomib and Rituximab vs Rituximab in Relapsed or Refractory Rituximab Naïve/Sensitive Follicular Lymphoma

R
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Arm A

- **Bortezomib 1.6 mg/m²** days 1, 8, 15, 22 for five 35-day cycles
- **Rituximab 375 mg/m²** days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2-5 (8 doses)

Arm B

- **Rituximab 375 mg/m²** days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2-5 (8 doses)

- Accrual goal = 670 pts
- Pts stratified by FLIPI, prior rituximab exposure, time from prior therapy (\leq or $>$ 1 year) and geographic region
- Primary study endpoint is PFS

Bendamustine Rituximab Plus Bortezomib vs Bendamustine Plus Rituximab (BR)

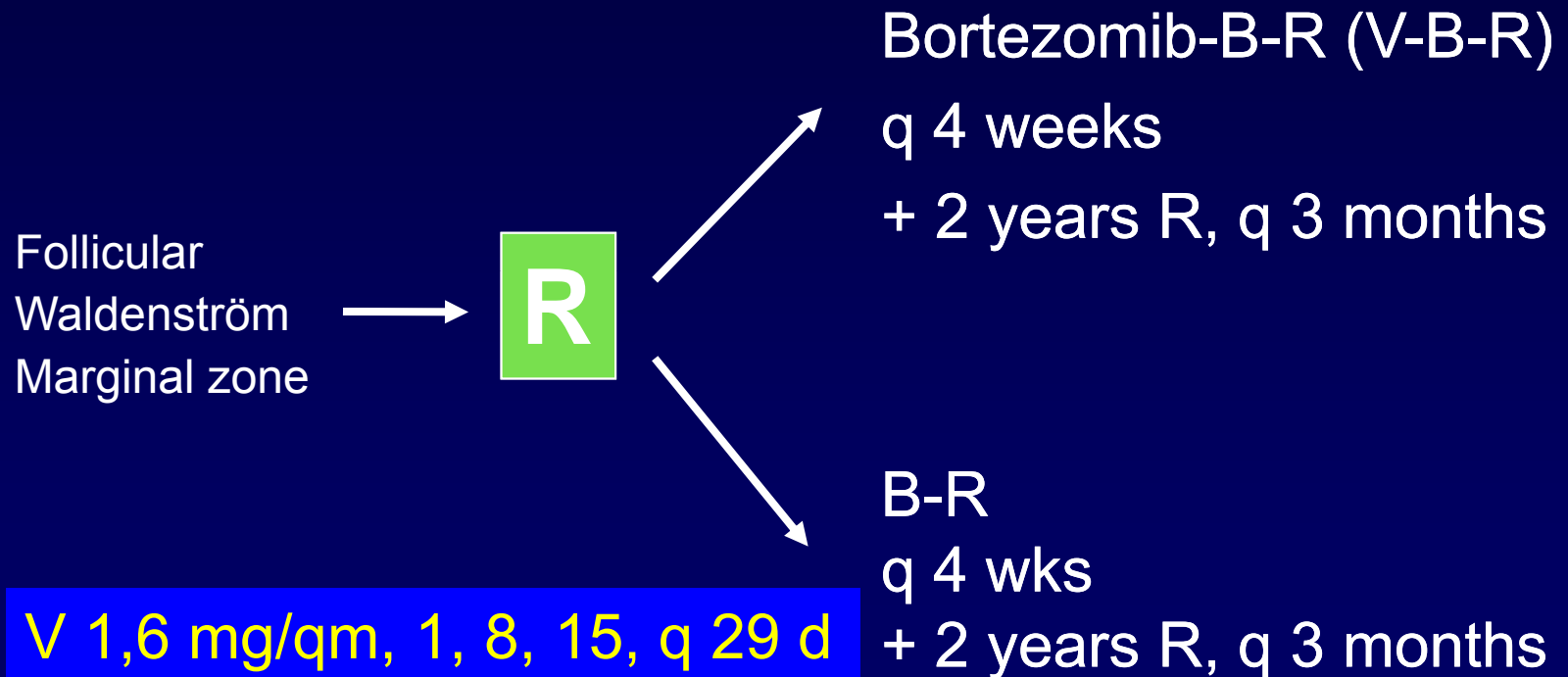
In relapsed follicular lymphoma
and Waldenström disease



NHL 8 - 2010

V-B-R + 2 Years R vs B-R + 2 Years R

StiL NHL 8-2010 Randomized Phase III Study



**Durable Response After
Lenalidomide Oral Monotherapy in
Patients With Relapsed or Refractory
DLBCL, MCL, FL III, T-NHL:
Results On An International Study
(NHL-003)**

ASH 2009, Abstract # 1676

**T. E. Witzig, J. M. Vose, P.L. Zinzani, C. B. Reeder, R. Buckstein, J.
Polikoff , P. Guo; D. Pietronigro, A. Ervin-Haynes,
M. S. Czuczman**

Patients

Lenalidomide 25mg/d d 1-21/ q28
Continuously until progress or intolerable toxicity

Total	N= 217	%
DLBCL	108	50
MCL	57	26
FL-III	19	9
TL	33	15

Median Age	69 (21-87)
Median time since diagnosis (years)	2,7 (0,04 – 20,6)
Median no of prior therapies n (range)	3 (1-13)
Rituximab pretreated, n (%)	94 (205/217)

Results

	n	ORR %	CR / Cru %	Median PFS	Median RD
Total	217	35	13	3.7	10.6
DLBCL	108	28	7	2.7	4.6
MCL	57	42	21	5.7	n.r.
FL-III	19	42	2	8.9	n.r.
TL	33	45	7	5.4	12.8

Standard of Care in Pts With Indolent Lymphomas

- There is still a role for watch & wait, despite new therapy modalities
- Combined Immuno-Chemotherapy is the standard of care
- No relevant role for high-dose therapy plus autologous stem cell support
- Bendamustine plus Rituximab has the potential to become a treatment of 1st-choice in these disease entities
- R-chemotherapy plus R-maintenance appears as the optimal approach for patients with relapsed disease and due to recently presented results of the PRIMA study also for patients after 1st-line R-chemotherapy
- Role of Lenalidomide, Bortezomib and Ofatumumab has yet to be defined