

# Case #1—Improving Outcomes in Mantle Cell Lymphoma

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# Disclosures for Mathias Rummel, MD, PhD

<b>Research Support / PI</b>	<b>Amgen, GSK, Roche, Mundipharma</b>
<b>Employee</b>	<b>N/A</b>
<b>Consultant / Scientific Advisory Board</b>	<b>N/A</b>
<b>Major Stockholder</b>	<b>N/A</b>
<b>Speakers' Bureau</b>	<b>N/A</b>

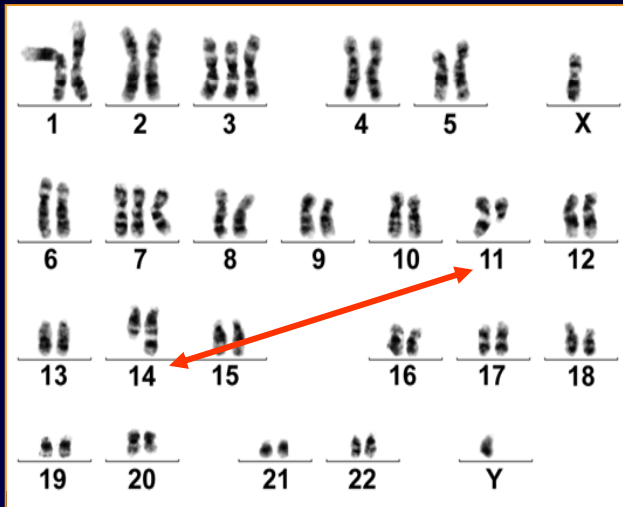
**N/A = Not Applicable (no conflicts listed)**

**Presentation includes discussion of the following off-label use of a drug or medical device: N/A**

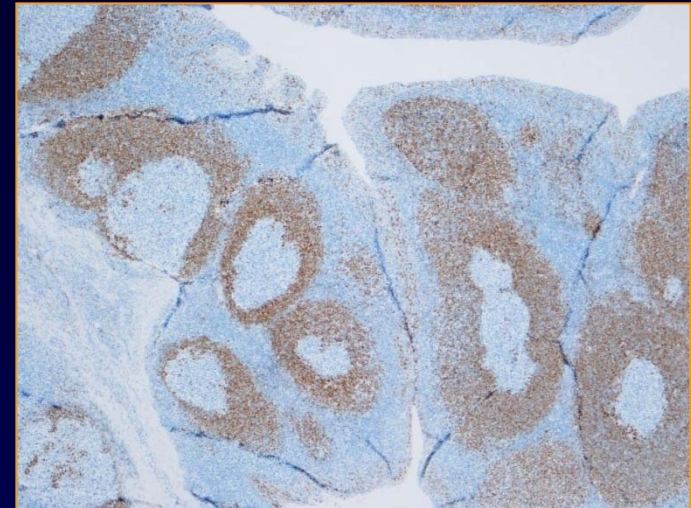
# Mantle Cell Lymphoma (MCL): Disease Characteristics

- Median age of onset: 68 years<sup>1</sup>
- Median survival: 5-7 years<sup>2</sup>
- Most patients present with advanced-stage disease at diagnosis
  - 90% have extranodal involvement (BM 50% to 80%, liver 25%, GI 25%)
  - 50% to 70% have evidence of circulating MCL cells at presentation
- Disease characterized as aggressive and incurable
  - Most patients treated immediately; watch-and-wait strategy possible
- Prognostic unfavorable: blastoid variant, high proliferation index Ki67
- Conventional chemotherapies have little benefit in patients with MCL
- Therapies such as autologous stem cell transplantation (SCT) are associated with improved outcomes, but most patients will relapse eventually

**t(11;14)(q13;q32)**

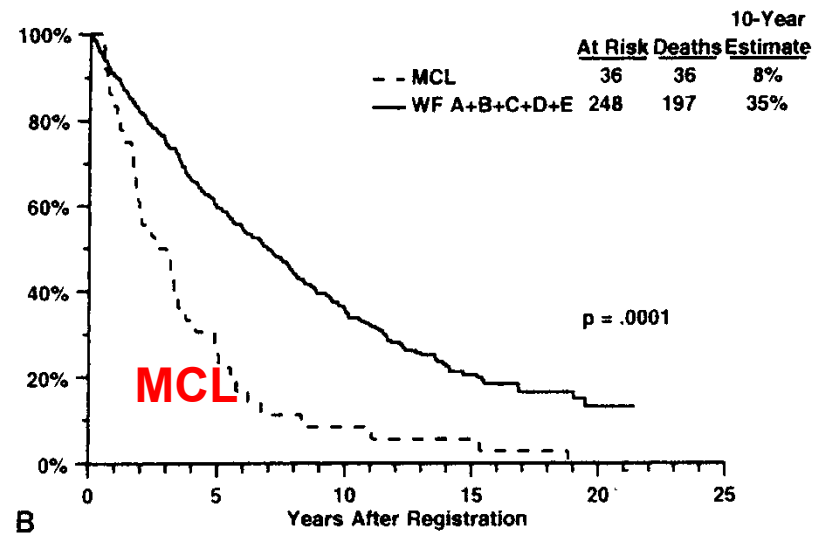
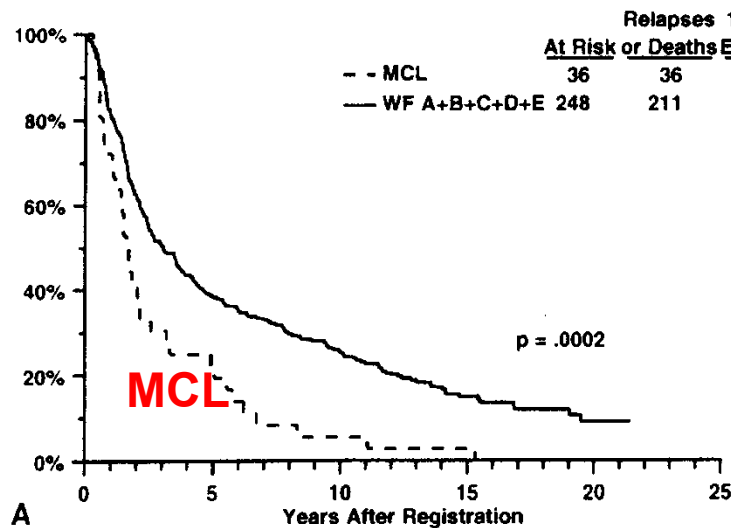


**Cyclin D1 staining**



**NHL Classification Project, Blood 1997**

MCL. (A) The failure-free survival curve for 36 patients with MCL compared with 248 patients with WF A through E is shown. (B) The overall survival of 36 patients with MCL compared with 248 patients with WF A through E is shown.



# MCL—Therapeutic Advances

Younger patients: Intensive chemotherapy ± HDT plus APBSCT

Elderly patients: New “old” compound bendamustine

Targeted therapy:

Anti-CD20:

Rituximab

Radioimmunotherapy:

Ibritumomab Tiuxetan

Microenvironment:

Thalidomide, Lenalidomide

Proteasome:

Bortezomib

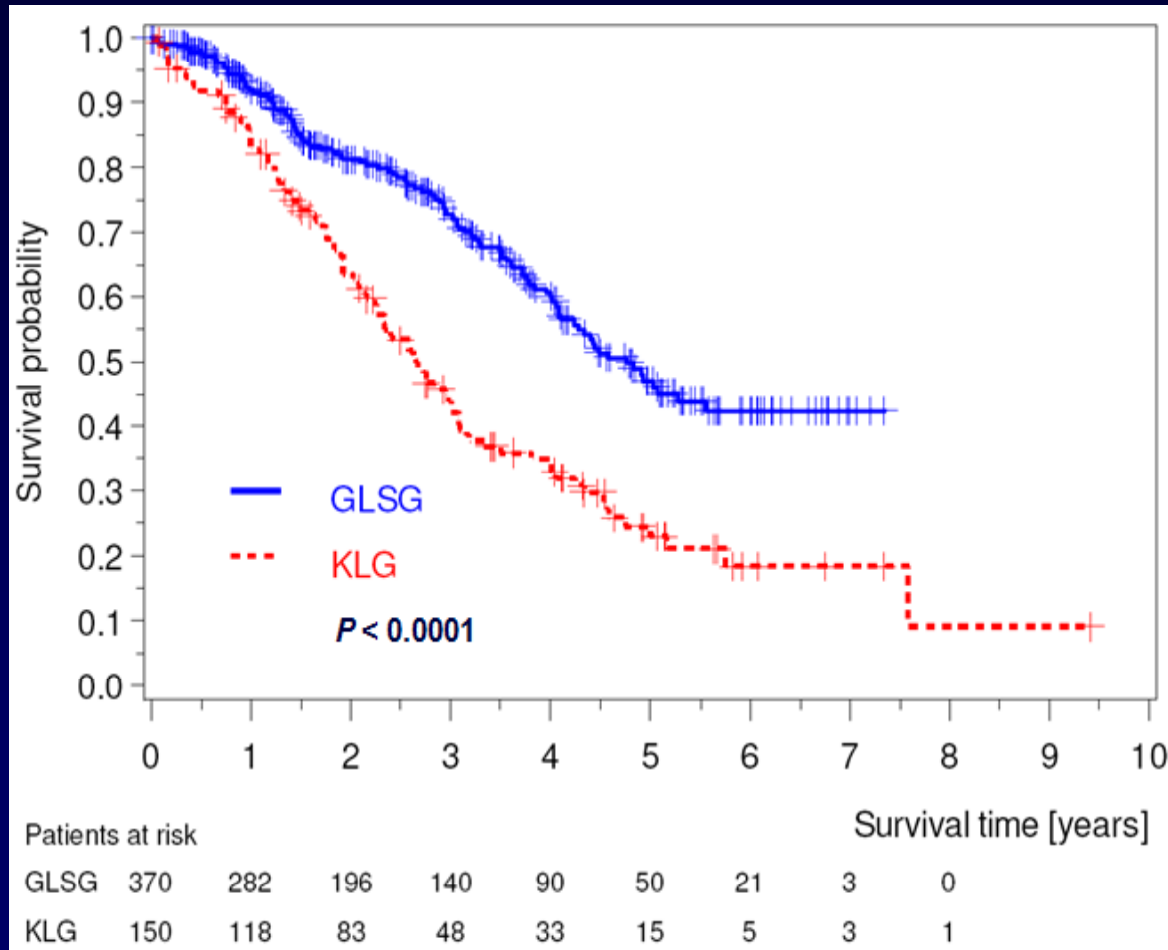
mTOR:

Temsirolimus

# Deferred Initial Treatment in MCL

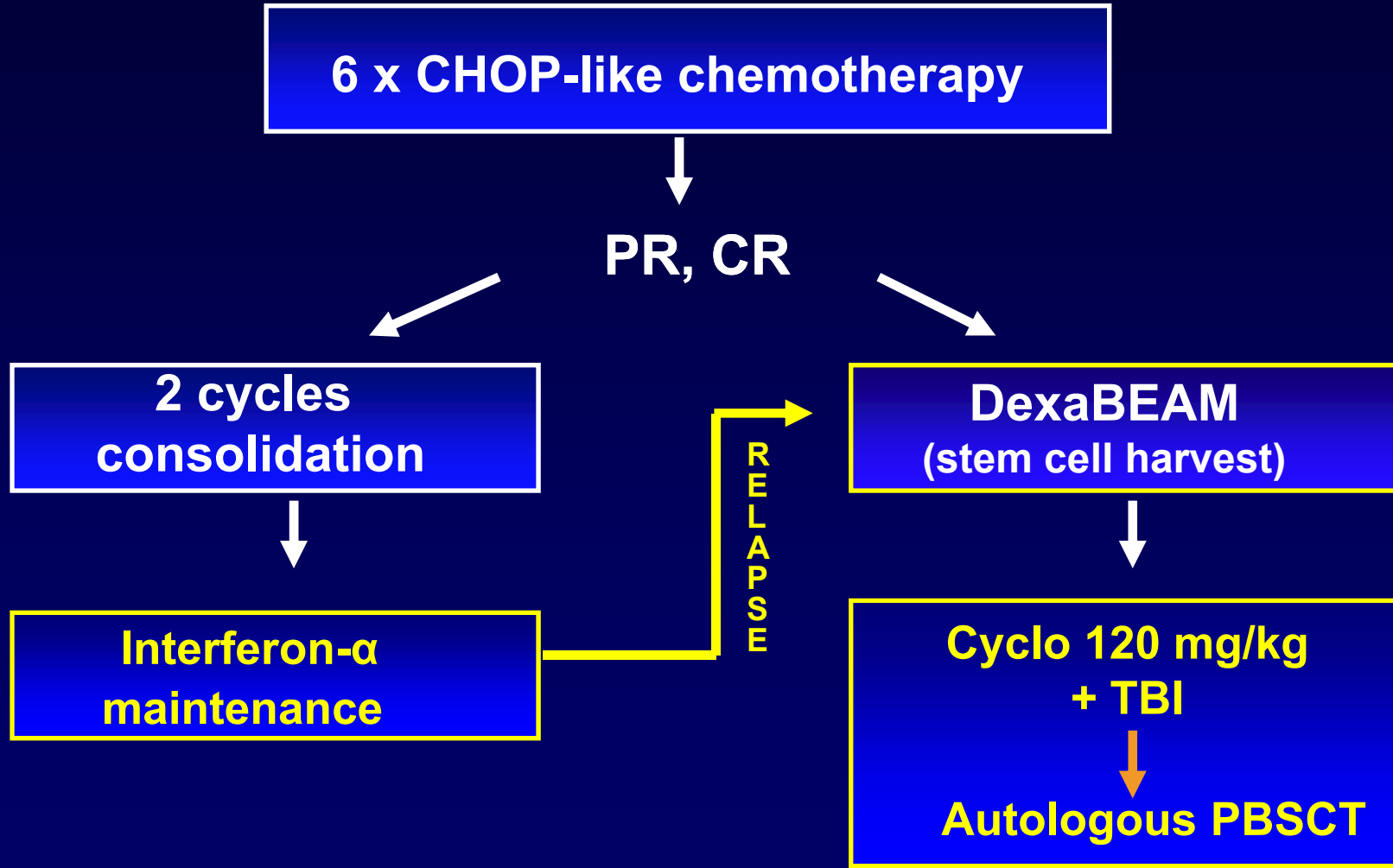
- 97 patients with MCL evaluated at Weill Cornell Medical Center
- 31 patients (32%) were observed for >3 months before initial therapy
  - Median time to treatment of 12 months (range, 4 to 128 months)
- Characteristics of the observation group (median follow-up, 55 months)
  - Median age 58 years, advanced stage (III/IV) in 75%, elevated LDH in 25%
  - Intermediate-risk or high-risk MIPI in 54%
  - Better performance status and lower-risk IPI more commonly
- Although time to treatment did not predict survival in a multivariate analysis, the survival profile of the observation group was statistically superior to that of the early treatment group (not reached v 64 months,  $P = .004$ )
- In selected asymptomatic patients with MCL, deferred initial treatment (“watch and wait”) is an acceptable approach

# Kiel (1975-1986) vs GLSG Cohort (1996-2004) Historical Comparison

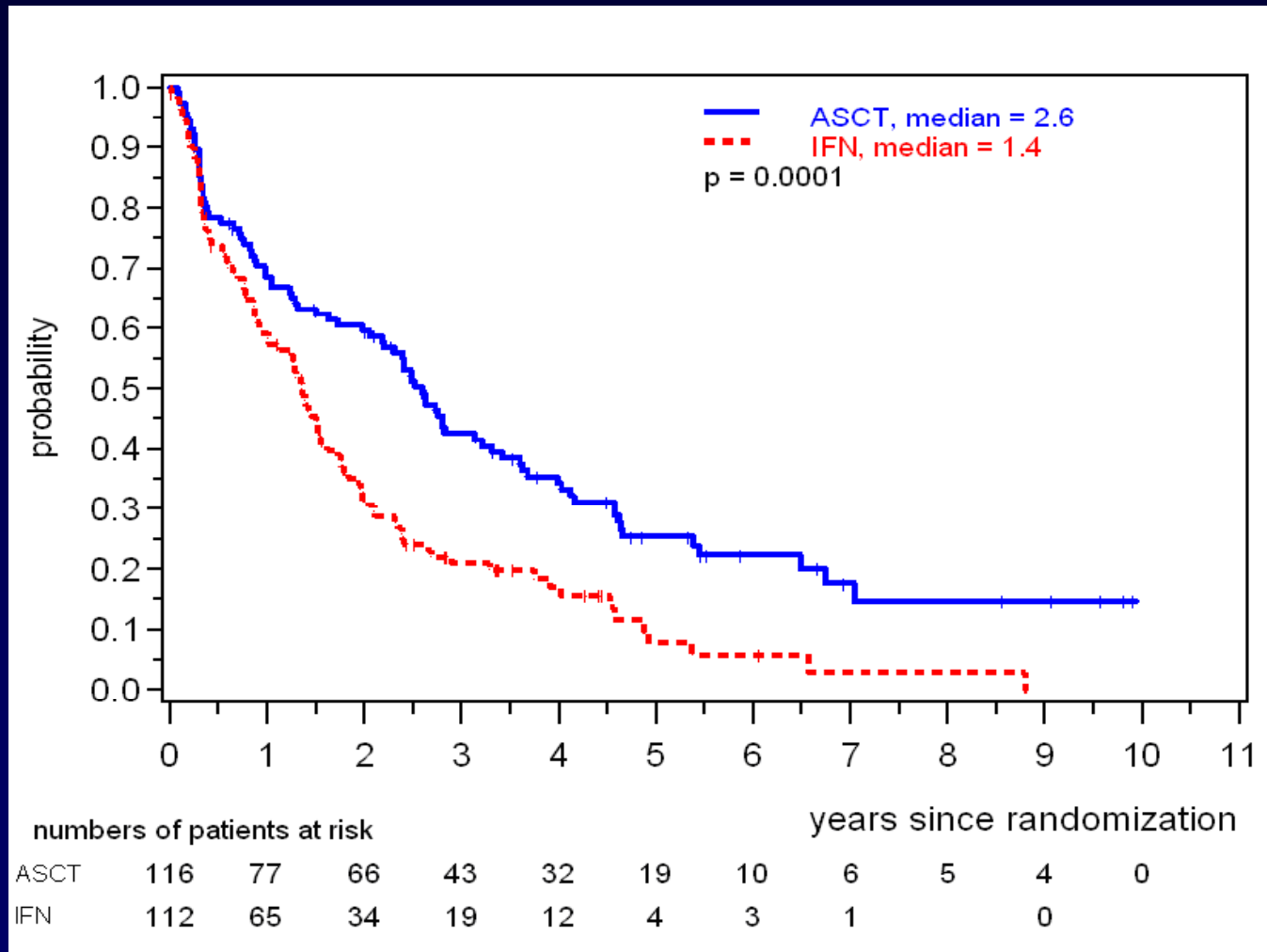


Kiel	GLSG
Age, years	
62	63
No of Patients	
150	370
COP vs CHOP	MCP vs CHOP
	CHOP vs R-CHOP
Median Survival, years	
2.7	4.8

# European MCL Network ASCT vs IFN

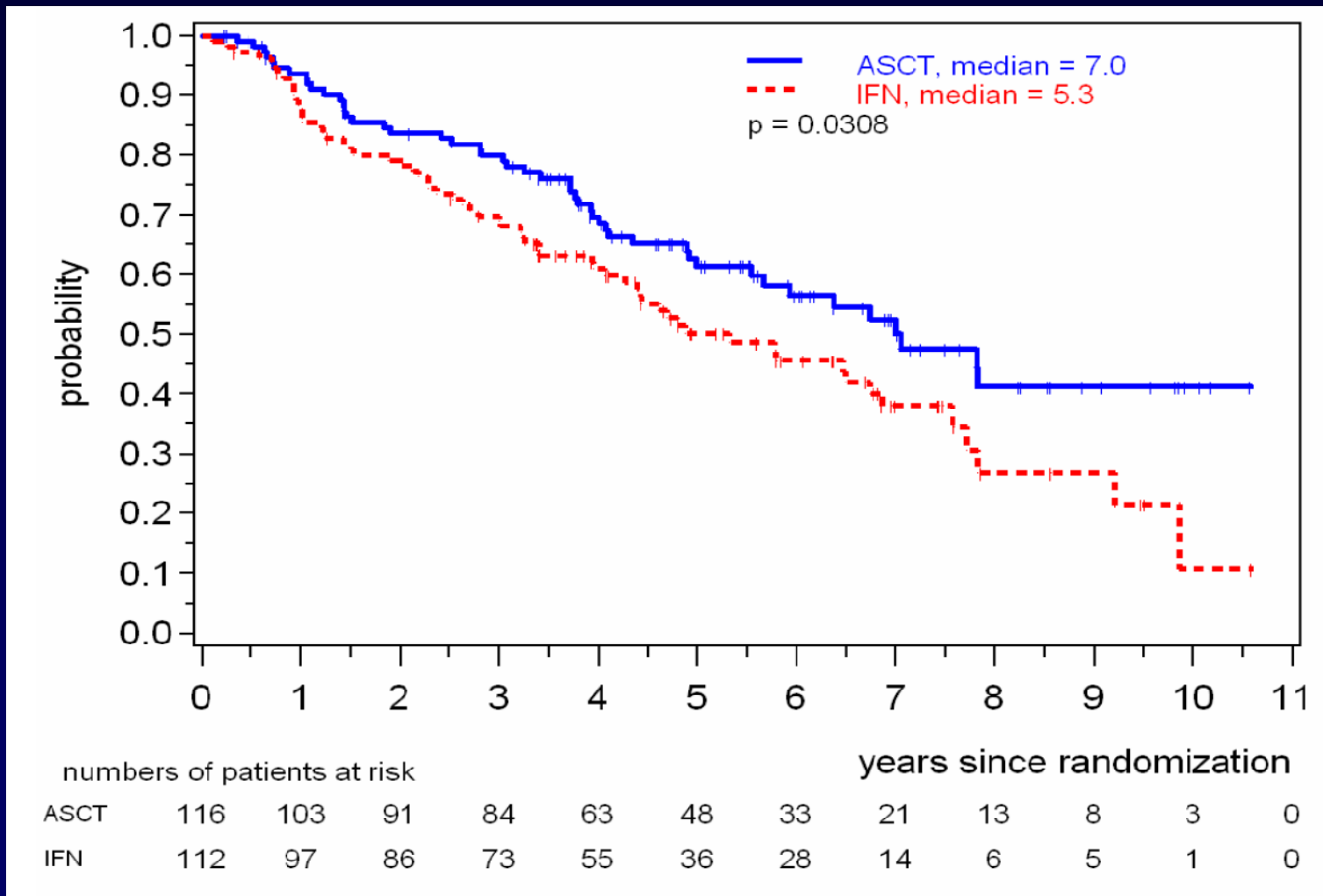


# European MCL Network: ASCT vs IFN Time to Treatment Failure (ITT)



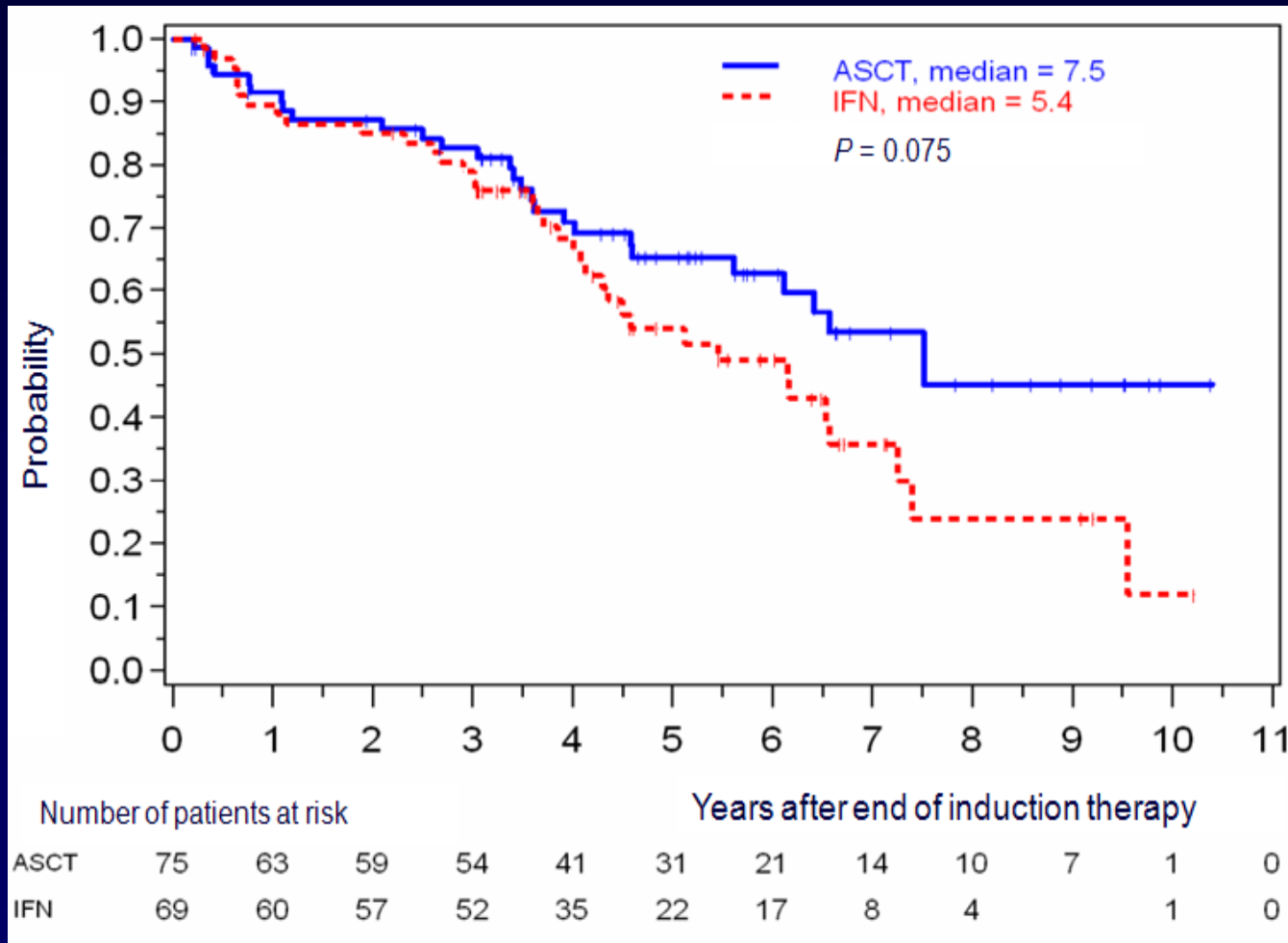
Dreyling M, et al. *Blood*. 2005;105(7):2677-2684 (updated).

# European MCL Network: ASCT vs IFN Overall Survival (ITT)



Dreyling M, et al. *Blood*. 2005;105(7):2677-2684 (updated).

# European MCL Network: ASCT vs IFN Overall Survival (PP)



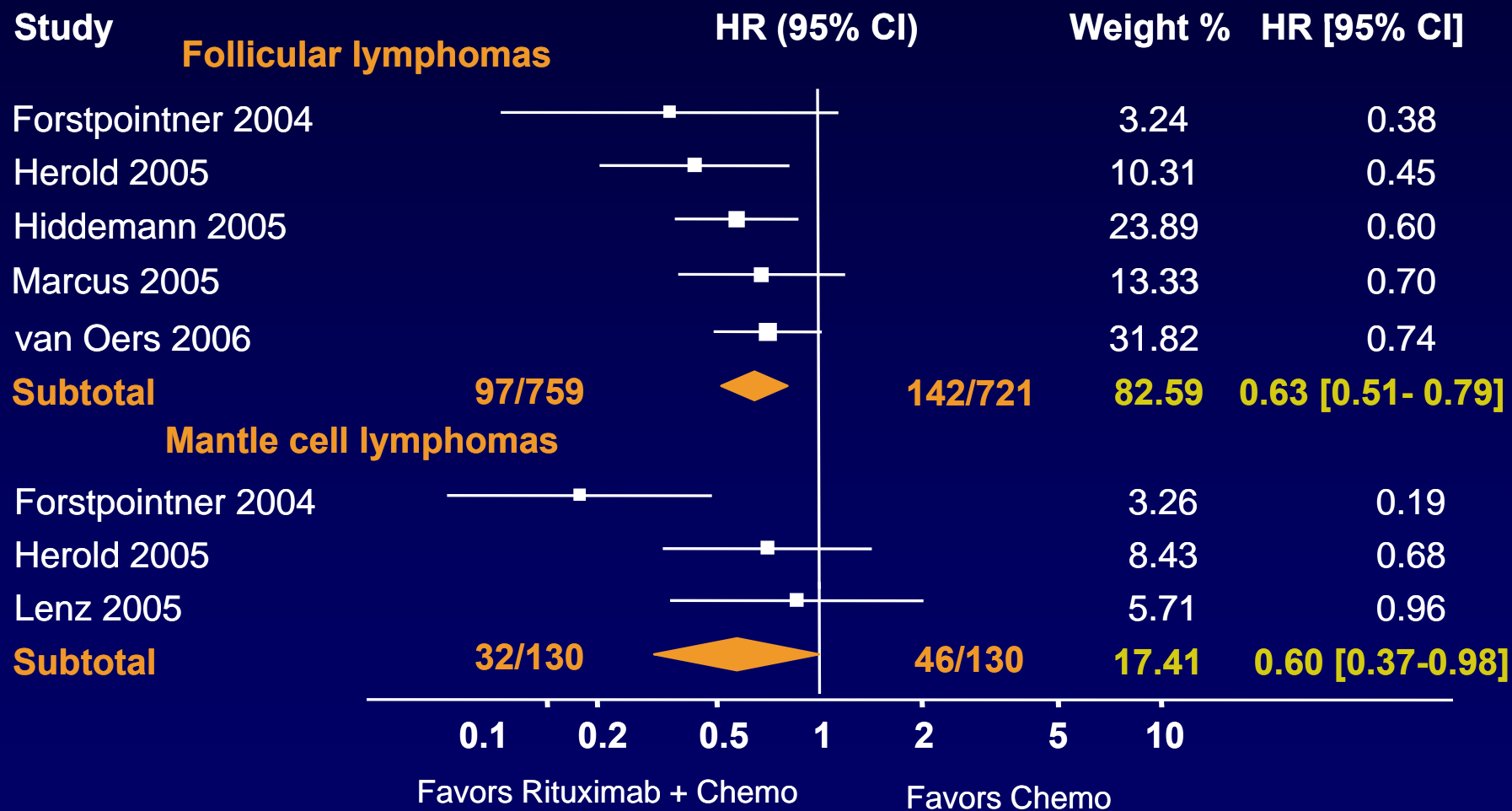
Dreyling M, et al. *Blood*. 2005;105(7):2677-2684 (updated).

# Transplant Setting in MCL

- **Comparison of early consolidation vs conventional maintenance<sup>1</sup>**
  - Consolidation with myeloablative radiochemotherapy followed by ASCT in first remission in MCL
    - Significantly prolonged response duration
    - Trend towards improved overall survival
- **Investigating different induction regimen<sup>2</sup>**
  - R-CHOP and R-DHAP followed by ASCT
    - Regimens containing AraC and rituximab are well tolerated and prolong survival and may even induce cure in patients with MCL

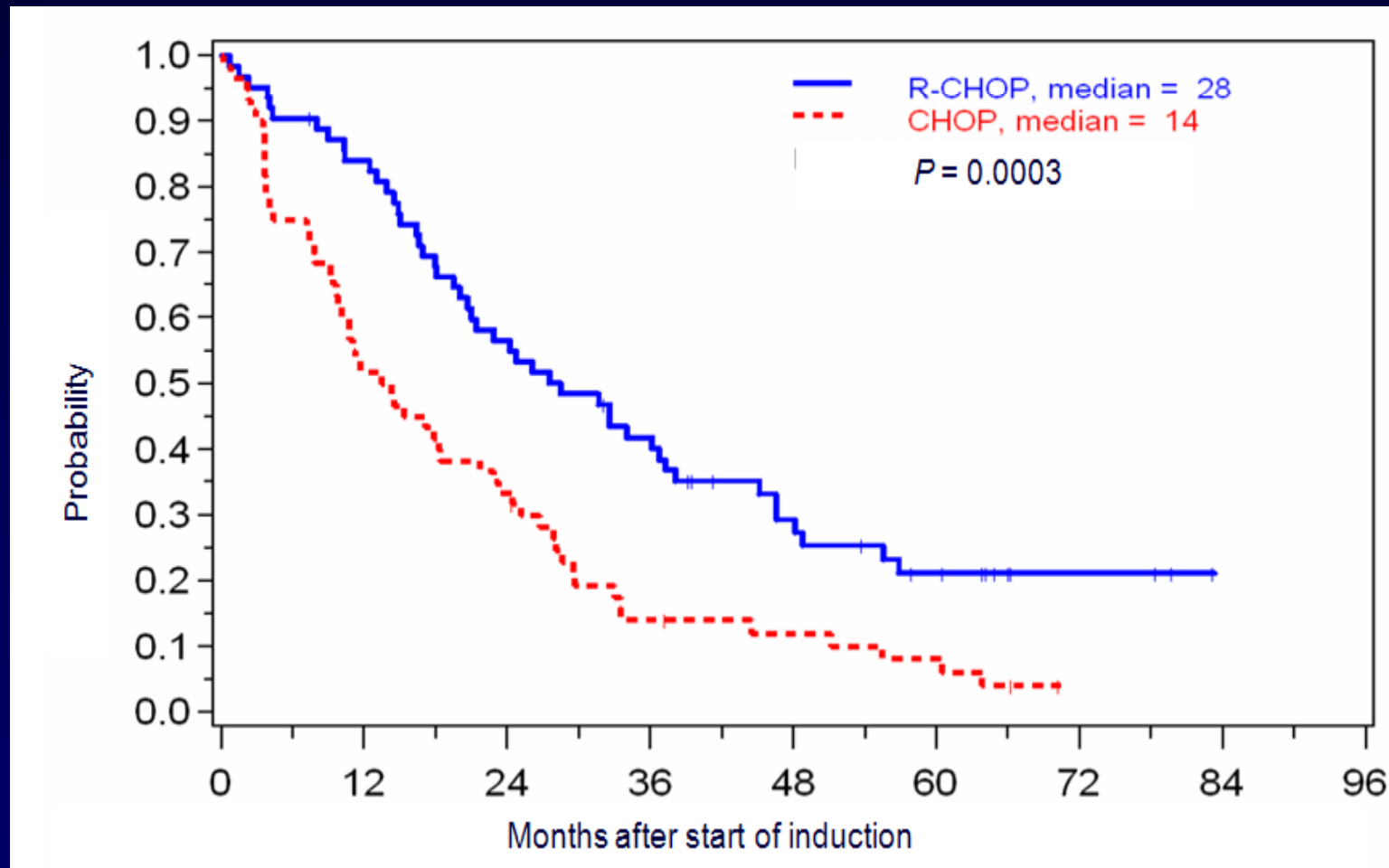
# Cochrane Meta-Analysis—Rituximab in MCL

## Overall Survival (Follicular and Mantle Cell Lymphoma)

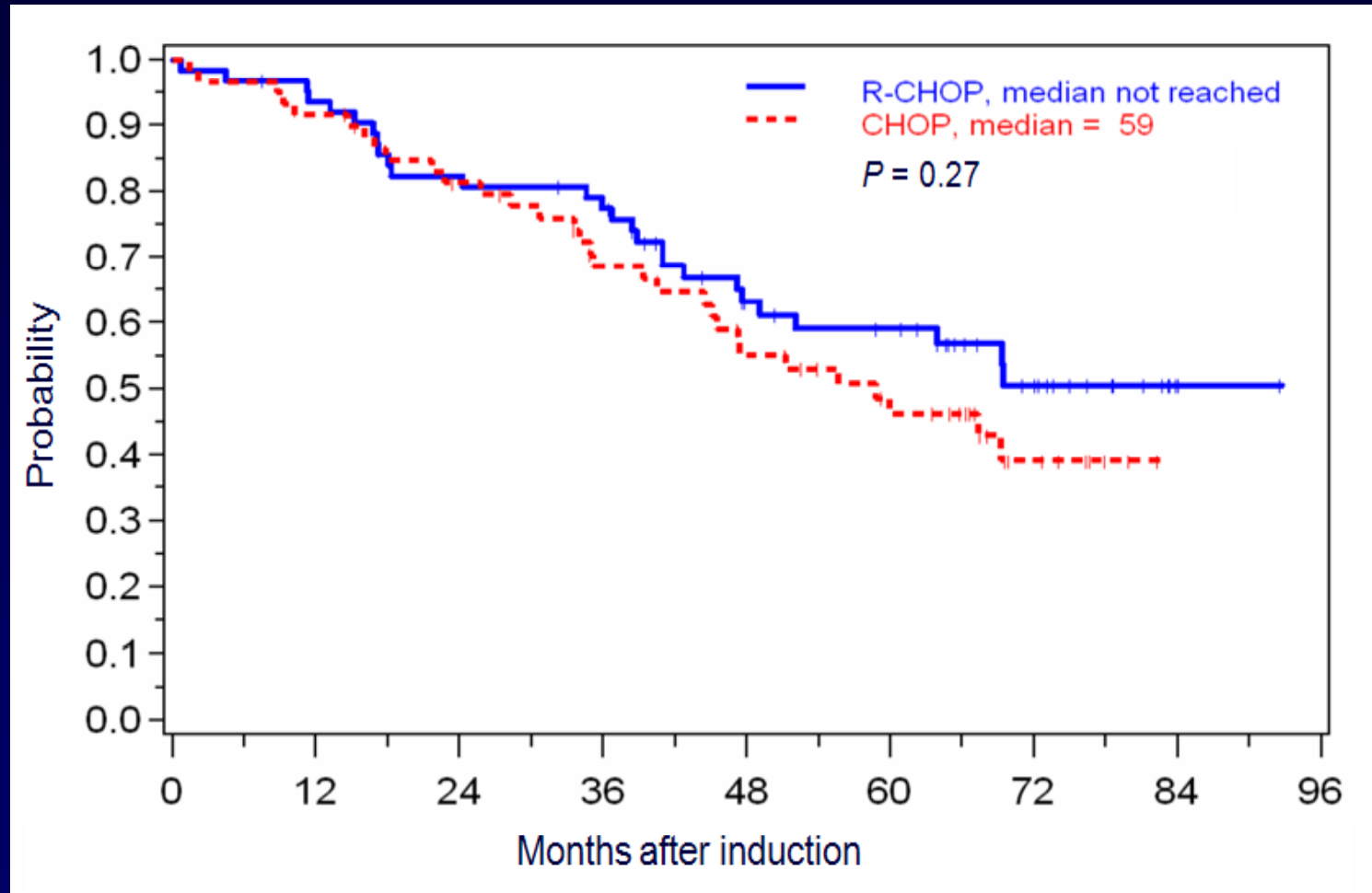


Schulz H, et al. *J Natl Cancer Inst.* 2007;99(9):706-714.

# CHOP vs R-CHOP: MCL—Time to Treatment Failure



# CHOP vs R-CHOP: MCL—Overall Survival



Hoster E, et al. *Blood*. 2008;112: Abstract 3049.

# MRD Assessment in MCL—Work Flow

## National reference labs

- Central sample collection
- 4 color flow of diagnostic blood and BM
- Consensus *IGH*, *t(11;14)* PCR and sequencing
- ASO Primer design
- Large scale RQ-PCR
  - Molecular marker in 90%
  - Sensitive ASO primer 90%
  - 80% quantifiable study patients

# EU-MCL Study Group: Trial Details

## Inclusion Criteria

- Histologically confirmed MCL
- Ann Arbor Stage II – IV
- previously untreated

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graph TD; A[Inclusion Criteria] --> B[EU-MCL Younger Trial]; A --> C[EU-MCL Elderly Trial];
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EU-MCL Younger Trial  
<65 years and eligible  
for high-dose therapy

R-CHOP vs R-CHOP / R-DHAP  
plus TBI and PBSCT

EU-MCL Elderly Trial  
>65 years or 60-65 years and  
not eligible for high-dose therapy

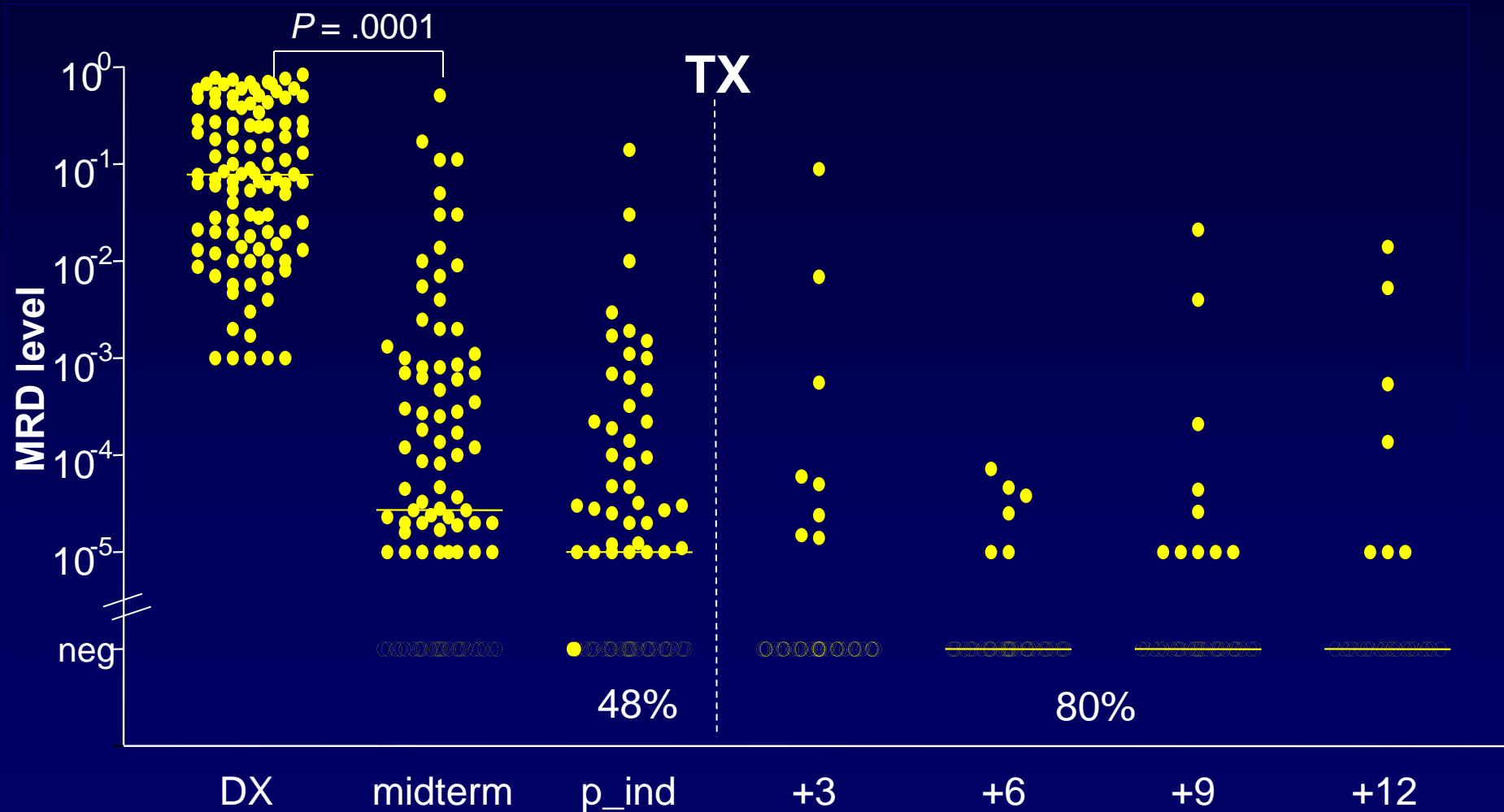
R-CHOP vs R-FC  
plus IFN or rituximab maintenance

# European MCL Network Molecular Remission After Induction

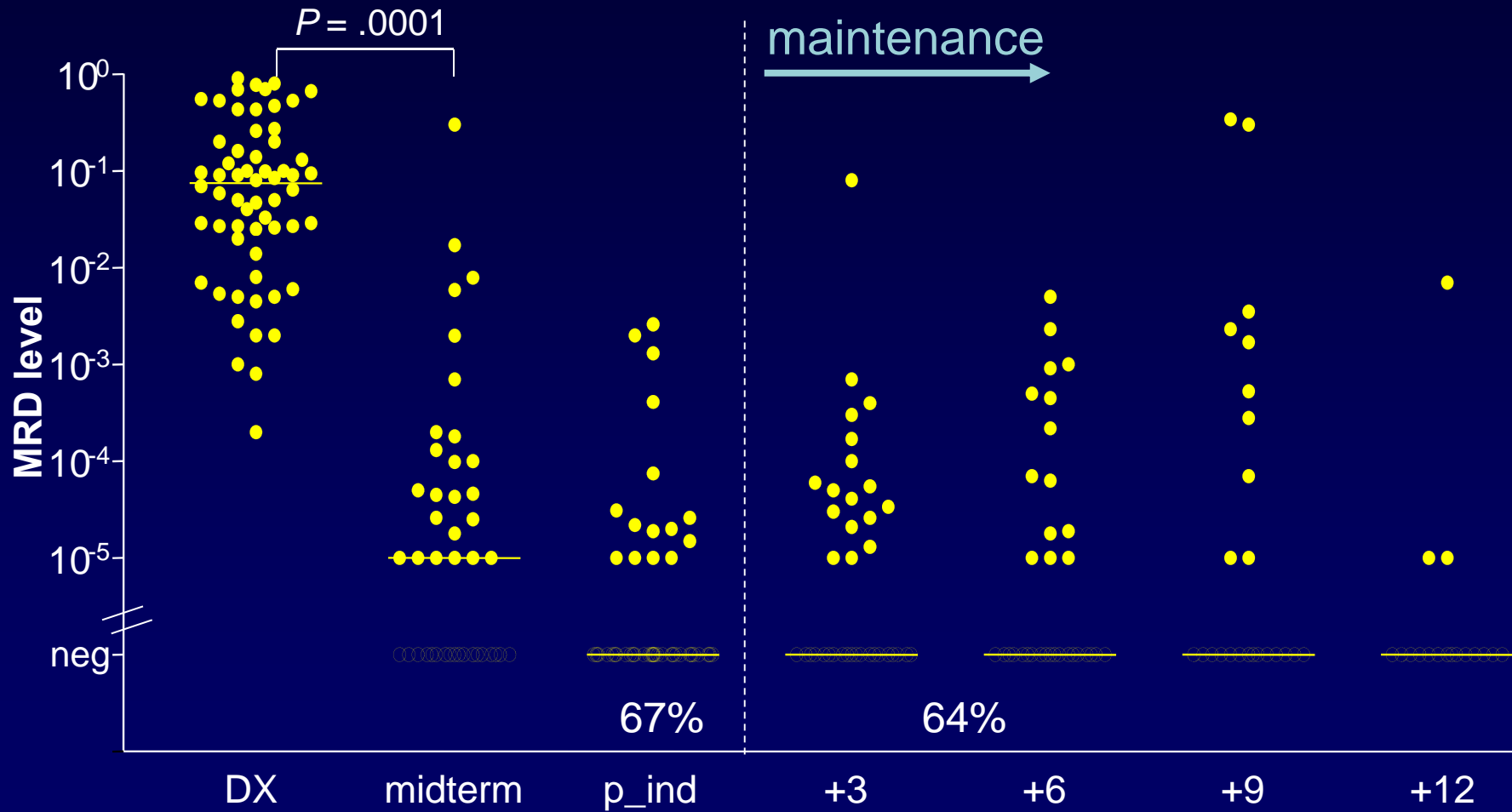
N = 190

	RR	CR	MRD-	MRD+	N
Younger	91%	34%	52 (48%)	57 (52%)	109
Elderly	84%	32%	54 (67%)	27 (33%)	81
Overall			106 (56%)	84 (45%)	190

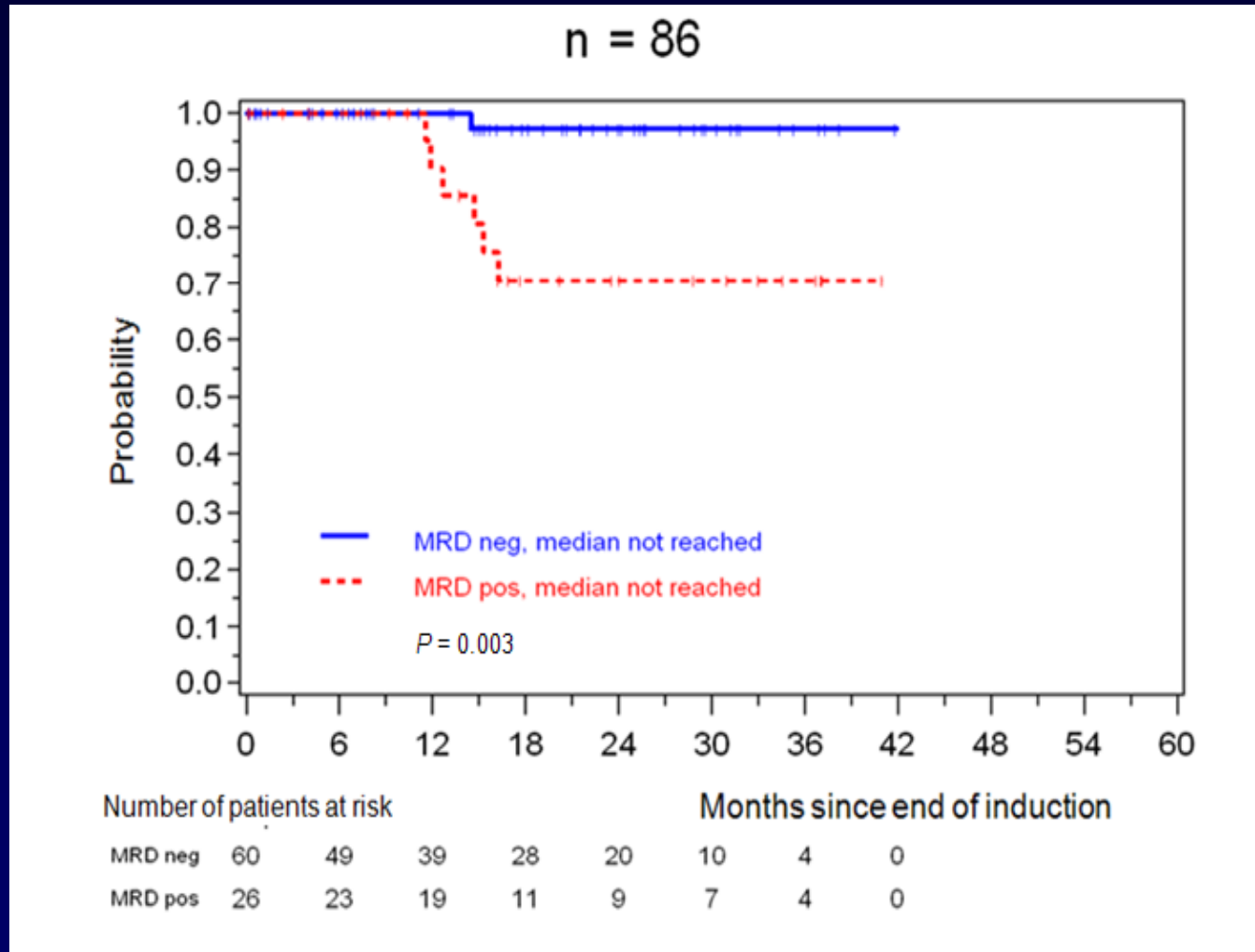
# MRD Detection in MCL—Follow-Up Younger Patients (n = 109)



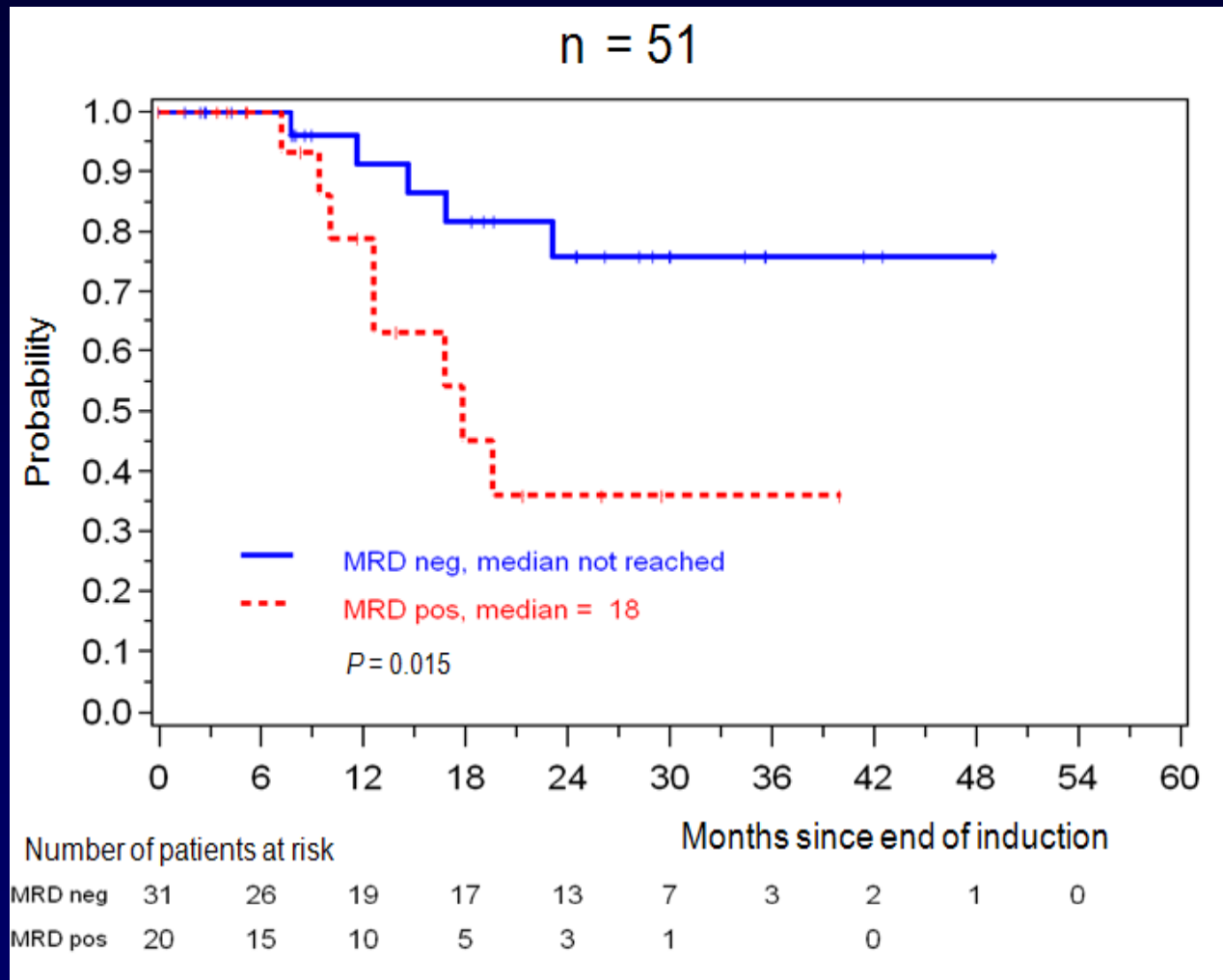
# MRD Detection in MCL—Follow-Up Elderly Patients (n = 81)



# Remission Duration According to MRD Status After ASCT—Younger Patients



# Remission Duration According to MRD Status During Maintenance—Elderly Patients





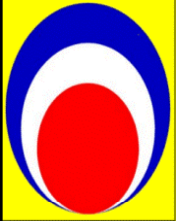
# Nordic Lymphoma Group MCL2 Trial

[www.nordic-lymphoma.org](http://www.nordic-lymphoma.org)

**Long-term progression-free survival in mantle cell lymphoma following front-line intensive immunochemotherapy with *in vivo* purged stem-cell support**

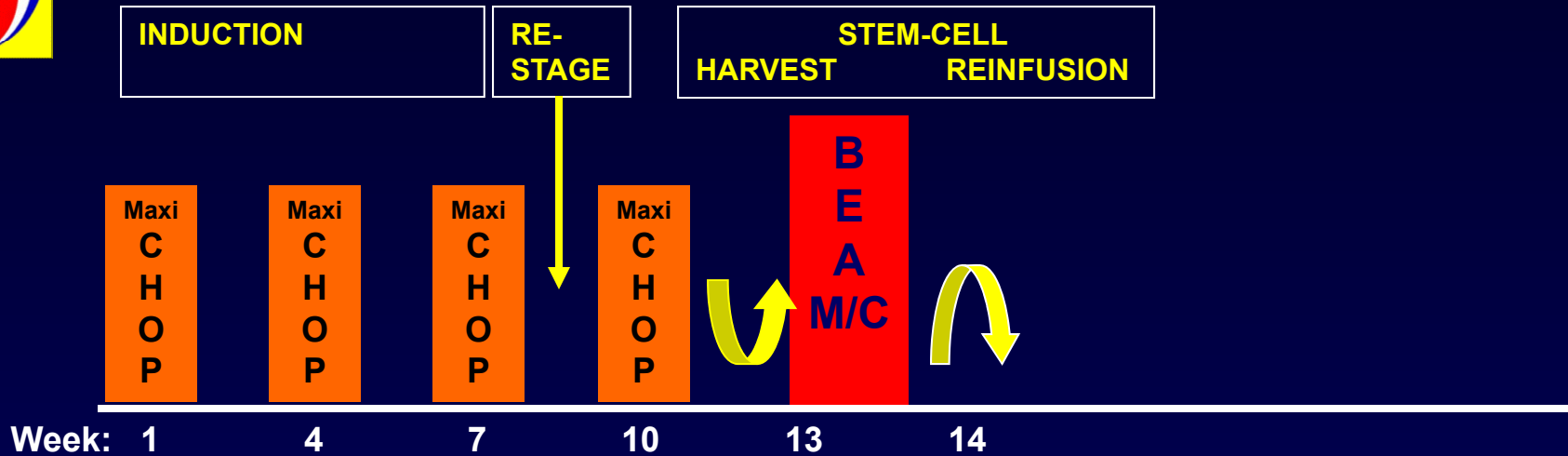
Using the MCL1 (previous nordic MCL trial) results as historic control **Rituximab** plus **high-dose AraC** was included in the MCL-2 protocol aiming to improve:

EFS, PFS, OS, and the proportion of PCR-negative stem cell products

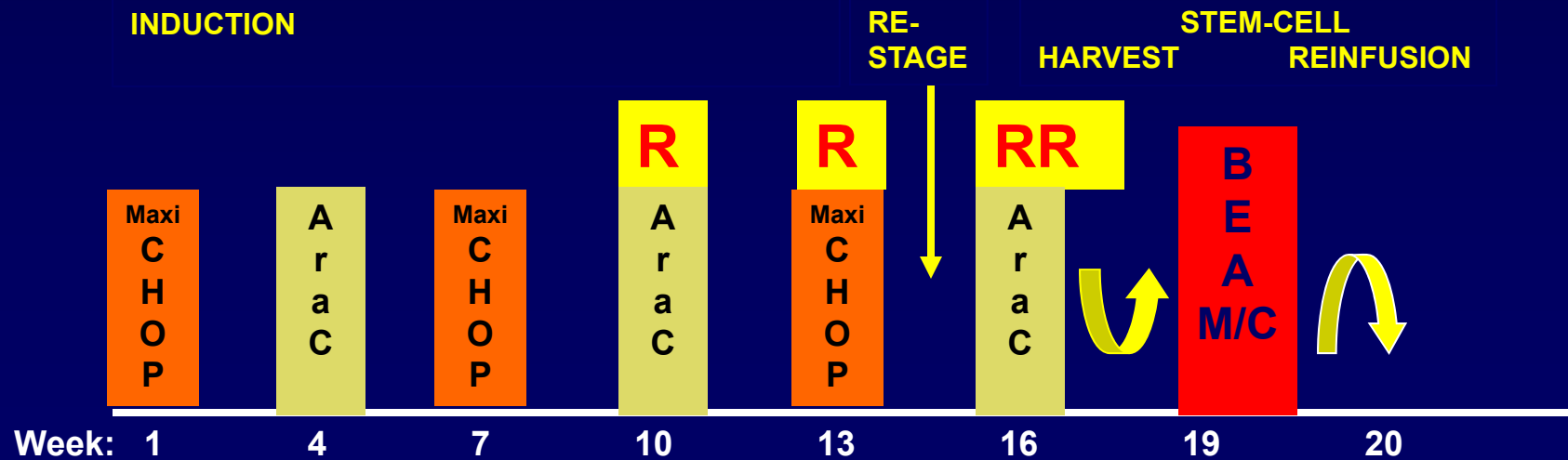


Treatment:

# MCL-1 TRIAL 1996-2000



# MCL-2 TRIAL 2000-2006



AraC: 4 Infusions:  $\leq 60$  years  $3 \text{ g/m}^2$ ,  $> 60$  years  $2 \text{ g/m}^2$

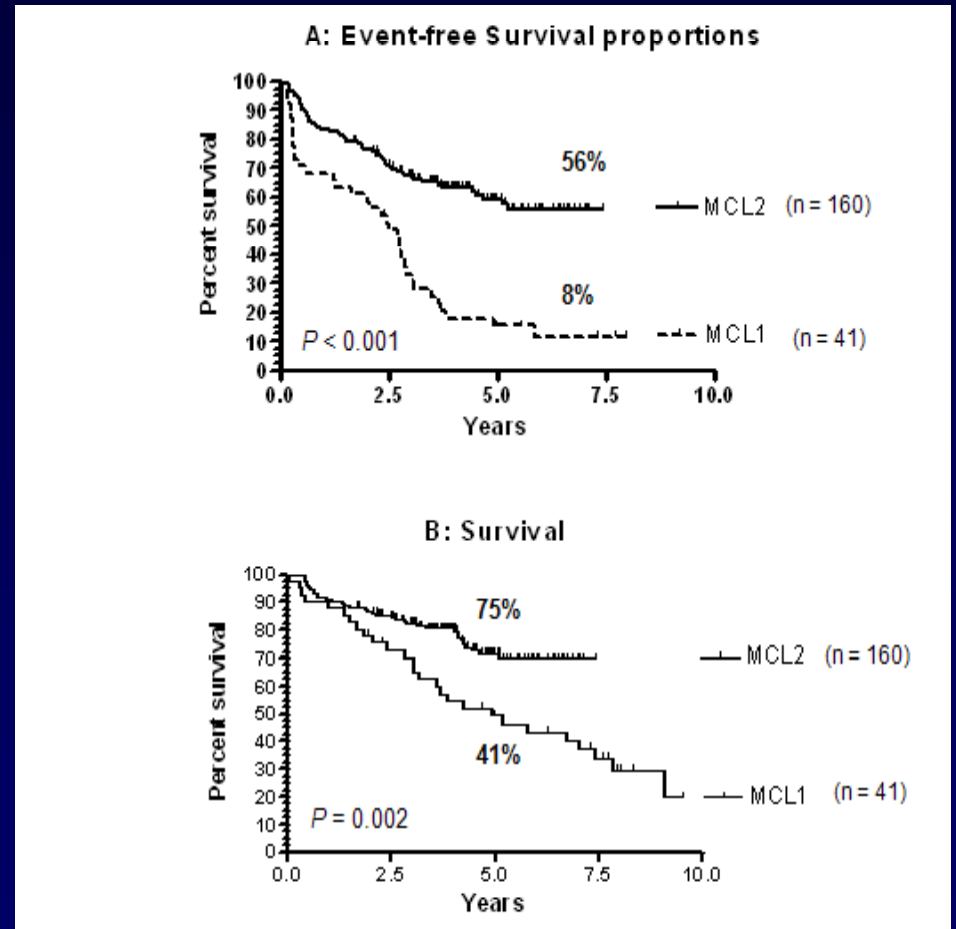


# Nordic MCL Project

## EFS and OS as an Intent-to-Treat Analysis

<b>Events:</b>	<b>61 (38%)</b>
<b>Relapse/PD</b>	<b>48 (30%)</b>
<b>Non-relapse events</b> Off due to: Toxicity 7 Harv. fail. 4 Graft fail.1 Pulm emb 1	<b>13 (8%)</b>

<b>Deaths:</b>	<b>39 (24%)</b>
<b>Lymphoma</b>	<b>31</b>
<b>Non-relapse deaths</b> Infection 3 Vasc. Inc.2 Graft fail. 1 Pulm. emb. year + 5: 1	<b>8 →</b> <b>NRM: 5%</b>



# **Bendamustine Plus Rituximab Versus CHOP Plus Rituximab in the First-Line Treatment of Patients with Indolent and Mantle Cell Lymphoma – Final Results of a Randomized Phase III Study of the StiL (Study Group indolent Lymphomas, Germany)**

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**Mathias J. Rummel, N. Niederle, G. Maschmeyer, G. A. Banat, U. von Grünhagen,  
C. Losem, G. Heil, M. Welslau, C. Balsler, U. Kaiser, H. Ballo, E. Weidmann,  
H. Dürk, D. Kofahl-Krause, F. Roller, J. Barth, D. Hoelzer, A. Hinke,  
and W. Brugger**

**on behalf of the StiL**



## B-R vs CHOP-R—Hematotoxicity Grades 3+4

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

# B-R vs CHOP-R—Toxicities

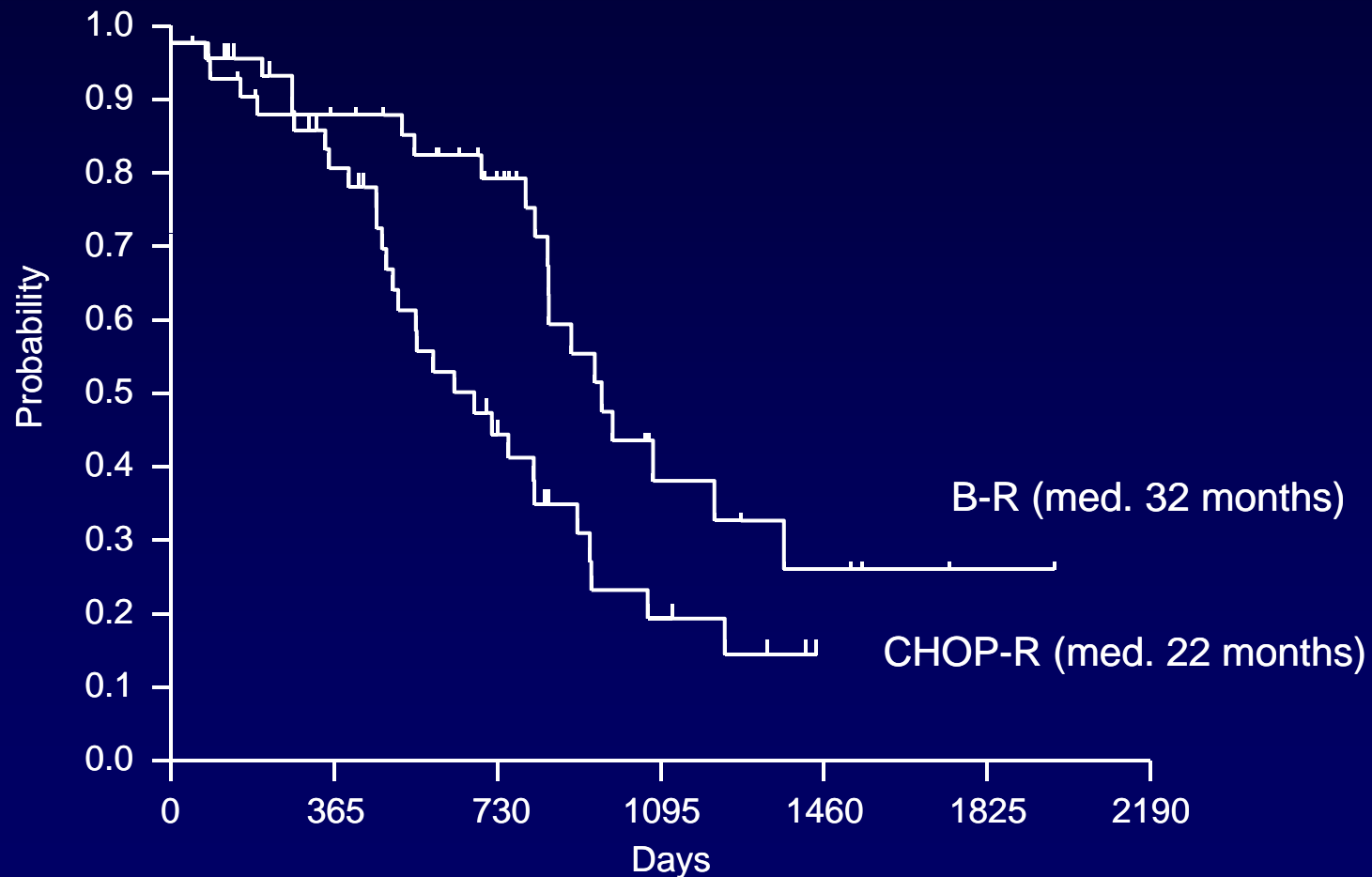
(all CTC-grades)

	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: B-R vs CHOP-R

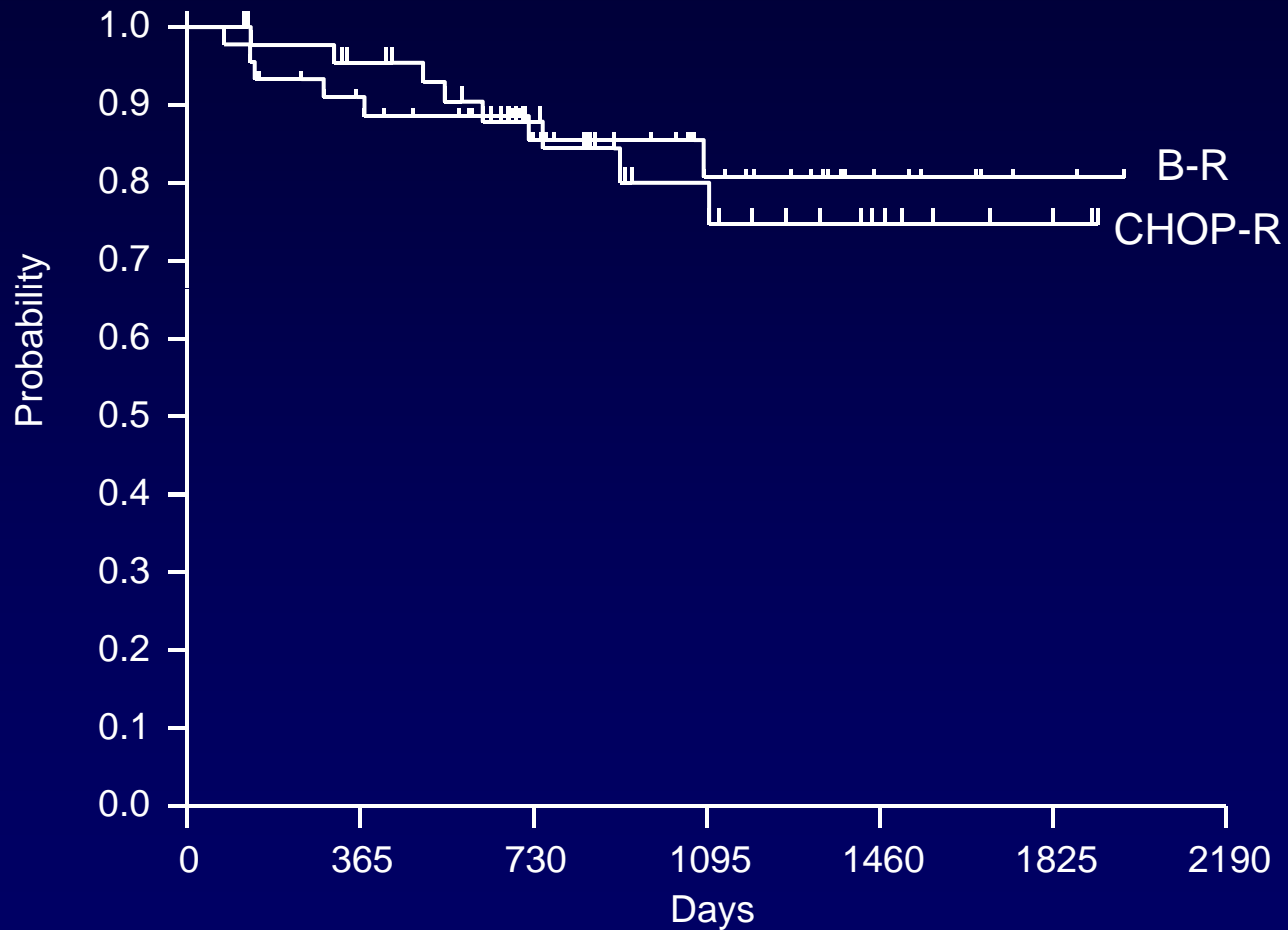
	B-R (n = 45)	CHOP-R (n = 47)
Age (median)	71	67
ORR	91%	96%
CR	32%	34%
SD	7%	2%
Prim. Refractory	2%	2%
PD/relapse	n = 20	n = 29
Deaths	n = 7	n = 8

# PFS for Mantle Cell Lymphoma: B-R vs CHOP-R



Rummel MJ, et al. *Blood*. 2008;112: Abstract 2596.

# OS for Mantle Cell Lymphoma: B-R vs CHOP-R



Rummel MJ, et al. *Blood*. 2008;112: Abstract 2596.

# B-R + Watch & Wait vs B-R + 2 Years Rituximab

## Randomized Phase II Study of the StiL

Mantle cell  
(not eligible for APBSCT)



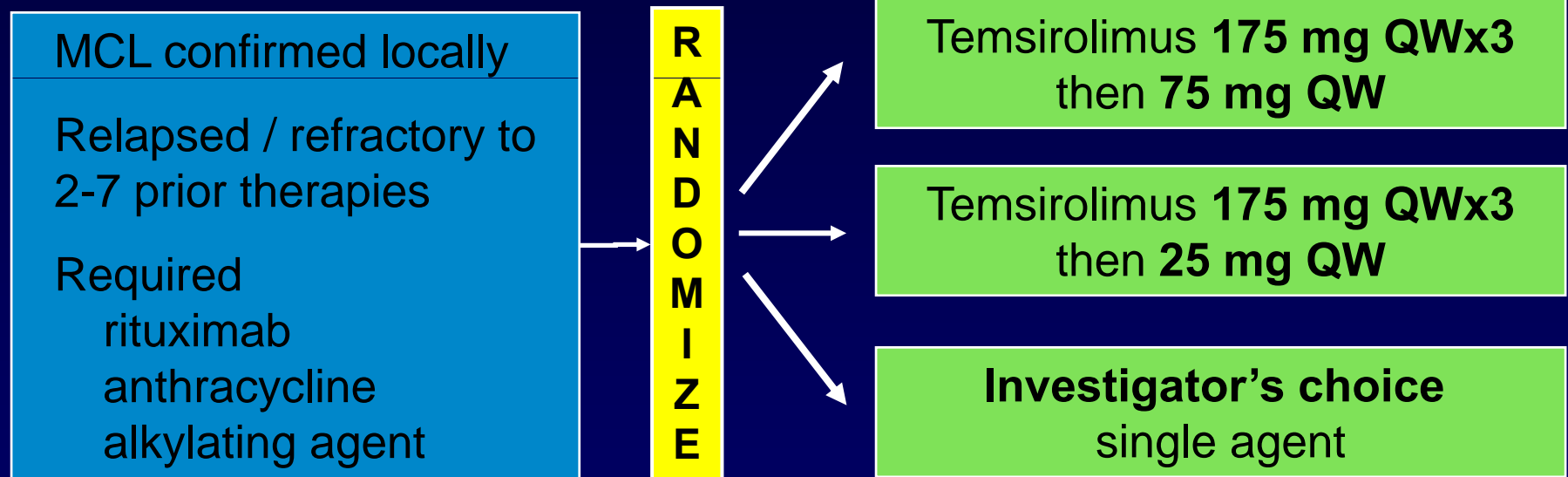
Bendamustine-  
Rituximab  
+ Watch & Wait

Bendamustine-Rituximab  
+ 2 years Rituximab  
q 2 months



# Phase III Study of Temsirolimus Compared With Investigator's Choice in Relapsed, Refractory MCL

## Study Design

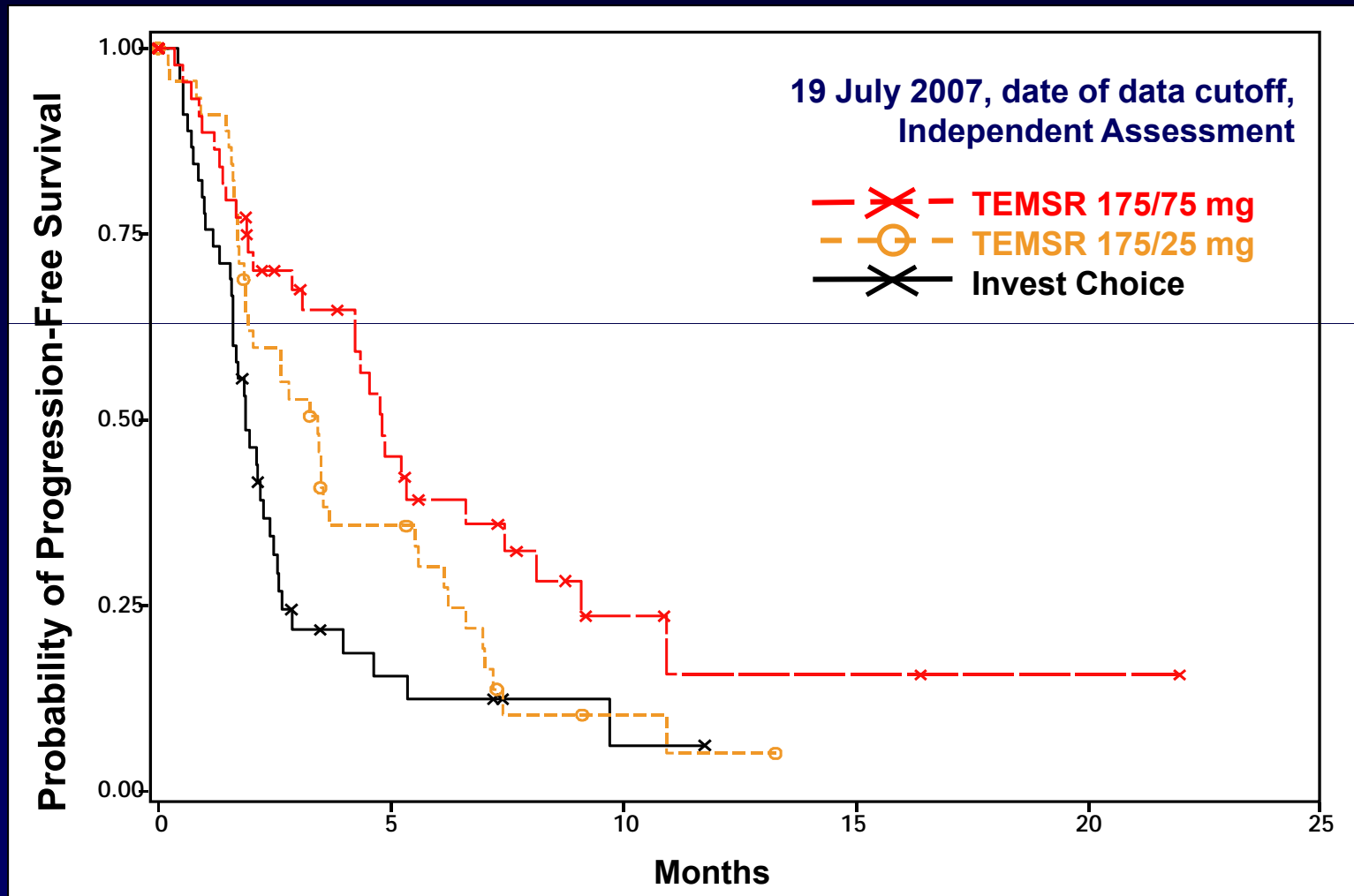


—————→  
Temsirolimus treatment to continue until progression, death, or unacceptable toxicity

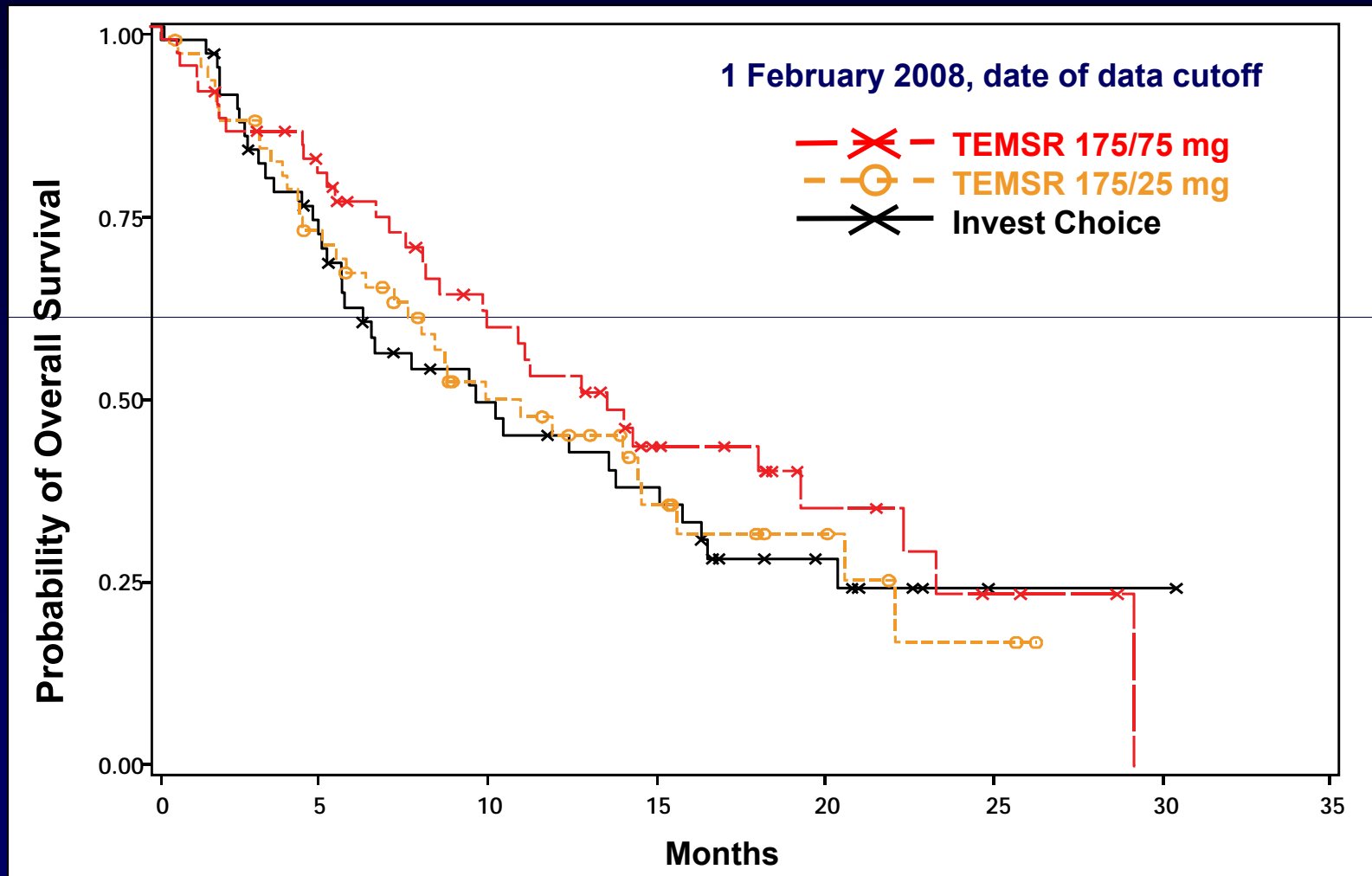
# Response Rates and Duration (ITT)

	TEMSR 175/75 n = 54	TEMSR 175/25 n = 54	Invest Choice n = 54
<b>Objective response rate</b>	<b>22%</b>	<b>6%</b>	<b>2%</b>
<b>95% CI for response rate</b>	<b>11 - 33</b>	<b>0 - 12</b>	<b>0 - 5</b>
<b>P value</b>	<b>.0019</b>	<b>.6179</b>	
<b>Complete response, n</b>	<b>1</b>	<b>0</b>	<b>1</b>
<b>Partial response, n</b>	<b>11</b>	<b>3</b>	<b>0</b>
<b>Duration of response, median (95% CI), mo</b>	<b>7.1 (4.1 - NA)</b>	<b>3.6 (3.2 - 10.6)</b>	<b>NA</b>

# Progression-Free Survival (ITT Population)



# Overall Survival (ITT Population)



# Temsirolimus

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Median PFS 4.9 months, which was 2.9 months longer than with standard of care (SOC)

No survival difference against SOC

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Costs of therapy (1.253 mg)	Euro
First month of treatment	58.755
Each consecutive month	23.502
Mean total dose in the study	98.160
Calculated costs per year	317.277

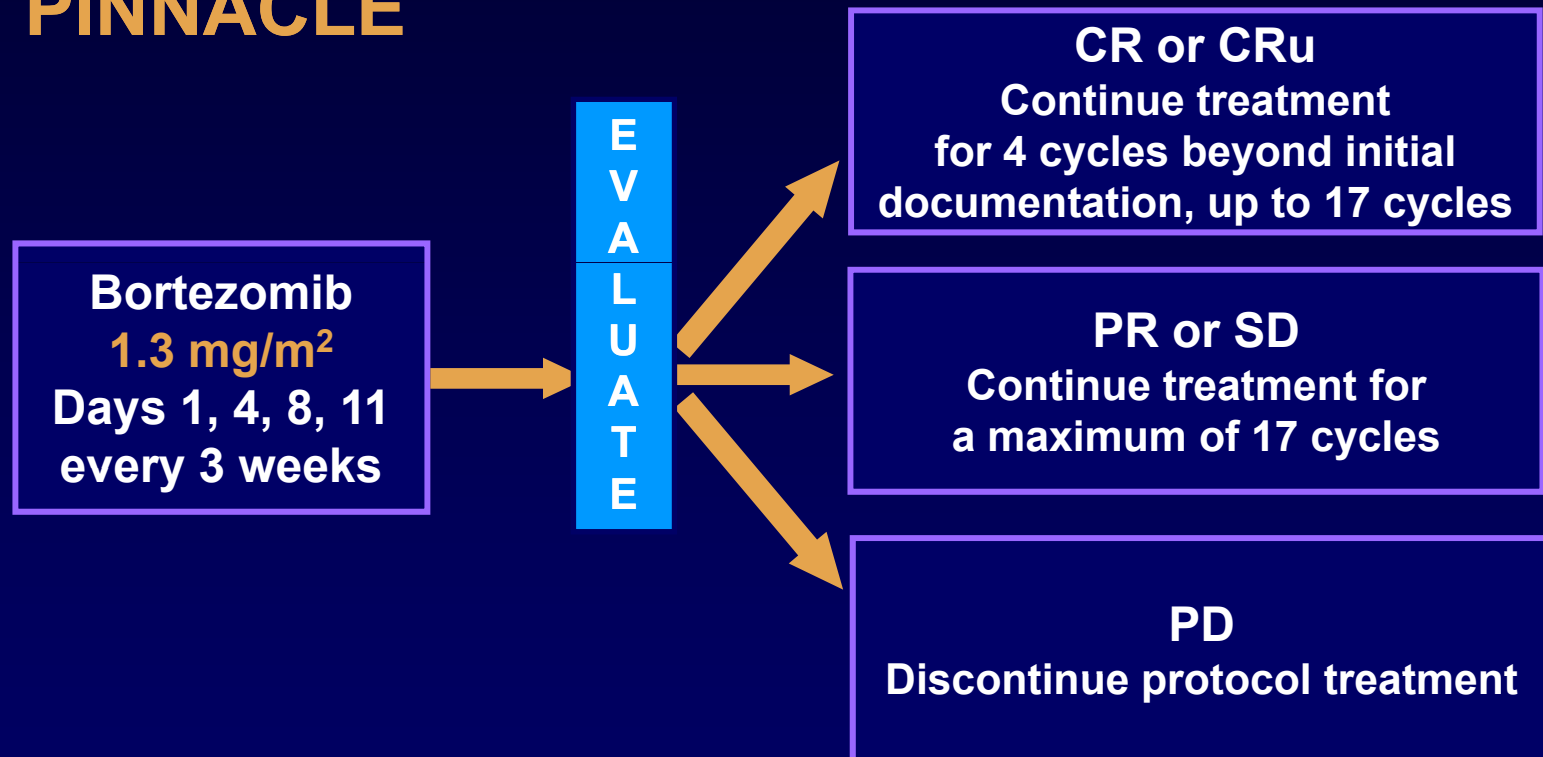
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# Single-Agent Bortezomib in Mantle Cell Lymphoma

Study	Bortezomib Regimen	Evaluable Pts (n)	CR/CRu	PR	ORR
O'Connor (JCO 2005; ICML 2005)	1.5 mg/m <sup>2</sup> days 1, 4, 8, 11 21-day cycle	37	14%	27%	41%
Goy (JCO 2005)	1.5 mg/m <sup>2</sup> days 1, 4, 8, 11 21-day cycle	29	21%	21%	41%
Strauss (JCO 2006)	1.3 mg/m <sup>2</sup> days 1, 4, 8, 11 21-day cycle	24	4%	25%	29%
Belch (Ann Onc 2007)	1.3 mg/m <sup>2</sup> days 1, 4, 8, 11 21-day cycle	28	4%	43%	46%
Fisher (JCO 2006)	1.3 mg/m <sup>2</sup> days 1, 4, 8, 11 21-day cycle	141	8%	26%	33%

# Bortezomib in Relapsed or Refractory MCL

## PINNACLE



Enrollment completed in June 2005 (N = 155)  
35 centers in the US, UK, and Germany

# Bortezomib in Relapsed or Refractory MCL

Best Response (n = 141)	Algorithm* n (%)	Investigator n (%)
CR	9 (6%)	8 (6%)
CRu	2 (1%)	3 (2%)
PR	36 (26%)	46 (33%)
ORR	47 (33%) <sup>†</sup>	57 (40%)

\*Response, date of response, and PD were determined by a computer algorithm that applied the IWRC (Cheson criteria) and using tumor measurements from an independent radiology review. <sup>†</sup>ORR reported in the prescribing information is based on the ITT population (n = 155).

— Median time to 1<sup>st</sup> response: 1.3 months (within 2 cycles, rapid onset)

# Bortezomib in Relapsed or Refractory MCL

## DOR, TTP, and Survival

Parameter	Algorithm	Investigator
DOR, mos	9.2	8.9
CR/CRu	13.5	15.5
TTP, mos	6.2	6.2
CR/CRu	14.6	18.2
Median OS, mos*		NYR
Estimated 1-year survival*		69%
CR/CRu/PR	94%	94%
CR/CRu	100%	100%

**Median follow-up of 13.4 months, 103/155 (66%) were alive**

**Durable Responses After Lenalidomide Oral  
Monotherapy in Patients with Relapsed or  
Refractory DLBCL, MCL, FL III, T-NHL:  
Results From 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**

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

<b>Median age</b>	<b>69 (21-87)</b>
<b>Median time since diagnosis, years (range)</b>	<b>2.7 (0.04 – 20.6)</b>
<b>Median no of prior therapies, n (range)</b>	<b>3 (1-13)</b>
<b>Rituximab pretreated, n (%)</b>	<b>94 (205/217)</b>

# Results

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

# Lenalidomide Plus Rituximab in MCL

## Rationale:

- Both lenalidomide and rituximab have activity as single agents in MCL

## Regimen and patients:

- Rituximab and lenalidomide (10 mg, 15 mg, 20 mg, and 25 mg)
- Median age 66 years; 91% males; with prior rituximab exposure

## Results: (median follow-up 12 months; 36 patients evaluable)

- Two DLTs occurred at 25 mg; MTD was 20 mg
- ORR 53%; 78% achieved stable disease or better
- Median duration of response was 18 months; PFS was 14 months

## Conclusions:

- Lenalidomide plus rituximab resulted in durable responses in relapsed/refractory MCL with a favourable toxicity profile

## Summary and Conclusions. How I Would Treat

- Survival almost doubled within the past 3 decades, even though MCL is still considered to be a noncurable disease
- Progress has been achieved by intensification of therapy
  - Anthracycline containing
  - Rituximab
  - High-dose cytarabine } Eg, Nordic lymphoma treatment approach
  - Stem cell transplantation
- Achievement of a molecular response is a major favorable prognostic indicator, regardless of treatment
- Bendamustine is well tolerated and shows promising activity in the elderly patient subgroup in combination with rituximab
- Bortezomib, temsirolimus, lenalidomide need to be studied further