

Hannover-Meeting 2009

Niedrig-malignes NHL



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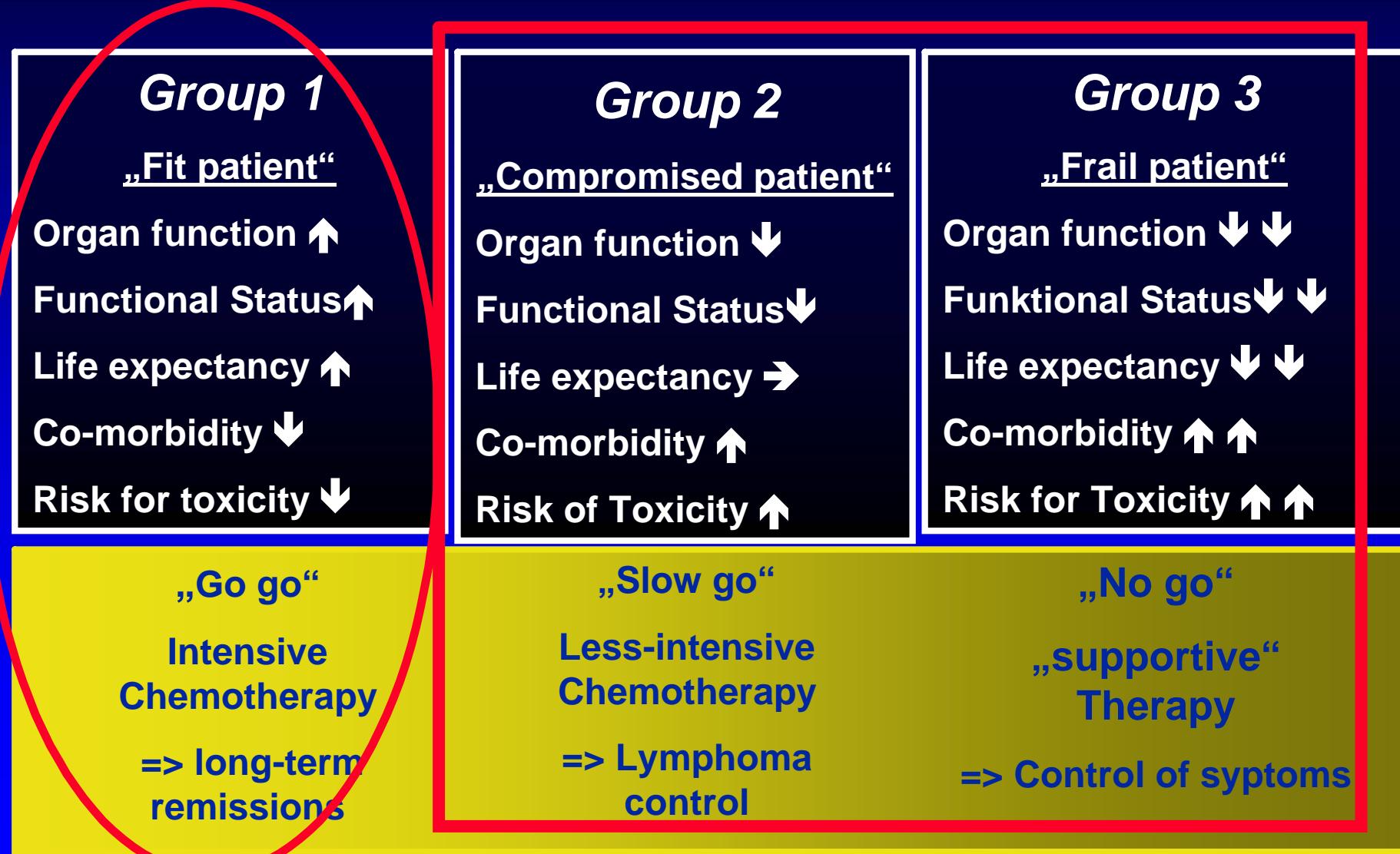


Follikuläres Lymphom

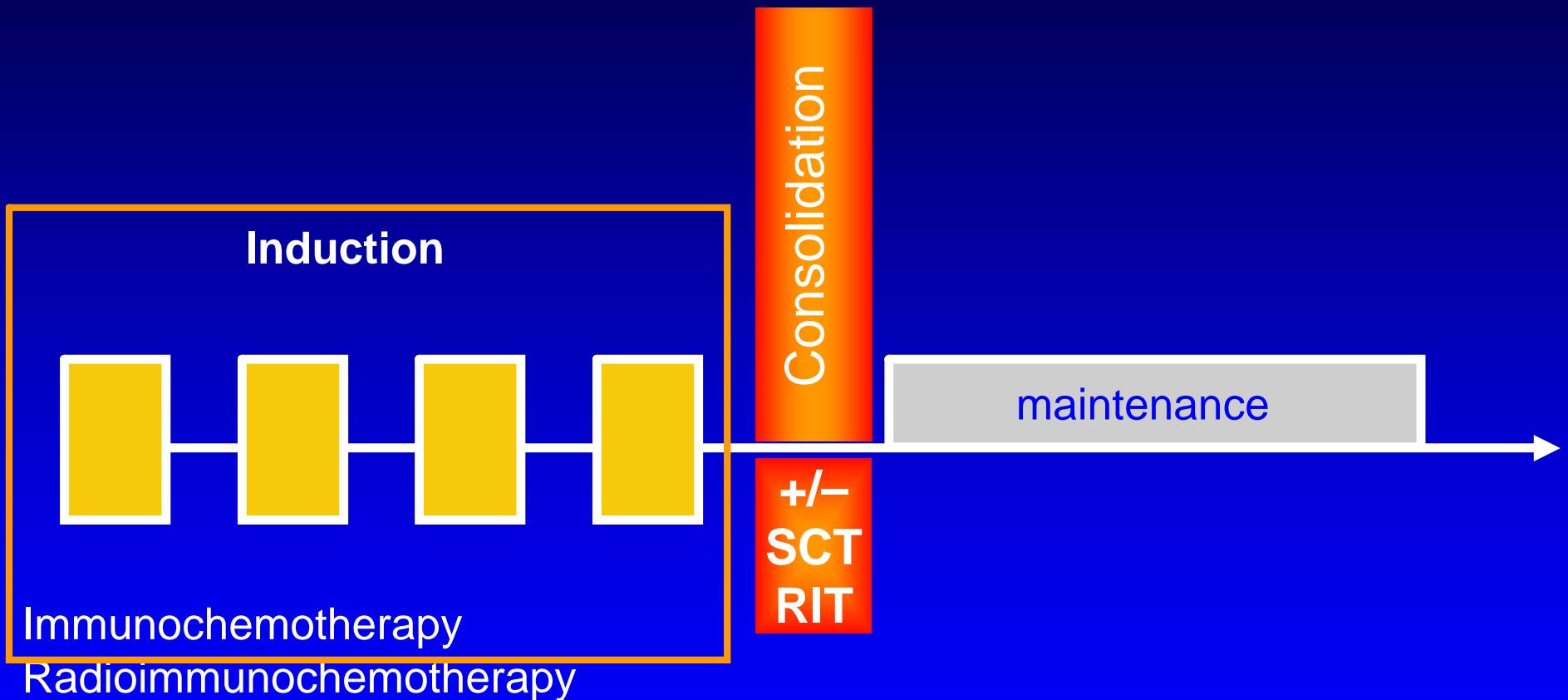
Konzepte

**Wenn wir behandeln müssen
– was sollen wir initial dem
Patienten anbieten?**

Two patient groups: Fit and Non-Fit Patients



Optimal treatment in follicular lymphoma ?



→ Tumor reduction

→ MRD

Follicular Lymphoma Therapeutic Options

Medically Fit

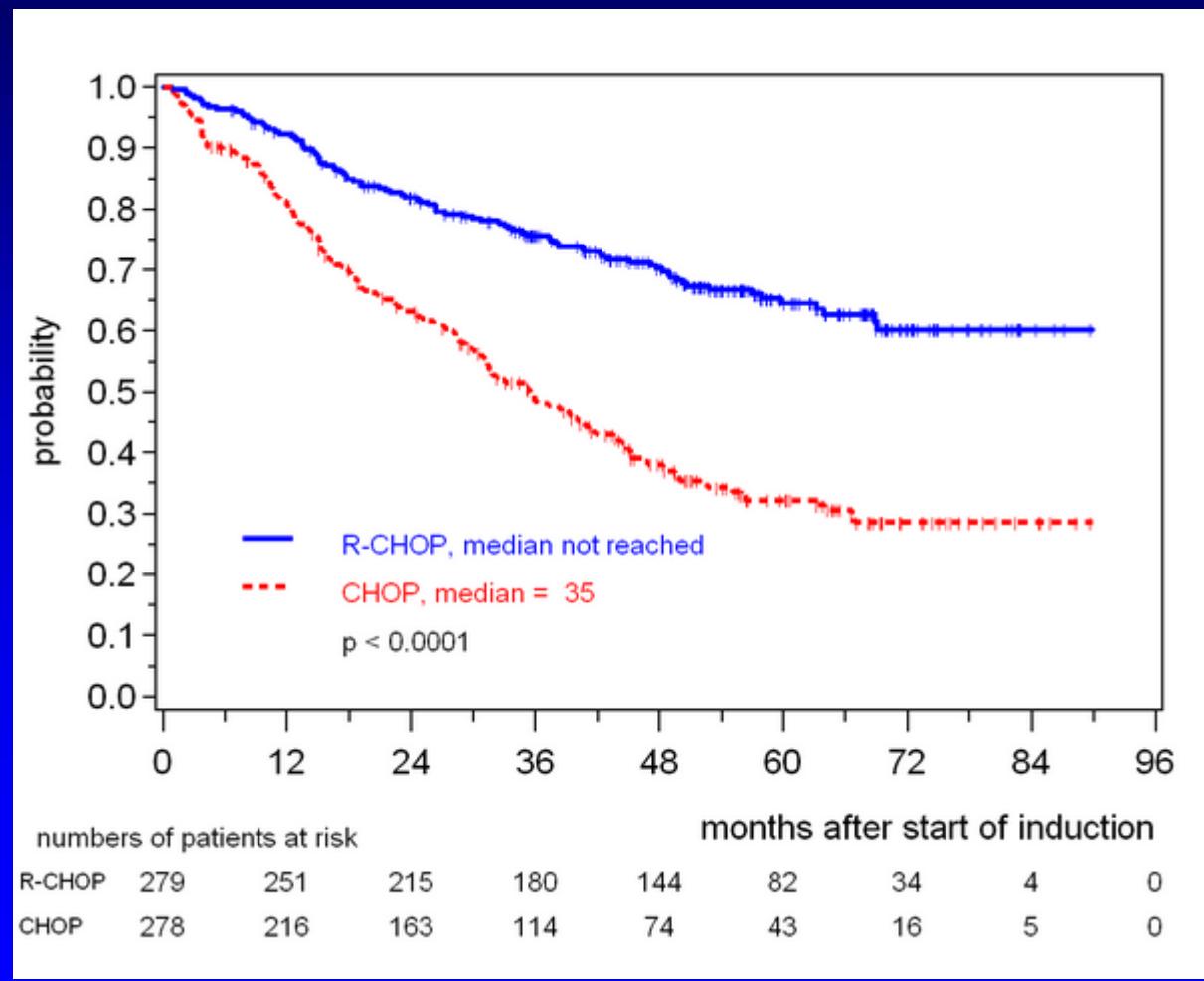
- Chemotherapy
- Rituximab single agent
- Rituximab plus chemotherapy
- Radioimmunotherapy

First-line treatment for follicular lymphoma: R-chemotherapy

| Hiddemann et al. | CHOP | R-CHOP | p |
|---------------------------------|------------|--------------|---------------------------------|
| Patients evaluable | 205 | 223 | |
| Response rate | 90% | 96% | 0.011 |
| Median TTF | 31 months | Not reached | < 0.0001 |
| OS (estimated 2-year OS) | 90% | 95% | 0.016 |
| Marcus et al. | CVP | R-CVP | p |
| Patients evaluable | 159 | 162 | |
| Response rate | 57% | 81% | < 0.0001 |
| Median time to progression | 15 months | 34 months | < 0.0001 |
| OS (median follow-up 53 months) | 71% | 81% | < 0.03 |
| Herold et al. | MCP | R-MCP | p |
| Patients evaluable | 96 | 105 | |
| Response rate | 75% | 92% | < 0.001 |
| Median EFS | 19 months | Not reached | < 0.0001 |
| OS (median) | 62 months | Not reached | 0.016 |
| Foussard et al. | CHVP/IFN-a | R-CHVP/IFN-a | p |
| Patients evaluable | 183 | 175 | |
| Response rate (CR/CRu) | 85% (49%) | 94% (76%) | < 0.0001 |
| Median EFS | 36 months | Not reached | < 0.0001 |
| OS (median follow-up 60 months) | 79% | 84% | n.s. For HR pts significant! |

R-CHOP vs CHOP

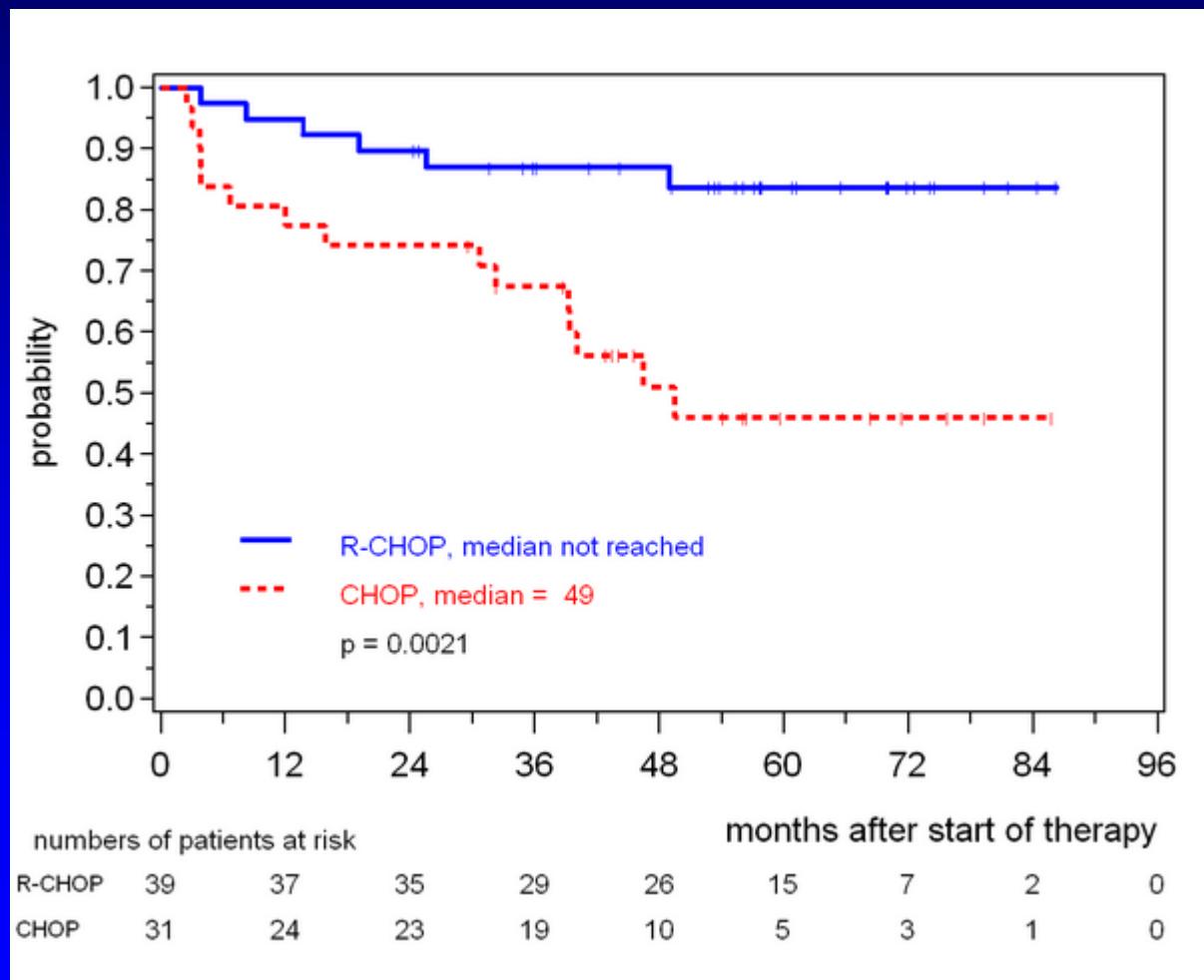
Time to Treatment Failure – 56 months follow-up



Buske et al., ASH 2008

R-CHOP vs CHOP

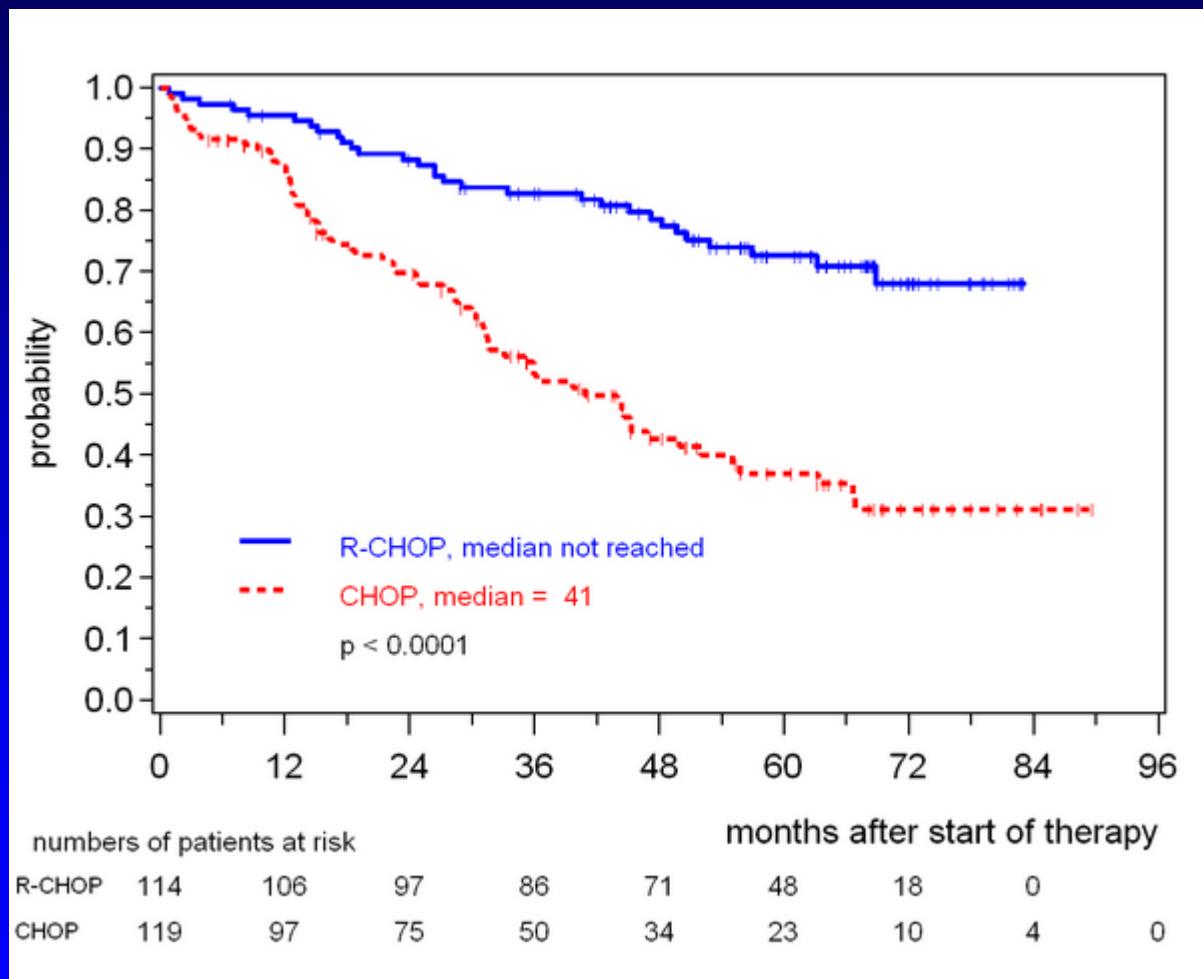
Time to Treatment Failure – Low Risk



Buske et al., ASH 2008

R-CHOP vs CHOP

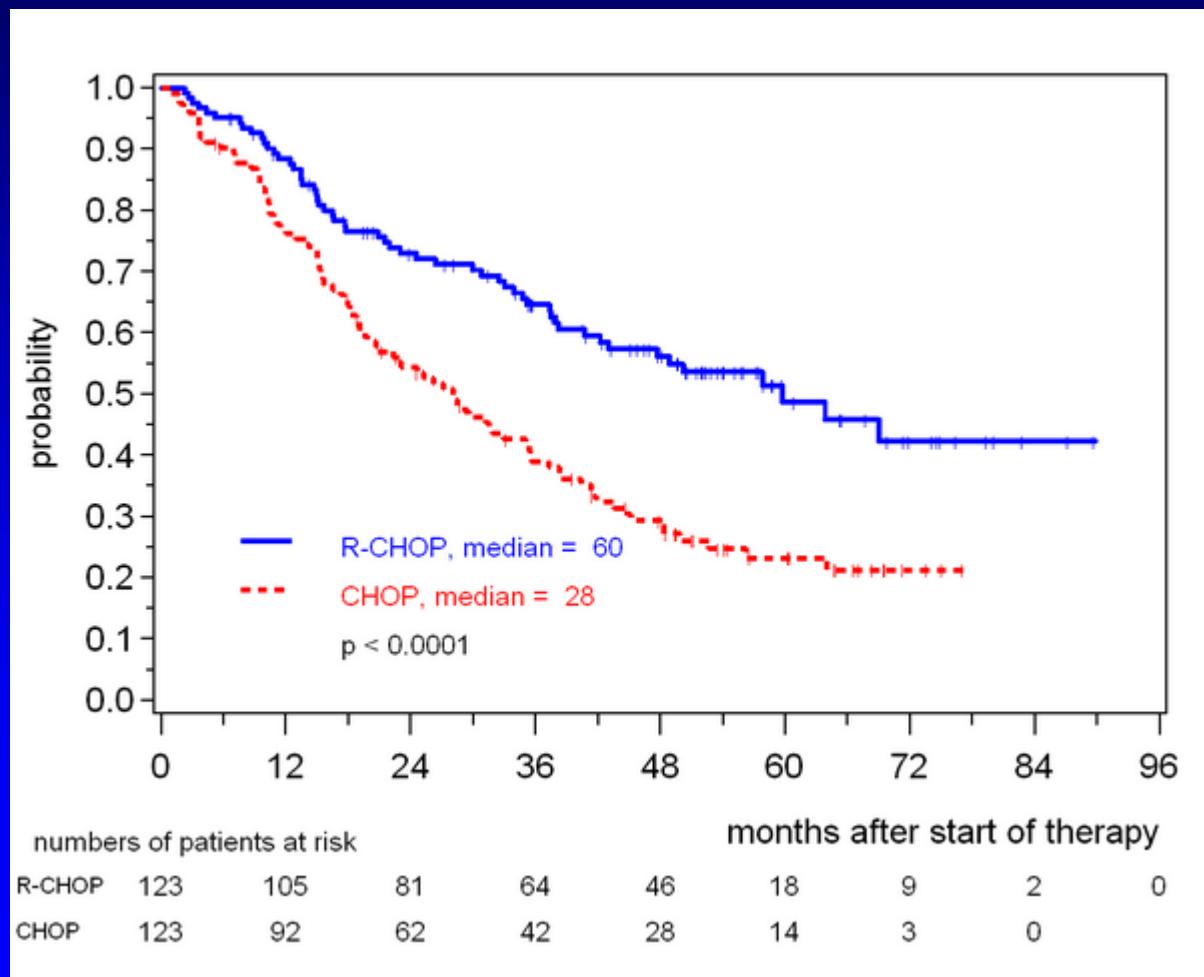
Time to Treatment Failure – Intermediate Risk



Buske et al., ASH 2008

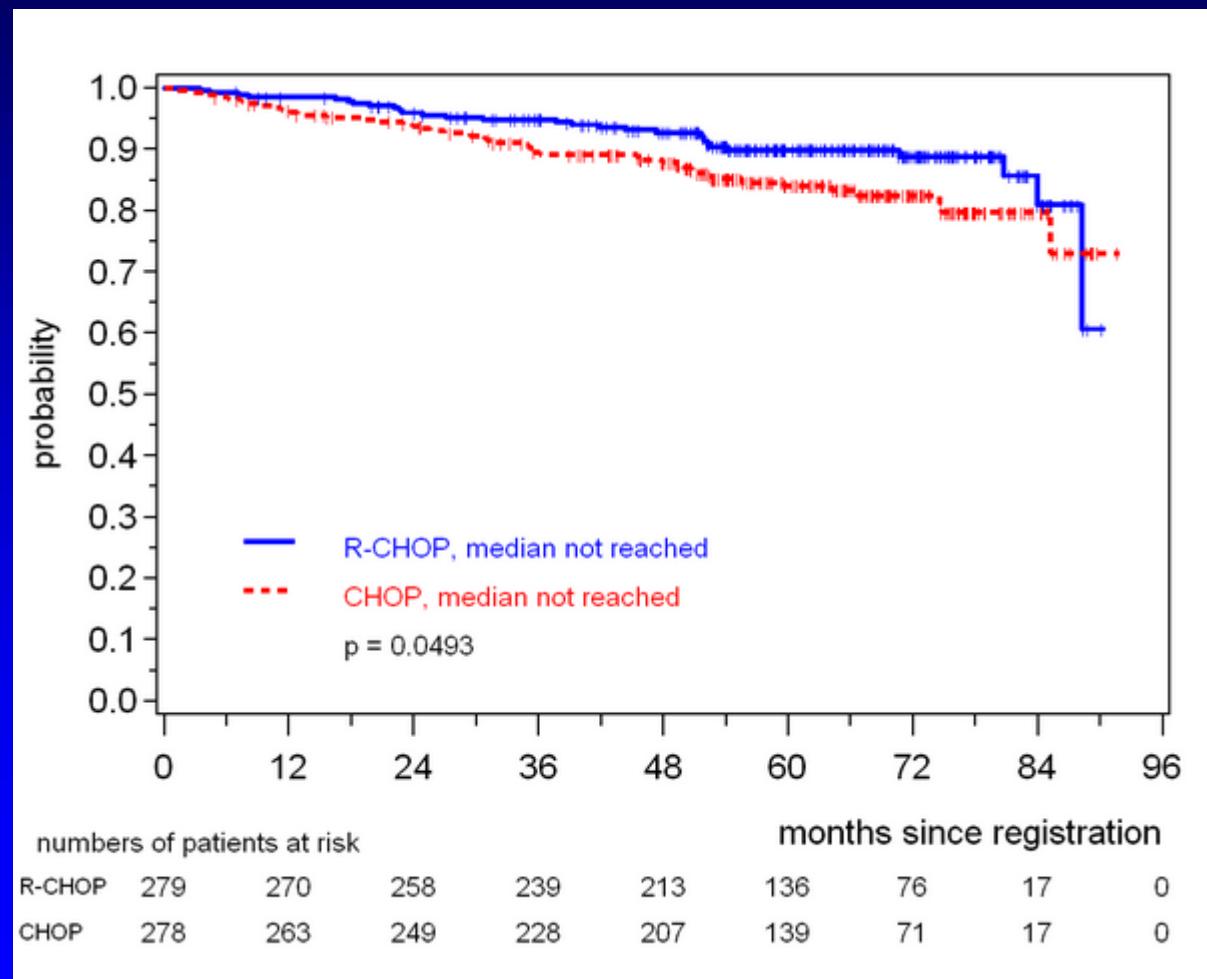
R-CHOP vs CHOP

Time to Treatment Failure – High Risk



Buske et al., ASH 2008

R-CHOP vs CHOP Overall Survival



Buske et al., ASH 2008

Conclusions

Several large prospectively randomized Phase III studies

→demonstrating superiority of Rituximab plus standard chemotherapy compared to chemotherapy alone

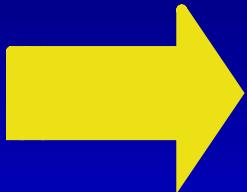
**Immuno-chemotherapy standard in the first line
and salvage treatment of advanced stage
follicular lymphoma in the medically fit patient**

Konzepte

Welche
Immunchemotherapie ist die
Beste...?

Which immunochemotherapy?

- CVP plus Rituximab
- CHOP plus Rituximab
- FC(m) plus Rituximab
- Bendamustine plus Rituximab

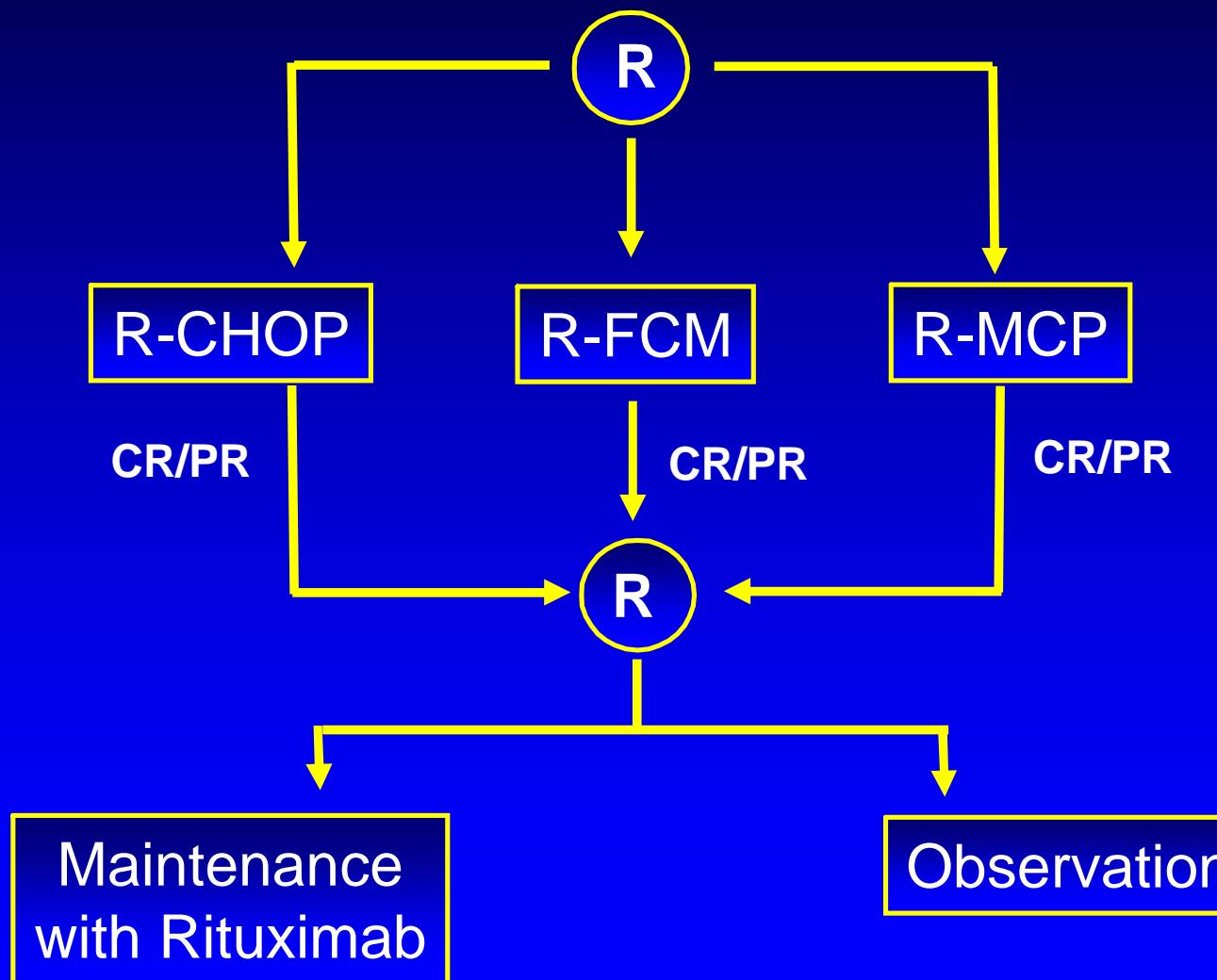


However, which
immunochemotherapy
is best?

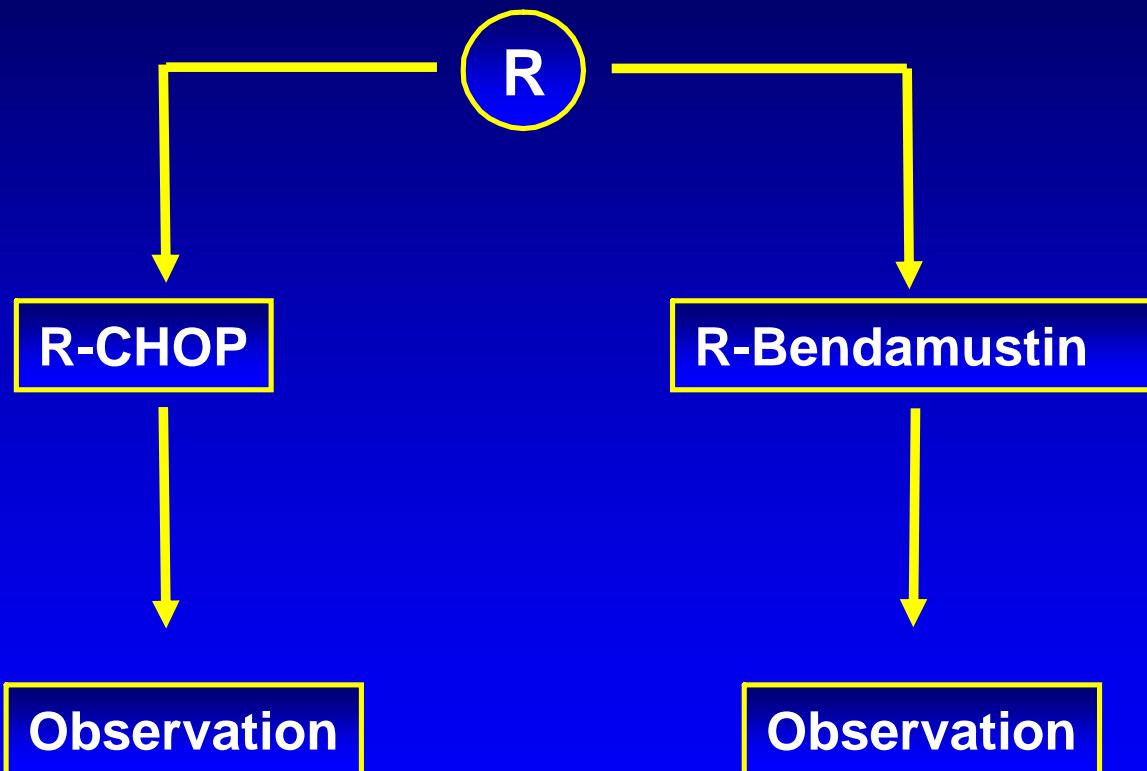
There are now randomized studies comparing
different immunochemotherapies in FL,
but so far no data !

OSHO/GLSG Study Concepts

(Follicular Lymphoma, Patients > 65 years)



StiL study concept (Follicular lymphoma)



Konzepte

**Reicht es nicht aus initial eine
optimale Zytoreduktion
durchzuführen?**

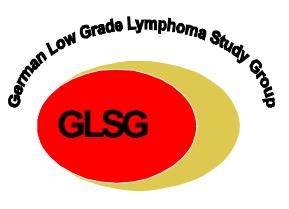
**Brauchen wir
Konsolidierung/Erhaltung?**

Follicular Lymphomas Stage III/IV Response Rates

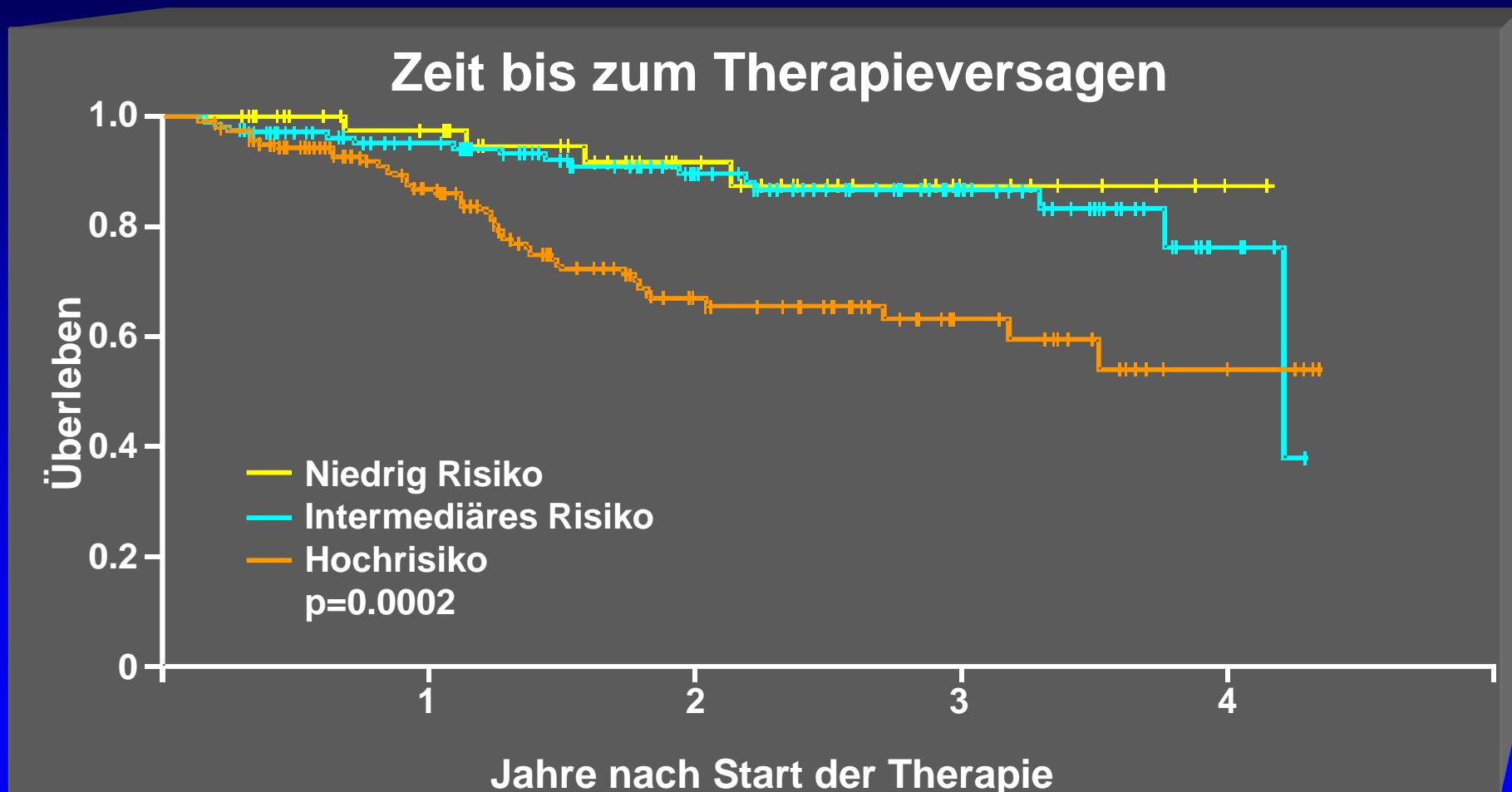
Best Response rates with rituximab/chemotherapy:

| | OR | CR | CR/CRu |
|-----------|------|------|---------------|
| R-CVP | 81% | 30% | 41% |
| R-CHOP | 96 % | 20% | <i>CRu=PR</i> |
| R-MCP | 92 % | 50% | n.a. |
| RCVHP/IFN | 94 % | n.a. | 76 % |

n.a. = Not available



Therapieverlauf nach Risikoprofil – R-CHOP



C. Buske et al. Blood 2006

How to treat – Medically Fit Follicular Lymphomas Stage III/IV

Part 1

Initial cytoreduction

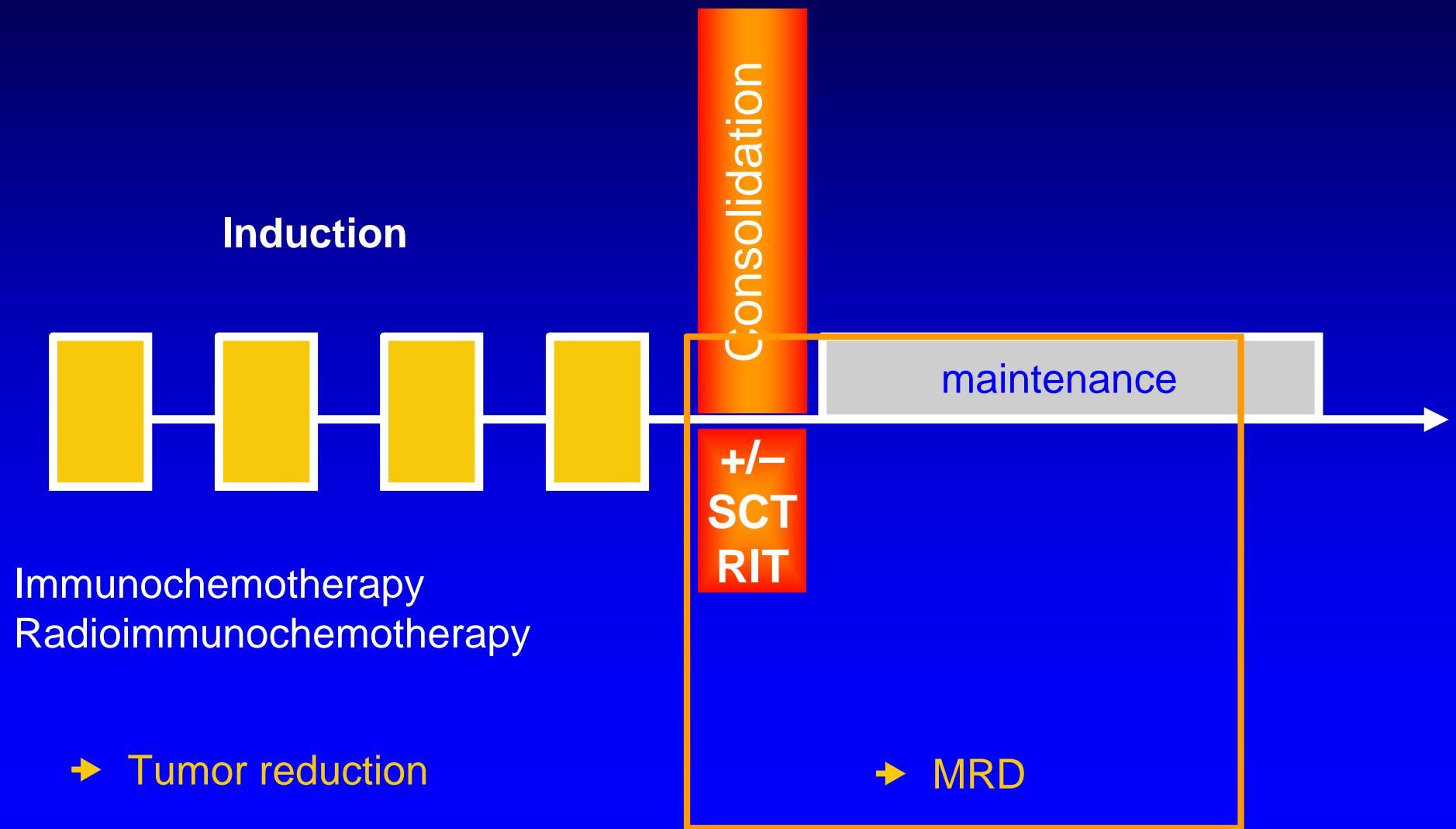
Part 2

Consolidation

Part 3

Maintenance

Optimal treatment in follicular lymphoma ?



ASCT in Follicular Lymphoma in 1st Remission

GOELAMS: CHVP + IFN vs. HD + ASCT

→ 5-years EFS prolonged (59 vs. 37 %), but no difference in OS

GELA: CHVP + IFN vs. HD/TBI + ASCT

→ EFS no difference, OS no difference

GLSG: CHOP/R-CHOP cytoreduction: ASCT vs IFN consolidation

→ PFS significant improvement, OS ?

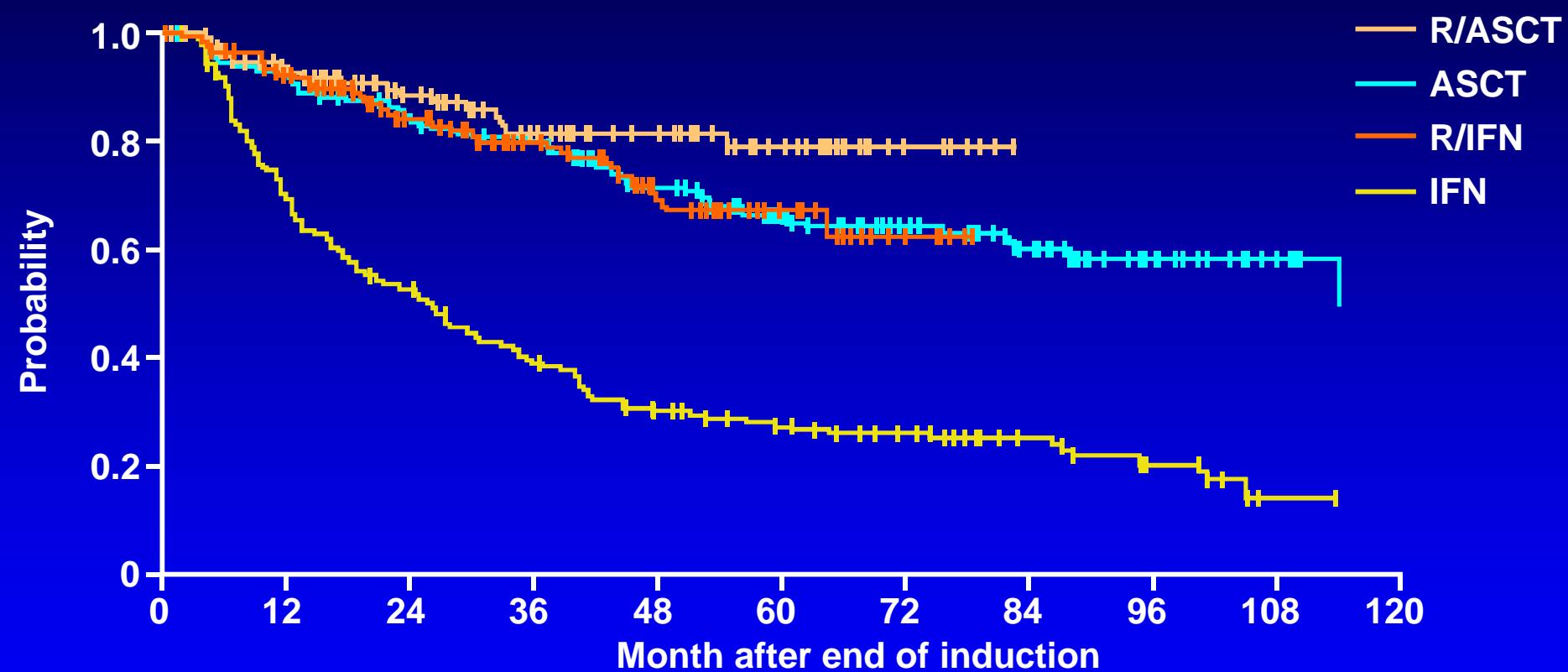
Follicular lymphoma ASCT?

This is a difficult time for ASCT in advanced stage FL

BUT:

- it stays a most important therapeutic concept**
- it has to be re-evaluated in clinical trials in the era of monoclonal antibody therapy**

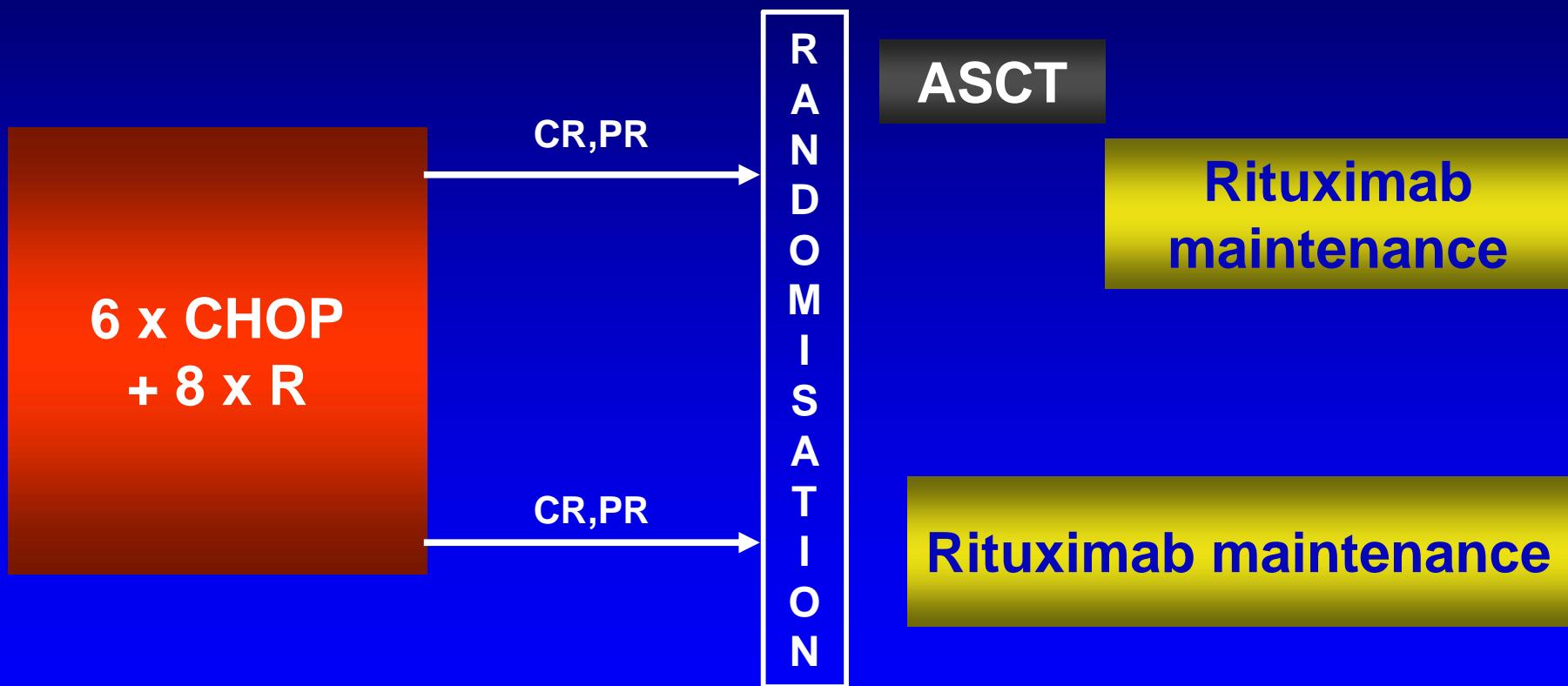
GLSG studies 1996 and 2000 response duration 08-08



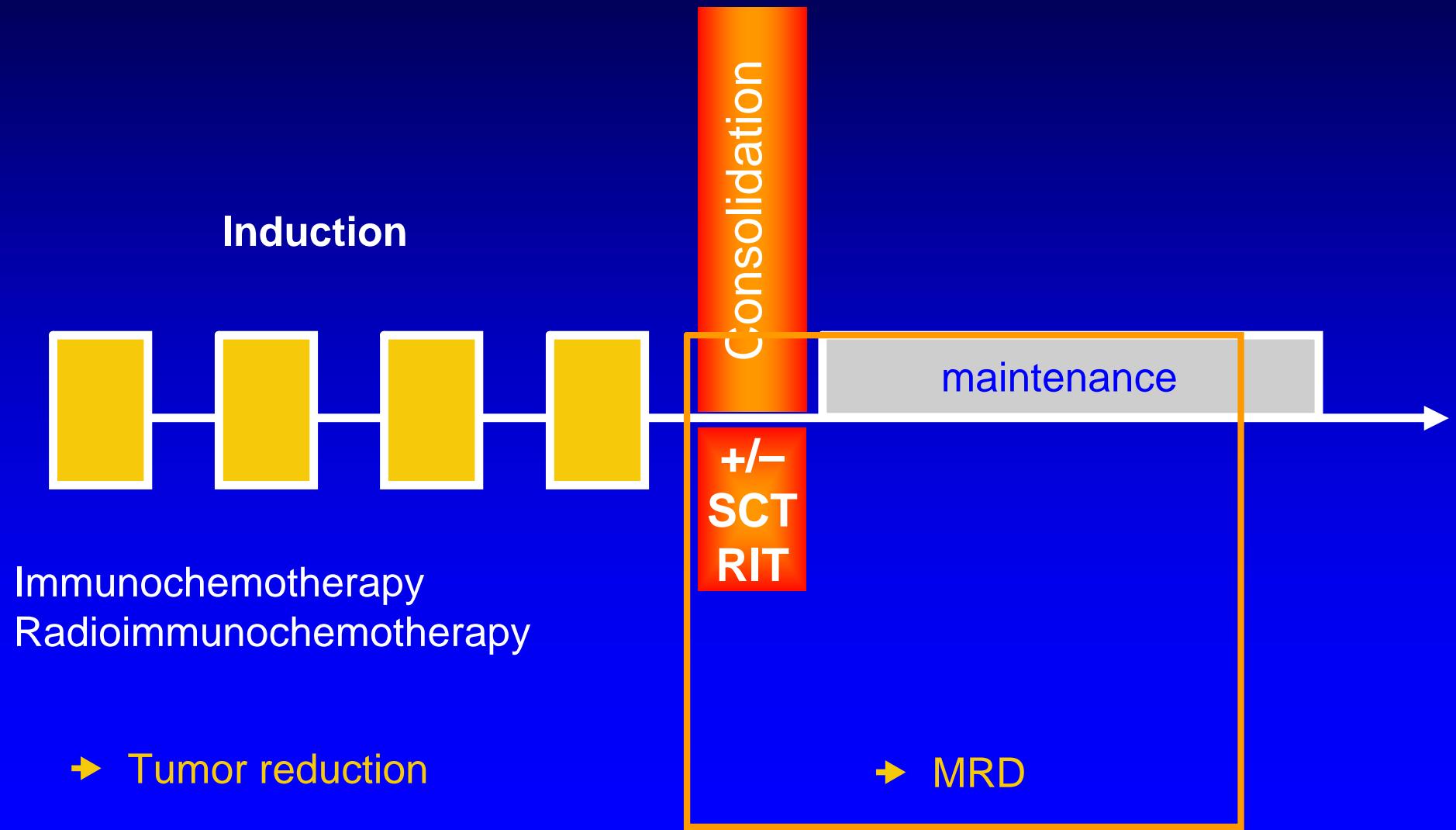
No. of patients at risk

| | | | | | | | | | | |
|--------|-----|-----|-----|-----|----|----|----|----|----|----|
| R/ASCT | 116 | 97 | 76 | 52 | 39 | 26 | 7 | 0 | | |
| ASCT | 145 | 132 | 118 | 107 | 87 | 69 | 54 | 38 | 22 | 12 |
| R/IFN | 152 | 120 | 86 | 62 | 32 | 17 | 5 | 0 | | |
| IFN | 167 | 114 | 85 | 62 | 44 | 36 | 28 | 17 | 9 | 2 |

RiCHOP study 2008 for first-line therapy of FL patients aged <65 years

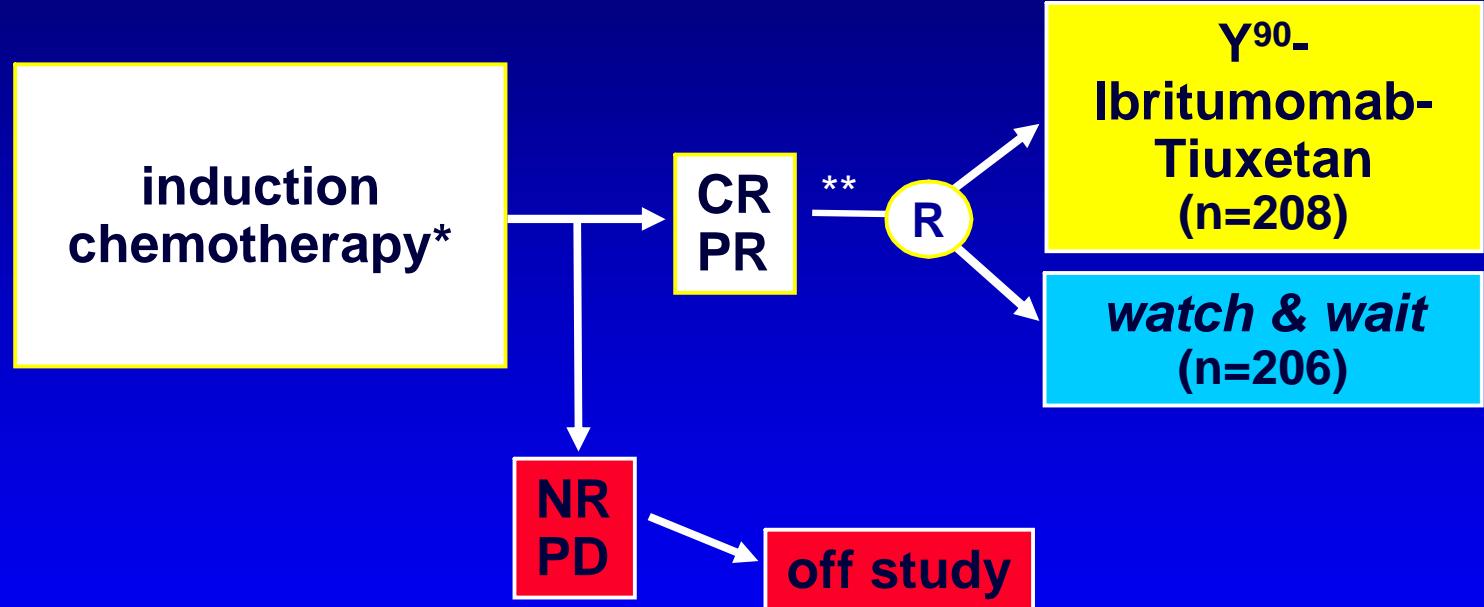


Optimal treatment in follicular lymphoma ?



FIT: ^{90}Y -Ibritumomab-Tiuxetan as first-line consolidation

newly diagnosed follicular lymphoma stage III/IV



FIT: *First-line Indolent lymphoma Trial*

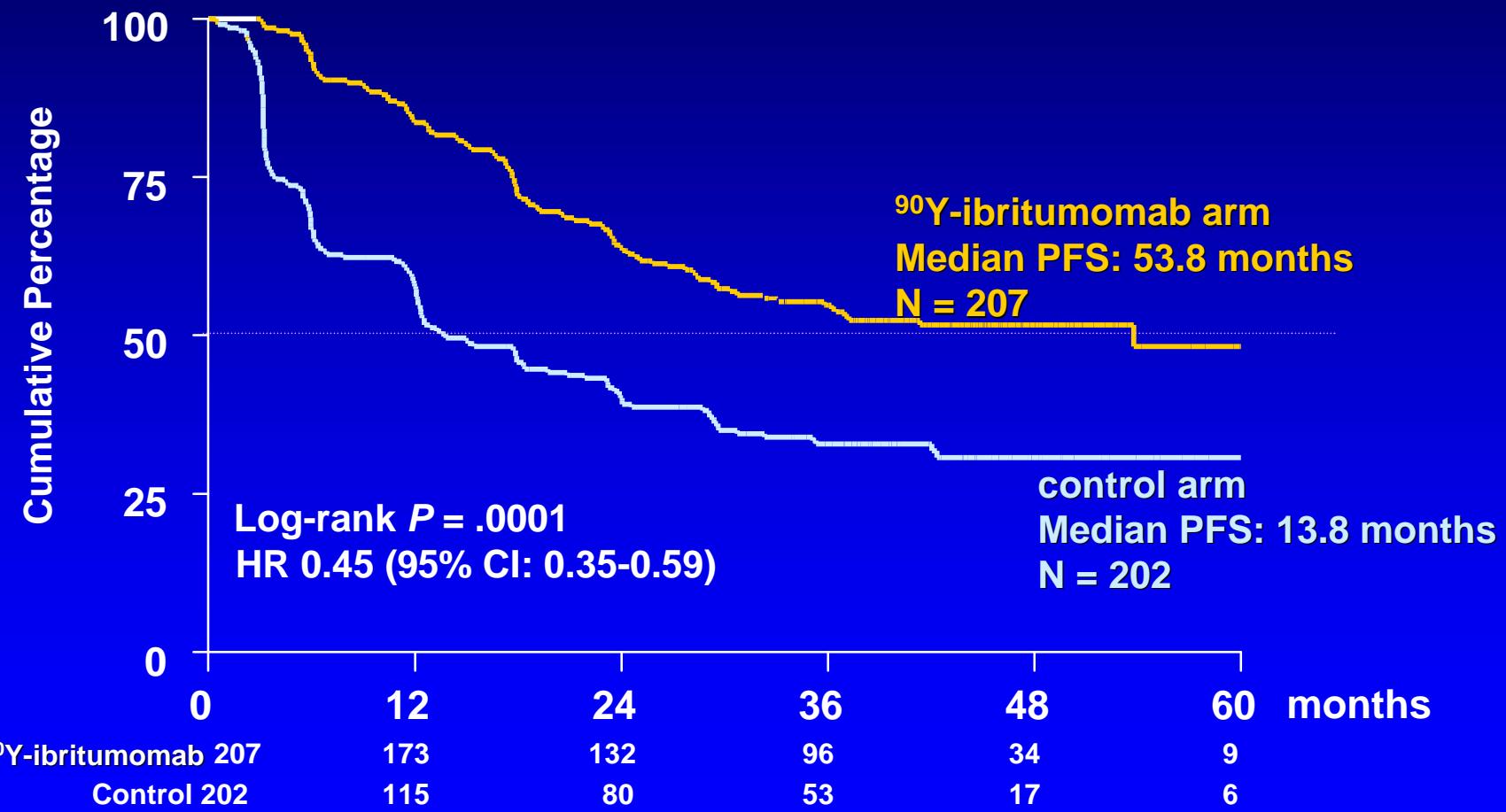
* CVP, CHOP, Fludarabin (combination), etc.

** n = 414

Hagenbeek, ASH 2007 #693

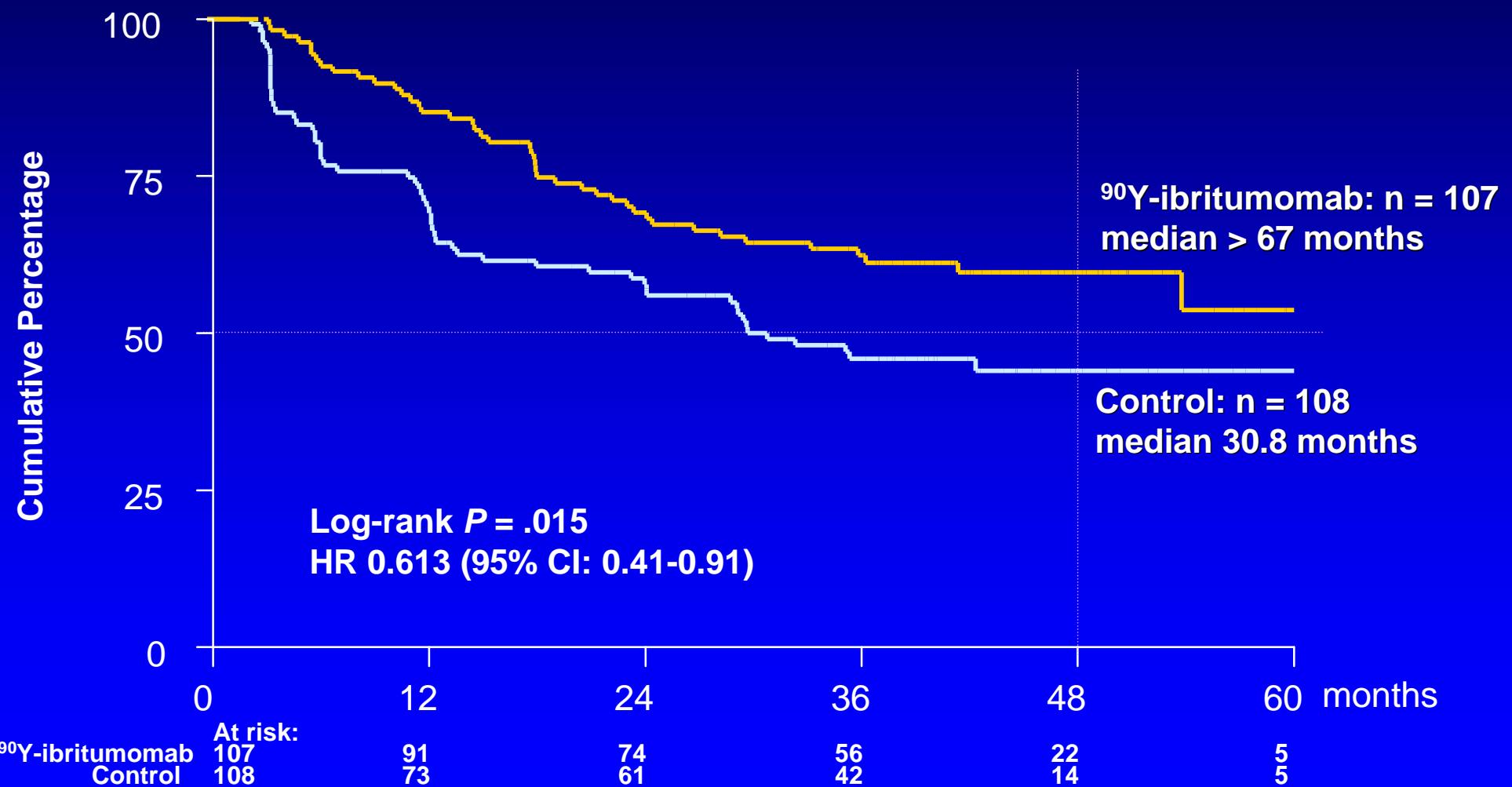
Overall PFS for Treatment Groups

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



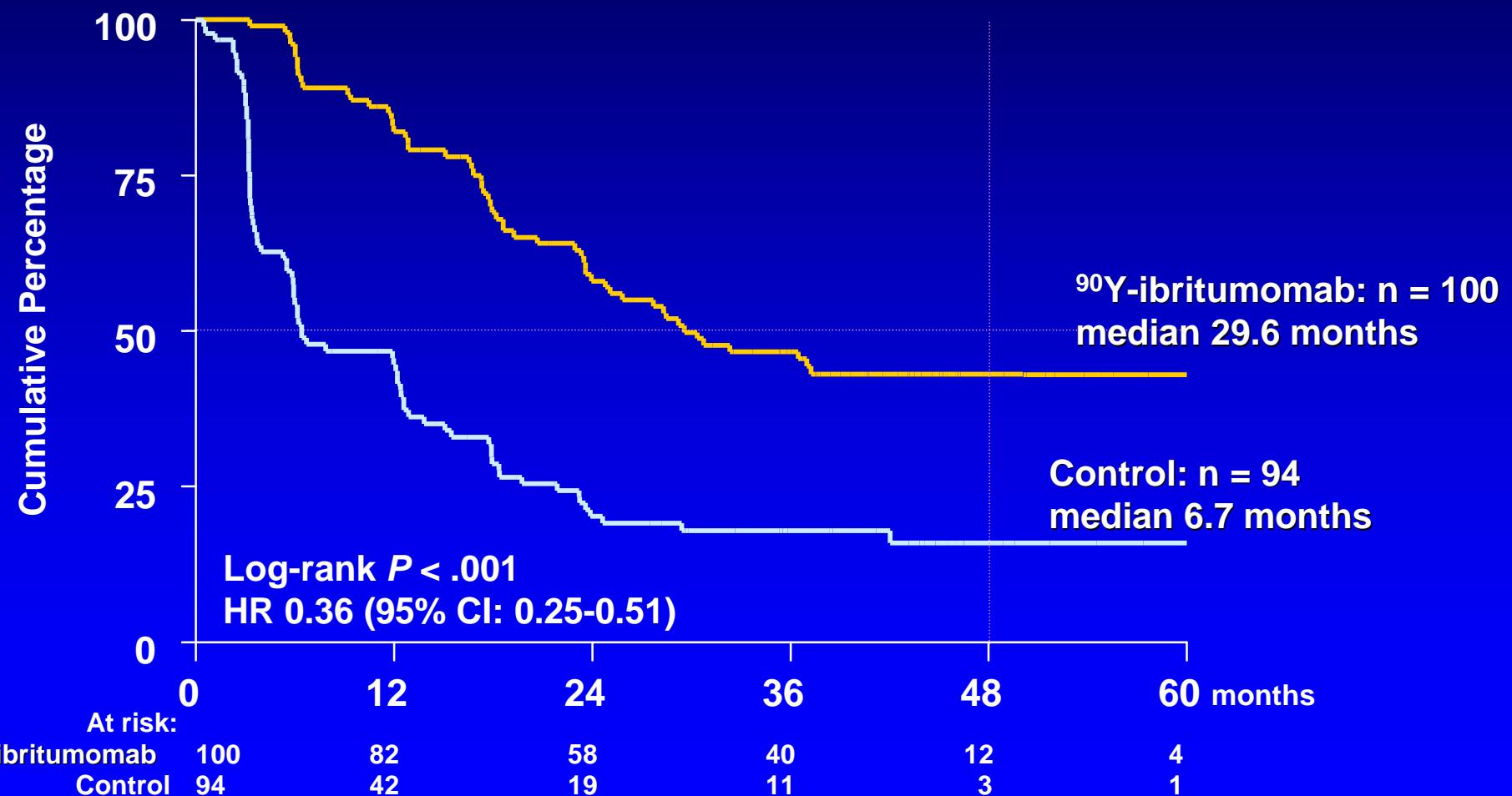
PFS for Patients in CR/CRu After Induction

The 4-year PFS among patients with a CR after induction
is 60% in the ^{90}Y -ibritumomab arm compared with 44% in the control arm



PFS for Patients in PR After Induction

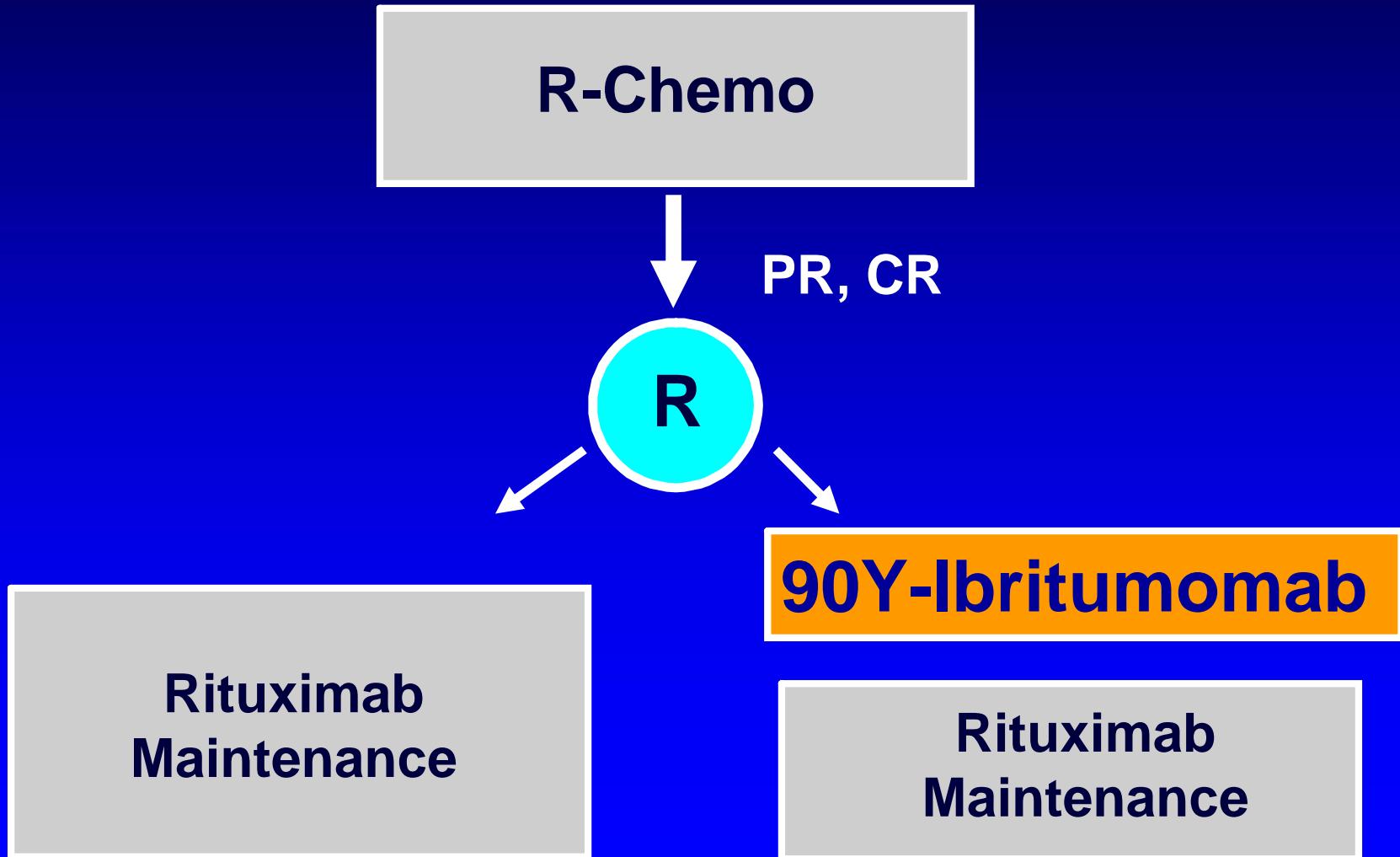
The 4-year PFS among patients with a PR after induction
is 43% in the ⁹⁰Y-ibritumomab arm compared with 15% in the control arm



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

| | Control | | | ⁹⁰Y-Ibritumomab | | | Hazard Ratio |
|------------------------------|-----------------|------------|----------------|-----------------|------------|----------------|-----------------------------|
| PFS | No. of Patients | No. Failed | Median PFS, mo | No. of Patients | No. Failed | Median PFS, mo | (95% CI)* |
| 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) |

RITZ - Trial



Konzepte. IV.

**Wie sollen wir ‚medically
non-fit‘ Patienten
behandeln?**



PRIMÄRTHERAPIE DES FOLLIKULÄREN LYMPHOMS IM FORTGESCHRITTENEN STADIUM BEI PATIENTEN MIT EINGESCHRÄNKTER BEHANDLUNGSFÄHIGKEIT

*Prospektiv randomisierte Prüfung der Wirksamkeit einer initialen
Chemotherapie mit Bendamustin in Kombination mit Rituximab
im Vergleich zu
einer initialen Monotherapie mit Rituximab*

Studiendesign

Randomisierung

$R = 8 \times 375 \text{mg/m}^2$

R-Benda
 $R = 8 \times 375 \text{mg/m}^2$
4x Benda 90 mg/m^2 d1+2

Mantelzell-Lymphome

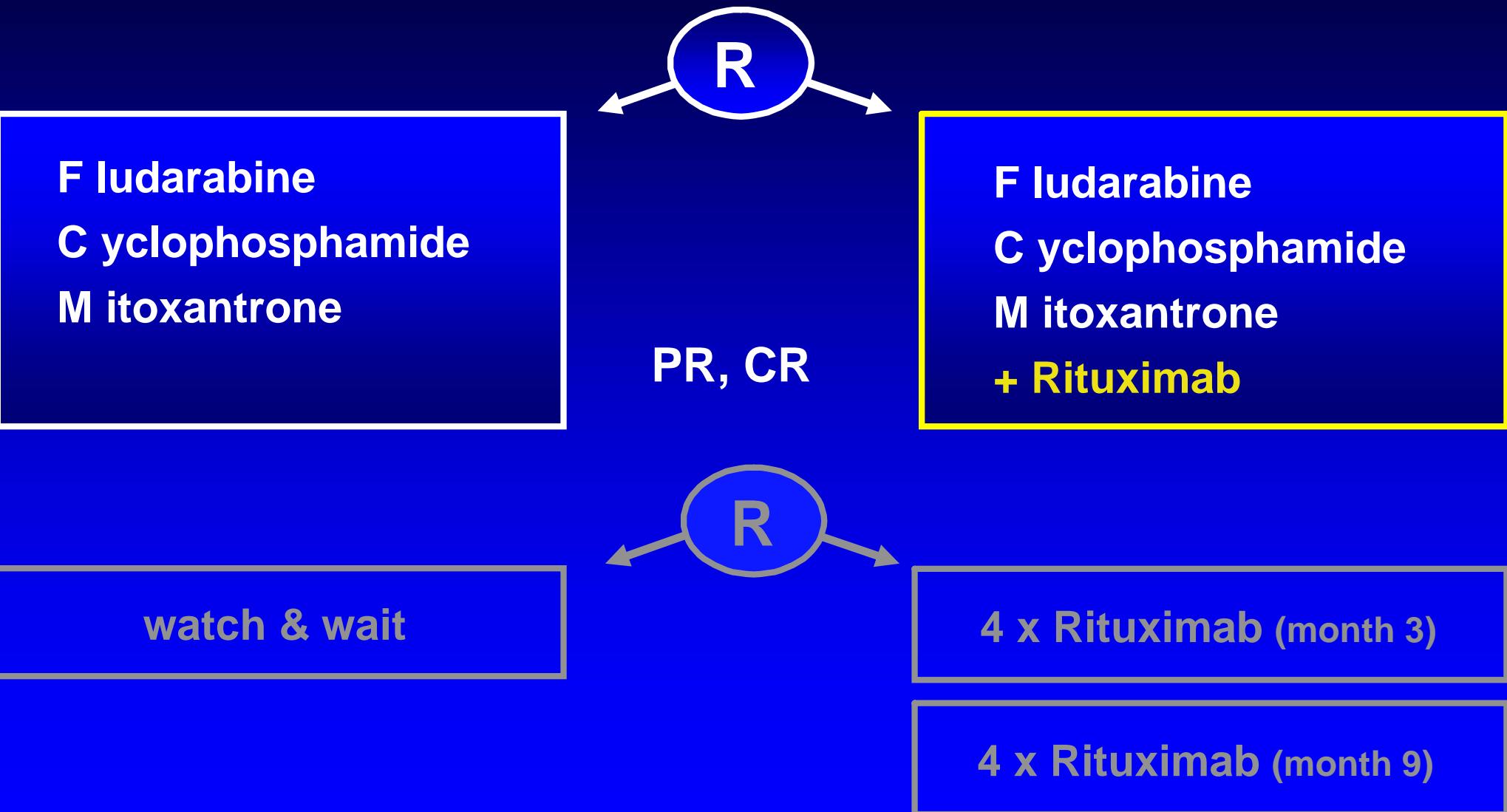
Konzepte

**Was sollen wir initial dem
Patienten anbieten?**

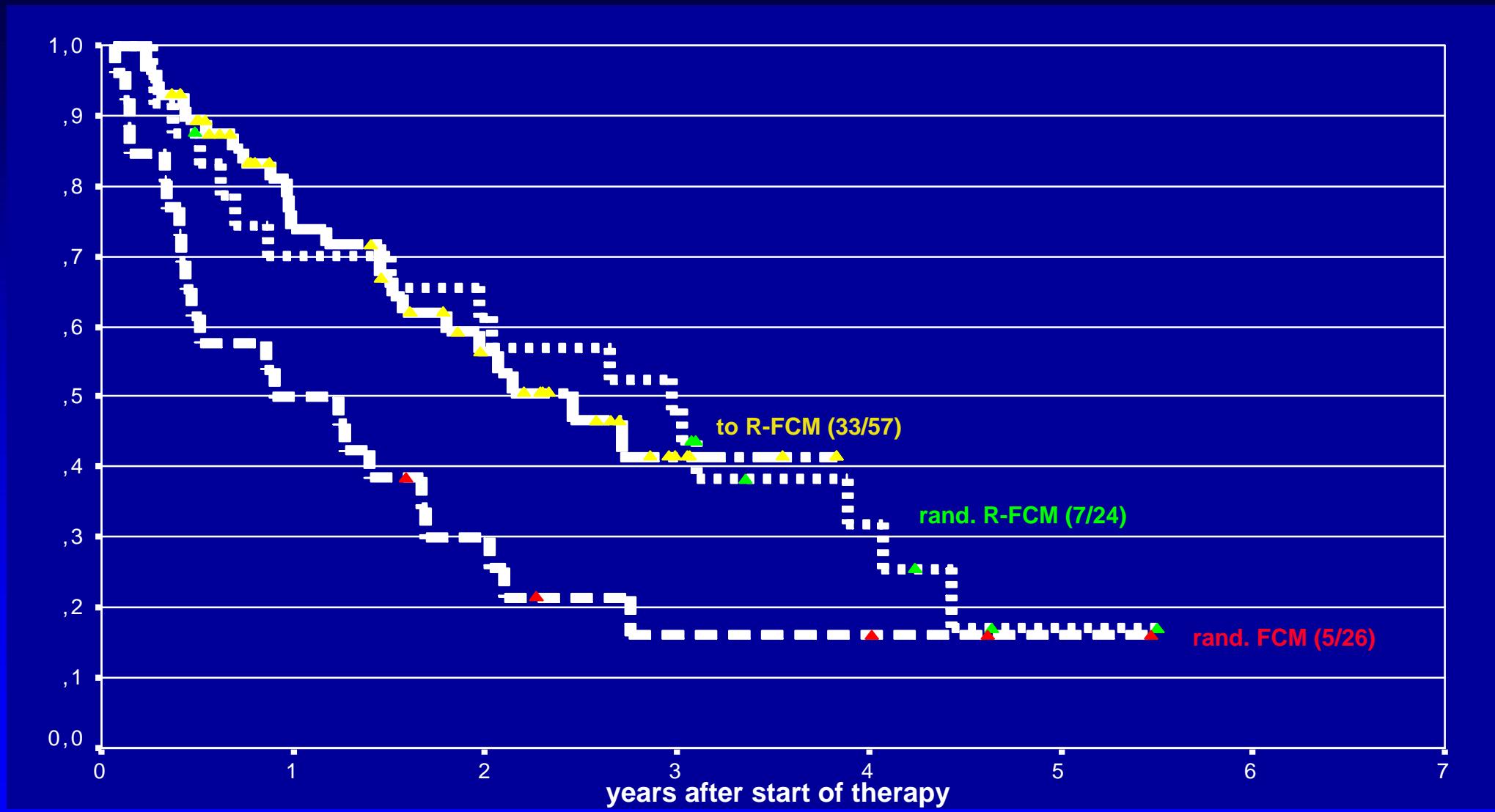
Immuno-chemotherapy in MCL

| <i>Lenz, JCO 2005</i> | CHOP | R – CHOP | p-value |
|----------------------------------|------------|------------|-----------------|
| Patients evaluable | 65 | 159 | |
| Response rate | 77% | 92% | p= 0.016 |
| CR | 9% | 32% | p= 0.002 |
| <i>Forstpointner, Blood 2004</i> | FCM | R-FCM | p-value |
| Patients evaluable | 26 | 79 | survival ! |
| Response rate | 57% | 81% | p= 0.28 |
| CR | 0 | 29% | p= 0.004 |
| <i>Herold, ASH 2004</i> | MCP | R-MCP | p-value |
| Patients evaluable | 46 | 44 | |
| Response rate | 63% | 71% | p=0.51 |
| CR | 15% | 32% | p= 0.08 |

FCM vs. R-FCM
Relapsed MCL



FCM vs. R-FCM: MCL Overall survival



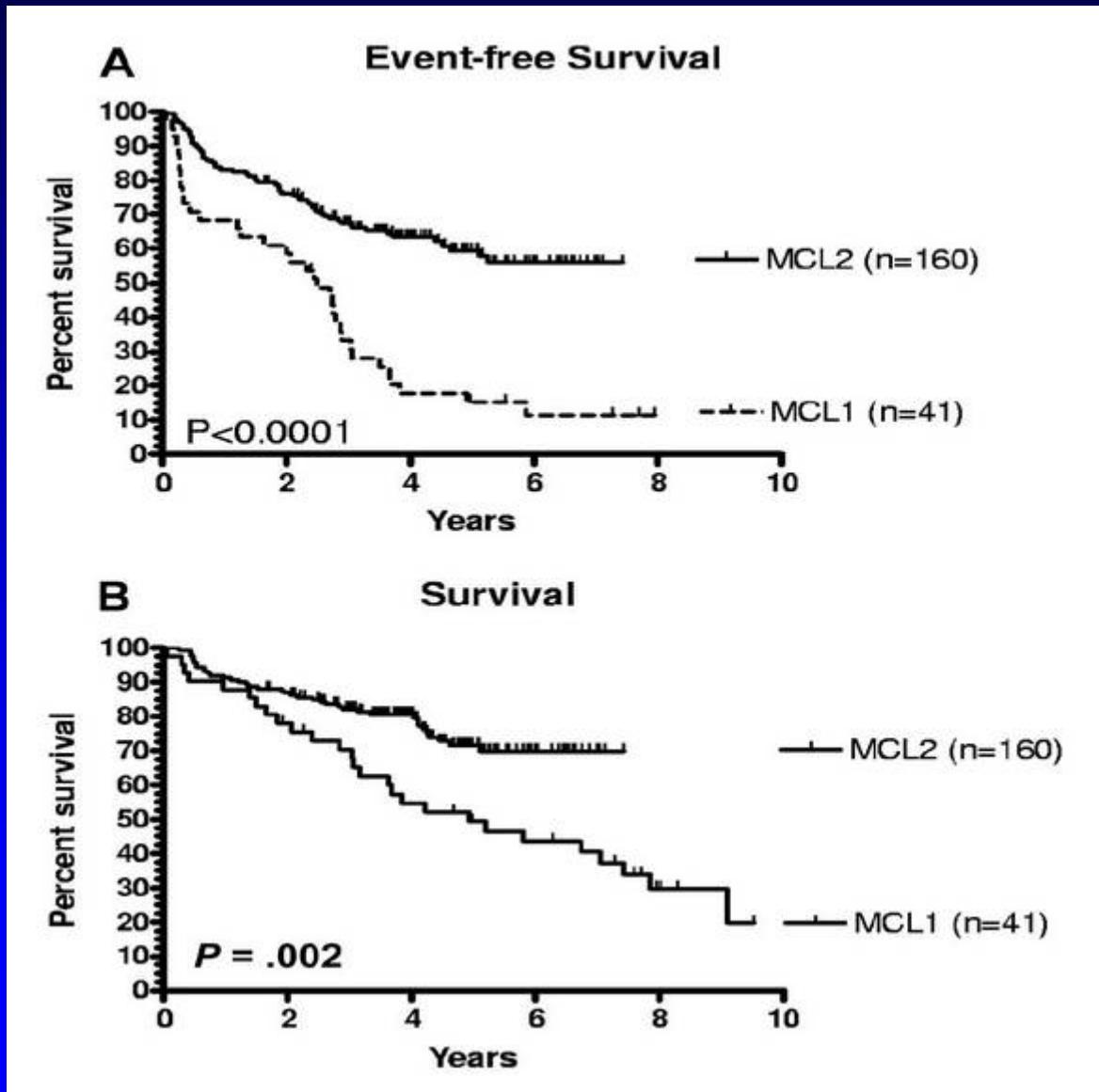
Dreyling, ASCO 2005 (update)

$p=0.0577$ ($p=0.0033$)

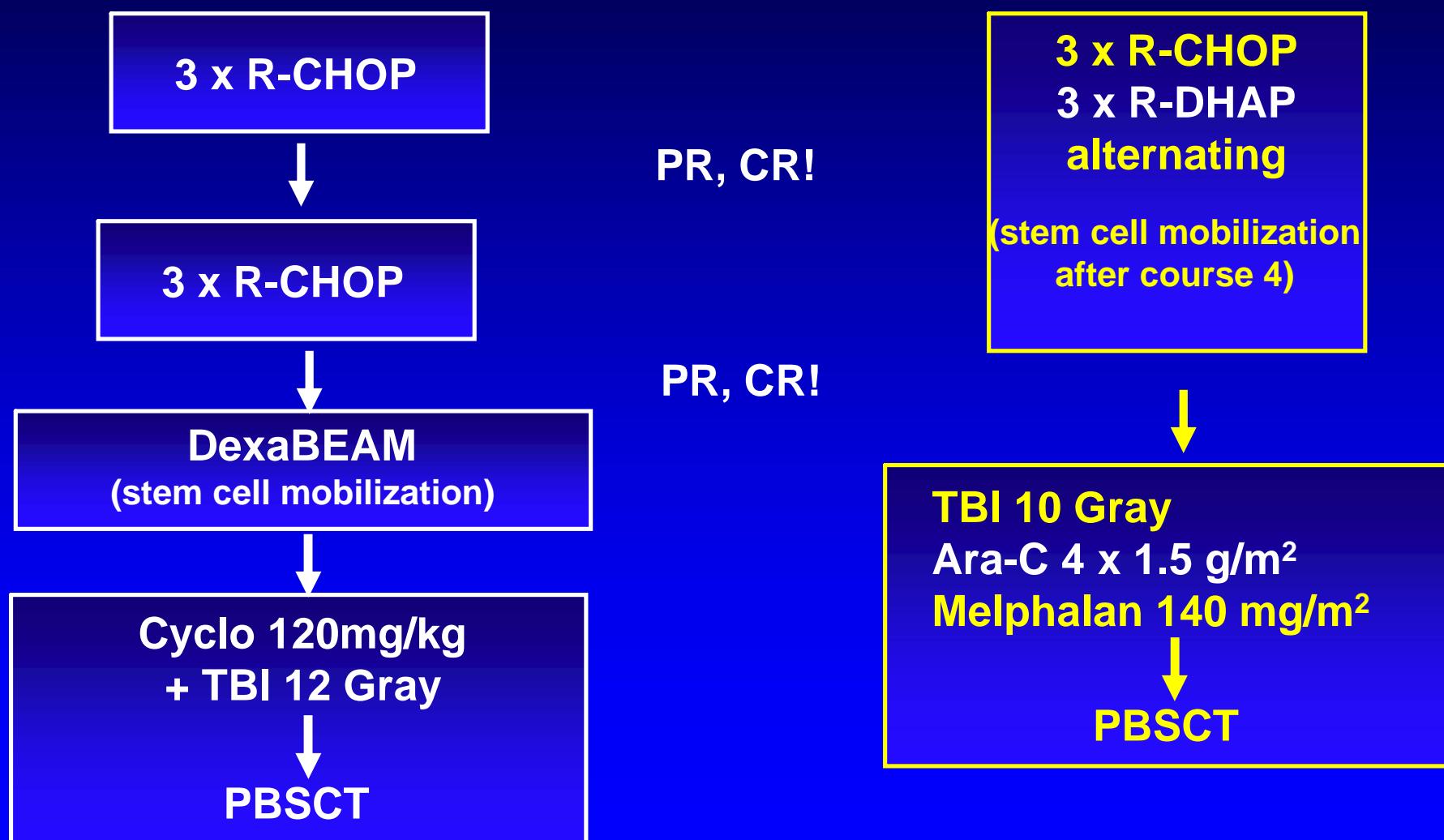
Konzepte

Welche
Immunchemotherapie ist die
Beste...?

Mantle cell lymphoma R-CHOP/High dose Ara-C => ASCT



European MCL Network
patients <65 years



MCL Younger

Response rate of induction

| Documented response | 250 | 64% | |
|-----------------------|-----|-----|----------------|
| Abort without staging | 6 | | |
| CR | 78 | 32% | |
| CRu | 46 | 19% | CR+CRu: 51% |
| PR | 98 | 40% | CR+CRu+PR: 91% |
| SD | 10 | 4% | |
| PD | 12 | 5% | |
| ED | 0 | 0% | |

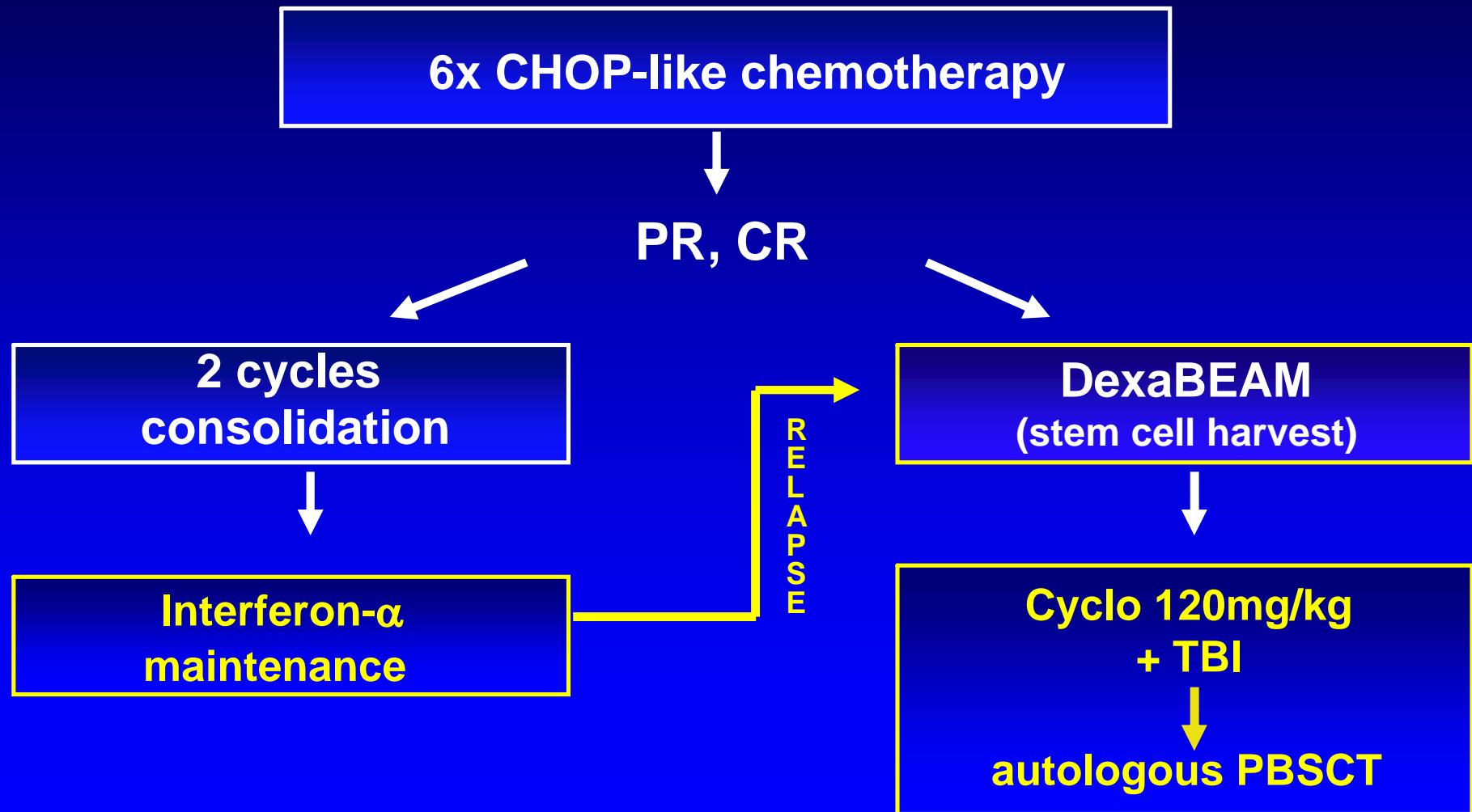
Konzepte

**Reicht es nicht aus initial eine
optimale Zytoreduktion
durchzuführen?**

**Brauchen wir
Konsolidierung/Erhaltung?**

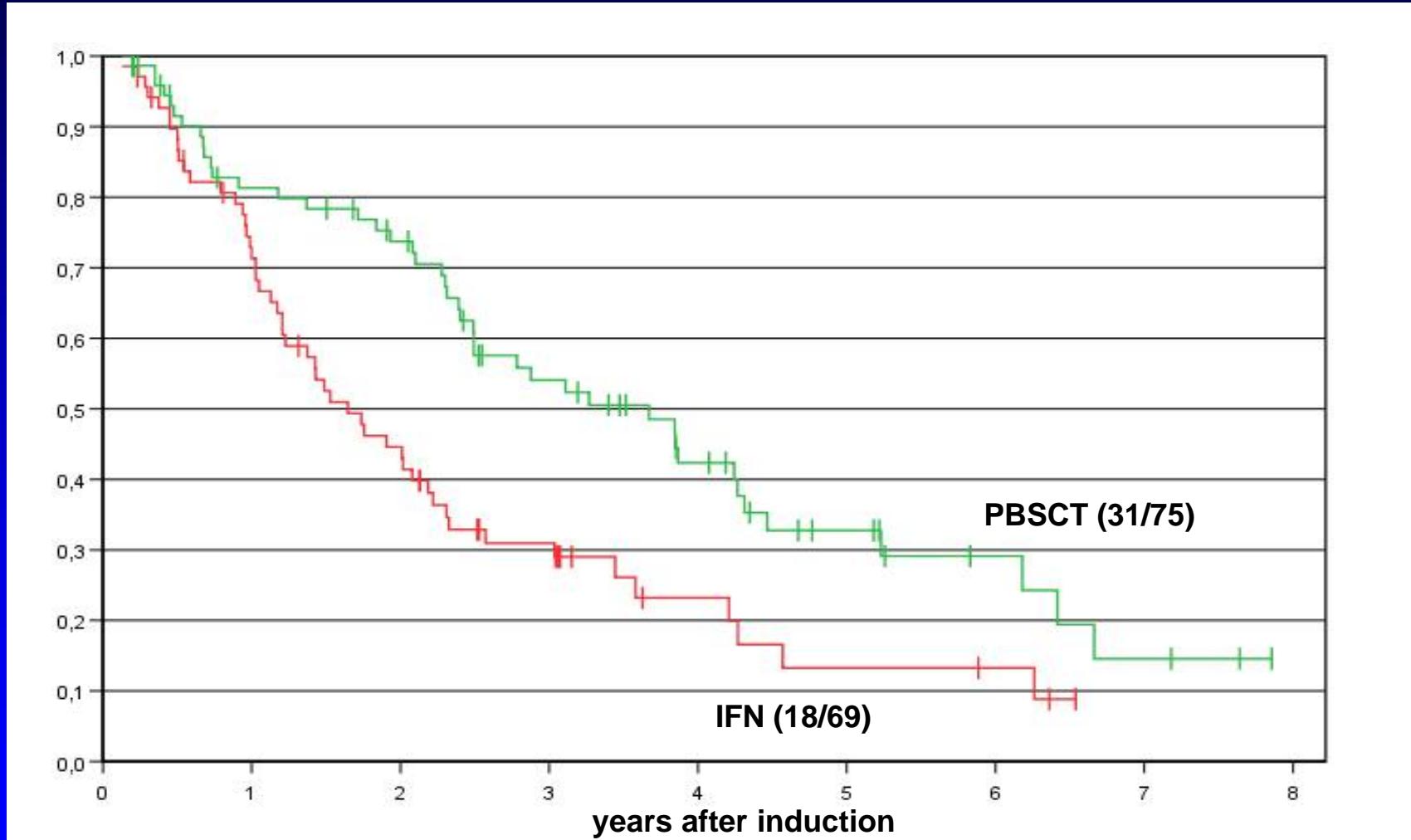
European MCL Network

ASCT vs. IFN



Dreyling, Blood 2005

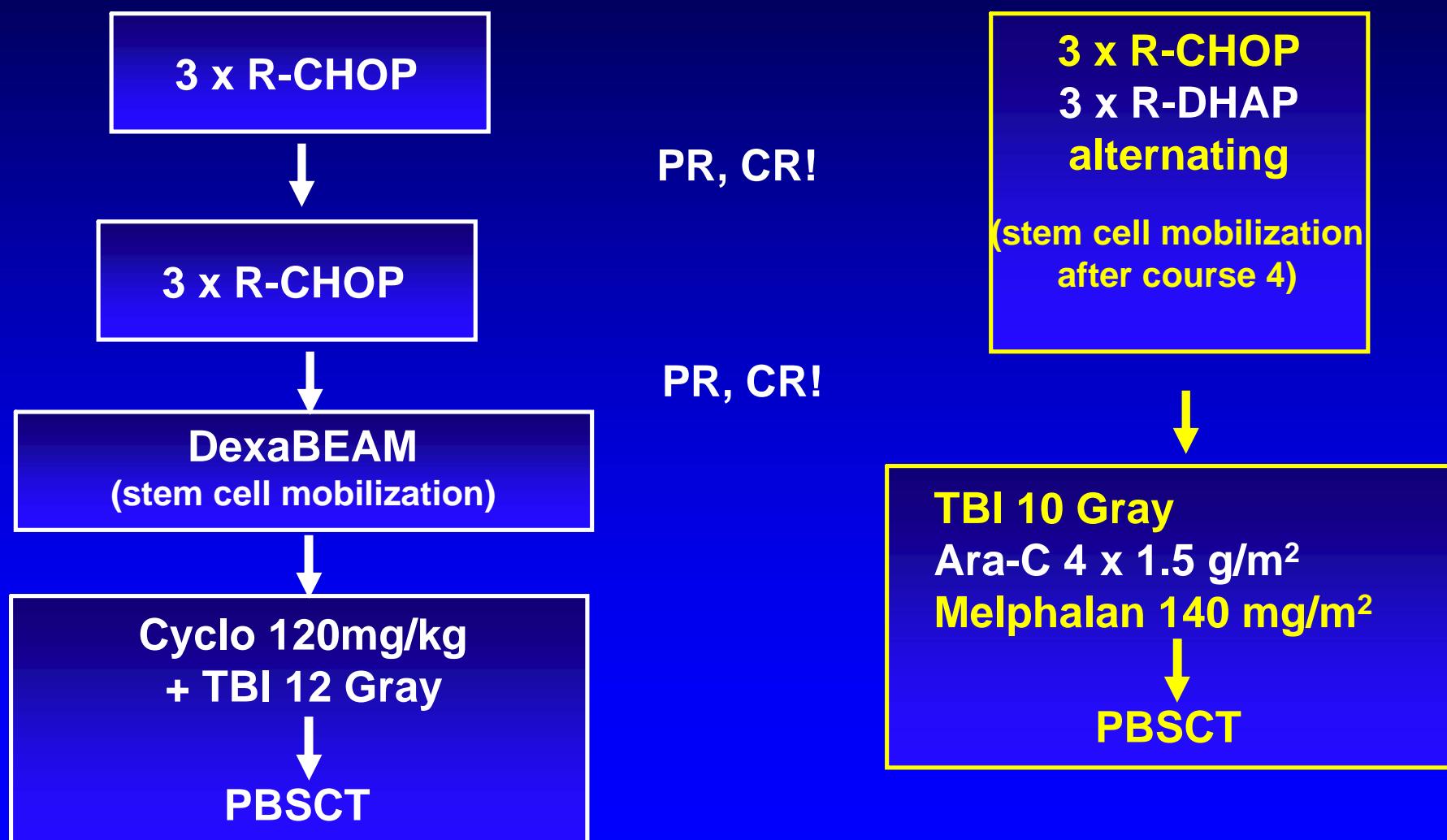
Progression-free survival (after consolidation)



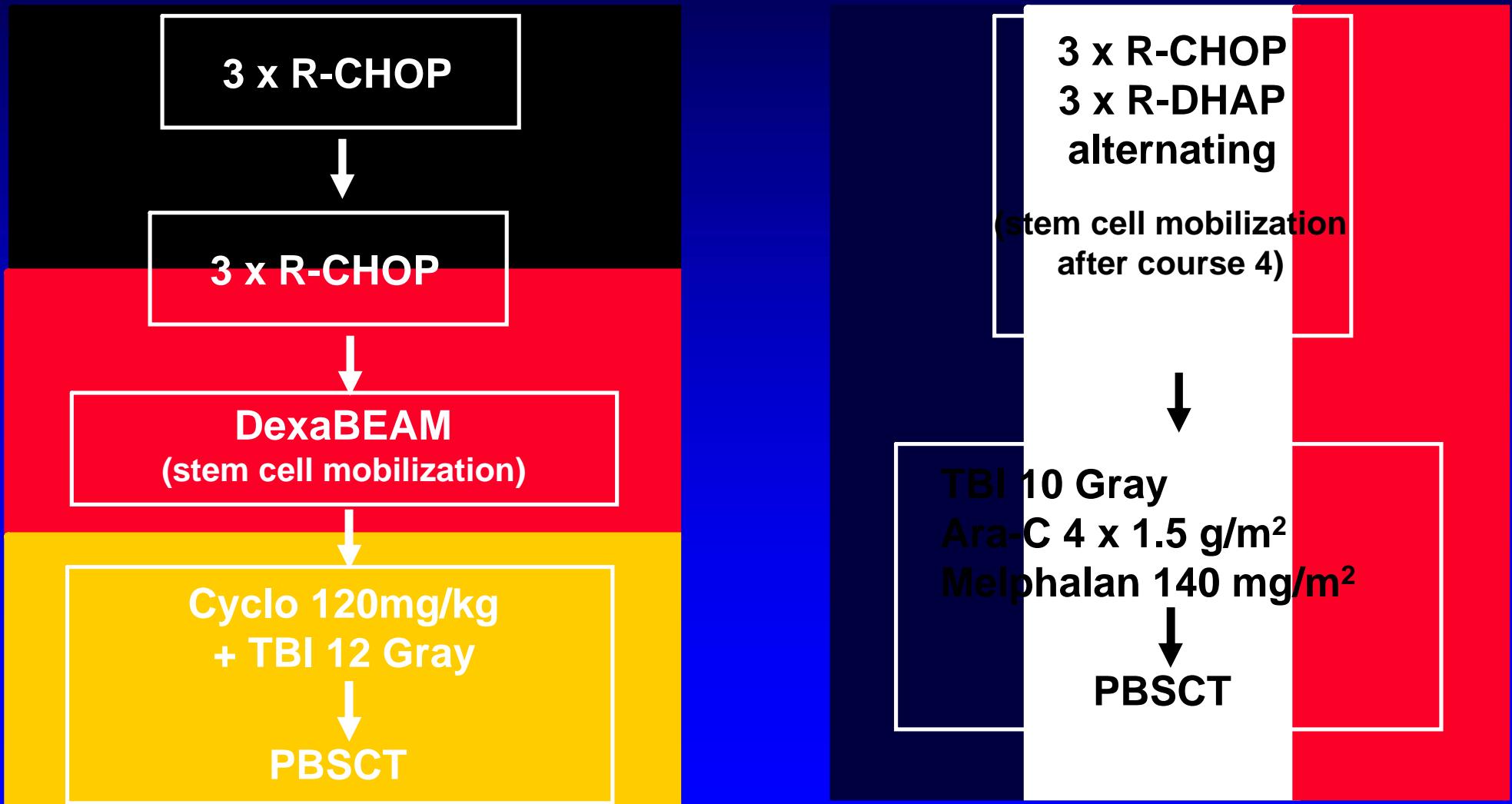
p=0,002

Dreyling, Blood 2005 (updated)

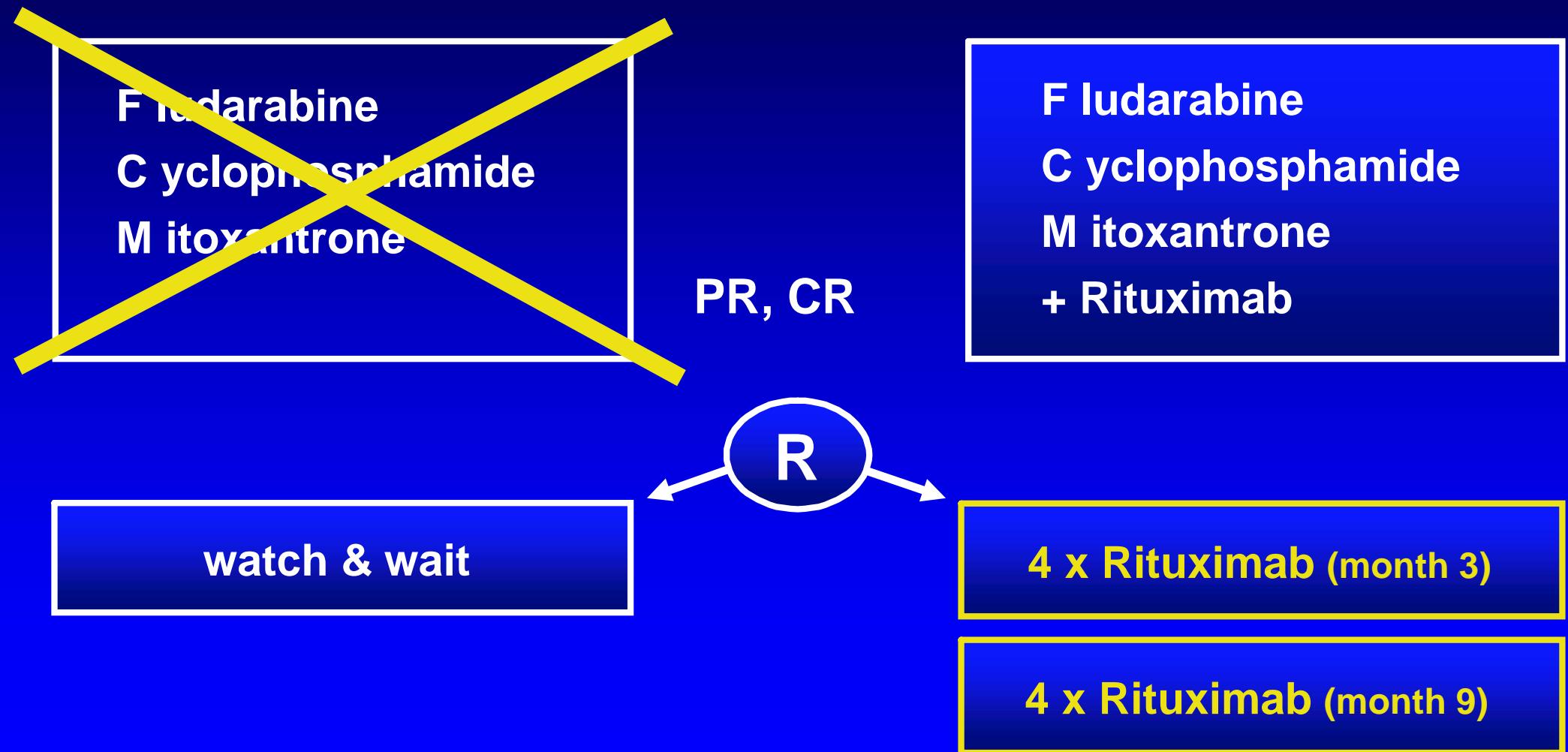
European MCL Network
patients <65 years



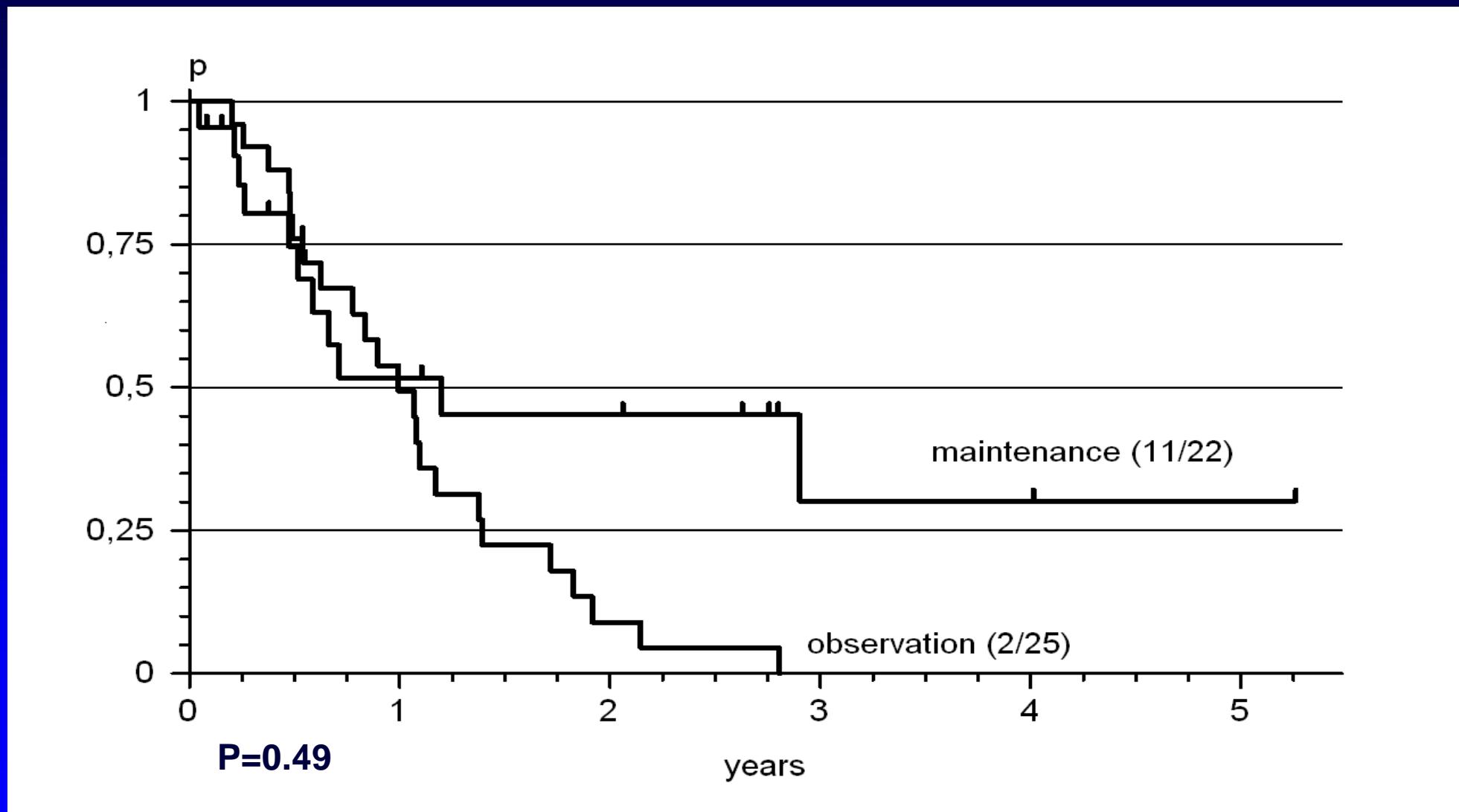
European MCL Network
patients <65 years



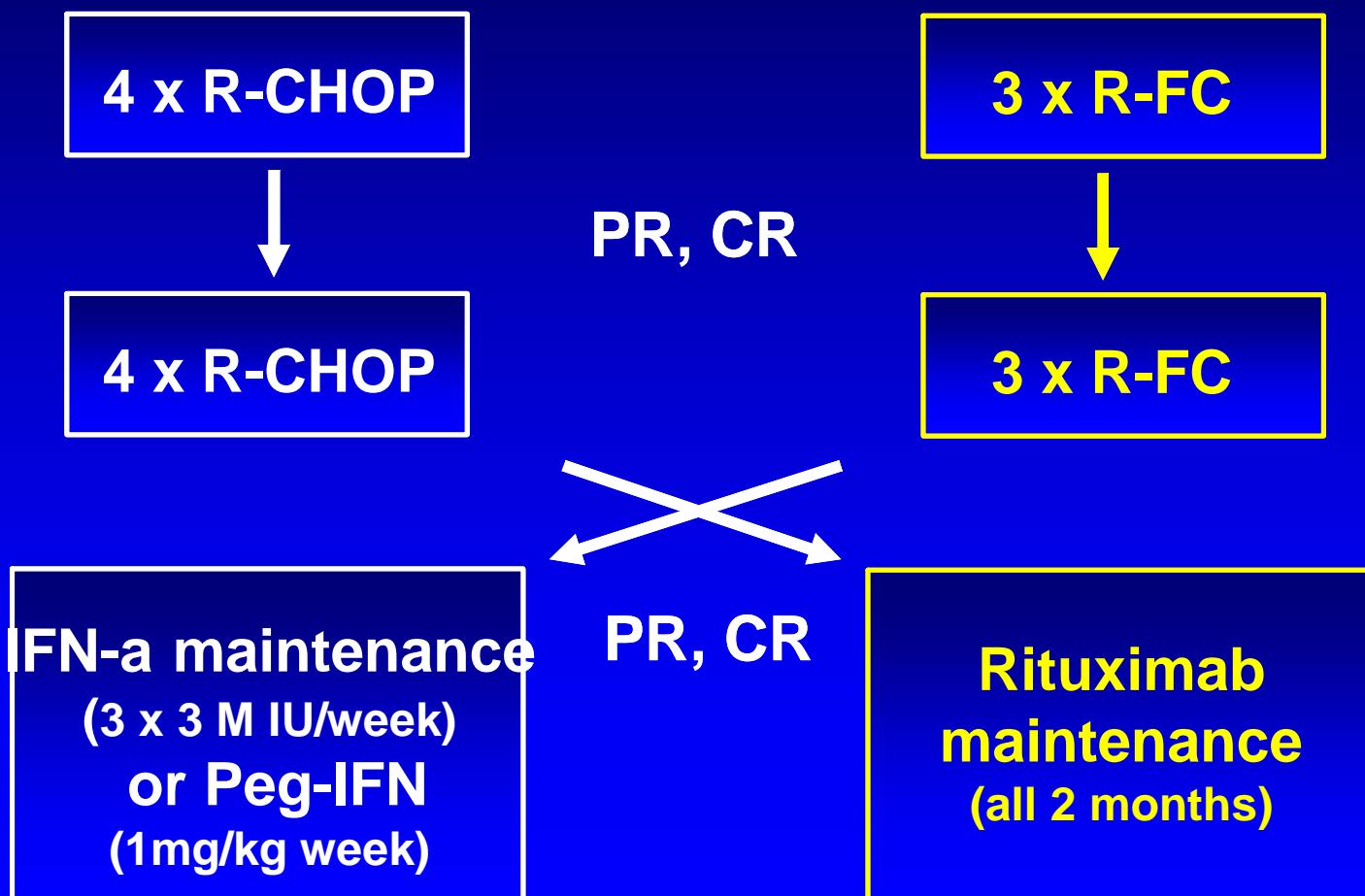
FCM vs. R-FCM Relapsed MCL



Maintenance vs. Observation in MCL Response duration (R-FCM)



European MCL network studies patients >65 years



MCL Elderly

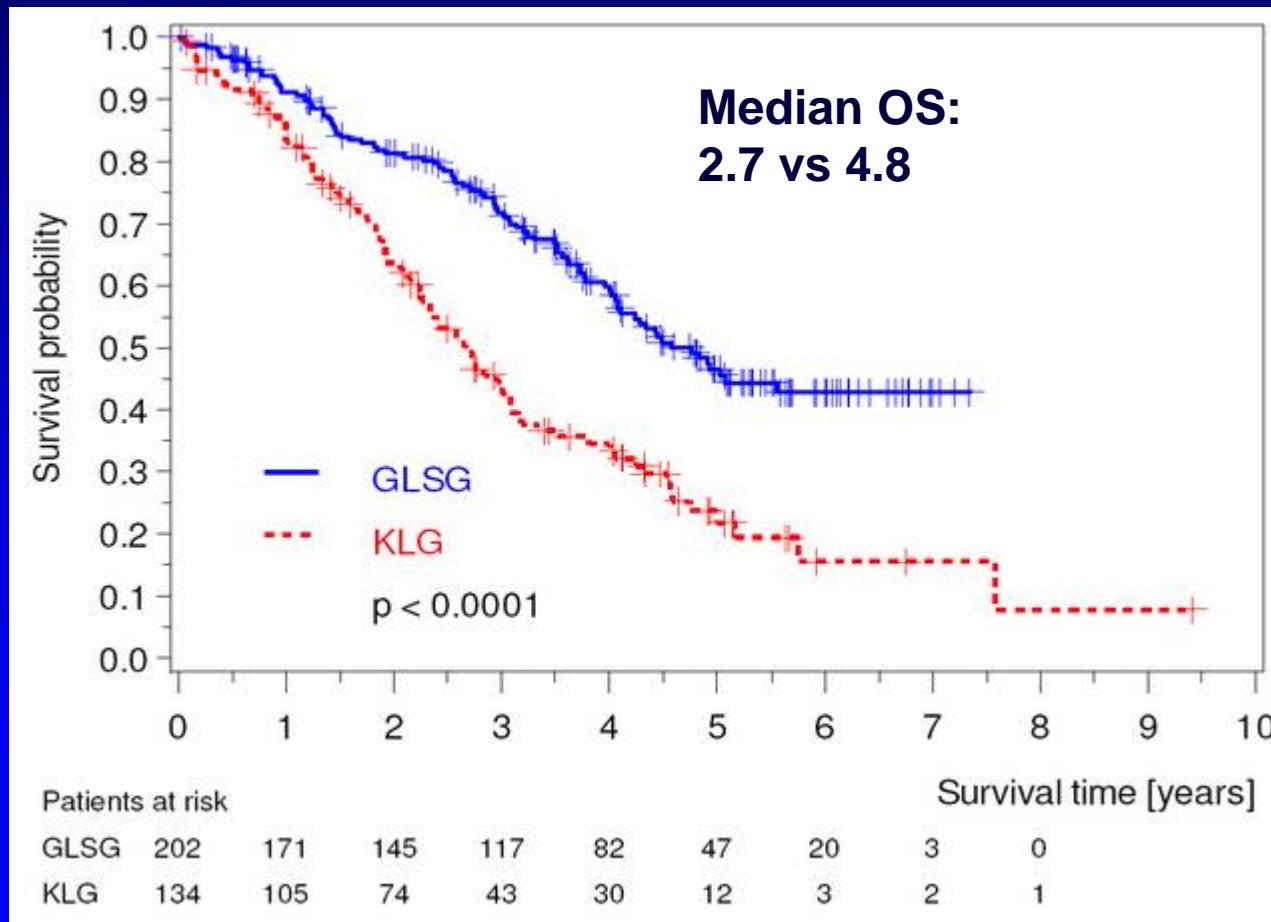
Response rate of induction

| | | | |
|------------------------------|------------|------------|-----------------------|
| Documented Response | 215 | 58% | |
| Abort without staging | 8 | | |
| CR | 71 | 34% | |
| CRu | 30 | 14% | CR+CRu: 49% |
| PR | 72 | 35% | CR+CRu+PR: 84% |
| SD | 6 | 3% | |
| PD | 19 | 9% | |
| ED | 9 | 4% | |

Kiel vs. GLSG cohort

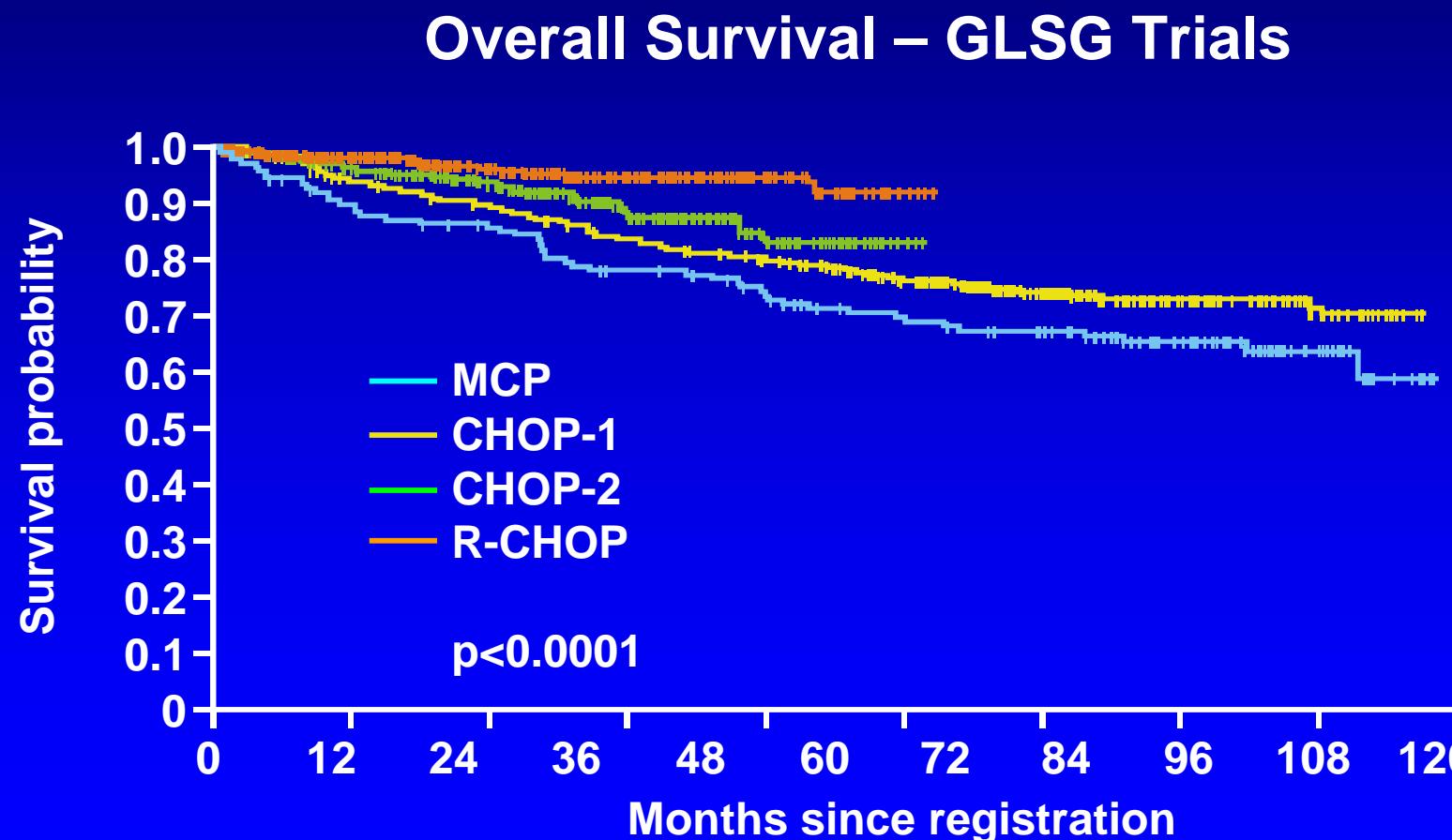
MCL - Historical comparison

Kiel/GLSG studies (balanced)



Herrmann, JCO 2008

GLSG cohort
FL - Historical comparison

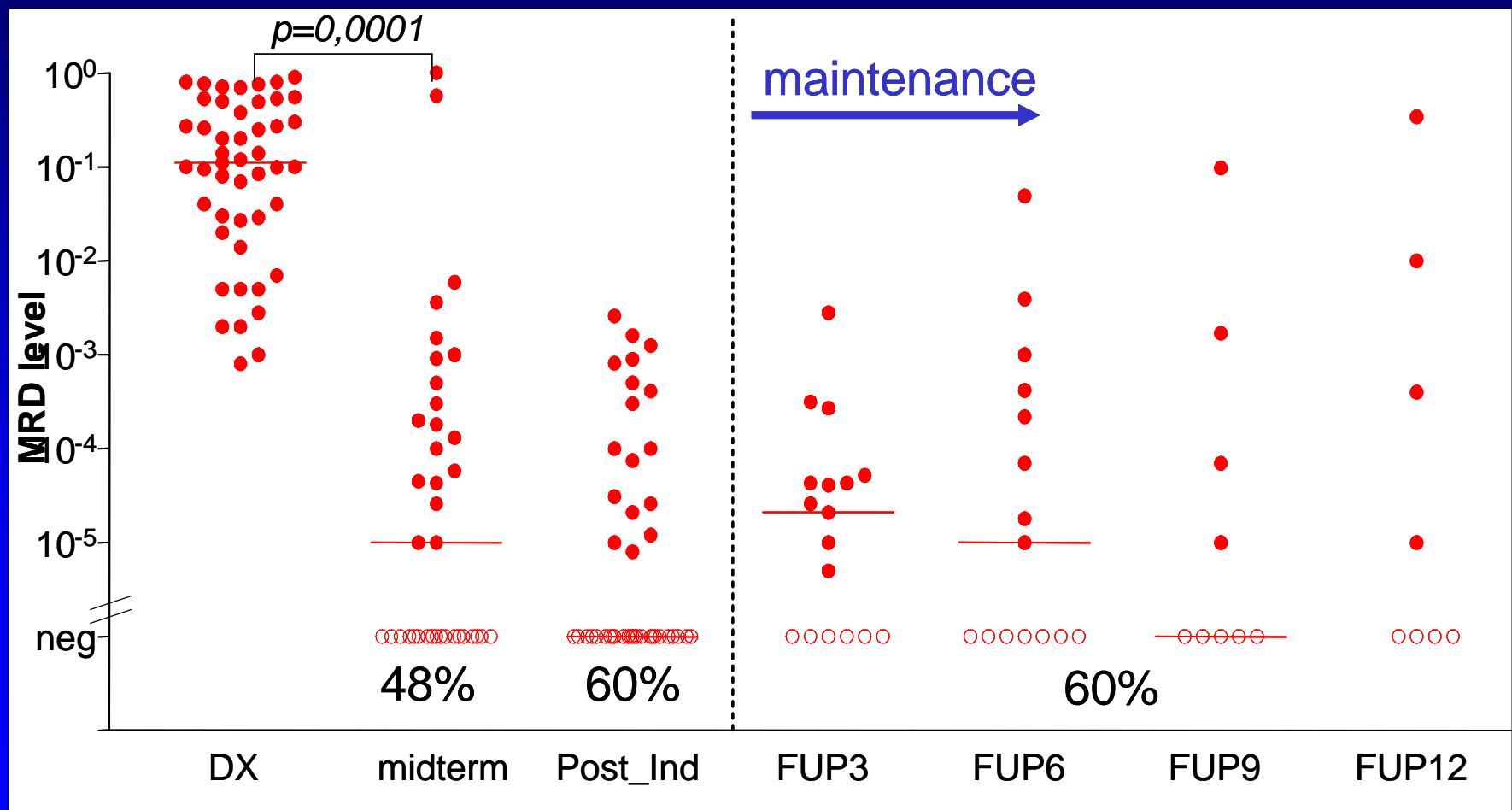




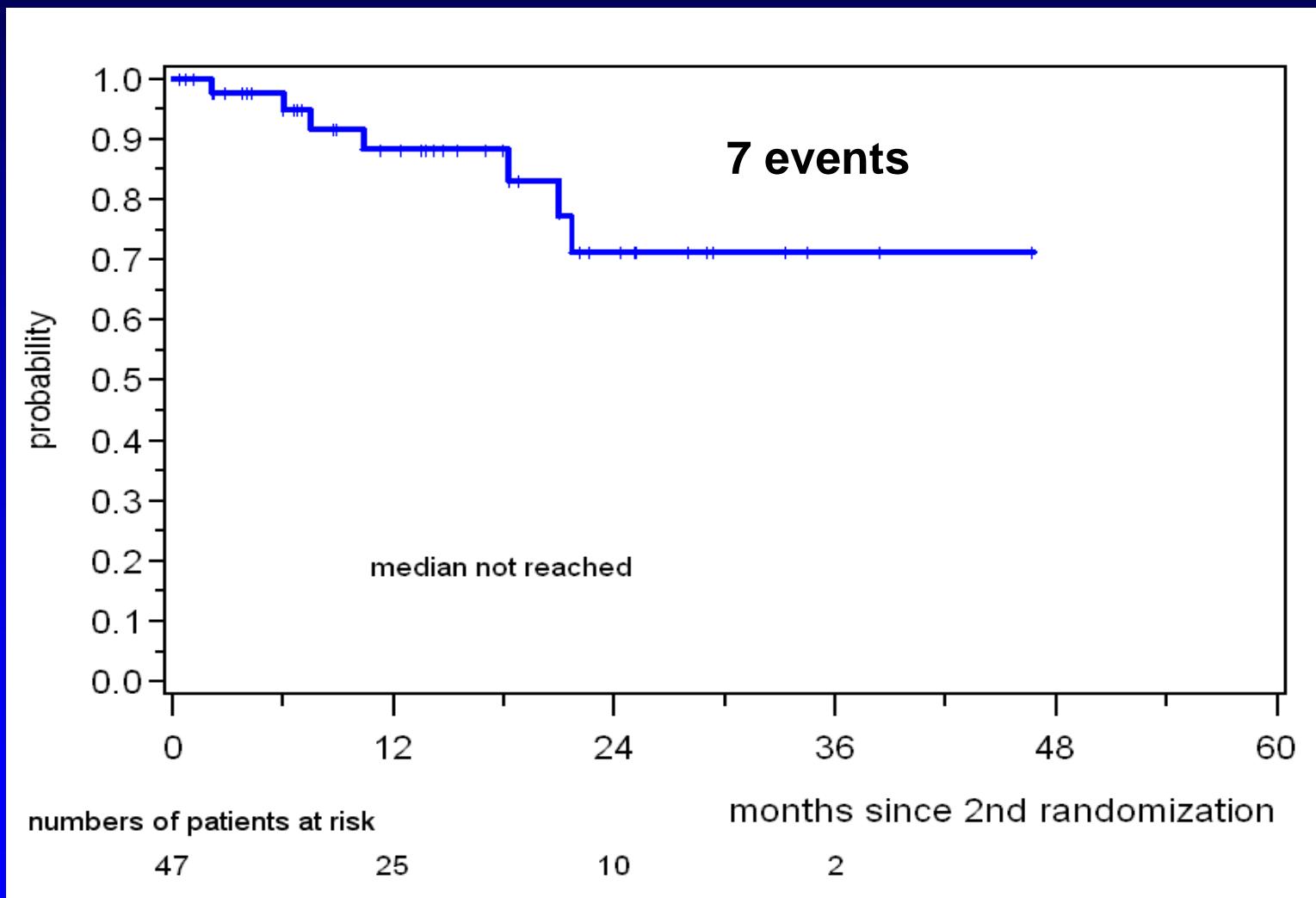
MRD detection in MCL

MRD follow-up elderly patients

n = 55



MCL Elderly
Response duration in CR



young patient (<65)

elderly patient (>65)

compromised patient

First line treatment

dose-intensified
immuno-chemotherapy
(either sequential:
e.g. R-CHOP =>PBSCT
or R-Hyper-CVAD)

conventional
immuno-chemotherapy
(e.g. R-CHOP)
↓
Rituximab maintenance ?
radioimmunotherapy ?

watch & wait ?
Rituximab monotherapy
Chlorambucil
Bendamustine

high tumor load:
immuno-chemotherapy
(e.g. R-FC)
↓
allo-transplant ?
radioimmunotherapy ?
Rituximab maintenance ?

immuno-chemotherapy
(e.g.
R-Bendamustine)
molecular approaches

higher relapse

molecular approaches: Bortezomib, CCI-779, Thalidomide/
Lenalidomide, Flavopiridol (preferable in combination)
repeat previous therapy (long remissions)

Mantle cell lymphoma

Lenalidomide

Table 4. Objective Response of Patients Receiving Lenalidomide Therapy by Histology Type (N = 49)

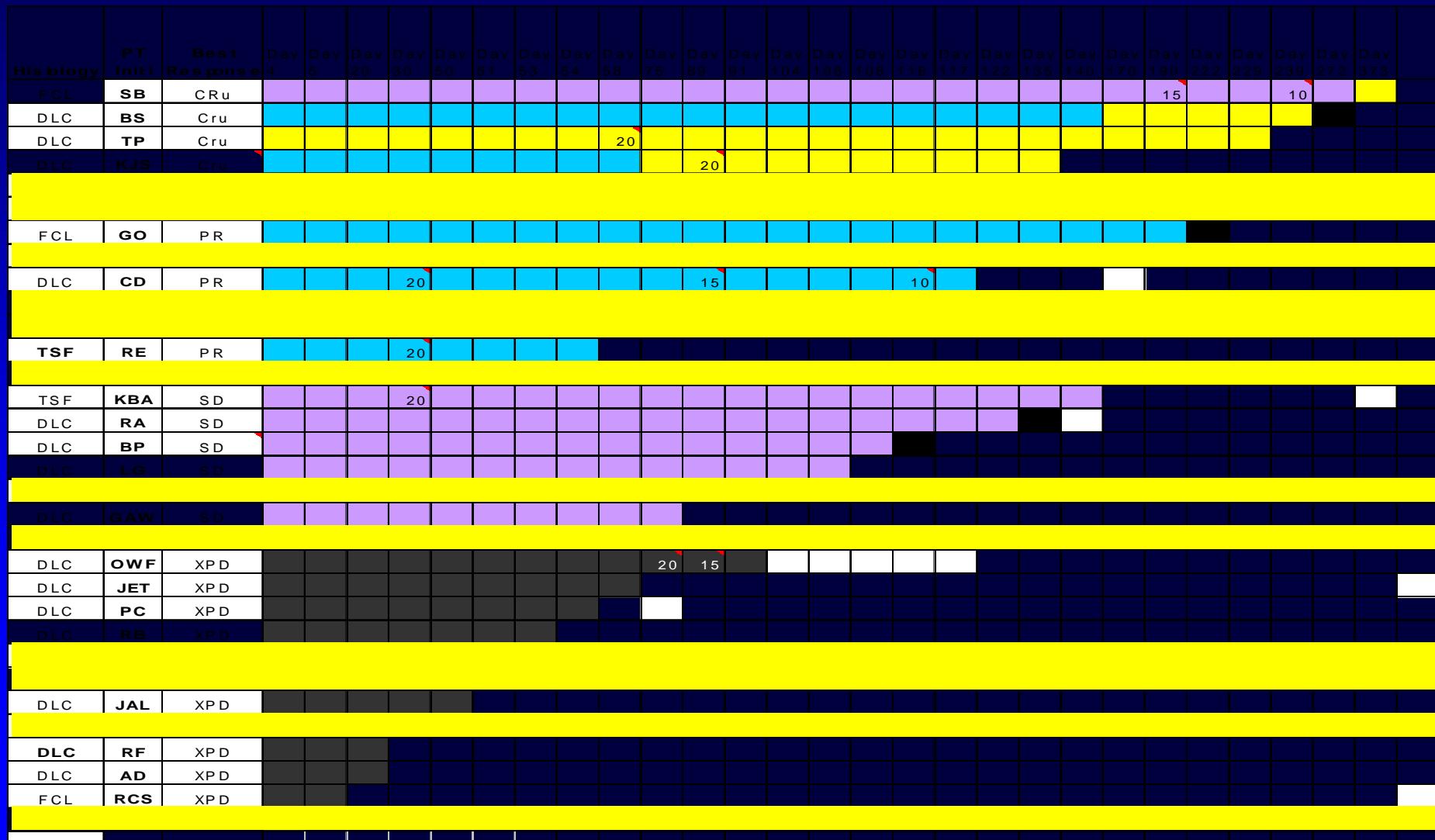
| Histology | No. of Patients | CR | CRu | PR | SD | PD | ORR (%) |
|-------------------------------------|-----------------|----|-----|----|----|----|---------|
| Aggressive NHL | 49 | 2 | 4 | 11 | 11 | 21 | 35 |
| Diffuse large B-cell lymphoma | 26 | 1 | 2 | 2 | 7 | 14 | 19 |
| Follicular center lymphoma, grade 3 | 5 | 0 | 1 | 2 | 0 | 2 | 60 |
| Mantle-cell lymphoma | 15 | 1 | 1 | 6 | 2 | 5 | 53 |
| Transformed low-grade lymphoma | 3 | 0 | 0 | 1 | 2 | 0 | 33 |

Abbreviations: NHL, non-Hodgkin's lymphoma; CR, complete response; CRu, unconfirmed CR; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

Mantle cell lymphoma

Lenalidomide

Wiernik ASH 2006



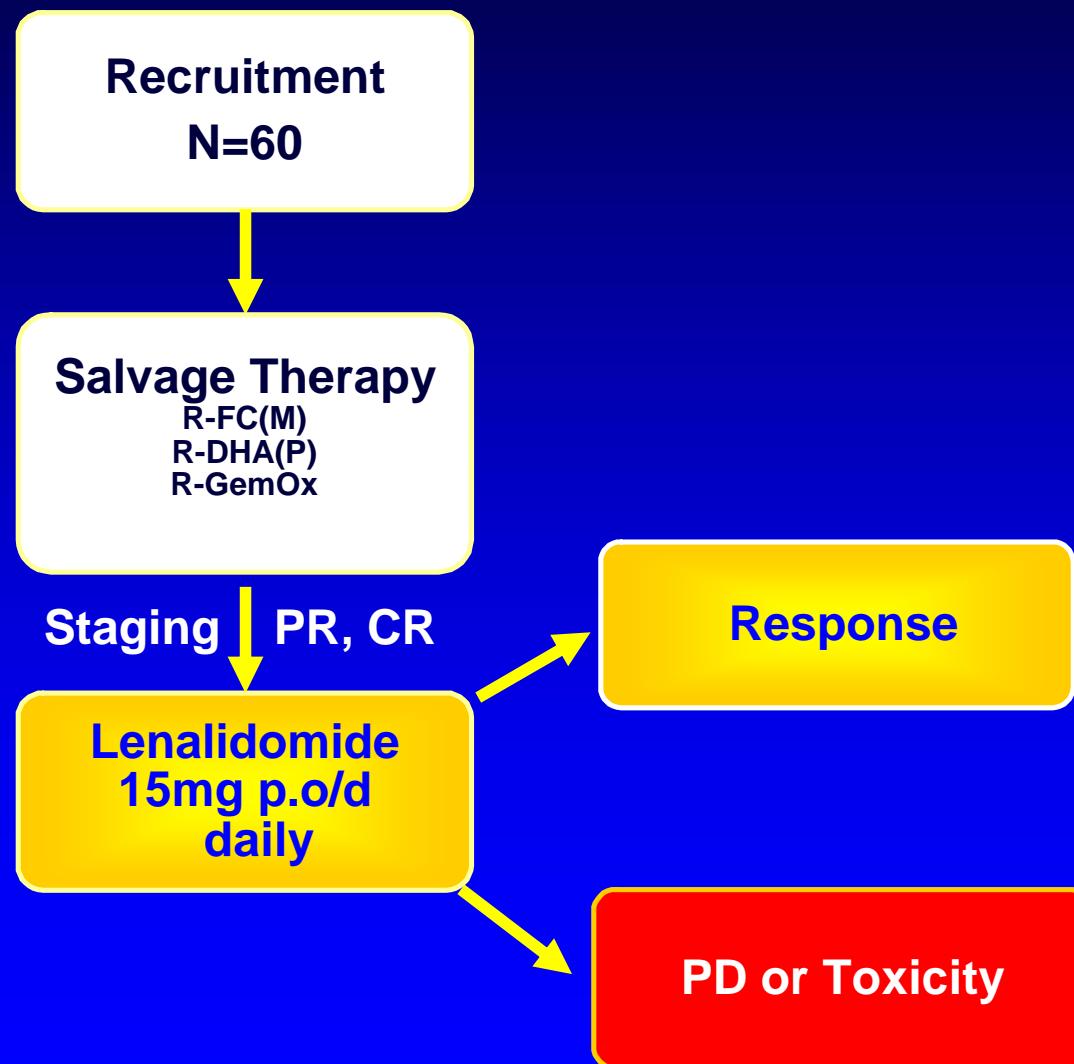
Feasability and efficacy of Lenalidomide maintenance after prior salvage in relapsed MCL

Inclusion Criteria

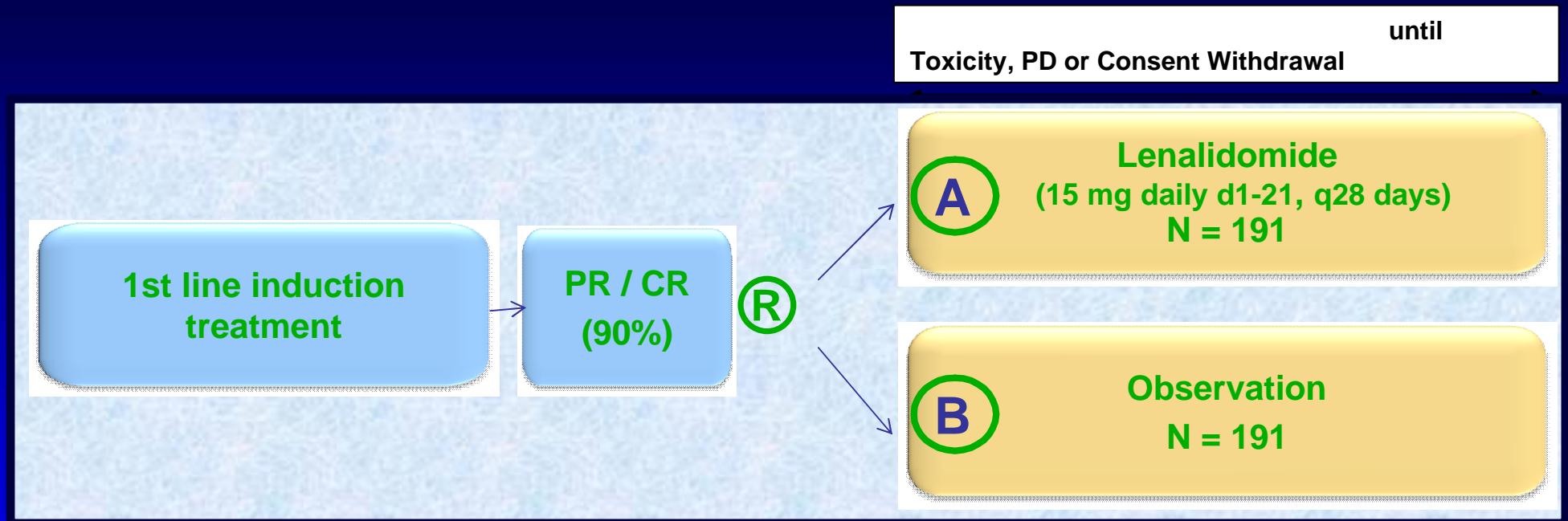
- histologically proven MCL
- ≥ 1 prior chemo Regimen
- Not eligible for/ relapse after ASCT

Endpoints

- Feasability
- Duration of Response
- TTP and PFS
- OS
- Safety



MCL-003 proposal: Study Design



- Phase 3, 1:1 Randomized, comparative, maintenance study post-completion of standard chemotherapy
- Newly Diagnosed MCL Patients with PR or CR after Initial Chemotherapy
- Transplant ineligible
- Primary endpoint: PFS
- Global Participation in Study: Europe, US, other countries around the world

MCL 003 protocol

European MCL Network

Ad hoc meeting at ICML in Lugano, June 6th 2008

Participants: M. Dreyling, E. Hoster, N. Ketter, C. Geisler, A. Kolstad, T. Lamy, St. Le Gouill, V. Ribrag, M. Silva, M. Trneny, M. van 't Veer, U. Vitolo, J. Walewski, P.L. Zinzani, Verena Voelter, N.N. (Chairwoman)

- so far, no maintenance approach is established. However, the current MCL elderly study of the *European MCL Network* might answer this question within the next couple of years (currently, more than 300 patients recruited).

- if the current trial proves the superiority of rituximab maintenance, this scheme (375 mg/m² every 2 months up to 2 years) will be added to both study arms.

MCL 002 protocol

European MCL Network

Ad hoc meeting at ICML in Lugano, June 6th 2008

Participants: M. Dreyling, E. Hoster, N. Ketter, C. Geisler, A. Kolstad, T. Lamy, St. Le Gouill, V. Ribrag, M. Silva, M. Trneny, M. van 't Veer, U. Vitolo, J. Walewski, P.L. Zinzani, Verena Voelter, N.N. (Chairwoman)

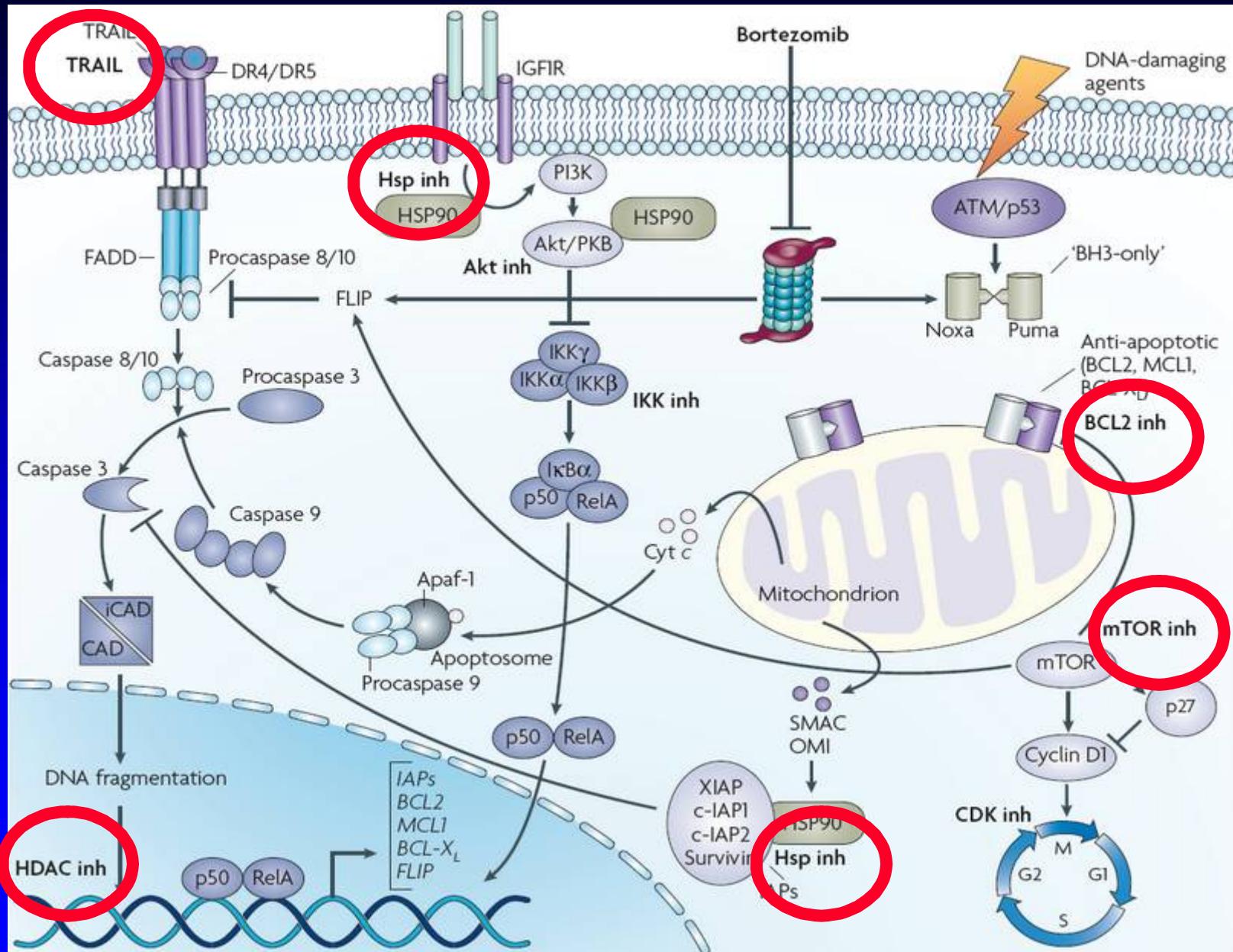
- accordingly, the *European MCL Network* is willing to act as leading group of an international first line trial in MCL patients comparing lenalidomide maintenance vs. observation after initial R-chemo in (elderly) patients not appropriate for autologous stem cell transplantation.

- this study may be performed as a registration trial (full monitoring etc.)
- however, the data center of the *European MCL Network* will have full insights into the data set.

European MCL Network
Discussion of lenalidomide maintenance

| | |
|---------------------|---|
| Italian | Inclusion criteria: Ara-C (e.g. DHAP) instead of chlorambucil Treatment: Lenalidomide <u>15 (-20)</u> mg 4 – 8 cycles induction chemotherapy |
| GELA | agreed |
| GOELAMS | Inclusion criteria: Ara-C (e.g. DHAP) Treatment: Lenalidomide 25 => <u>15</u> mg |
| PLSG | agreed Treatment: lower dose of Lenalidomide |
| SAKK | interested Treatment: Lenalidomide <u>10-15</u> mg (continuously) |
| BNLI | interested Treatment: lower dose of Lenalidomide R optional during induction ? |
| Portugal | agreed Treatment: Lenalidomide <u>10-15</u> mg Inclusion criteria: Ara-C (e.g. DHAP) instead of chlorambucil |
| Nordic group | agreed |
| Israel | agreed Treatment: Lenalidomide <u>15</u> mg (3 weeks on- 1 week off) |
| Catalanian | will not participate |

Altered pathways in MCL

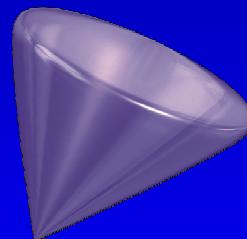


Jares, Nature Reviews 2007

Bortezomib: Mechanism of action



26S proteasome:
degrades tagged proteins



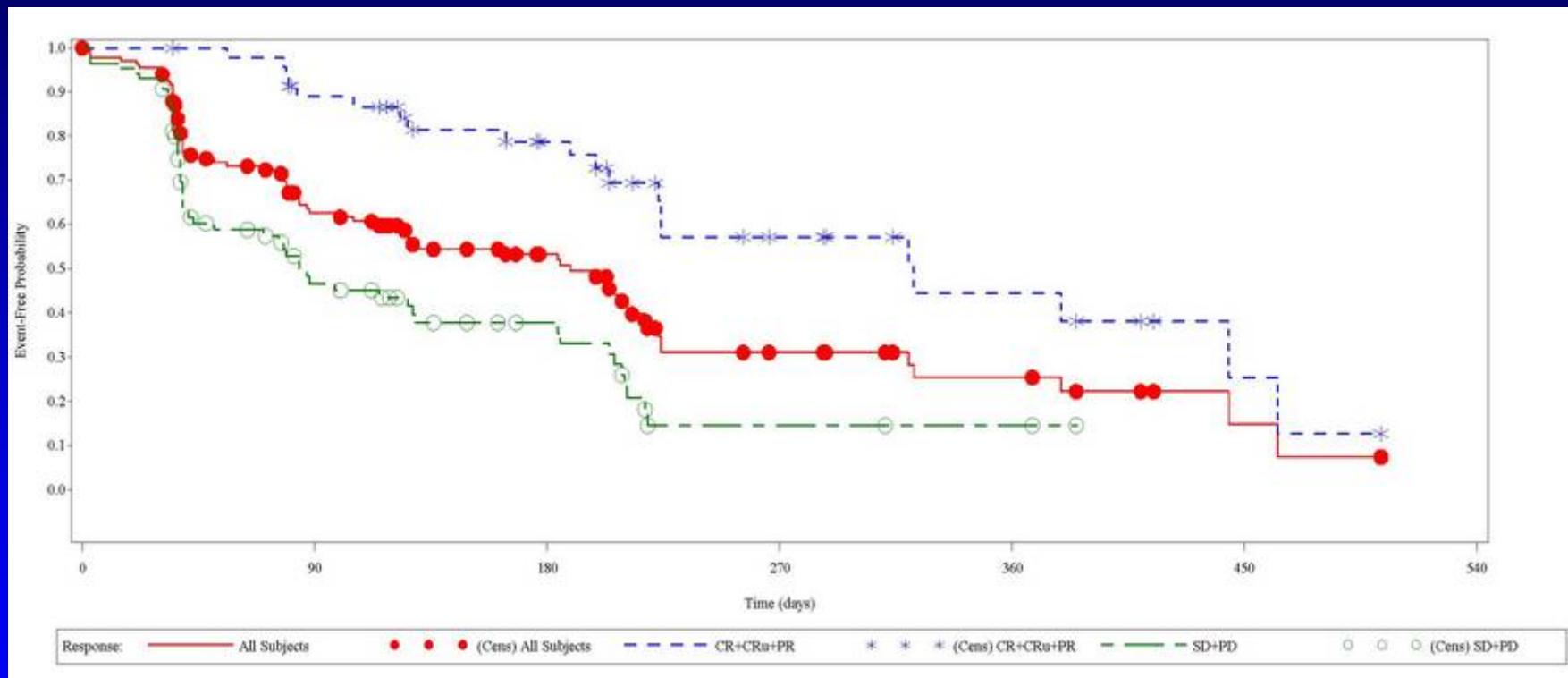
Bortezomib:
reversible inhibitor
of the proteasome



Inhibition:
prevents proteolysis
of tagged proteins

Clinical studies: bortezomib cytotoxic to a variety of lymphomas !

Progression-free survival (red) responders (blue), non-responders (green)



median TTP 6.2 months (median follow-up 13.4 months)

Goy ASCO 2006, Fisher JCO 2006

Bortezomib Ara-C combination in MCL **Pilot phase**

| | |
|---|--|
| Recruited patients (obtained informed consent) | 8 |
| Evaluable patients (obtained documentation) | 8 |
| Median time since start of treatment | 265 days |
| No. of applied cycles | 24 |
| Patients with 2 cycles | 4 |
| Patients with 4 cycles | 4 |
| Best response after 2 cycles (n=8) | |
| CR | 0 / 8 |
| PR | 4 / 8 |
| MR | 1 / 8 |
| SD | 1 / 8 |
| PD | 2 / 8 |
| Best response after 4 cycles (n=4) | |
| CR | 1 / 4 |
| PR | 3 / 4 |
| Event (progression/relapse/death) | 6 / 8 |
| Time to event | 49, 51, 119, 130, 147, 271 days |
| Salvage therapy | 4 / 8 |
| Ongoing remission | 2 / 8 |
| Time in remission | 233+ (PR), 311+ (SD) days |
| Alive | 5 / 8 |
| Death | 3 / 8 |
| | 2 deaths 75 and 314 days after start of treatment (both PD after 2 cycles) |
| | 1 death 271 days after start of treatment (in PR after 4 cycles) after allogeneic hematopoietic stem cell transplantation from HLA identical sibling |

Weigert, ASH 2006

European MCL network
relapsed MCL (DHAB = R-HAD)

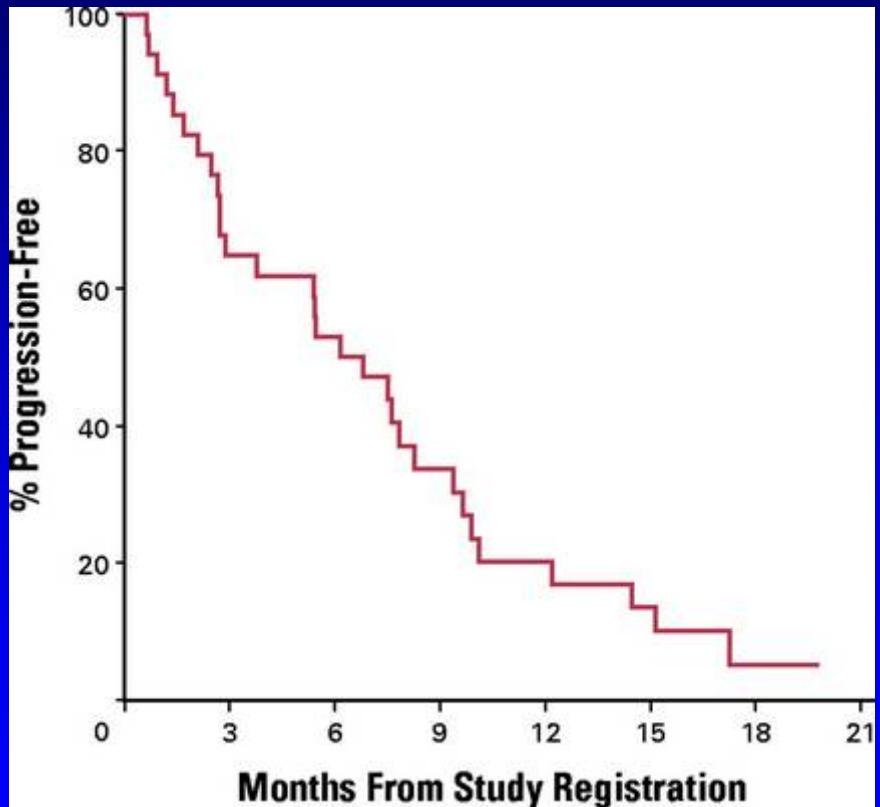
Patients: n=250, relapsed MCL
after/not appropriate for autologous PBSCT

| | | | |
|-----------------|----------------------|--------------------------|----------|
| Therapy: | Dexamethasone | 40 mg | day 1-4 |
| | Rituximab | 375 mg/m ² | day 1 |
| | Ara-C | 2 x 1–2 g/m ² | day 2 |
| | +/- | | |
| | Bortezomib | 1,5 mg/m ² | day 1, 4 |

Study aim: - Response rate
- Progression-free/overall survival
- Toxicity/feasability

Targeting protein Translation

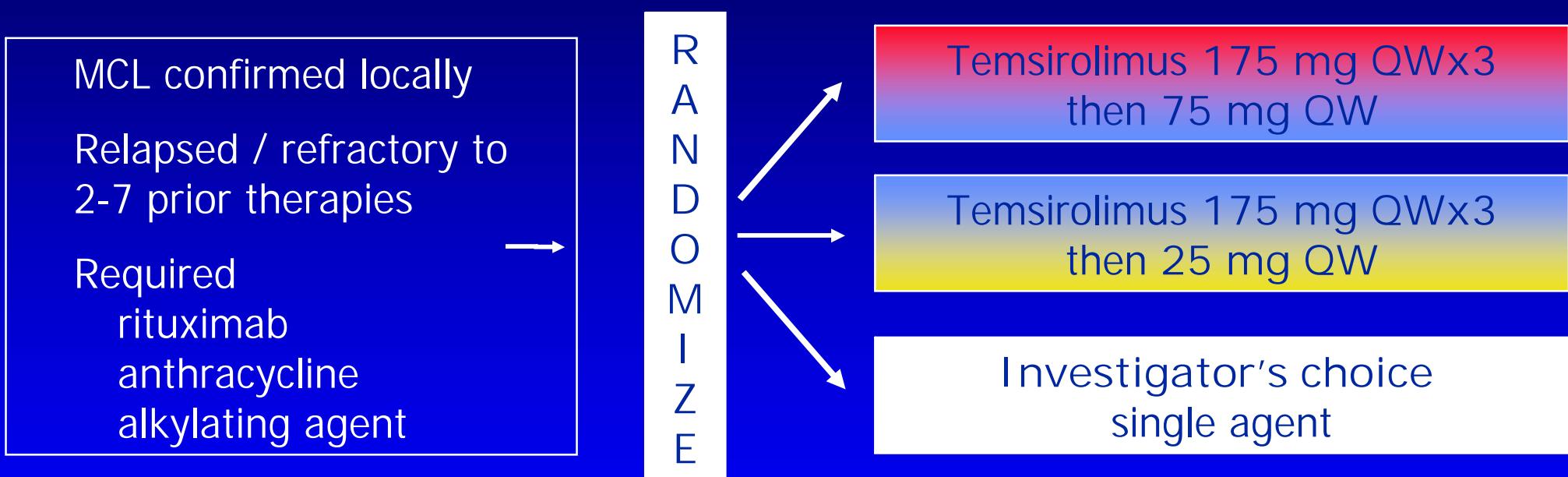
mTOR inhibitors: CCI-779 (Temsirolimus)



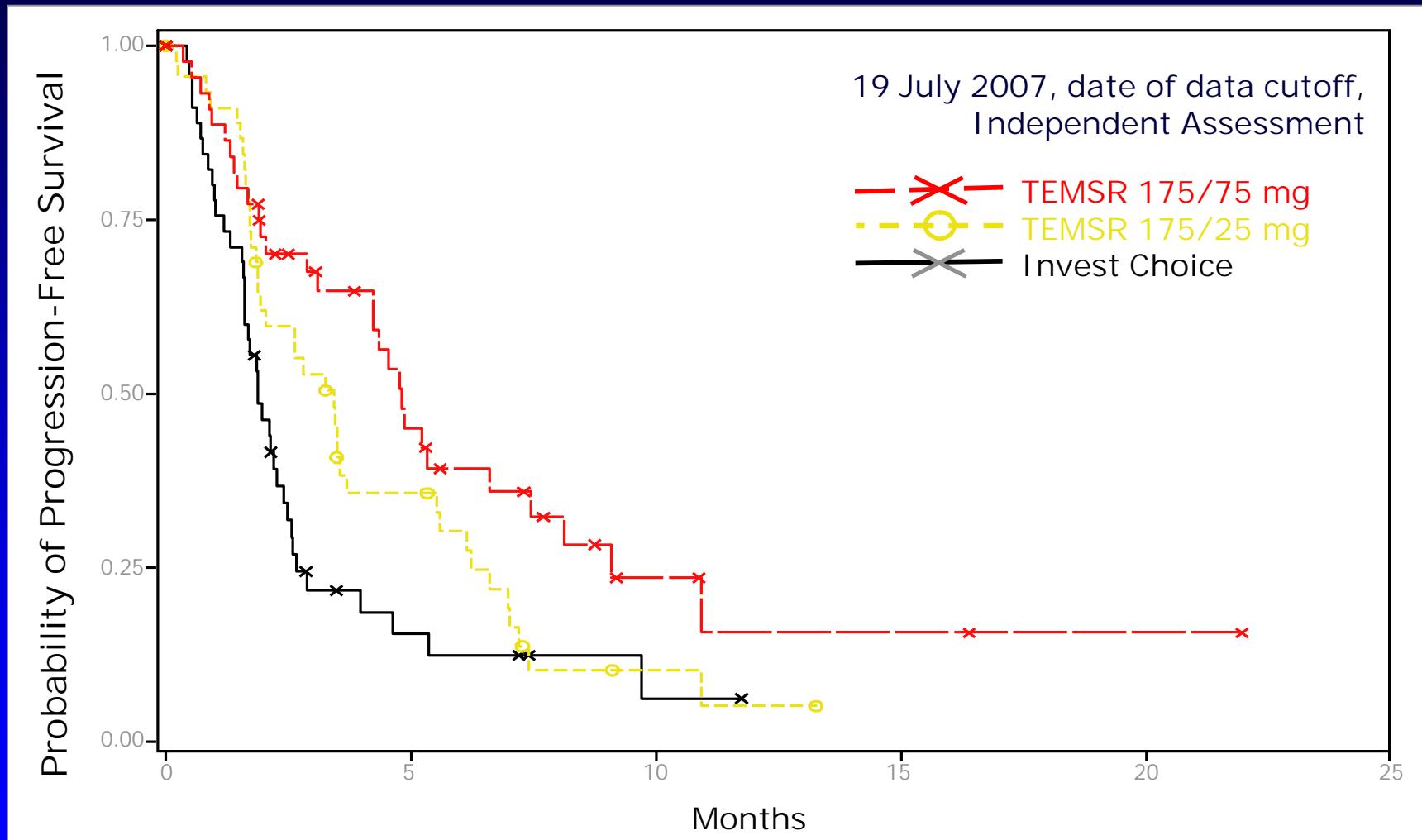
- response rate: 38% (13/34 pts),
1 CR, 12 PR
- duration of response: 6.9 months
- median follow-up 11 months
(range, 6.7 to 24.6+)
- thrombocytopenia ?

Witzig, JCO 2005

Study Design



Progression Free Survival (ITT)



Hess, ASCO 2008

BERT: Bendamustine/ rituximab/ temsirolimus (phase II)

BERT: Full target dose in phase II, 4 cycles

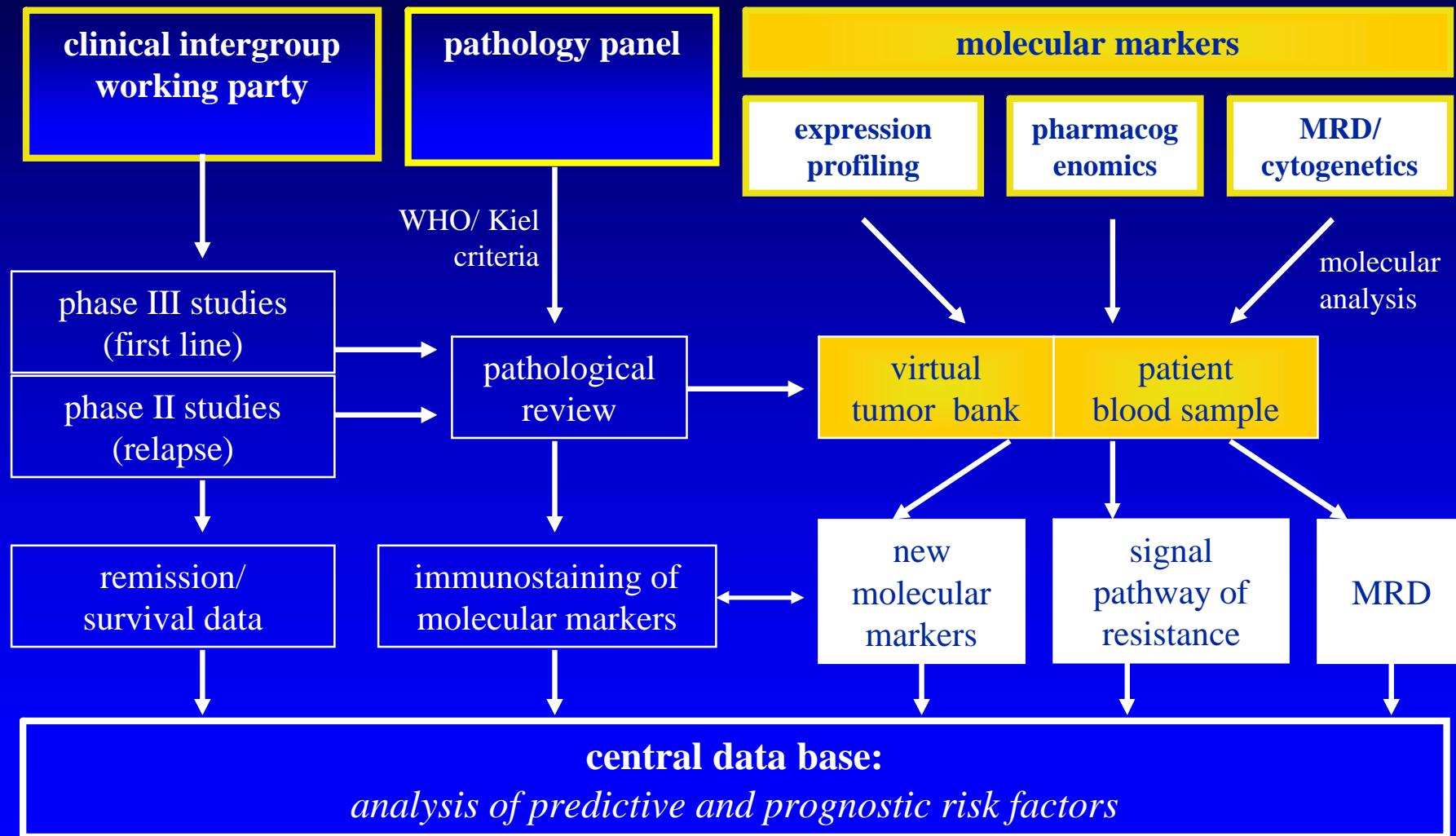
Bendamustine 90mg/m² day 1-2, repeat day 29 – 30

Rituximab 375mg/m² day 0 or 1, repeat day 28 or 29

Temsirolimus 75mg, Day 2, 9, 16, repeat day 30

European MCL Network

www.european-mcl.net



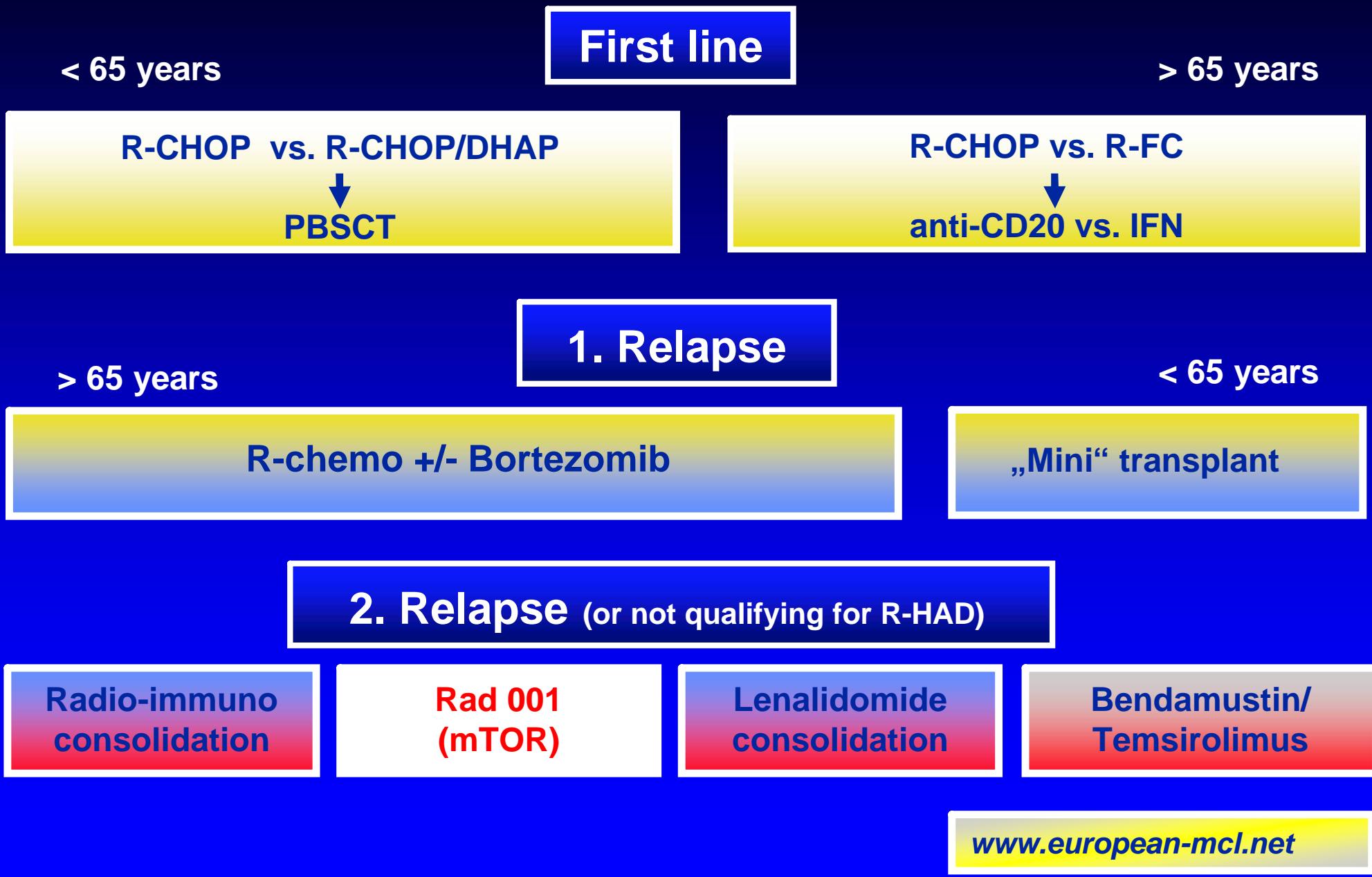


European MCL Network

annual conference in Munich 2007



European MCL Network: Clinical studies 2008/9



young patient (<65)

elderly patient (>65)

compromised patient

First line treatment

dose-intensified
immuno-chemotherapy
(either sequential:
e.g. R-CHOP =>PBSCT
or R-Hyper-CVAD)

conventional
immuno-chemotherapy
(e.g. R-CHOP)
↓
Rituximab maintenance ?
radioimmunotherapy ?

watch & wait ?
Rituximab monotherapy
Chlorambucil
Bendamustine

1. relapse

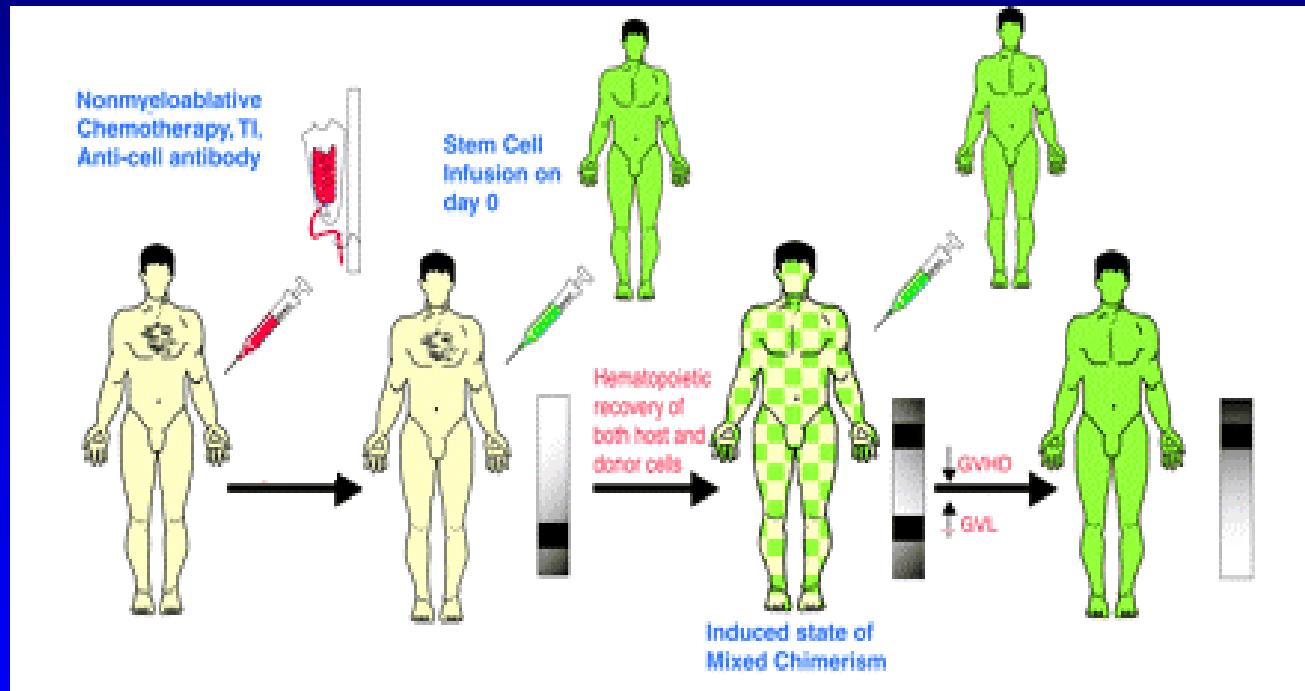
immuno-chemotherapy
(e.g. R-FC,
R-Bendamustine)
↓
molecular approaches ?
autologous PBSCT
radioimmunotherapy ?
Rituximab maintenance ?

immuno-chemotherapy
(e.g.
R-Bendamustine)
molecular approaches

higher relapse

molecular approaches: Bortezomib, CCI-779, Thalidomide/
Lenalidomide, Flavopiridol (**preferable in combination**)
repeat previous therapy (long remissions)

Allogeneic transplantation Dose-reduced conditioning



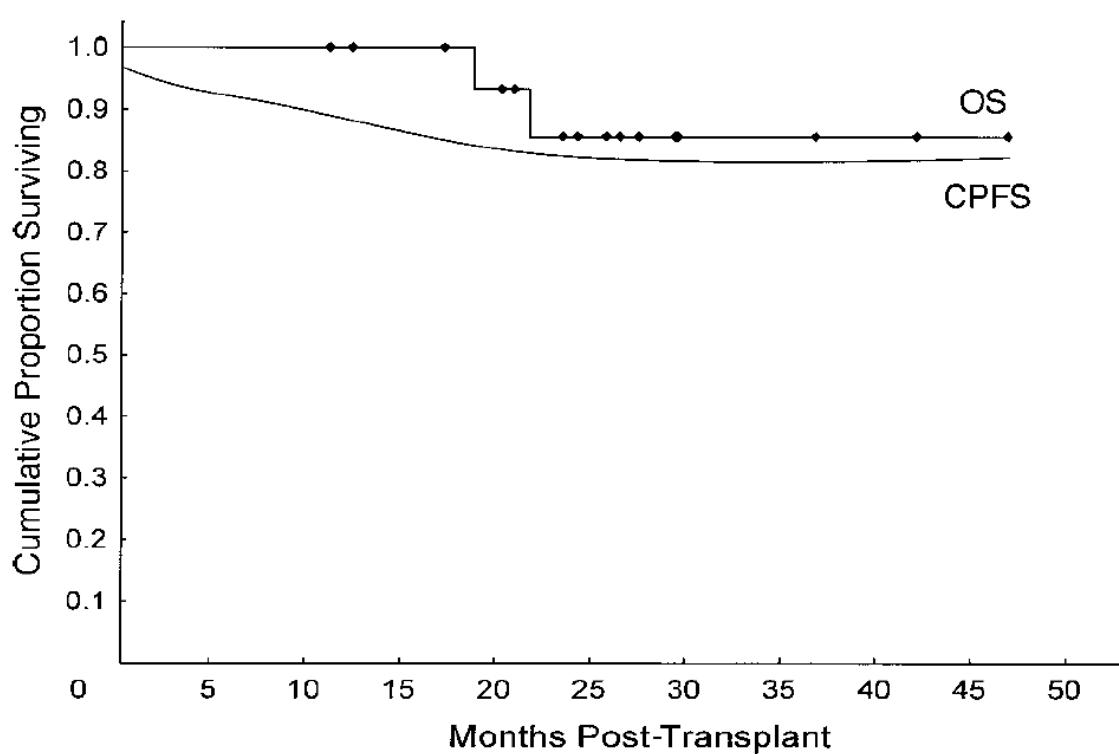
concept:

- reduced conditioning
(Flu/Cy, Flu/Bus, Flu/Mel)
- focus on
immunosuppression
(2 GyTBI, MMF, CyA)
- tandem (auto-allo)
transplantation

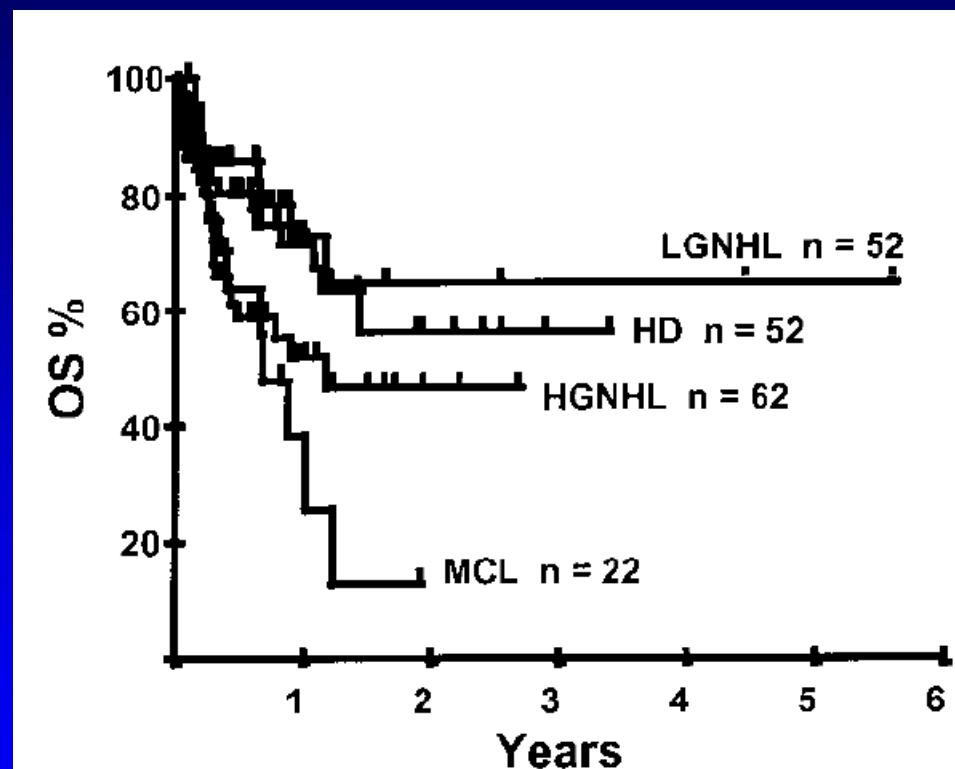
Spitzer, Oncologist, 2000

Allogeneic transplantation

Dose-reduced conditioning



Khoury et al, JCO 2003



Robinson et al, Blood 2002

young patient (<65)

elderly patient (>65)

compromised patient

First line treatment

conventional
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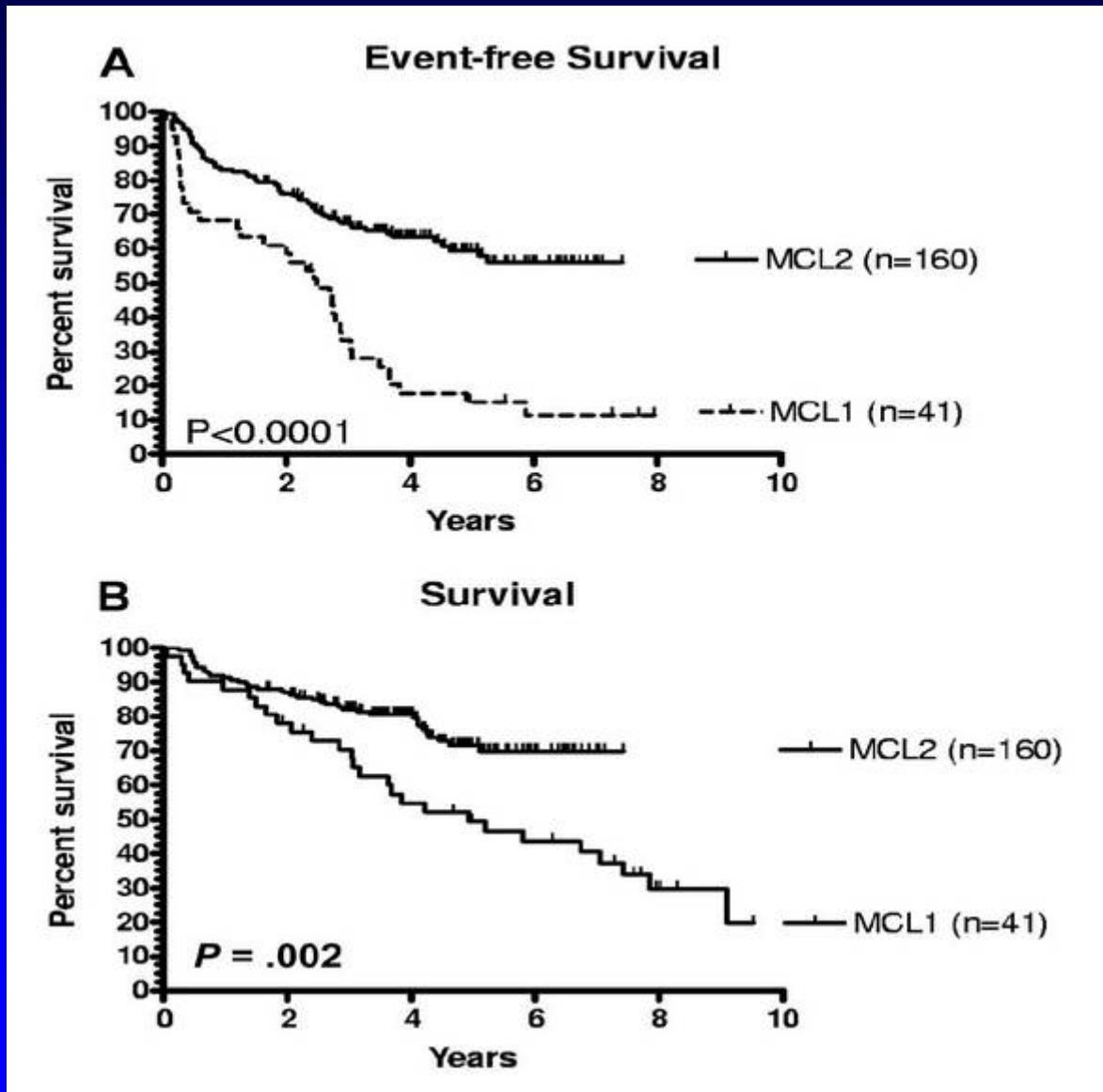
molecular approaches

high tumor load:
immuno-chemotherapy
(e.g. R-FC)
↓
allo-transplant ?
radioimmunotherapy ?
Rituximab maintenance ?

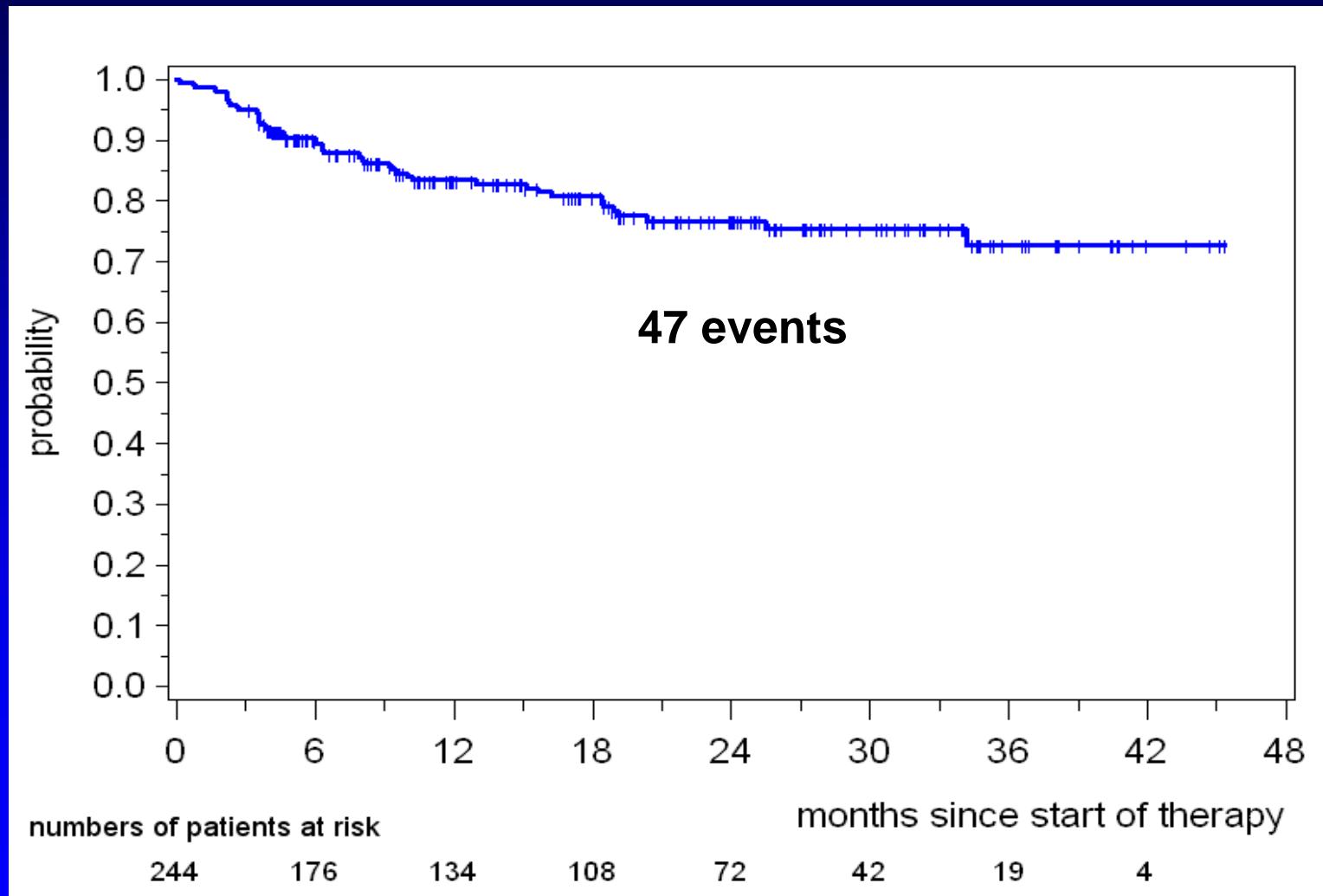
higher relapse

molecular approaches: Bortezomib, CCI-779, Thalidomide/
Lenalidomide, Flavopiridol (preferable in combination)
repeat previous therapy (long remissions)

Mantle cell lymphoma
CHOP/High dose => ASCT



MCL younger
Time to treatment failure



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dose-intensified
immuno-chemotherapy
(either sequential:
e.g. R-CHOP =>PBSCT
or R-Hyper-CVAD)

elderly patient (>65)

high tumor load:
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compromised patient

watch & wait ?
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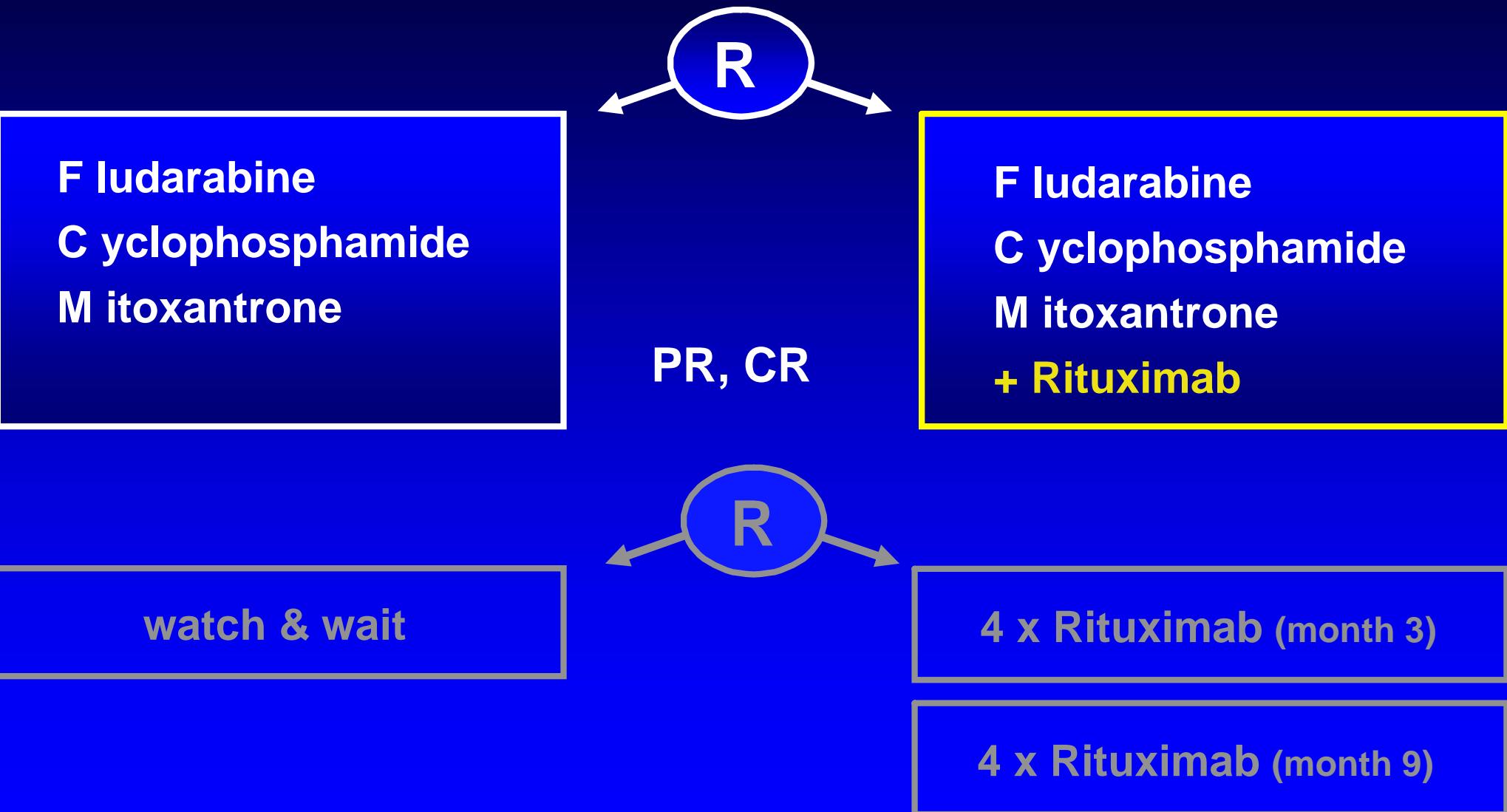
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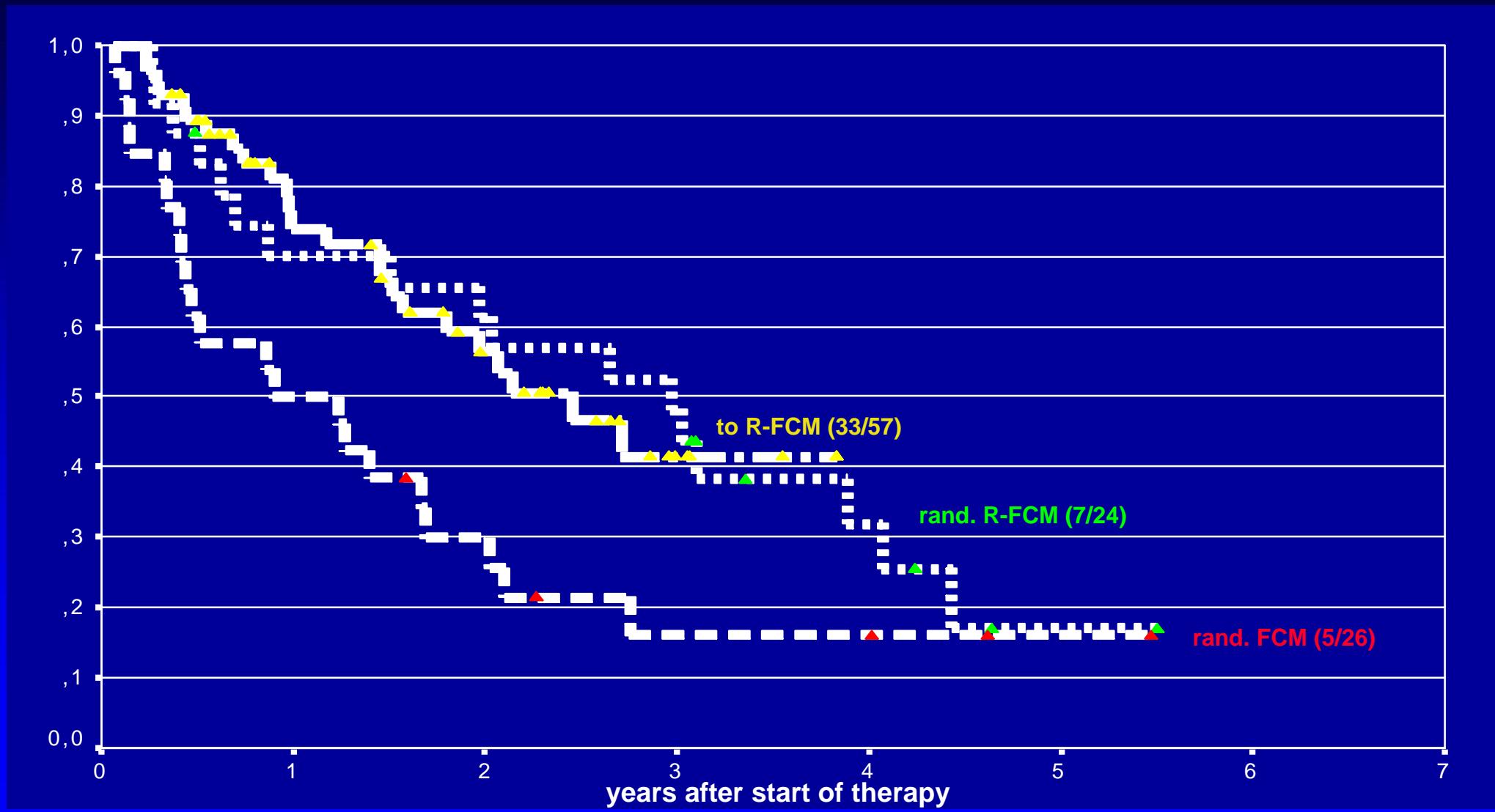
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FCM vs. R-FCM
Relapsed MCL



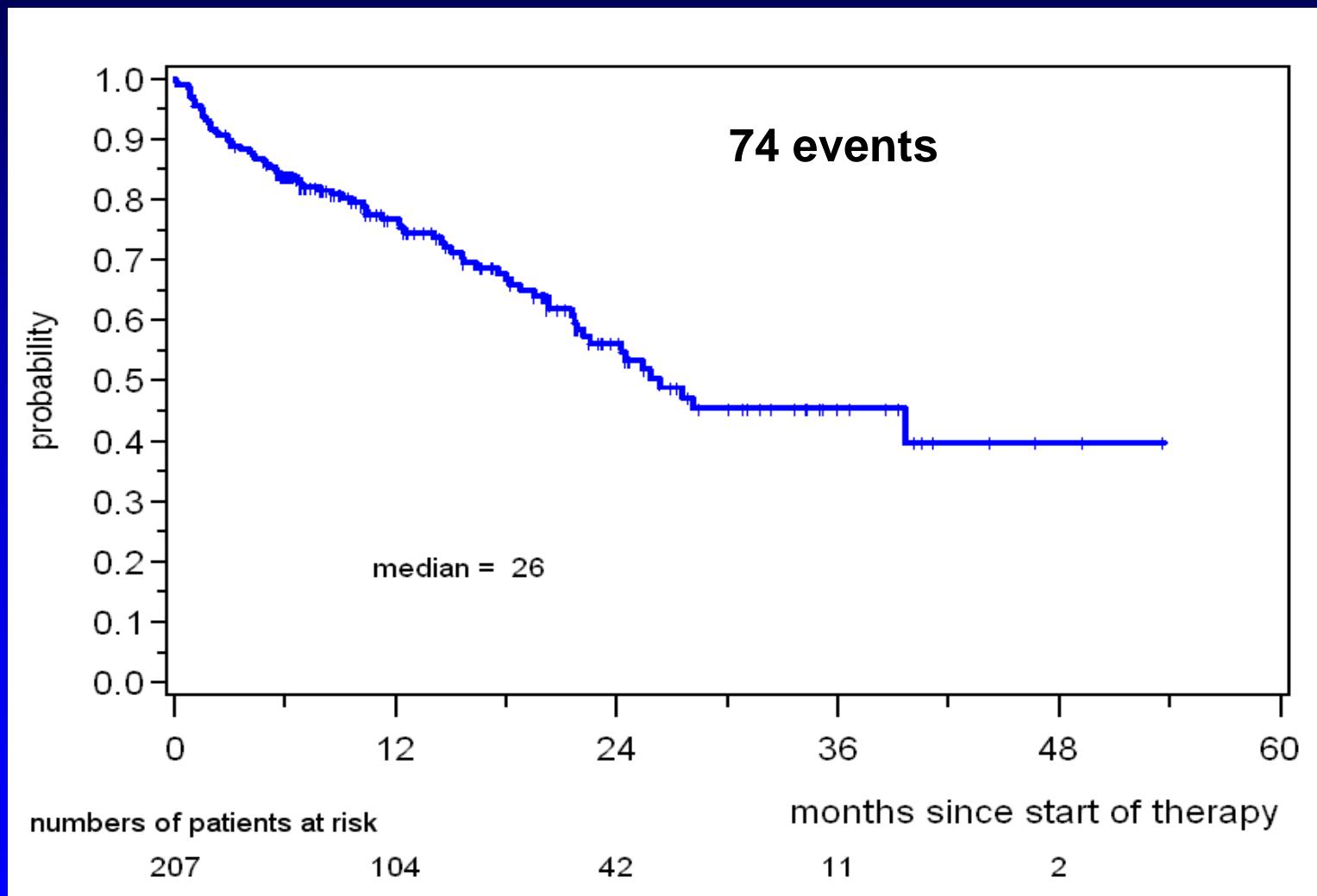
FCM vs. R-FCM: MCL Overall survival



Dreyling, ASCO 2005 (update)

$p=0.0577$ ($p=0.0033$)

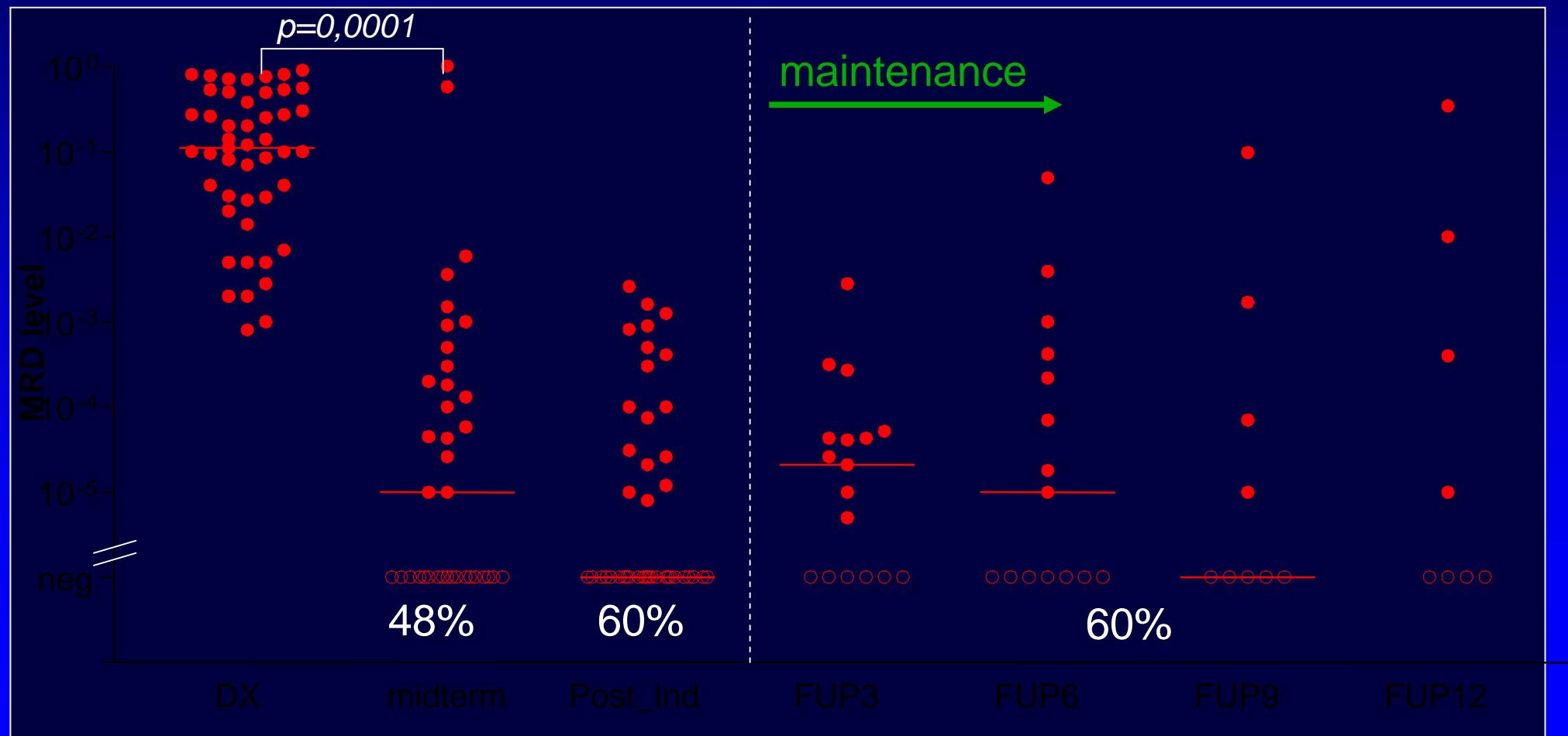
MCL elderly
Time to treatment failure



MRD detection in MCL

MRD follow-up elderly patients

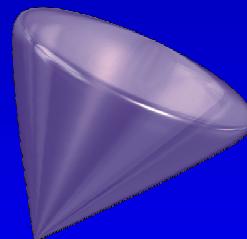
n = 55



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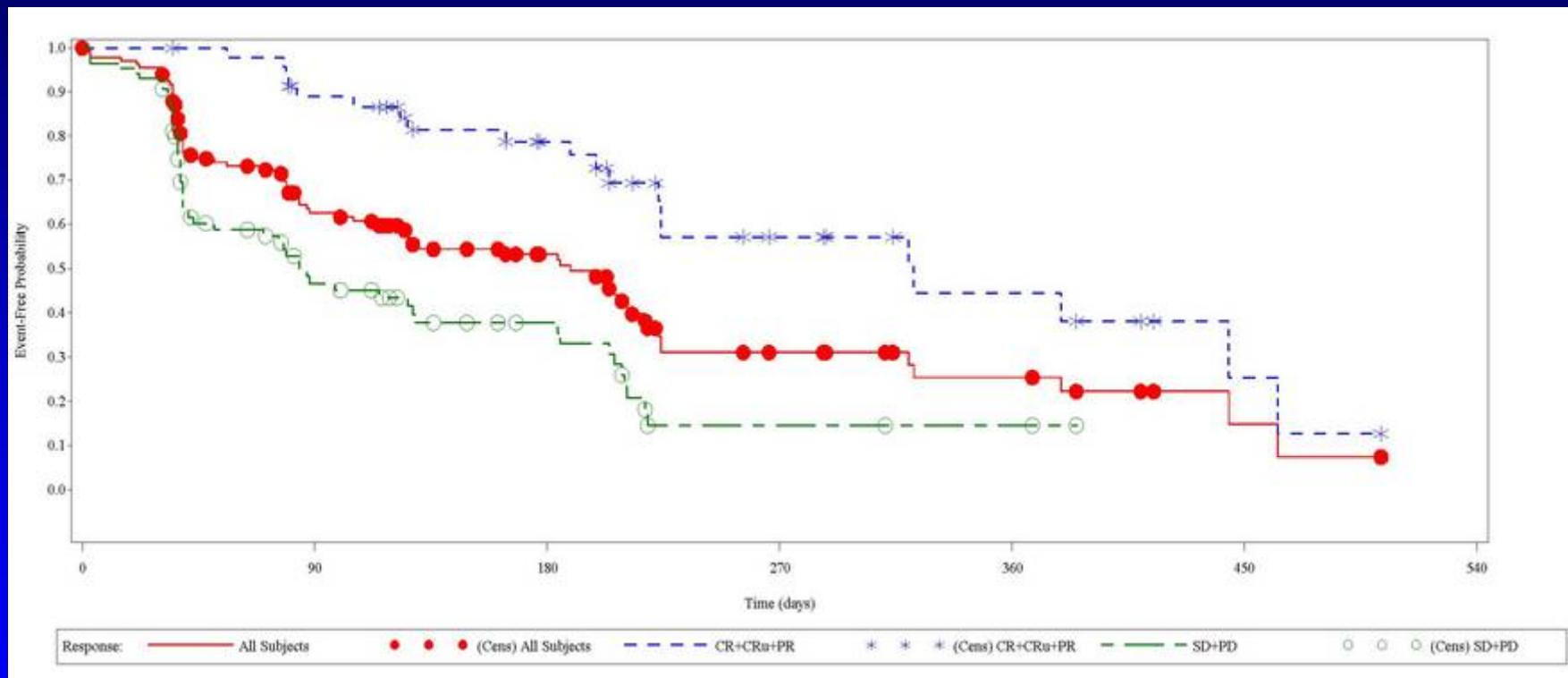
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European MCL Network: Clinical studies 2008/9

