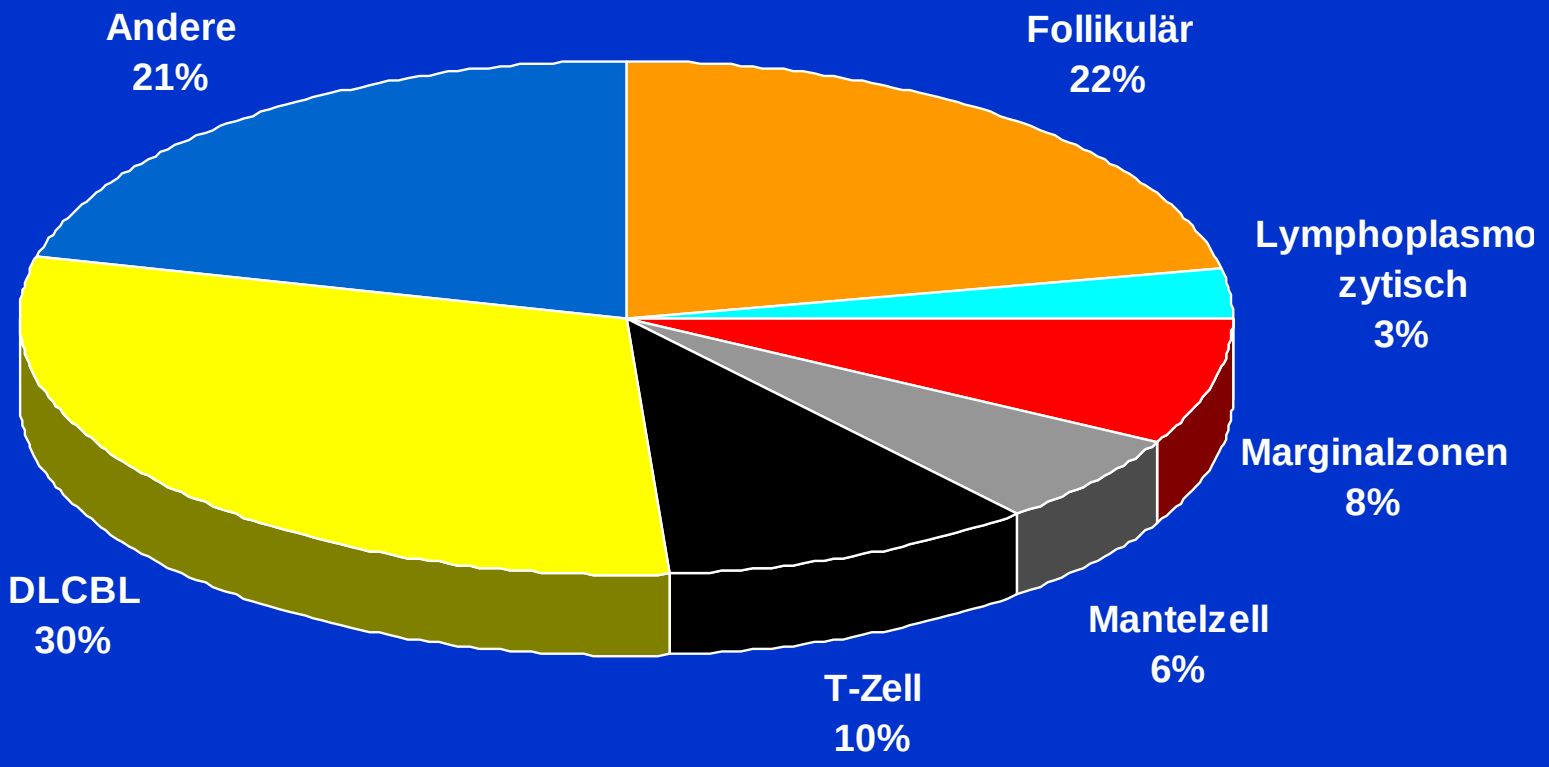
Niedrig maligne Lymphome

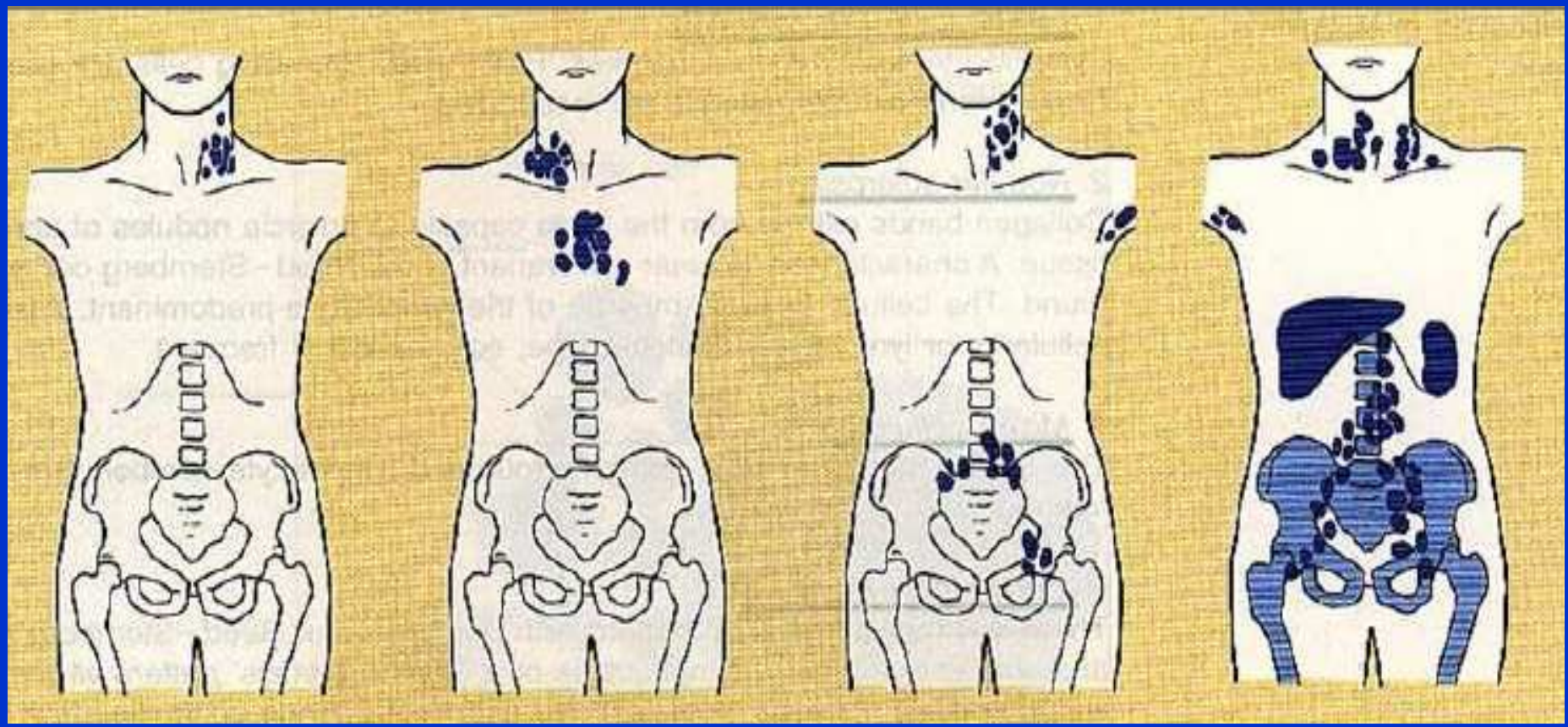
Dr. G. Schmidt
Onkologische Schwerpunktpraxis
Muhr am See / Weißenburg

Gemeinschaftspraxis
Muhr am See
Weißenburg

Non-Hodgkin Lymphome

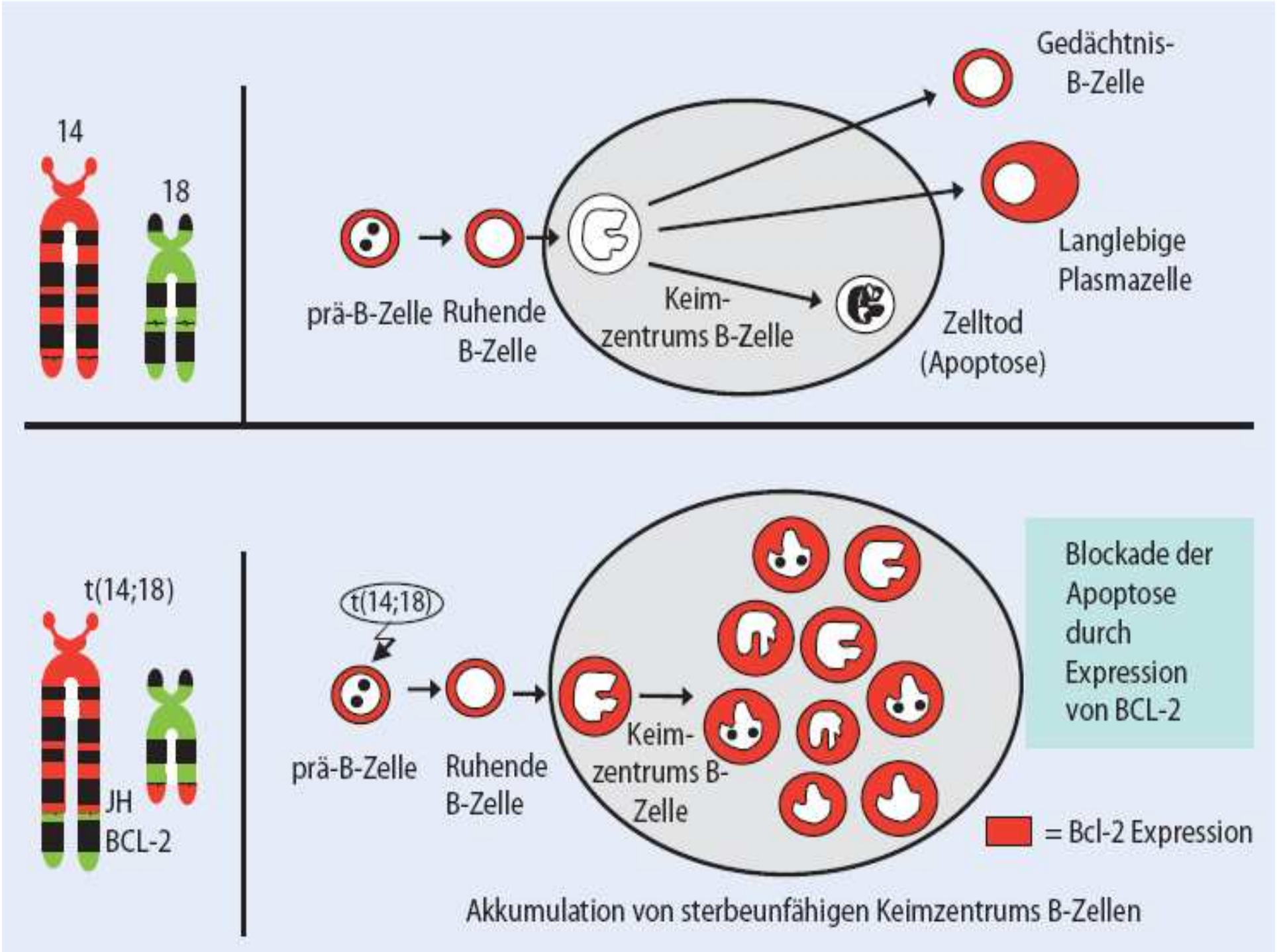


Stadien: Ann-Arbor Klassifikation

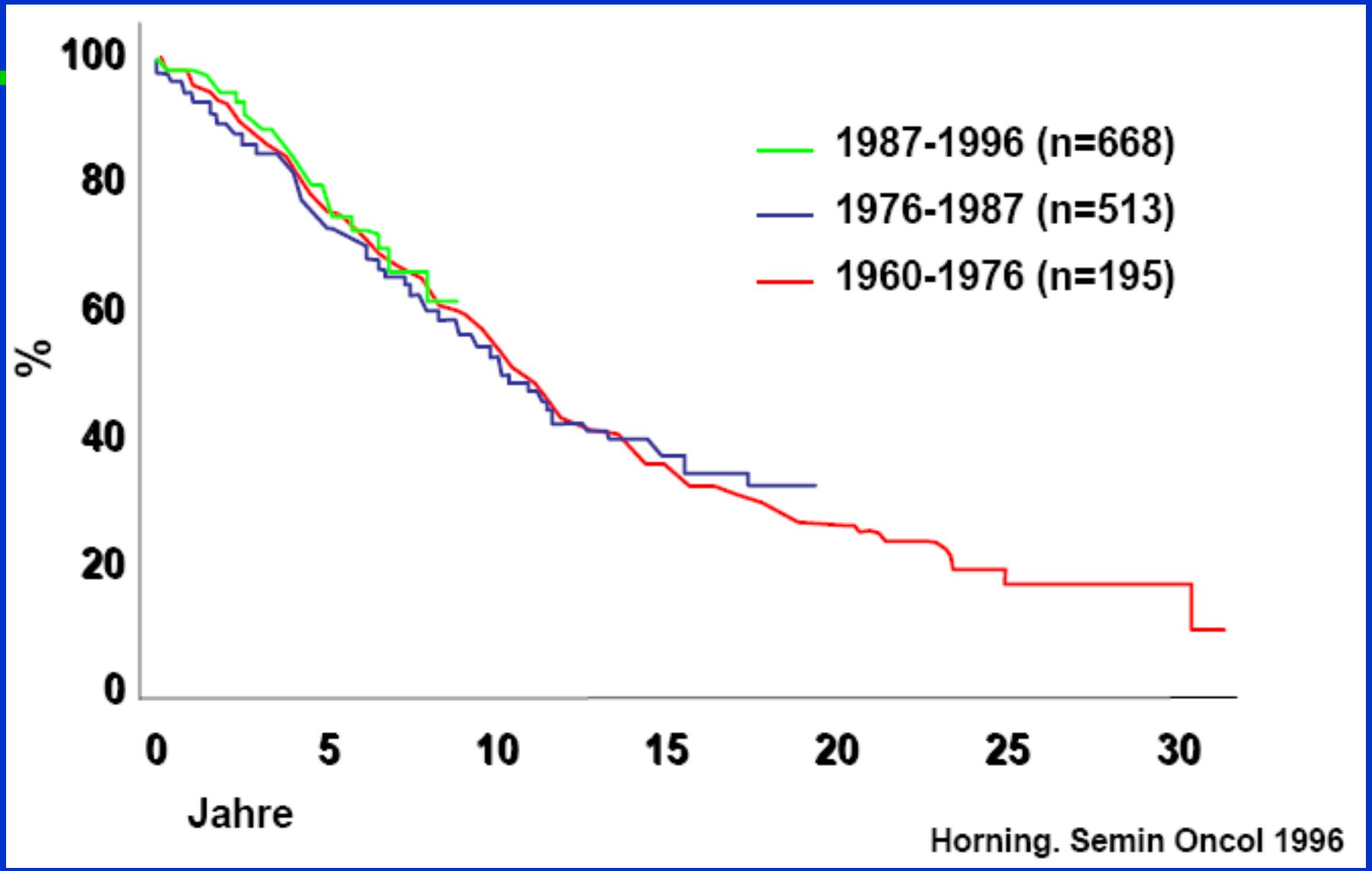


Follikuläres NHL

- Grading!
- 20-30% Transformation in hochmal. NHL (3% pro Jahr)
- St. I/II nur 20% bei Diagnosestellung
- auch im Stadium III / IV medianes ÜL 8-12J.
- 80-90% t(14;18) -> Überexpression des antiapotptotischen bcl-2 Proteins, Akkumulation langlebeiger Centrocyten (14: IgH-Promotor / 18: bcl-2)


14
18
prä-B-Zelle
Ruhende B-Zelle
Keim-zentrums B-Zelle
Zelltod (Apoptose)
Gedächtnis-B-Zelle
Langlebige Plasmazelle
t(14;18)
JH
BCL-2
t(14;18)
prä-B-Zelle
Ruhende B-Zelle
Keim-zentrums B-Zelle
Blockade der Apoptose durch Expression von BCL-2
= Bcl-2 Expression
Akkumulation von sterbeunfähigen Keimzentrums B-Zellen

Gesamtüberleben



Therapie: Stadium I / II

- Kurative Intention
- Strahlentherapie: IF, EF, TNI
- Hohe lokale Kontrolle (95%)
- bis 50% Langzeitremissionen

Therapie: Stadium III / IV

- watch & wait
  - kein negativer Einfluß auf Gesamtüberleben; 10J.-ÜLR 70%, Spontanremissionen 20%
- Therapieindikation bei:
  - B-Symptomen
  - rasche Progredienz
  - Hämatopoetische Insuffizienz
  - Drohende Organschäden

Was ist die beste Erstlinientherapie?

Primärtherapie: Vor Rituximab

GLSG Erfahrungen

	COP	CHOP	MCP	PmM
CR	21%	20%	16%	35%
PR	65%	71%	62%	5%
OR	86%	91%	78%	80%

Brittinger 1984, Unterhalt 1996

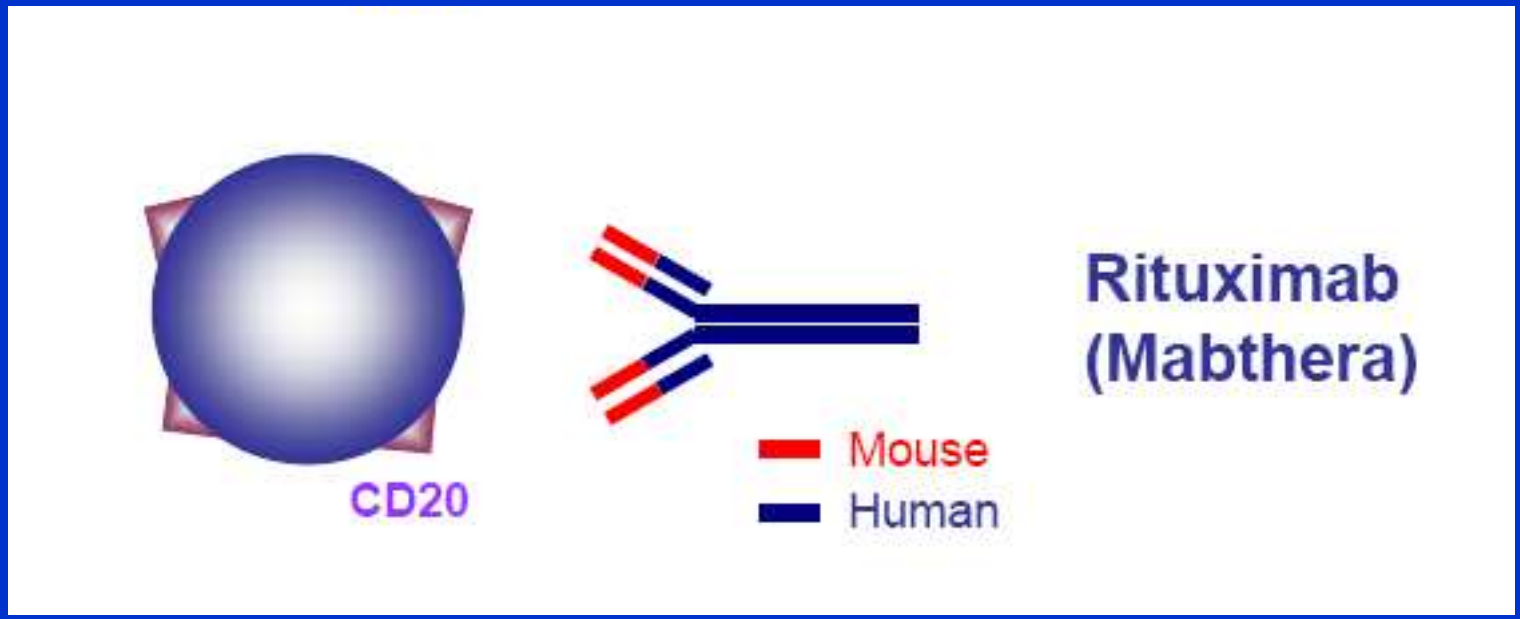
Primärtherapie

- CHMB mono: RR 50-75%
- CVP: OR =, CR ↑, PFS ↑, OS =
- Fludara mono: 65-85% RR, CR 37-47%, aber: F < CHOP (RR, OS)
- Rituximab mono: OR 50%, PFS 13 mo.
- R-Benda ≈ R-CHOP (Rummel, ASH2007)
- RIT: PFS 40% 10J., OS 90%

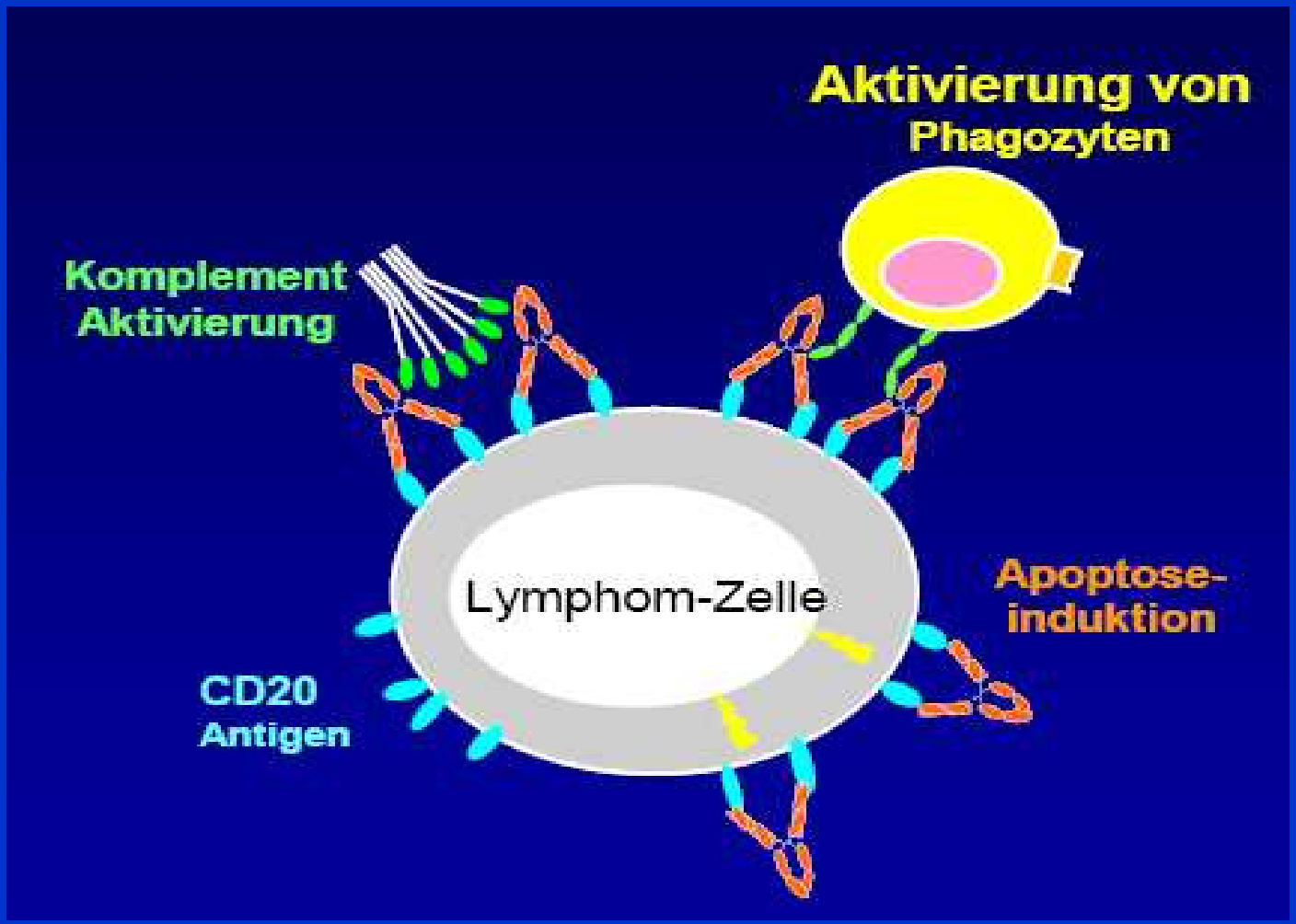
Primärtherapie: Anthracycline?

- Keine Verbesserung v. RR, PFS, OS
- Höhere Toxizität
- Evtl. niedrigeres Risiko einer Transformation
- Möglichkeit späterer PBSCT !

Rituximab



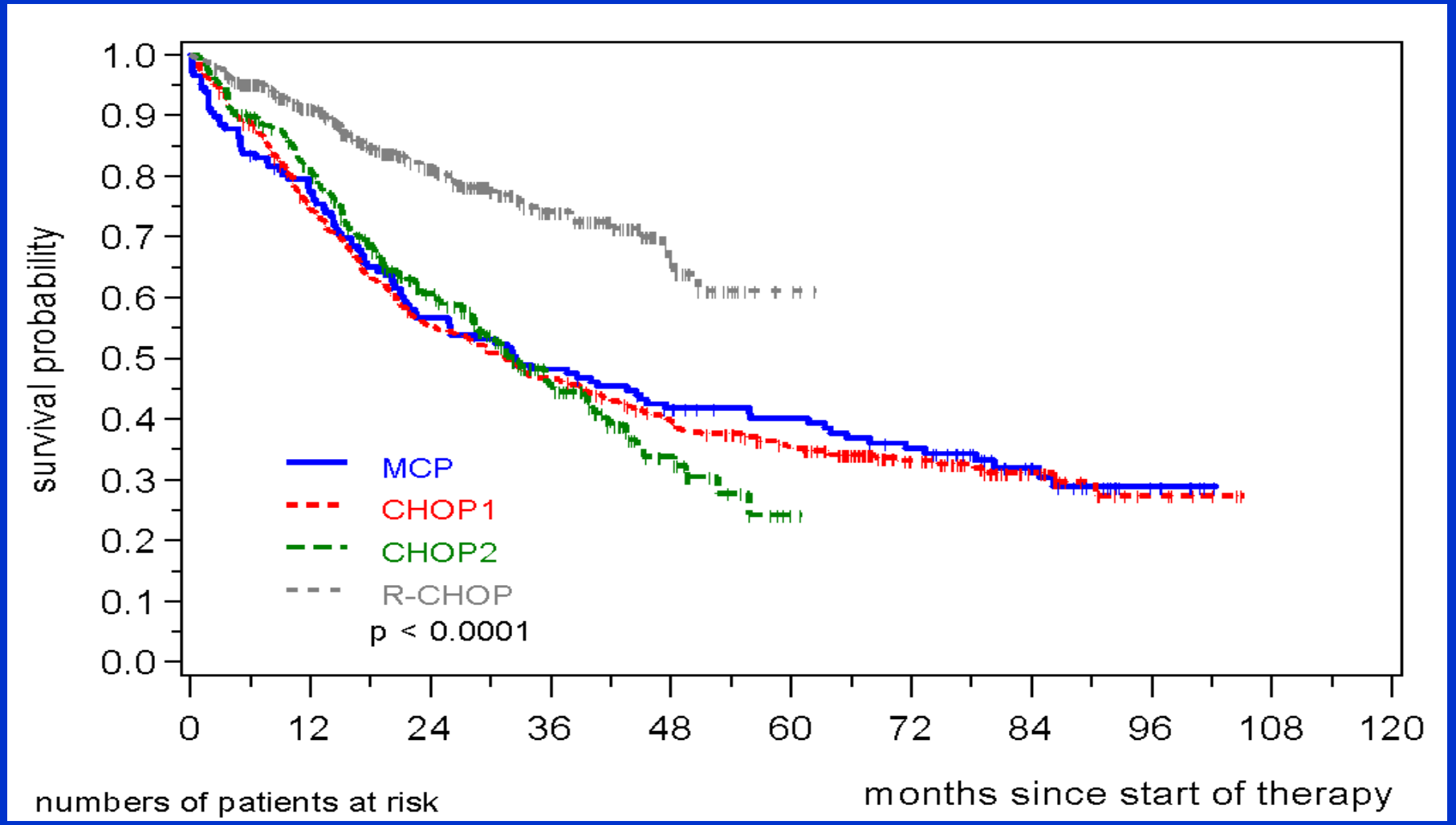
Rituximab


Aktivierung von
Phagozyten
Komplement
Aktivierung
Lymphom-Zelle
Apoptose-
induktion
CD20
Antigen

Phase III: Chemo vs. R- Chemo

Studie	Therapie, n	Medians FU (Monate)	ORR (%)	CR (%)	TTP (Median, Monate)	OS
Marcus et al. (2006)	CVP (159) R-CVP (162)	53	57 81	10 41	15 34 (p<0,0001)	77% 83% (4-Jahre#; p=0,0293)
Hiddemann et al. (2005) Buske et al (2006)	CHOP (205) R-CHOP (222)	48	90 96	17* 20*	5,0 Jahre 2.1 (TTF; p<0,0001)	81% 90% (4-Jahre#; p=0,039)
Herold et al. (2006)	MCP (96) R-MCP (105)	48	75 92	25 50	39% 70% (EFS; p<0,01)	74% 87% (4-Jahre#; p=0,0096)
Foussard et al. (2006)	CHVP-IFN (175) R-CHVP-IFN (183)	42	72 81	60 75	46% 67% (EFS; p<0,0001)	84% 91% (p=0,029)

GLSG Studien: TTF



Erhaltungstherapie

- IFN
- Rituximab
- PBSCT
- Radioimmuntherapie

Erhaltungstherapie: IFN - Metaanalyse -

- 10 Ph.-III Studien, 1922 Pt.
- Kein Einfluß auf RR
- Remissionsdauer länger mit IFN
- OS besser wenn
  - gegeben mit intensiverer Chemoth.
  - in höherer Dosis
  - mit statt nach Chemoth.

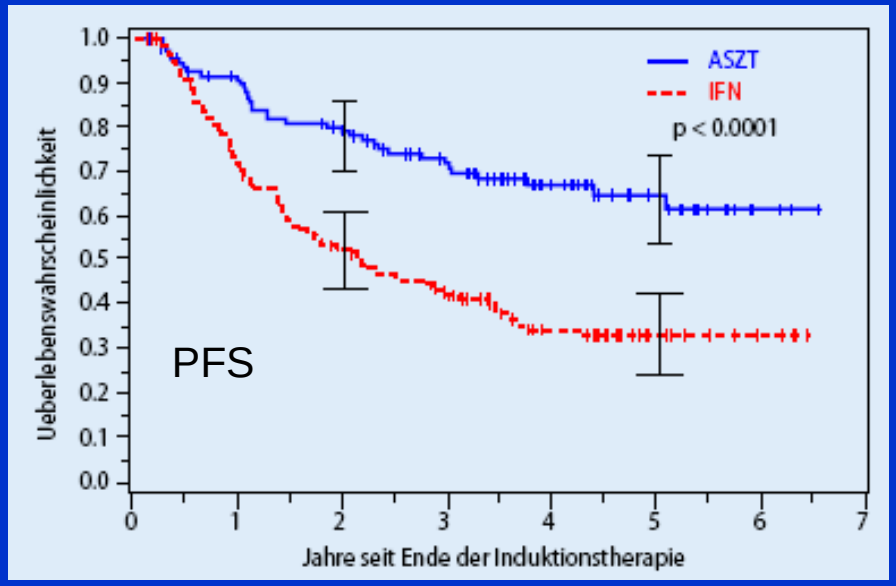
Rohatiner, JCO 2005

PBSCT in 1. Remission

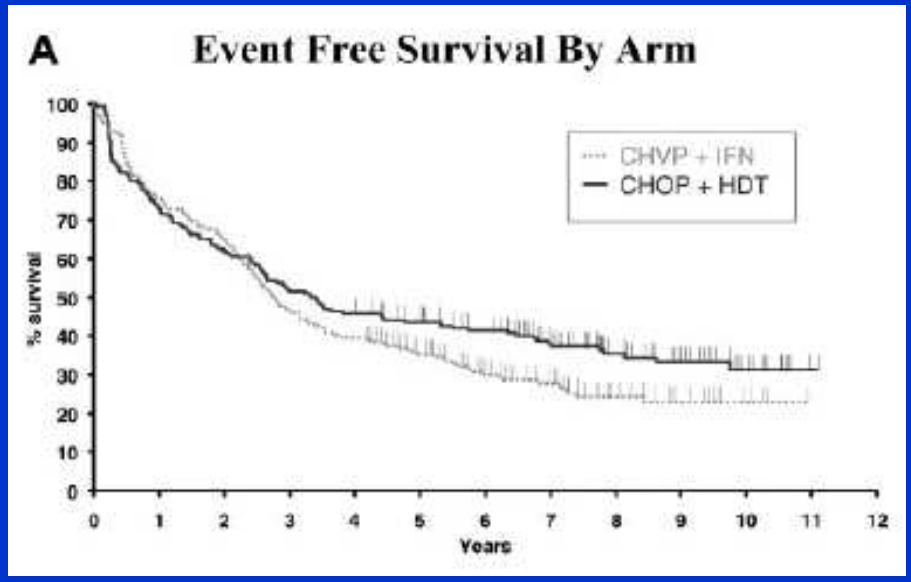
Comment on Sebban et al, page 2540

Autologous transplantation for follicular lymphoma? Not too soon!

Koen van Besien UNIVERSITY OF CHICAGO

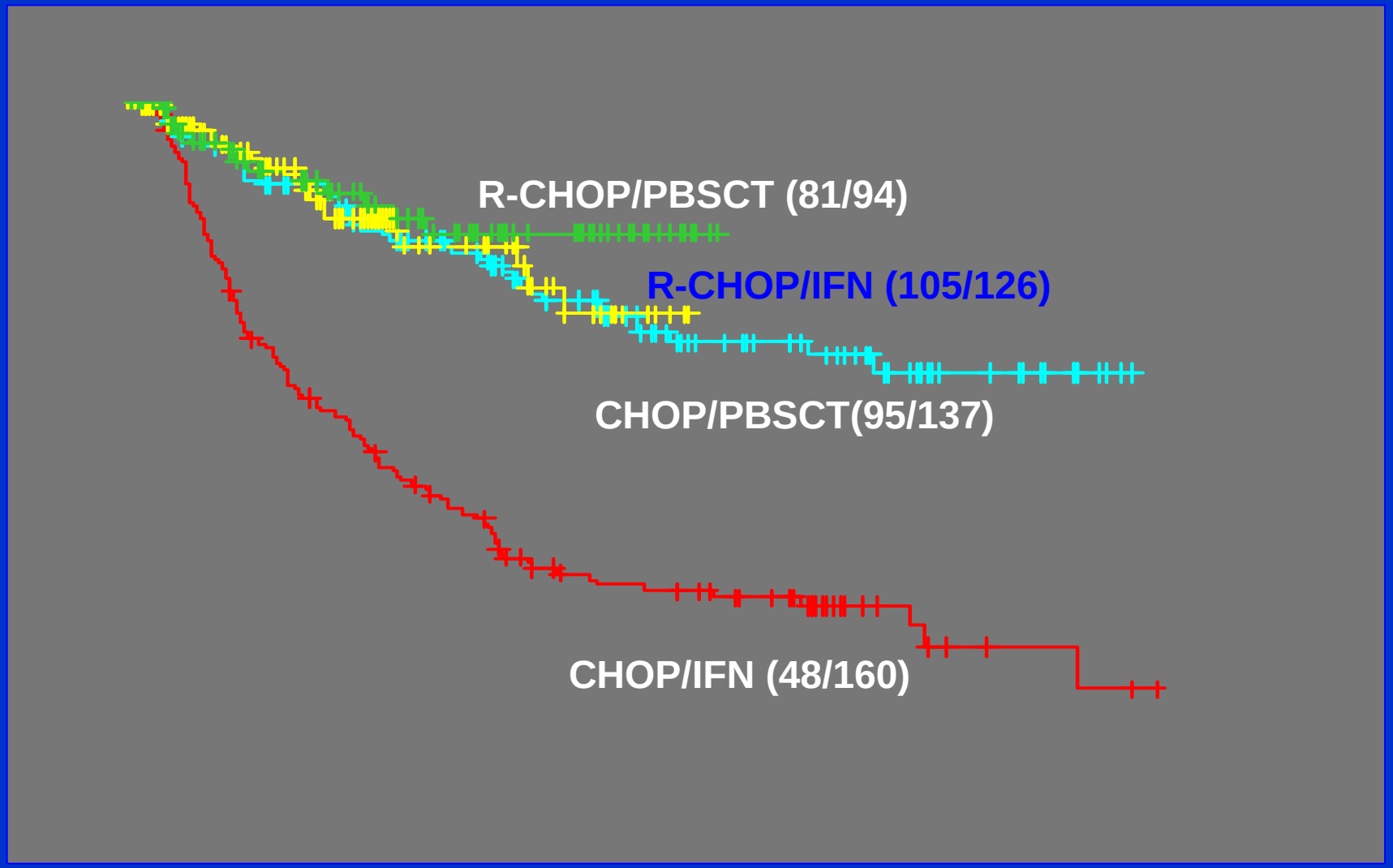


GLSG



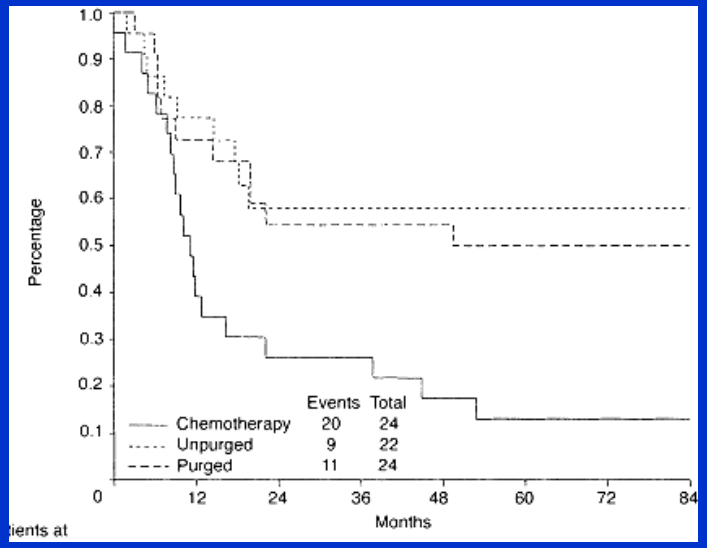
GELA

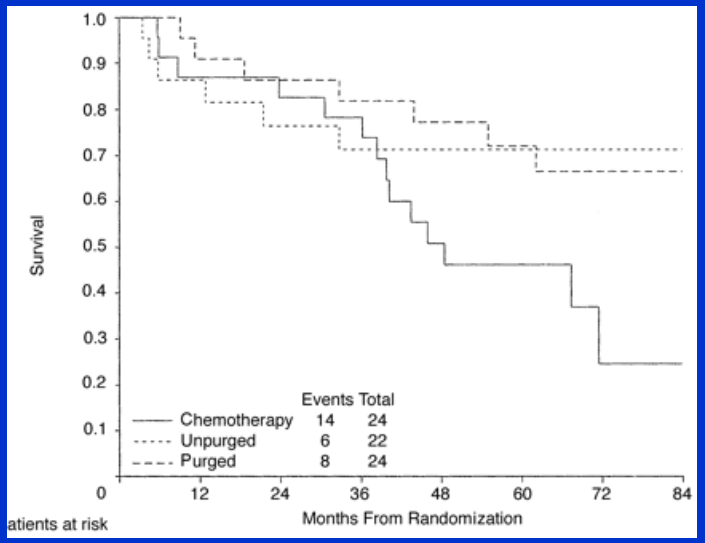
CHOP vs. R-CHOP Followed by PBCT vs. IFN
Response Duration



HDT in ≥ 2. Remission

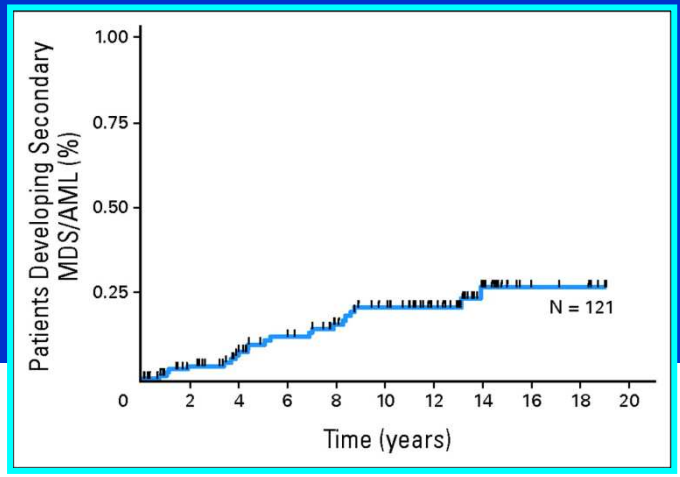
- Signifikante Verlängerung von PFS, OS

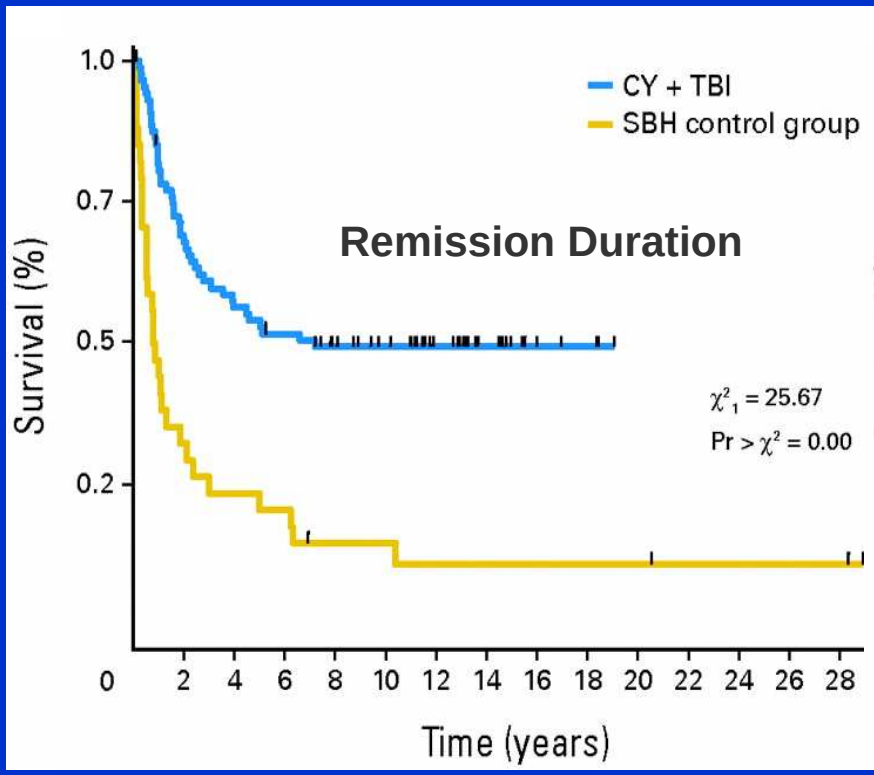


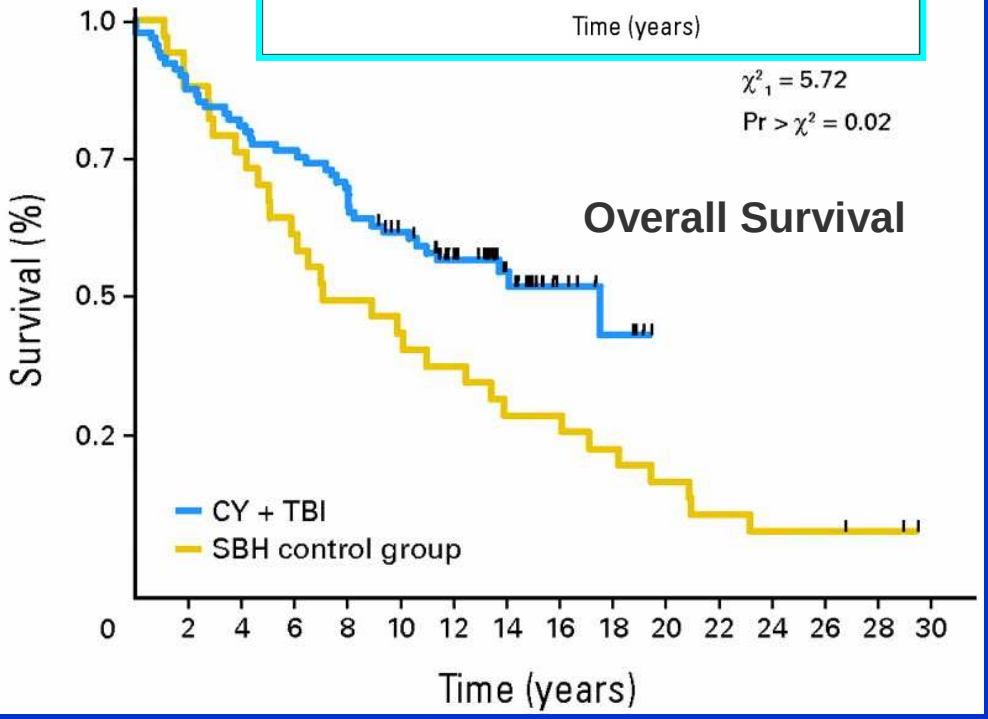


Schouten JCO 2003

PBSCT in ≥ 2. Remission





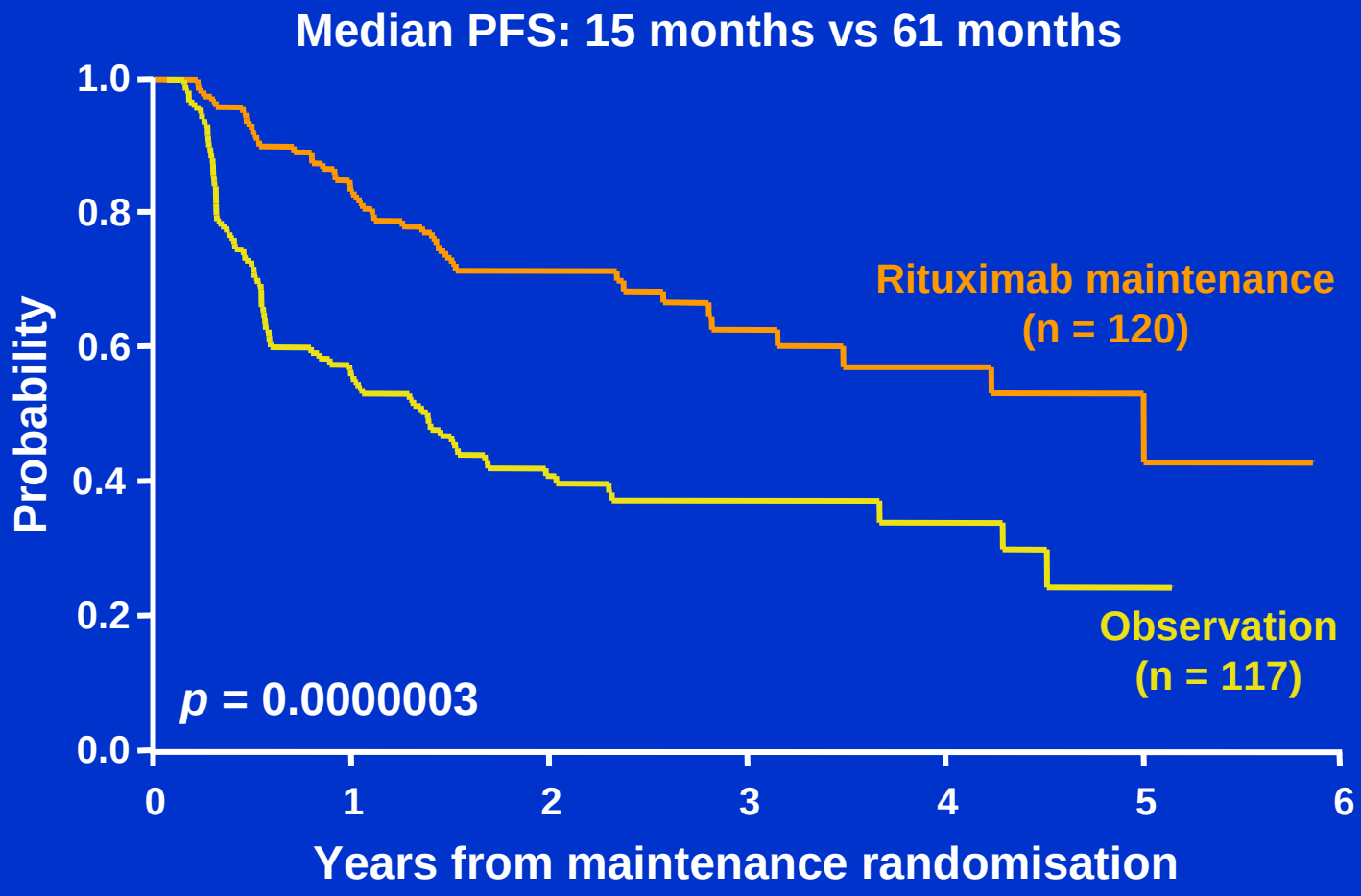


Rohatiner J Clin Oncol; 2007

Rituximab Erhaltung

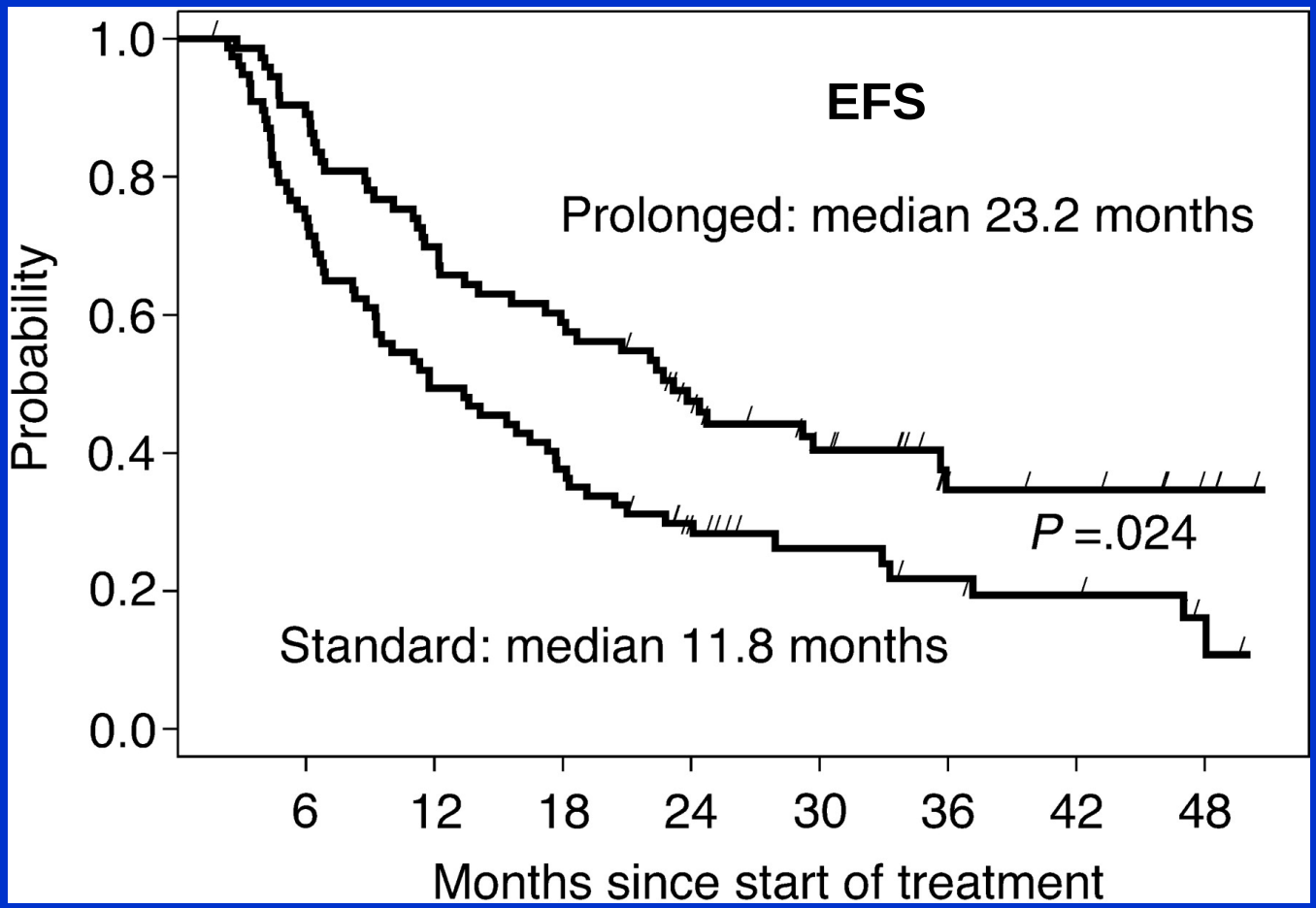
	N=	Induktion	Regime	PFS	OS
Primärtherapie					
Ghielmini	151	4x R	R q 2mo.	++ (3J)	n.a.
Hainsworth	90	4x R	4x R q 6mo.	+(3,5J)	n.a.
Hochster	304	6-8x CVP	4x R q 6mo.	+++(4J.)	(p=0,09)
	237 FL	6-8x CVP	4x R q 6mo.	+++(4J.)	+(4J.)
Rezidivtherapie					
Hiddemann	174	R-FCM	4x R q 6mo.	++	-
Van Oers	396	R-CHOP	R q 3mo.	+++ (3J.)	+ (3J.)

Rituximab maintenance therapy significantly prolongs PFS in first-line FL



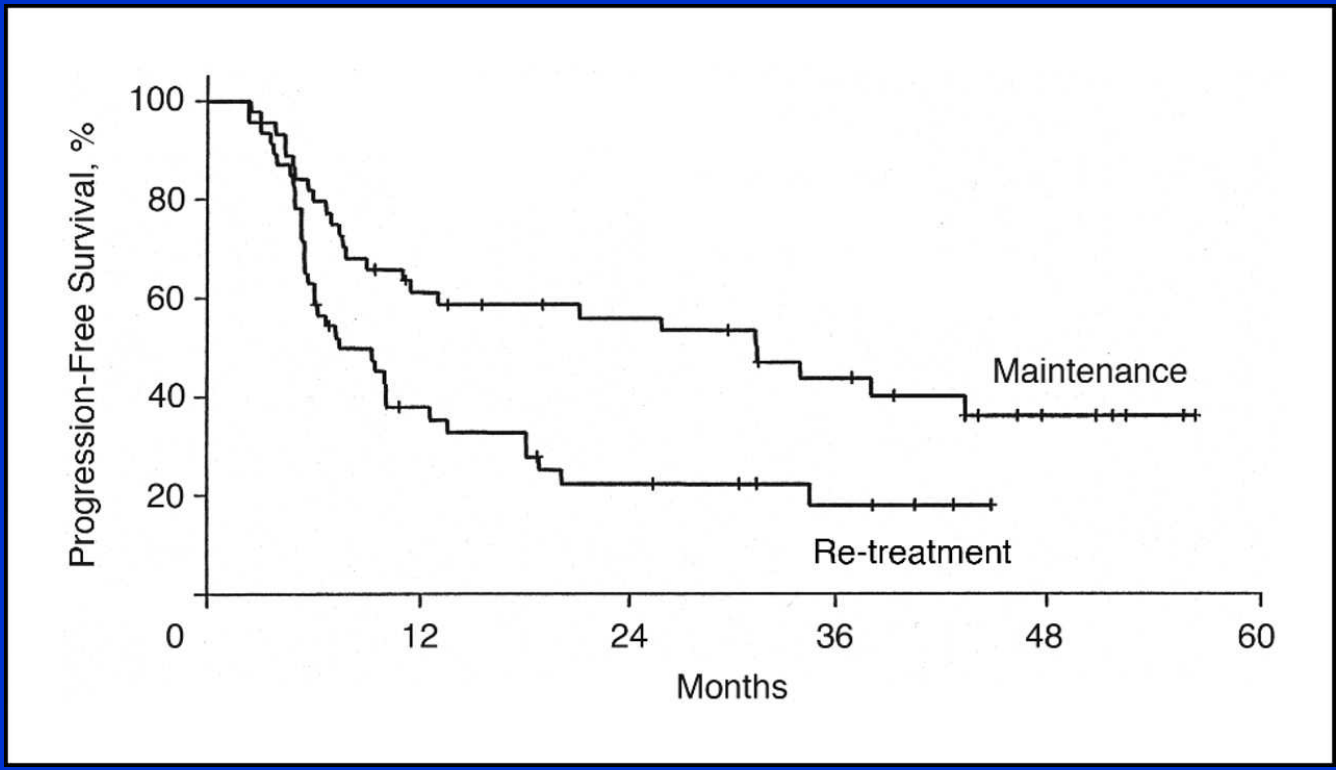
Hochster: Blood 2005

Rituximab Erhaltungstherapie nach Rituximab bei Chemotherapie-naiven und vorbehandeltem FL



Ghielmini, M. et al. Blood 2004;103:4416-4423

Erhaltungstherapie versus Therapie im Rezidiv mit Rituximab bei follikulärem Lymphom



Actuarial progression-free survival (PFS)

114 Patienten mit CT-vorbehandeltem FL

Standard: 4 x R,

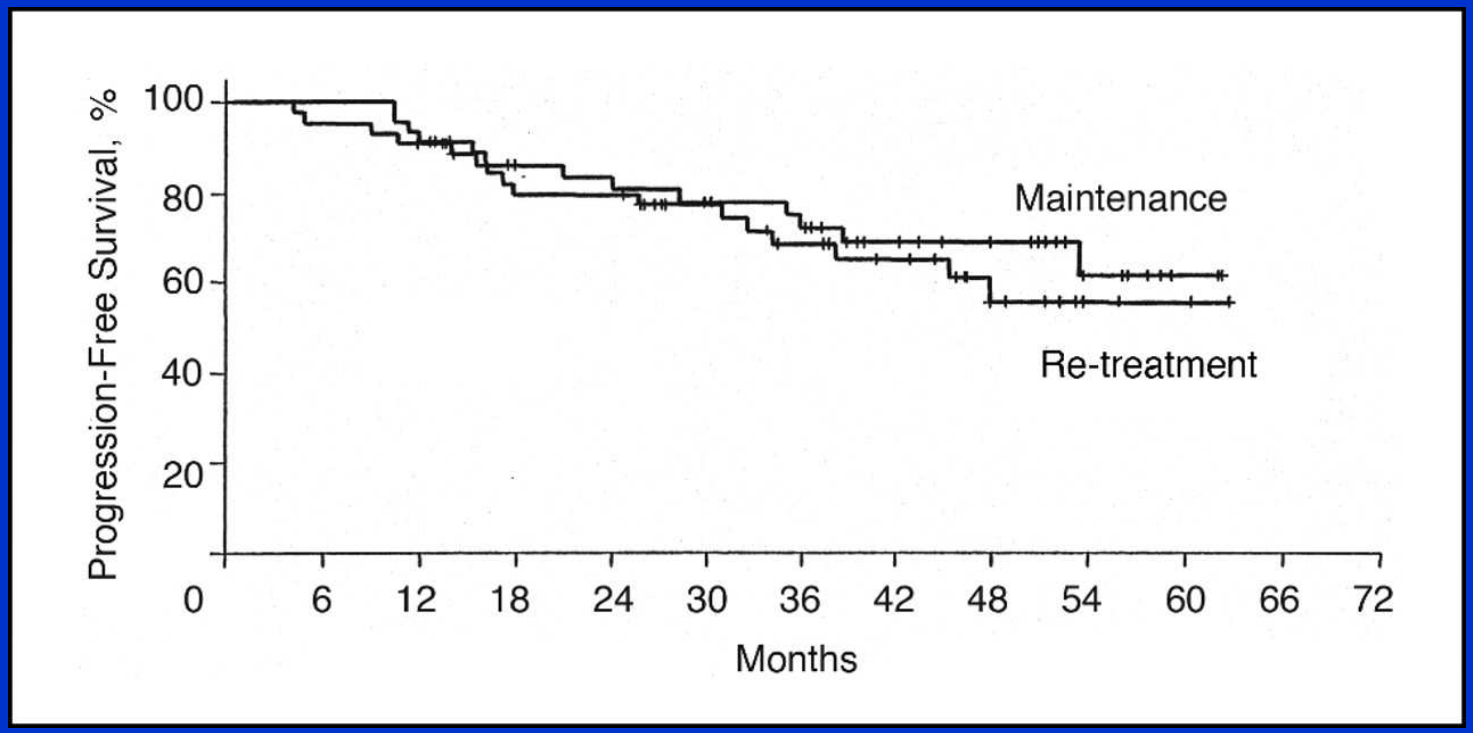
4 x R im Rezidiv

Erhaltung: 4 x R

Erhaltung 4 x R/ 6 Mo

Hainsworth, J. D. et al. J Clin Oncol; 2005

Erhaltungstherapie versus Therapie im Rezidiv mit Rituximab bei follikulärem Lymphom

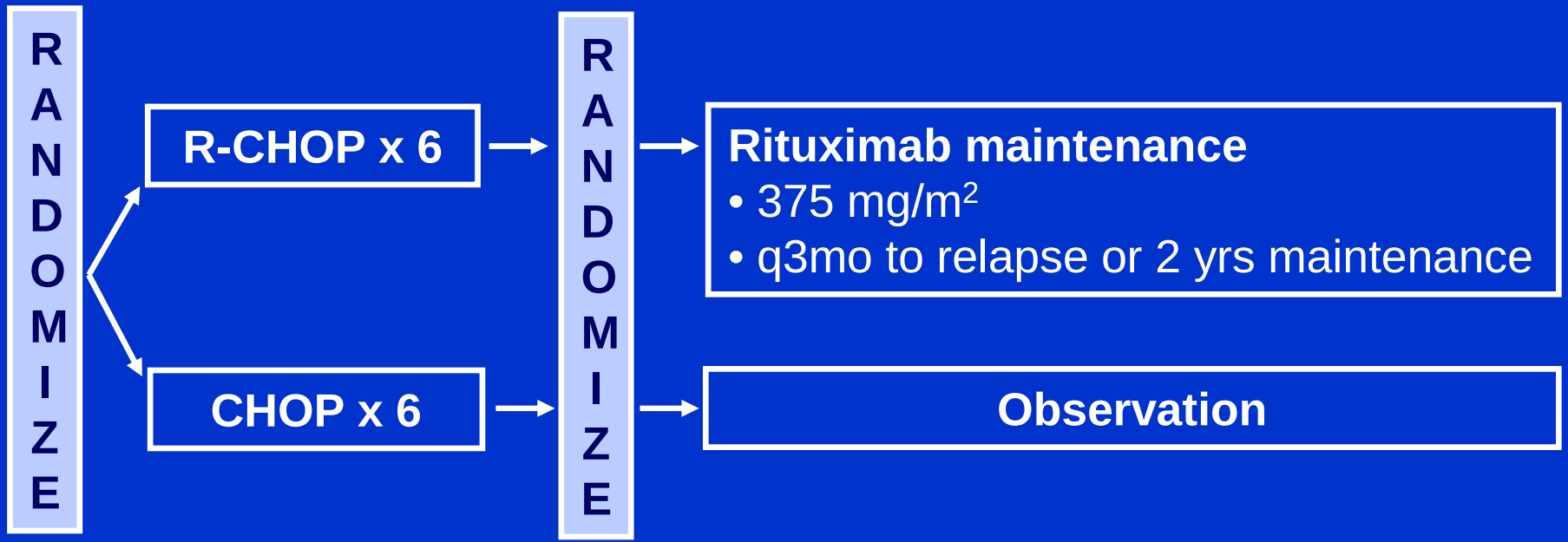


Actuarial survival curves: 3-year actuarial survival for the maintenance versus re-treatment groups are 72% and 68%, respectively

Hainsworth, J Clin Oncol; 2005

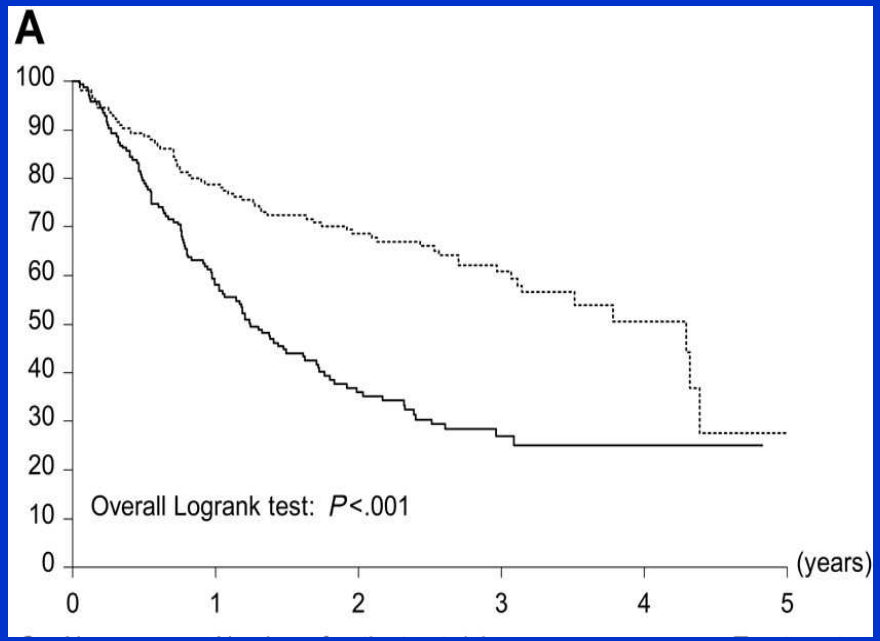
EORTC 20981

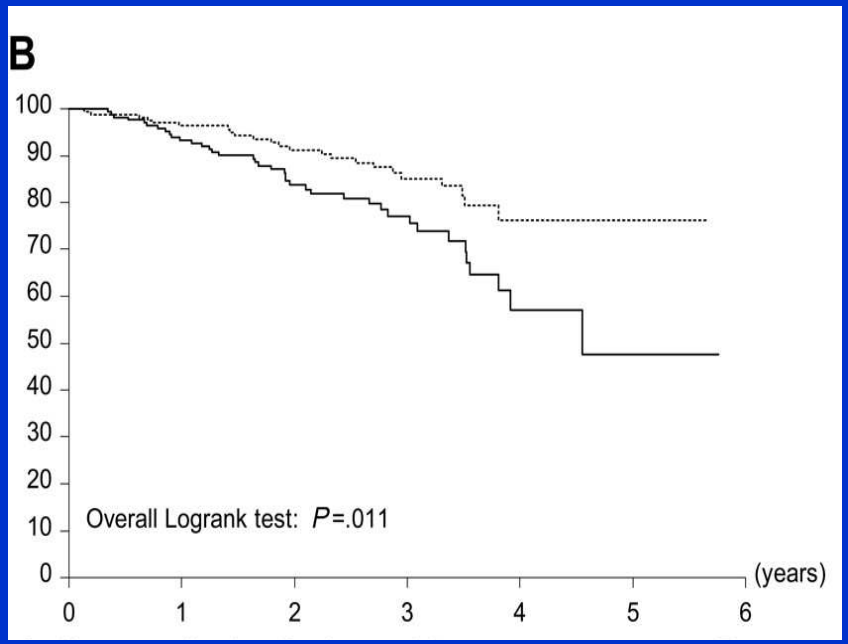
- **Phase III trial of CHOP ± R, with or without rituximab maintenance**
- **474 patients with relapsed/refractory follicular NHL, 316 randomized for maintenance/observation**



van Oers MHJ, *et al*. *Blood* 2004; **104:**Abstract 586.

Effect of R (rituximab) maintenance treatment on progression-free survival and overall survival





van Oers, M. H. J. et al. Blood 2006;108:3295-3301

GLSG: FCM vs R-FCM
Relapsed indolent lymphoma

F ludarabine
C yclophosphamide
M itoxantrone

F ludarabine
C yclophosphamide
M itoxantrone
+ Rituximab

PR, CR

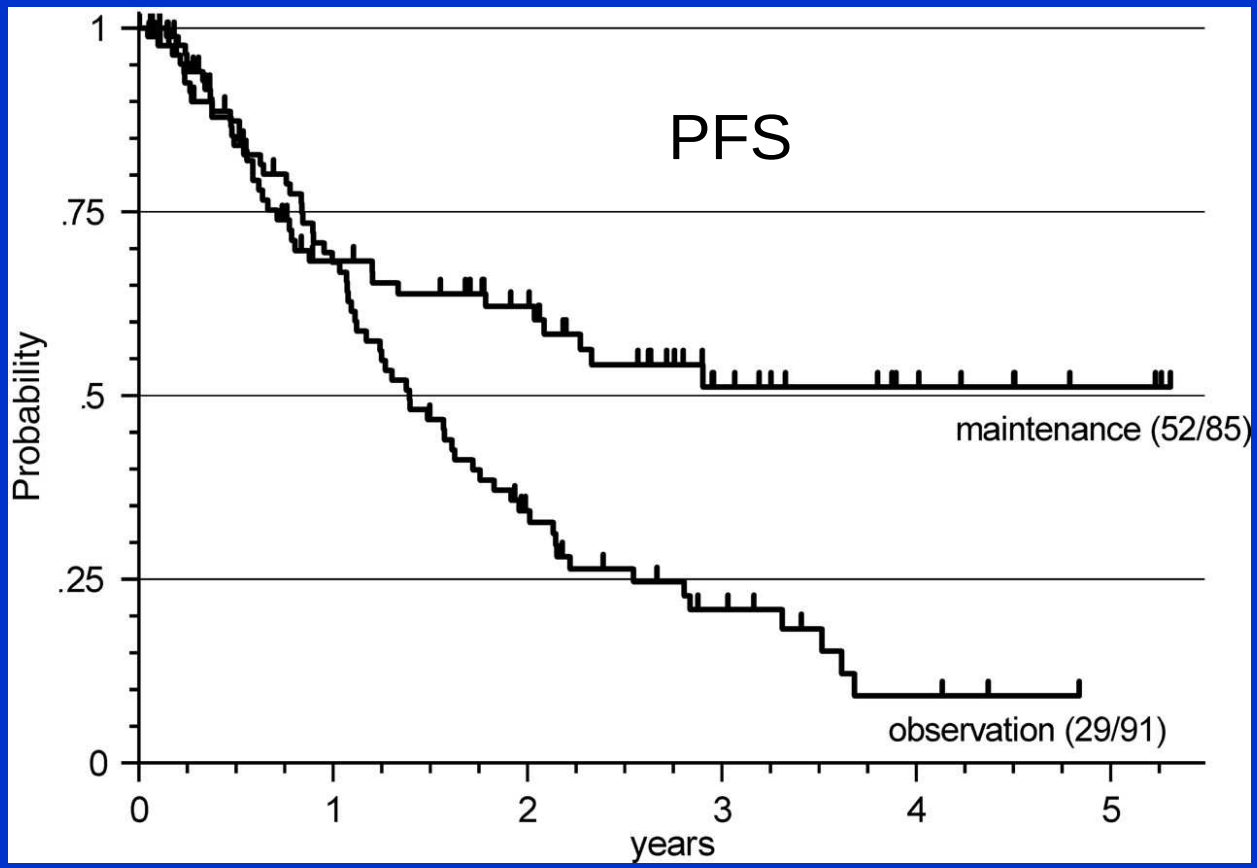
RANDOMISE

4 x Rituximab
(months 3 & 9)

Watch & wait

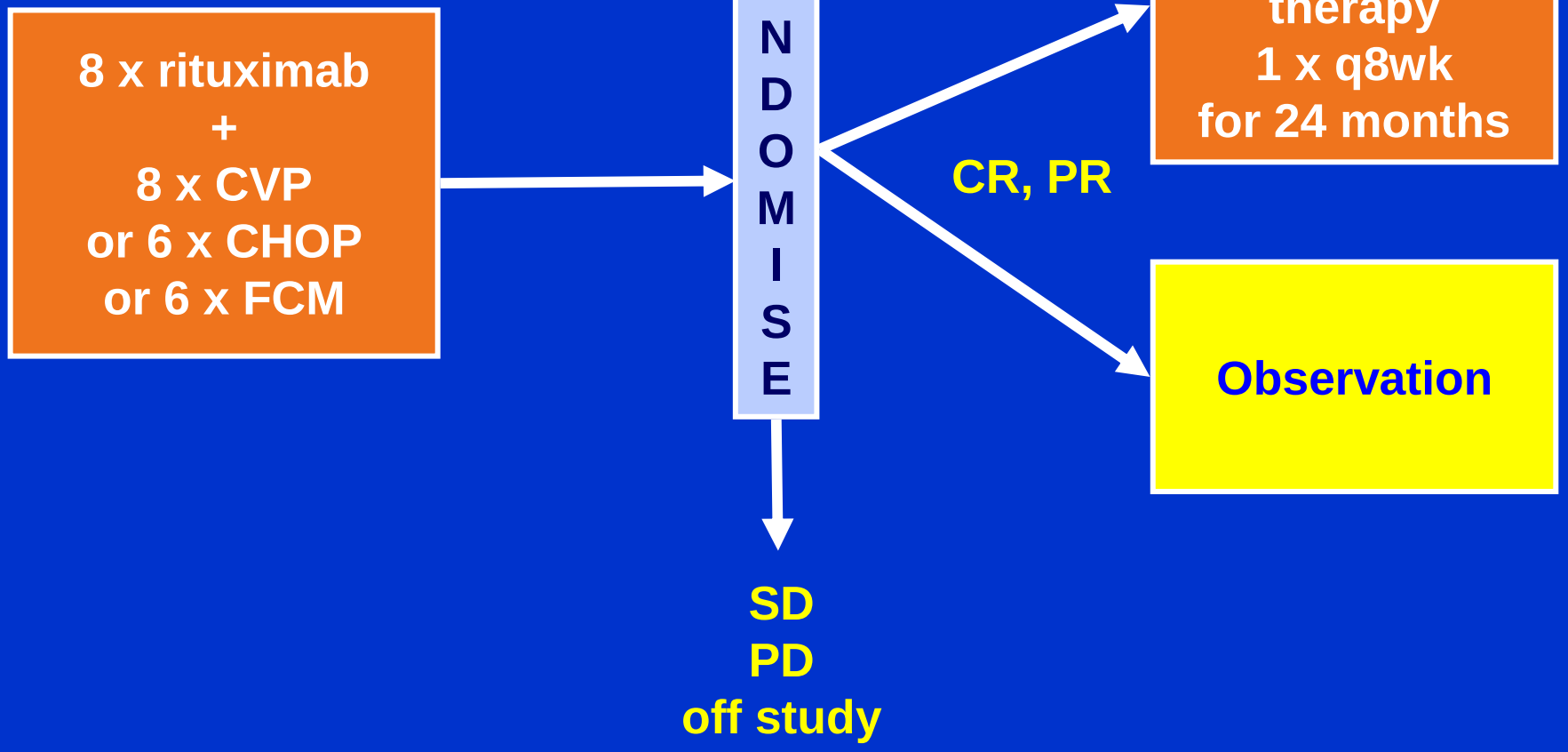
Blood 2006; 108:4003–4008.

Stellenwert einer Rituximab-Erhaltung nach R-FCM bei rezidiviertem NHL

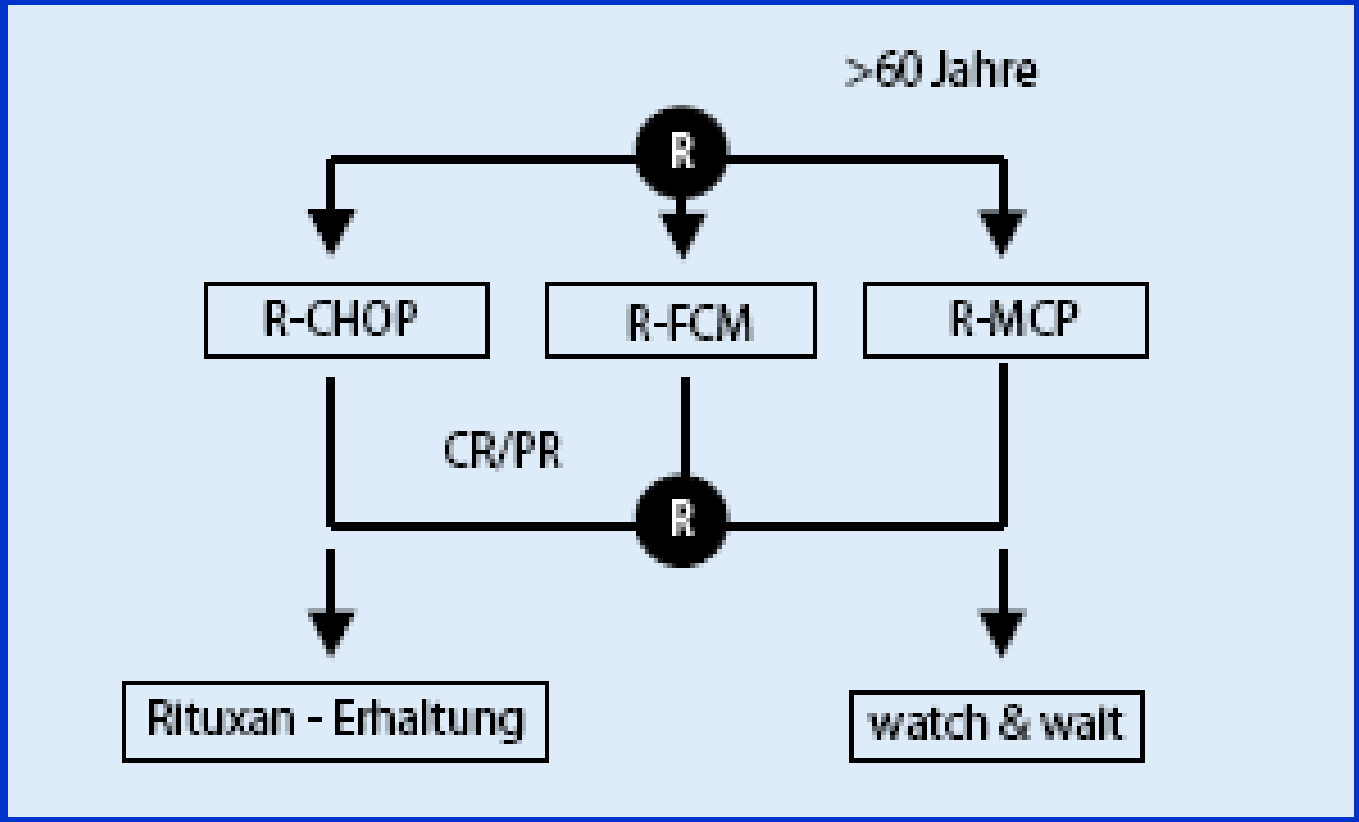


Forstpointner, R. et al. Blood 2006;108:4003-4008

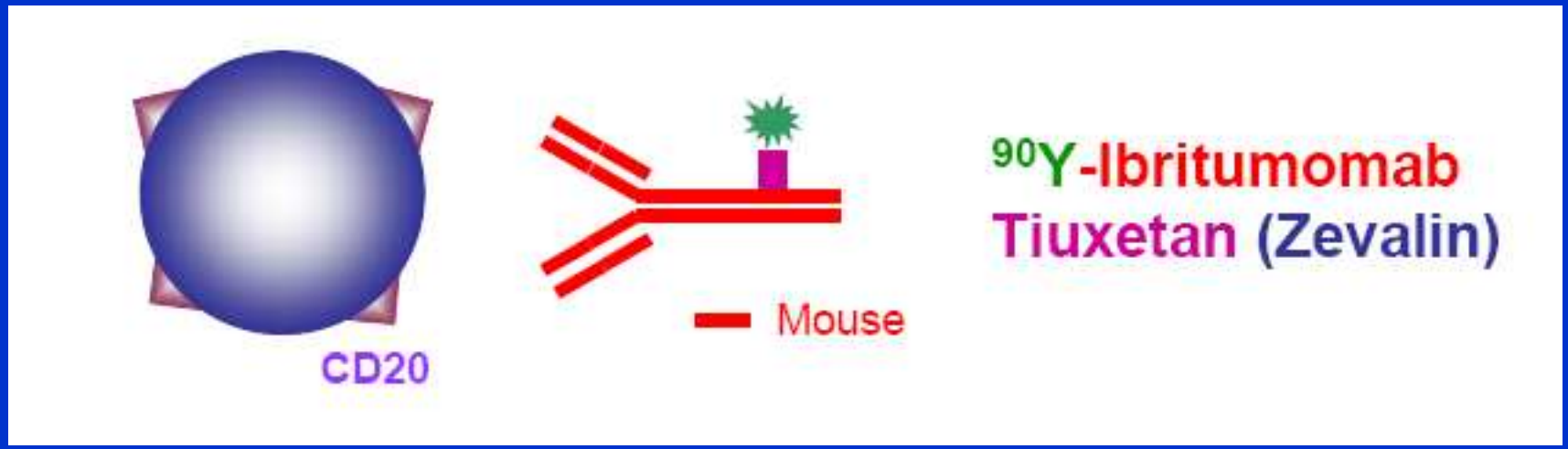
PRIMA Studie: Rituximab Induktion und Maintenance in first-line



Aktuelle Studie der GLSG: > 60 J.



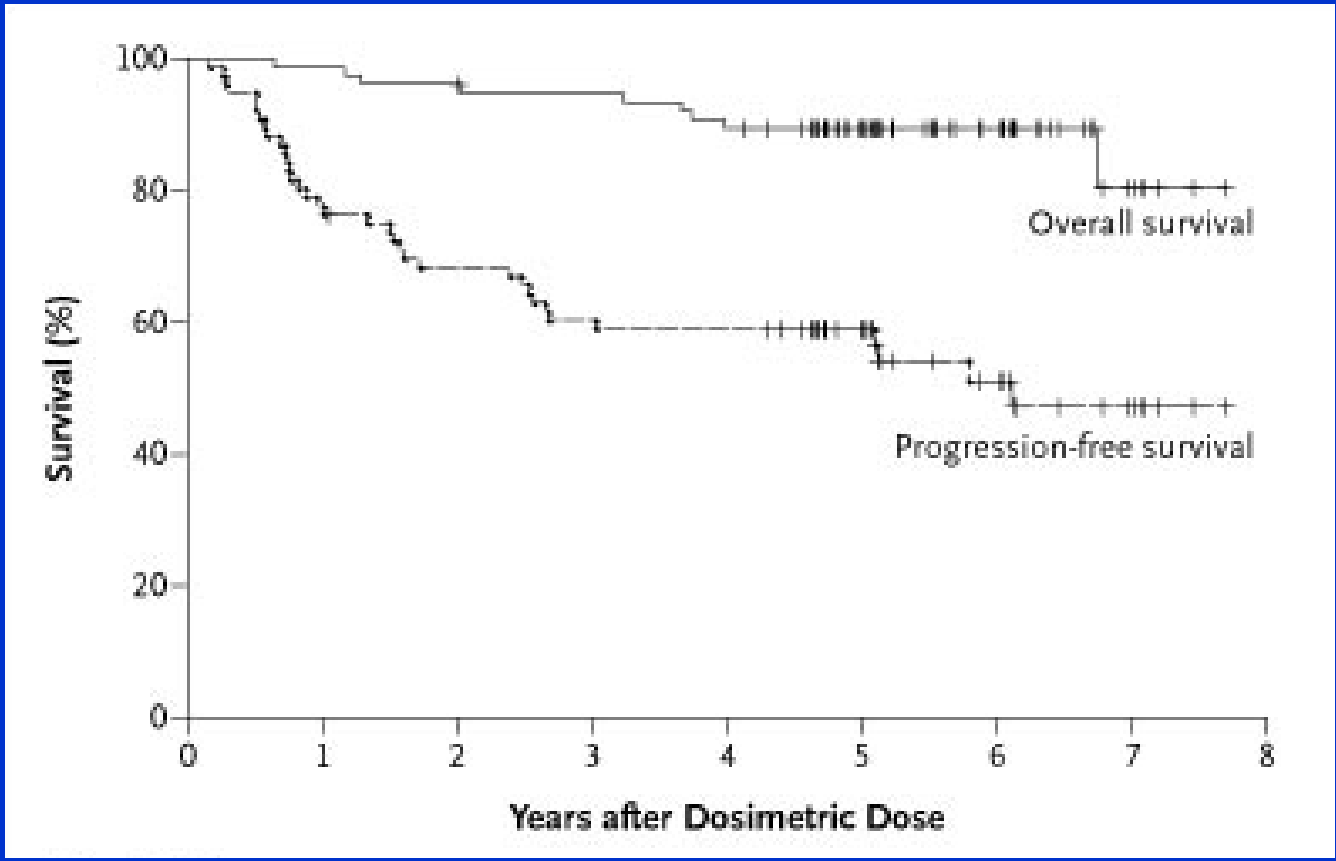
Radioimmuntherapie



- Yttrium-90: reiner Beta-Strahler, Reichweite 5mm, HWZ= 64h

Bexxar 1st line: PFS und OS

- CR 75%
- PR 20%
- Medianes PFS 6,1 J.



Kaminski M et al. N Engl J Med 2005

RIT: Zevalin

- ORR 80%, 20-30% CR,
  PFS meist 1J., mehr als 3 J. in 25-30%
- Bei R- refraktären Pt.: RR 74%,
  15% CR (Witzig JCO 2002)
- Zevalin vs. R (1st line): RR ↑
  (Witzig JCO 2003)
- Konsolidierung nach PR /CR:
  FIT - Studie

RIT – Konsolidierung in 1. Remission (FIT)

- Ph III, n= 414
- Chemo -> PR, CR -> RIT vs. Ktr.
- PR 29,3 vs. 6,2mo, CR 53,9 vs. 29,5 mo
- PFS 36,5 vs. 13,3 mo
- PR -> in 77% CR
- Schwächen: Diverse Chemo-Reg. (CHMB bis R-CHOP); OS (noch) nicht sign., medianer FU 3,5J.,
  nur 15% R als Teil der Induktionstherapie
- Kein Vergleich mit R- Erhaltung

Morschhauser, JCO Nov. 2008