Therapeutic Strategies for Elderly Patients with DLBCL

Michael Pfreundschuh

German High-Grade Non-Hodgkin Lymphoma Study Group
Internal Medicine I, Saarland University Medical School
Homburg (Saar), Germany

DSHNHL

Aggressive Lymphomas in the Elderly

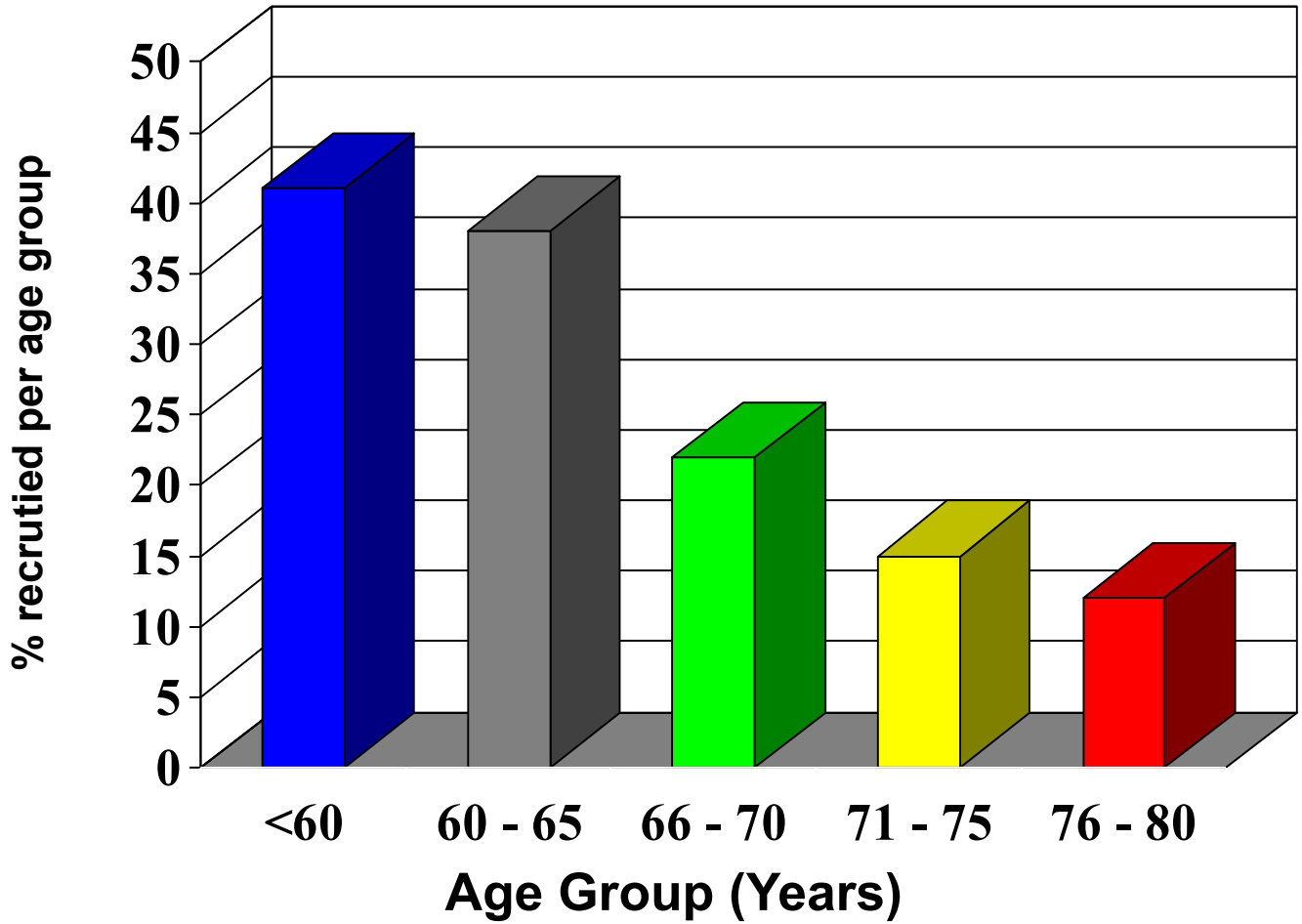
- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
- **Perspectives**

Aggressive Lymphomas in the Elderly

Clinical Relevance:

- **~ 40% of all lymphomas**
- **> 50% diagnosed >65 years**
- **> 15% dignosed >80 years**
- **Octa- and nona-generians: fast-growing population**
- **Under- or no presentation in studies**

*Patients recruited for prospective trials**



*** Prospective population based KML Study (Saarland 2000-2003)**

Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
- **Perspective**

Aggressive Lymphomas in the Elderly

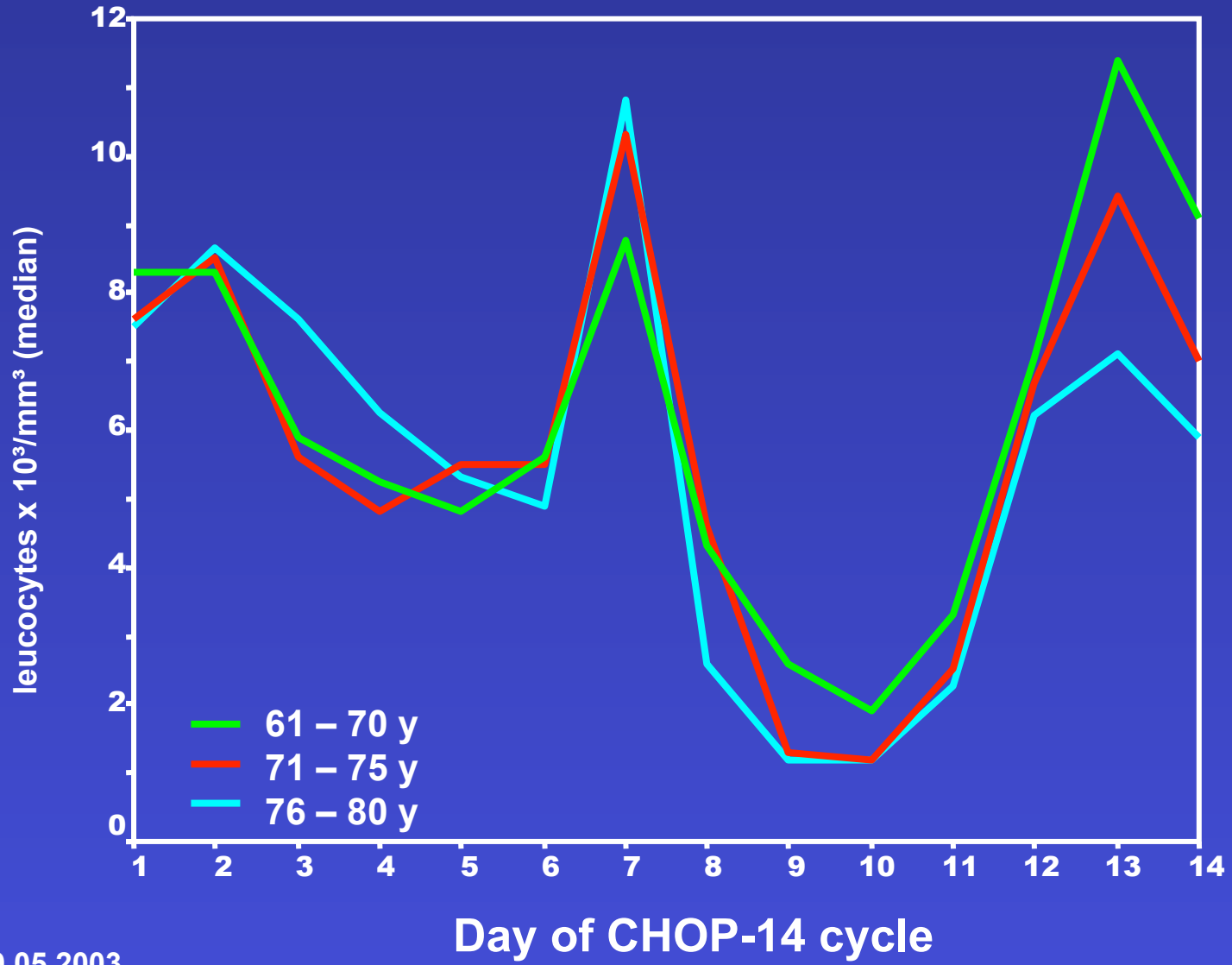
Age groups analyzed*:

- **61 – 65 years**
- **66 – 70 years**
- **71 – 75 years**
- **76 – 81 years**
- **>80 years [?]**

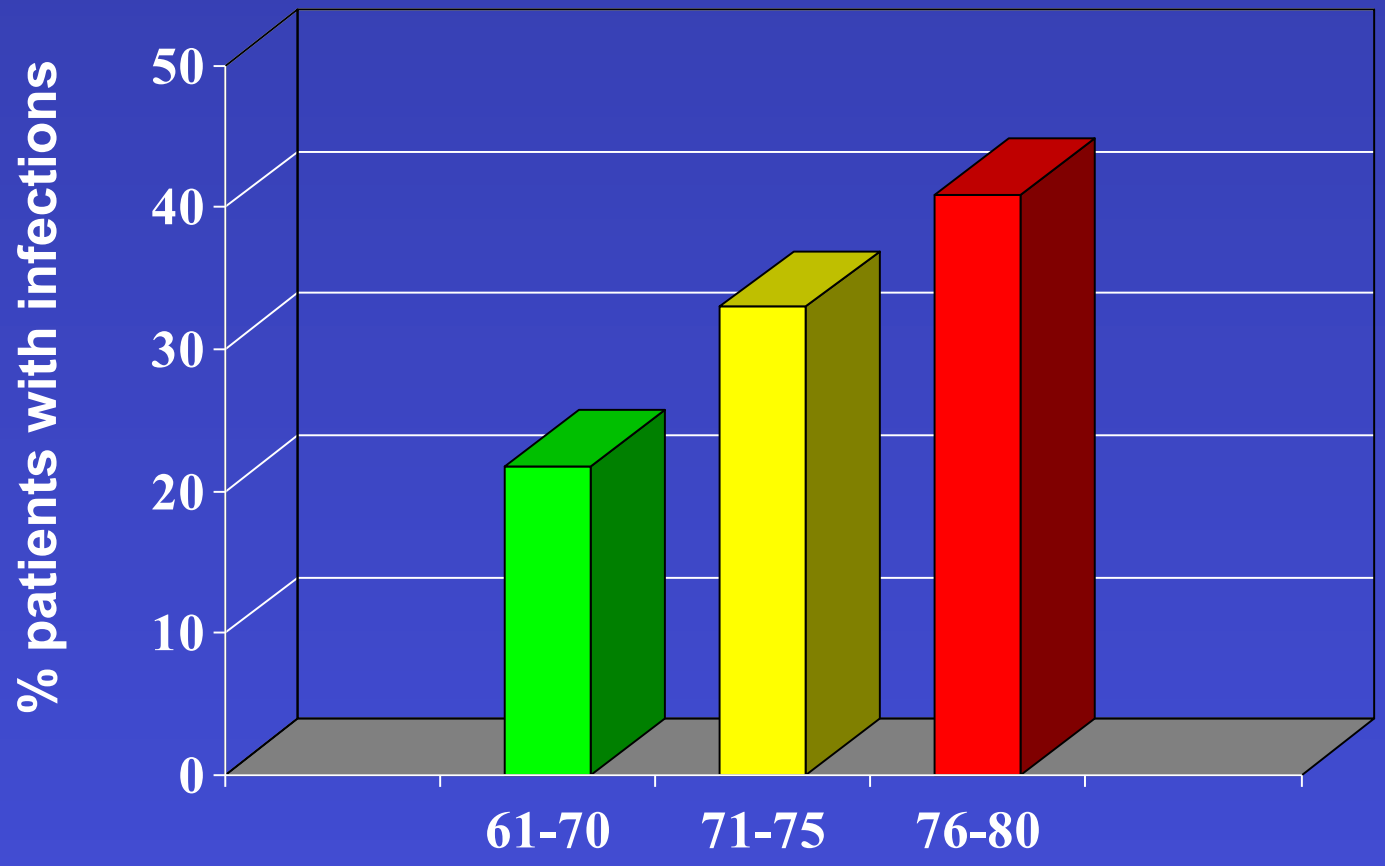
} **no difference**

RICOVER-60 Trial

Course of leukocytes

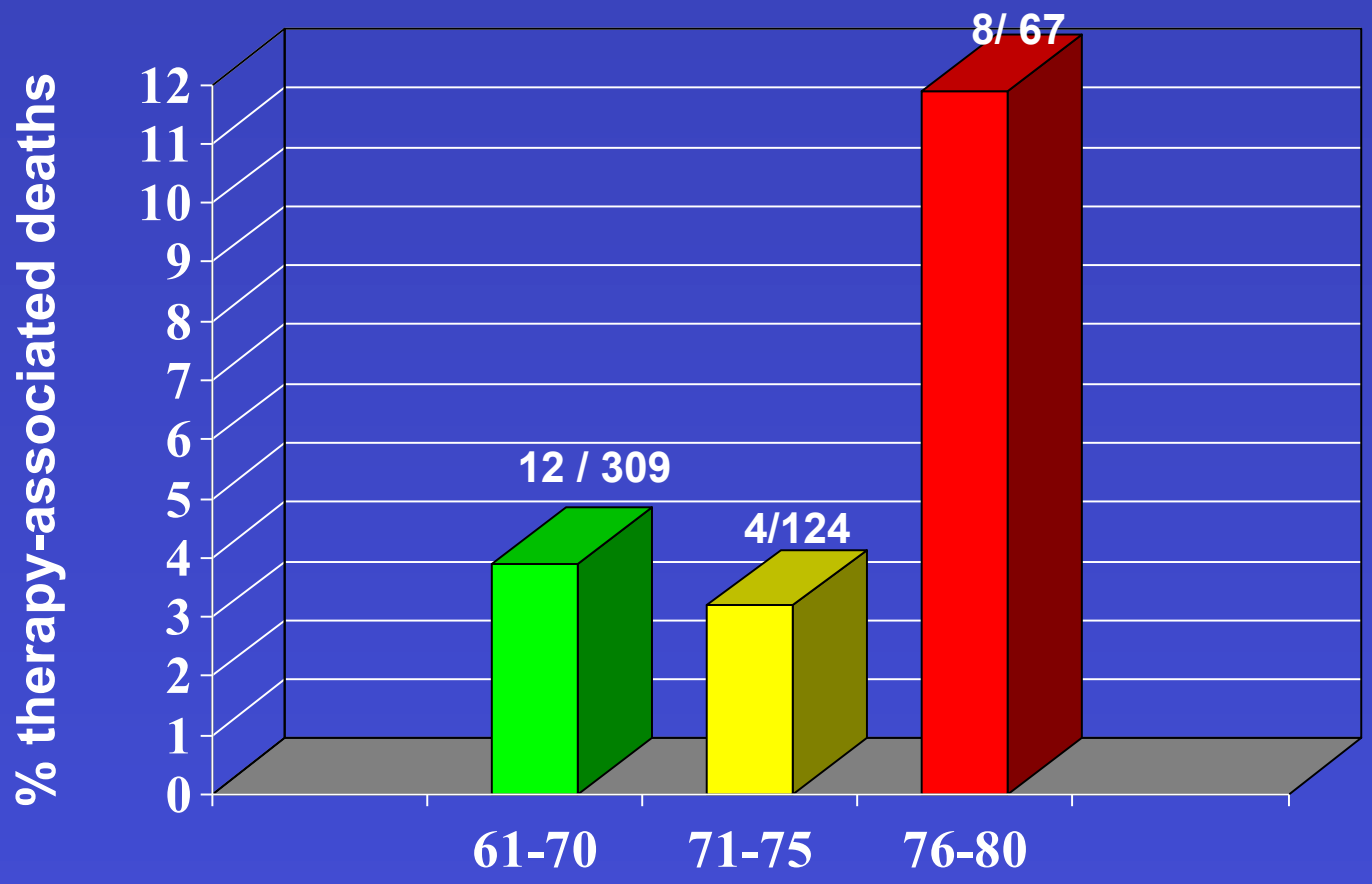


Grade 3&4 Infections*



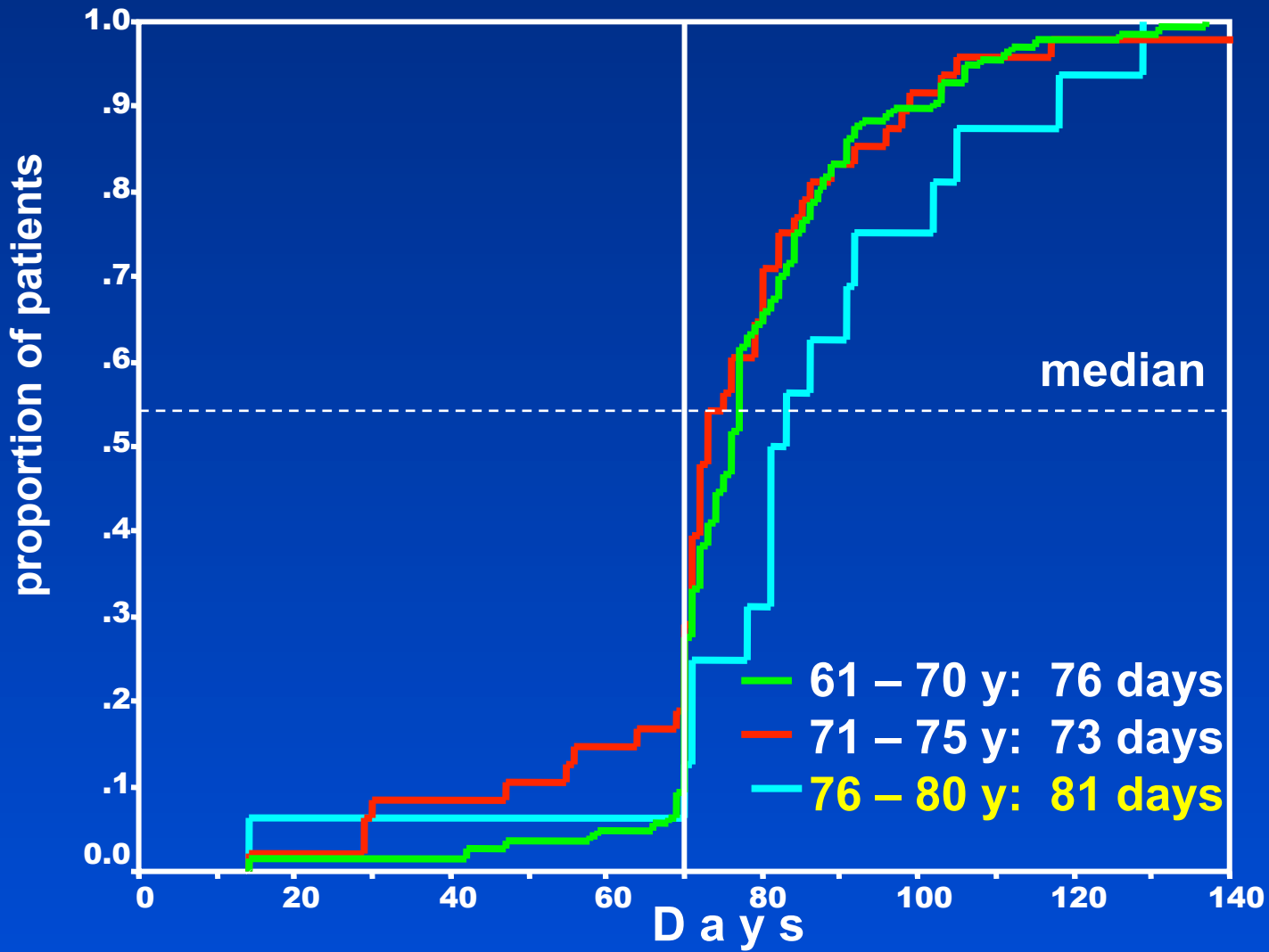
* RICOVER-60 Trial (Pats. # 001-500)

Therapy-associated deaths*



* RICOVER-60 Trial (Pats. # 501-1000)

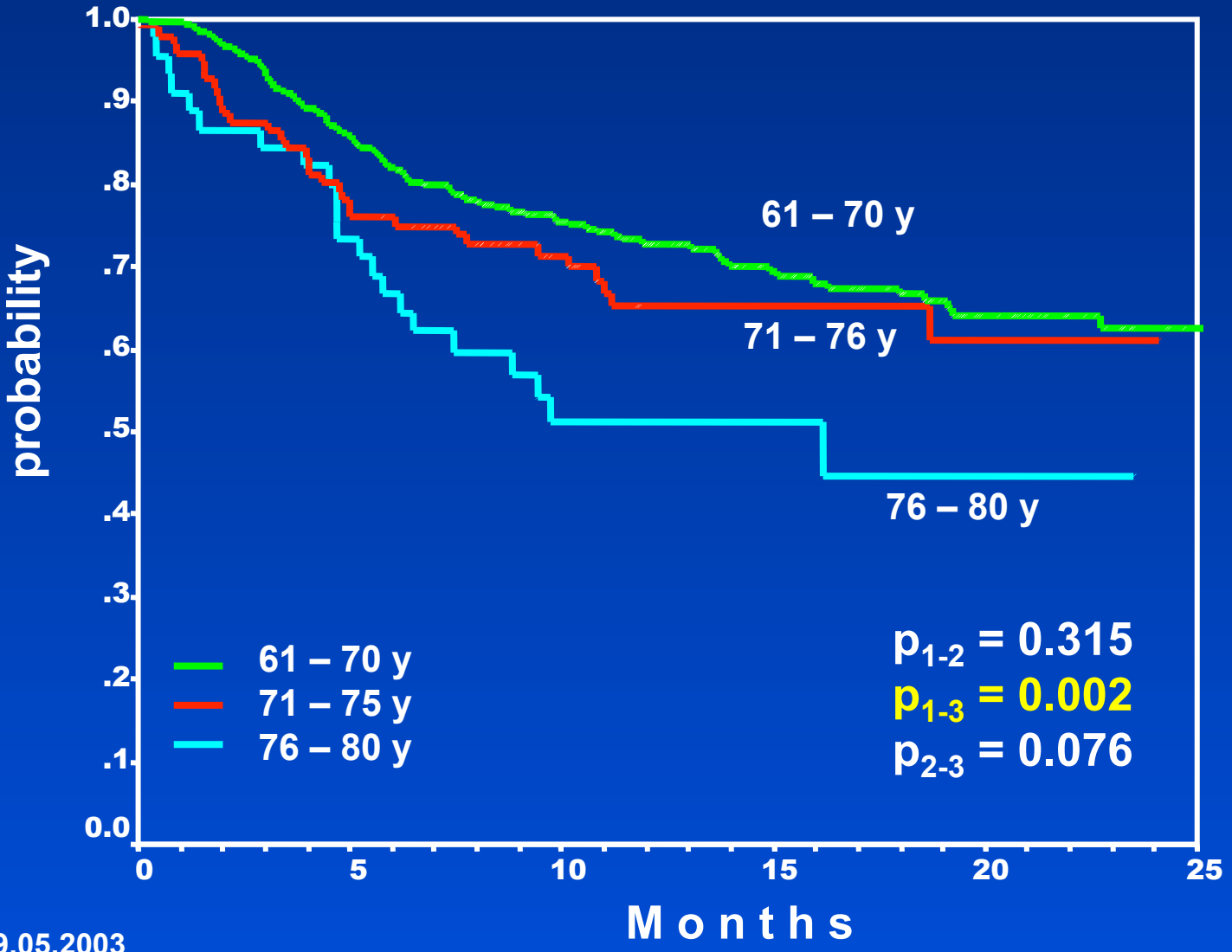
RICOVER60 Trial
Treatment duration – 6 cycles CHOP-14 ± rituximab



DSHNHL 19.05.2003

RICOVER60 Trial

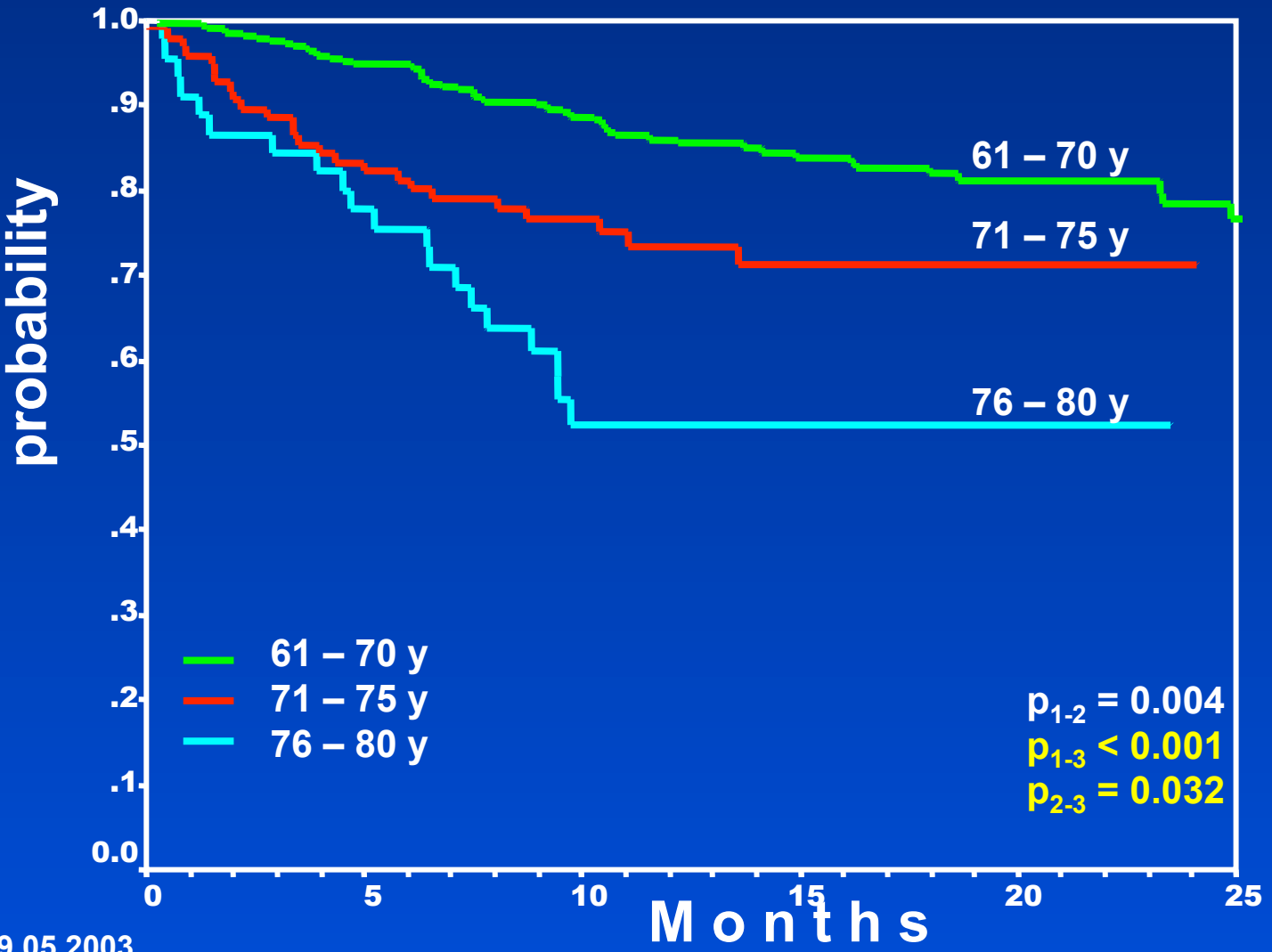
Event–free Survival



DSHNHL 19.05.2003

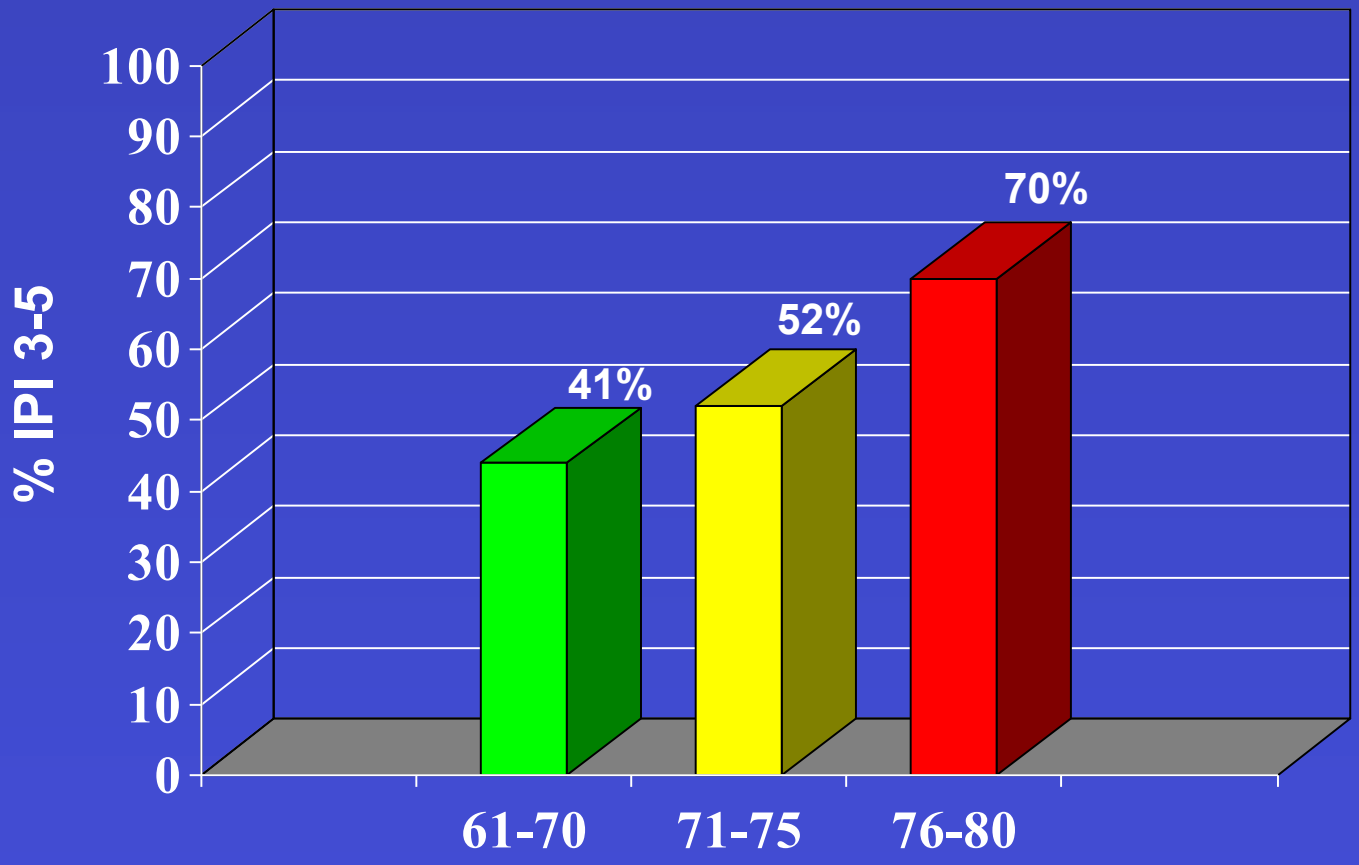
RICOVER60 Trial

Overall Survival



DSHNHL 19.05.2003

IPI according to age groups*



* RICOVER-60 Trial (Pats. # 001-500)

Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
- **Perspectives**

Aggressive Lymphomas in the Elderly

Specific features of „elderly“ DLBCL:

- **prognosis worsening with age**
- **hardly explained by protocol adherence**
- **partially explained by:**
  - **different biology**
  - **poorer risk profile**
  - **higher deather rate**

Aggressive Lymphomas in the Elderly

Specific features of „elderly“ DLBCL:

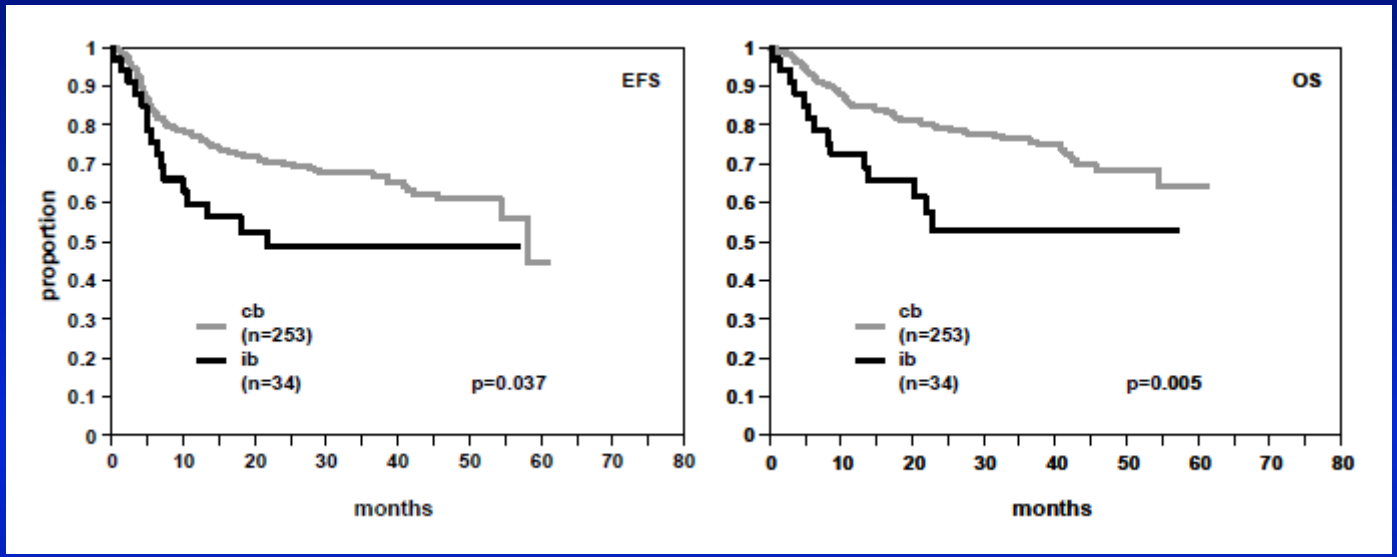
- **prognosis worsening with age**
- **hardly explained by protocol adherence**
- **partially explained by:**
  - **different biology**
  - **poorer risk profile**
  - **higher deather rate**

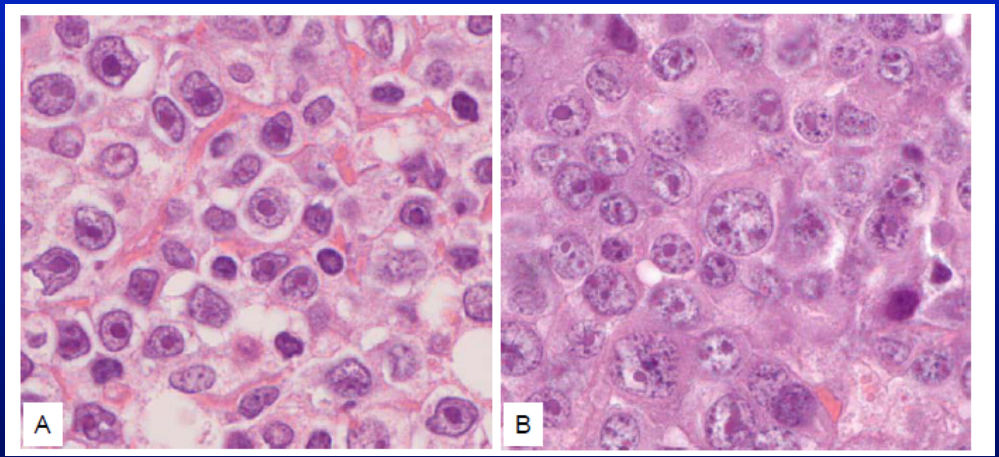
Aggressive Lymphomas in the Elderly

Specific features of „elderly“ DLBCL:

- **prognosis worsening with age**
- **hardly explained by protocol adherence**
- **partially explained by:**
  - **different biology**
  - **poorer risk profile**
  - **higher death rate**

Outcome Prediction: Molecular vs. Cytological





Ott et al., *Blood 2010 (in press)*

Aggressive Lymphomas in the Elderly

DLBCL biology in the elderly:

- **immunoblastic subtype ⇑**
- **ABC type ⇑**
- **BCL2/MYC double expressors ⇑**

Specific Measures:

1. **Prephase Treatment**
2. **Anti-infective Prophylaxis**
3. **Hydrocortison Substitution**

Aggressive Lymphomas in the Elderly

Prephase treatment:

~~Vincristin~~	~~1 mg~~	~~i.v.~~	~~day –7~~
Prednisone	100 mg	p.o.	days –7 to –1

Effects:

- Improvement of performance state
- Ameliorization of 1st-cycle effect

Aggressive Lymphomas in the Elderly

Prephase treatment:

Vincristin	**1 mg**	**i.v.**	**day –7**
Prednisone	**100 mg**	**p.o.**	**days –7 to –1**

Effects:

- **Improvement of performance state**
- **Ameliorization of 1st-cycle effect**

Aggressive Lymphomas in the Elderly

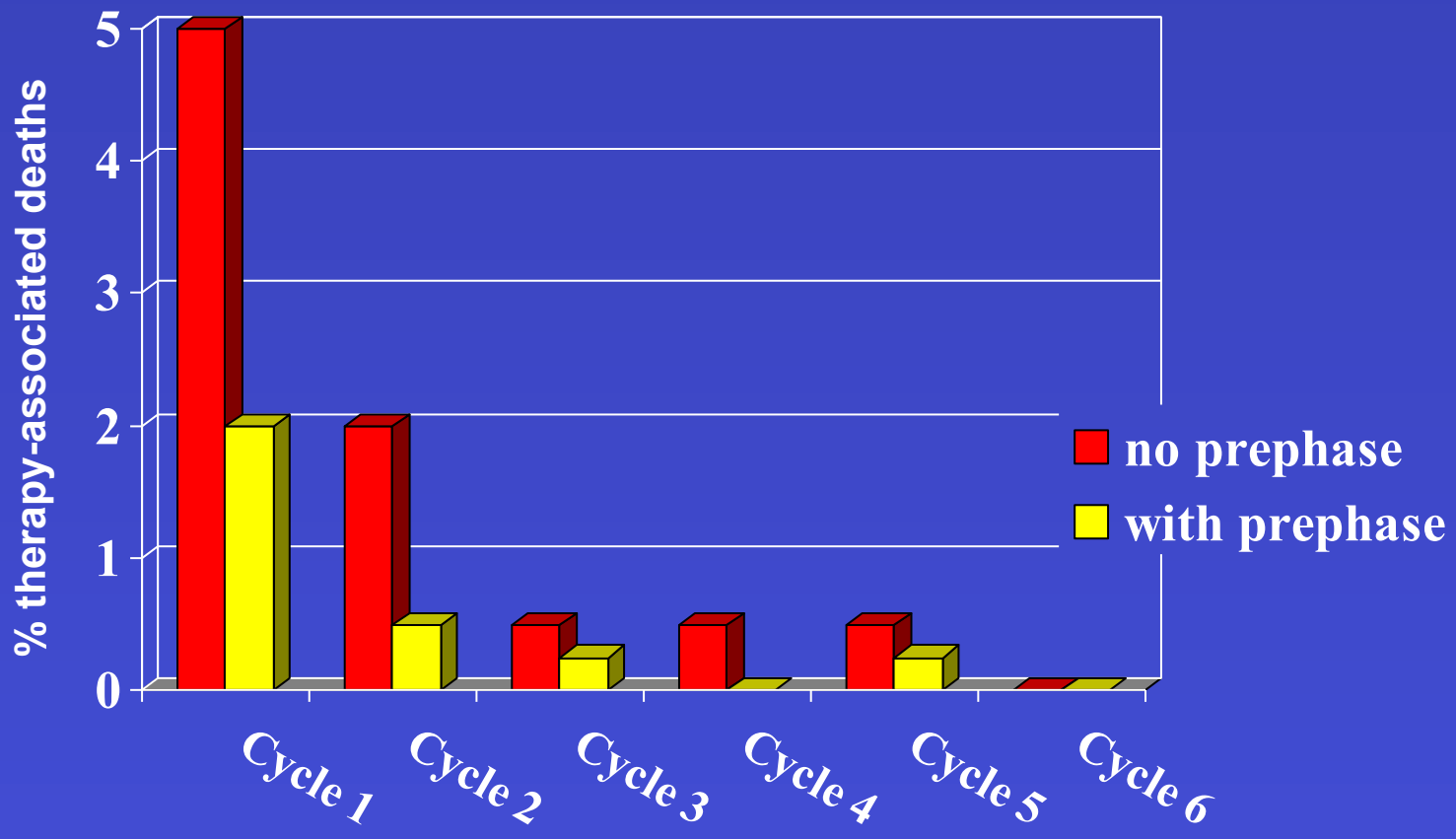
Prephase treatment:

Vincristin	**1 mg**	**i.v.**	**day –7**
Prednisone	**100 mg**	**p.o.**	**days –7 to –1**

Effects:

- **Improvement of performance state**
- **Ameliorization of 1st-cycle effect**

Therapy-associated Deaths before and after Introduction of Prephase Therapy*



* DSHNHL NHL-B2 Trial

Specific Measures:

1. **Prephase Treatment**
2. **Anti-infective Prophylaxis**
   (Cotrimoxazole & Aciclovir)

DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections

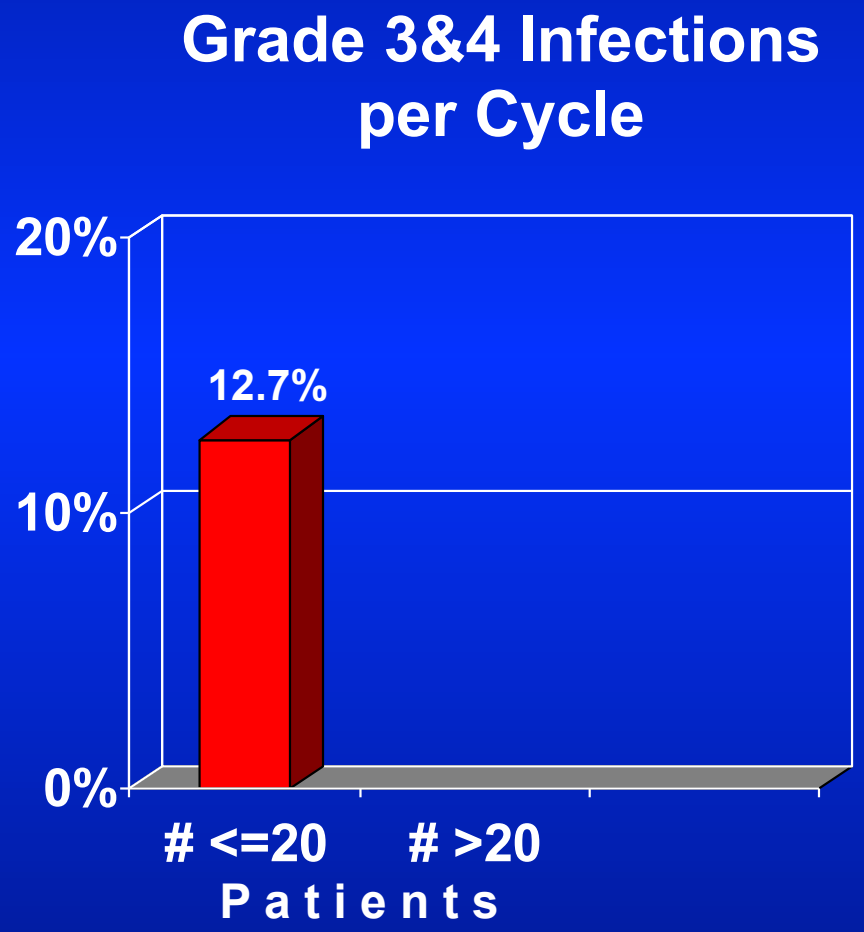
Grade 3&4 Infections per Cycle

DSHNHL

Supported by

DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections

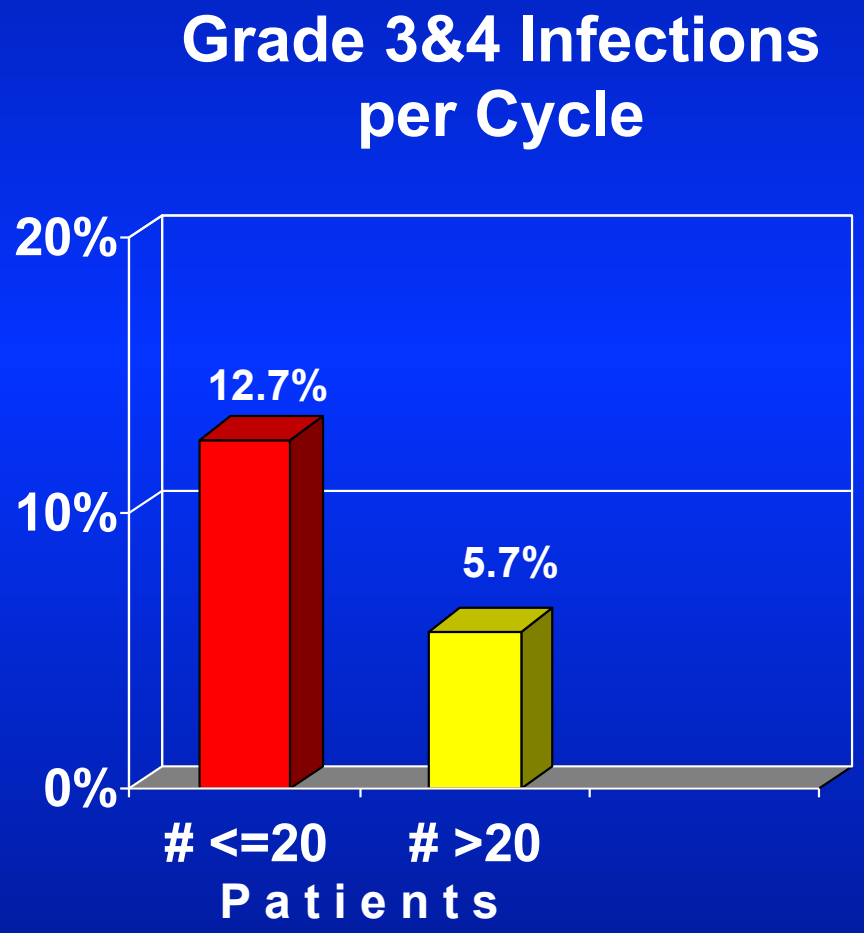


DSHNHL

Supported by

DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections

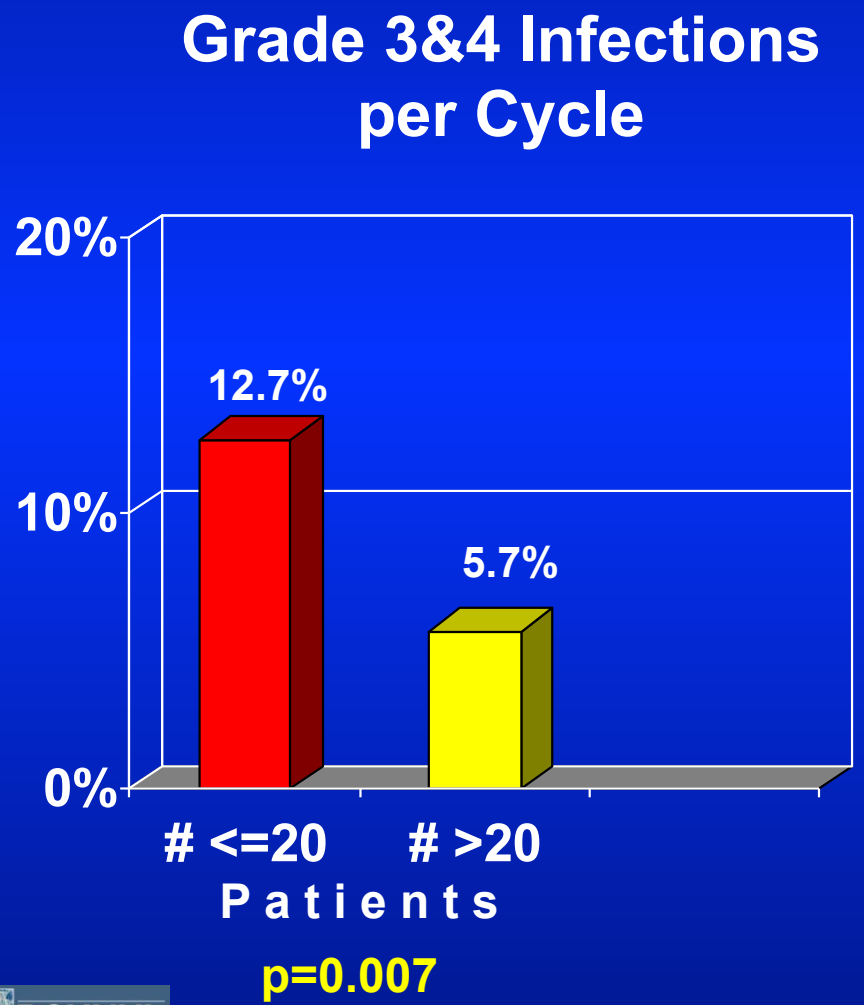


DSHNHL

Supported by

DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections



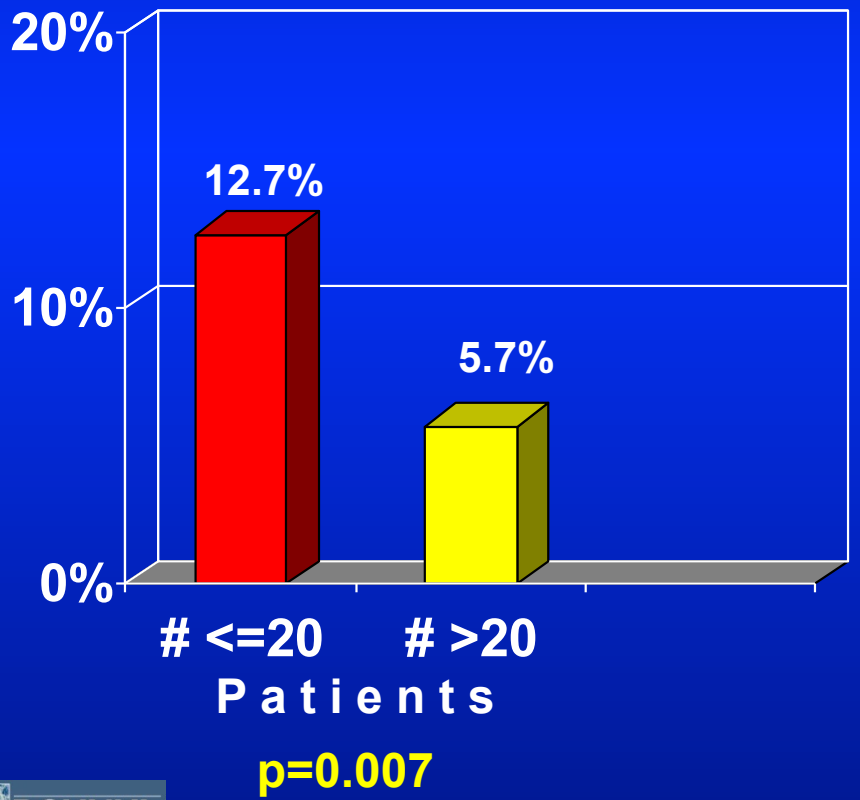
DSHNHL

Supported by

DENSE-R-CHOP-14

Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle



p=0.007

Grade 3&4 Infections per Patient

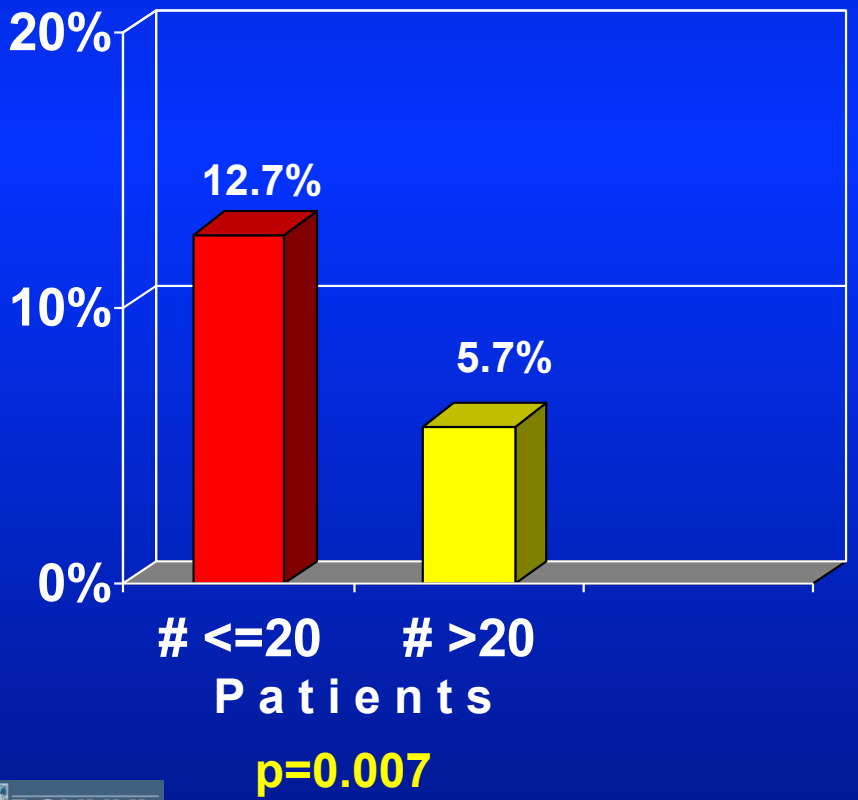
DSHNHL

Supported by

DENSE-R-CHOP-14

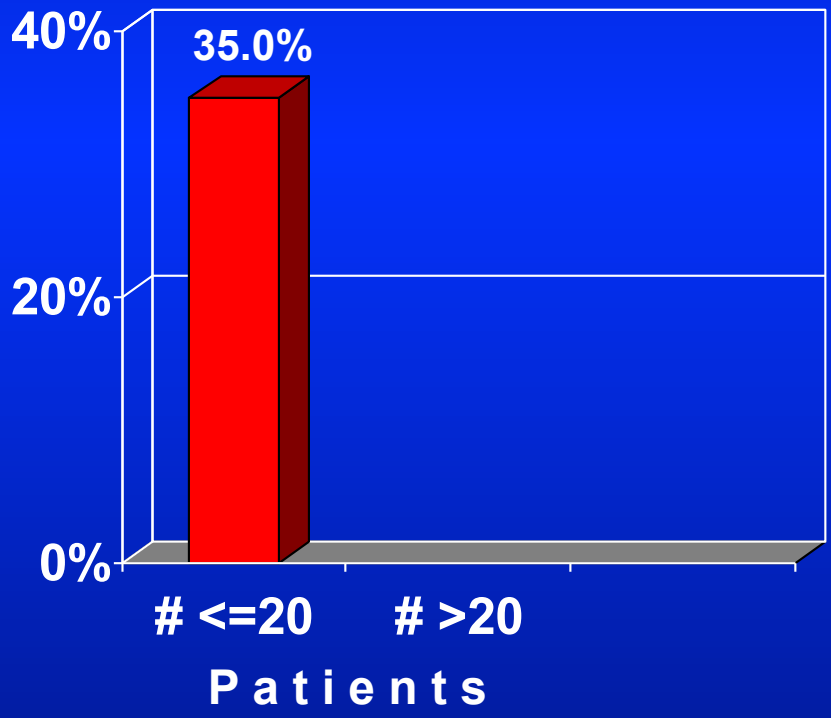
Effect of Prophylaxis on Grade 3&4 Infections

Grade 3&4 Infections per Cycle



p=0.007

Grade 3&4 Infections per Patient



DSHNHL

Supported by

Specific Measures:

1. **Prephase Treatment**
2. **Anti-infective Prophylaxis**
3. **Hydrocortisone Substitution for intercycle fatigue**

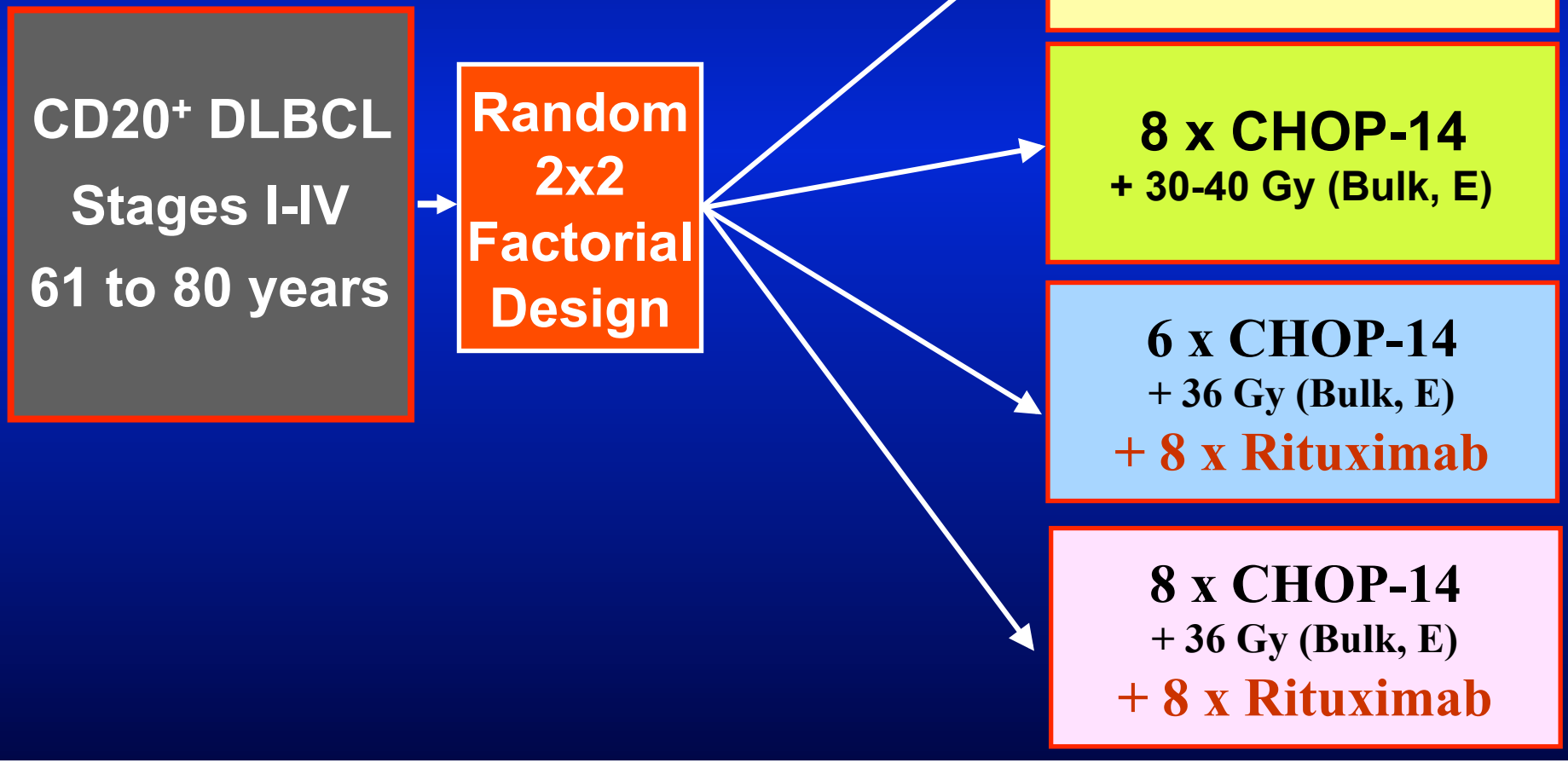
Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**

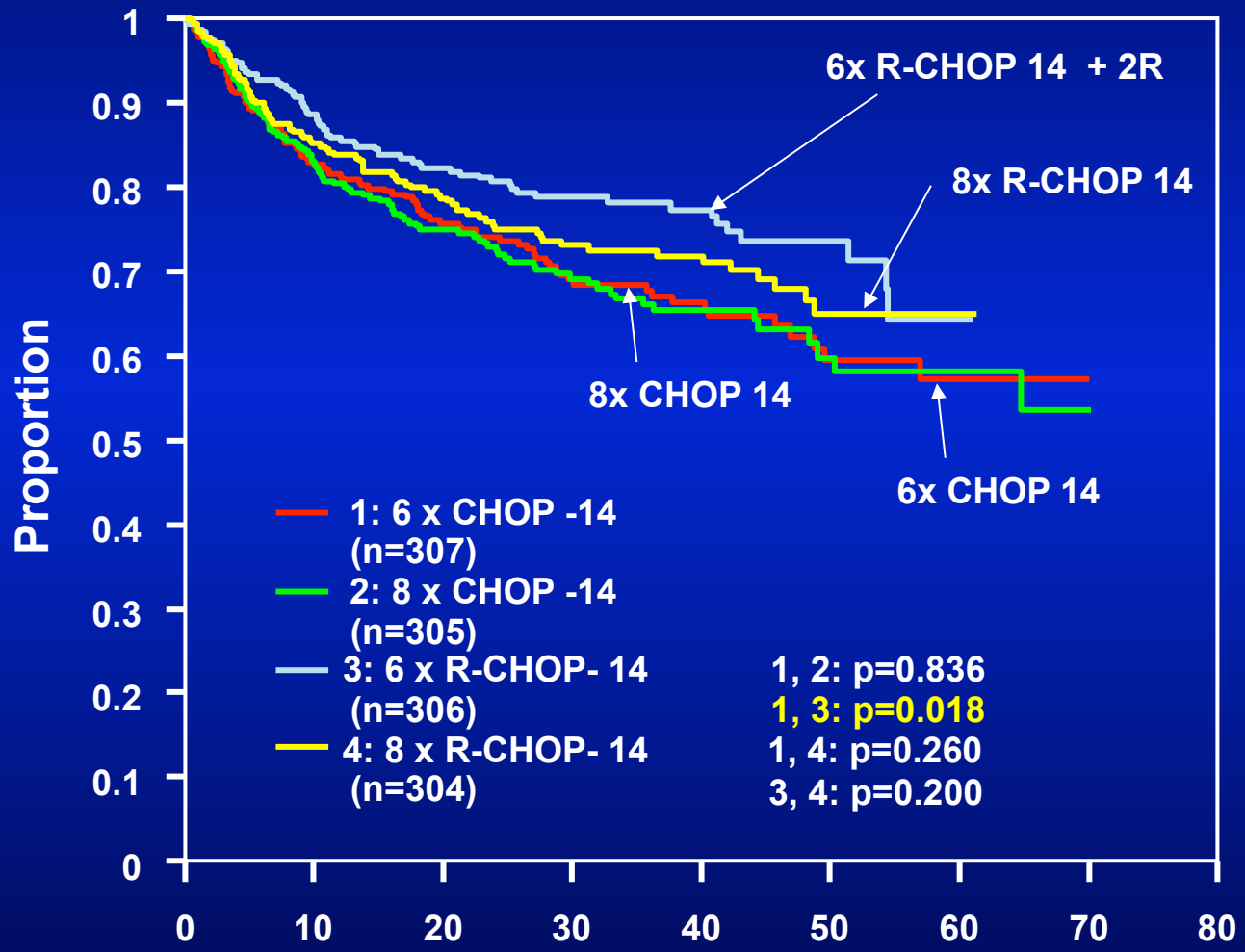
Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
  - **fit elderly**
  - **unfit elderly / very old**

RICOVER-60 Study Design



RICOVER-60
Overall Survival



Pfreundschuh et al., Lancet Oncol. (2008)

III. Elderly Patients:

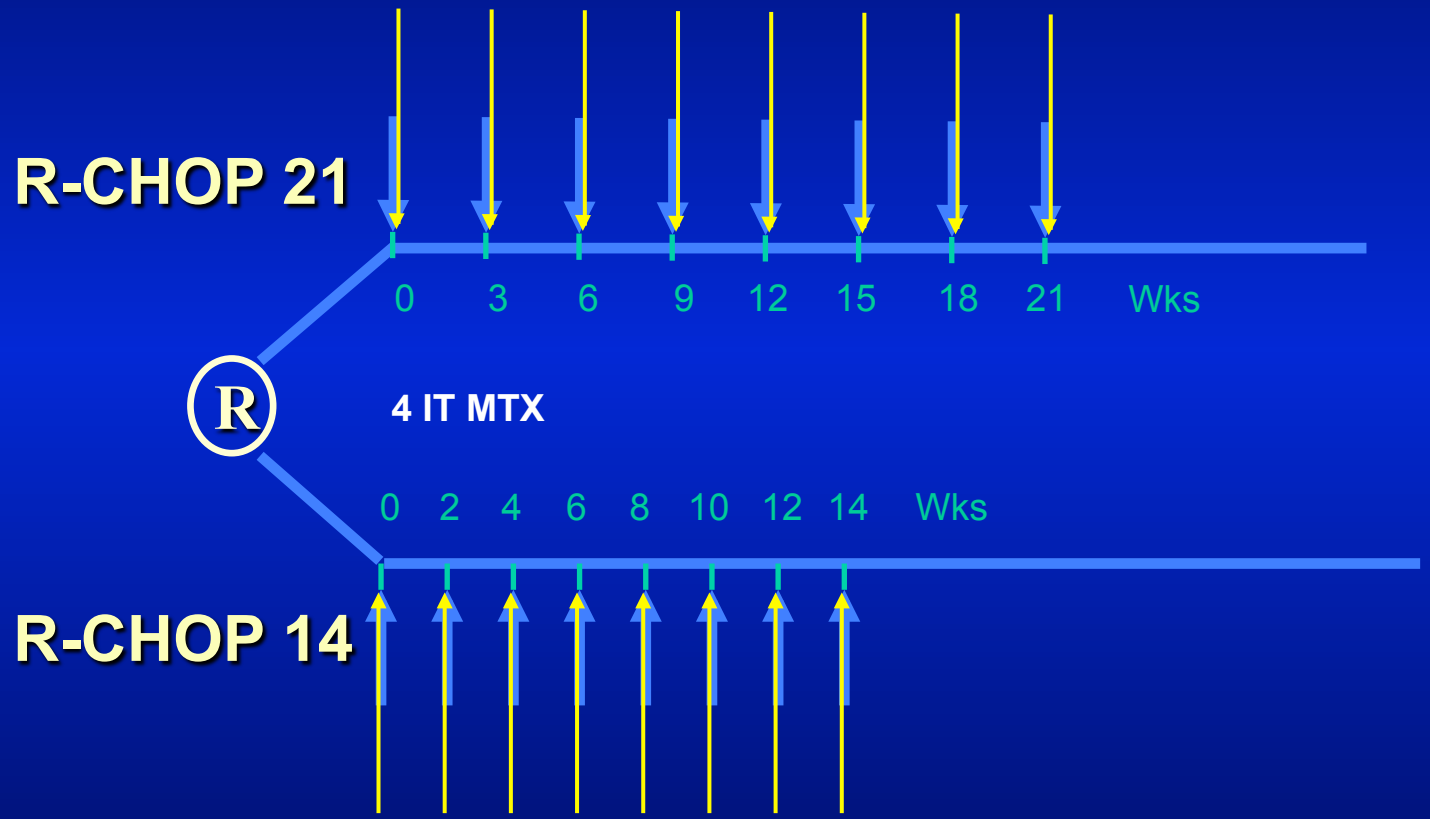
Do we still need Dose Densification / Interval Reduction?

[R-CHOP-14 vs. R-CHOP-21]

LNH 03-6B

66-80 years, aaIPI = 1,2,3

R. Delarue, A. Bosly



Primary endpoint: EFS

Expected improvement: 10% at 3 years with R-CHOP 14 (55 to 65%)

600 patients required (over 4 years)

LNH-03 6B

The French Learning Curve (I) …

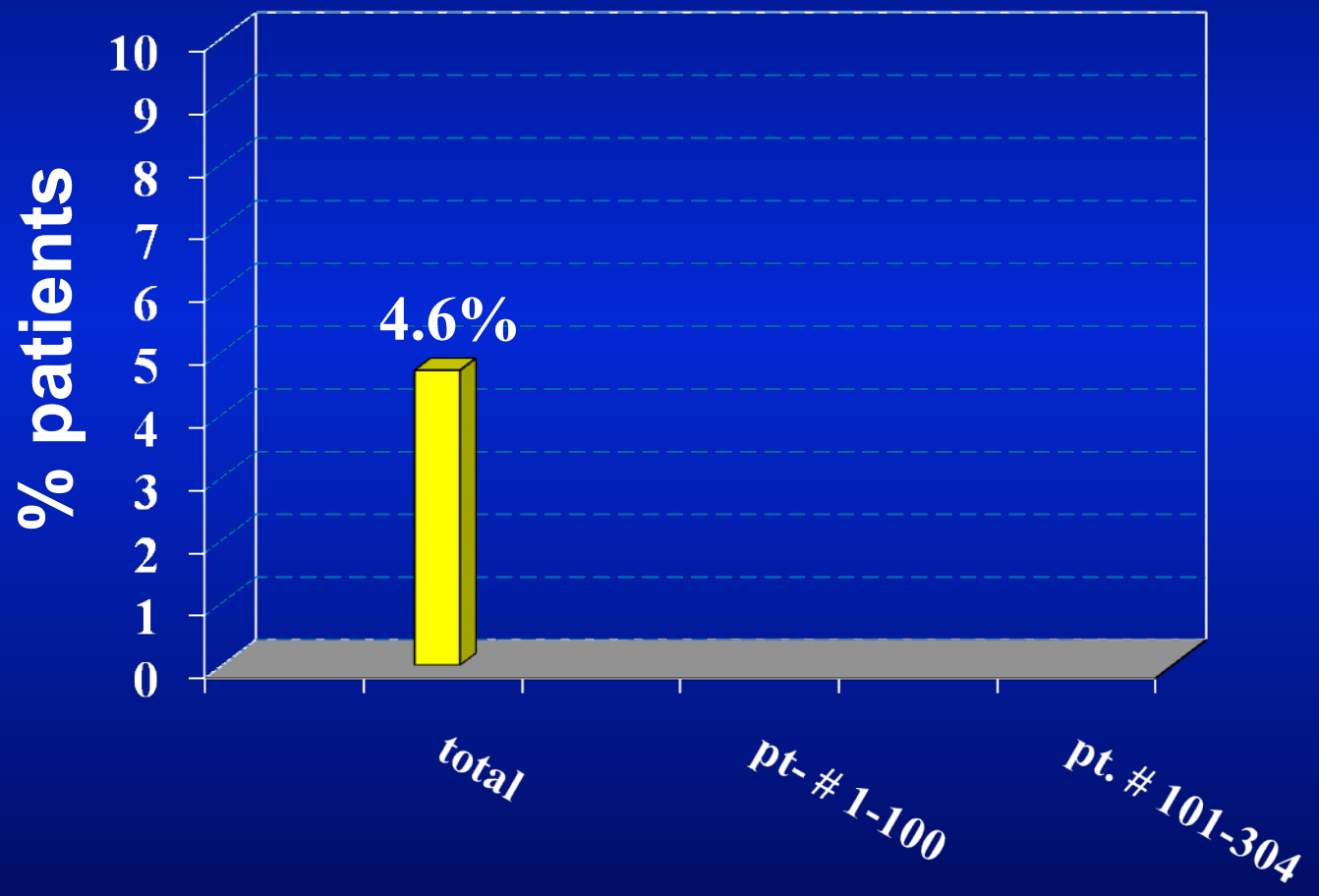
Toxic Deaths with R-CHOP-14

Delarue et al., ASH 2009 / Lancet Oncology 2013

LNH-03 6B

The French Learning Curve (I) …

Toxic Deaths with R-CHOP-14

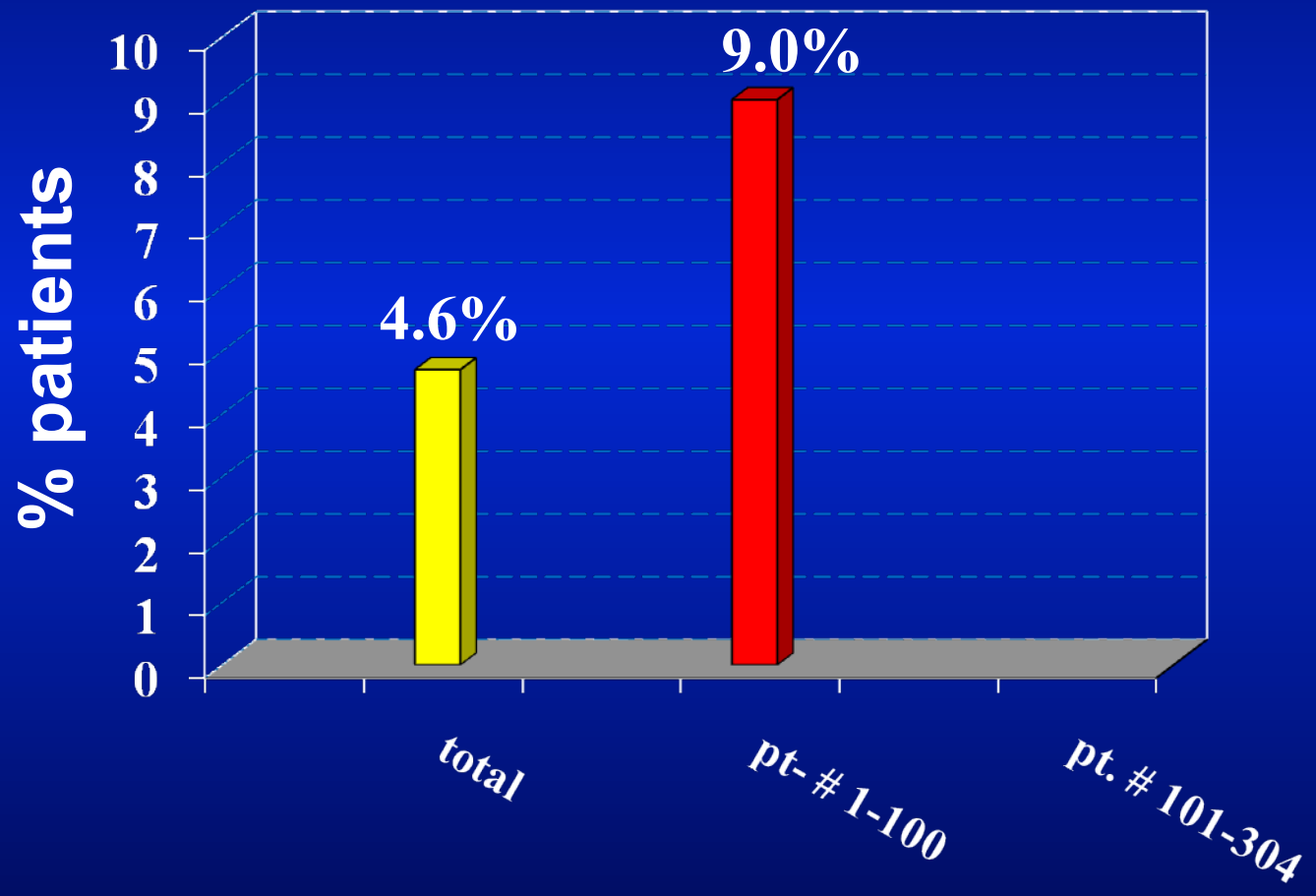


Delarue et al., ASH 2009 / Lancet Oncology 2013

LNH-03 6B

The French Learning Curve (I) …

Toxic Deaths with R-CHOP-14

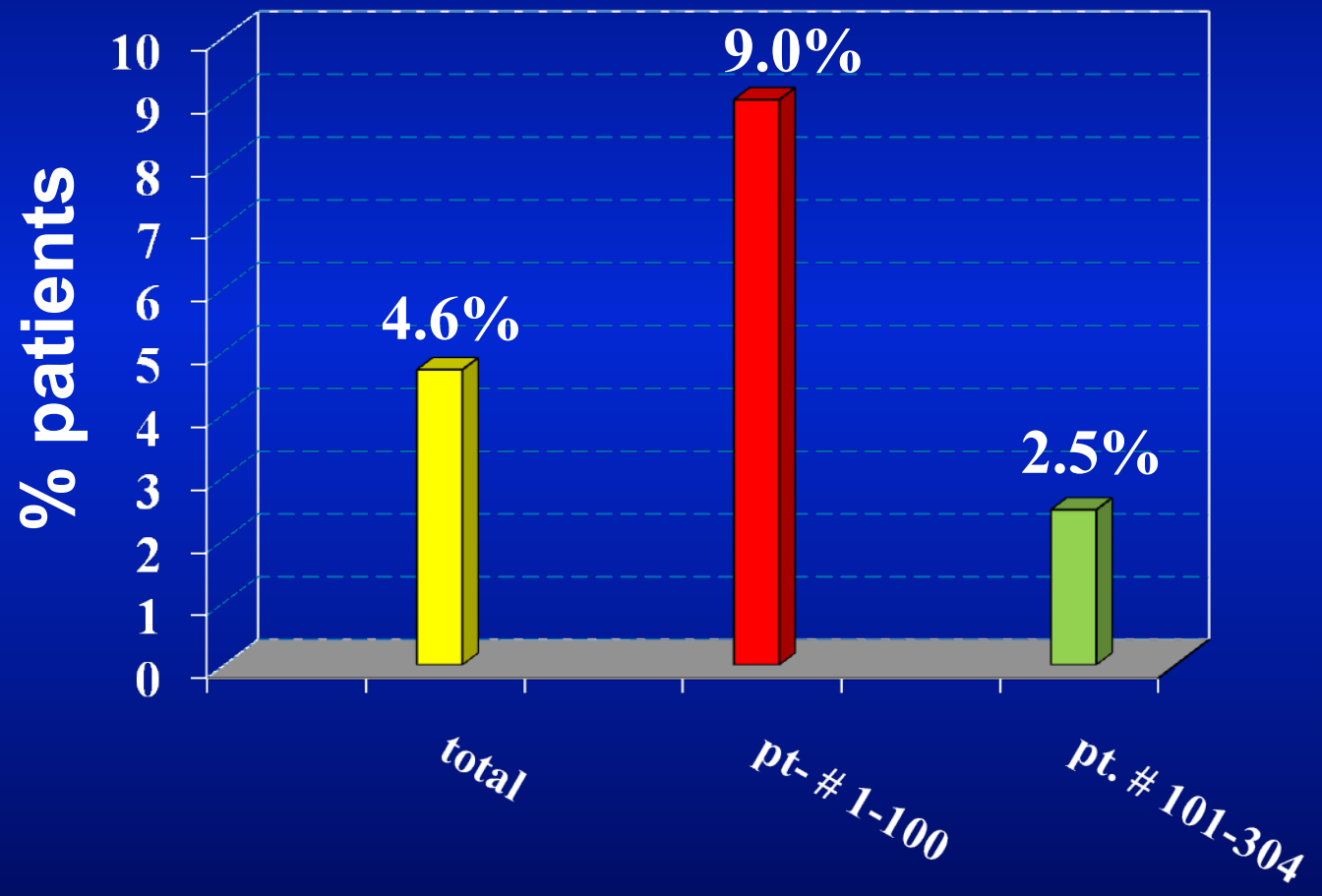


Delarue et al., ASH 2009 / Lancet Oncology 2013

LNH-03 6B

The French Learning Curve (I) …

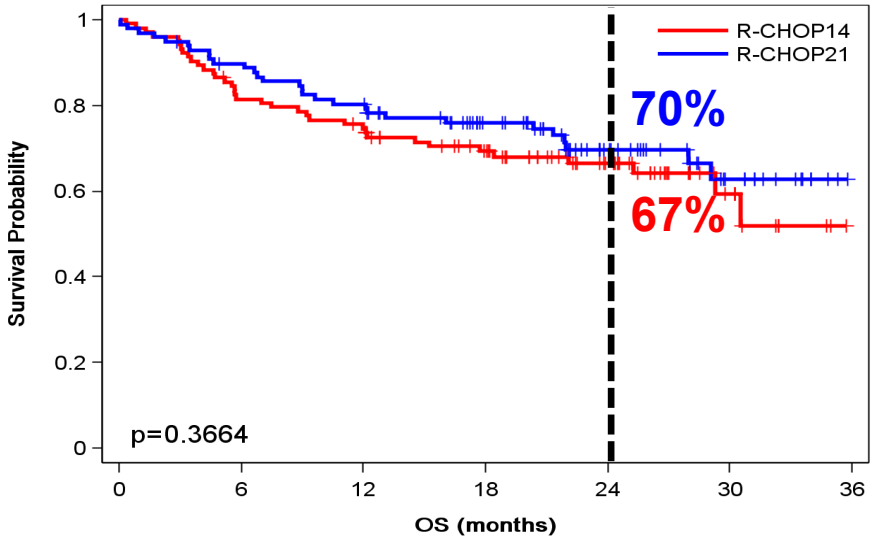
Toxic Deaths with R-CHOP-14



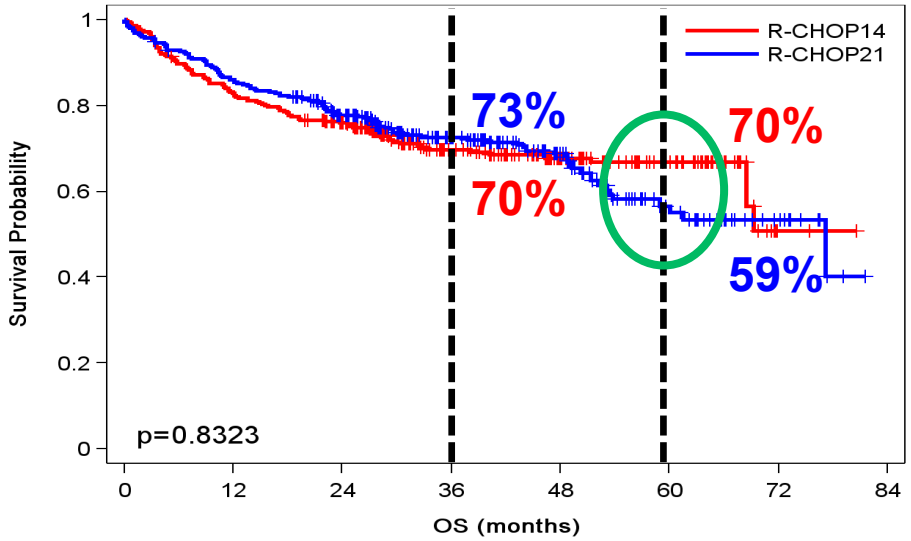
Delarue et al., ASH 2009 / Lancet Oncology 2013

GELA LNH03-6B:
The French CHOP-14 Learning Curve (II)

OS Pts. #1-200



OS Pts. #1-600



2-year OS:
67% (R-CHOP14) vs 70% (R-CHOP21)

3y-OS : 70% vs 73%
HR: 0.98 (95%CI: 0.74-1.30);
p=0.89

Delarue et al., ASH 2009 / Lancet Oncology 2013

RICOVER-60

Adherence to Protocol

Relative Dose Cyclophosphamide (median)

6 x CHOP-14	99%
6 x R-CHOP-14	99%
8 x CHOP-14	96%
8 x R-CHOP-14	96%
GELA 8xR-CHOP-14	83%

RICOVER-60

Adherence to Protocol

Relative Dose Cyclophosphamide (median)

6 x CHOP-14	99%
6 x R-CHOP-14	99%
8 x CHOP-14	96%
8 x R-CHOP-14	96%
GELA 8xR-CHOP-14	83%

Are German patients tougher ?

RICOVER-60

Adherence to Protocol

Relative Dose Intensity Cyclophosphamide (median)

6 x CHOP-14	99%
6 x R-CHOP-14	99%
8 x CHOP-14	96%
8 x R-CHOP-14	96%

- supportive measures as discussed
- no dose reductions unless delay >7 days
- strict adherence to G-CSF schedule

Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- **Equal efficacy**

Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- **Equal efficacy**
- **Equal acute toxicity**

ESMO GUIDELINES 2015

Recommendation Elderly DLBCL:

- **6 cycles R-CHOP-14 + 2 R**
- **8 cycles R-CHOP-21**

Tilly et al., *Ann Oncol 2015*

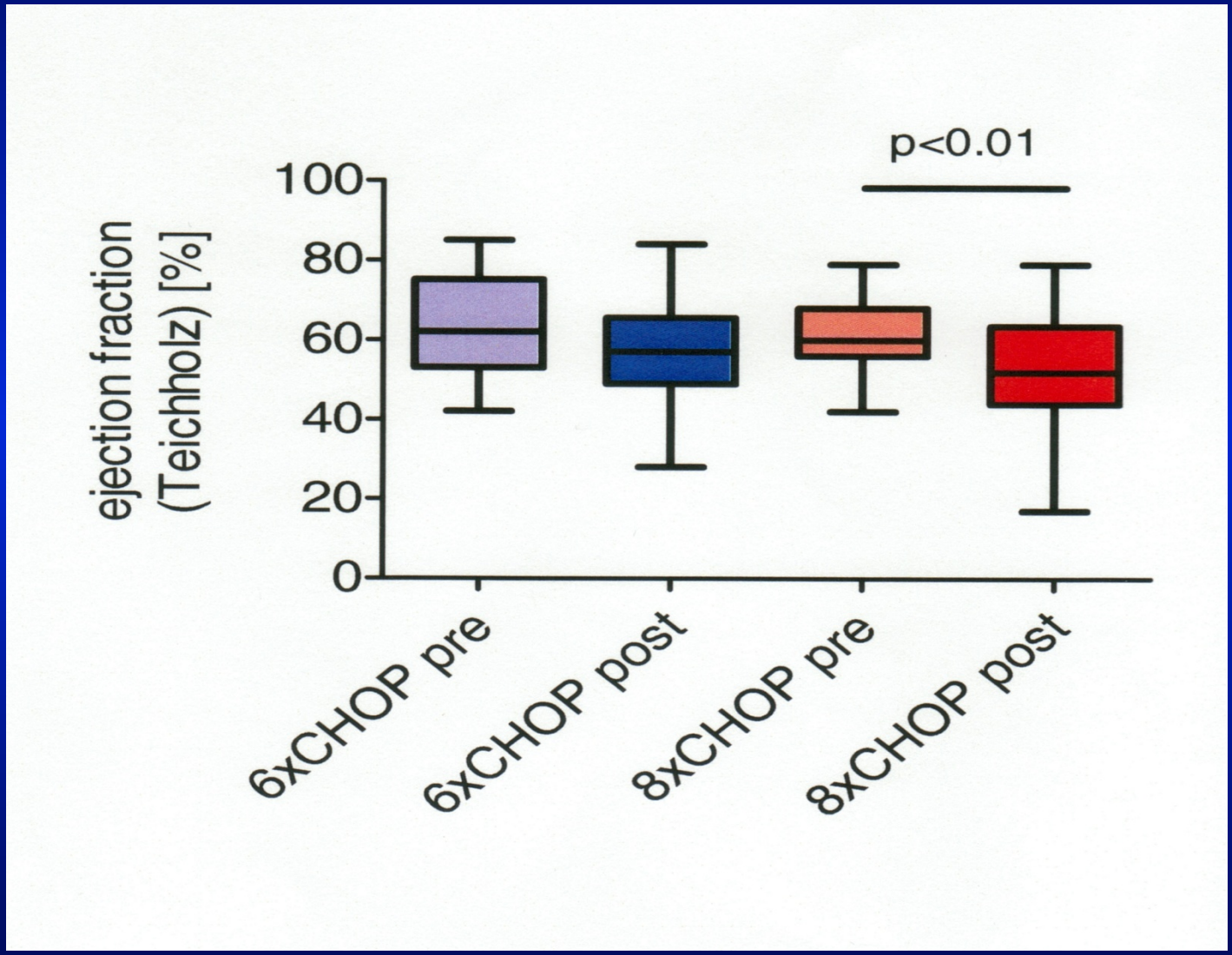
Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- **Equal efficacy**
- **Equal acute toxicity**

What about long-term toxicity ?

R-CHOP: Reduction of EF



Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- **Equal efficacy**
- **Equal acute toxicity**
- **Less long-term toxicity (cardiac: yes; second neoplasms: probably)**

Unresolved Issues in DLBCL

R-CHOP-14 vs R-CHOP-21 in Elderly:

- **Equal efficacy**
- **Equal acute toxicity**
- **Less long-term toxicity (cardiac: yes; second neoplasms: probably)**
- **Shorter time under chemo (10 vs. 21 weeks)**

Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
  - **fit elderly**
  - **unfit elderly / very old (>80 years?)**

Rituximab and reduced dose R-miniCHOP for patients aged over 80 with DLBCL

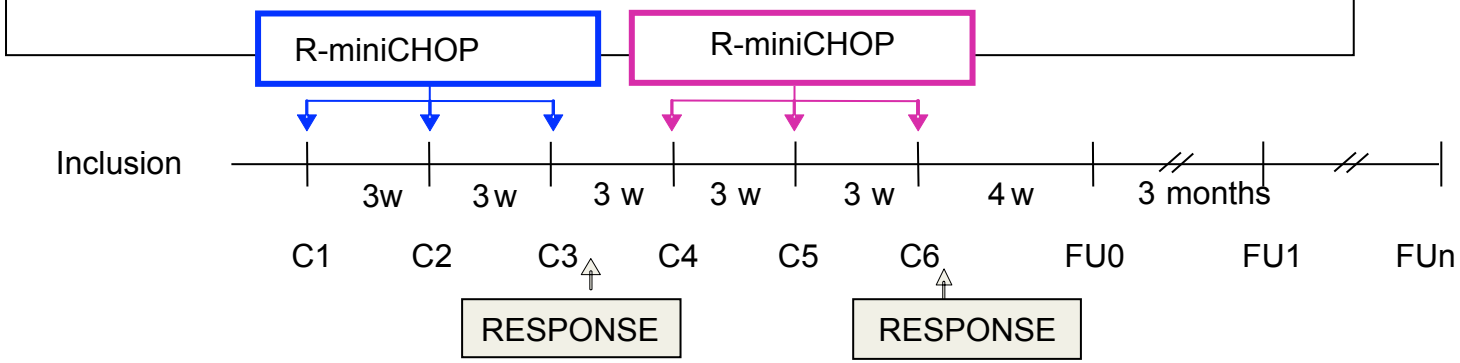
Groupe d'Etude Des Lymphomes De l'Adulte (GELA)
Study LNH03-7B

Frédéric Peyrade, Fabrice Jardin, Christian Gisselbrecht, Antoine Thyss, Jean François Emile, Sylvie Castaigne, Bertrand Coiffier, Corinne Haioun, Serge Bologna, Olivier Fitoussi, Gérard Lepeu, Christophe Fruchart, Dominique Bordessoule, Michel Blanc, Richard Delarue, Maud Janvier, Bruno Salles, Andre Bosly, and Hervé Tilly

Gela

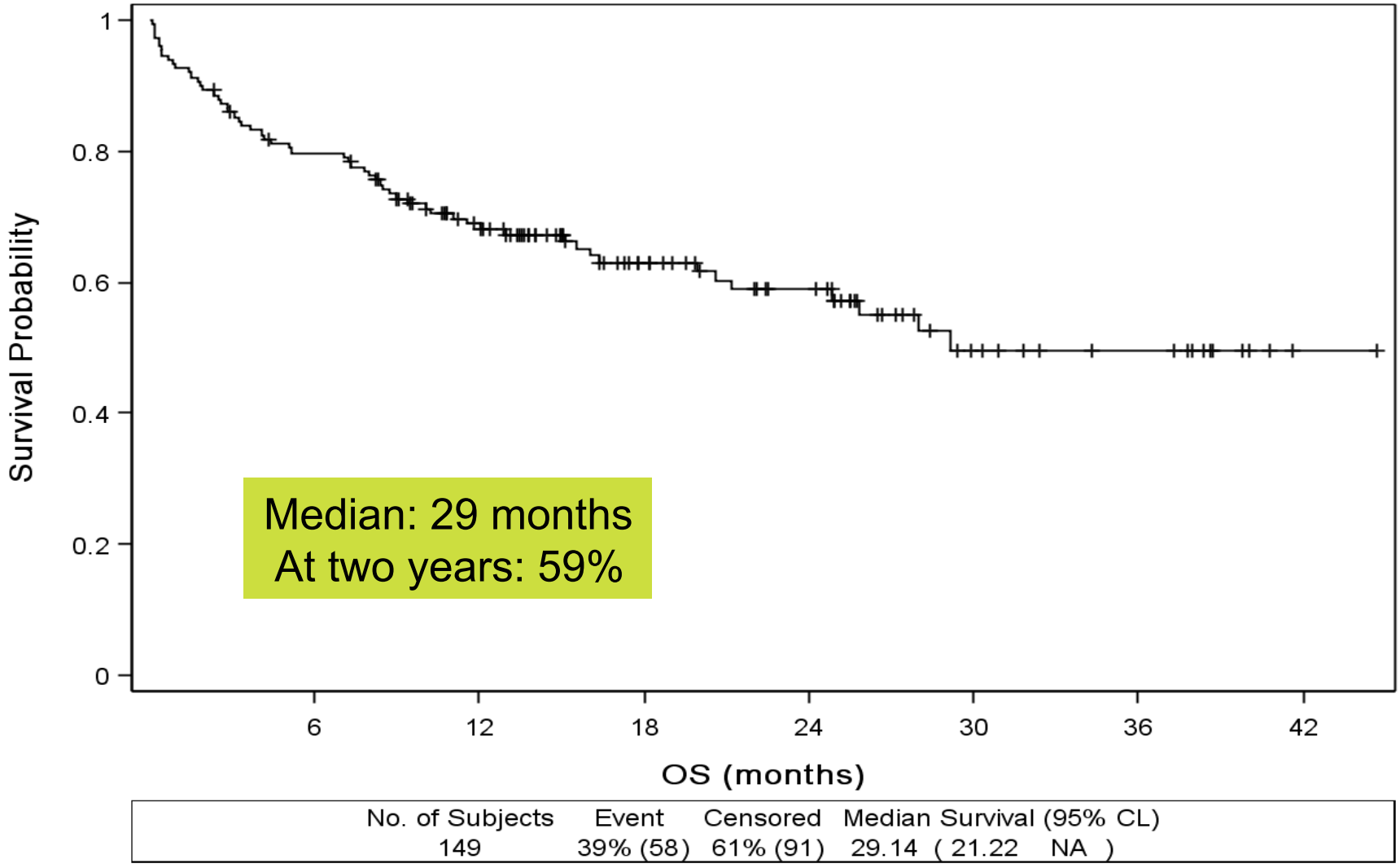
Treatment

R-miniCHOP	Dose	D1	D2	D3	D4	D5
Prednisone	40 mg/m²	X	X	X	X	X
Rituximab	375 mg/m²	X				
Doxorubicin	25 mg/m²	X				
Cyclophosphamide	400 mg/m²	X				
Vincristine	1 mg DT	X				



Primary endpoint: overall survival

Primary endpoint: Overall survival
Intent-to-treat population



Conclusions

- **R-miniCHOP : adapted regimen for DLBCL patients older 80 years**
- **Acceptable toxicity, but first treatment cycles represent a crucial period**
- **59% patients are alive at two years**
- **Less toxicity with perphase treatment***

*** ASH 2014**

Aggressive Lymphomas in the Very Old

Specific evaluation:

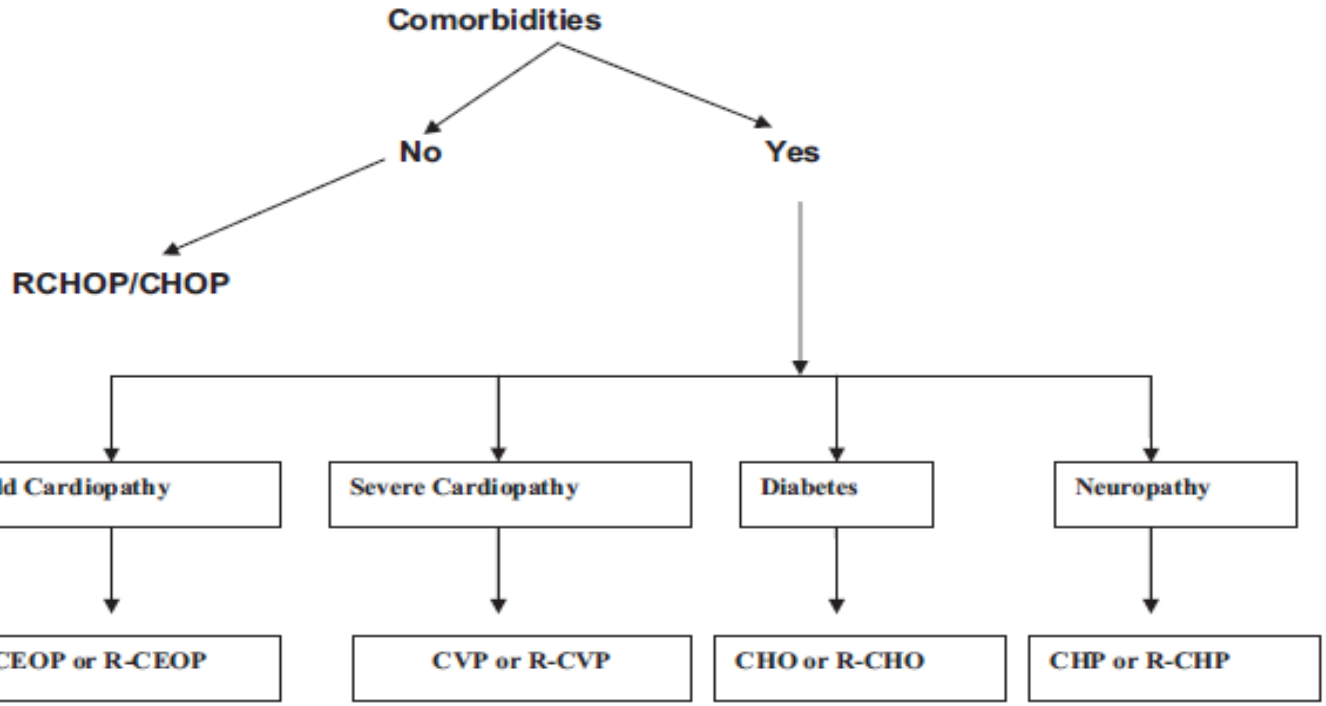
- **Comprehensive geriatric assessment (CGA)**
- **Activities of daily life (ADL)**
- **Instrumental acitivties of daily linving (IADL)**
- **Cumulative illness rating score (CIRS)**

Aggressive Lymphomas in the Elderly

Basic geriatric evaluation:

- **Gait speed**
- **Timed up and go**
- **Hand grip**
- **Tinetti gait and blance test**
- **Hurria Self Assessment Test**

Geriatric Assessment-modified Strategy

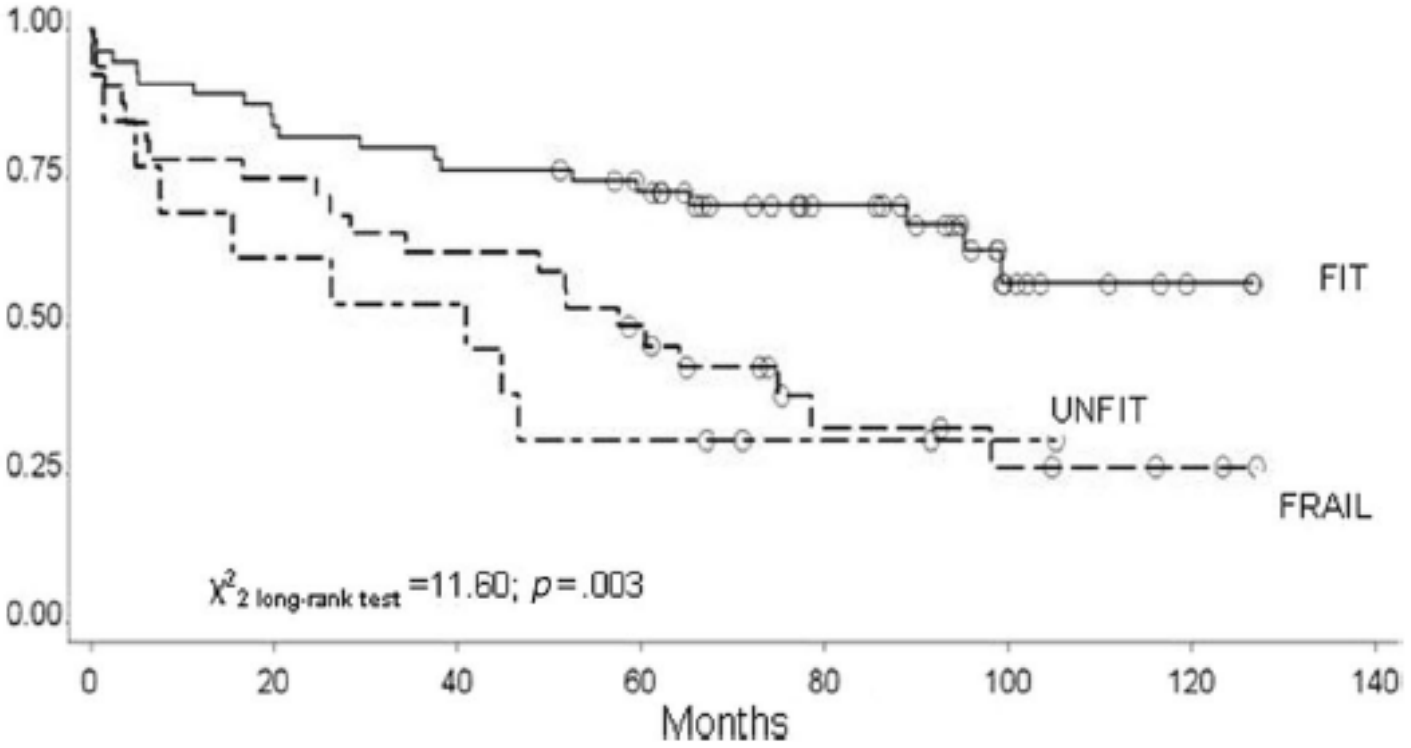


Step 2: Dosage of chemotherapy

ADL	6	5	<5
or			
IADL	7-8	5-6	<5
	100%	75%	50%

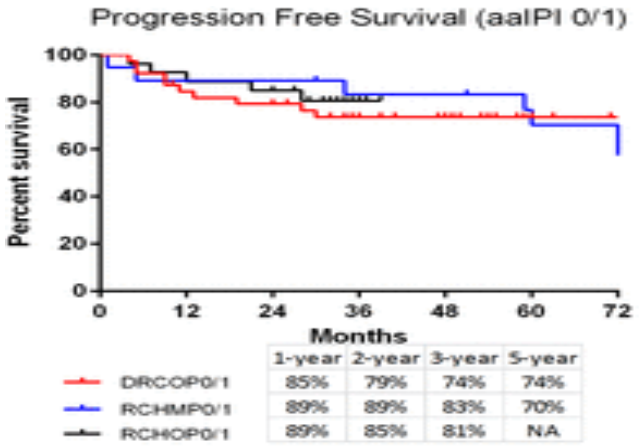
Spina et al. 2012

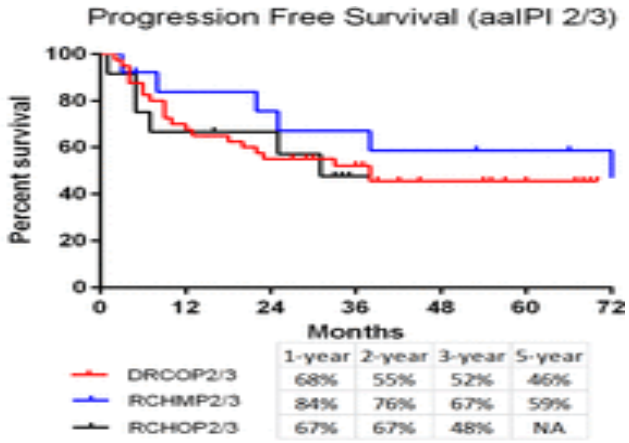
Geriatric Assessment-modified Strategy

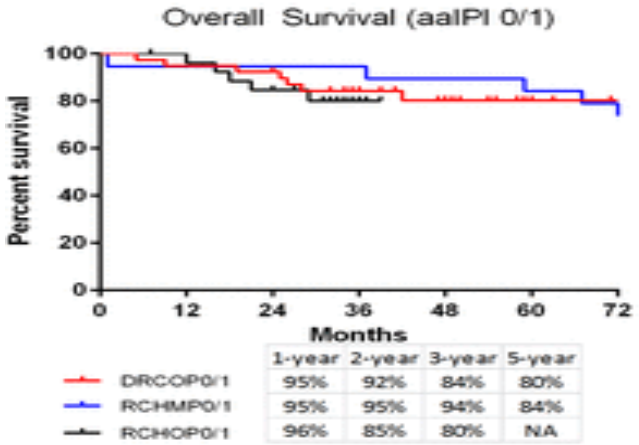


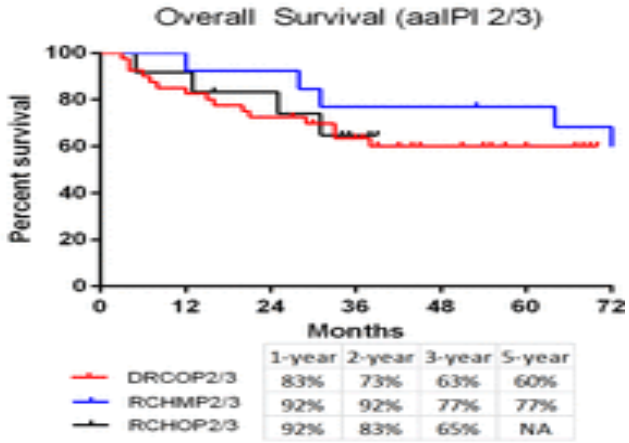
Spina et al. 2012

Patients >60 Years of Age with Diffuse Large B-Cell Lymphoma (DLBCL) Treated with Standard or Liposomal Chemotherapies





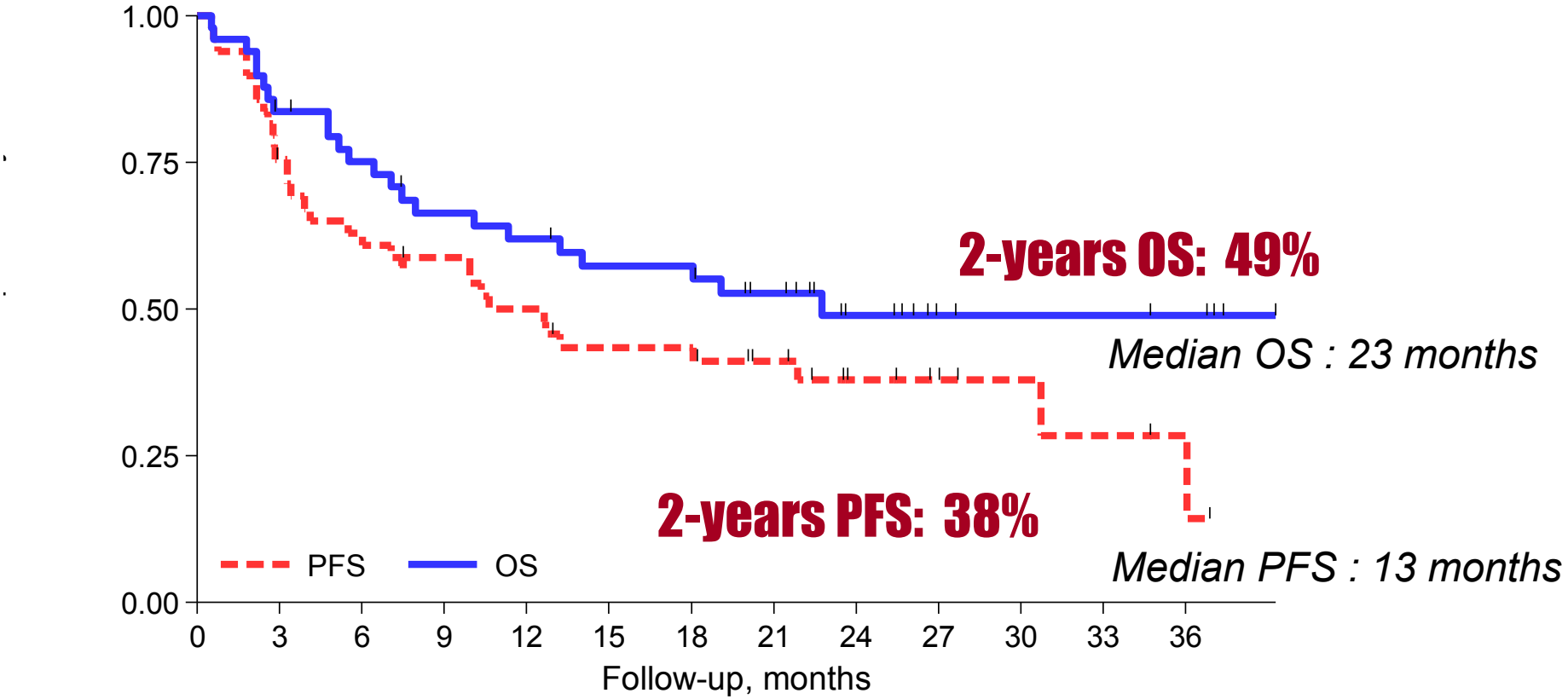




Romega et al. ASH 2015

R-BENDA Frail: Outcome

Median follow-up: 23 months (range 1-39)



PFS	49	36	30	26	23	19	19	15	8	6	4	3	2
OS	49	40	35	30	28	25	25	20	11	6	5	5	4

R-BENDA Frail, Sergio Storti, Campobasso -Italy

Aggressive Lymphomas in the Elderly

- **Clinical relevance**
- **Definition of „elderly“ patients**
- **Specific features of elderly patients**
- **Treatment options**
- **Perspectives**

Improvement Strategies In Elderly DLBCL

1. Intensified chemotherapy ?

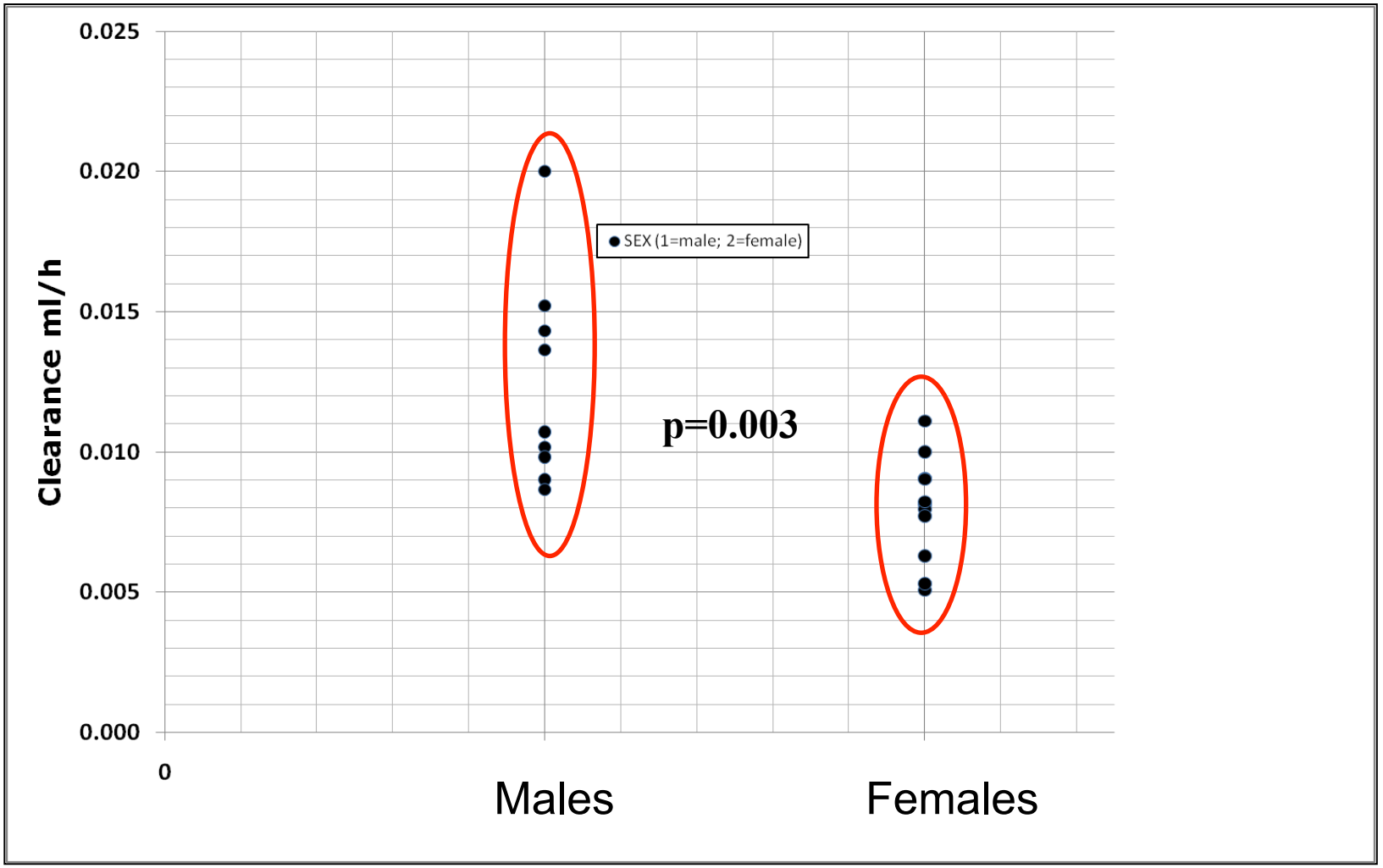
2. Intensified rituximab ?

Improvement Strategies In Elderly DLBCL

1. Intensified chemotherapy ?

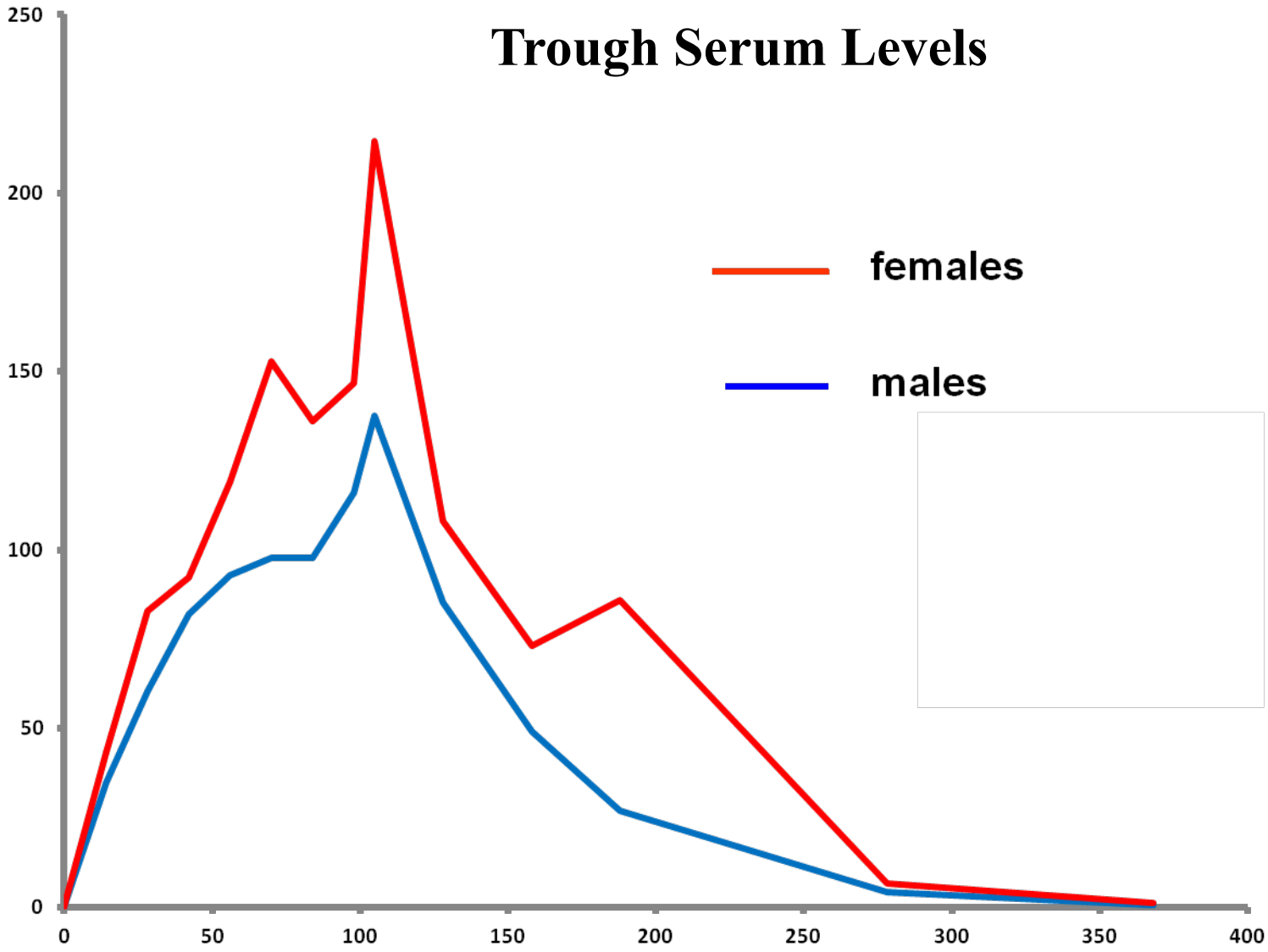
2. Intensified rituximab ?

RICOVER-60 Trial: Rituximab Clearance

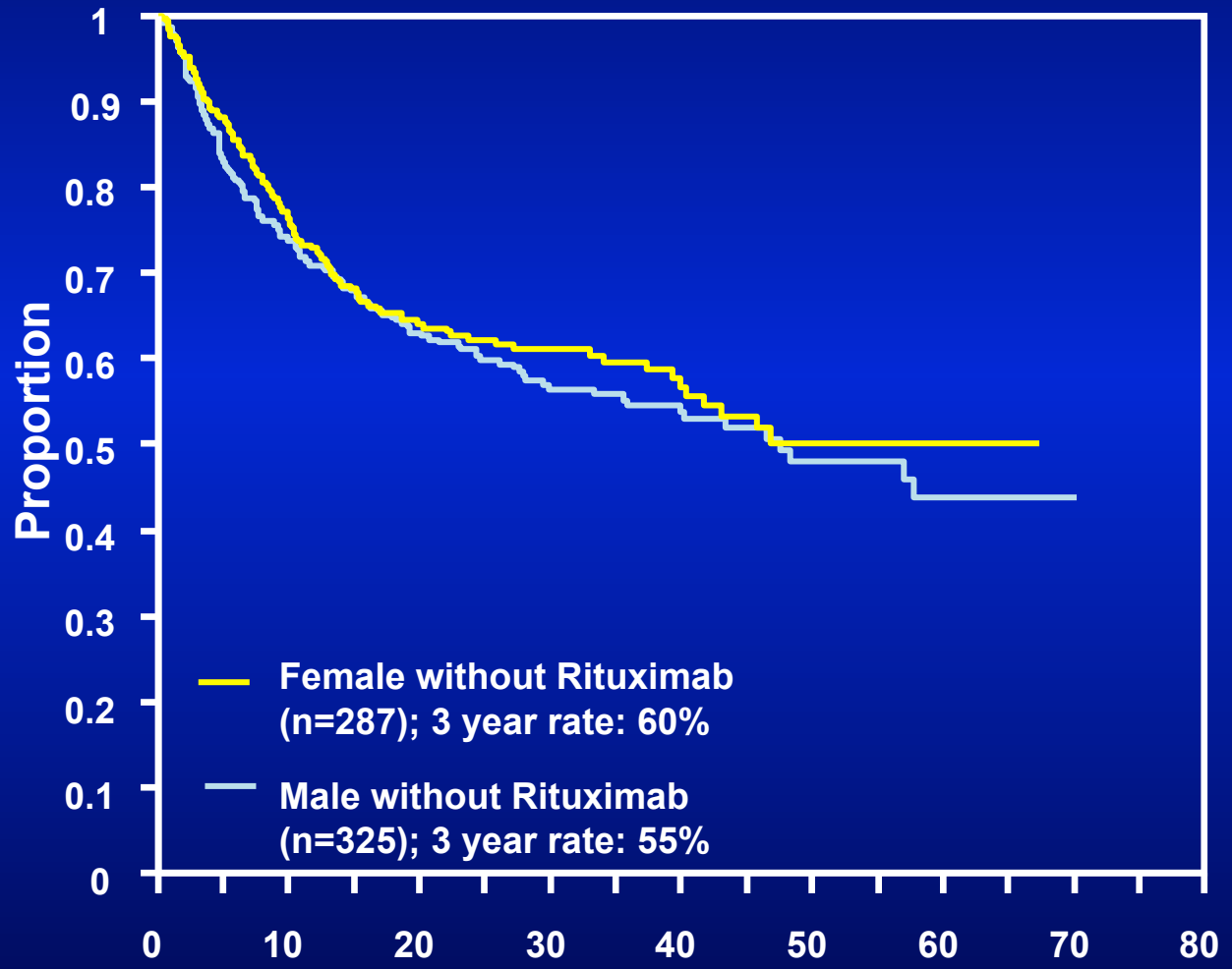


Müller et al., Blood 2012

RICOVER-60

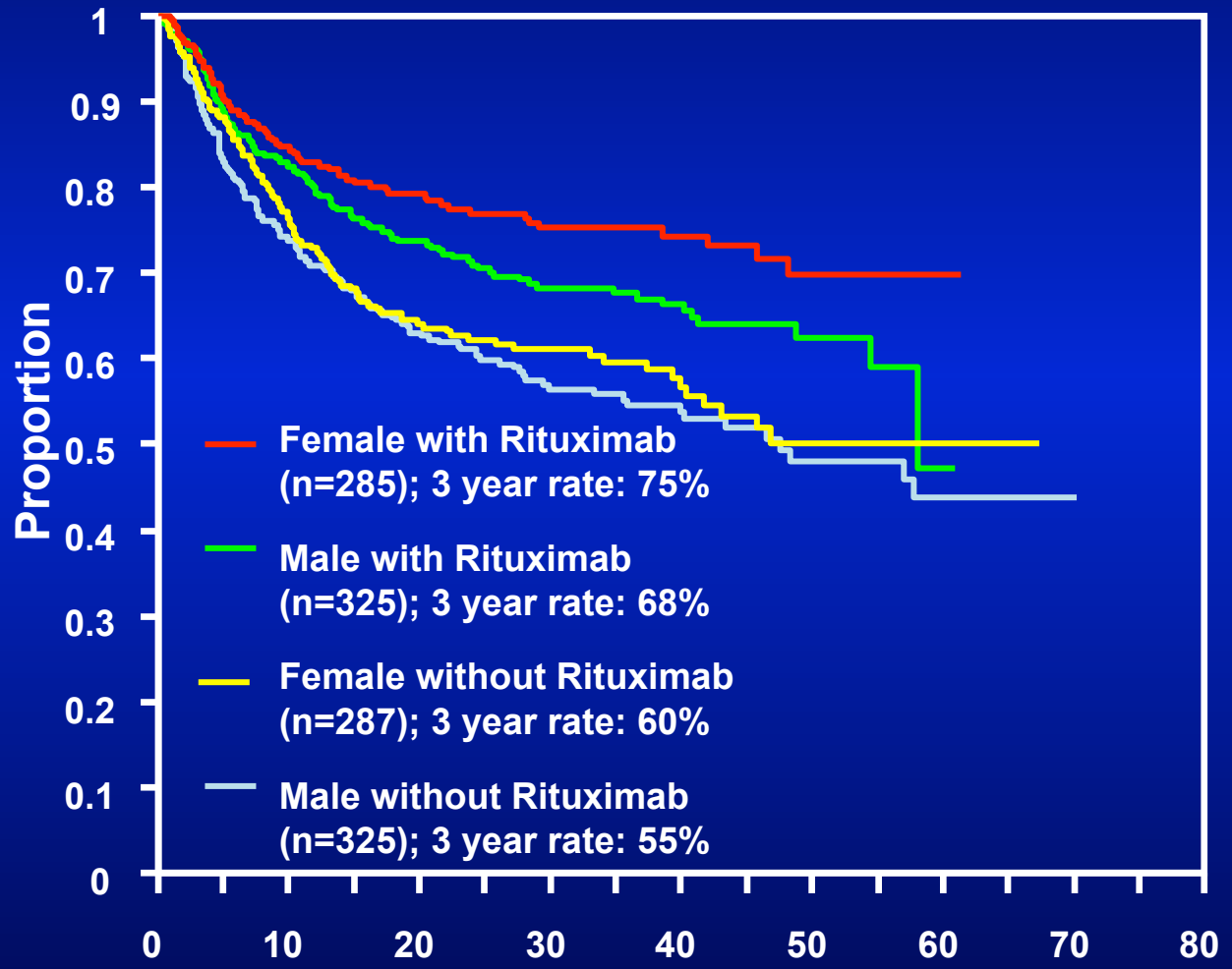

Trough Serum Levels
250
200
150
100
50
0
0
50
100
150
200
250
300
350
400
females
males

RICOVER-60 Trial (n=1222)
PFS according to Sex and Rituximab



Müller et al, Blood 2012

RICOVER-60 Trial (n=1222)
PFS according to Sex and Rituximab



Müller et al, Blood 2012

RICOVER-60 Trial (n=1222)
Multivariate Analysis PFS

Without **Rituximab**

	RR	p
LDH	1.526	0.002
ECOG	1.672	0.001
Stage	1.957	<0.001
Ex>1	1.650	0.001
Male vs. Female	1.127	0.348

Müller et al, Blood 2012

RICOVER-60 Trial (n=1222)
Multivariate Analysis PFS

Without Rituximab

	RR	p
LDH	1.526	0.002
ECOG	1.672	0.001
Stage	1.957	<0.001
Ex>1	1.650	0.001
Male vs. Female	1.127	0.348

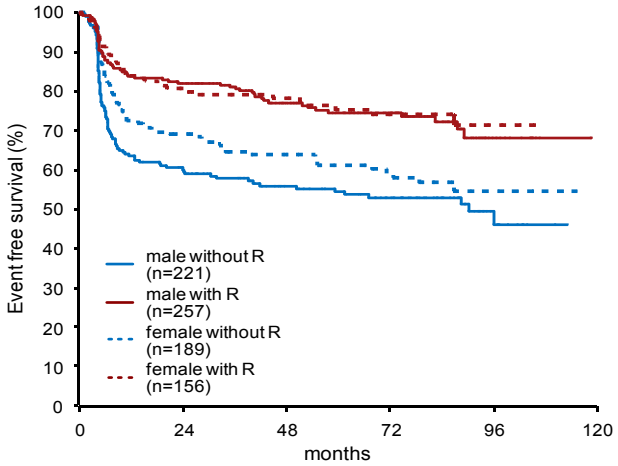
With Rituximab

	RR	p
LDH	2.210	<0.001
ECOG	1.743	0.004
Stage	1.450	0.045
Ex>1	1.075	0.724
Male vs. Female	1.592	0.004

Müller et al, Blood 2012

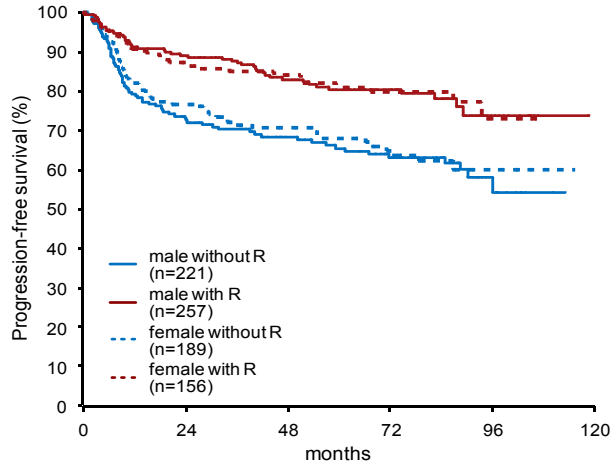
Outcome of Young Females and Males with DLBCL in the MInT Study

E F S



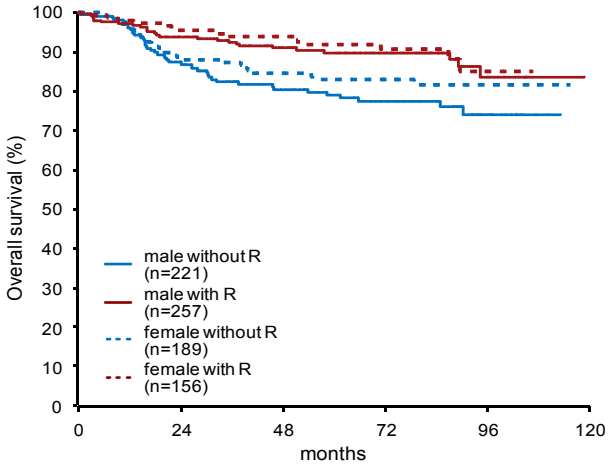
Number at risk					
male without R	115	82	63	14	0
male with R	189	130	94	17	0
female without R	118	81	54	11	0
female with R	116	84	56	13	0

P F S



Number at risk					
male without R	137	98	75	15	
male with R	202	138	100	17	
female without R	127	85	57	11	
female with R	124	89	61	13	

O S



Number at risk					
0 male without R	170	118	94	20	0
0 male with R	221	157	119	27	0
0 female without R	153	108	81	20	0
0 female with R	144	102	71	14	0

Females without rituximab

Males without rituximab

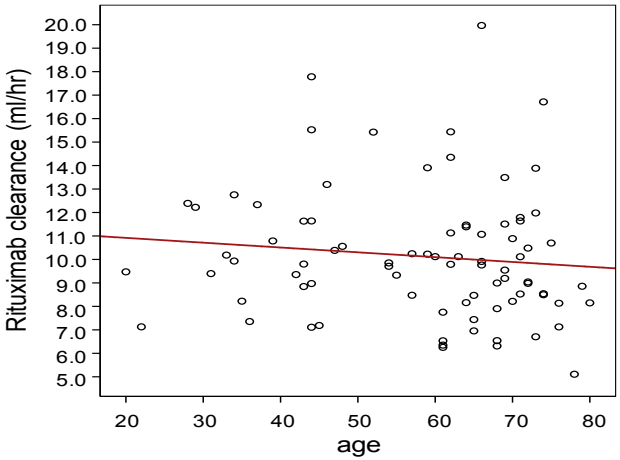
Femals with rituximab

Males with rituximab

Rituximab Clearance in DLBCL according to Age

Rituximab Clearance in DLBCL according to Age

All Patients

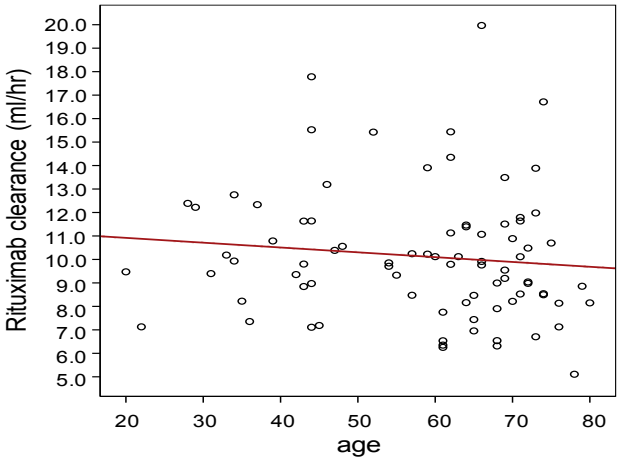


p=0.320

Pfreundschuh et al., *Blood 2014*

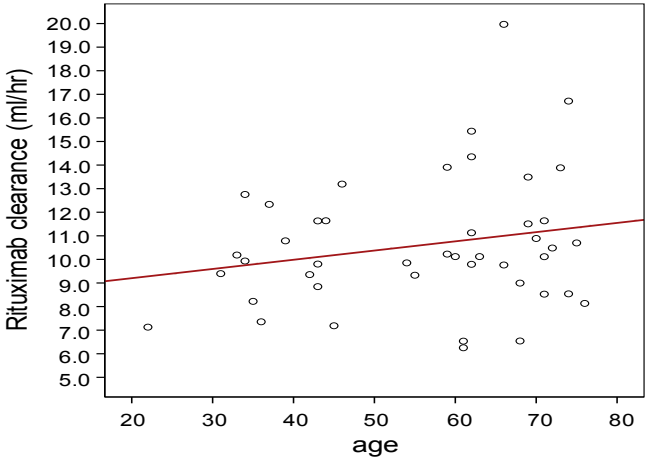
Rituximab Clearance in DLBCL according to Age

All Patients



p=0.320

Males

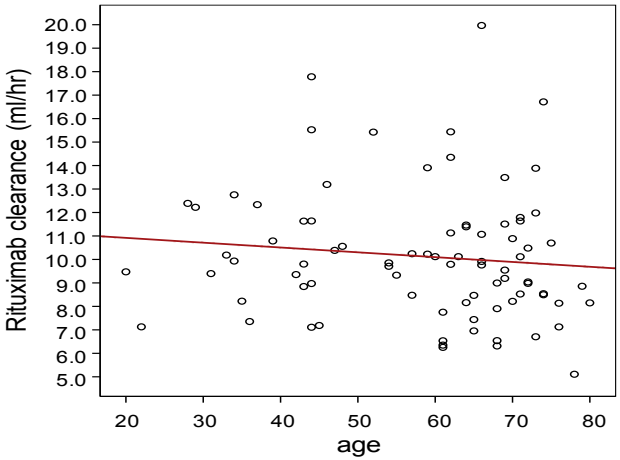


p=0.168

Pfreundschuh et al., *Blood 2014*

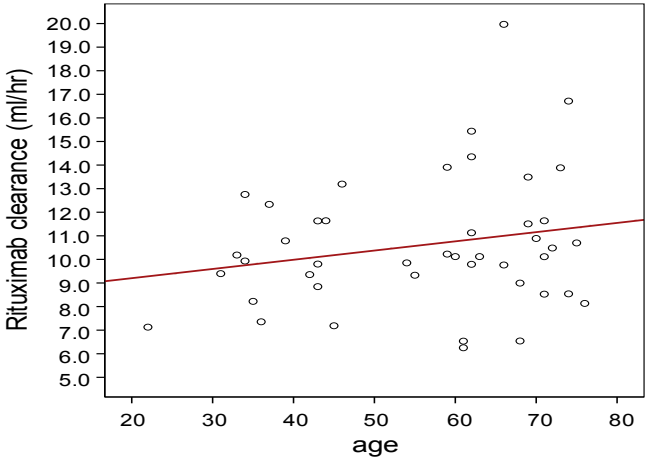
Rituximab Clearance in DLBCL according to Age

All Patients



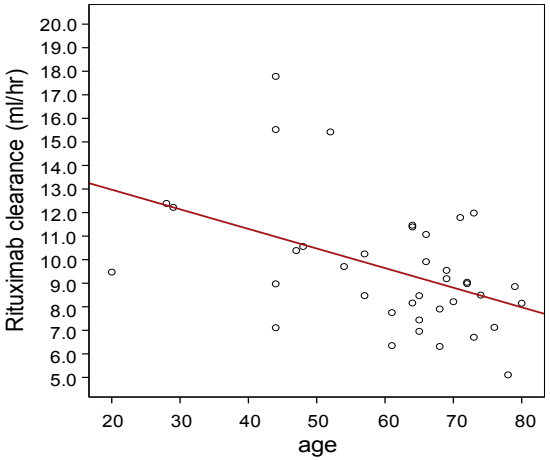
p=0.320

Males



p=0.168

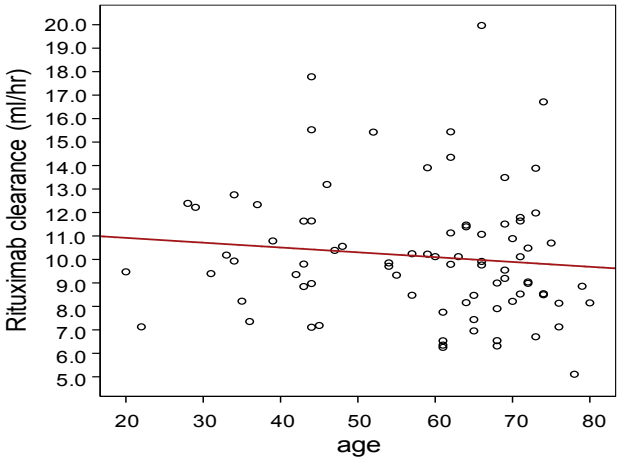
Females



Pfreundschuh et al., *Blood 2014*

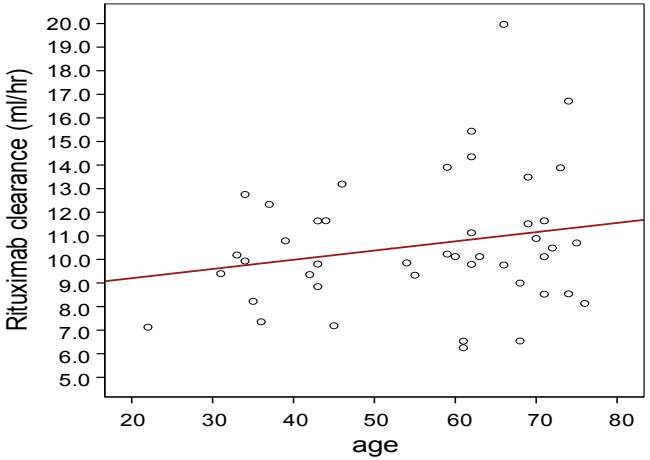
Rituximab Clearance in DLBCL according to Age

All Patients



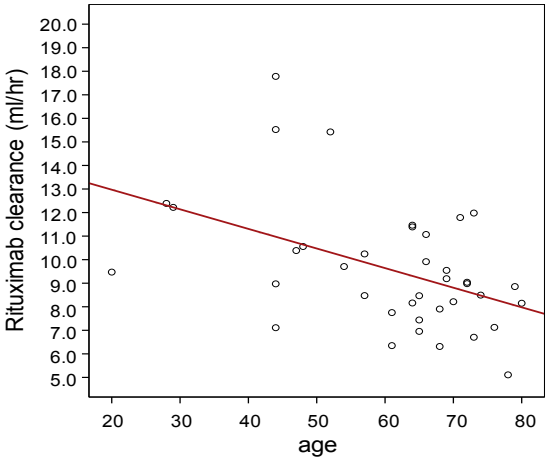
p=0.320

Males



p=0.168

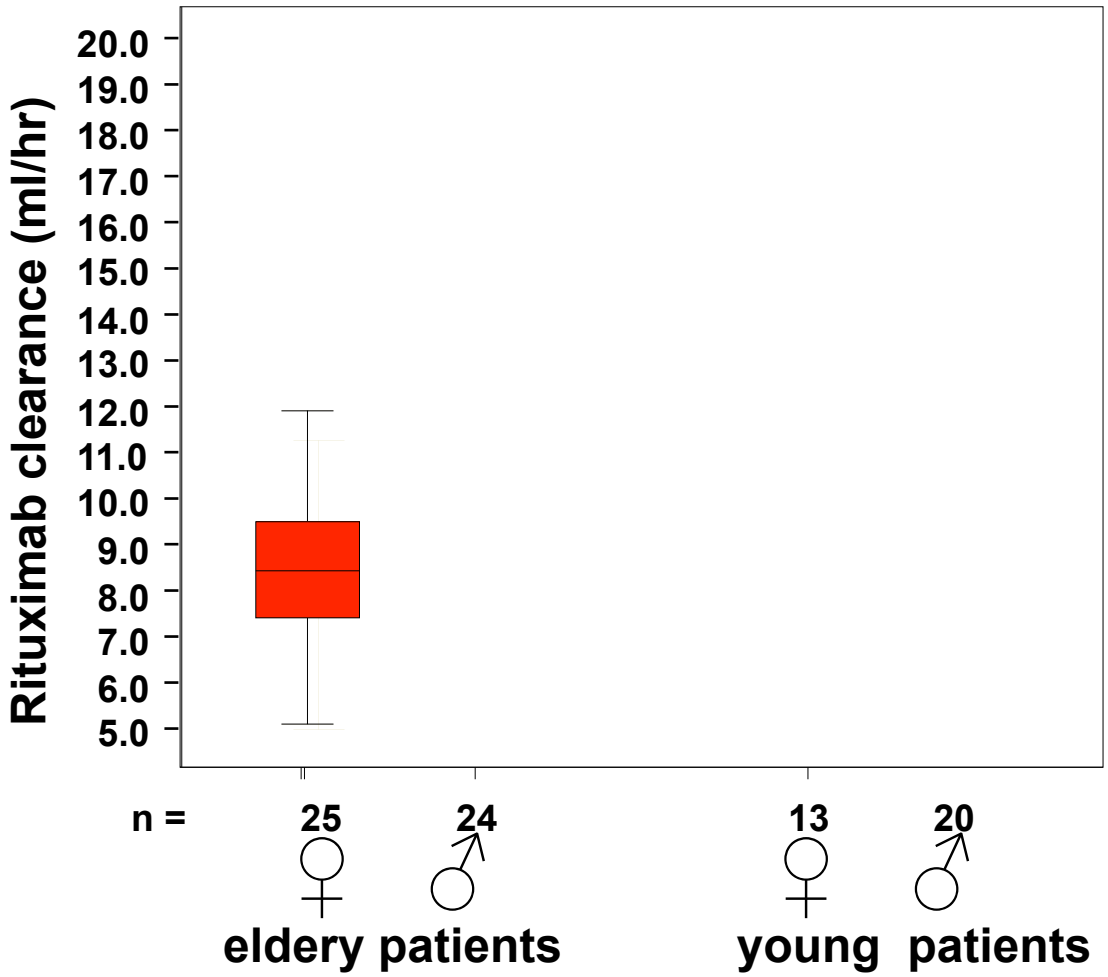
Females



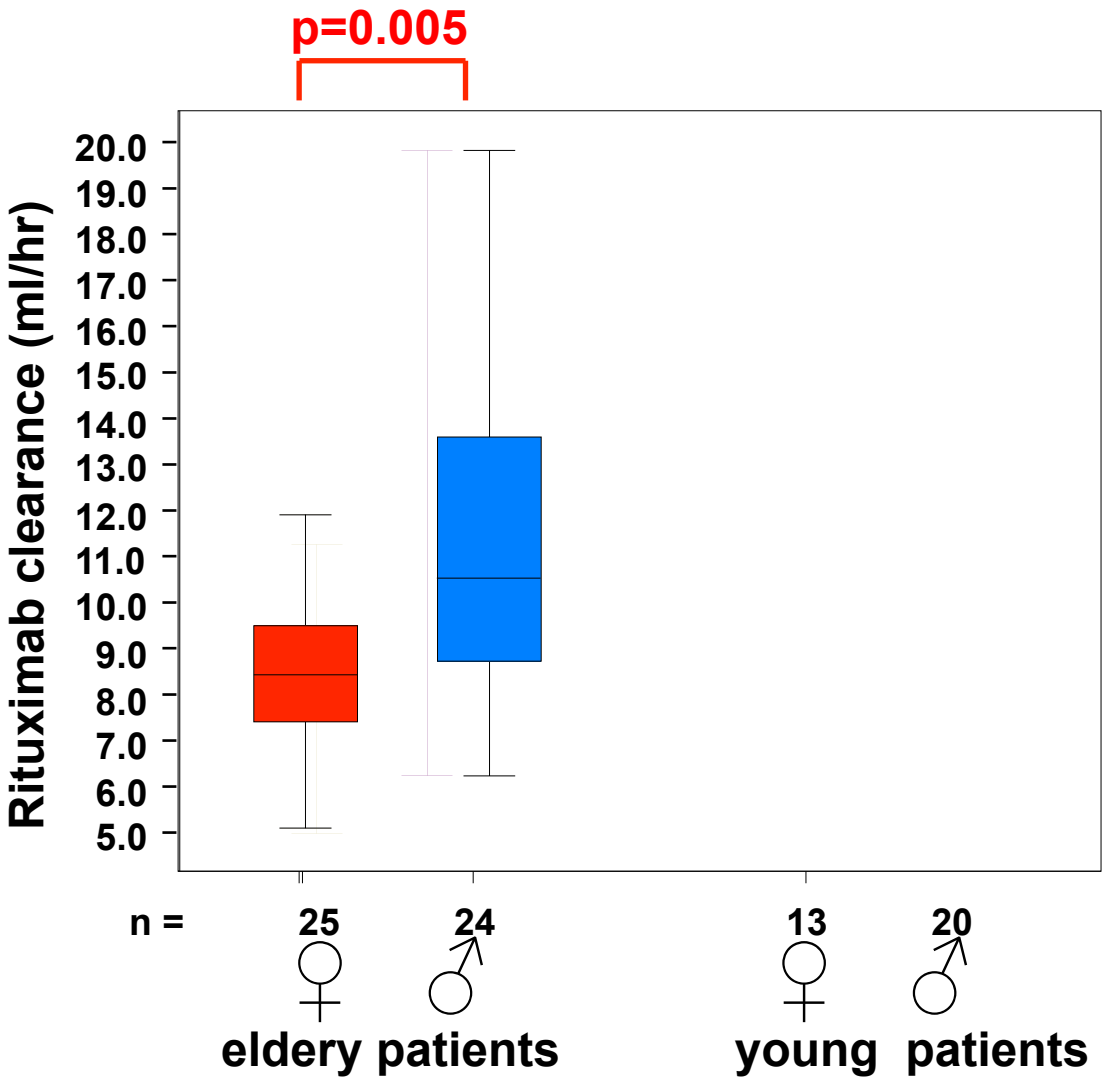
p=0.004

Pfreundschuh et al., *Blood 2014*

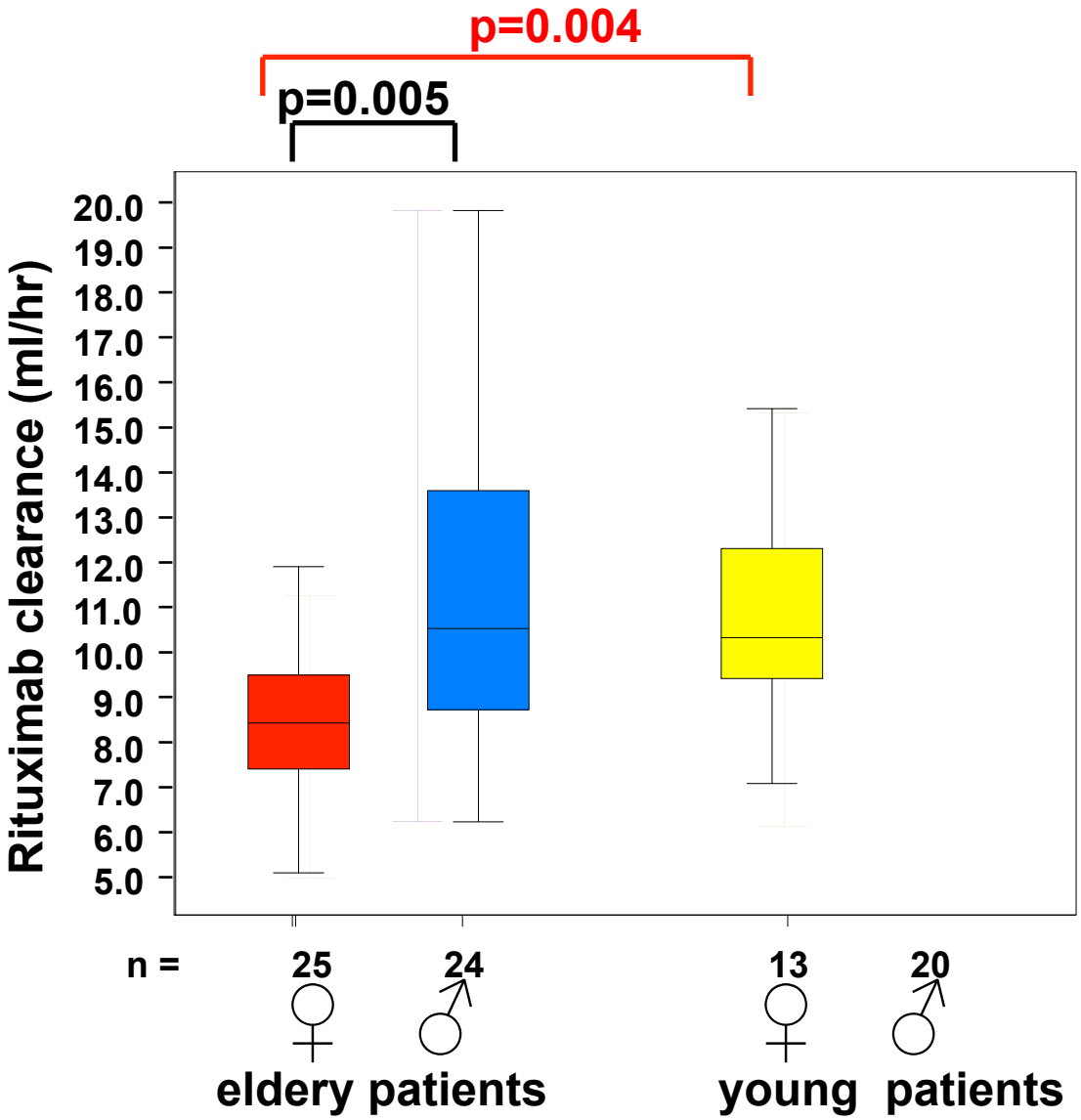
Rituximab Clearance in DLBCL Subgroups



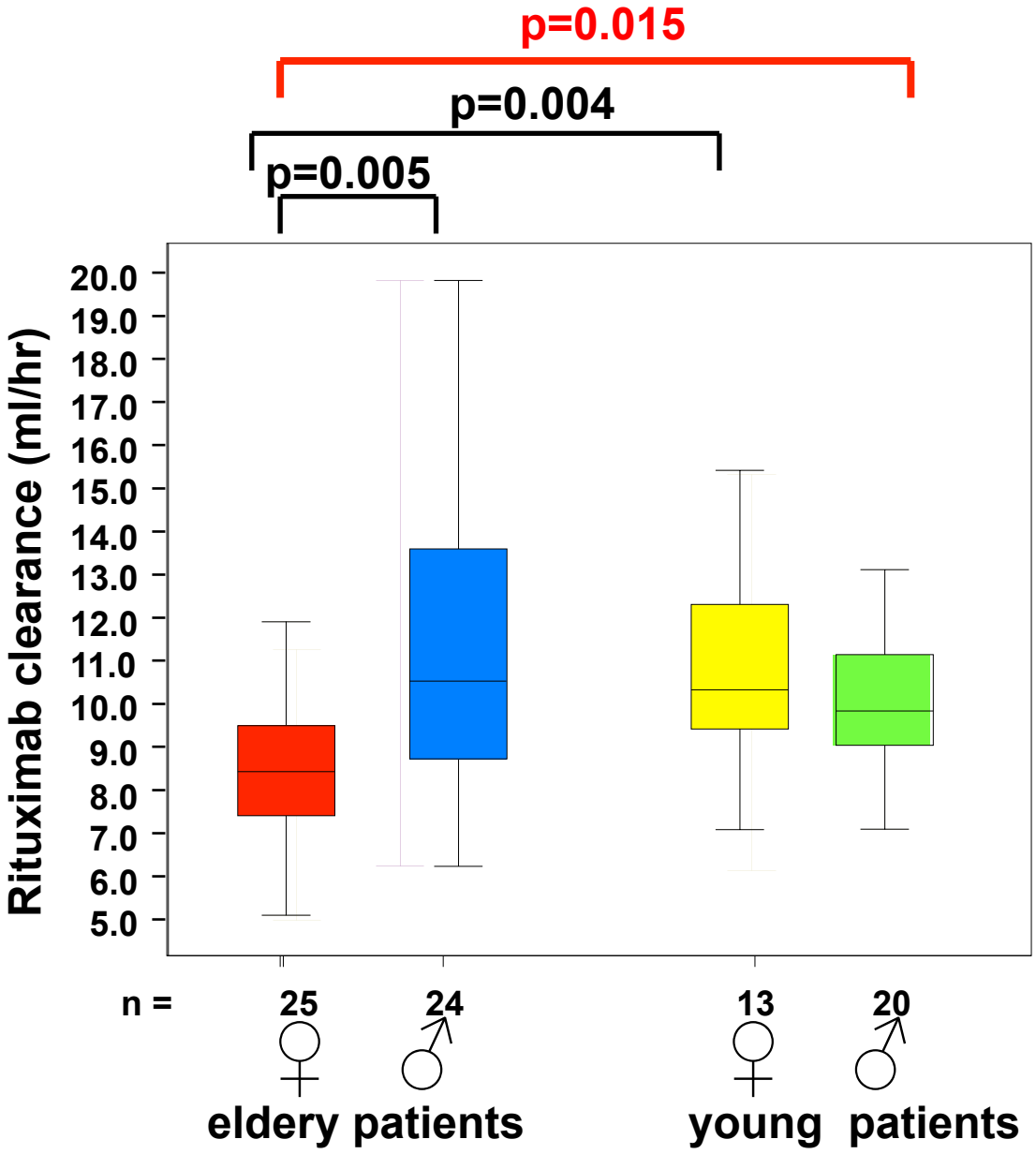
Rituximab Clearance in DLBCL Subgroups



Rituximab Clearance in DLBCL Subgroups



Rituximab Clearance in DLBCL Subgroups



Rituximab Pharmacokinetics in DBLC

Clinical Consequences

?

DSHNHL

Rituximab Pharmacokinetics in DBLC

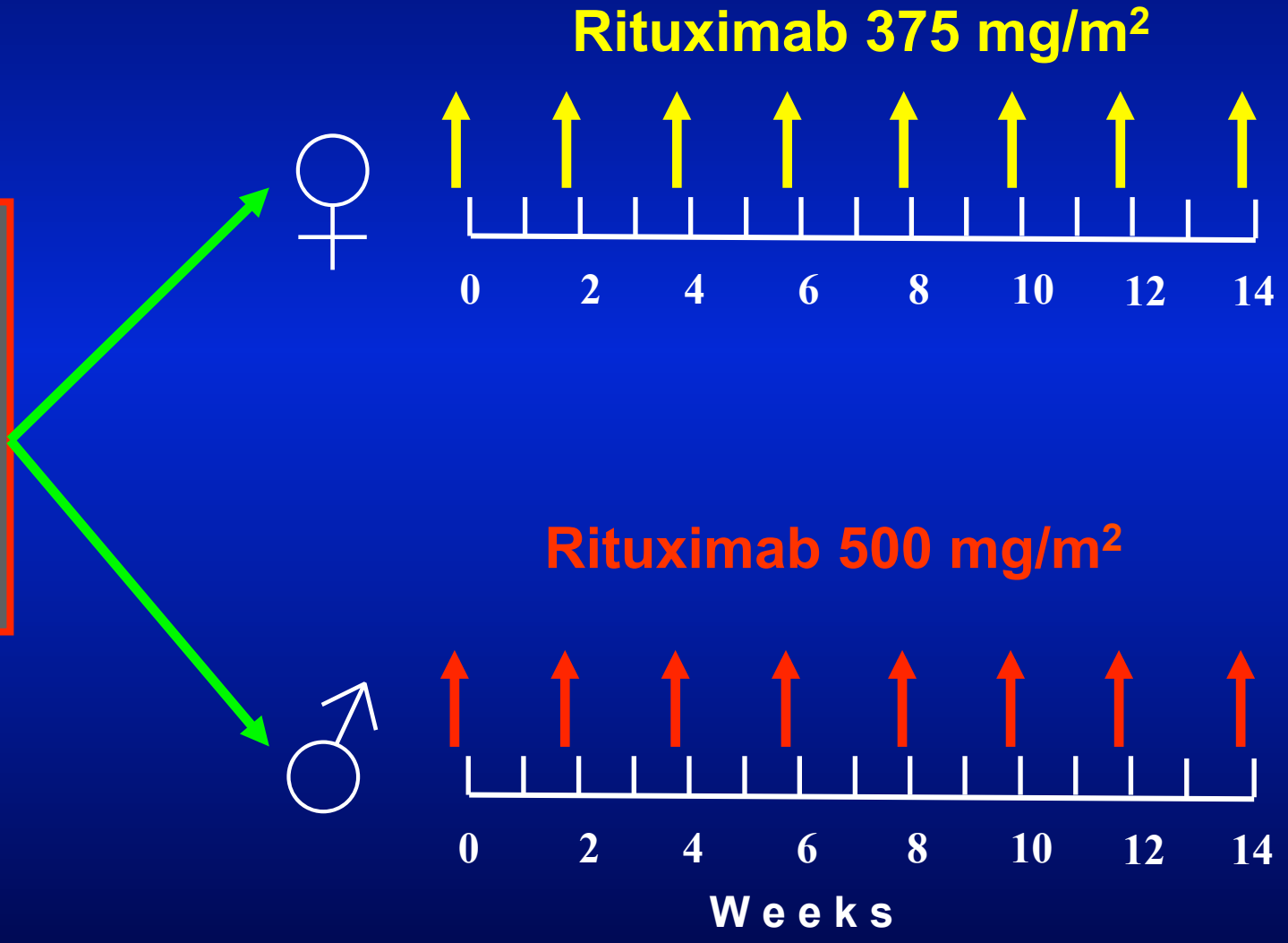
Clinical Consequences (I):

SEXIER-CHOP-14

DSHNHL

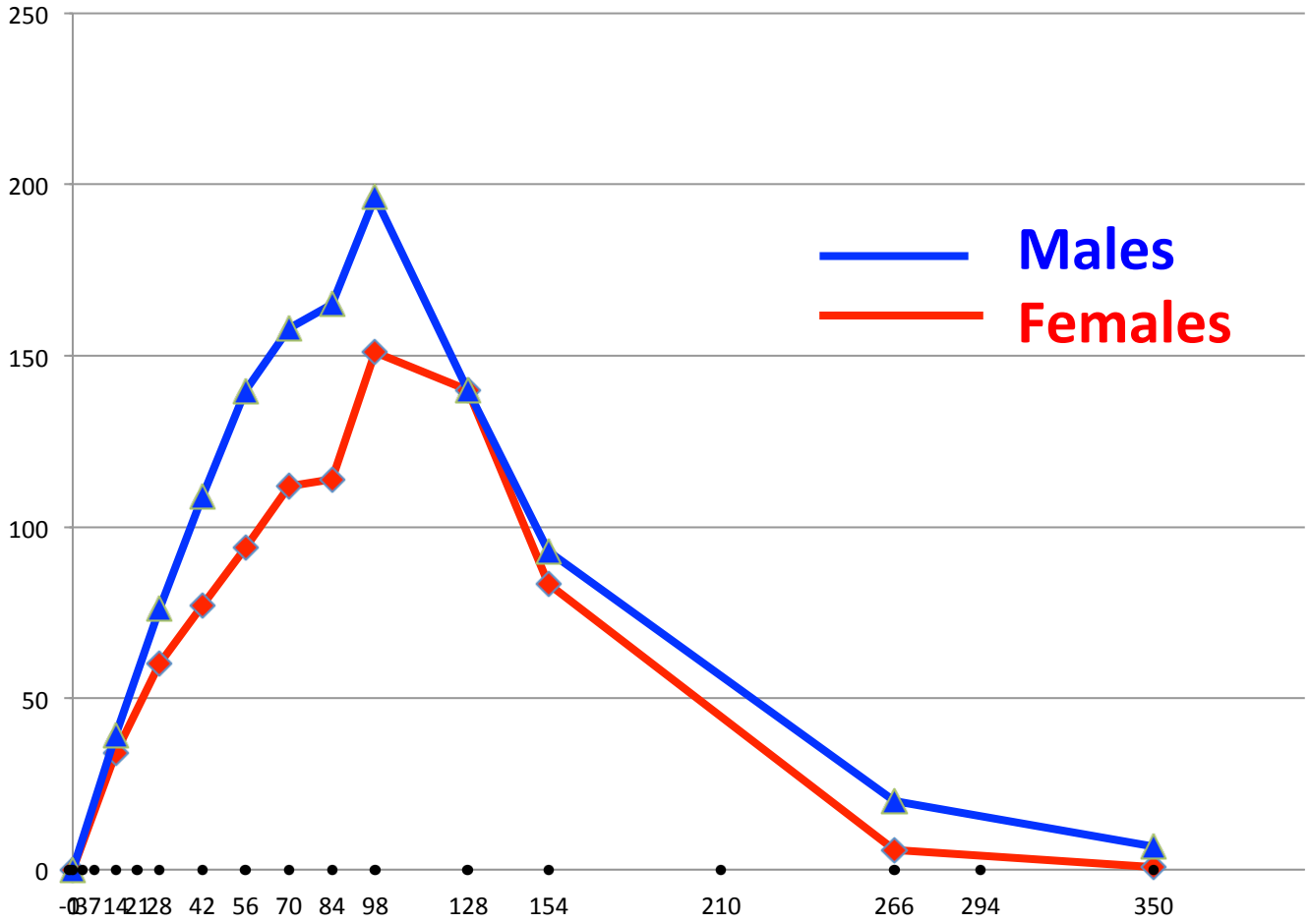
SEXIE-R-CHOP-14 Study Design

CD20+ DLBCL
Stages I-IV
61 to 80 years



SEXIE-R-CHOP-14

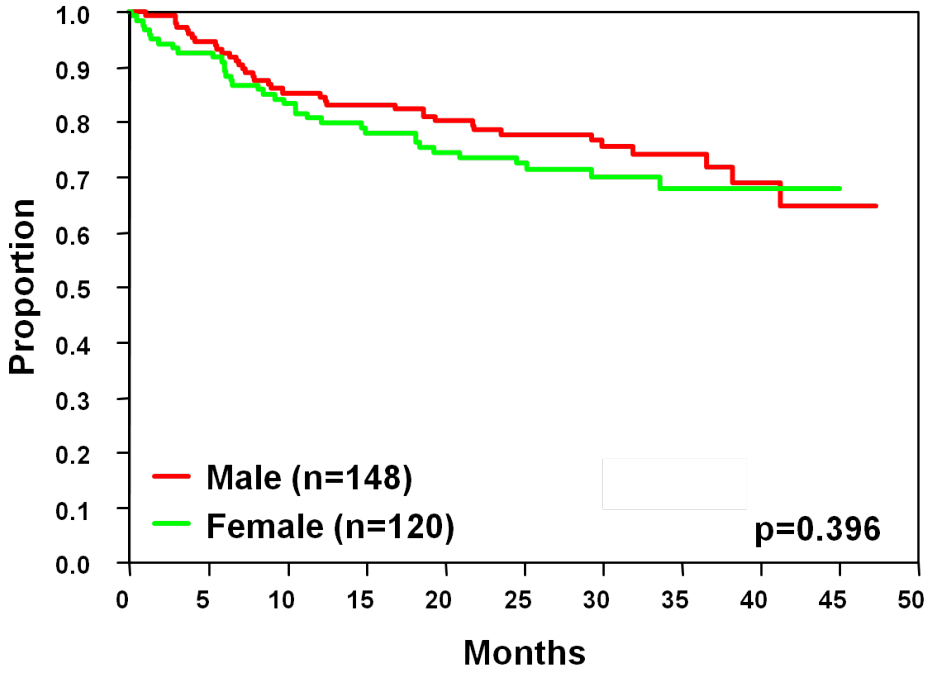
Trough Serum Levels



Pfreundschuh et al., ASCO 2014

SEXIE-R-CHOP-14: PFS

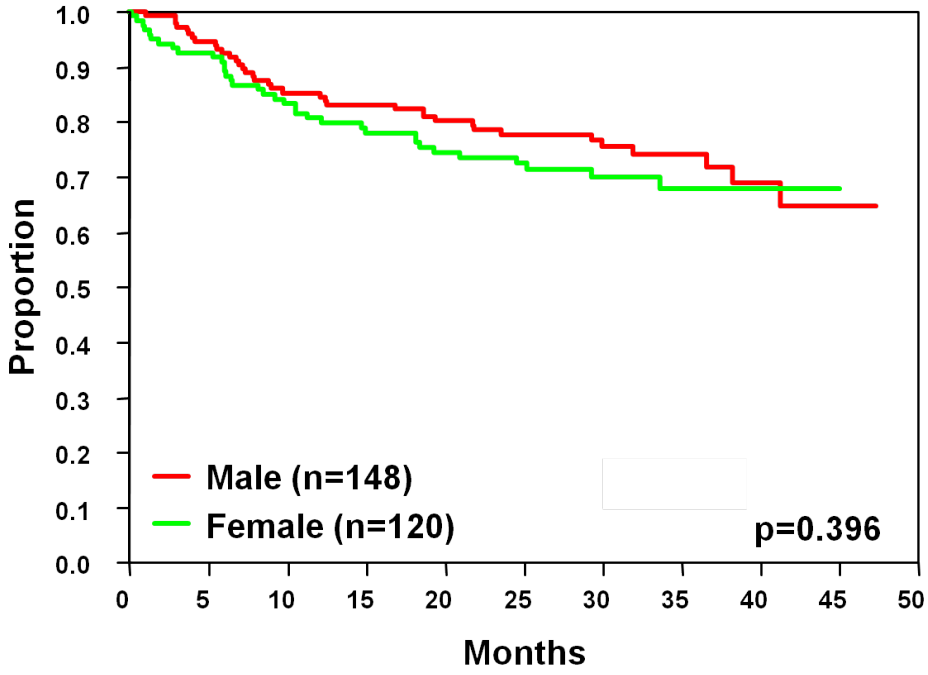
SEXIE-R



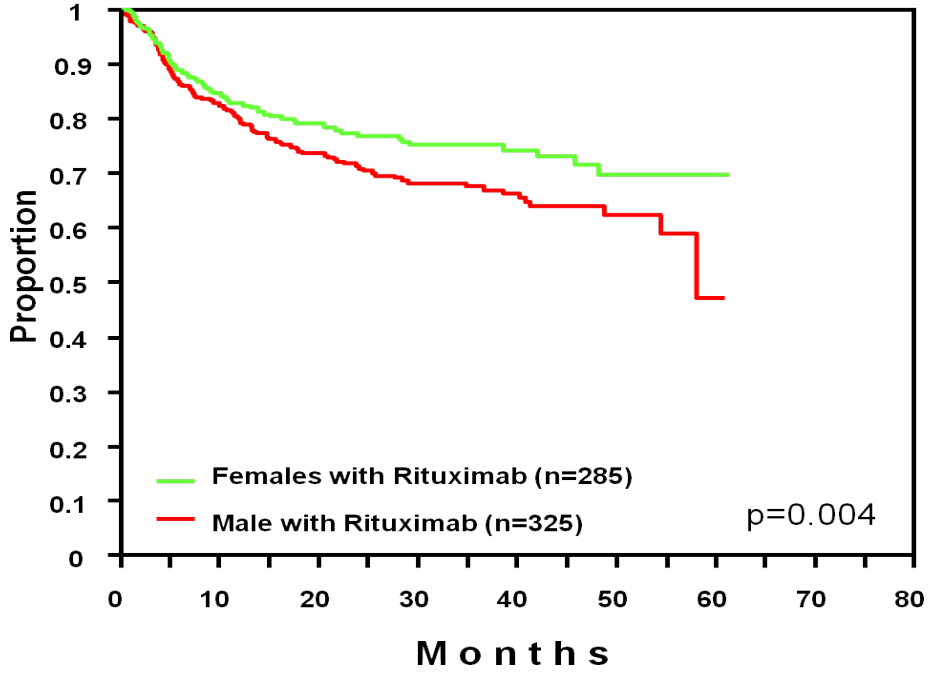
Pfreundschuh et al., ASCO 2014

SEXIE-R-CHOP-14: PFS

SEXIE-R



RICOVER-60



Pfreundschuh et al., ASCO 2014

Sex as a Risk Factor in Elderly DLBCL Patients

Multivariable Analysis: RICOVER-60 (375mg/m^2) vs. SEXIE-R-CHOP-14 (500 mg/m^2)

	EFS		PFS		OS	
	Hazard ratio [95%-CI] RICOVER (n=610)	Hazard ratio [95%-CI] SEXIE-R (n=168)	Hazard ratio [95%-CI] RICOVER (n=610)	Hazard ratio [95%-CI] SEXIE-R (n=168)	Hazard ratio [95%-CI] RICOVER (n=610)	Hazard ratio [95%-CI] SEXIE-R (n=168)
Elevated LDH	1.8 (p<0.001)	1.7 (p=0.170)	2.2 (p<0.001)	1.6 (p=0.238)	2.1 (p<0.001)	2.2 (p=0.107)
ECOG>1	1.8 (p=0.001)	1.1 (p=0.873)	1.7 (p=0.004)	1.2 (p=0.719)	1.9 (p=0.001)	1.3 (p=0.644)
Stages III&IV	1.5 (p=0.011)	1.2 (p=0.755)	1.5 (p=0.045)	1.2 (p=0.686)	1.5 (p=0.047)	1.1 (p=0.791)
>1 extra-lymphatic site	1.0 (p=0.937)	1.9 (p=0.121)	1.1 (p=0.724)	2.0 (p=0.103)	1.1 (p=0.817)	1.5 (p=0.420)
Male vs. female	1.4 p=0.016	0.9 p=0.708	1.6 p=0.004	0.8 p=0.613	1.4 p=0.063	0.7 p=0.252

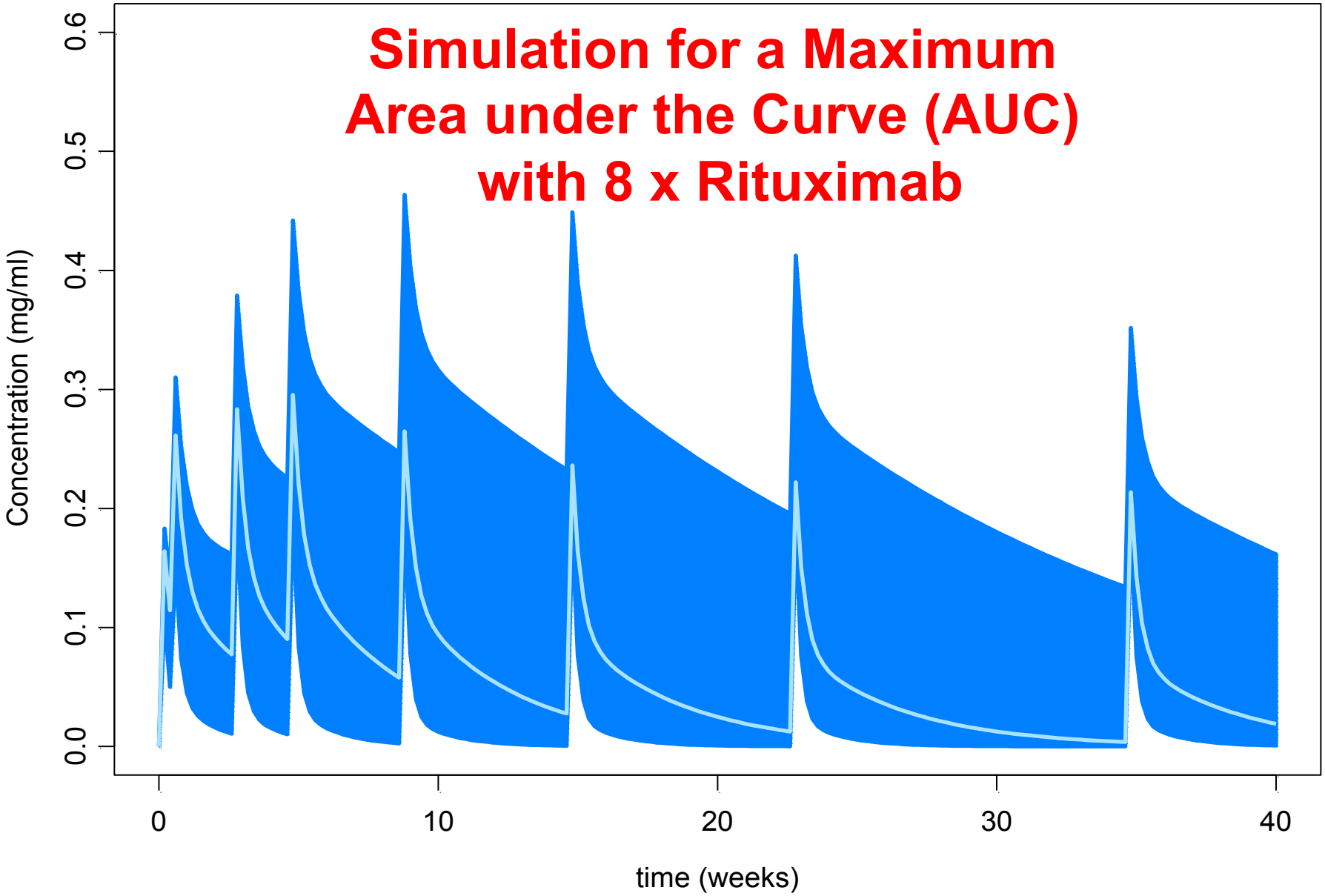
Rituximab Pharmacokinetics in DBLC

Clinical Consequences (II):

SMARTE-R-CHOP-14

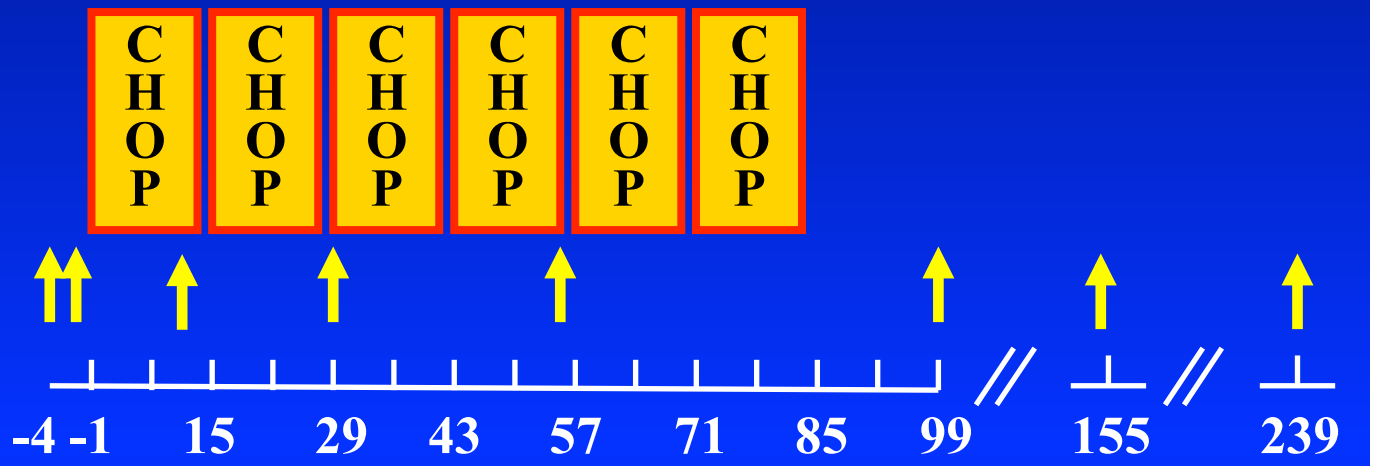
DSHNHL

SMARTE-R-CHOP-14



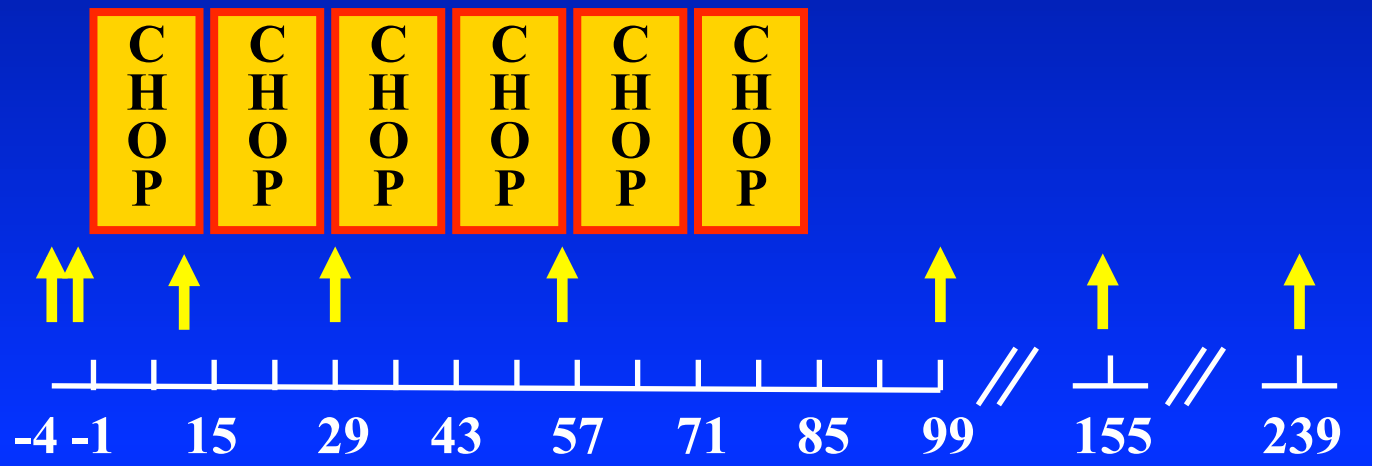
Rituximab Schedules for DLBCL

SMARTE-R-CHOP-14 (8 x R)

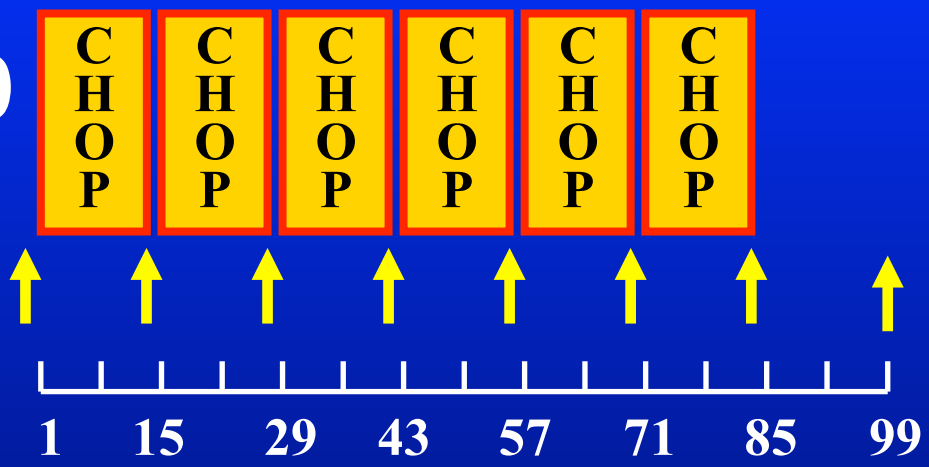


Rituximab Schedules for DLBCL

SMARTE-R-CHOP-14 (8 x R)



RICOVER-60 R-CHOP-14 (8 x R)

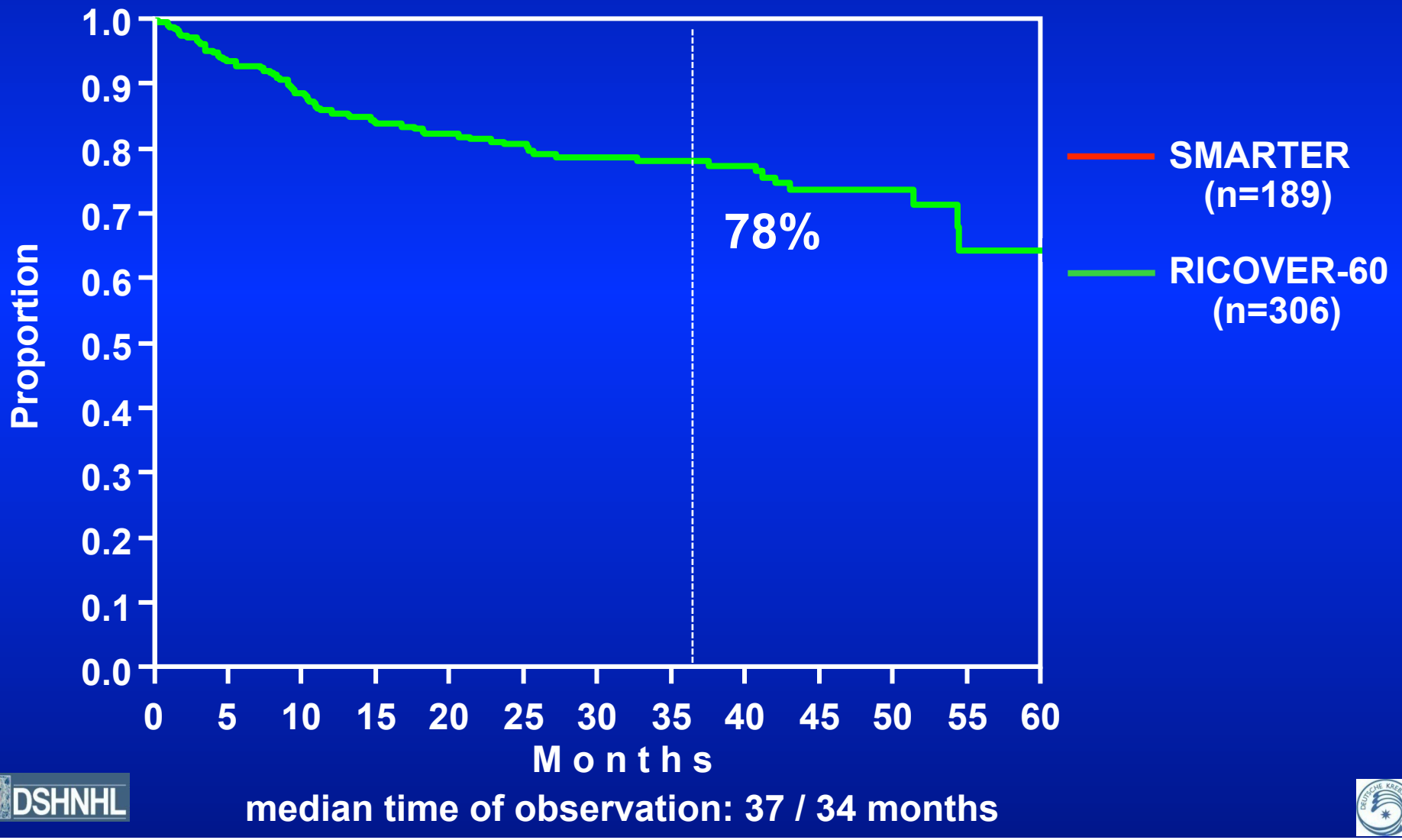


DSHNHL

Supported by

SMARTE-R-CHOP-14

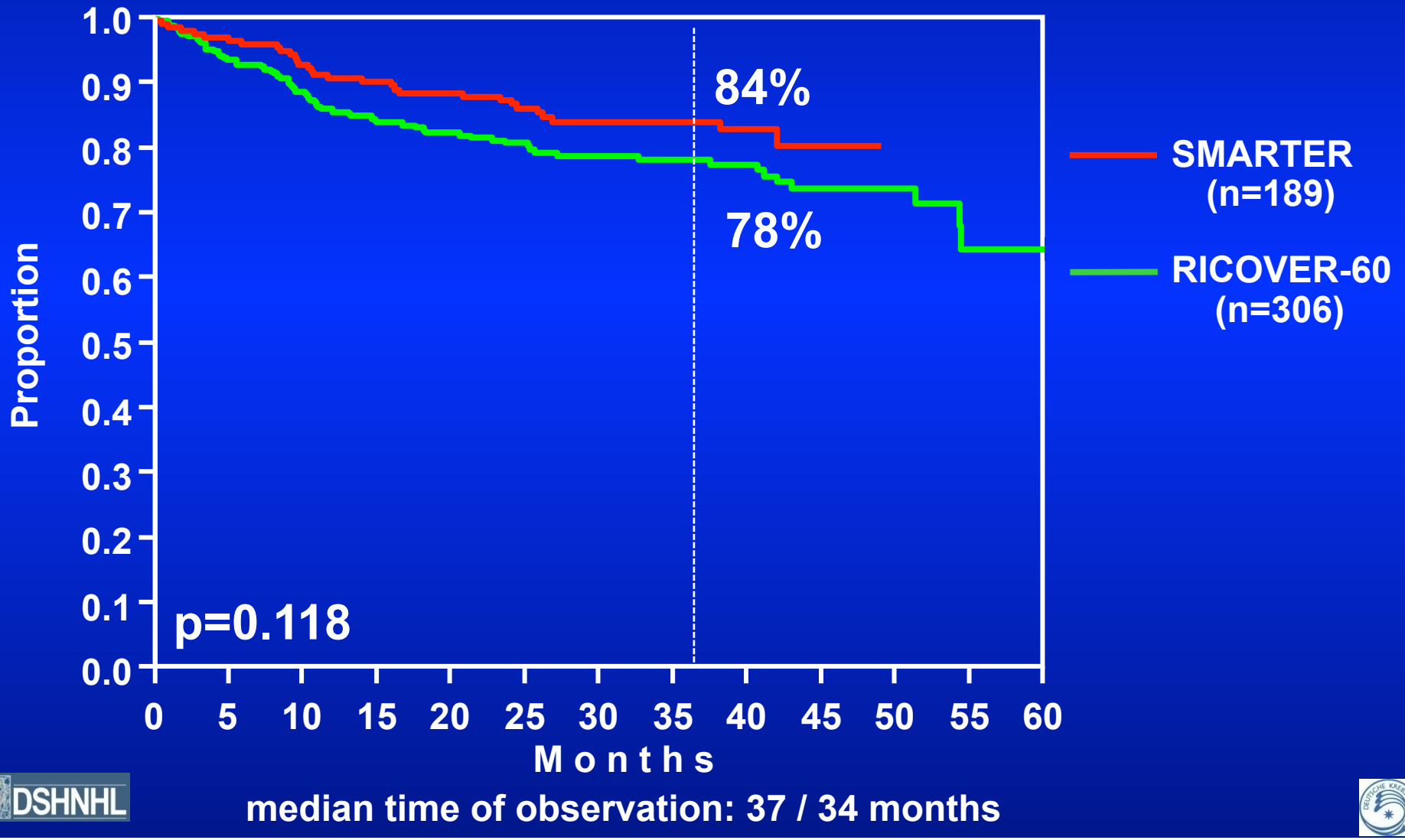
Overall Survival



median time of observation: 37 / 34 months

SMARTE-R-CHOP-14

Overall Survival



DSHNHL

median time of observation: 37 / 34 months

SMARTE-R-CHOP-14

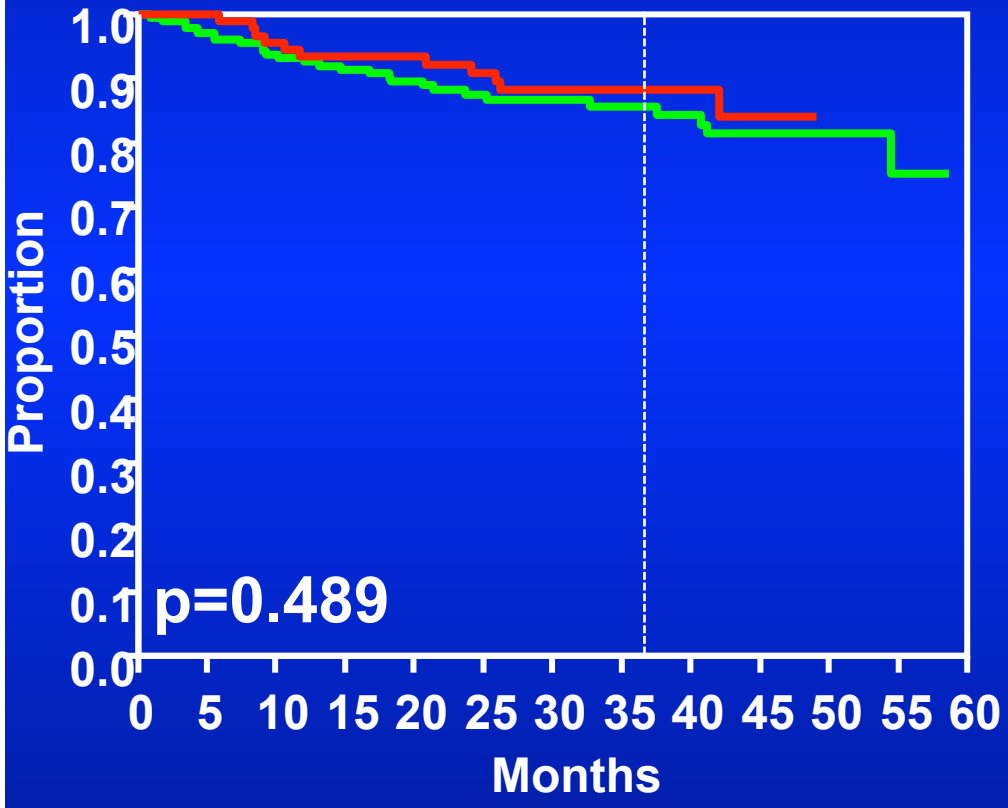
Overall Survival

IPI=1,2

SMARTE-R-CHOP-14

Overall Survival

IPI=1,2

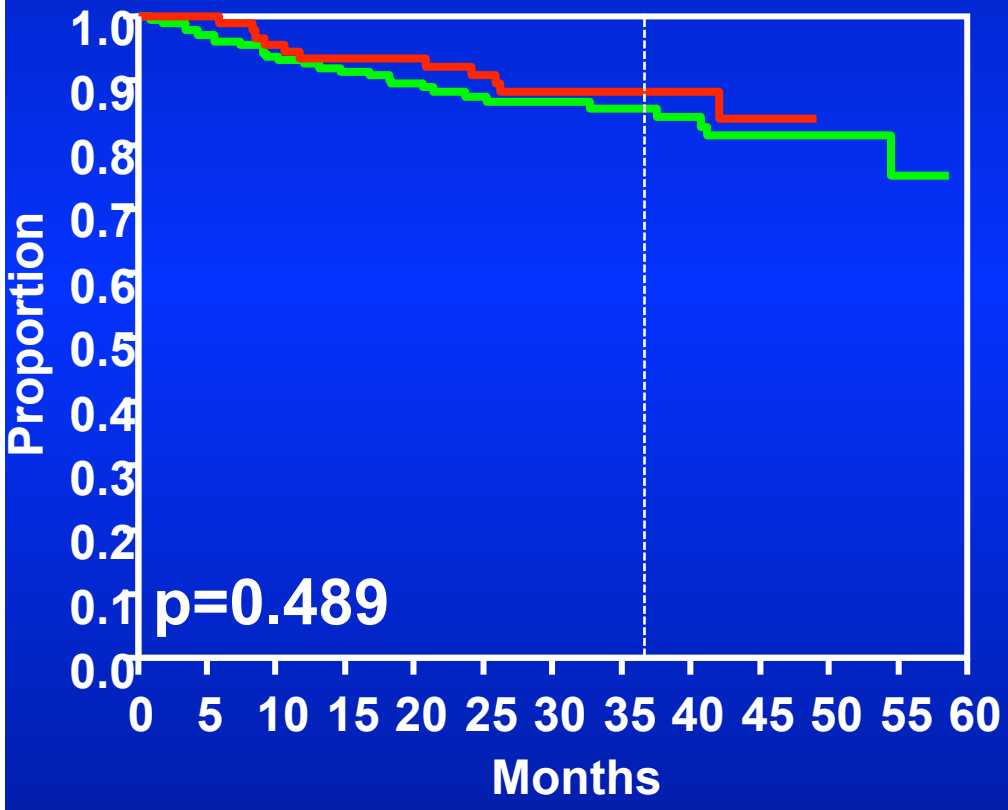


DSHNHL

SMARTE-R-CHOP-14

Overall Survival

IPI=1,2



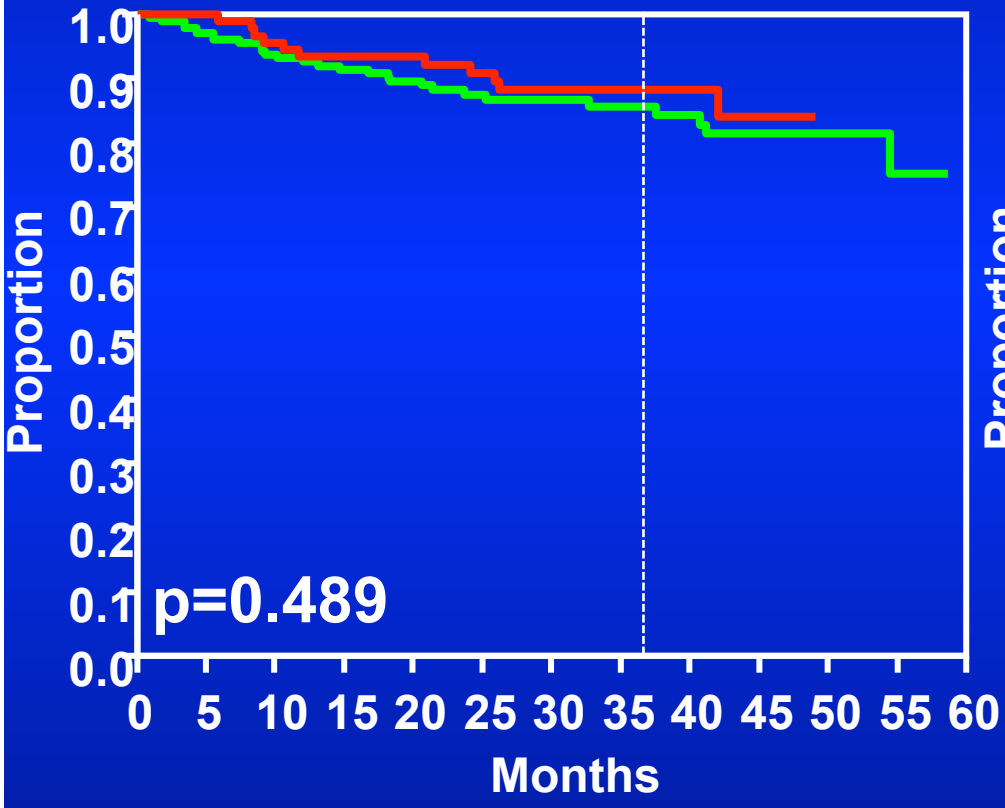
IPI>2

DSHNHL

SMARTE-R-CHOP-14

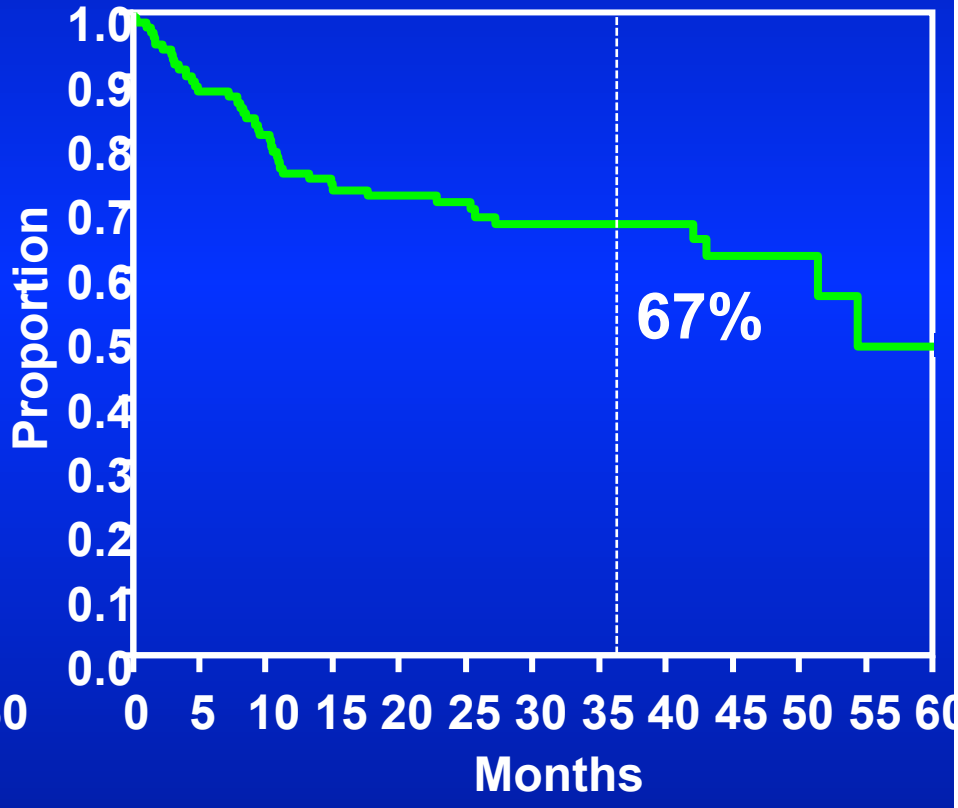
Overall Survival

IPI=1,2



SMARTER (n=90)
RICOVER-60 (n=183)

IPI>2



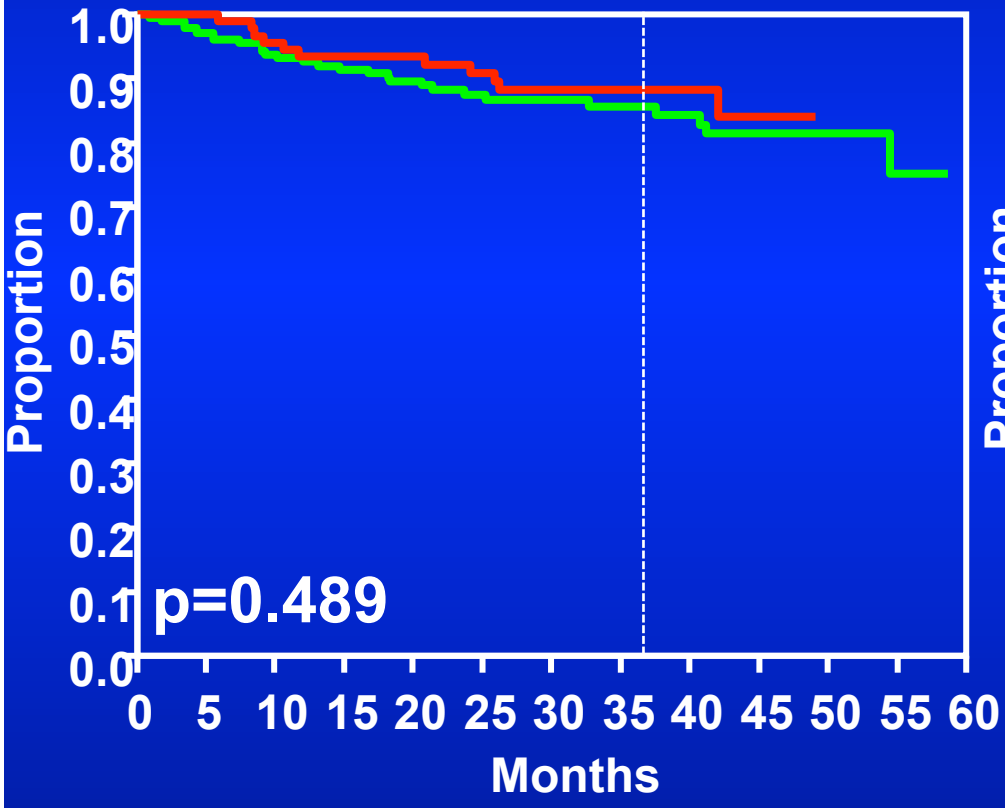
SMARTER (n=99)
RICOVER-60 (n=123)

DSHNHL

SMARTE-R-CHOP-14

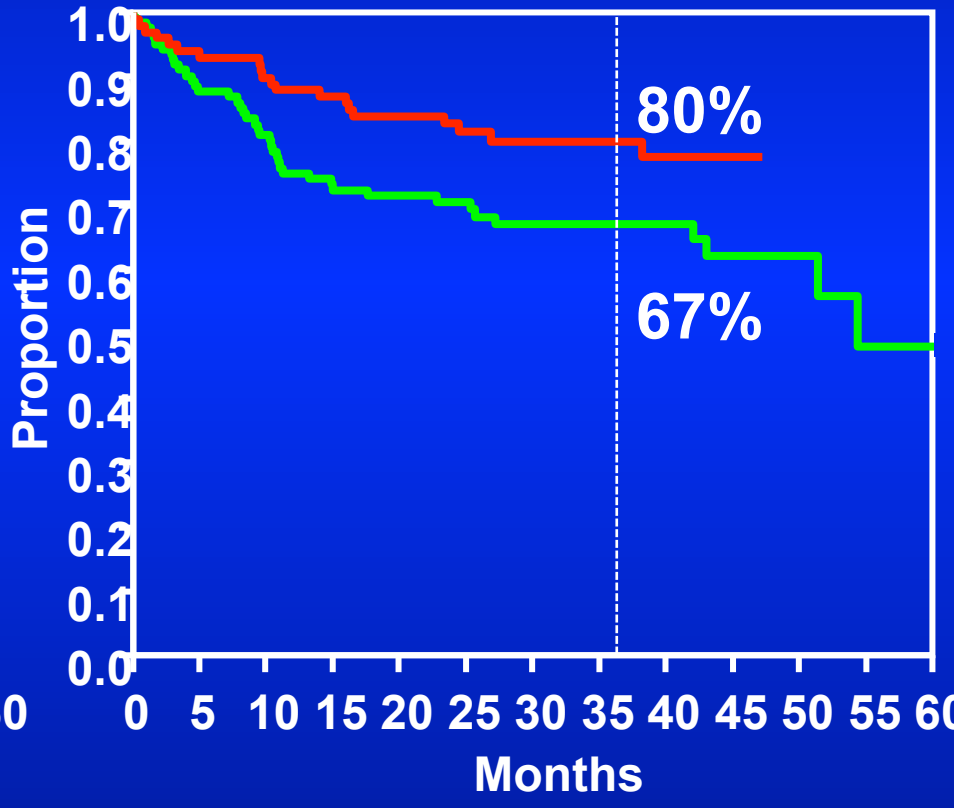
Overall Survival

IPI=1,2



SMARTER (n=90)
RICOVER-60 (n=183)

IPI>2



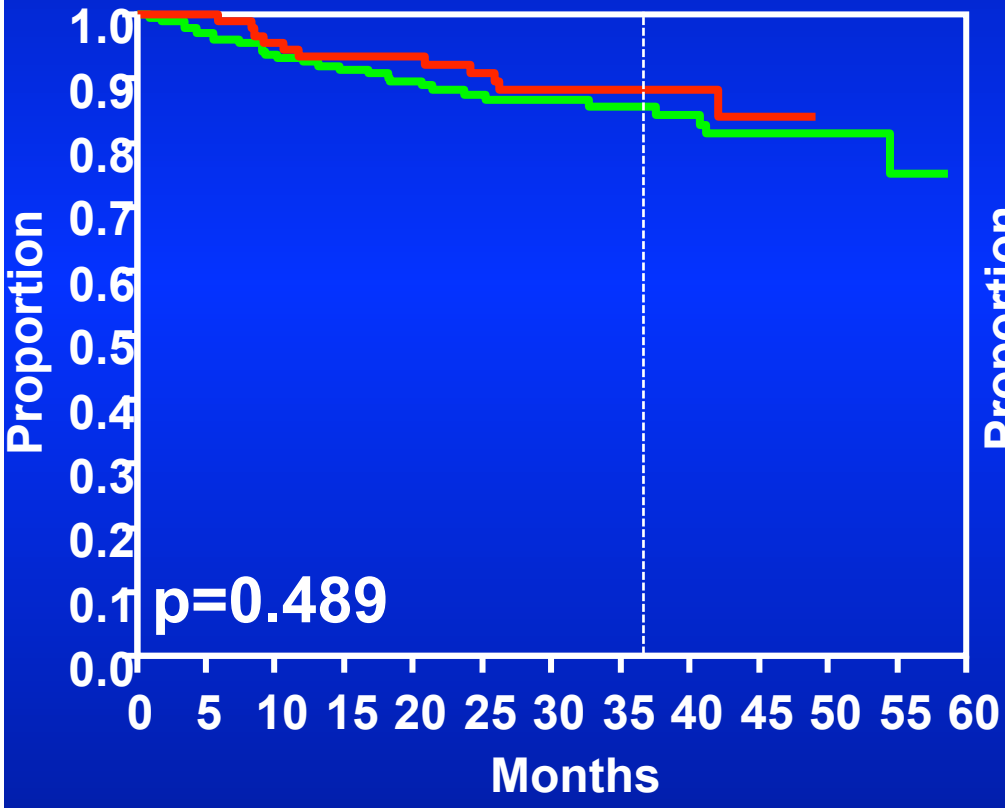
SMARTER (n=99)
RICOVER-60 (n=123)

DSHNHL

SMARTE-R-CHOP-14

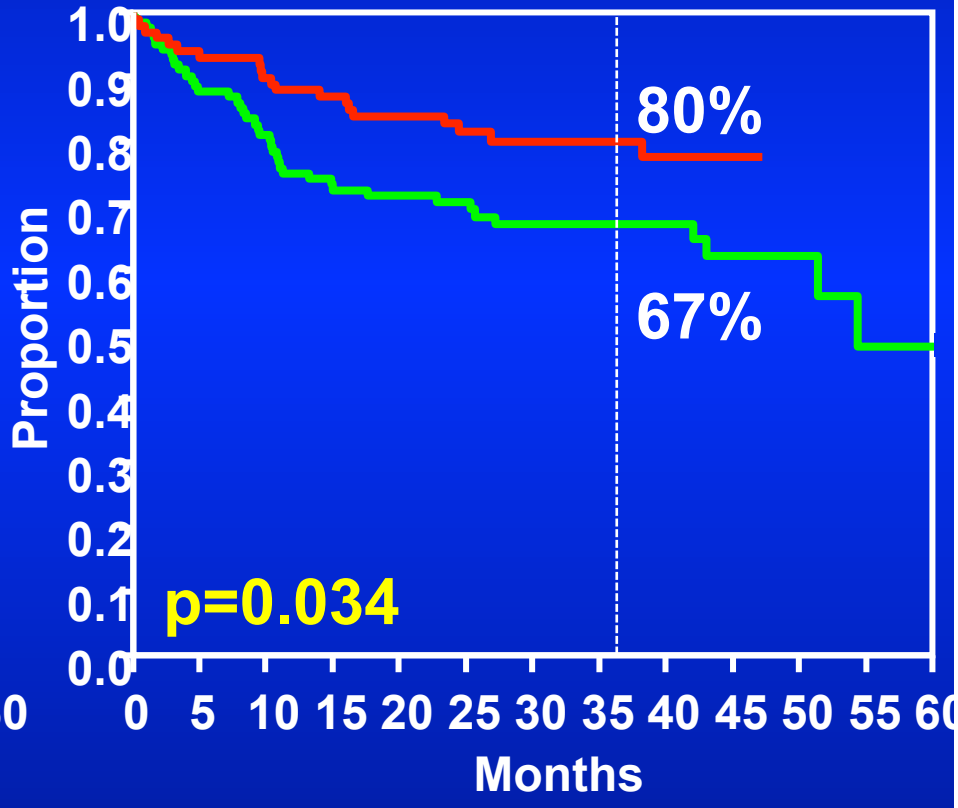
Overall Survival

IPI=1,2



SMARTER (n=90)
RICOVER-60 (n=183)

IPI>2



SMARTER (n=99)
RICOVER-60 (n=123)

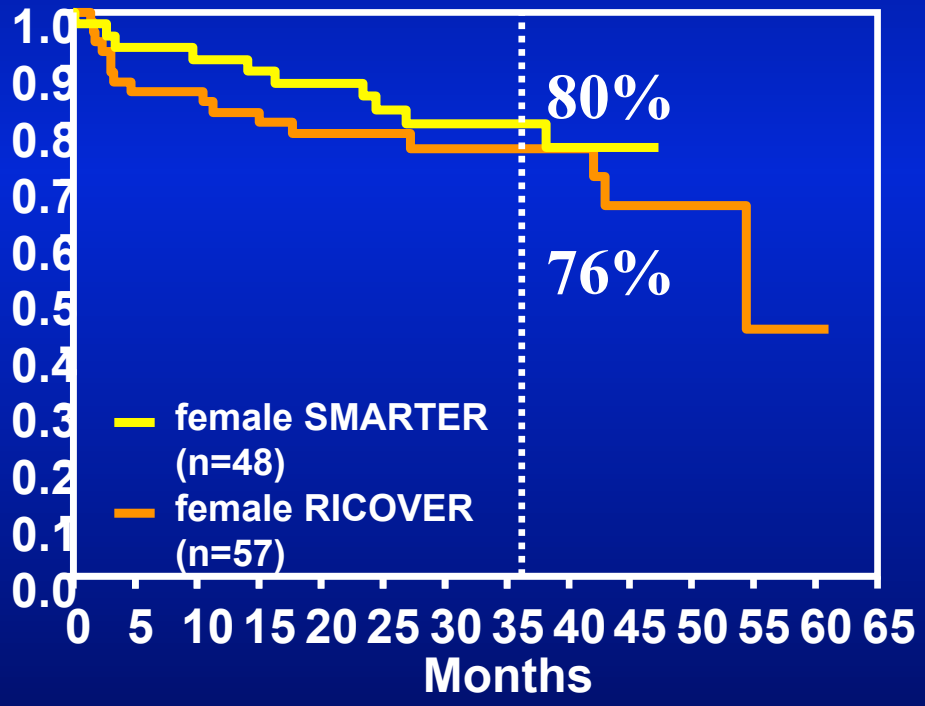
DSHNHL

SMARTE-R vs. RICOVER
Sex-differential Improvement

Pfreundschuh et al., J Clin Oncol 2014

SMARTE-R vs. RICOVER
Sex-differential Improvement

OS of Females (IPI=3-5)

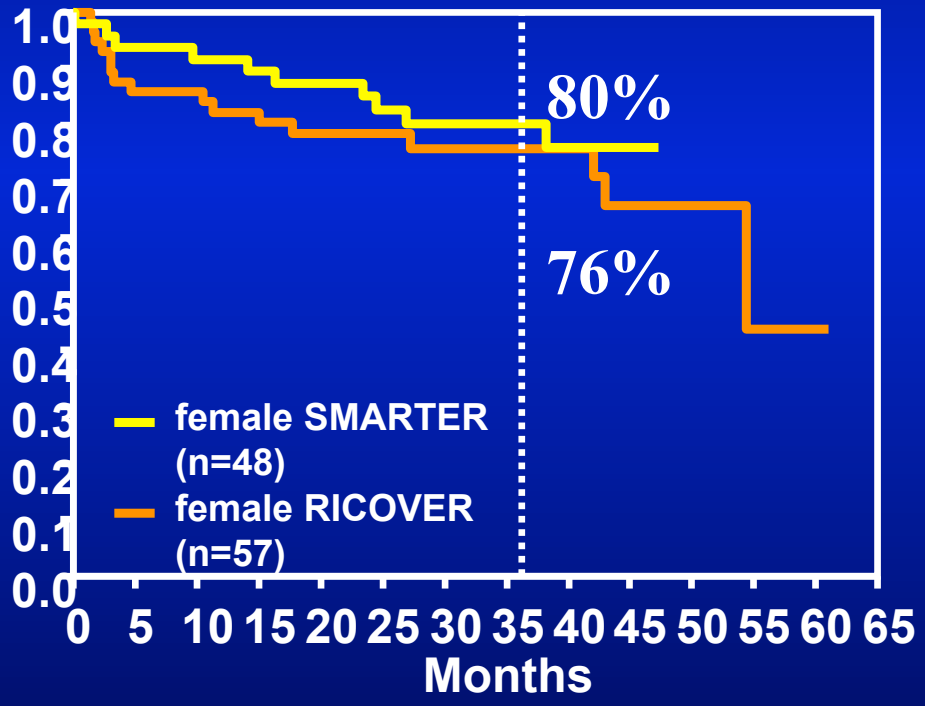


DSHNHL

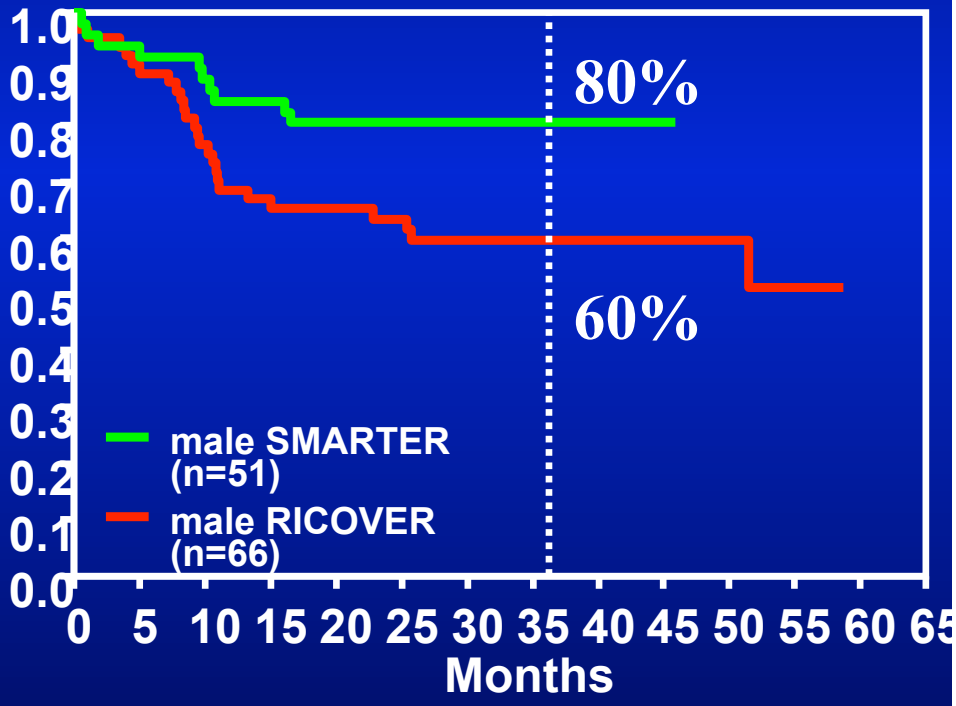
Pfreundschuh et al., J Clin Oncol 2014

SMARTE-R vs. RICOVER
Sex-differential Improvement

OS of Females (IPI=3-5)



OS of Males (IPI=3-5)



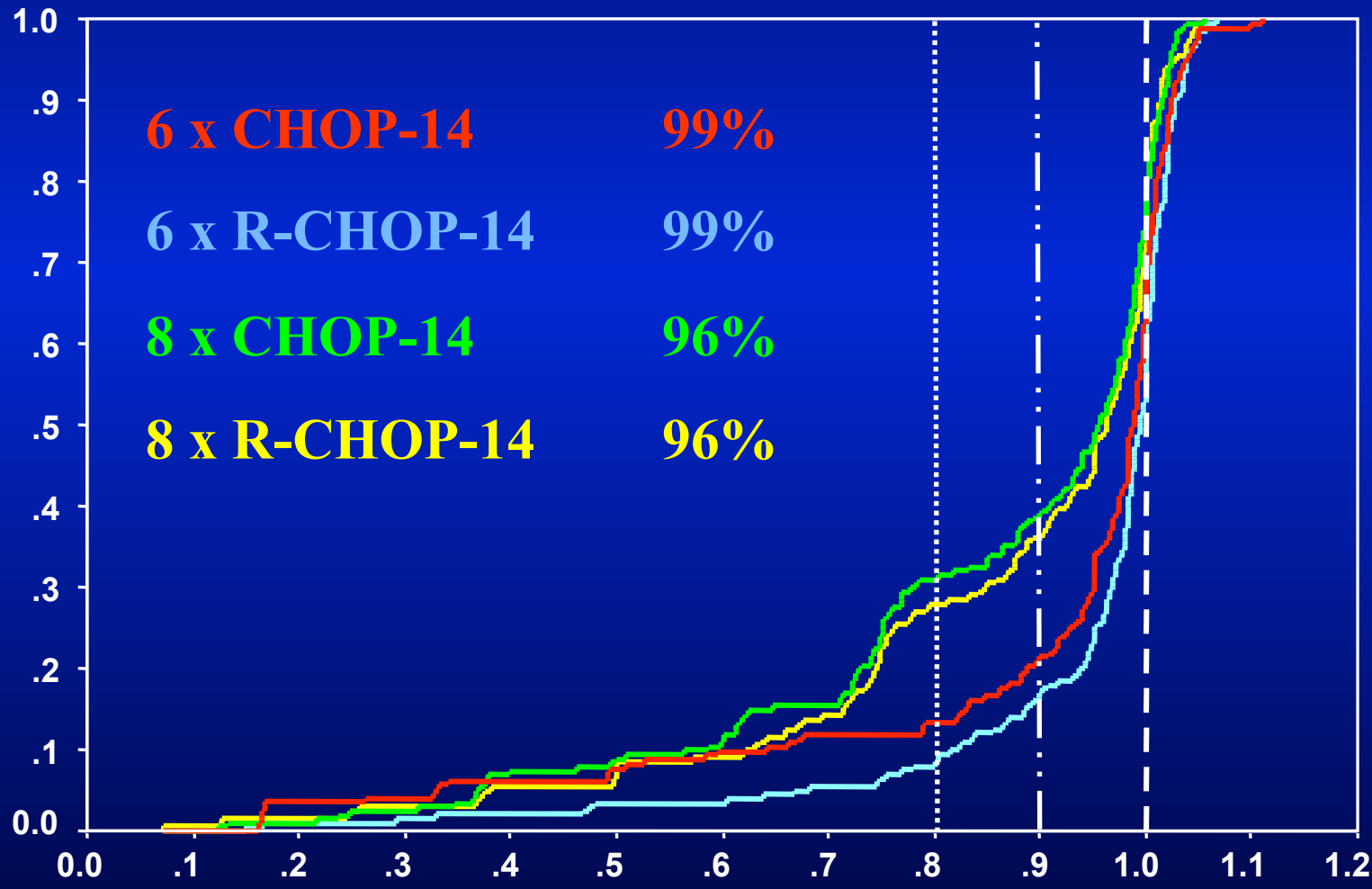
DSHNHL

Pfreundschuh et al., J Clin Oncol 2014

RICOVER-60

Adherence to Protocol

Relative Dose Cyclophosphamide (median)



RICOVER-60

Vincristine Administration

Dosage [mg]	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	total
0	2.5%	2.4%	5.3%	9.8%	16.4%	22.0%	30.4%	35.5%	11.8%
0.1 - 1.9	10.9%	12.5%	14.7%	17.0%	17.6%	17.4%	17.3%	15.2%	15.0%
2	86.5%	84.9%	79.5%	72.6%	65.3%	59.0%	51.0%	47.9%	72.5%
> 2	-	0.1%	0.2%	-	-	0.2%	-	0.3%	0.1%
Vinblastine	0.1%	0.2%	0.3%	0.6%	0.8%	1.4%	1.3%	1.1%	0.6%

DSHNHL

Towards the Cure of DLBCL

Vincristine polyneuropathy:

an unmet medical need

DSHNHL

OPTIMAL >60 Study Design

CD20+ DLBCL
IPI 2-4
IPI 1 Bulk
61 to 80 years

Random 2x2 Factorial Design

R-CHOP-14§
+ 36 Gy BULK-IN-RT*

Opti-R-CHOP-14§
+36 Gy BULK-INRT*

R-CHLIP-14&
+ 36 Gy BULK-IN-RT*

Opti-R-CHLIP-14&
+ 36 Gy BULK-IN-RT*

Except PET-neg.

§ conventional vincristine 2 mg (absol.)

& liposomal vincristine 2 mg/m²

DSHNHL

Towards the Cure of DLBCL

CHOP:

Cyclophosphamide	750 mg/m^2	i.v.	day 1
Doxorubicin	50 mg/m^2	i.v.	day 1
Vincristine	1.4 mg/m^2	i.v. (max. 2mg)	day 1
Prodniso(lo)ne	100 mg	p.o.	days 1-5

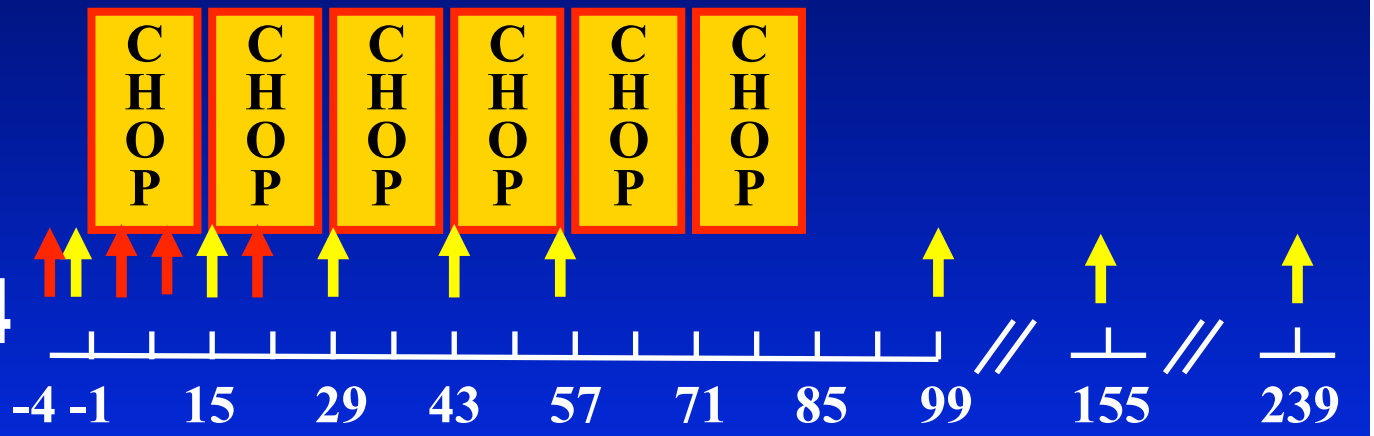
CHLIP:

Cyclophosphamide	750 mg/m^2	i.v.	day 1
Doxorubicin	50 mg/m^2	i.v.	day 1
liposomal Vincristine	2.0 mg/m^2	i.v.	day 1
Predniso(lo)ne	100 mg	p.o.	days 1-5

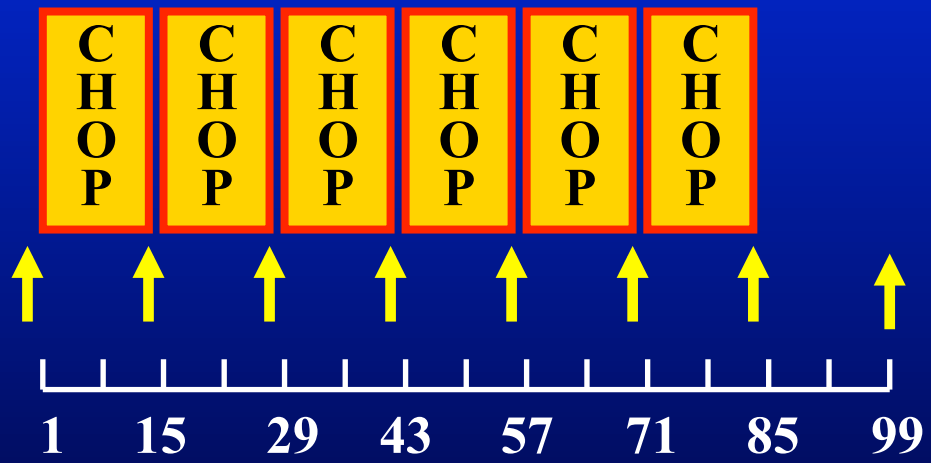
DSHNHL

OPTIMAL >60 Study Design

OPTIMAL
R-CHOP-14
R-CHLIP-14
(12 x R)



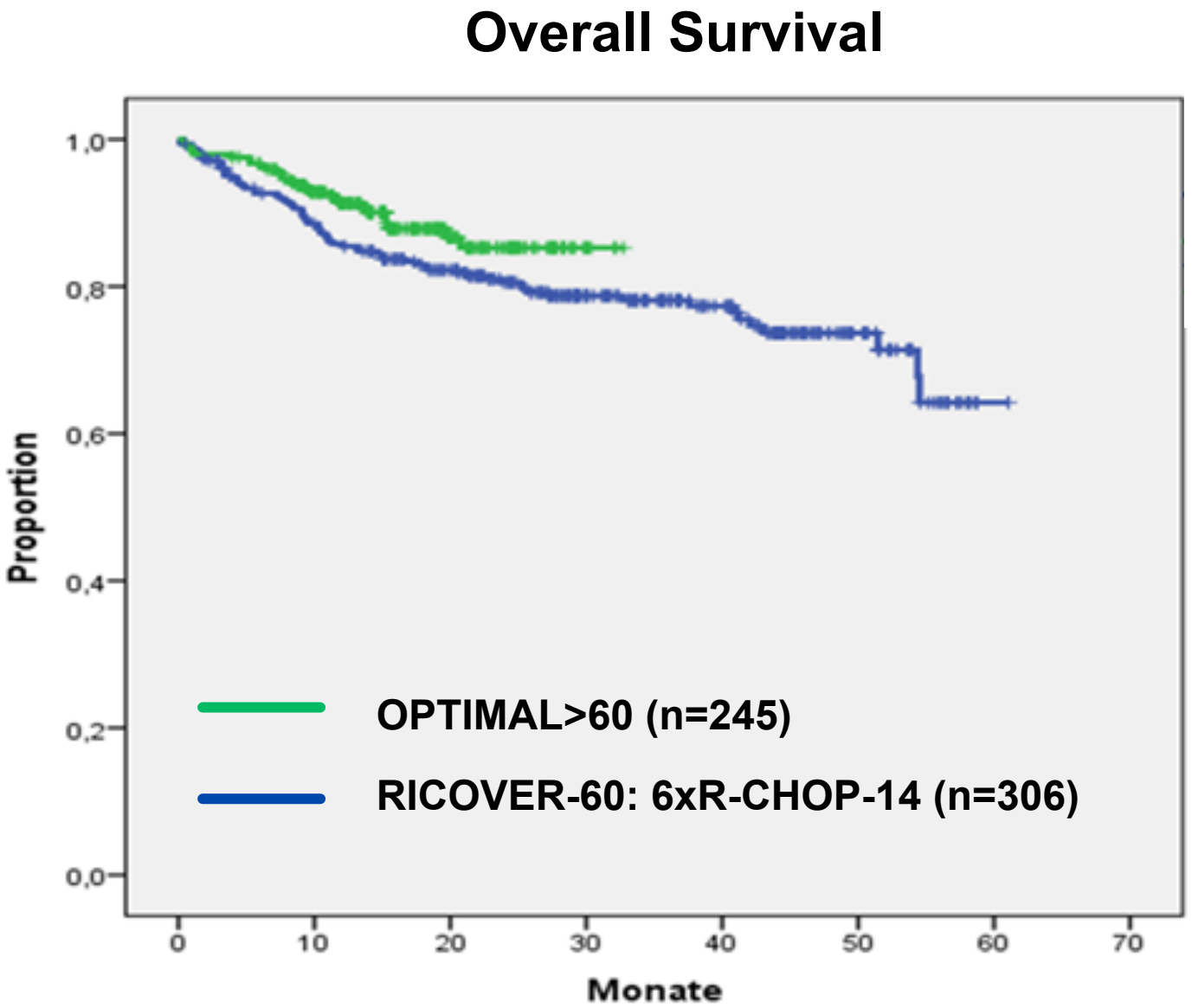
2-week
R-CHOP-14
R-CHLIP-14
(8 x R)



DSHNHL

Supported by

OPTIMAL>60: Further Improvement ?

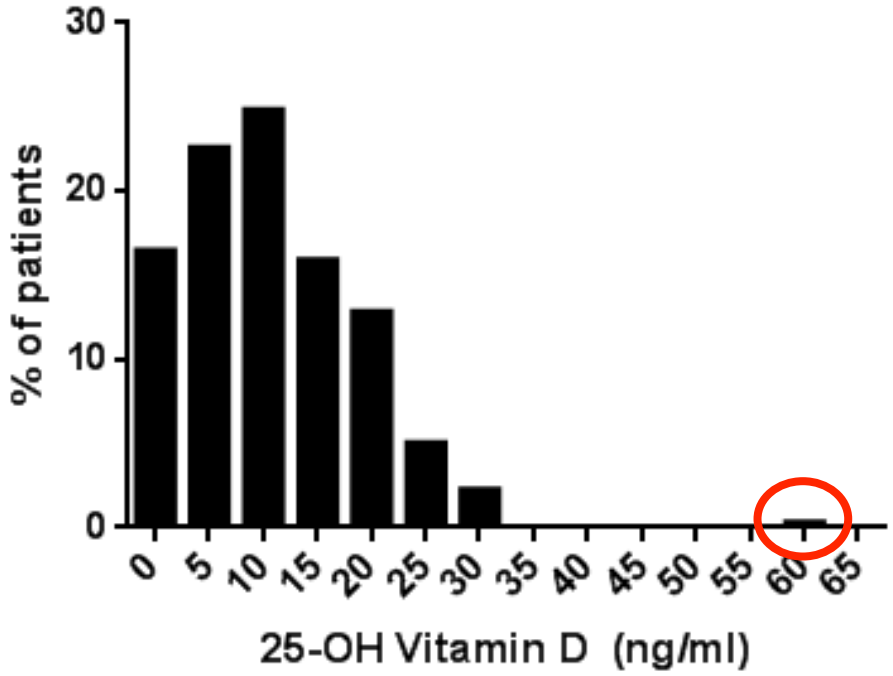


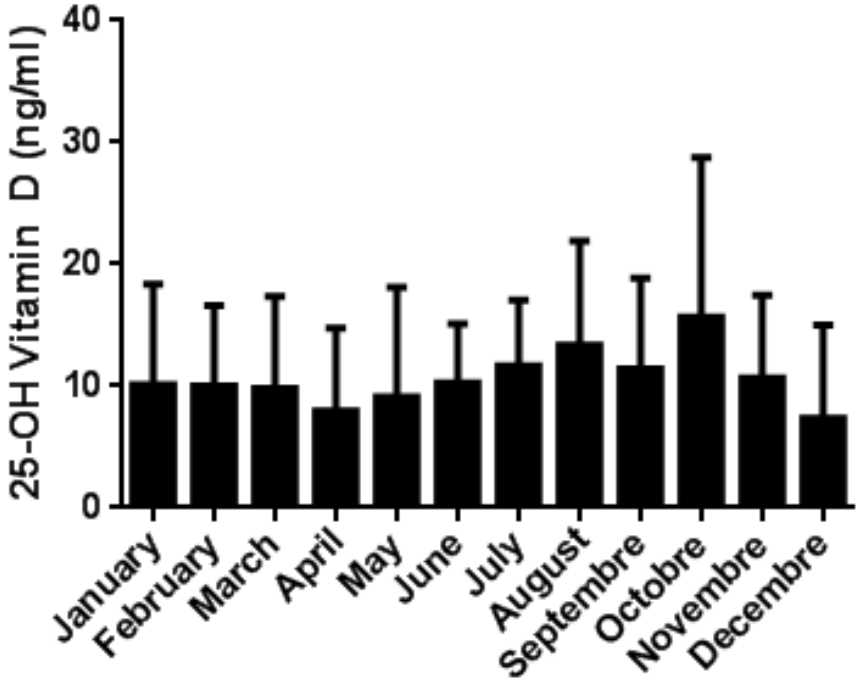
Beyond Rituximab Pharmacokinetics …

Vitamin D Deficiency:
Not a Problem in „Sunny Rimini“ ?

RICOVER-60:
Vitamin D serum levels (n=359)

Median: 9,2 ng/ml

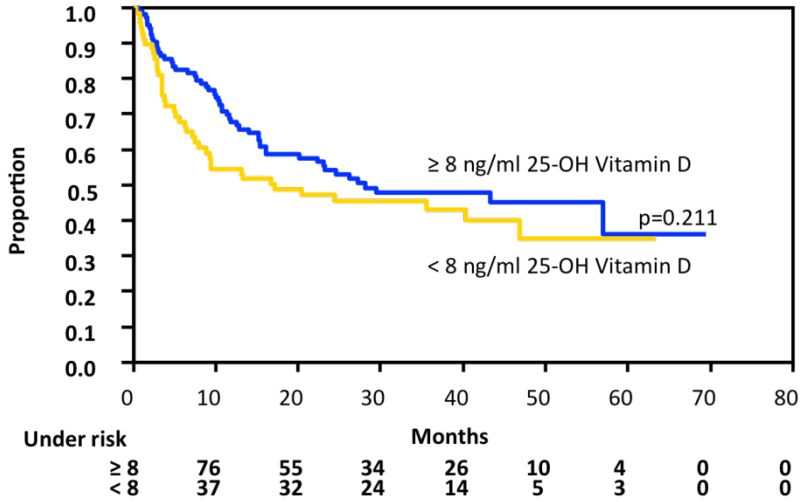




Bittenbring et al., *J Clin Oncol 2014*

RICOVER-60: Event-free Survival

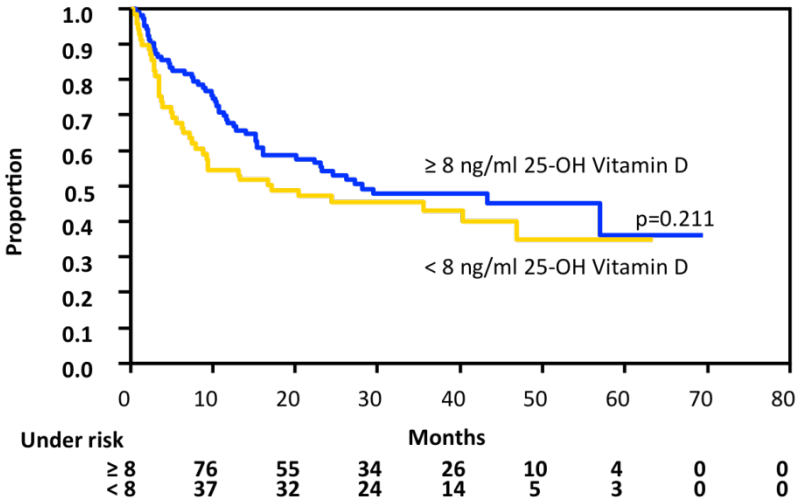
CHOP



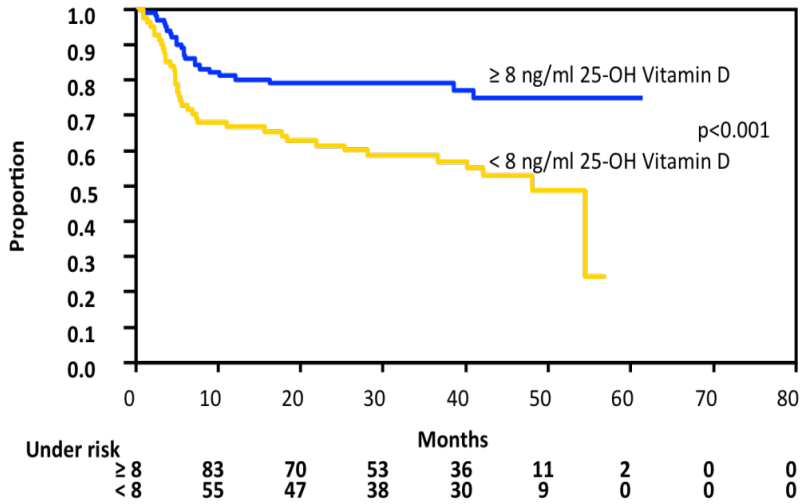
Bittenbring et al., *J Clin Oncol 2014*

RICOVER-60: Event-free Survival

CHOP

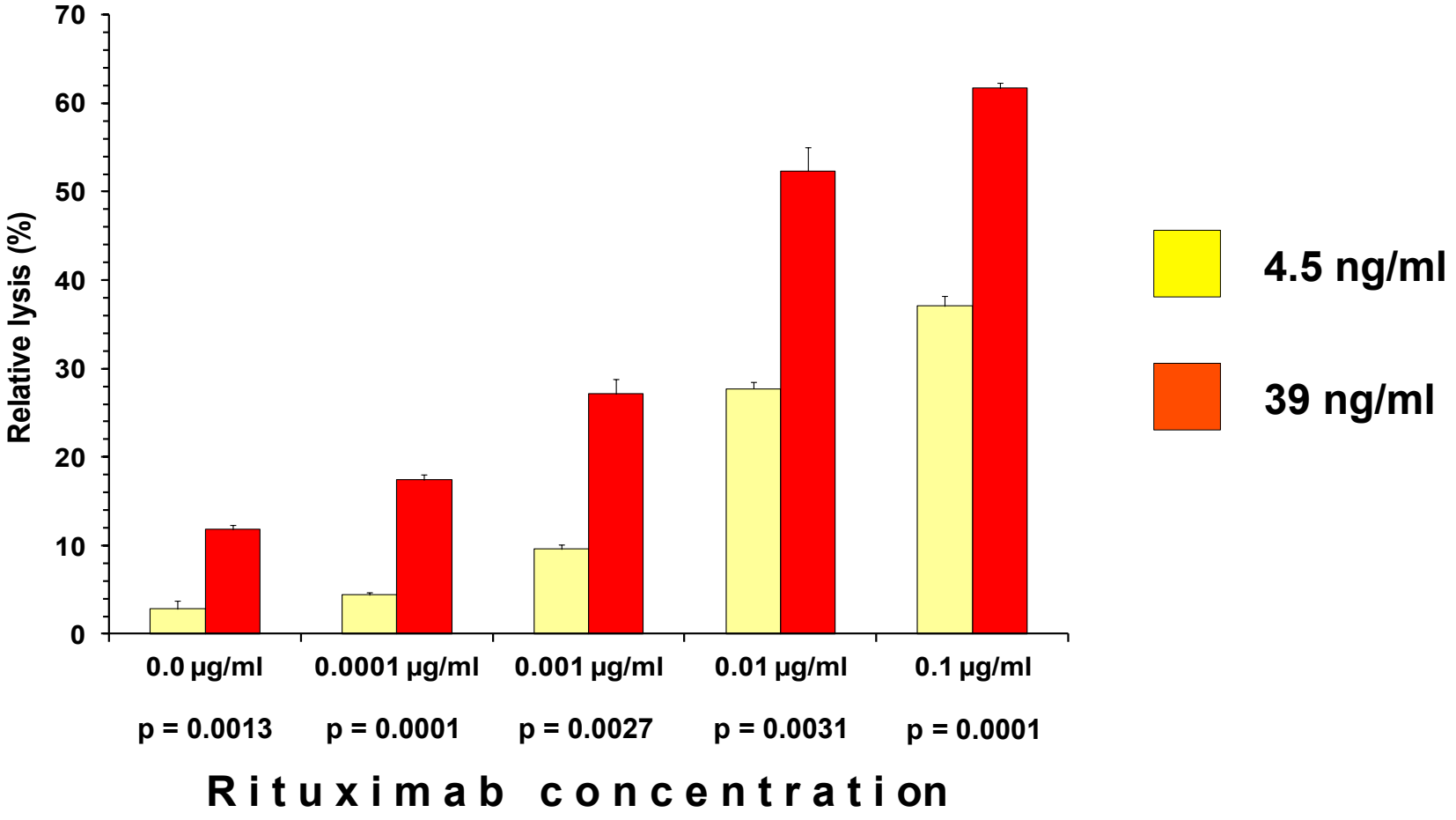


R-CHOP



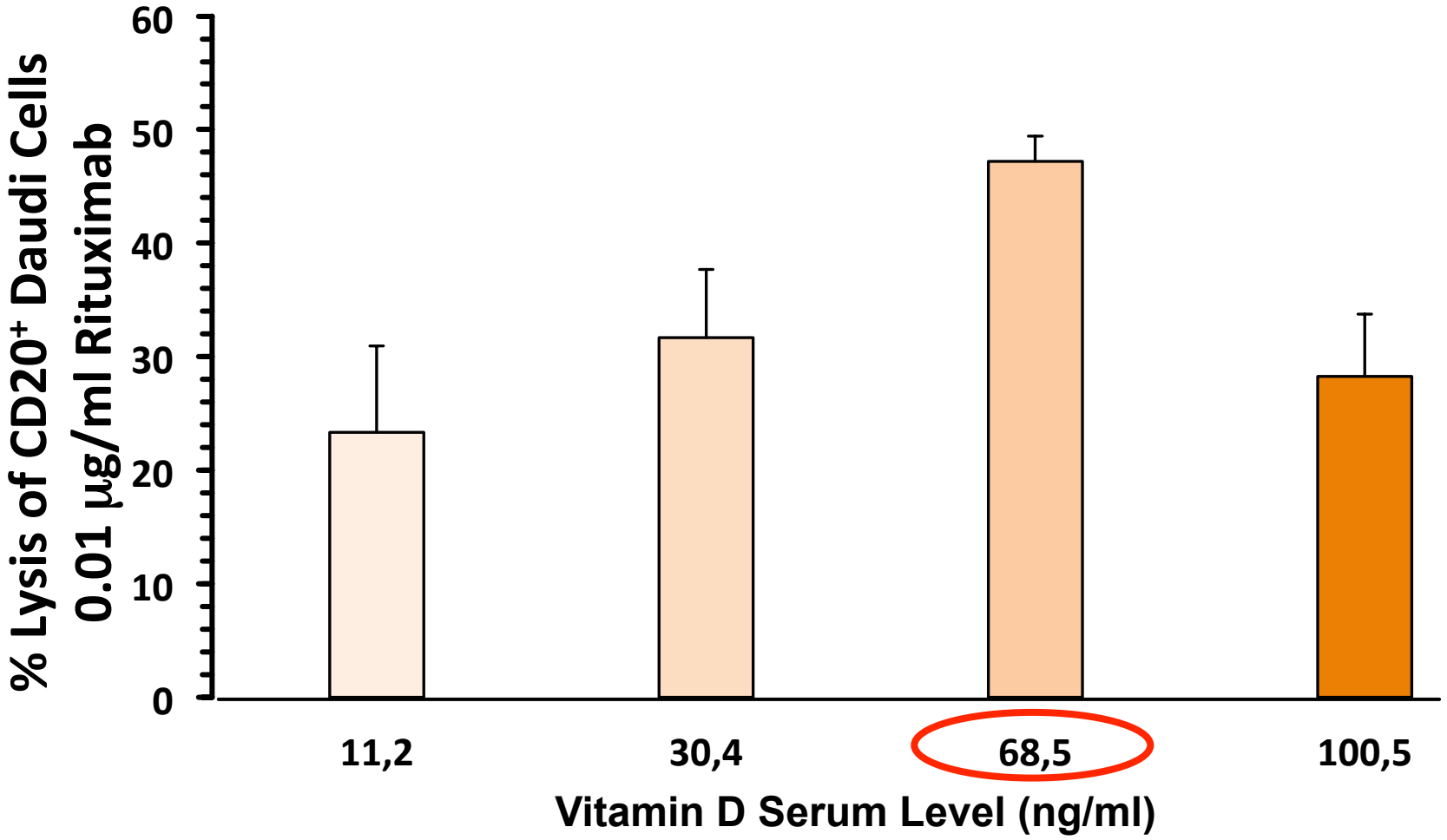
Bittenbring et al., *J Clin Oncol 2014*

Rituximab-mediated Cellular Cytotoxicity in Vitamin-D Deficient Individuals before and after Substitution



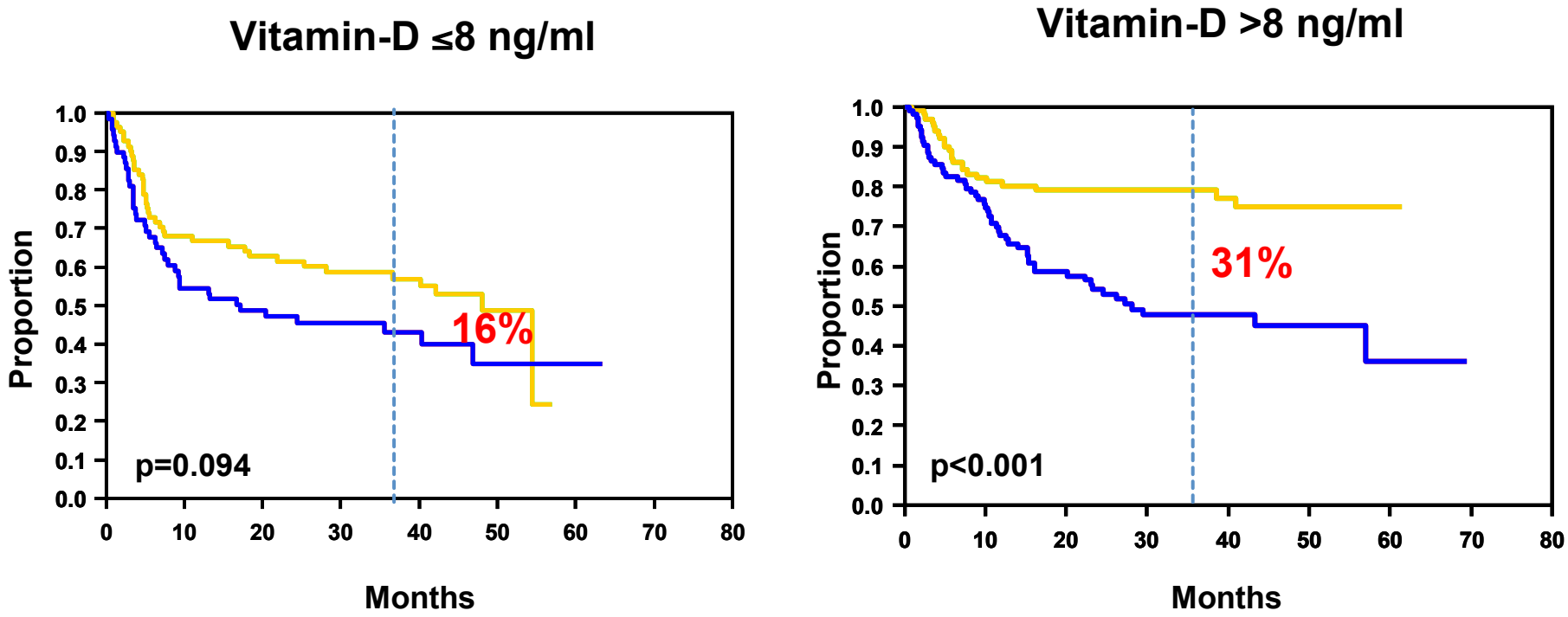
Bittenbring et al., *J Clin Oncol 2014*

Rituximab-mediated Cellular Cytotoxicity before and after Vitamin-D-Substitution



Bittenbring et al., *ASH 2015*

3-Year EFS Improvement by Rituximab in RICOVER-60



Bittenbring et al., *J Clin Oncol 2014*

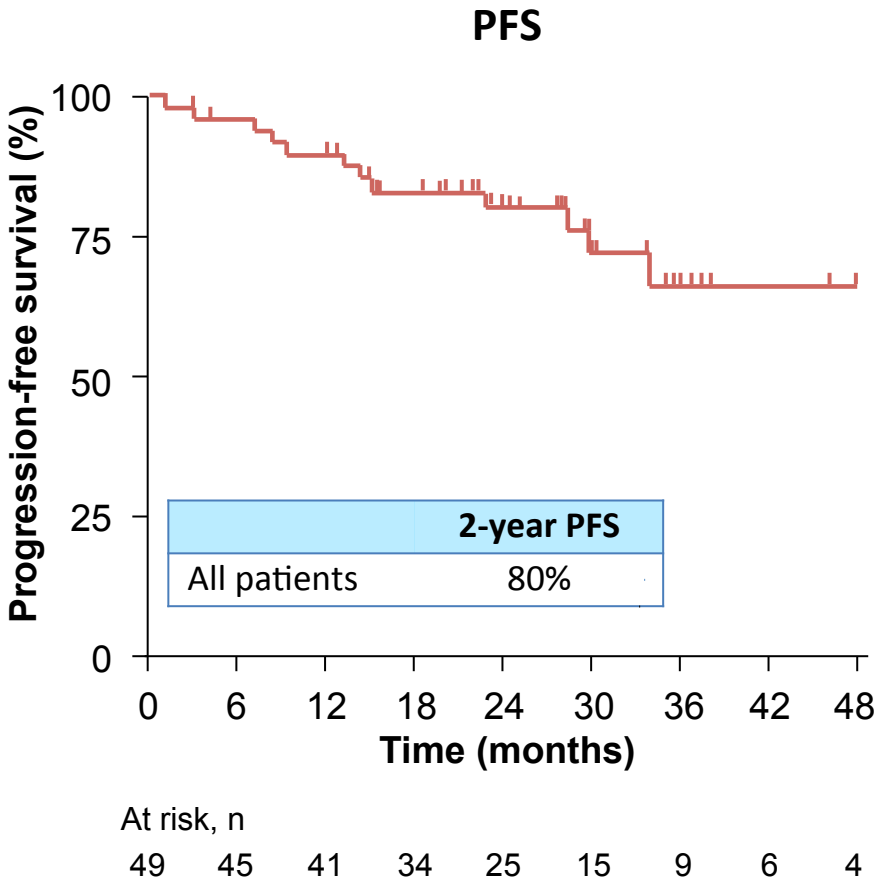
Towards the Cure of DLBCL

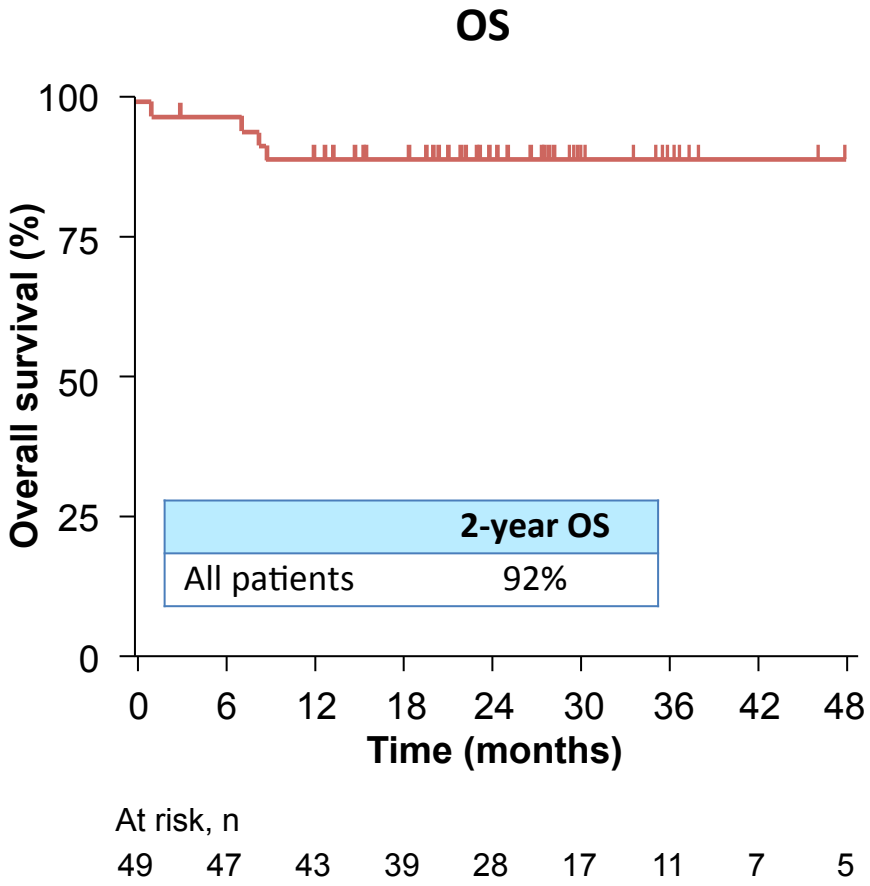
The future:

- [Vitamin D substitution: „DR.CHOP“]
- **Lenalidomide**
- BTK inhibitors (Ibrutinib)
- PI3K inhibitors
- Bcl-2 inhibitors
- Combos (PPM + BTK-I + mTor-I)

DSHNHL

REAL07 phase II R2-CHOP21 in elderly high risk untreated DLBCL





Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

Towards the Cure of DLBCL

The future:

- [Vitamin D substitution: „DR.CHOP“]
- Lenalidomide
- BTK inhibitors (Ibrutinib)
- PI3K inhibitors
- Bcl-2 inhibitors
- Combos (PPM + BTK-I + mTor-I)
- BARs

DSHNHL

Towards the Cure of DLBCL

The future:

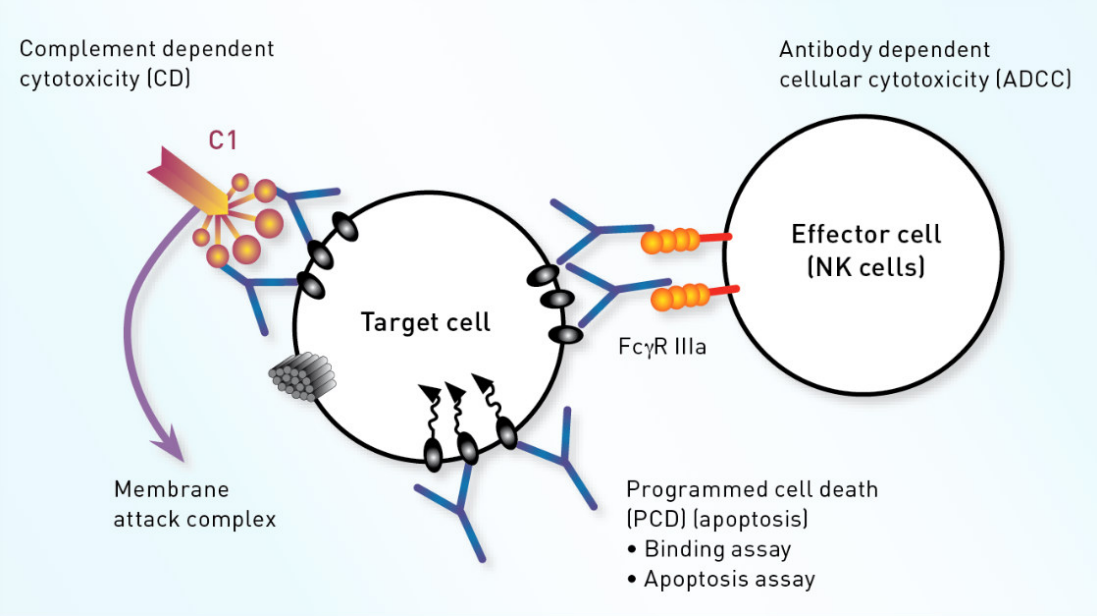
- **[Vitamin D substitution: „DR.CHOP“]**
- **BTK inhibitors (Ibrutinib)**
- **PI3K inhibitors**
- **Bcl-2 inhibitors**
- **Combos (PPM + BTK-I + mTor-I)**
- ***B*CR-*A*ntigens for *R*everse Targeting**

DSHNHL

Forward vs. Reverse Targeting

Forward Trageting

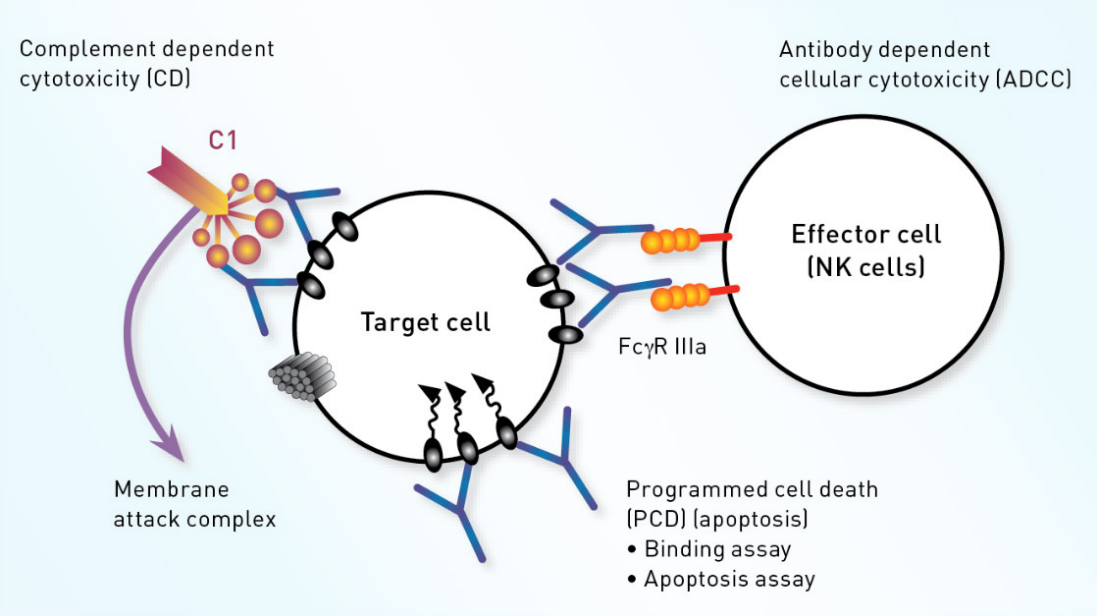
Antibody binds to Antigen, e. g. CD20



Forward vs. Reverse Targeting

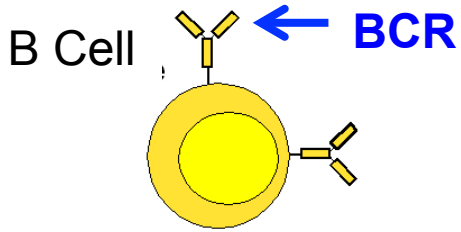
Forward Trageting

Antibody binds to Antigen, e. g. CD20



Reverse Targeting

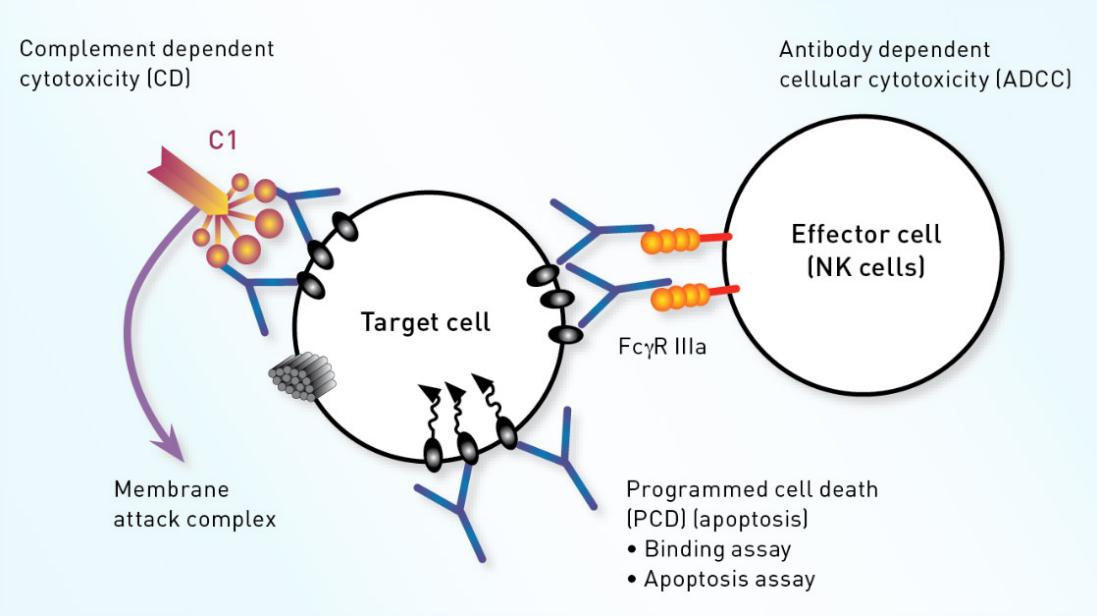
B-Cell Receptor Antigen binds to B-Cell Receptor



Forward vs. Reverse Targeting

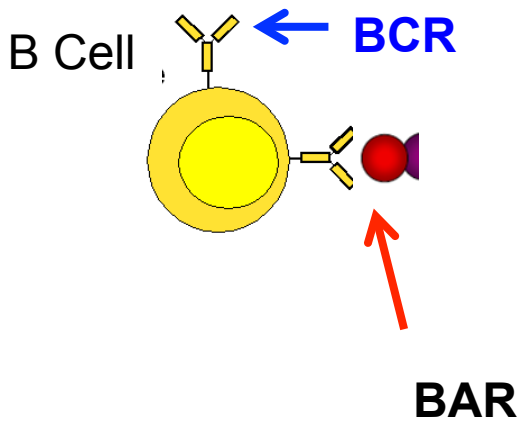
Forward Trageting

Antibody binds to Antigen, e. g. CD20



Reverse Targeting

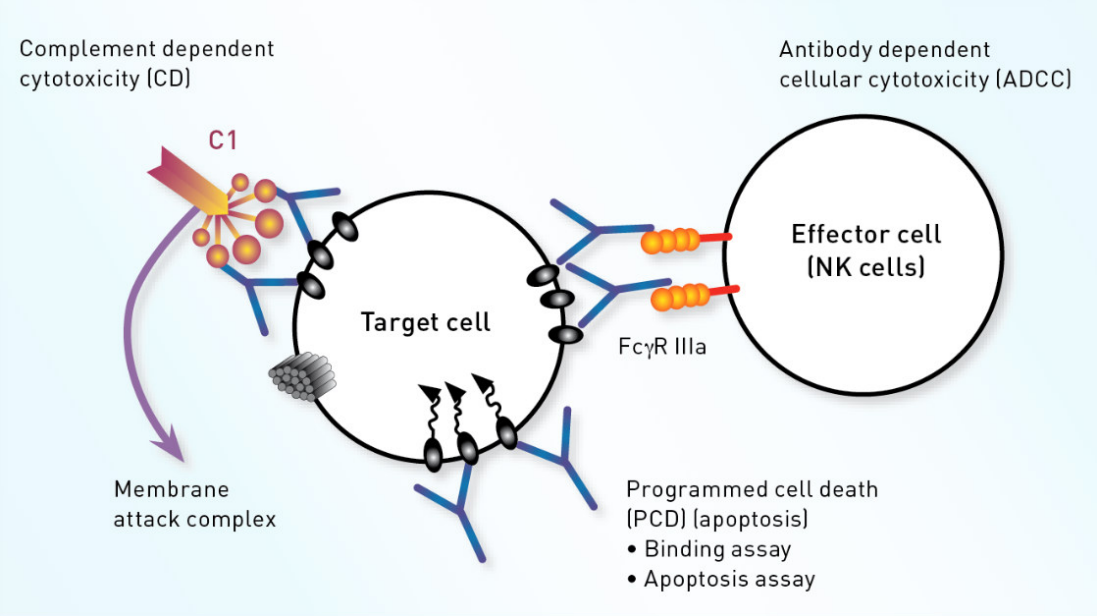
B-Cell Receptor Antigen binds to B-Cell Receptor



Forward vs. Reverse Targeting

Forward Trageting

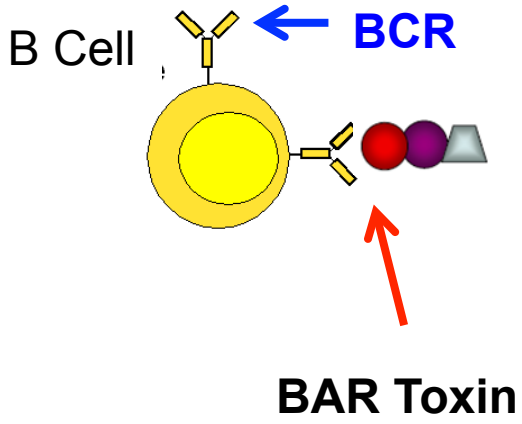
Antibody binds to Antigen, e. g. CD20



Reverse Targeting

B-Cell Receptor Antigen (with Toxin)

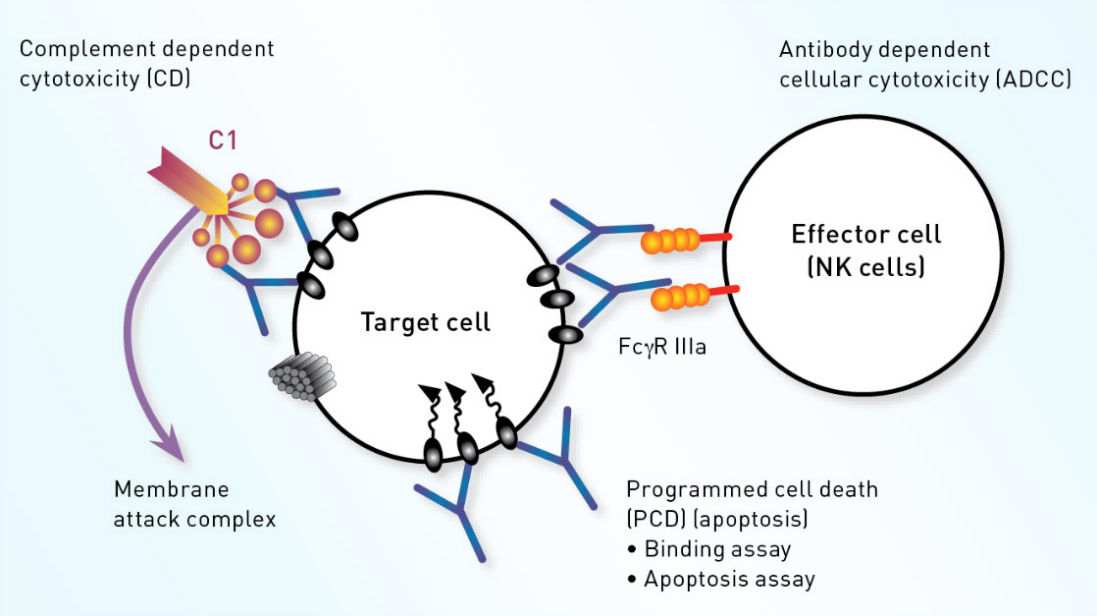
binds to B-Cell Receptor



Forward vs. Reverse Targeting

Forward Trageting

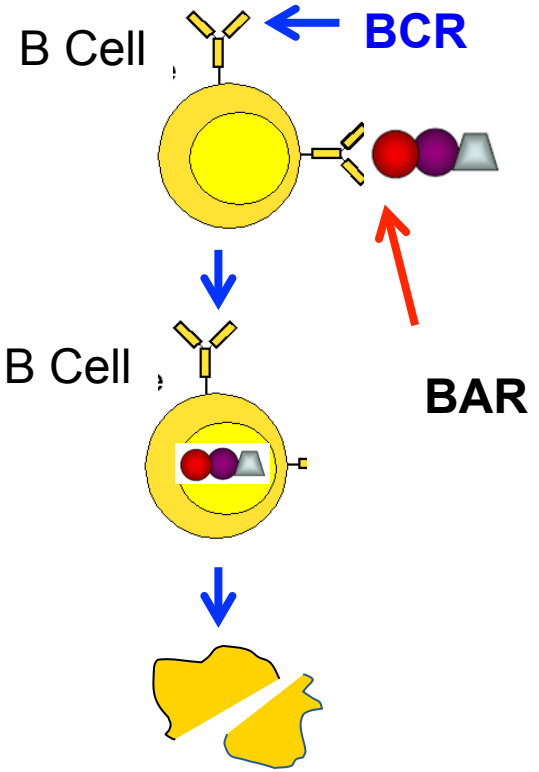
Antibody binds to Antigen, e. g. CD20



Reverse Targeting

B-Cell Receptor Antigen (with Toxin)

binds to B-Celr Receptor

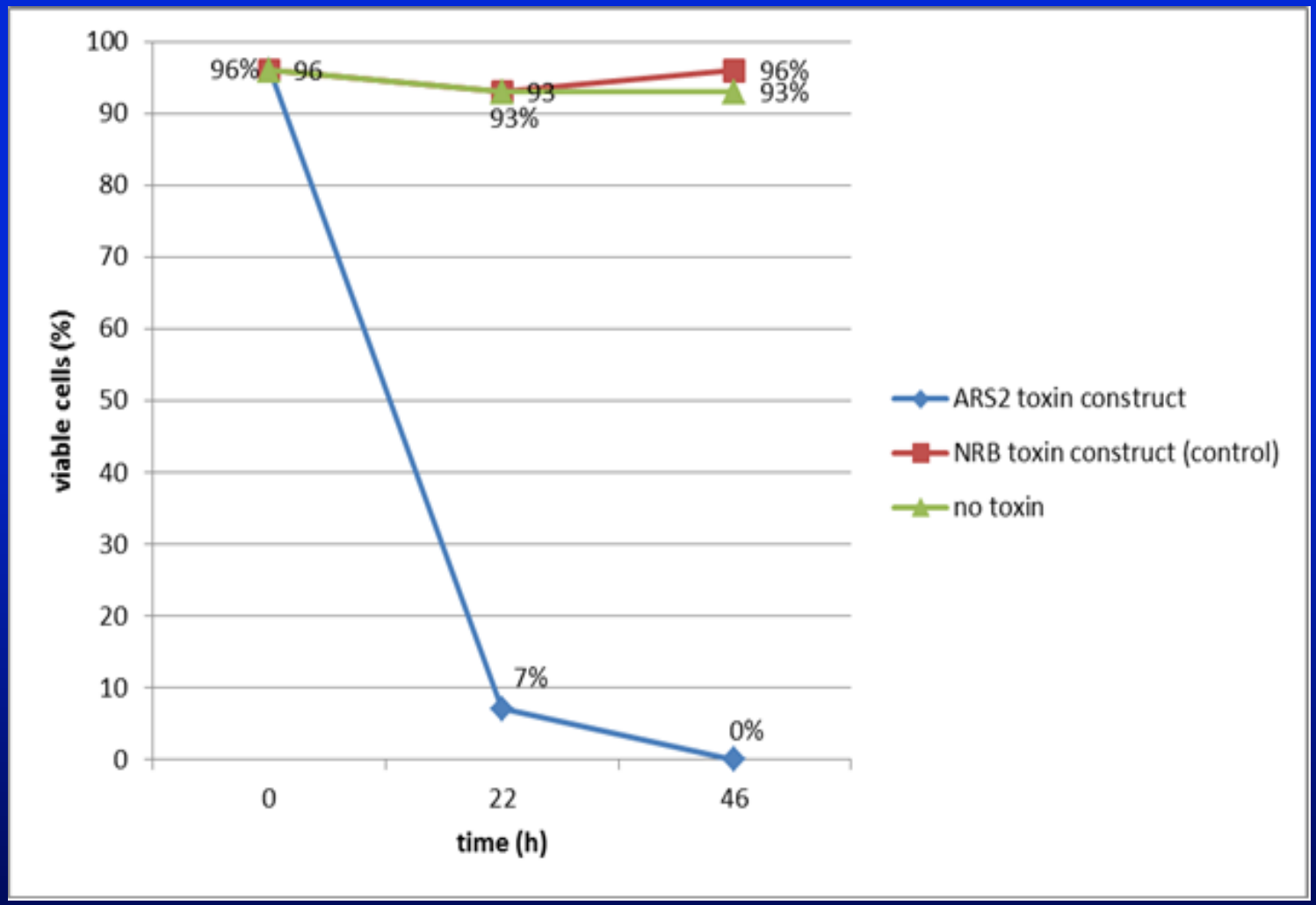


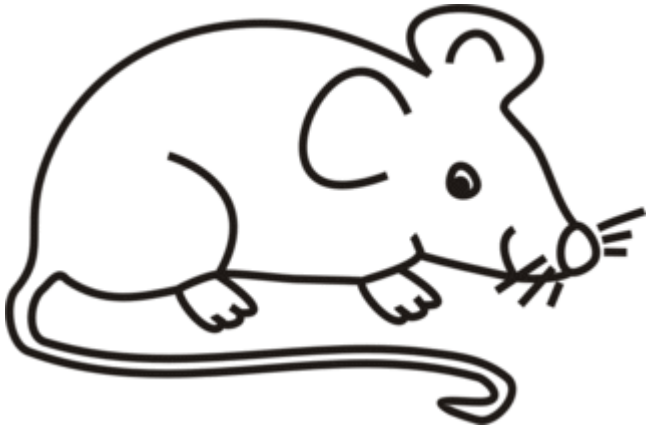
Clinical Relevance of BCR Antigens

Homburg BARs identified (25.03.15):

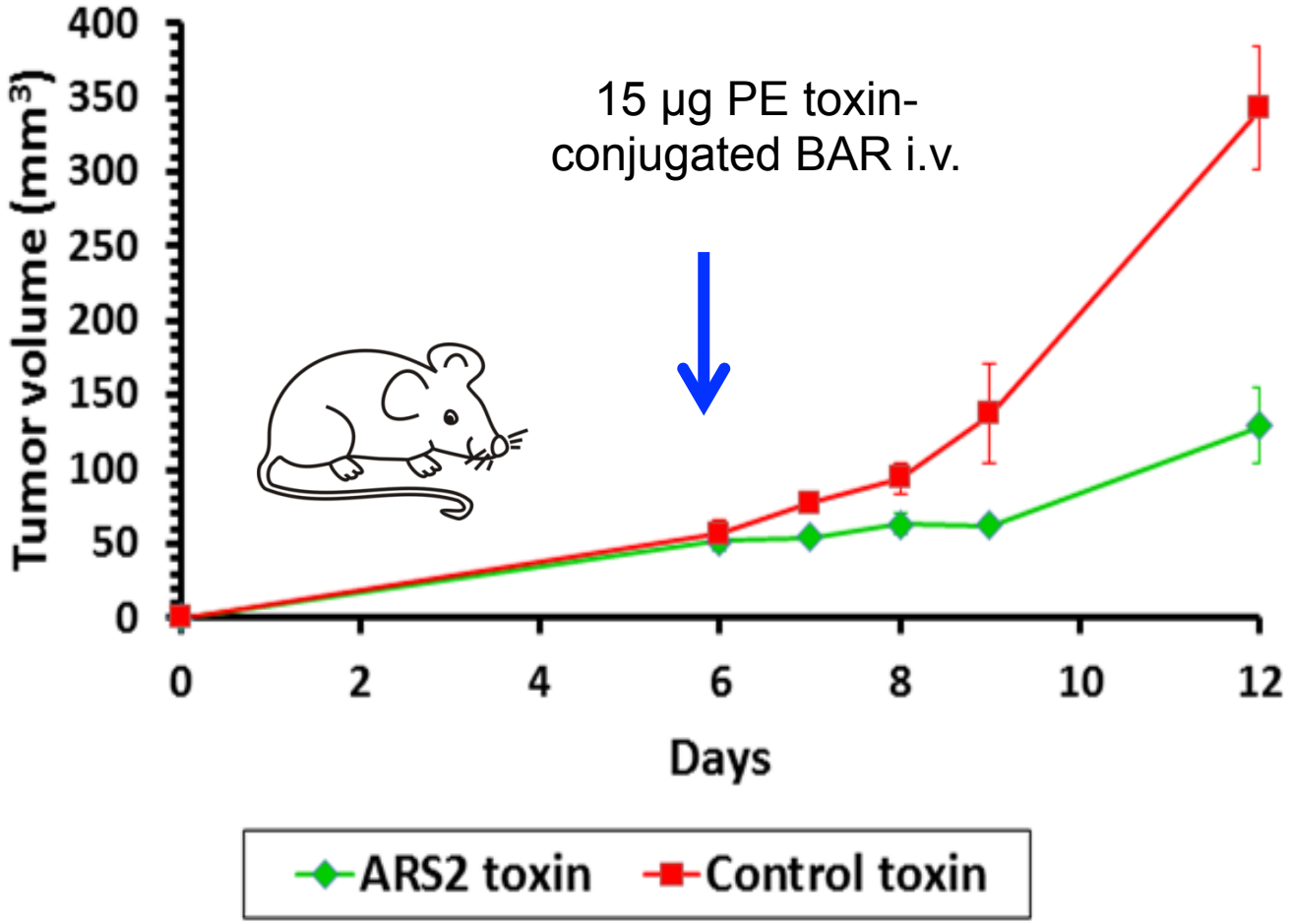
- 30-50% of MGUS/MM (2 antigens, 1 epitope)
- 30% of CLL (diverse, ≥2 epitopes each)
- 25% of FL (1 antigen, 1 epitope)
- 66% of all PCNSL (1 antigen, 1 epitope)
- 60% all ABC-DLBCL (1 antigen, 1 epitope)
- 45% of all MCL (1 antigen, 1 epitope)
- 90% of IgD-NLPHL (Moraxella catarrhalis)

Specific Killing of ARS2-pos ABC-DLBCL by BAR-Toxins (Pseudomonas Exotoxin)





Growth of heterotransplanted ARS2-pos. OCI-LY3 in SCID mice



BARs: A new dimension in the treatment for a broad spectrum of various B-cell malignancies

o r :

„Personalized and Precision Medicine at the Limits“

Thank you !