

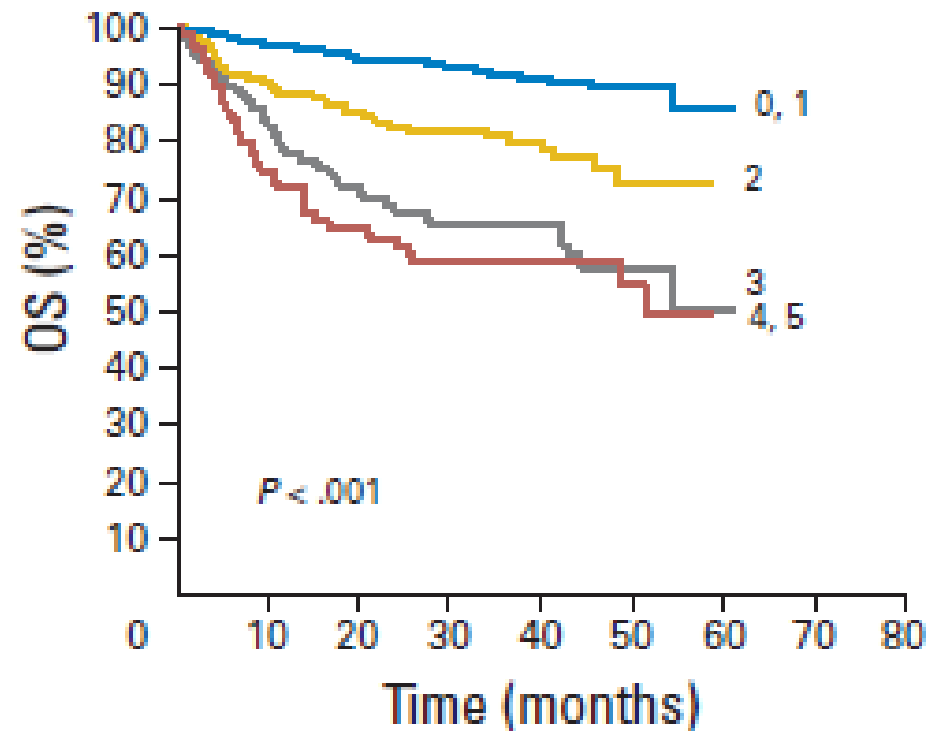
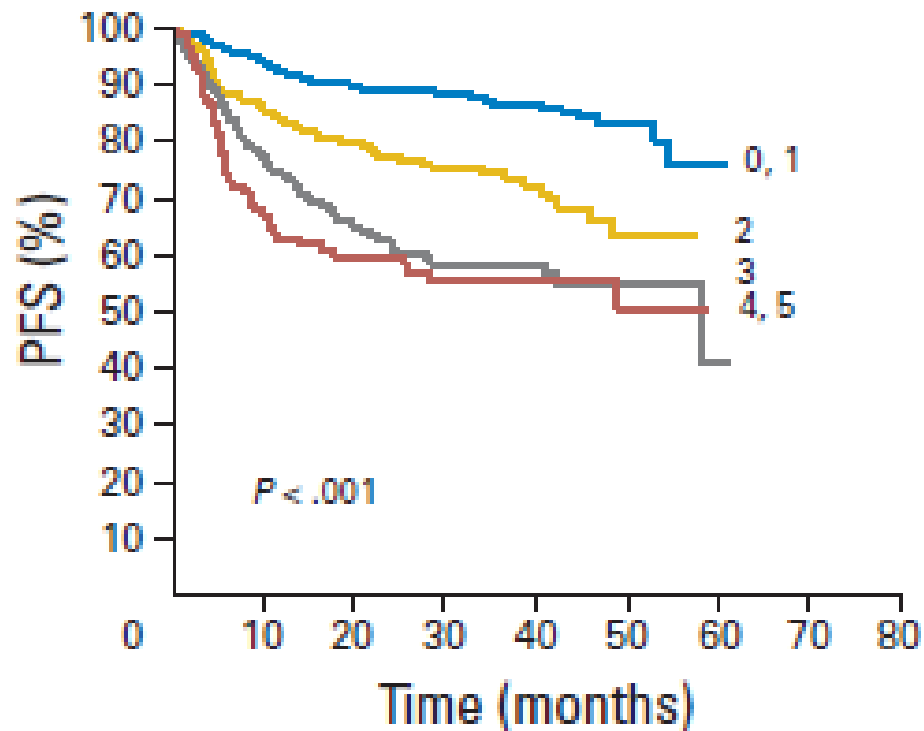
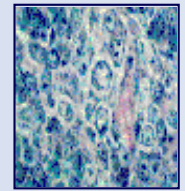
## Aktuelle Studien und Ergebnisse der DSHNHL: Aggressive Non-Hodgkin-Lymphome

Lorenz Trümper, Marita Ziepert, Zamira Zeylanova, Gerald Wulf, Bertram Glaß,  
Andreas Rosenwald, Markus Loeffler, Norbert Schmitz, Michael Pfreundschuh  
für die DSHNHL (Deutsche Studiengruppe Hochmaligne Lymphome)



- **Prognose**
  - **CB vs IB – und? ; „Risiko Alter“**
- Jüngere Patienten
  - MINT Follow Up, Mega CHOEP Auswertung
  - FLYER & UNFOLDER Status
- Ältere Patienten
  - Rituximab Modifikationen
  - OPTIMAL Studie
  - Non-fit Elderly: BRENDA Studie
- Periphere T Zell Lymphome

# IPI: gilt immer noch(R-IPI)!

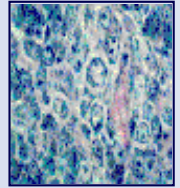


Marita Ziepert et al. *J Clin Oncol* 28:2373-2380.

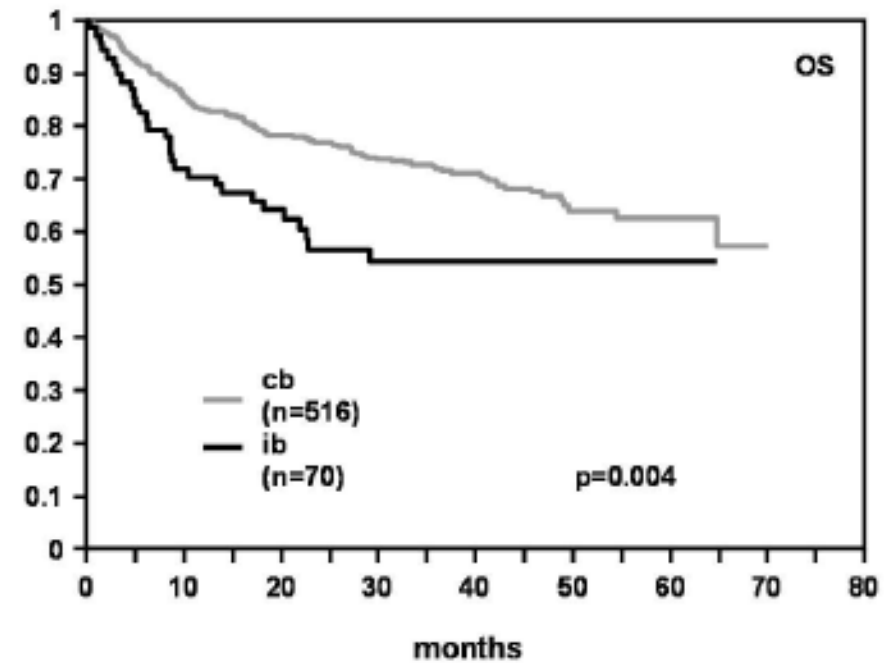
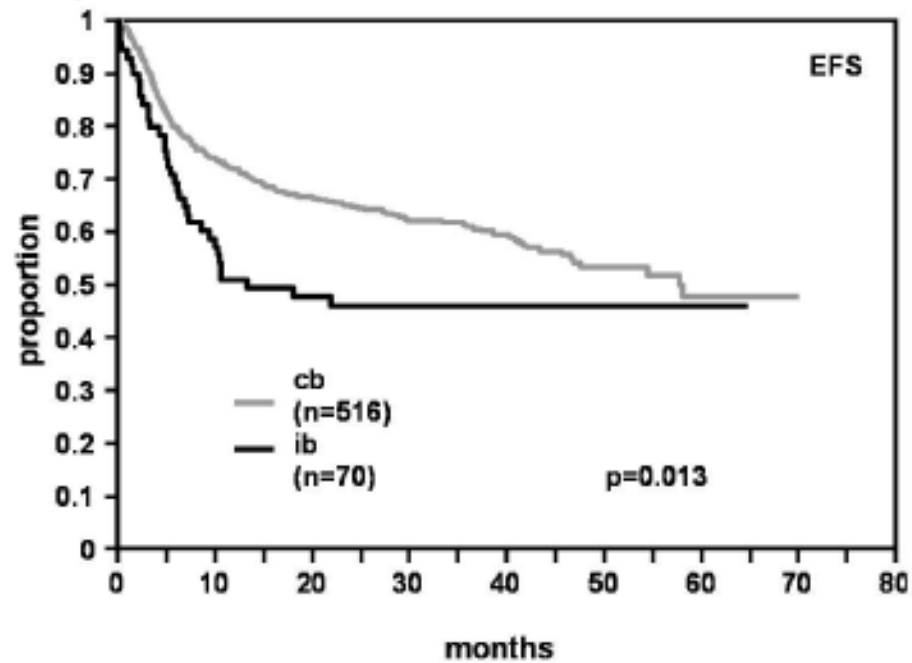
# Kiel „gilt immer noch“

GERMAN HIGH-GRADE NHL  
STUDY GROUP (DSHNHL)

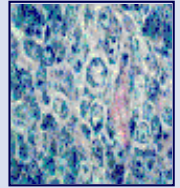
[www.lymphome.de/en/Groups/DSHNHL](http://www.lymphome.de/en/Groups/DSHNHL)



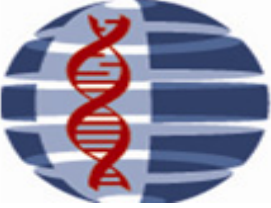
all patients:



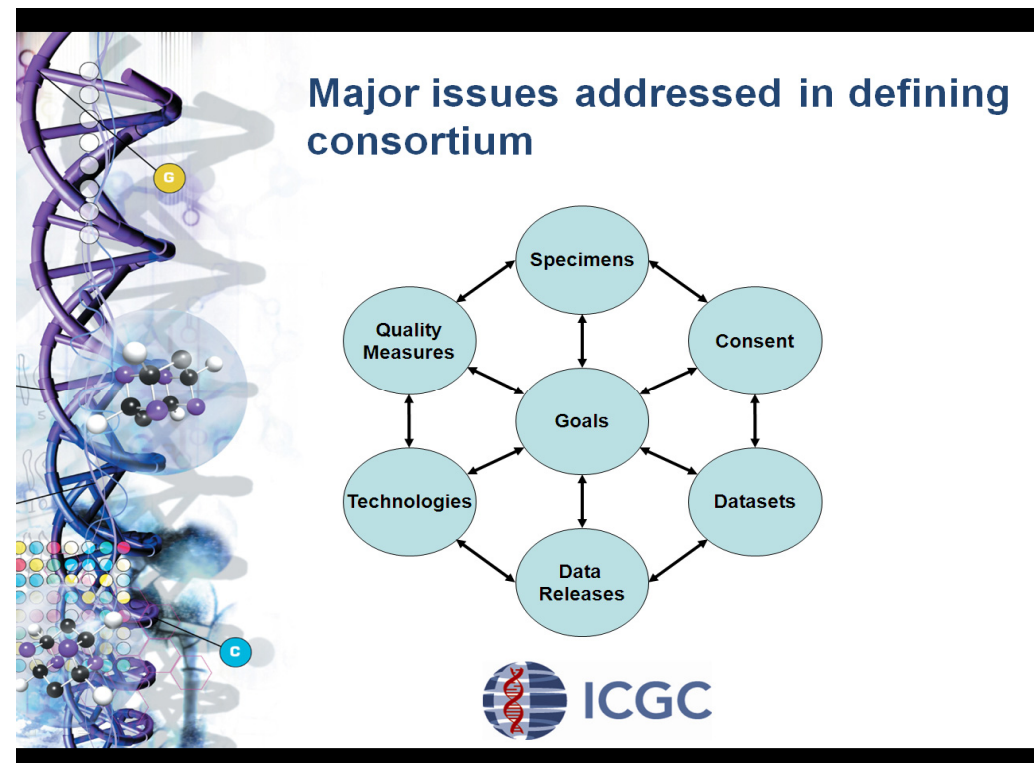
Ott et al, Blood 2010



- Internationales Krebsgenomkonsortium
- „Next Generation Sequencing“
- BMBF Förderung
- ... *Frischmaterial*
- ... *Keimbahn*



CIGGCTCCATCGTACG  
TGCAATCGTTATCGGC  
CGCGATATACTGAGTA  
GTCGCCTATATATCCA  
GCCCG**MMML\*SEQ**  
TCTAGTATATAAGCA

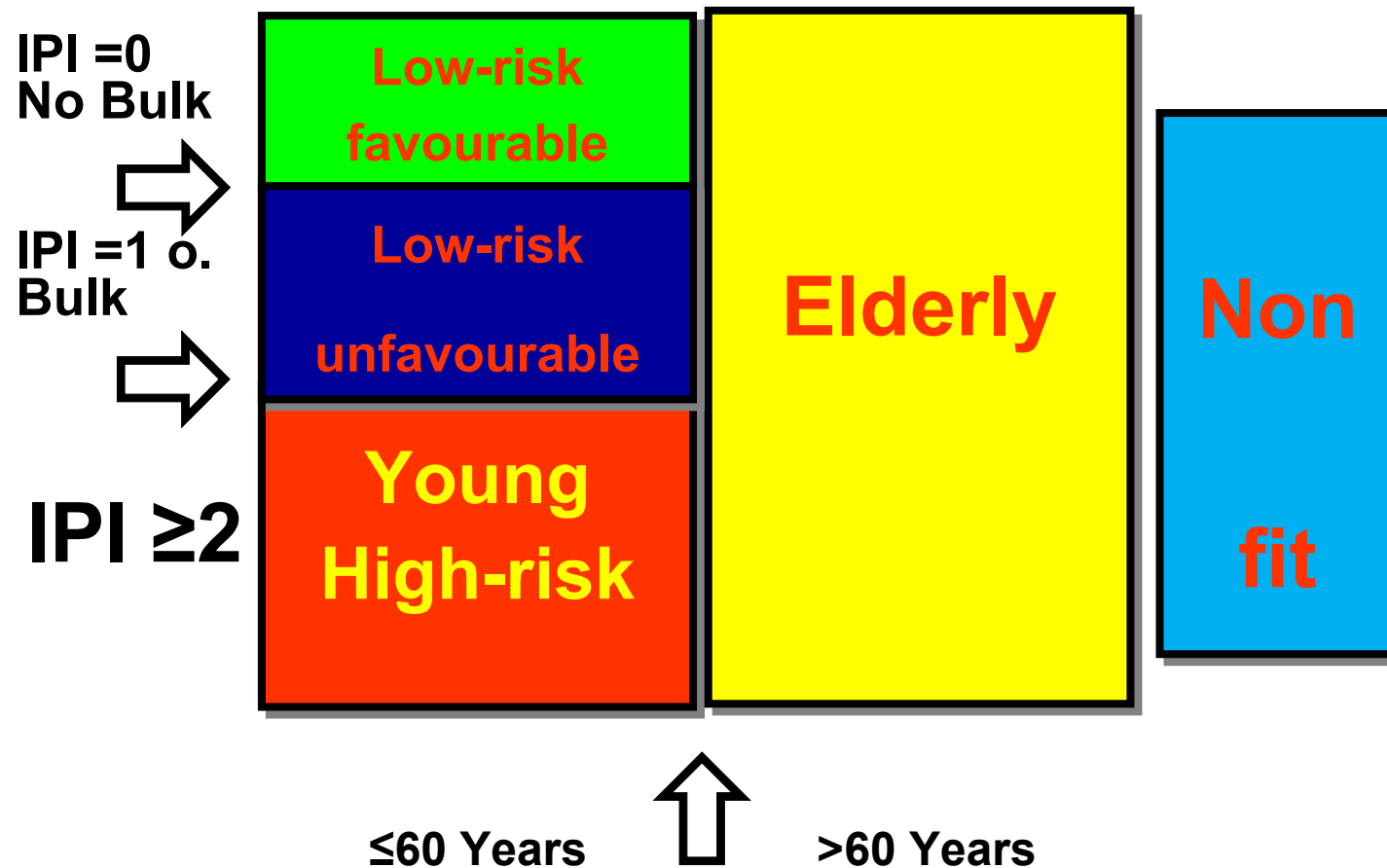
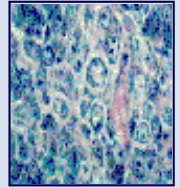


# Risikogruppen

## DSHNHL – Aggr. B NHL

GERMAN HIGH-GRADE NHL  
STUDY GROUP (DSHNHL)

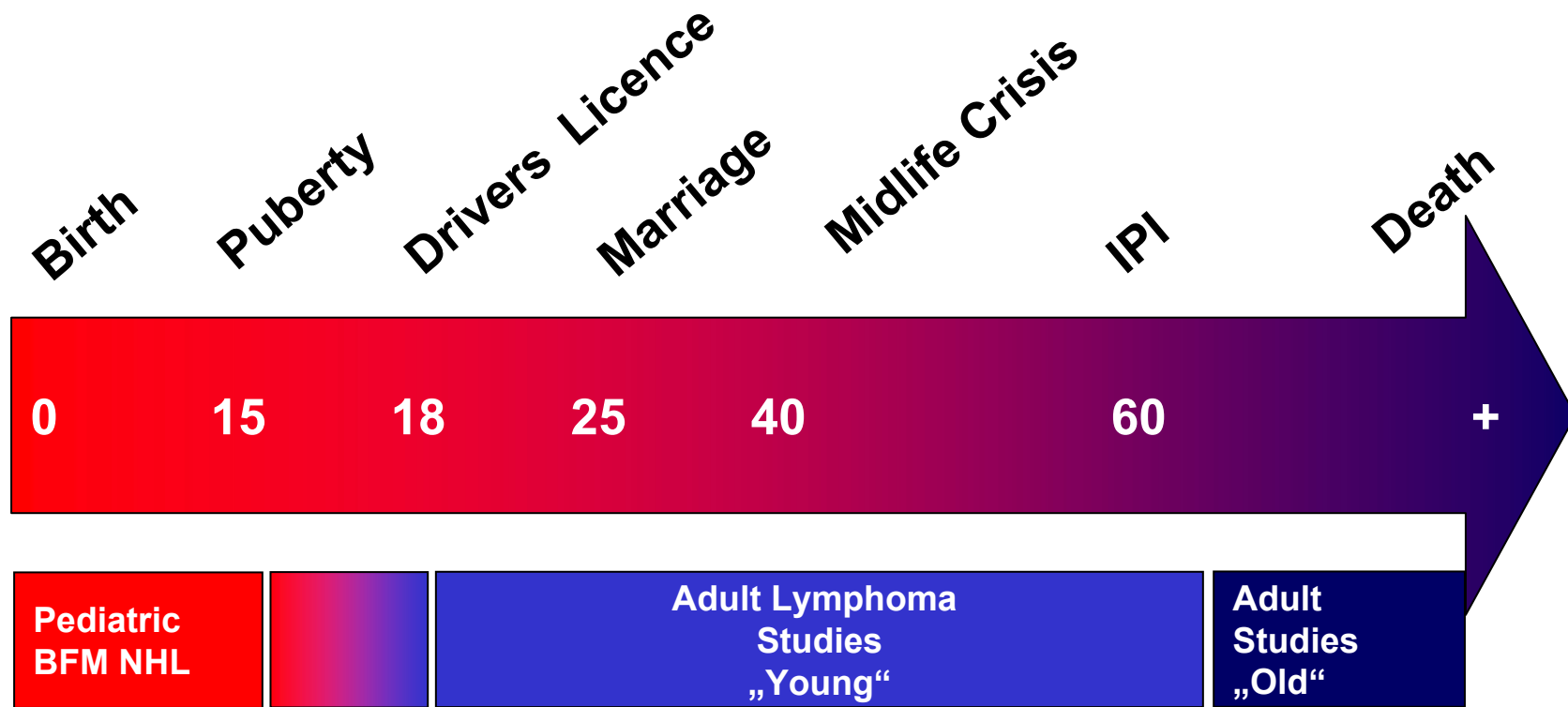
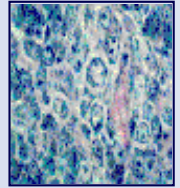
[www.lymphome.de/en/Groups/DSHNHL](http://www.lymphome.de/en/Groups/DSHNHL)

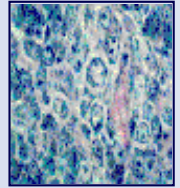


Where is the border between „pediatric“  
and „adult“ ?

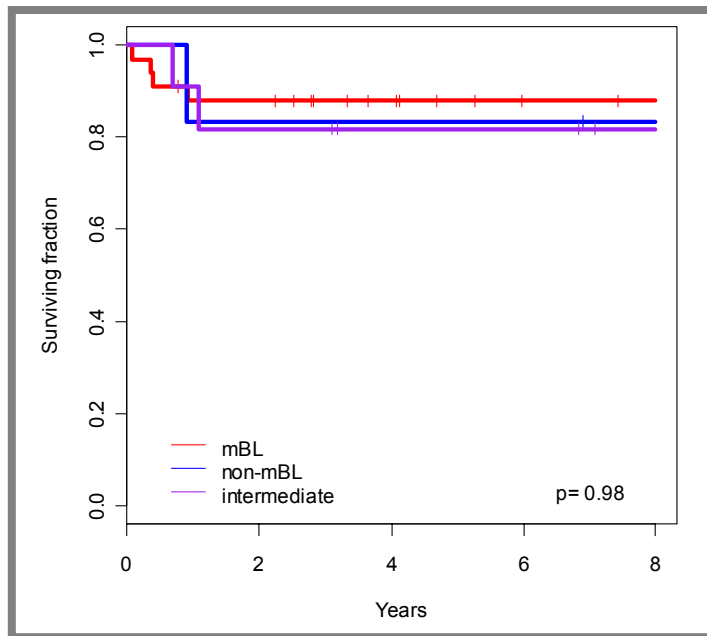
GERMAN HIGH-GRADE NHL  
STUDY GROUP (DSHNHL)

[www.lymphome.de/en/Groups/DSHNHL](http://www.lymphome.de/en/Groups/DSHNHL)

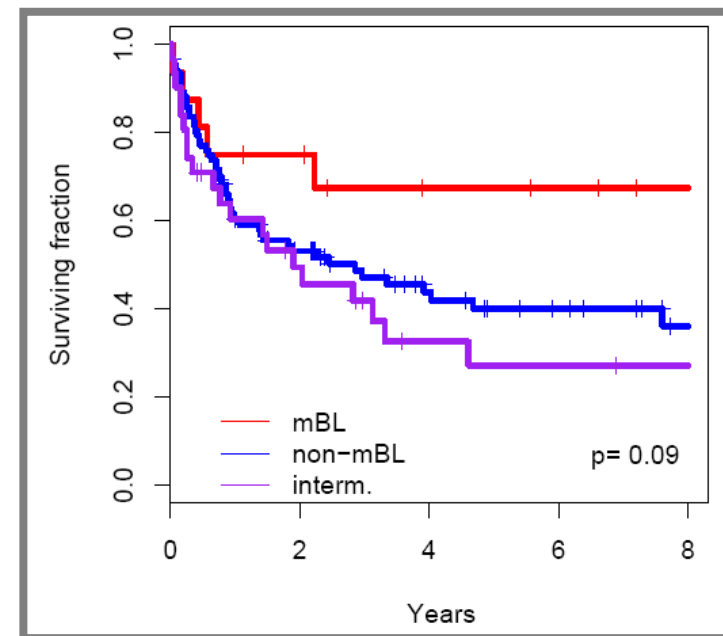




### Pediatric Patients (<15yrs) BFM-NHL trials

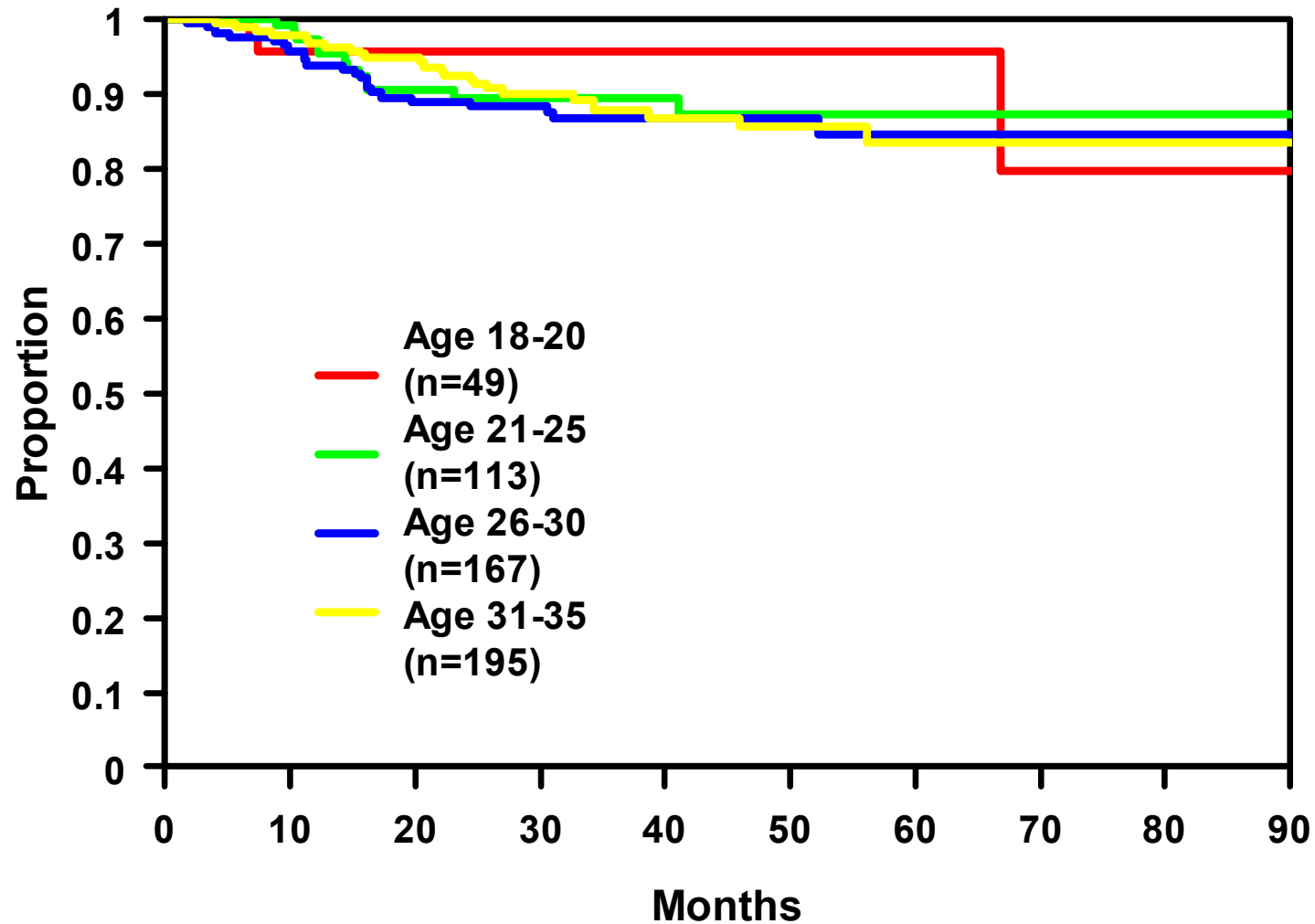
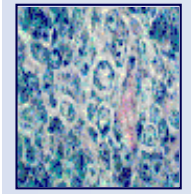


### Adult Patients (>18yrs)



# Age analysis

Patients  $\leq 35$  years from all DSHNHL studies (n=524)  
Overall Survival according to age





- Prognose
  - „Risiko Alter“
  - CB vs IB – und?
- **Jüngere Patienten**
  - **MINT Follow Up**
  - **FLYER & UNFOLDER Status**
  - **Mega CHOEP Auswertung**
- Ältere Patienten
  - Rituximab Modifikationen
  - OPTIMAL Studie
  - Non-fit Elderly: BRENDA Studie

# Aggressive B-NHL

Primärbehandlung: spielt Strahlentherapie doch eine Rolle ?

Behandlung junger Patienten mit intermediärer Prognose (IPI =1)

MINT:

R

6 x R-CHOP<sub>like</sub> 21

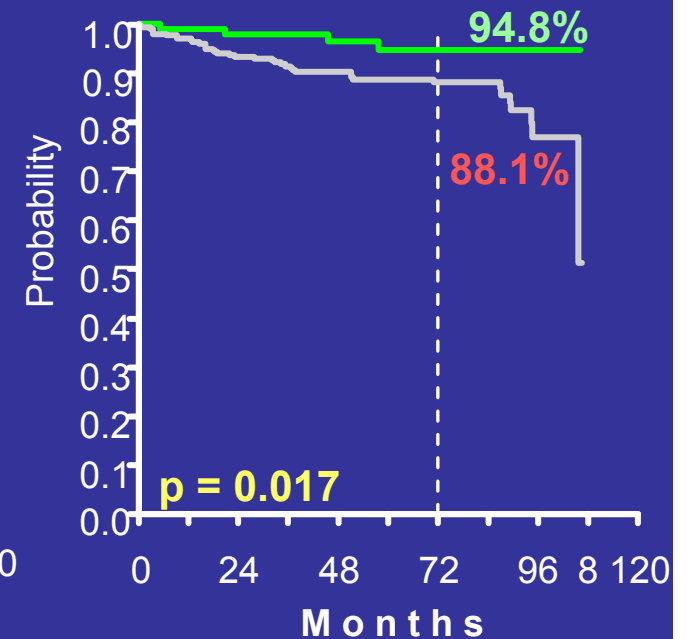
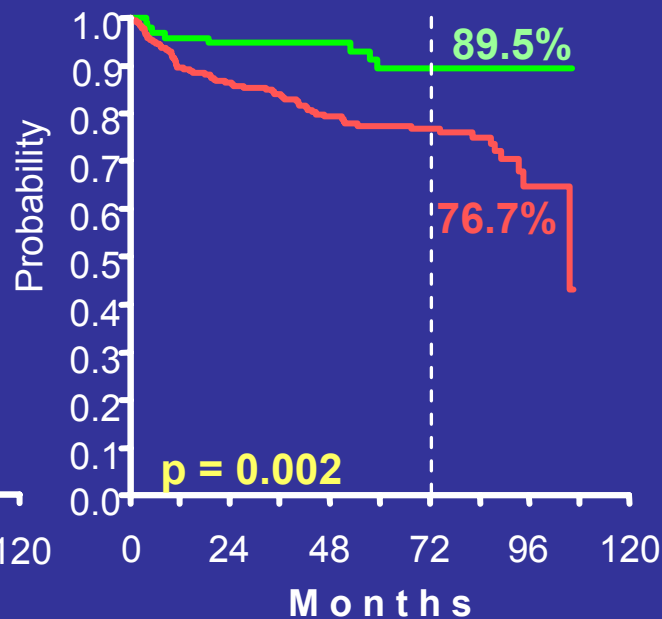
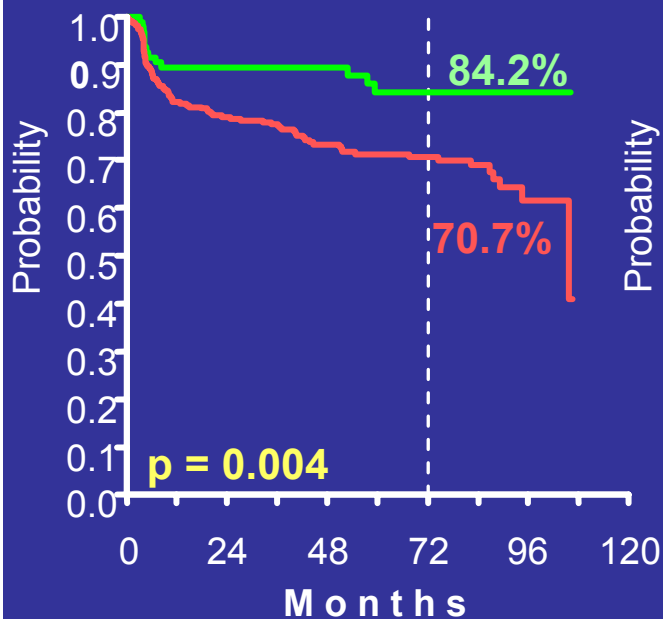
6 x CHOP<sub>like</sub> 21

RAD 40 Gy  
bulk, E-nodal

EFS

PFS

OS



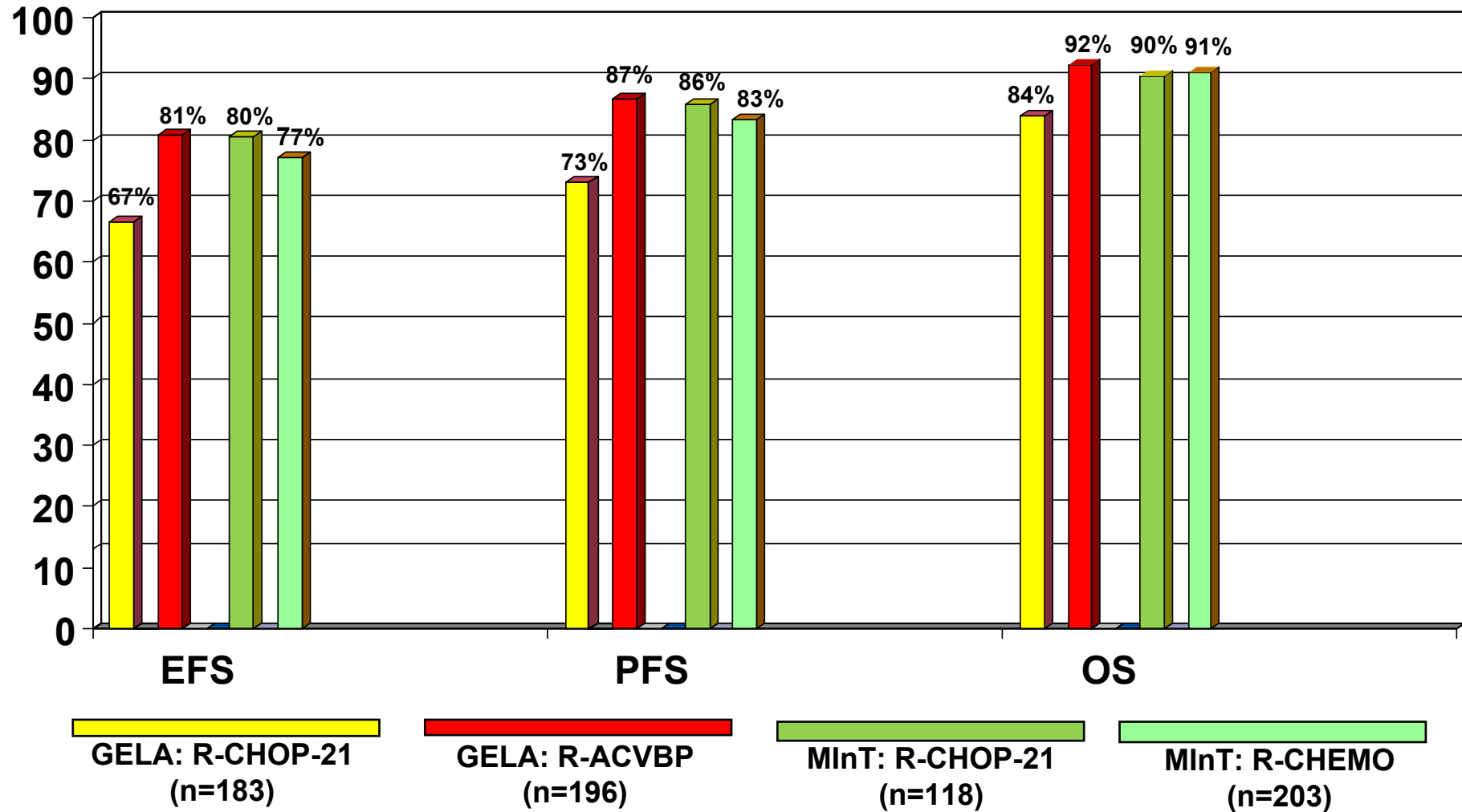
Favourable: IPI=0 / Ø bulk

Unfavourable: IPI=1 and / or bulk<sub>1</sub>

# Aggressive B-NHL

Primärbehandlung: spielt Strahlentherapie doch eine Rolle ?

Vergleich: Ergebnisse LNH 03-2B vs MINT für Patienten mit IPI =1

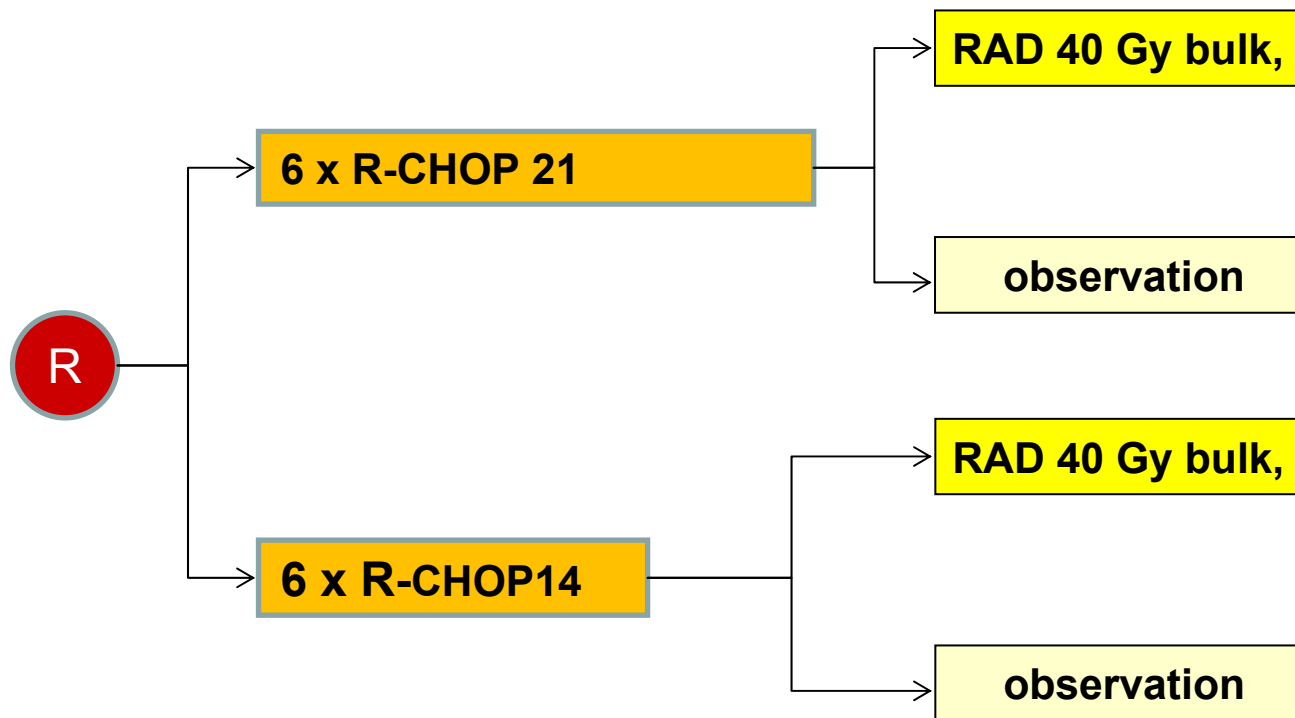


# Aggressive B-NHL

Primärbehandlung: spielt Strahlentherapie doch eine Rolle ?

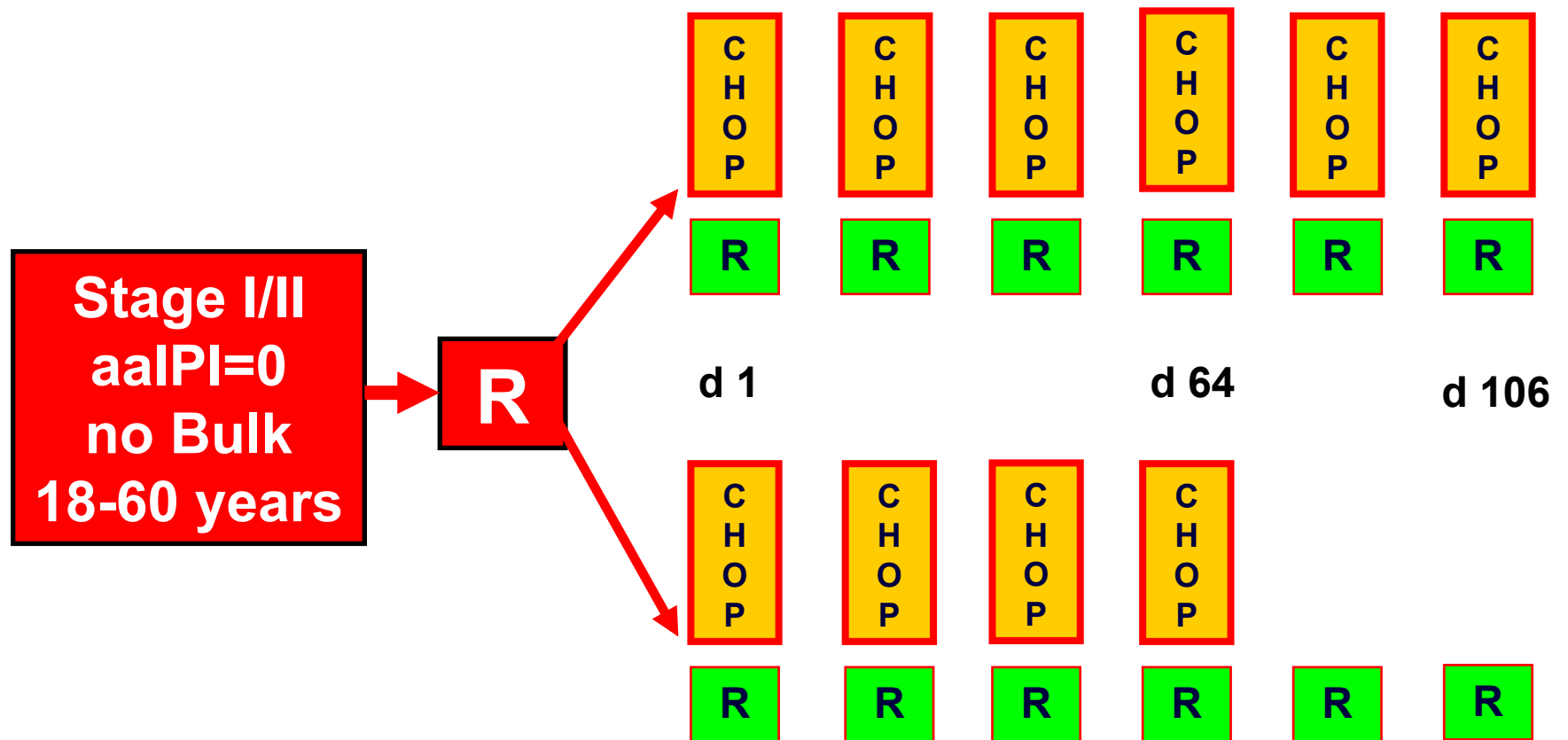
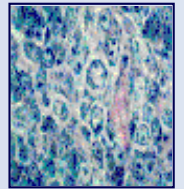
Behandlung junger Patienten mit intermediärer Prognose (IPI =1)

## UNFOLDER Study Design



# Recruitment UNFOLDER

- **Start of trial : 01.11.05**
- **Planned number of patients : 642**
- **Number of patients 04/11: 424**
- **First planned interim analysis: 07/11**



# FLYER (6-6/6-4) STUDY DESIGN

**FLYER (6-6/6-4):**

**PLANNED SAFETY ANALYSIS**

**200 Patients :**

**4 events**

**1 death (swine flu)**

**3 other events**

**worst-case scenario:**

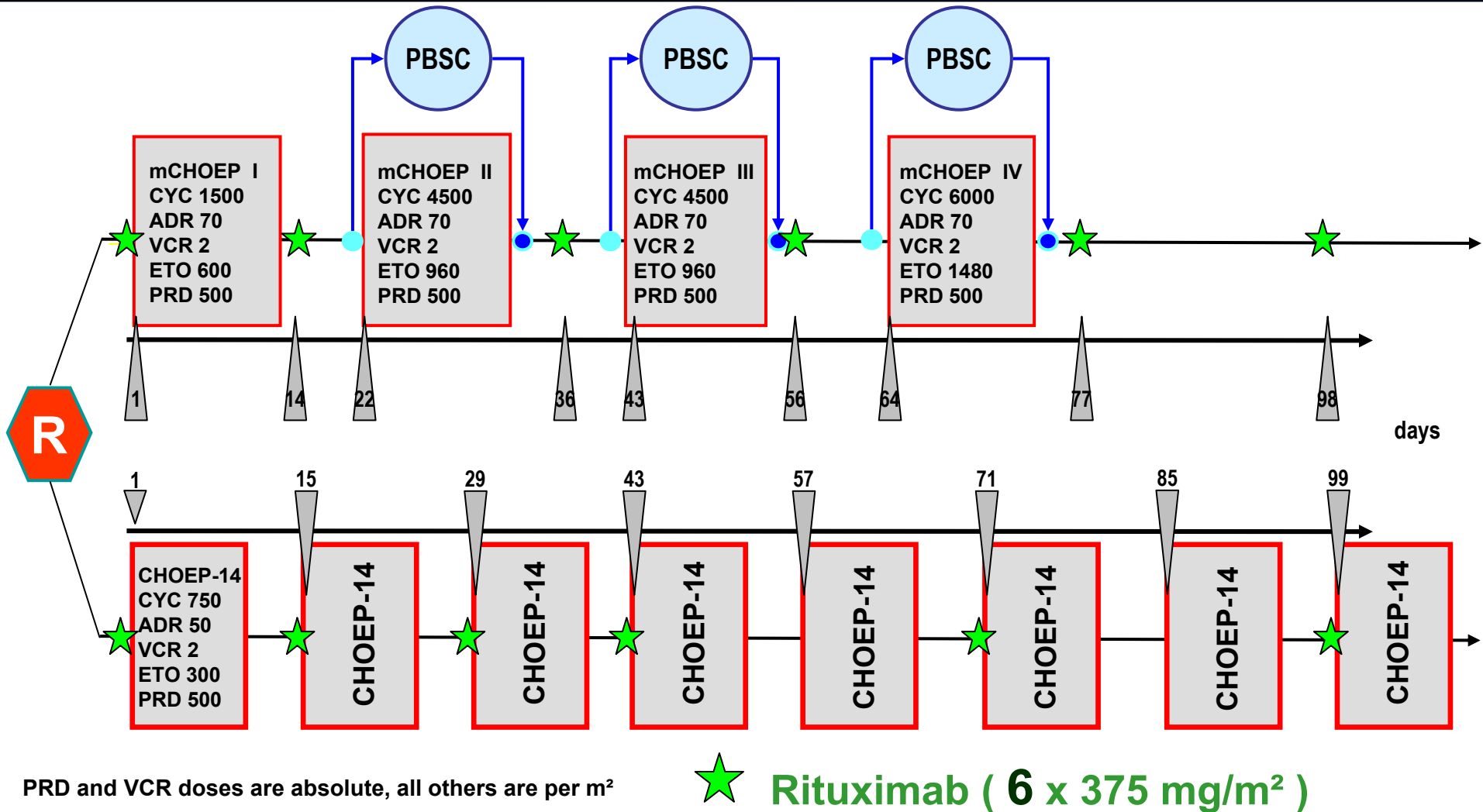
**4xR-CHOP+2R: EFS 97%, OS=100%**

# R-MegaCHOEP

## DESIGN OF THE RANDOMIZED STUDY

GERMAN HIGH-GRADE NHL  
STUDY GROUP (DSHNHL)

[www.lymphome.de/en/Groups/DSHNHL](http://www.lymphome.de/en/Groups/DSHNHL)



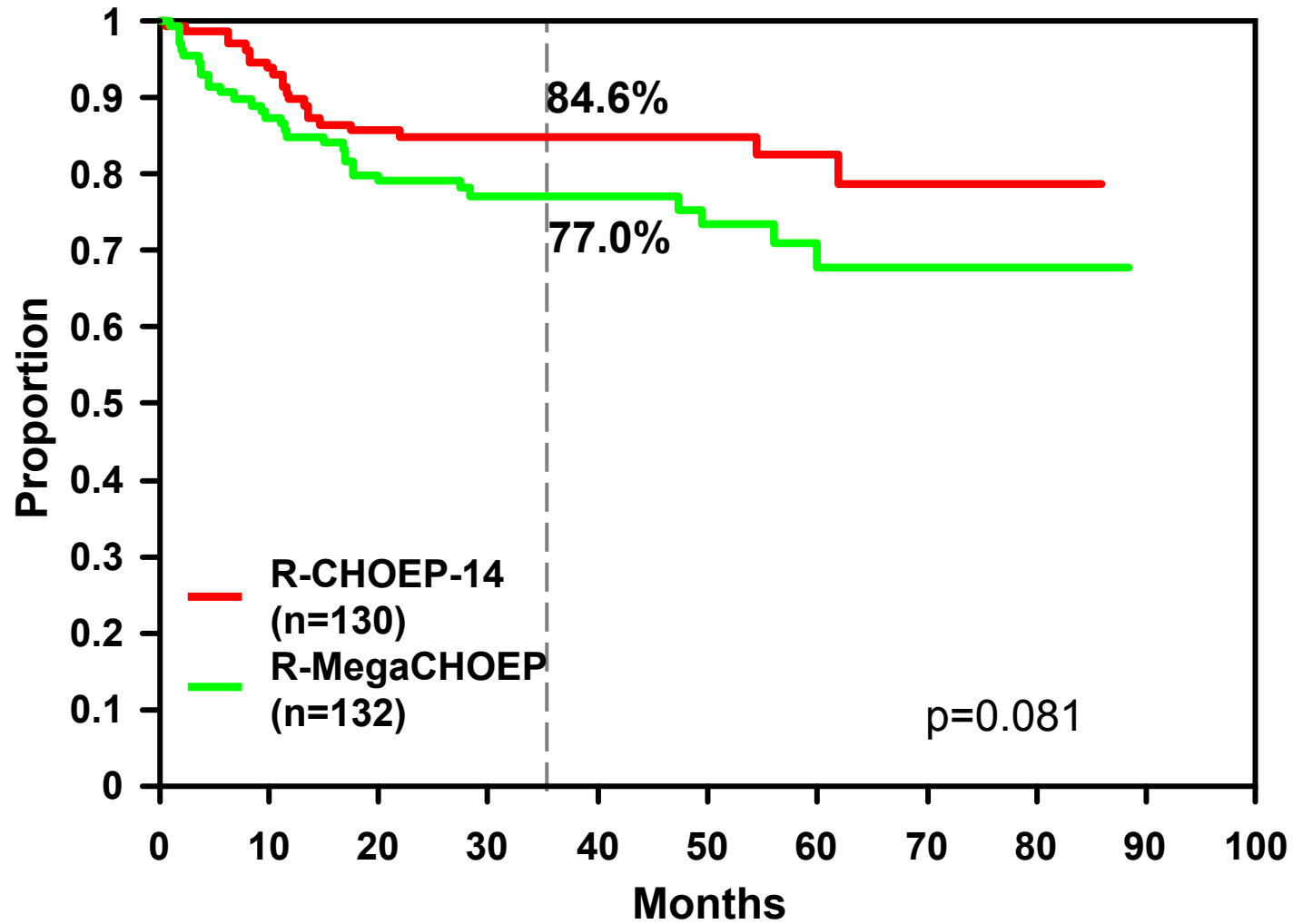
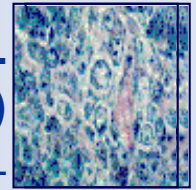
RADIOTHERAPY to bulky disease and EN involvement

# R-MegaCHOEP Study

## OS ACCORDING TO TREATMENT ARM

GERMAN HIGH-GRADENHL  
STUDY GROUP (DSHNHL)

[www.lymphoma-euro.com/Groups/DSHNHL](http://www.lymphoma-euro.com/Groups/DSHNHL)

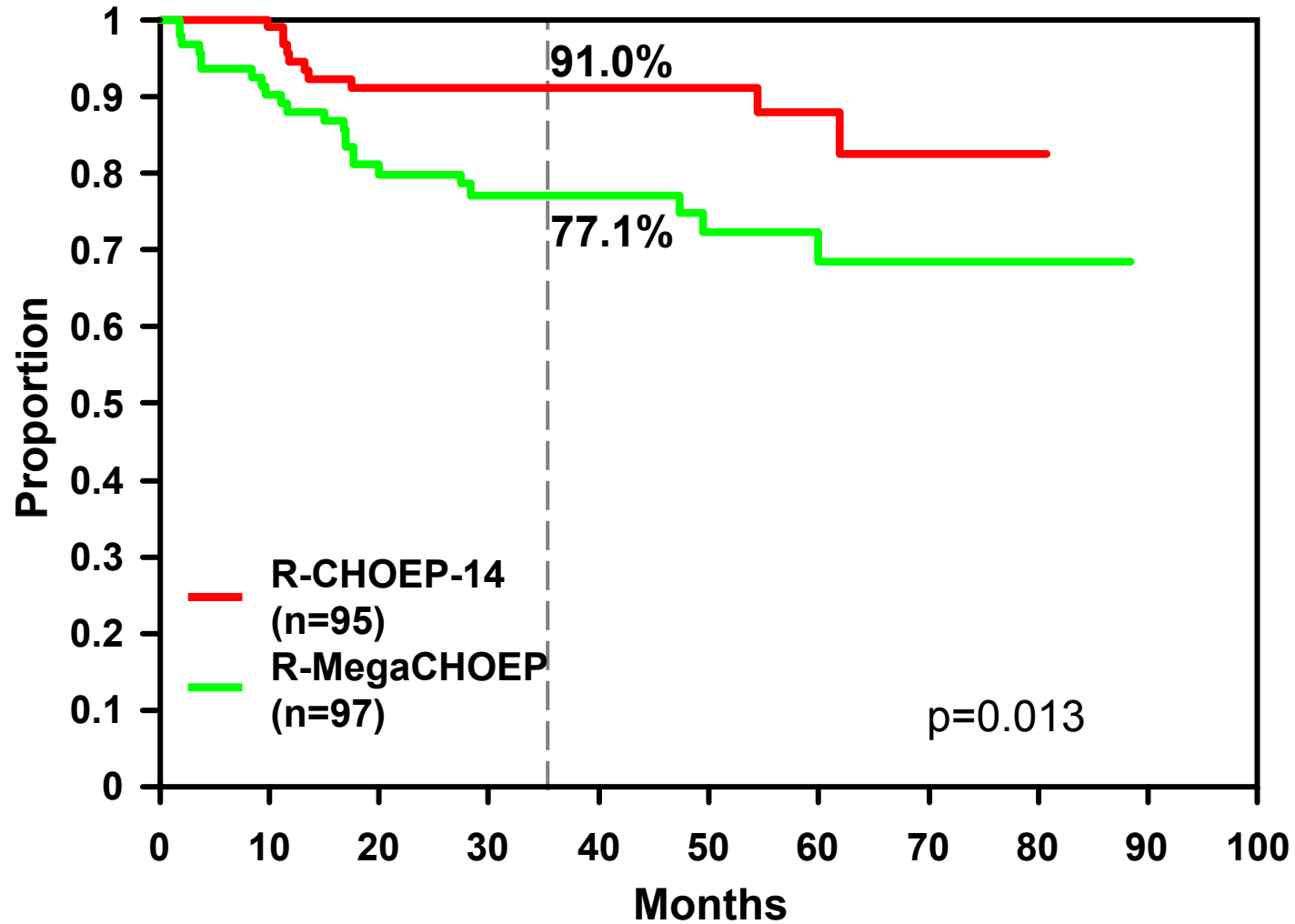
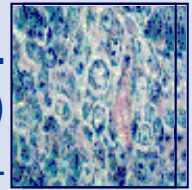


# R-MegaCHOEP Study

OS: PATIENTS WITH aaPI 2 ONLY!

GERMAN HIGH-GRADENHL  
STUDY GROUP (DSHNHL)

[www.lymphoma-euro.com/Groups/DSHNHL](http://www.lymphoma-euro.com/Groups/DSHNHL)

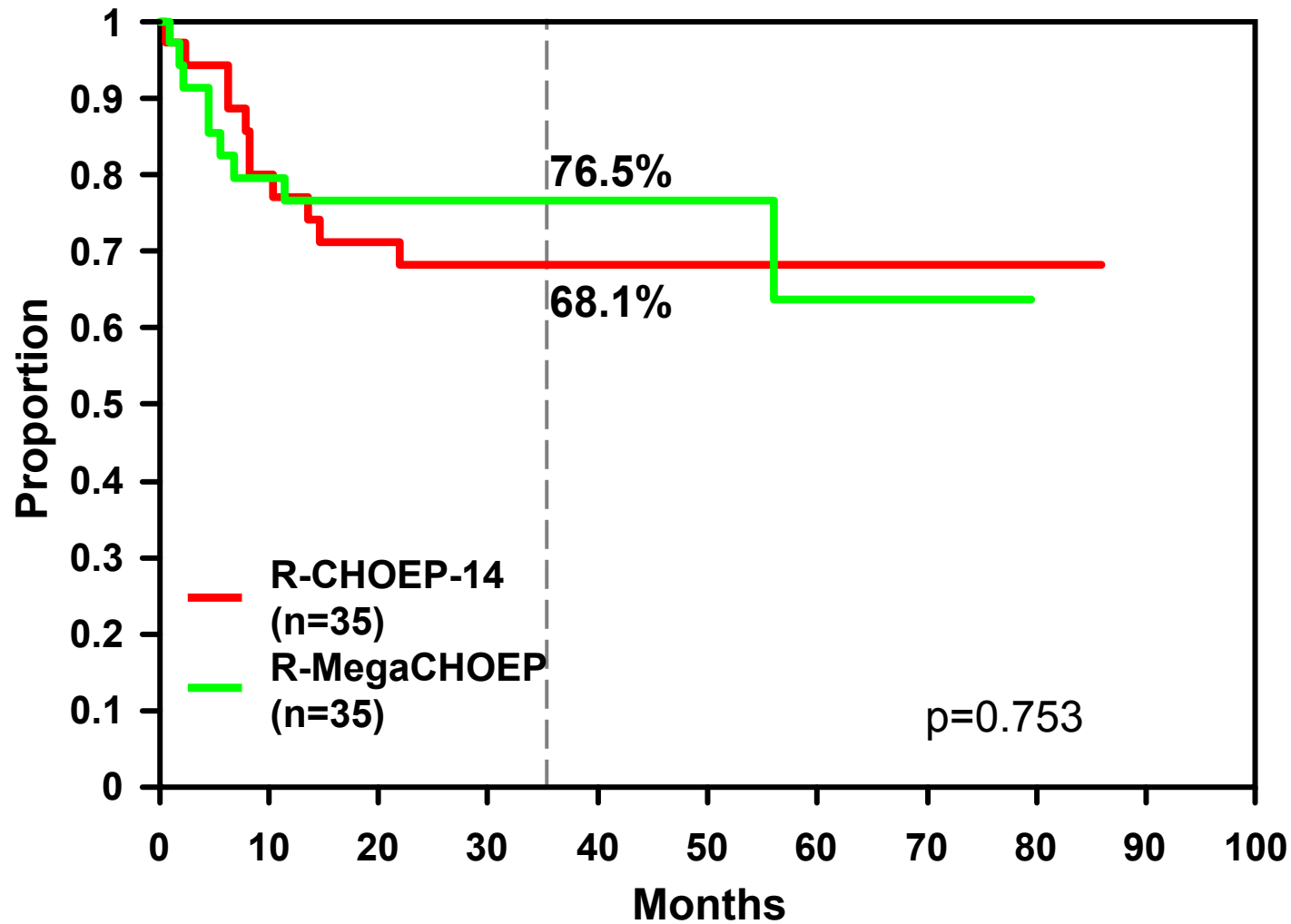
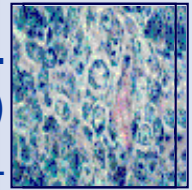


# R-MegaCHOEP Study

OS: PATIENTS WITH aaPI 3 ONLY!

GERMAN HIGH-GRADENHL  
STUDY GROUP (DSHNHL)

[www.lymphoma-europe.org/Groups/DSHNHL](http://www.lymphoma-europe.org/Groups/DSHNHL)



# DENSE-R-CHOEP-14



**CD20-pos.**

**B-NHL**

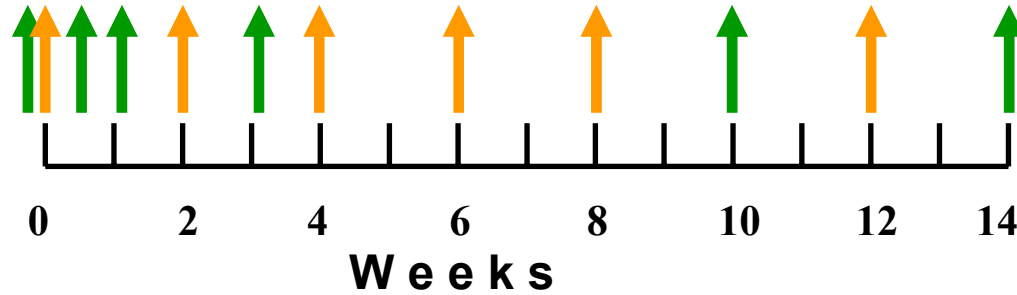
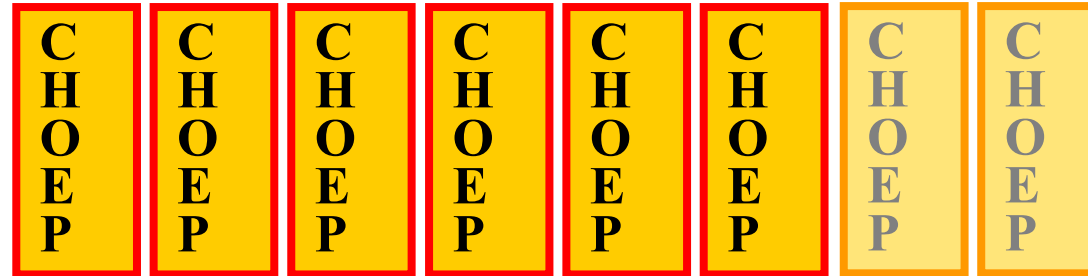
18-60 years

aaIPI 2-3:

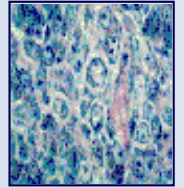
LDH > N

stage III / IV

ECOG 2 - 4



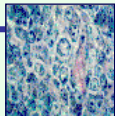
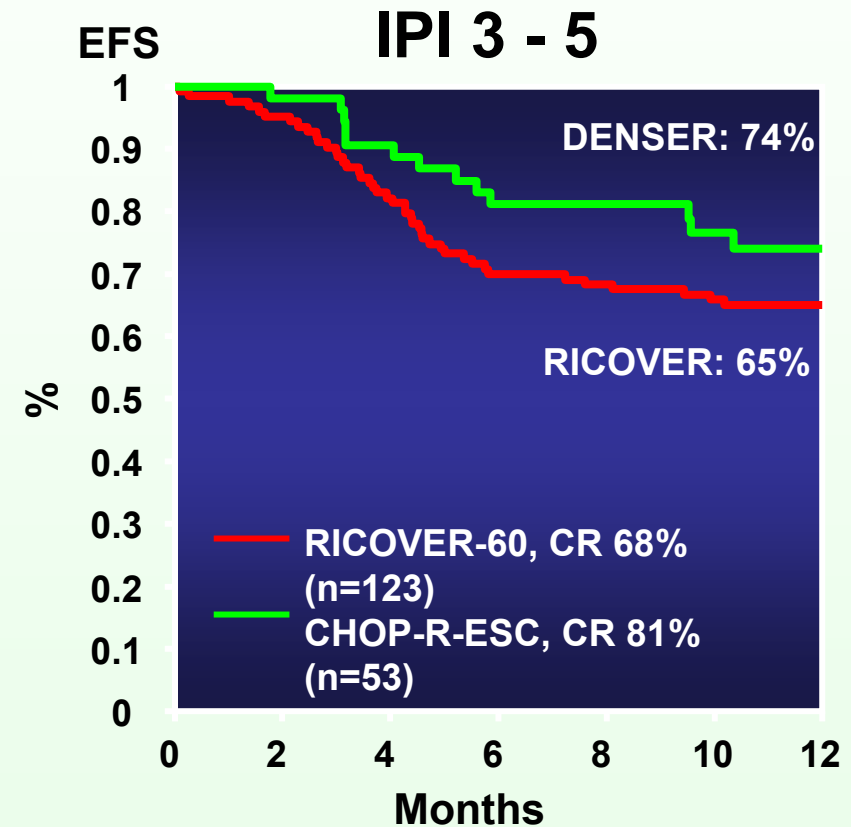
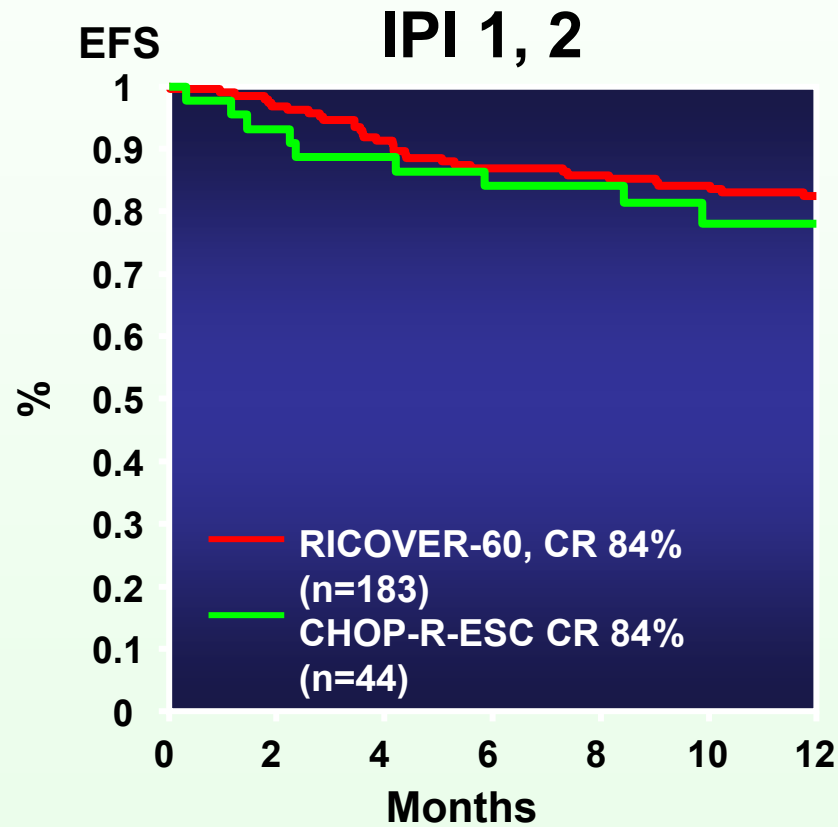
  Rituximab



- Prognose
  - „Risiko Alter“
  - CB vs IB – und?
- Jüngere Patienten
  - MINT Follow Up
  - FLYER & UNFOLDER Status
  - Mega CHOEP Auswertung
- **Ältere Patienten**
  - **Rituximab Modifikationen**
  - **OPTIMAL Studie**
  - **Non-fit Elderly: BRENDA Studie**

# Aggressive B-NHL

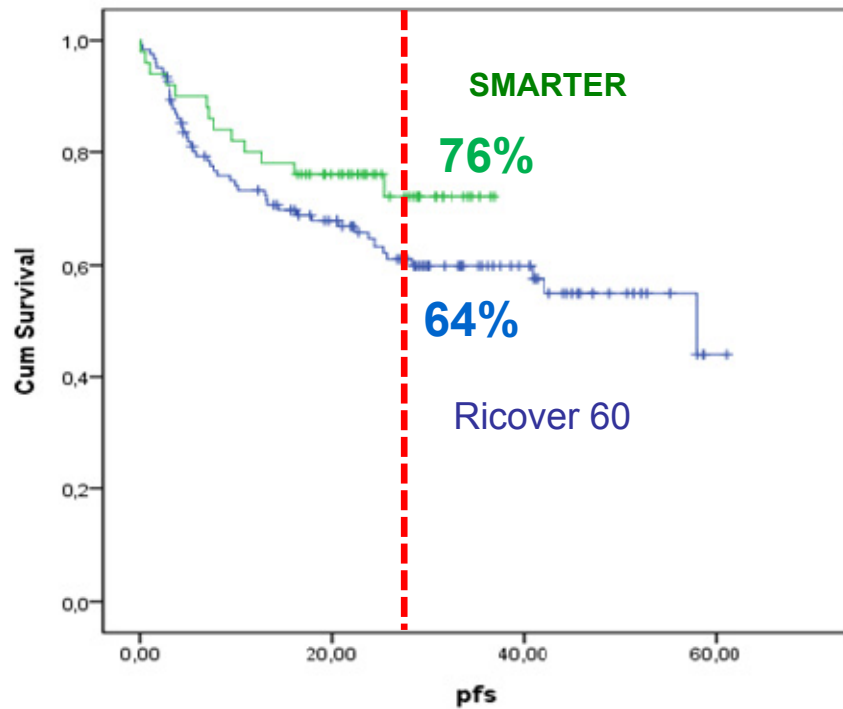
## DENSER-CHOP: Therapieoptimierung durch Intensivierung der Immuntherapie



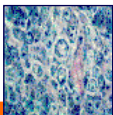
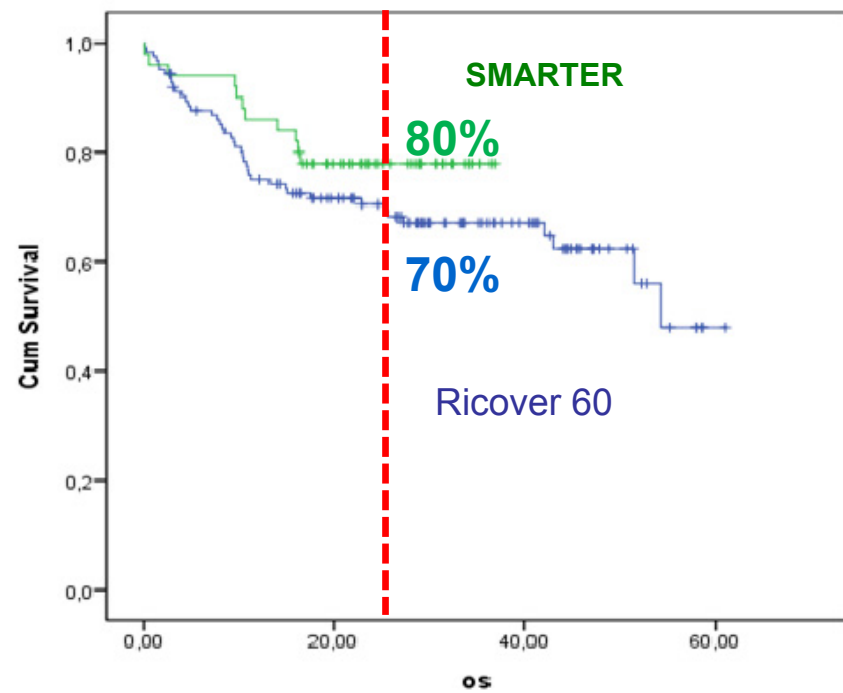
# Aggressive B-NHL SMARTER-CHOP: Ergebnisse Hochrisiko-Patienten IPI 3-5

Median Time of Observation: 28 Months

P F S



O S



DSHNHL Pfreundschuh et al, ASCO 2011, #8064, aktuelles Update

# RICOVER-60 Trial (n=1222)

## Multivariate Analysis PFS

### Without Rituximab

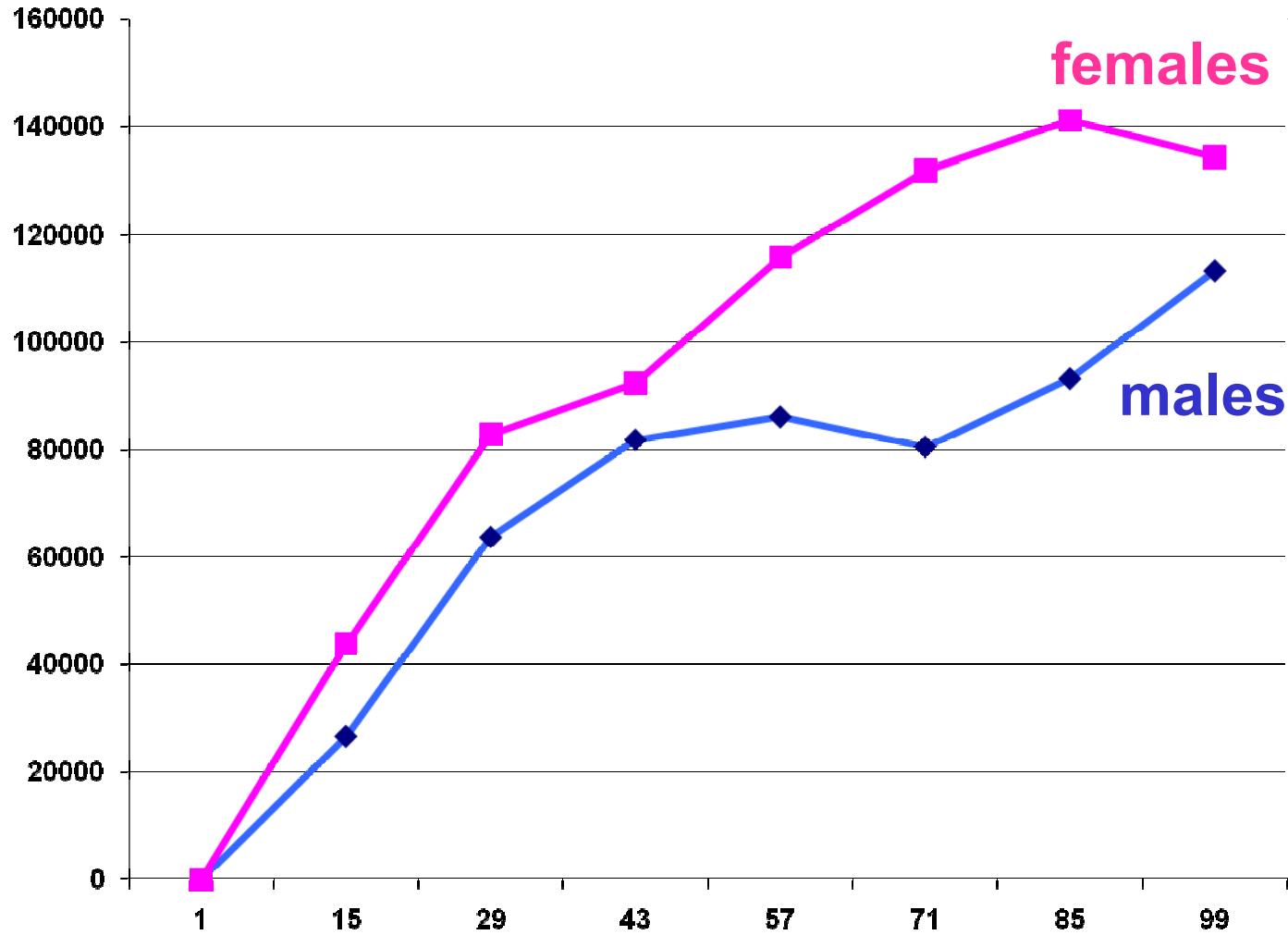
	RR	p
LDH	1.526	0.002
ECOG	1.672	0.001
Stage	1.957	<0.001
Ex>1	1.650	0.001
Male vs. Female	<b>1.127</b>	<b>0.348</b>

### 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	<b>1.592</b>	<b>0.004</b>

# RICOVER-60 Trial (n=1222)

## Rituximab Trough Serum Levels



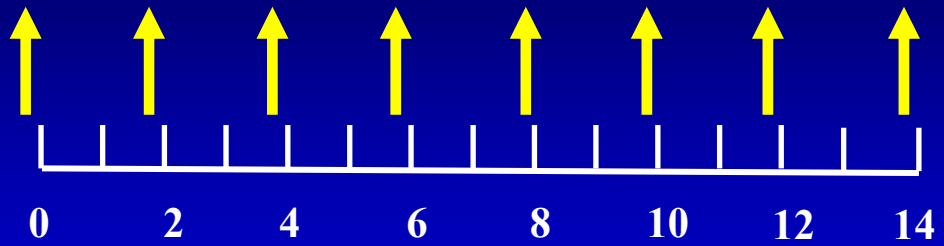
# DENSE-R-UP-CHOP-14

# Study Design

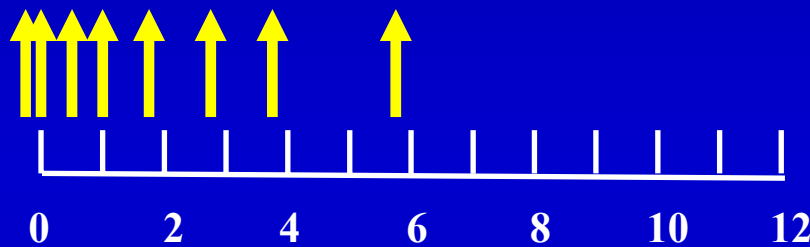
CD20<sup>+</sup> DLBCL  
Stages I-IV  
61 to 80 years



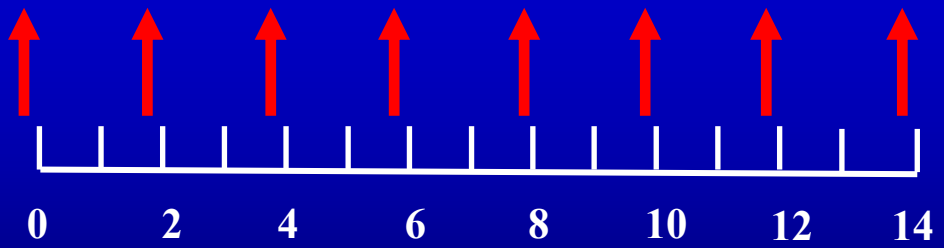
1



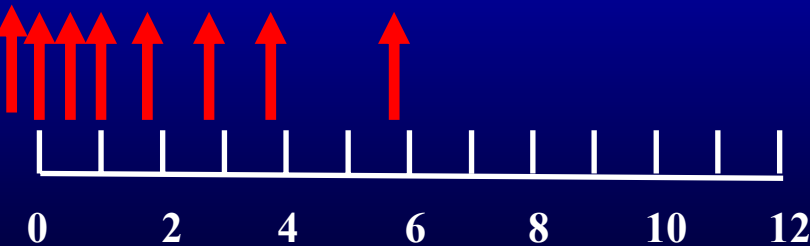
2



1



2

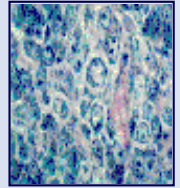


Rituximab 375 mg/m<sup>2</sup>

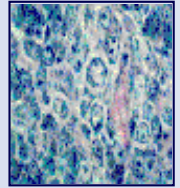


Rituximab 500 mg/m<sup>2</sup>

Weeks



- Standard : 6 Zyklen R-CHOP-14
  - (Ältere Low Risk: CHOP-21 oder 4 Zyklen – ungeprüft)
- Frühe, dichtere Gabe von Rituximab bei aggressiven NHL sinnvoll: Prüfung in Phase III
- Erhöhte Rate opportunistischer Infekte bei dosisdichtem R-CHOP:
  - *Infektprophylaxe* indiziert (i.e. G-CSF, Aciclovir, Cotrimoxazol, Gyrasehemmer)



## Studienziele - > 60 Jahre

- Verringerung der Toxizität (PNP!)
- Überprüfung der Dosisdichte Rituximab
- PET als NEGATIVER Prädiktor bei low risk
- Studie für „non-fit“ elderly

**DENSE-R-CHOP/CHLIP-14**  
**LESS FAVORABLE**

# Study Design

**CD20<sup>+</sup> DLBCL**  
**IPI 2-5**  
**IPI 1 Bulky**  
**61 to 80 years**

**Random**  
**2x2**  
**Factorial**  
**Design**

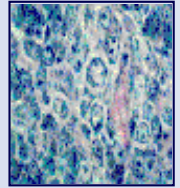
**R-CHOP-14**  
**+ 36 Gy BULK-IN-RT\***

**DENSE-R-CHOP-14**  
**+36 Gy BULK-INRT\***

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

**DENSE-R-CHLIP-14**  
**+ 36 Gy BULK-IN-RT\***

**\* Except Interim-PET-neg.**



- Phase II (PFS)
- 100 Patienten
- Geriatisches assessment
- Iniziiierung 2011
- Rituximab/Benda werden gestellt
- CRO Iomedico

Diagnose: **DLBCL**

Alter: > 81 Jahre alle Patienten

61-80 Jahre „nicht CHOP fähig“

### Vorphase

d-7 to -d-1 Prednisolon 100mg

d -3 i.v. Rituximab 375 mg/m<sup>2</sup>

### Therapiephase

6 x R-Benda

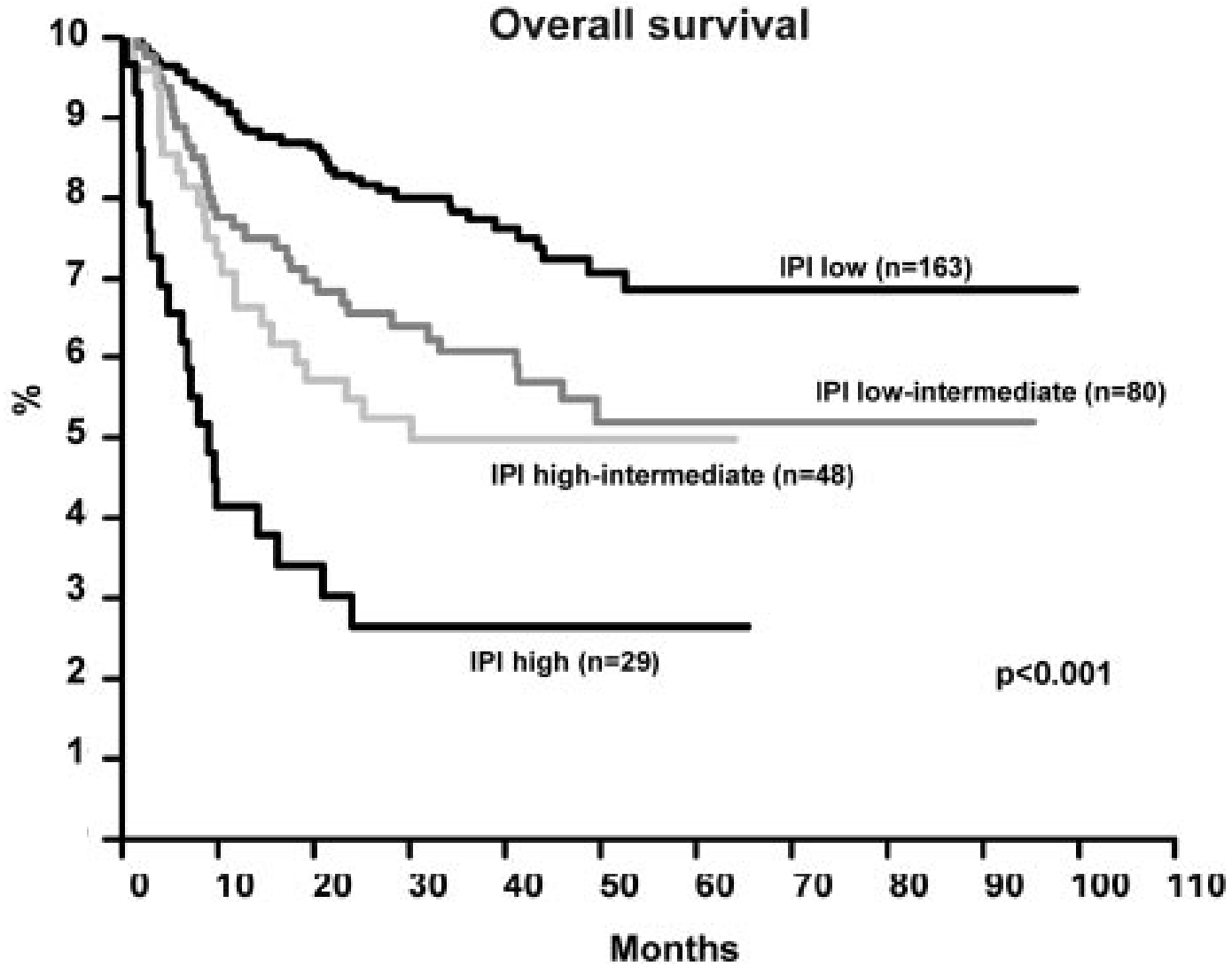
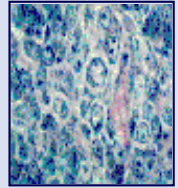
d 1 s.c. Rituximab 1400 mg

d 1-2 Bendamustin 90mg/m<sup>2</sup>

Wiederholung Tag 22

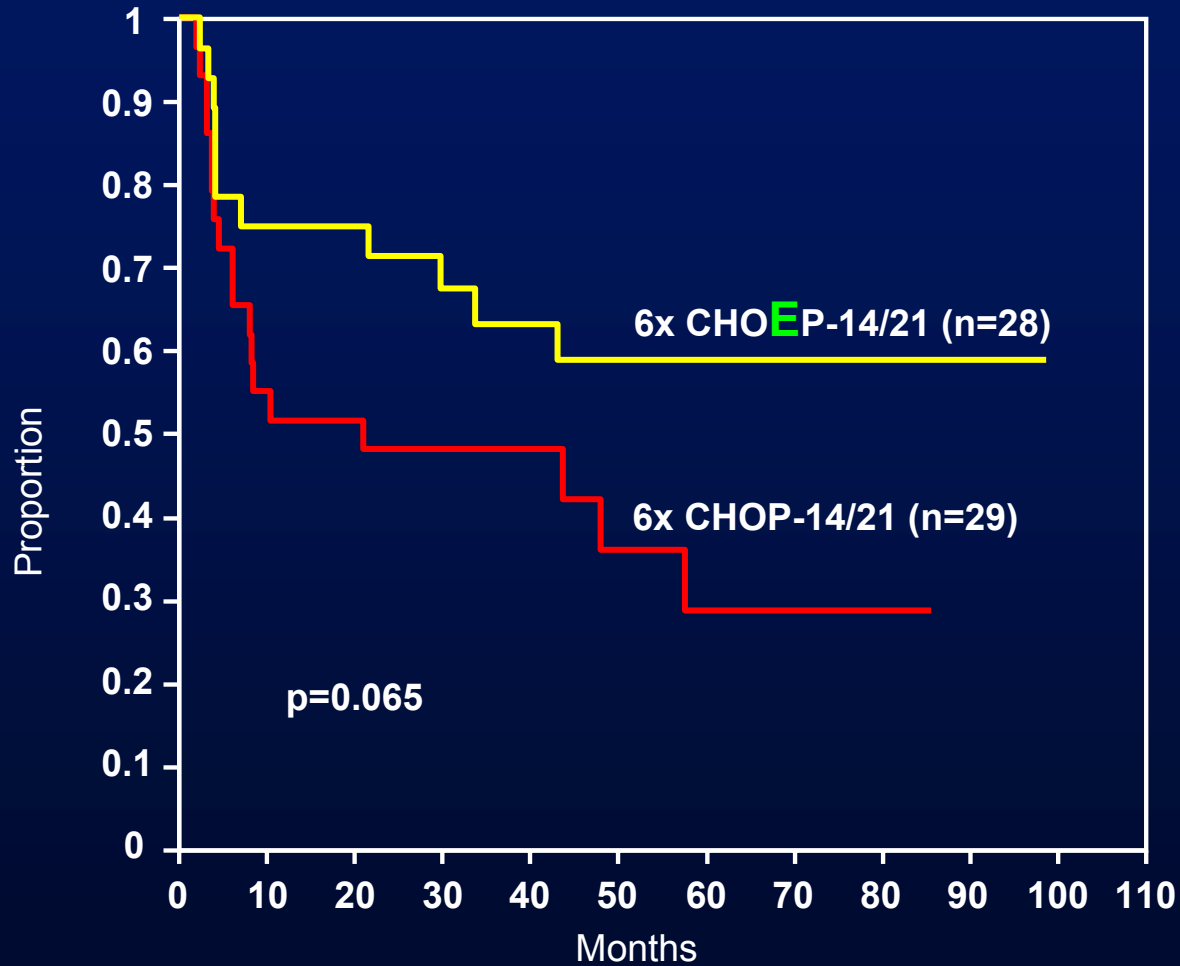


- Prognose
  - CB vs IB – und? ; „Risiko Alter“
- Jüngere Patienten
  - MINT Follow Up, Mega CHOEP Auswertung
  - FLYER & UNFOLDER Status
- Ältere Patienten
  - Rituximab Modifikationen
  - OPTIMAL Studie
  - Non-fit Elderly: BRENDA Studie
- **Periphere T Zell Lymphome**



# T-cell lymphomas in DSHNHL trials

ALK-negative ALCL and other T-cell lymphomas  
NHL-B1 trial ( $\leq 60$  years, LDH  $\leq N$ , n=57), EFS: role of etoposide



Schmitz, Trümper et al., Blood

3 years EFS rate:

with Etoposide:

63.2% (95% CI: 45.0%-81.4%)

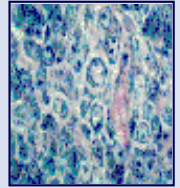
without Etoposide:

48.3% (95% CI: 30.1%-66.5%)

# Spezifische Subgruppen

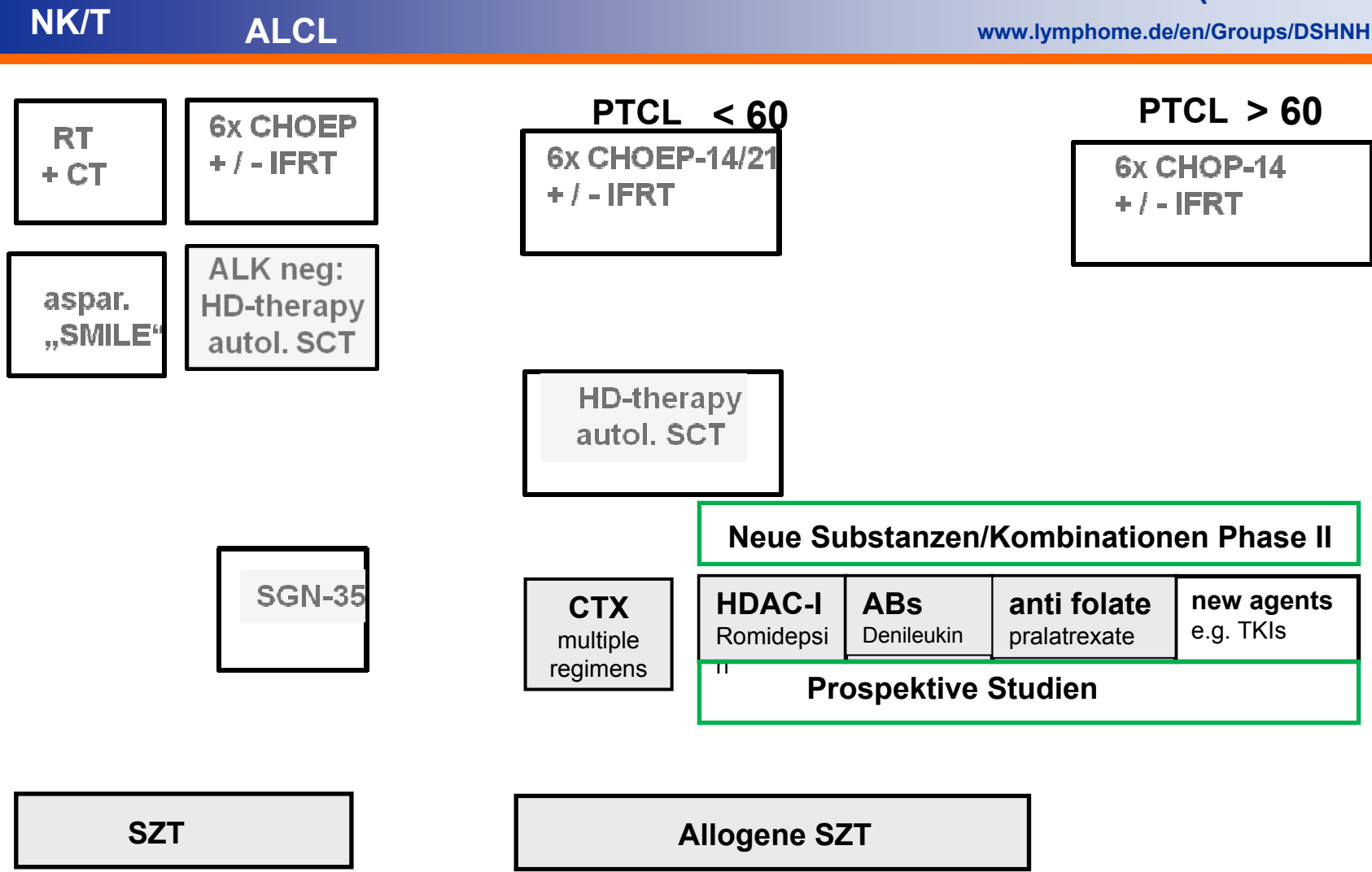
## GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

[www.lymphome.de/en/Groups/DSHNHL](http://www.lymphome.de/en/Groups/DSHNHL)



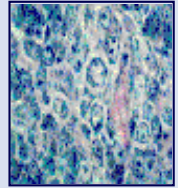
Primär  
Behandlung

Rezidiv  
Behandlung



# Spezifische Subgruppen

# GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)



www.lymphome.de/en/Groups/DSHNHL

NK/T

ALCL

Primär  
Behandlung

Rezidiv  
Behandlung

RT  
+ CT

6x CHOEP  
+ / - IFRT

PTCL < 60  
6x CHOEP-14/21  
+ / - IFRT

PTCL > 60  
6x CHOP-14  
+ / - IFRT

aspar.  
„SMILE“

ALK neg:  
HD-therapy  
autol. SCT

**AATT Studie  
Auto vs Allo**

**ACT-2 Studie  
Alemtuzumab**

HD-therapy  
autol. SCT

SGN-35

Neue Substanzen/Kombinationen Phase II

CTX  
multiple  
regimens

HDAC-I Romidepsi	ABs Denileukin	anti folate pralatrexate	new agents e.g. TKIs
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Prospektive Studien

SZT

Allogene SZT