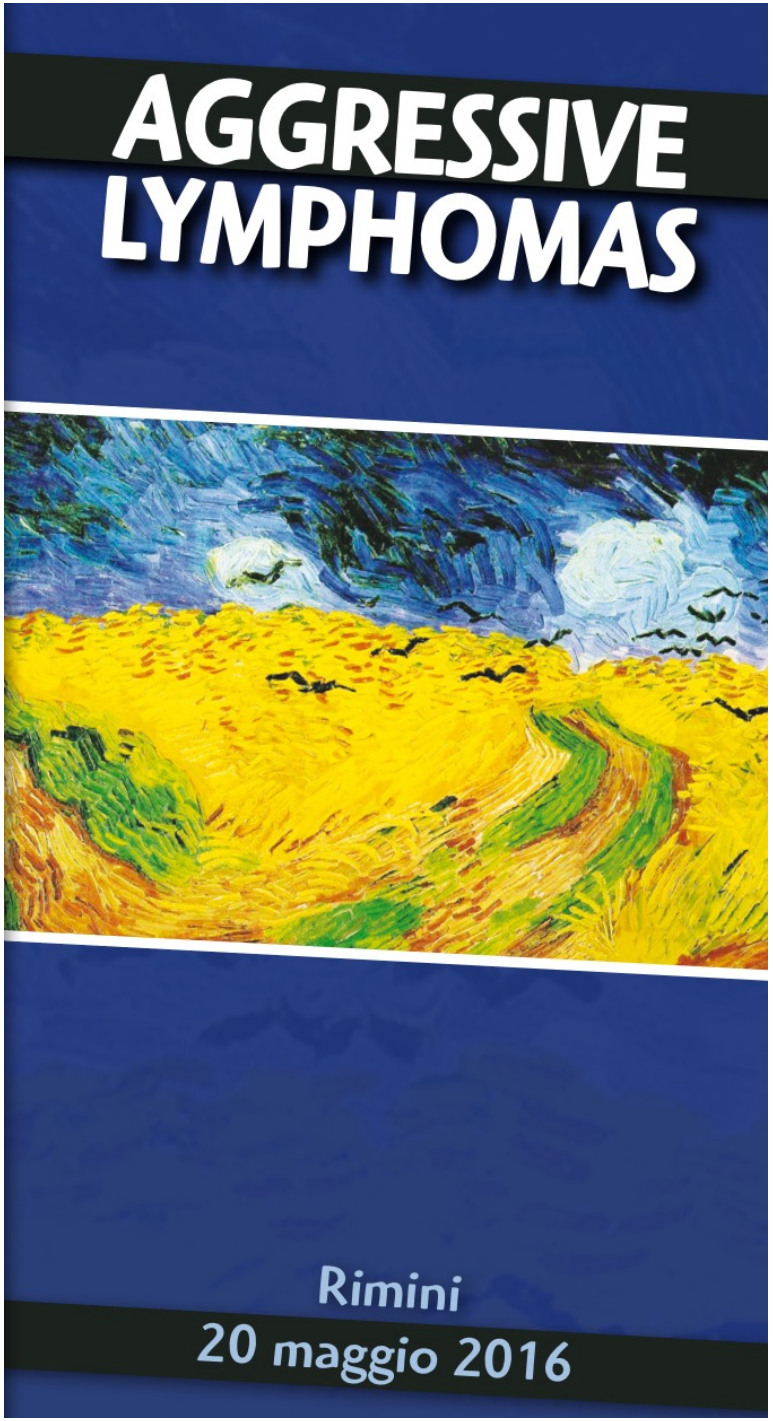
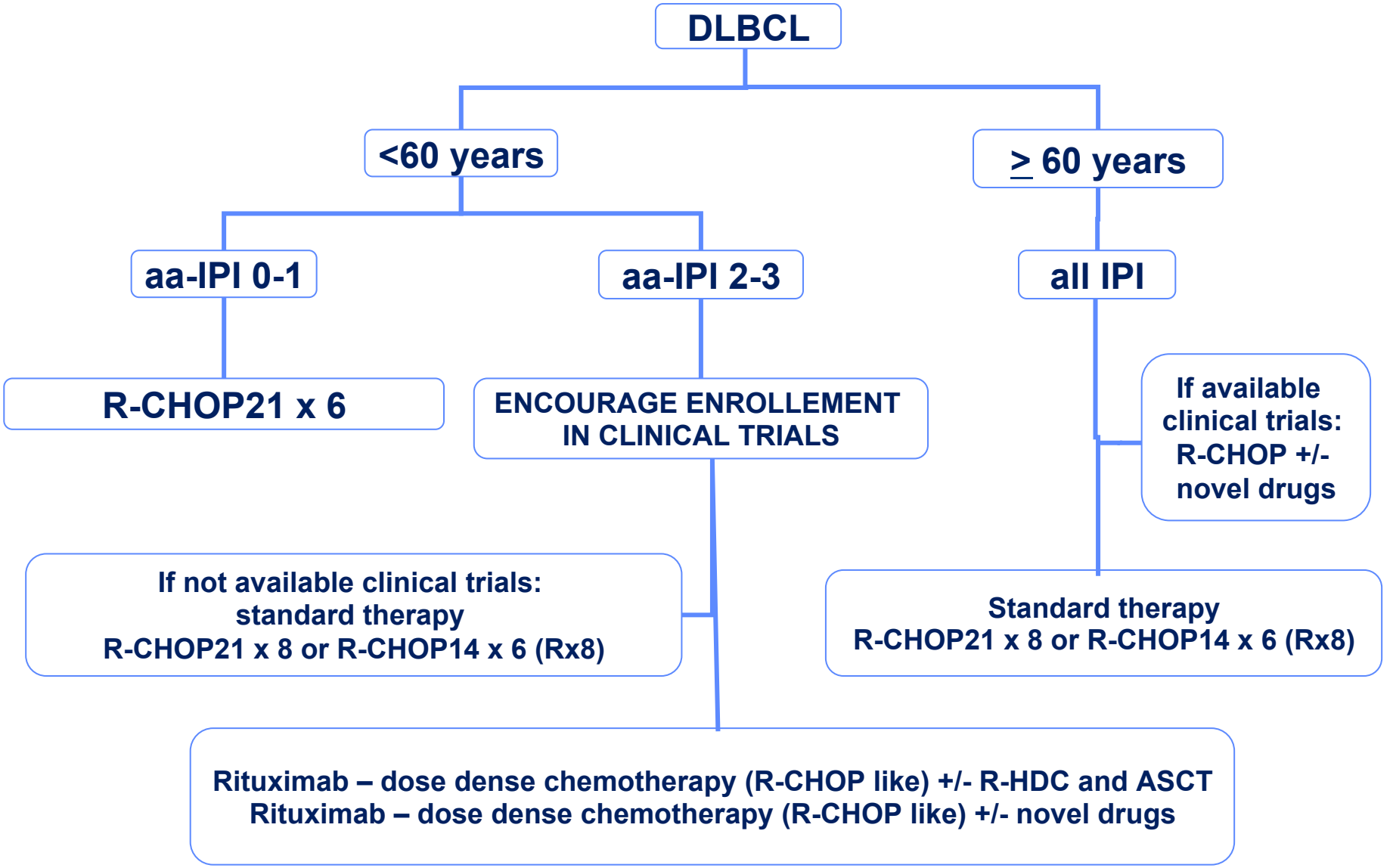


SESSION 1

DLBCL young patients: therapy for limited stages and IPI<2

Luigi Rigacci
AOU Careggi Firenze

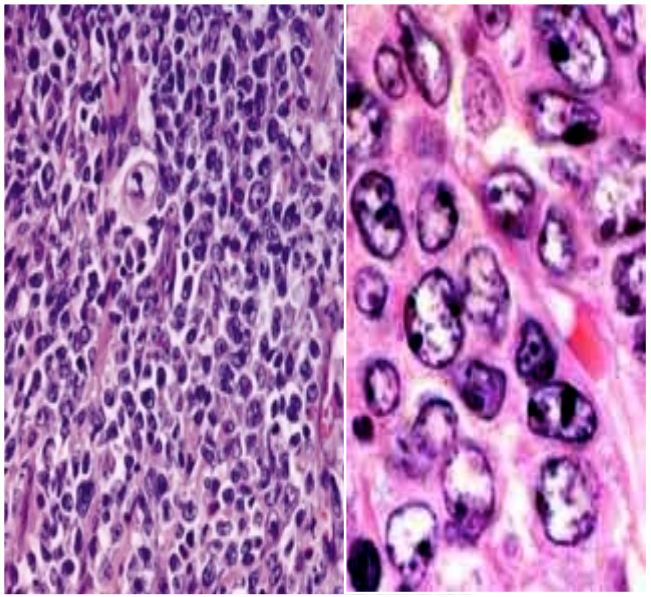
Management of DLBCL: first line treatment



Italian Society of Hematology Recommendations

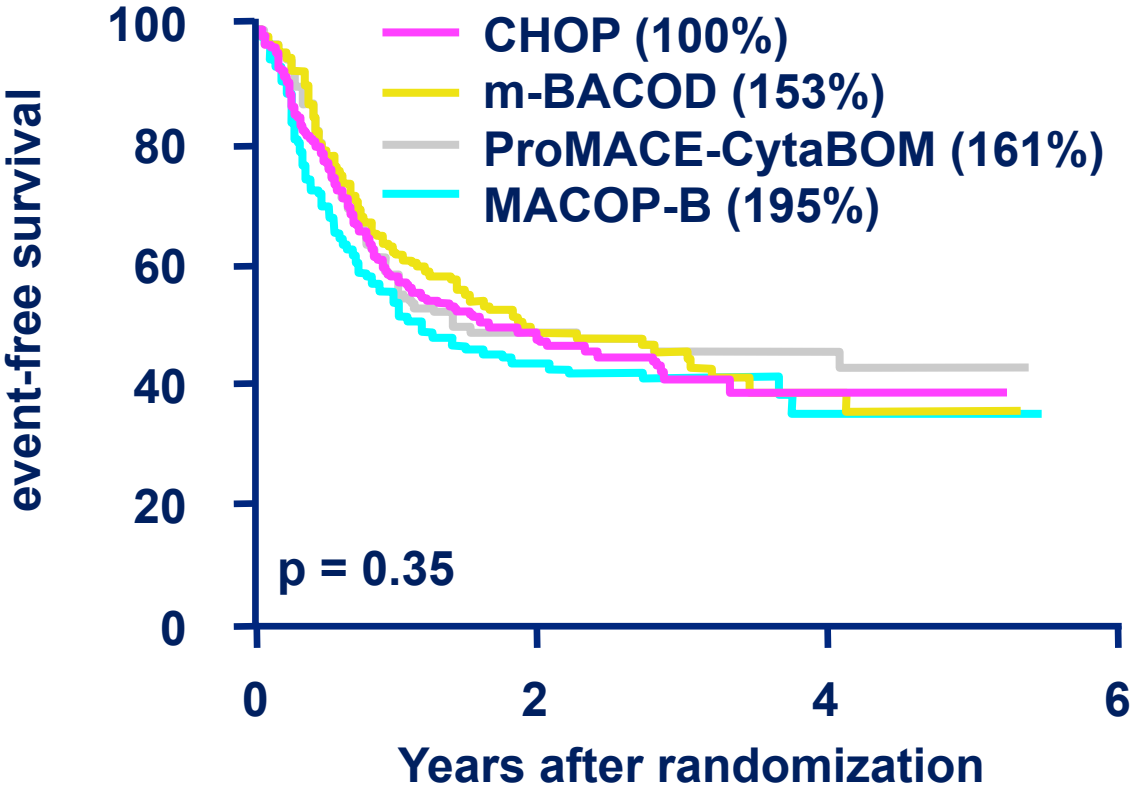
Diffuse Large B-Cell Lymphoma

- Most common NHL: 31%
  - Peak incidence in 6th decade
- Clinical outcomes and molecular features highly heterogeneous
- Large cells with loss of follicular architecture
  - 30% to 40% present with rapidly enlarging, symptomatic mass with B symptoms
  - May present as extranodal disease (stomach, CNS, testis, skin)
- Curable in 50% or more of cases
- Median survival: wks to mos if not treated



Michallet AS, et al. Blood Rev. 2009;23:11-23.

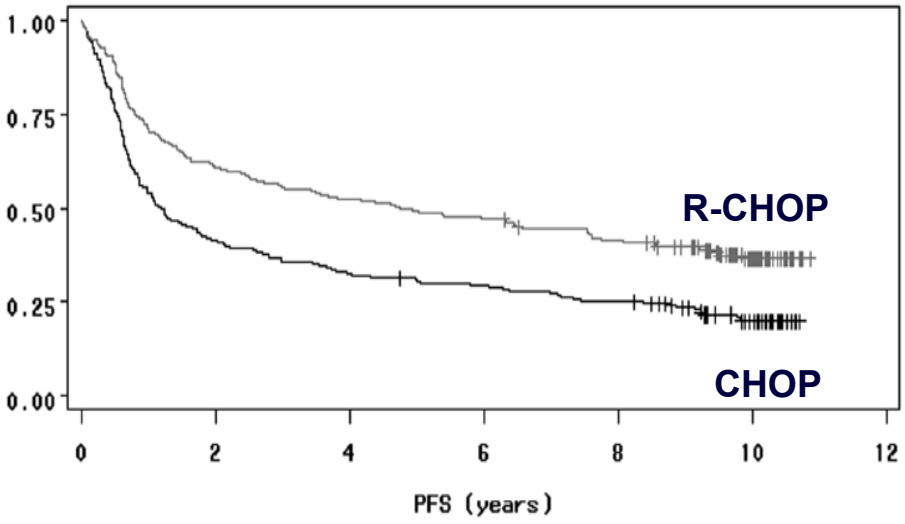
CHOP vs. Intensified Regimens

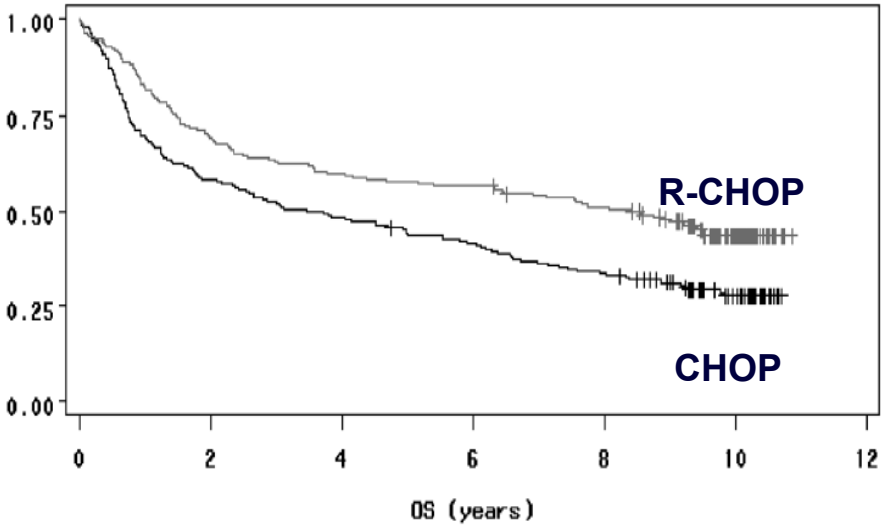


Fisher RI, NEJM 1993

R-CHOP is the standard of care in DLBCL

CHOP ± rituximab in DLBCL: 10-yr survival results (GELA LNH-98.5 study)



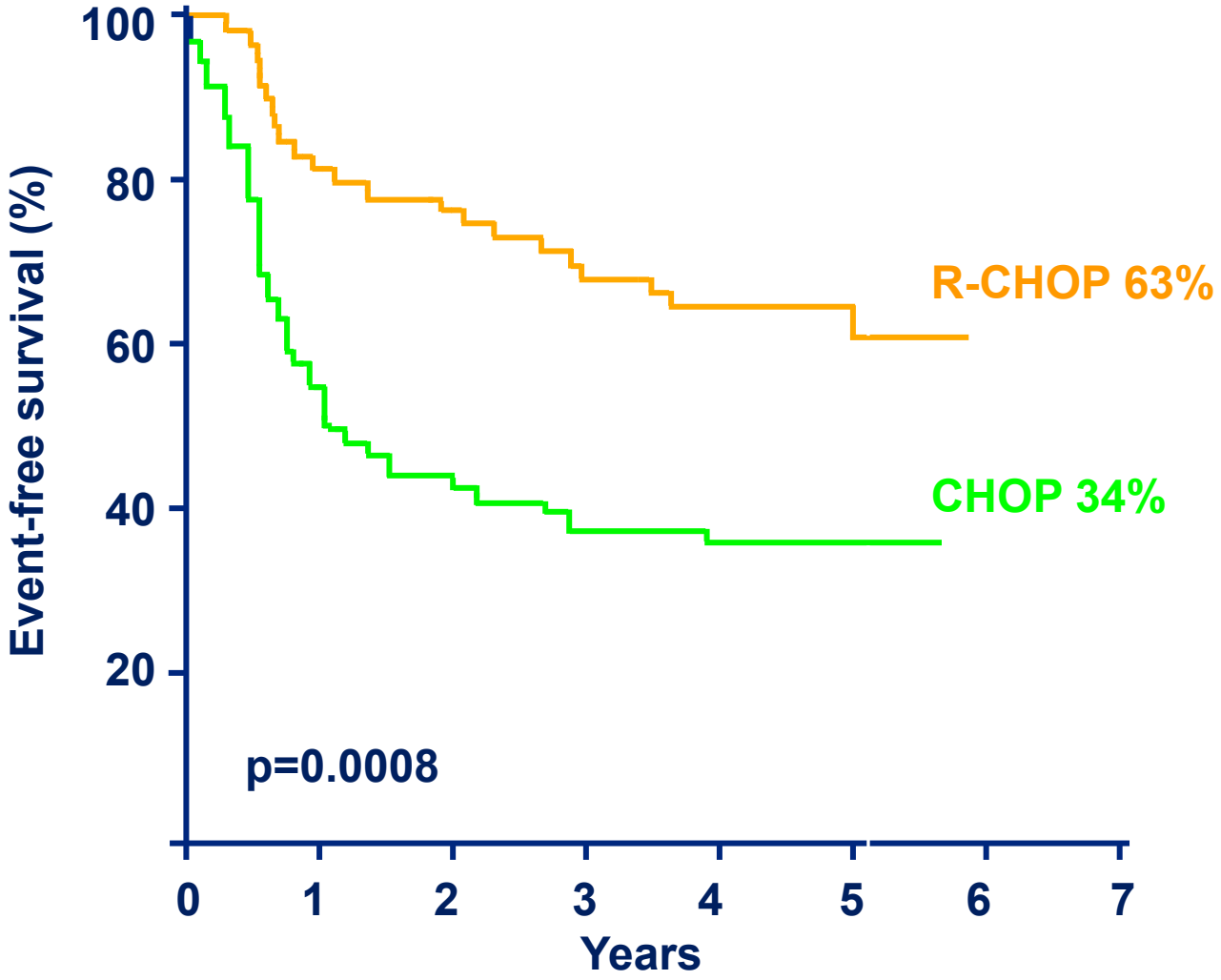


PFS: CHOP 20.0%
R-CHOP 36.5%

OS : CHOP 28%
R-CHOP 43.5%

Coiffier B et al., Blood. 2010;116(12):2040-2045

GELA-LNH 98.5: 5-year EFS in low-aaIPI patients (aaIPI 0/1)



Feugier P, et al. J Clin Oncol 2005;23:4117–26

DLBCL

Prognostic factors

- Clinical and biological factors

Treatment

- Young low risk (very favourable, less favourable)
- Role of radiotherapy
- Role of PET

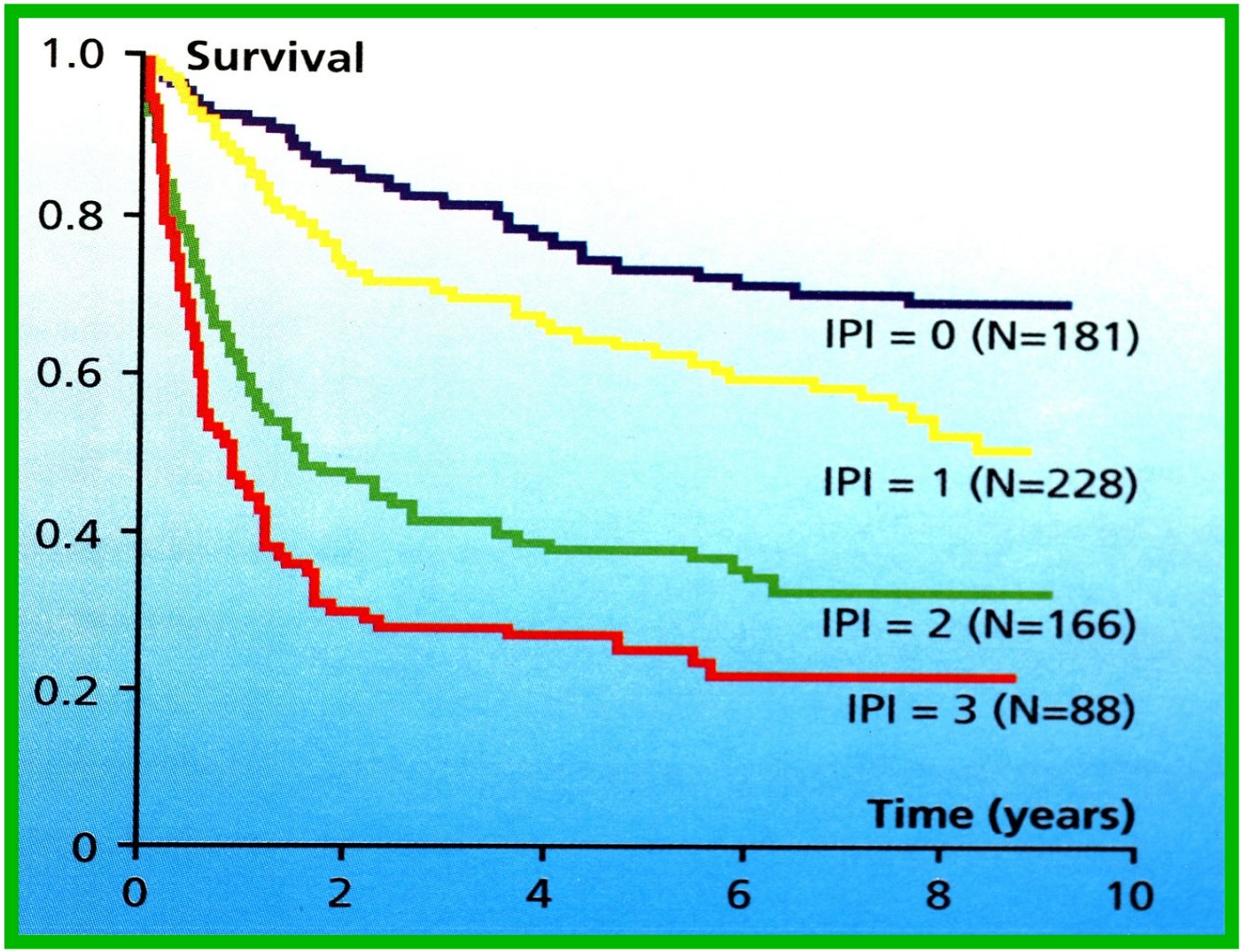
IPI in the Rituximab Era ?

Risk Group	Risk Factors, n	CR, %	5-Yr OS, %
Patients (all ages)			
▪ Low	0-1	87	73
▪ Low intermediate	2	67	51
▪ High intermediate	3	55	43
▪ High	4-5	44	26
Patients 60 yrs of age or younger			
▪ Low	0	92	83
▪ Low intermediate	1	78	69
▪ High intermediate	2	57	46
▪ High	3	46	32

International NHL Prognosis Factors Project. N Engl J Med. 1993;329:987-994.

Aggressive Non-Hodgkin Lymphomas:

Survival of IPI Risk Groups



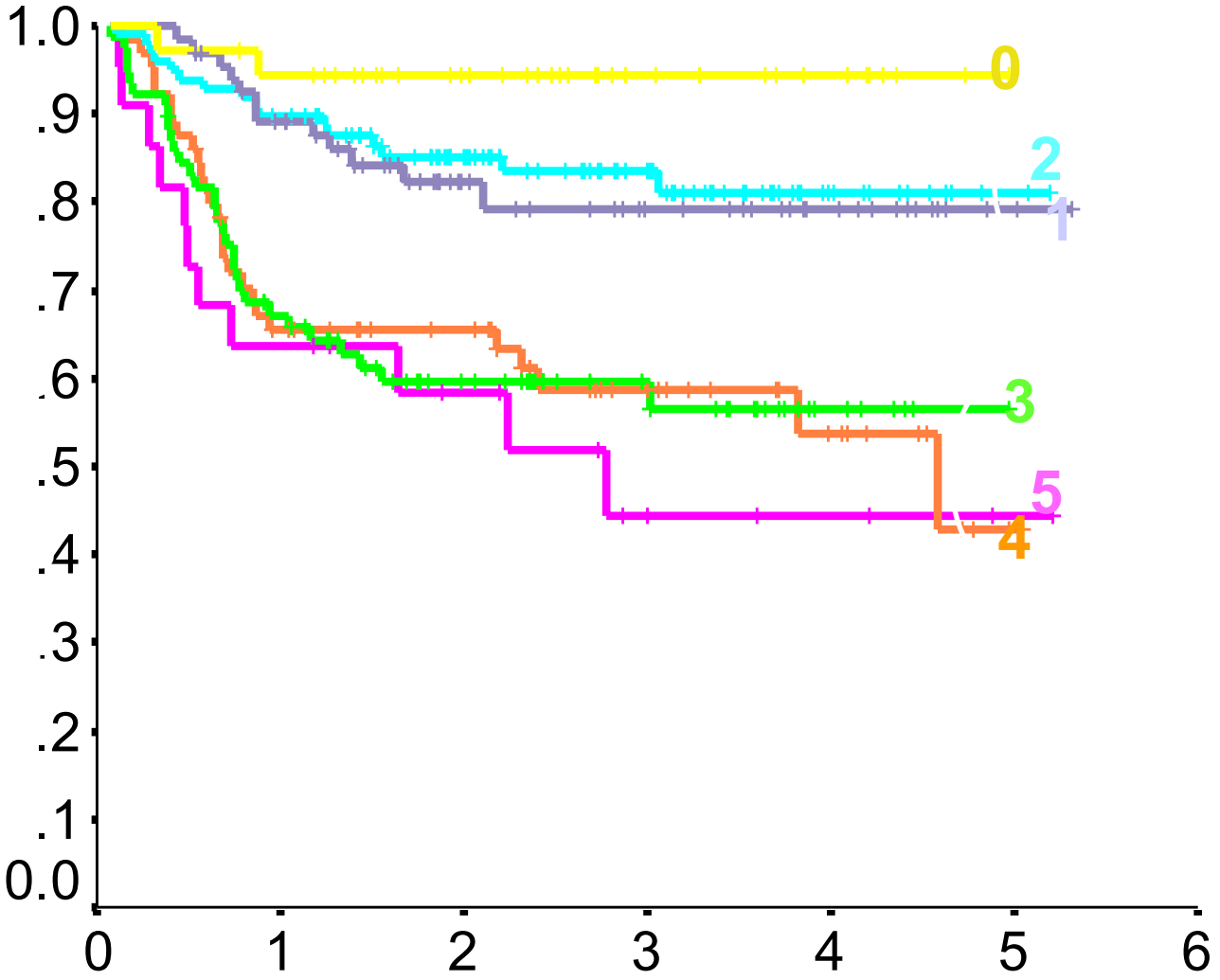
Revised International Prognostic Factors (R-IPI) vs Standard IPI

Group	Factors	5y PFS	5y-OS
IPI (Shipp 1993)			
Low	0-1	70%	73%
Low-int	2	50%	51%
High-int	3	49%	43%
High	4-5	40%	26%

R-IPI (Sehn 2006)	Factors	4y-PFS	4y-OS
Very-good	0	94%	94%
Good	1-2	80%	79%
Poor	3-5	53%	55%

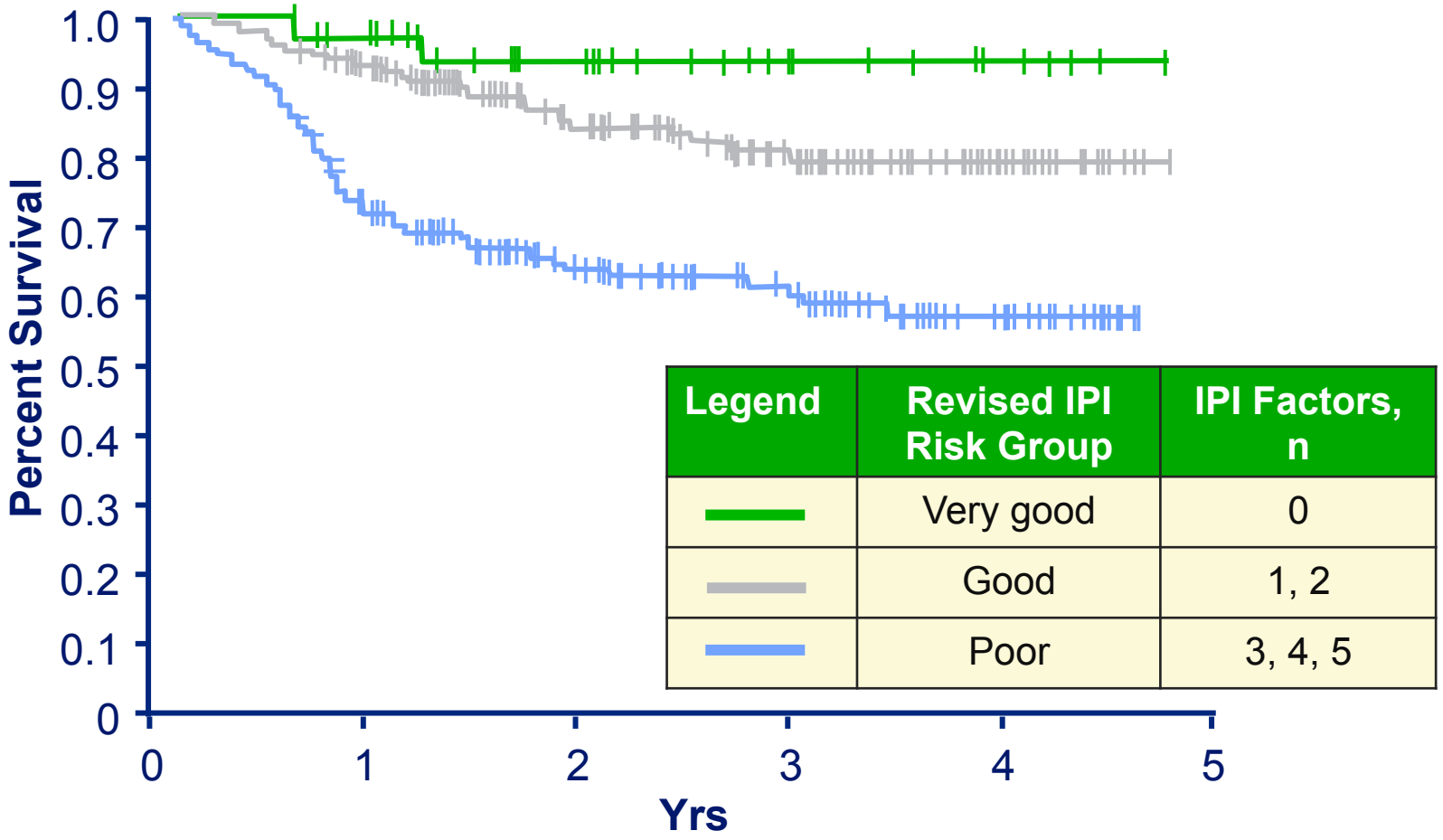
Sehn et al JCO 2007

Progression-Free Survival of 365 Patients According to Number of IPI Factors



Sehn et al, Blood, 2007

OS According to Revised IPI



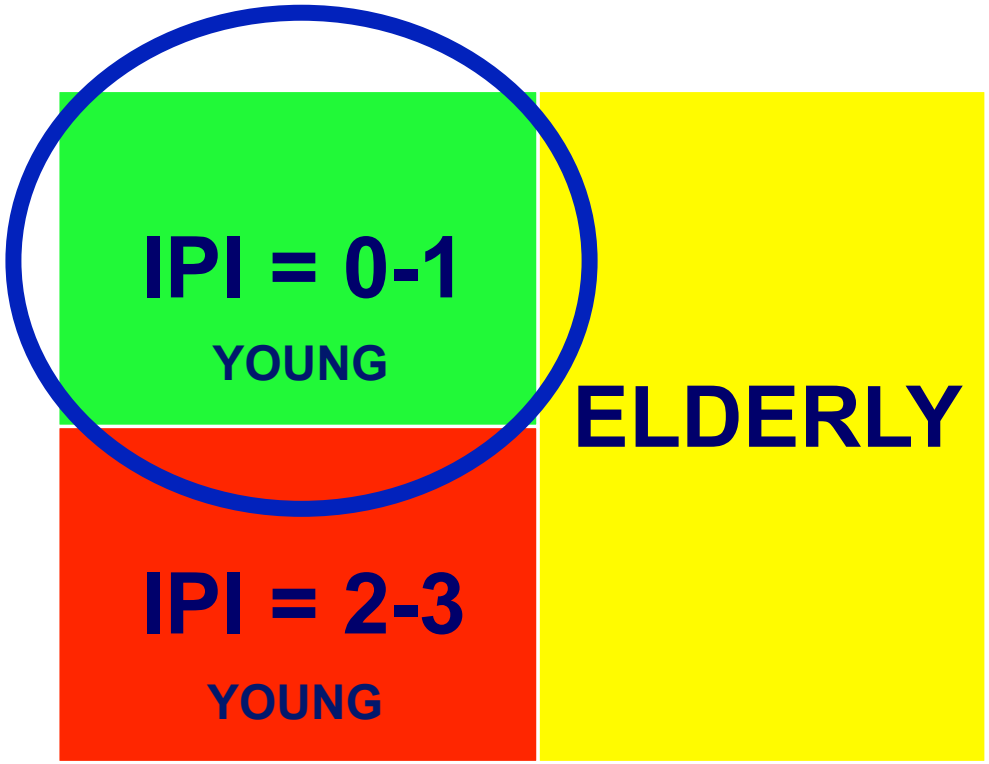
Sehn LH, et al. Blood. 2007;109:1857-1861.

Risk Factors in the Rituximab Era

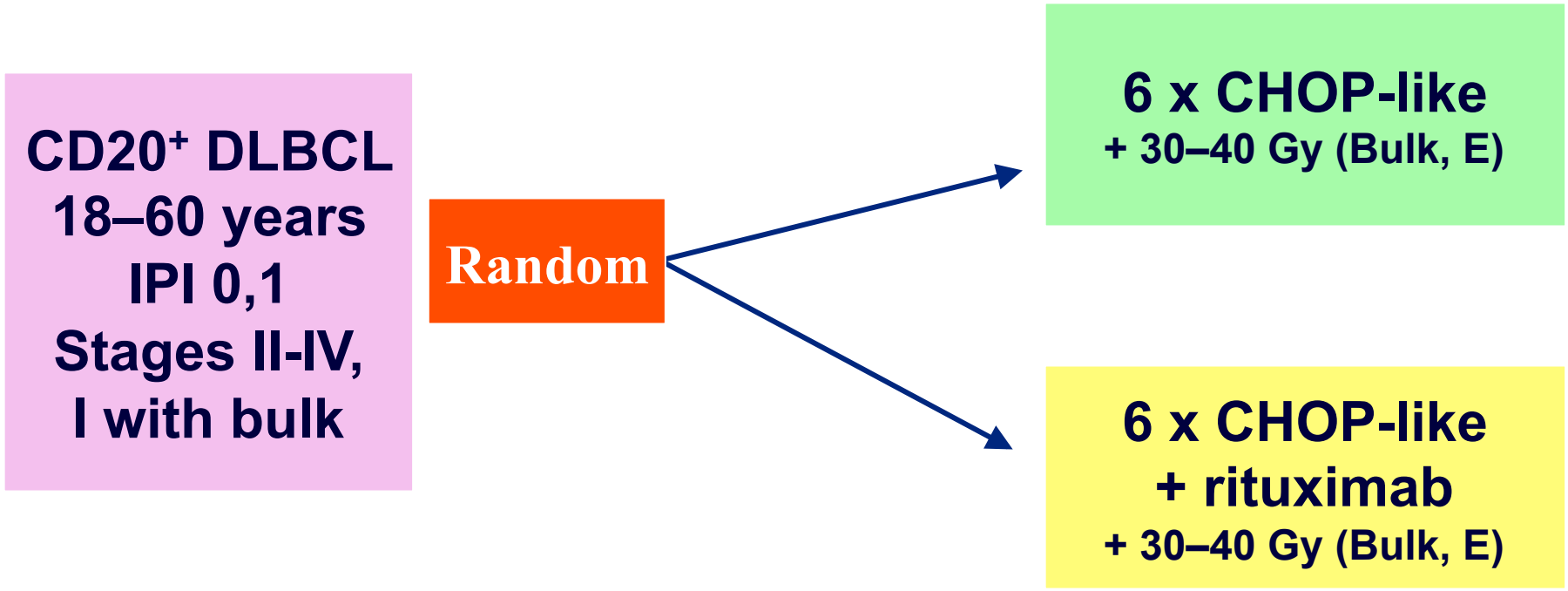
Conclusion:

- **The „R-IPI“ (365 pts.) does not hold scrutiny**
- **The IPI (4500 pts.) is alive and valid in the rituximab era (1068 pts.)**

Risk-adapted Approaches



MInT Trial Design

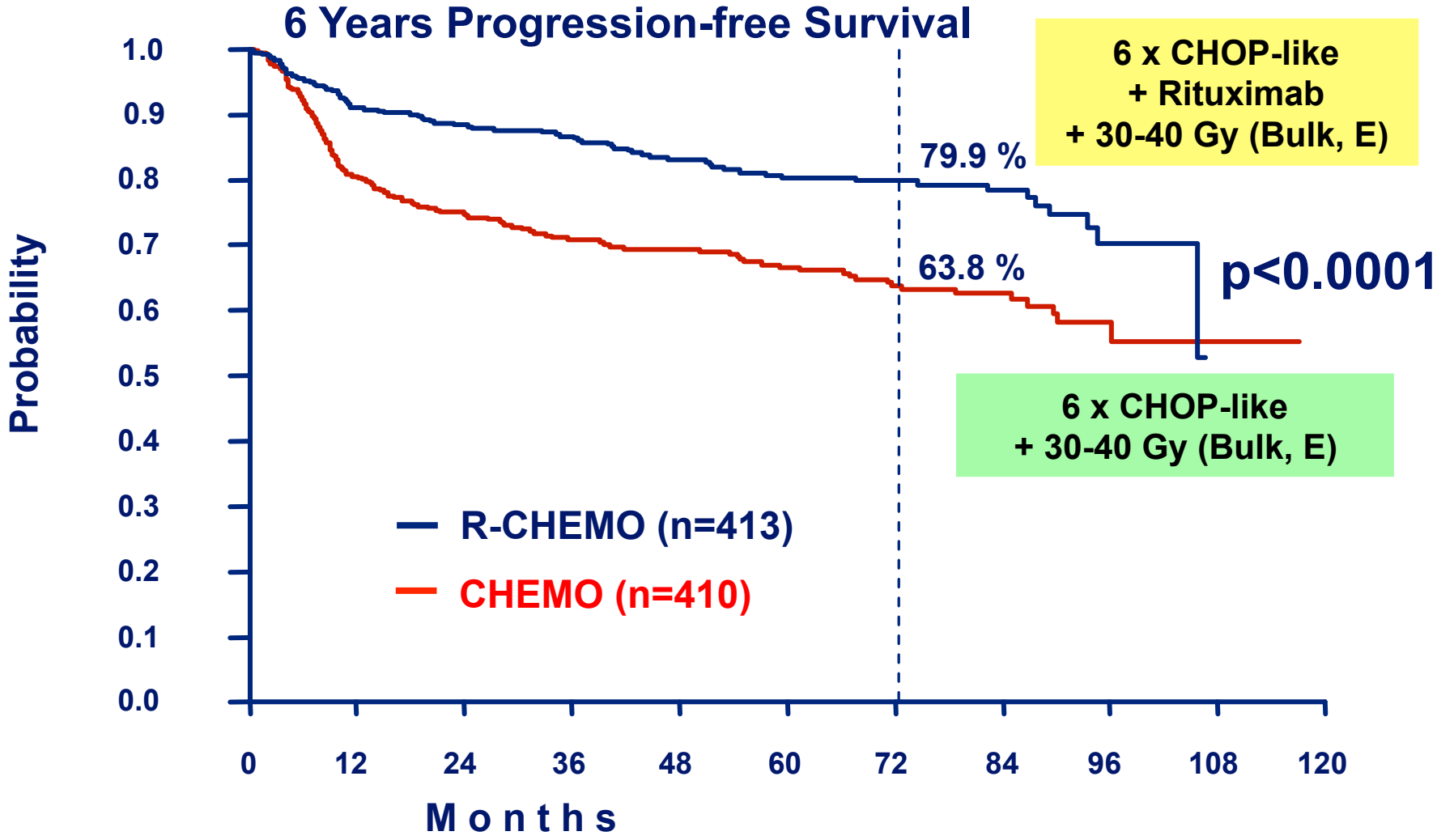


MInT Chemotherapy

	Chemo (n=410)	R-Chemo (n=413)
CHOEP-21	44%	44%
CHOP-21	48%	48%
MACOP-B	4%	4%
PMitCEBO	4%	4%

MInT

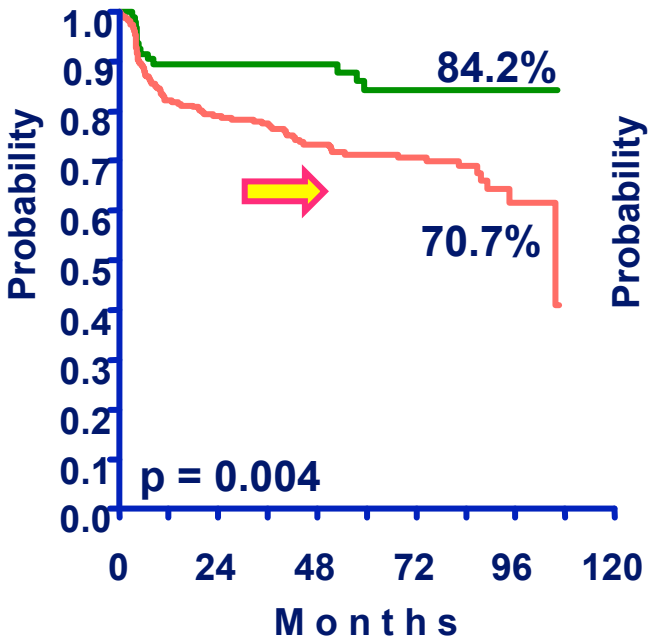
6-YEAR FOLLOW-UP OF THE MInT STUDY OF THE MABTHERA INTERNATIONAL TRIAL (MInT) GROUP in Young Good-Prognosis Patients with Aggressive Lymphomas.



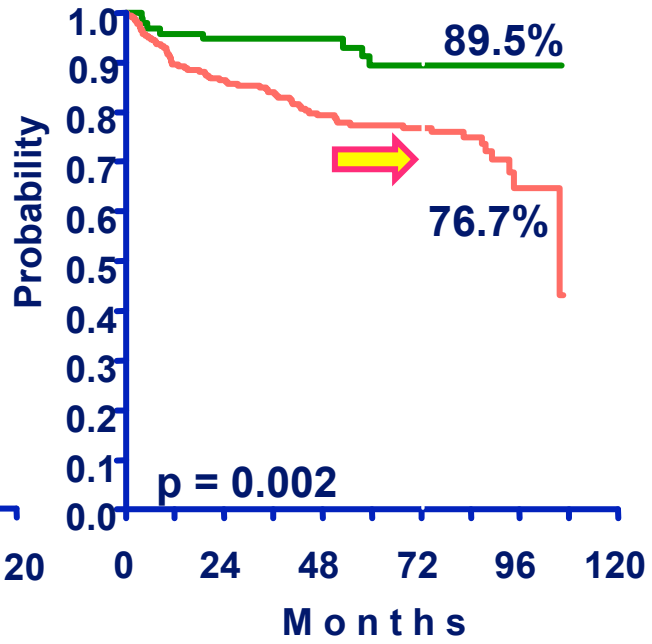
Prognostic Groups in the Rituximab Era: Favourable vs. Unfavourable

MInT

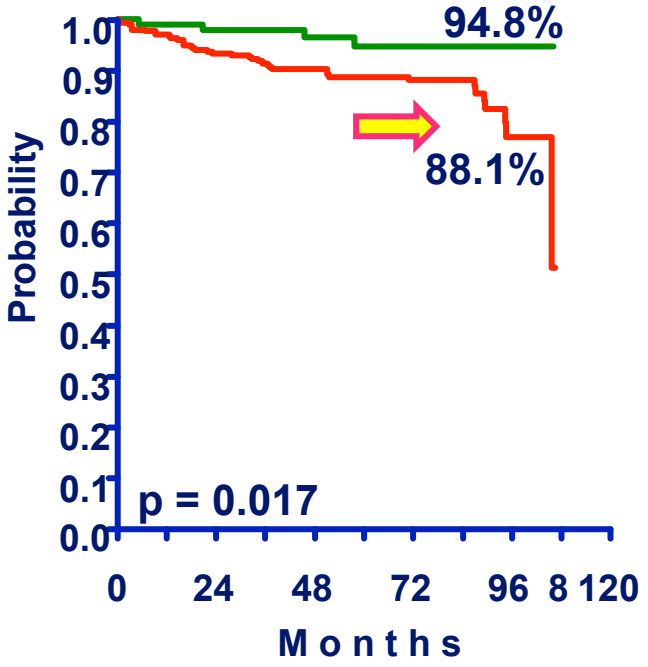
EFS



PFS



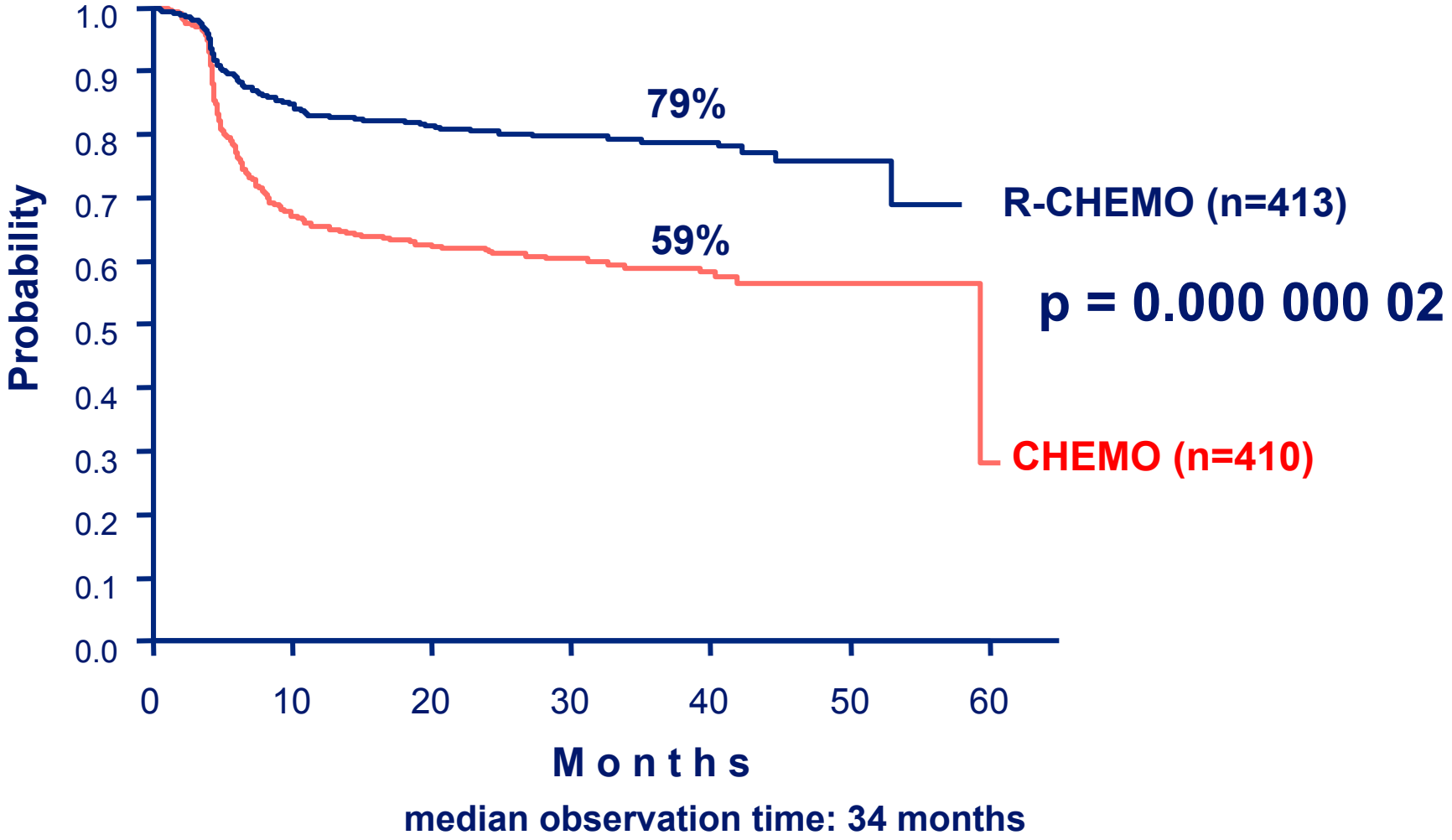
OS



Favourable: IPI=0 / ∅ bulk

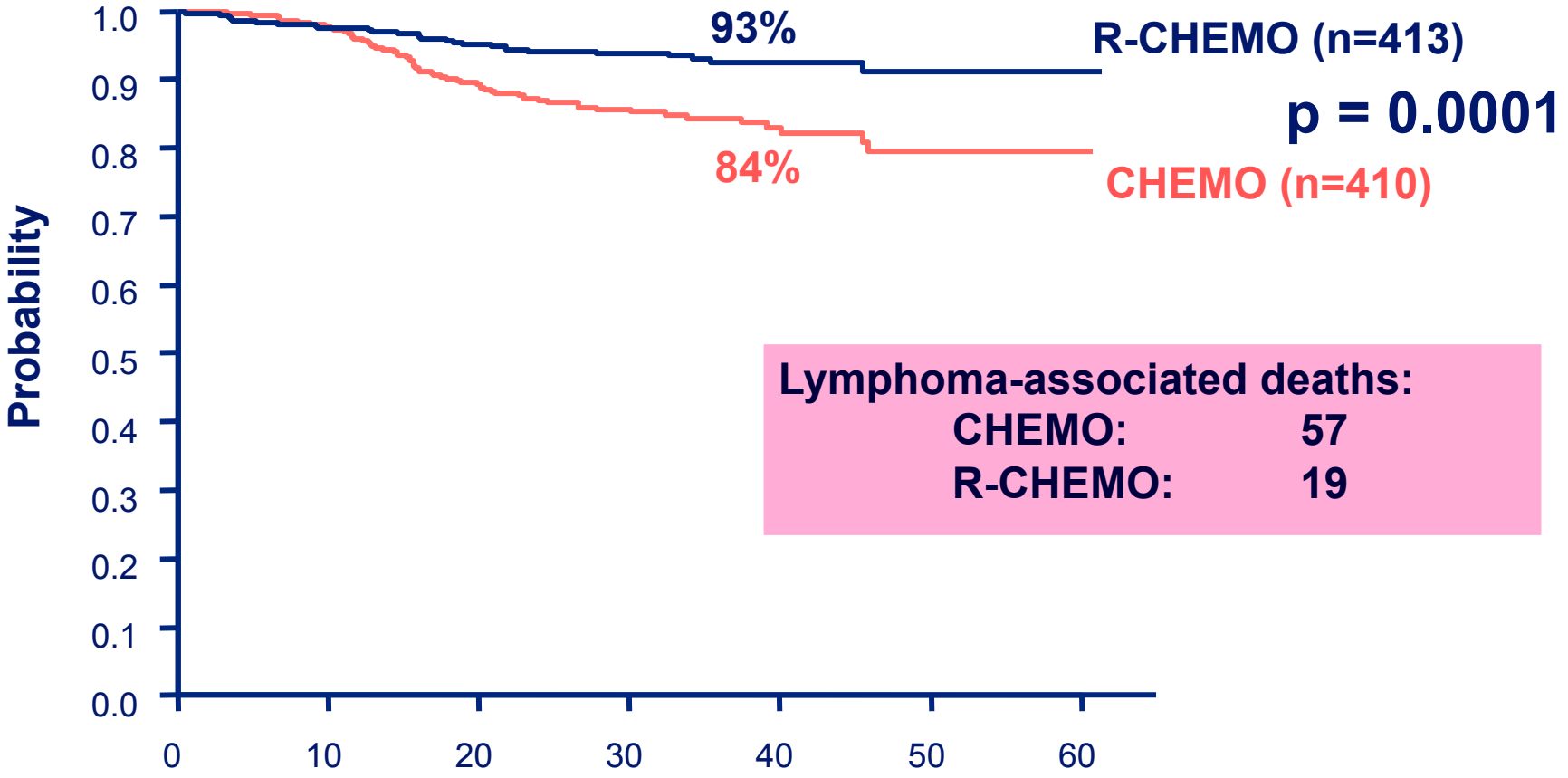
Unfavourable: IPI=1 and / or bulk

MInT Event-free Survival



median observation time: 34 months

Overall Survival



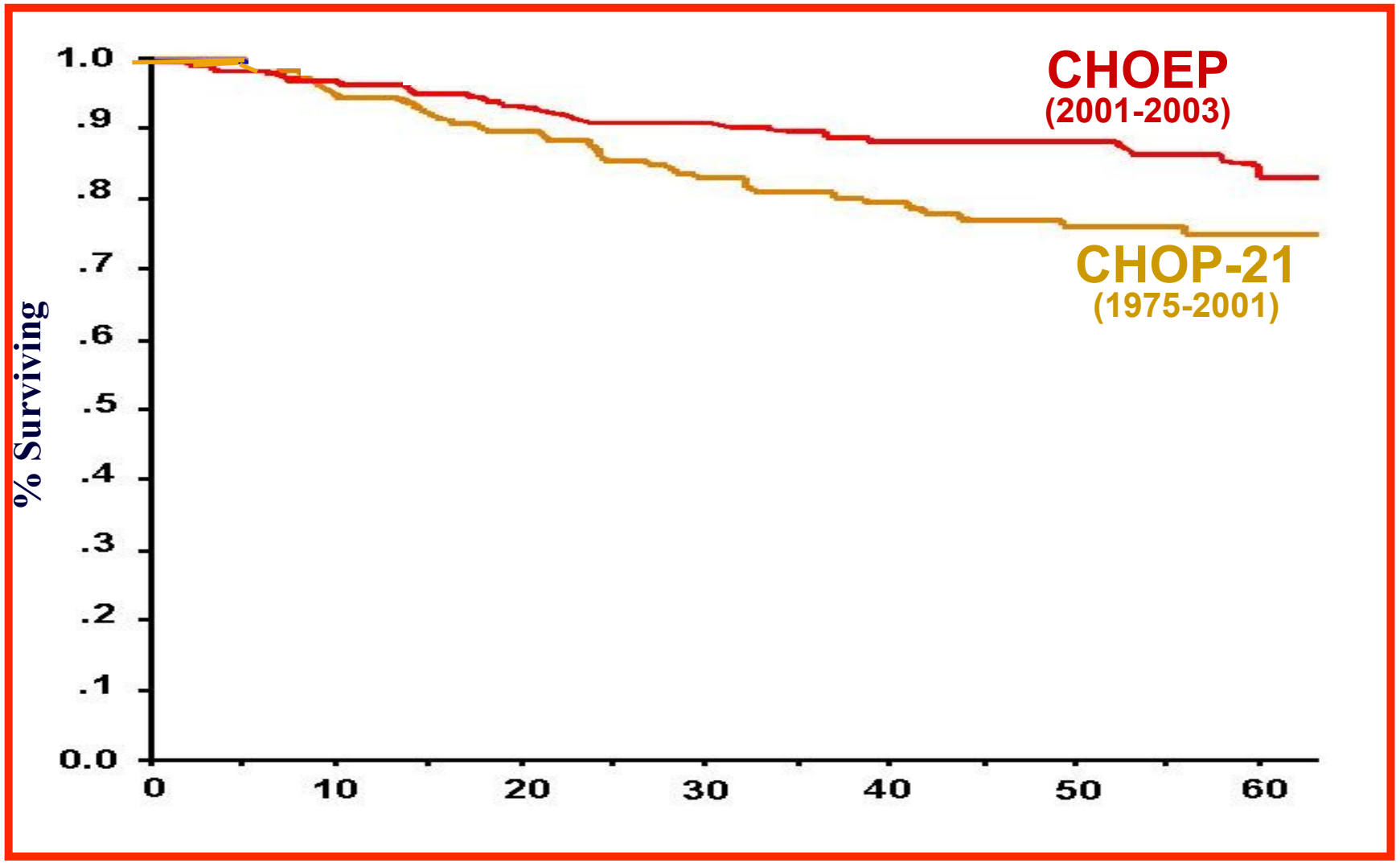
Lymphoma-associated deaths:

CHEMO:	57
R-CHEMO:	19

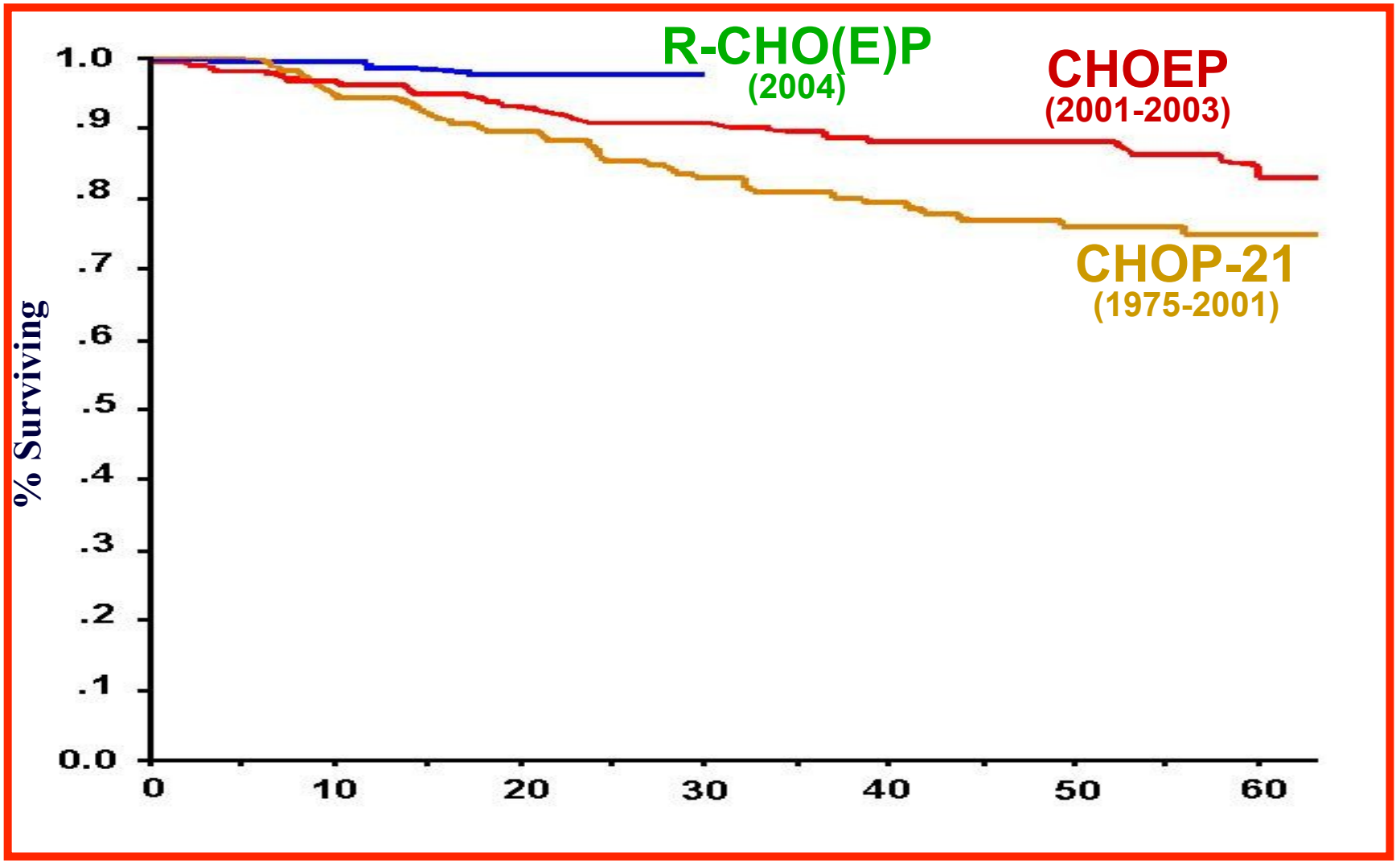
median observation time: 34 months

MInT

Progress in the treatment of Young good-prognosis DLBCL



Progress in the treatment of Young good-prognosis DLBCL

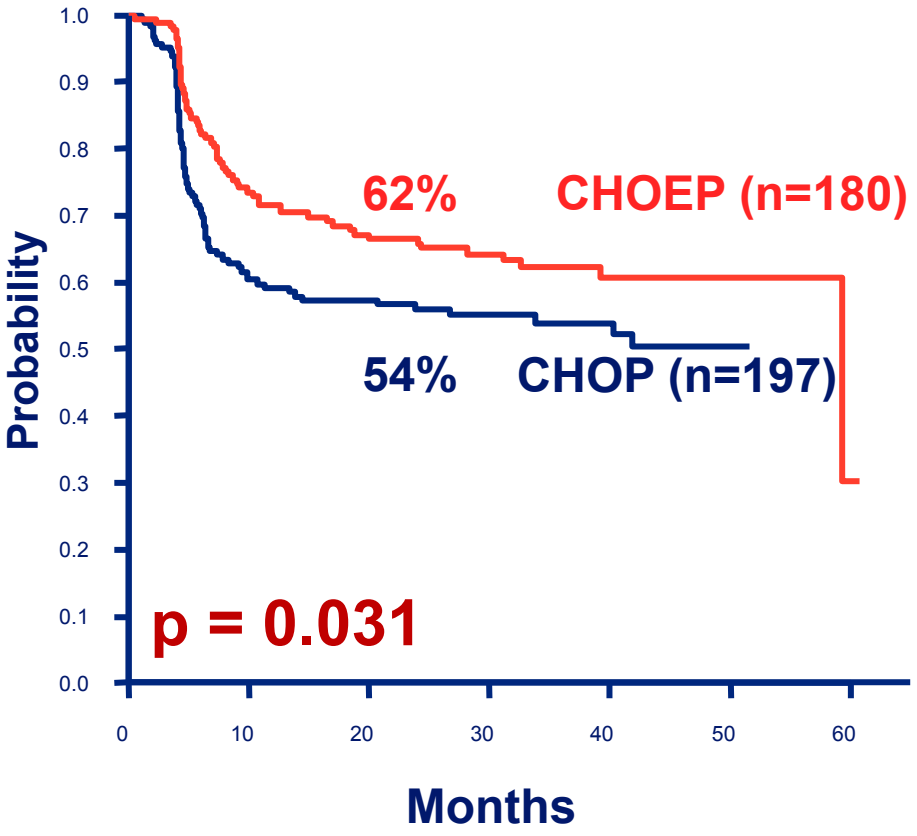


Risk-adapted Treatment in the Rituximab Era

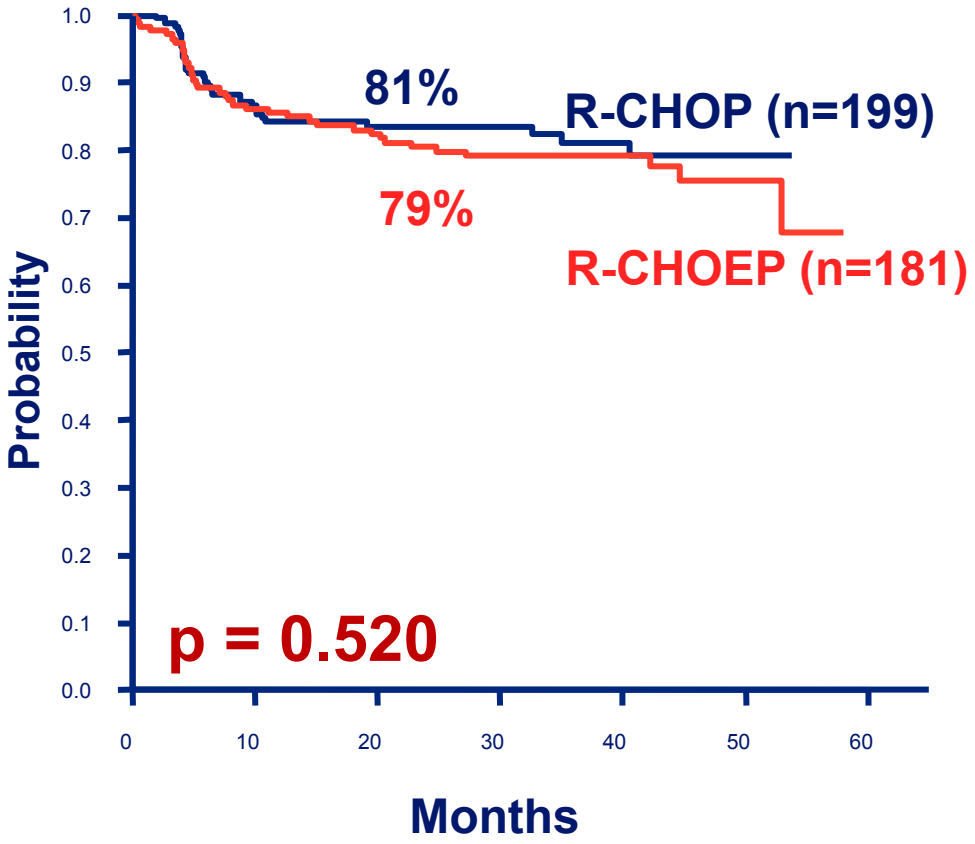
Do we still need etoposide ?

MInT Event-free Survival

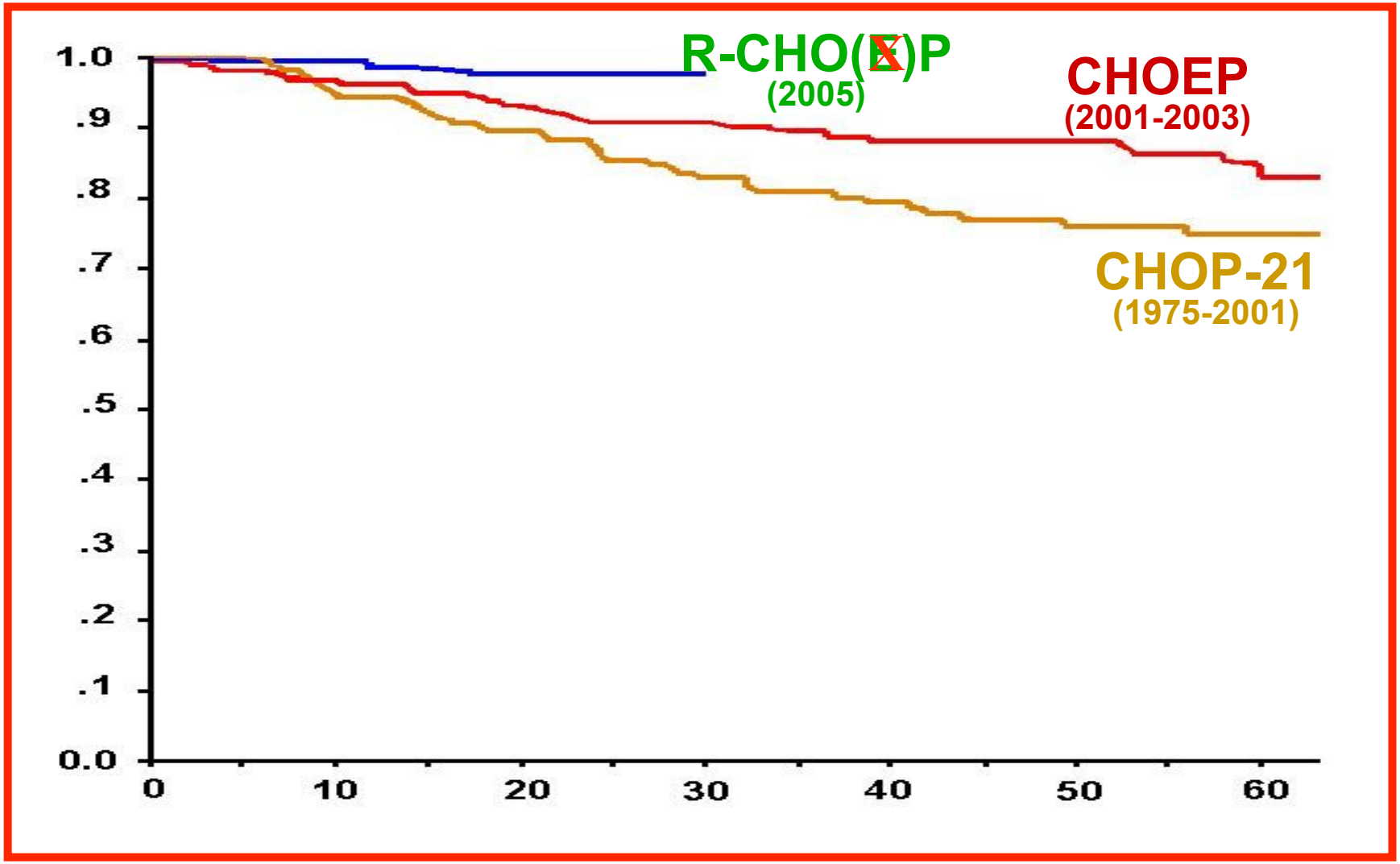
CHOP vs. CHOEP



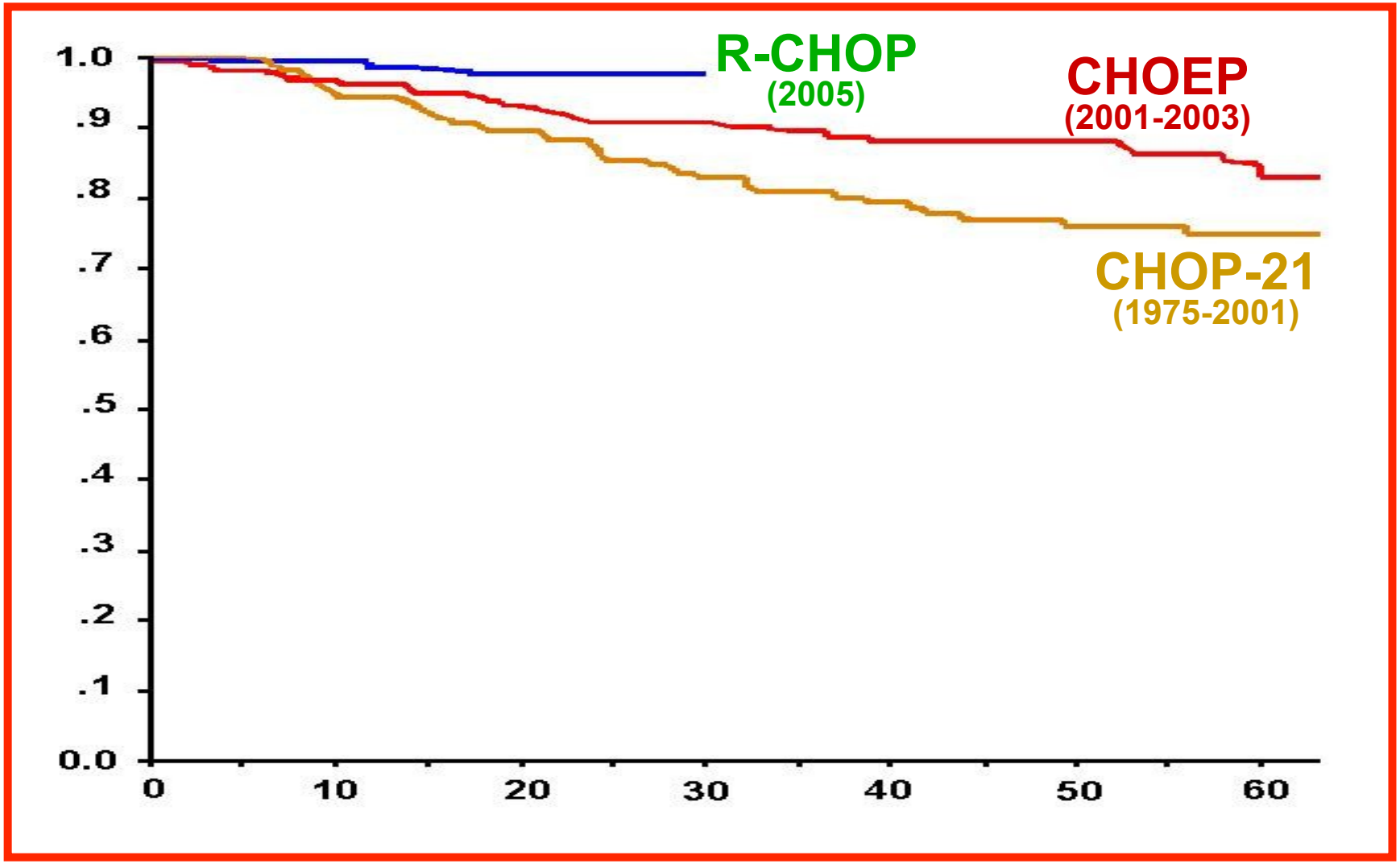
R-CHOP vs. R-CHOEP



Progress in the treatment of Young good-prognosis DLBCL



Progress in the treatment of Young good-prognosis DLBCL



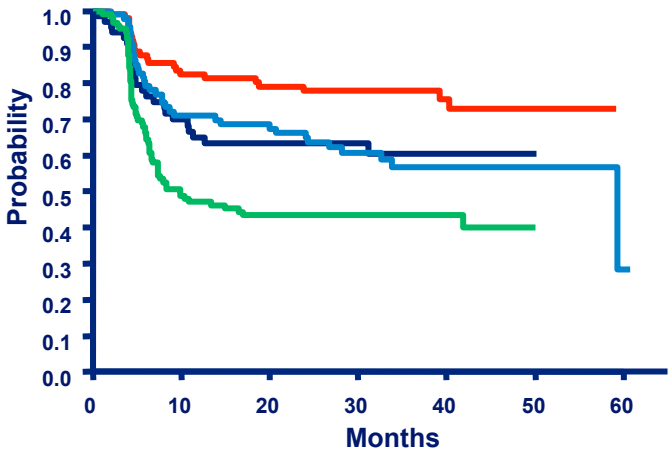
MInT Conclusions

- R-CHOEP is not superior to R-CHOP
- The addition of rituximab: „equalizer“ in all subgroups of young good-prognosis patients
- R-CHOP-21 preferred combination

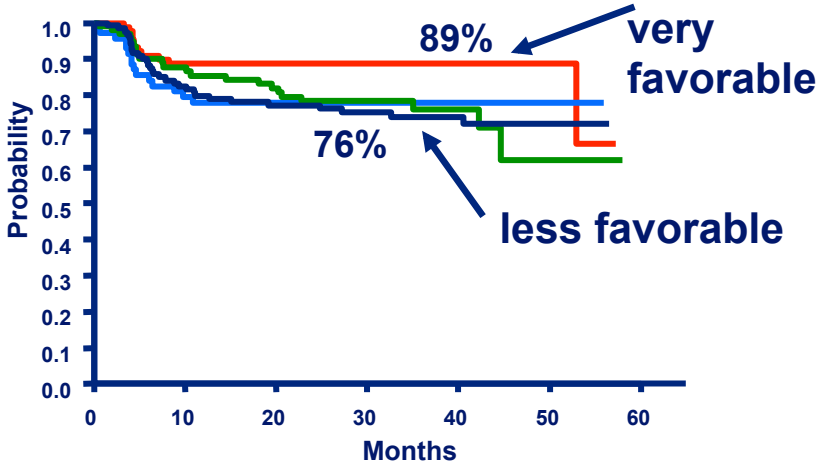
R-CHOP 21 x 6 reference for future trials

MInT EFS: subgroup analysis

CHEMO: EFS



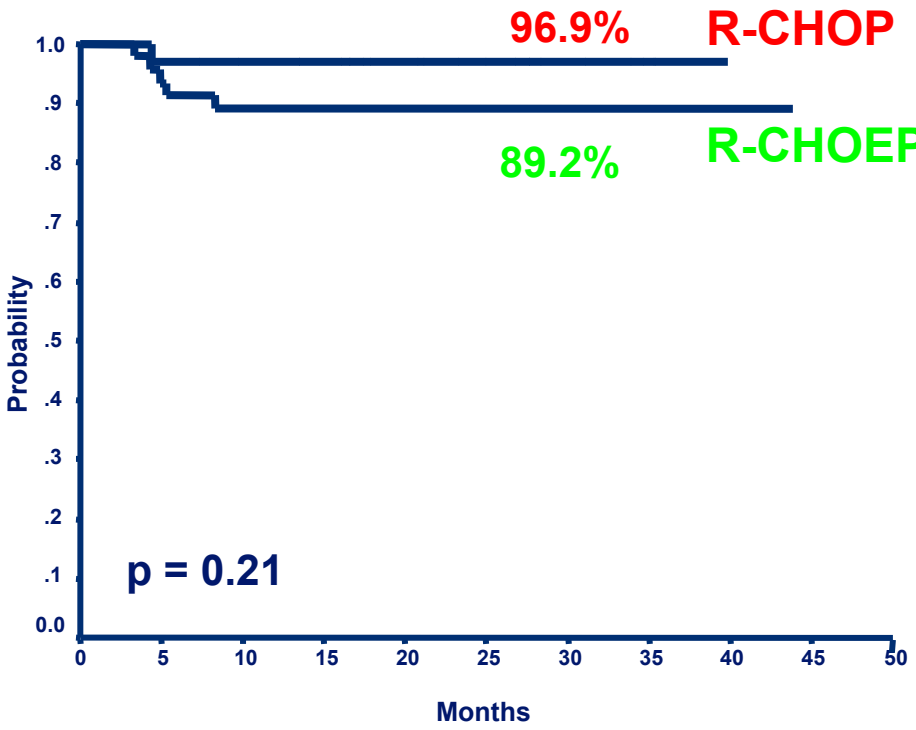
R-CHEMO: EFS



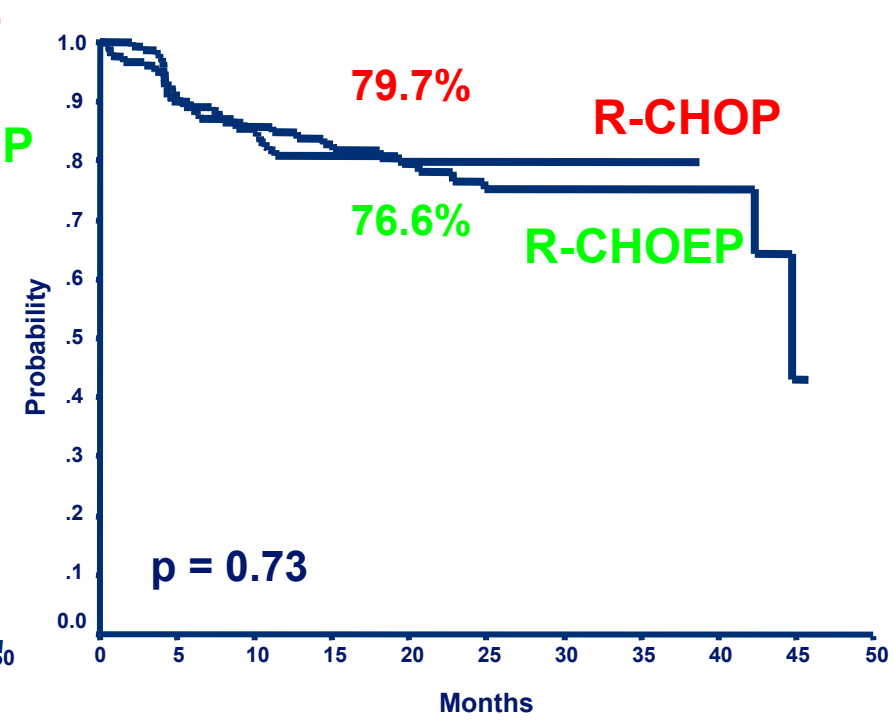
		Chemo	R-Chemo	p
IPI = 0 and no Bulk	(n=108/101)	78%	89%	0.054
IPI = 0 and Bulk	(n=70/73)	61%	78%	0.064
IPI = 1 and no Bulk	(n=105/107)	57%	76%	0.034
IPI = 1 and Bulk	(n=127/132)	44%	74%	0.000 000 3

MInT EFS prognostic subgroups

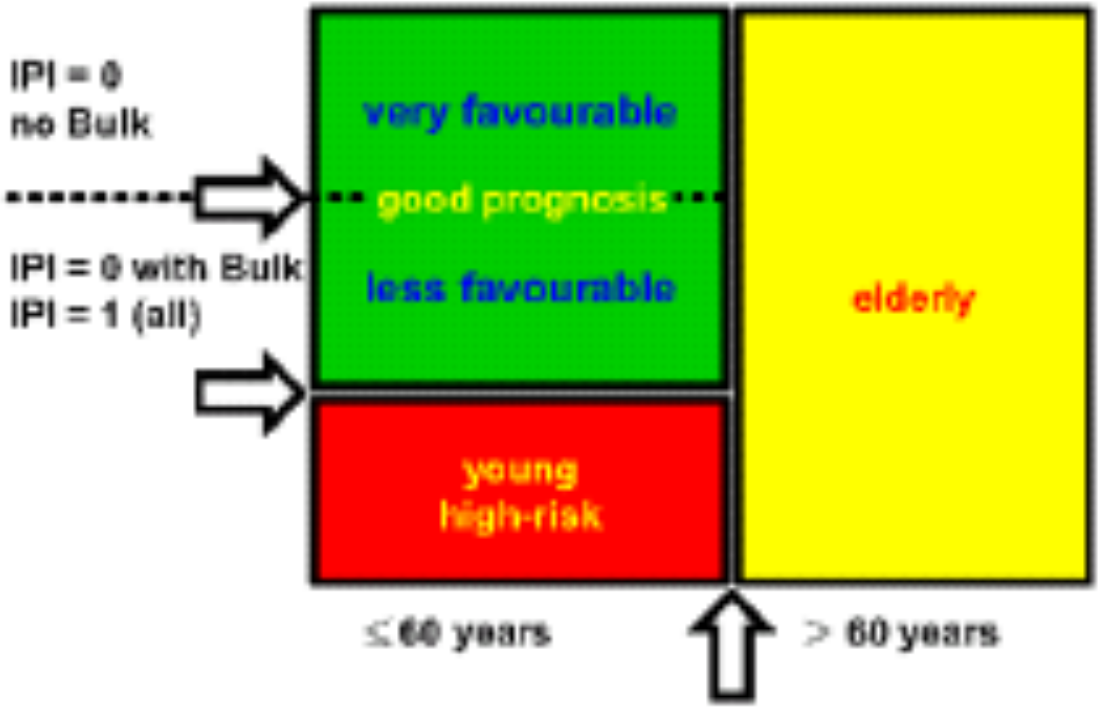
Very Favorable (IPI=0, no bulk)



Less Favorable (IPI=1 and/or bulk)



TREATMENT OF DIFFUSE LARGE B LYMPHOMAS



STANDARD TREATMENT: R-CHOP +/- RT

Risk-adapted Treatment in the Ritxuimab Era

New Risk Factors in the Rituximab Era?

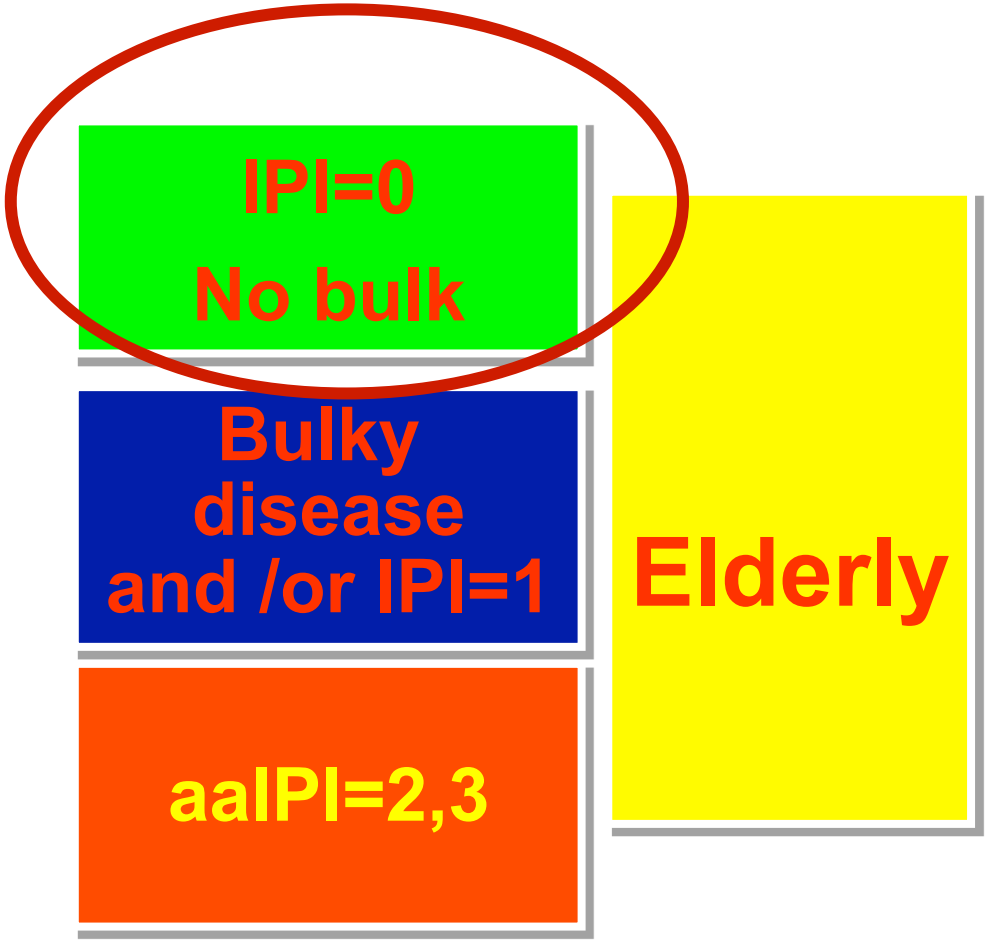
Multivariate Analysis*

Parameter	Hazard Ratio (95%-CI)	Significance
Treatment arm	0.4 (0.3;0.6)	p=0.000 000 003
Bulky disease	1.7 (1.3;2.2)	p=0.0003
IPI	1.6 (1.2;2.2)	p=0.0008

* for primary endpoint EFS

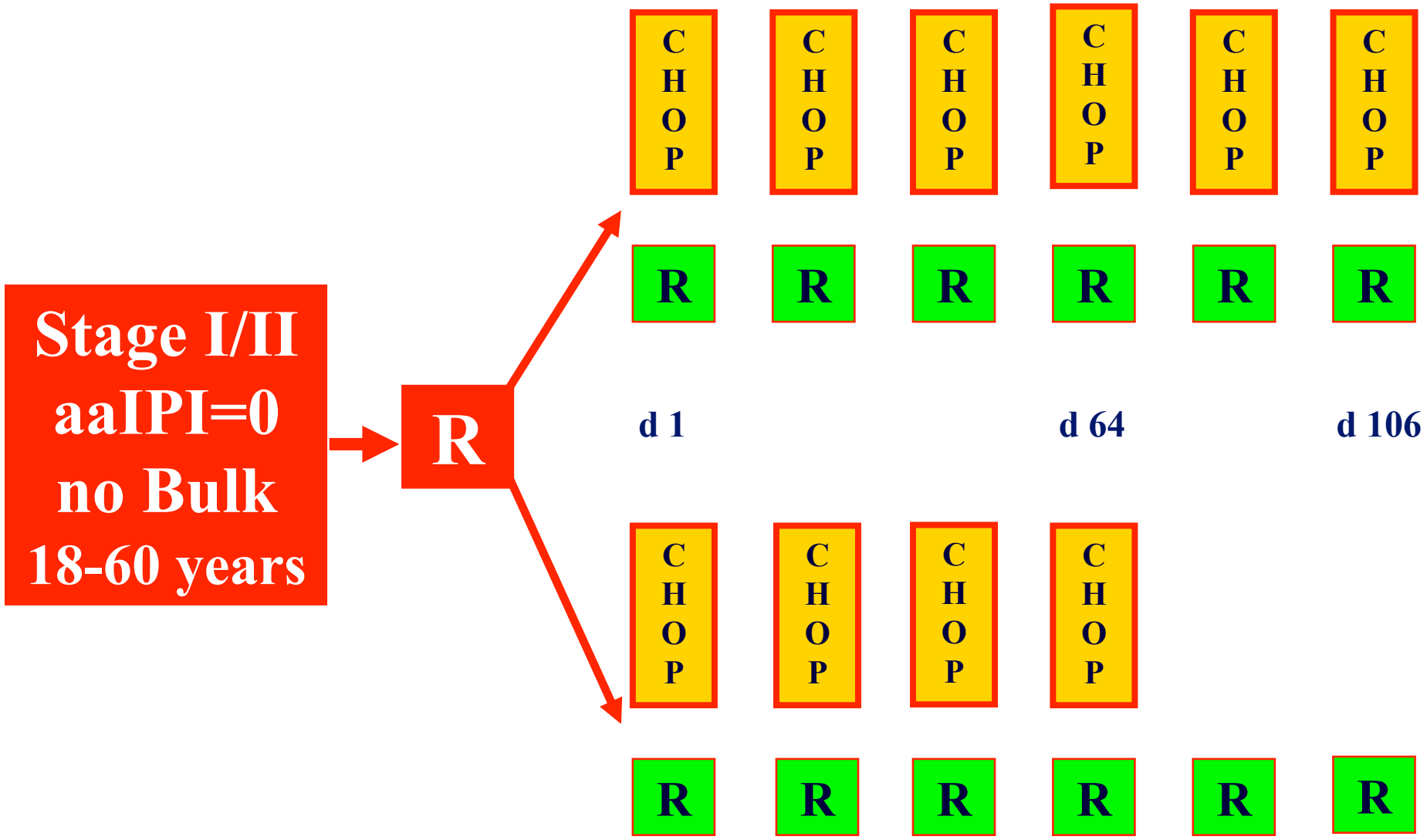
Risk-adapted Approaches

OS~ 100%
EFS >95%



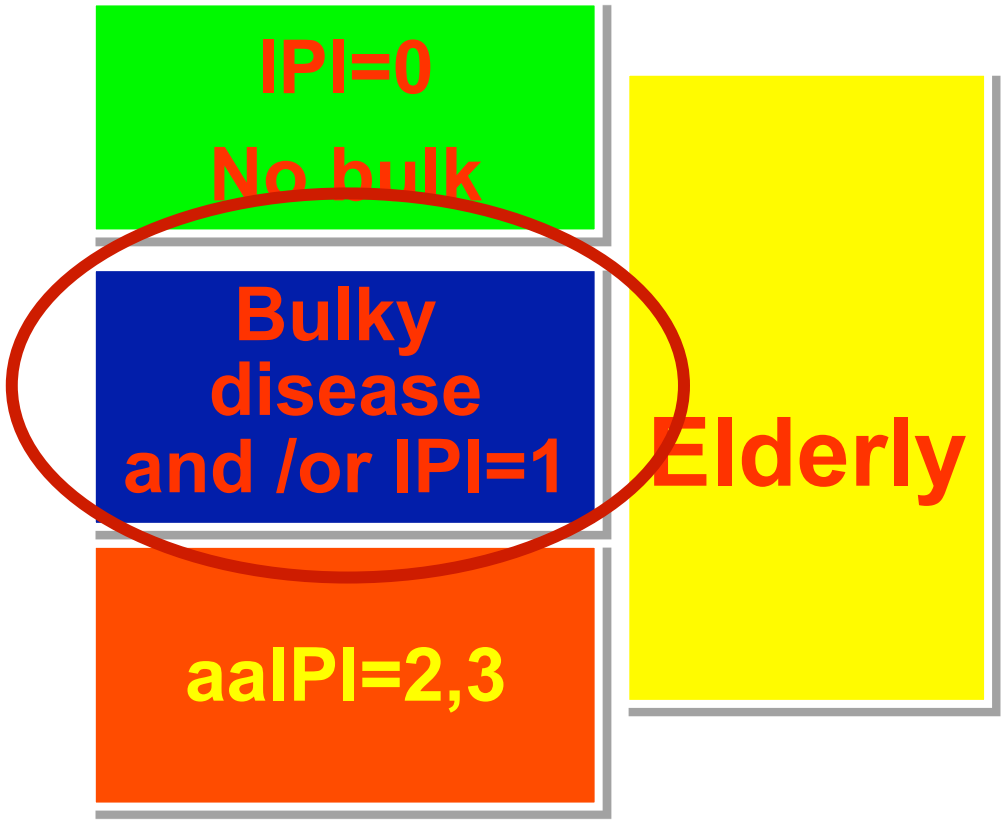
post-MInT

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



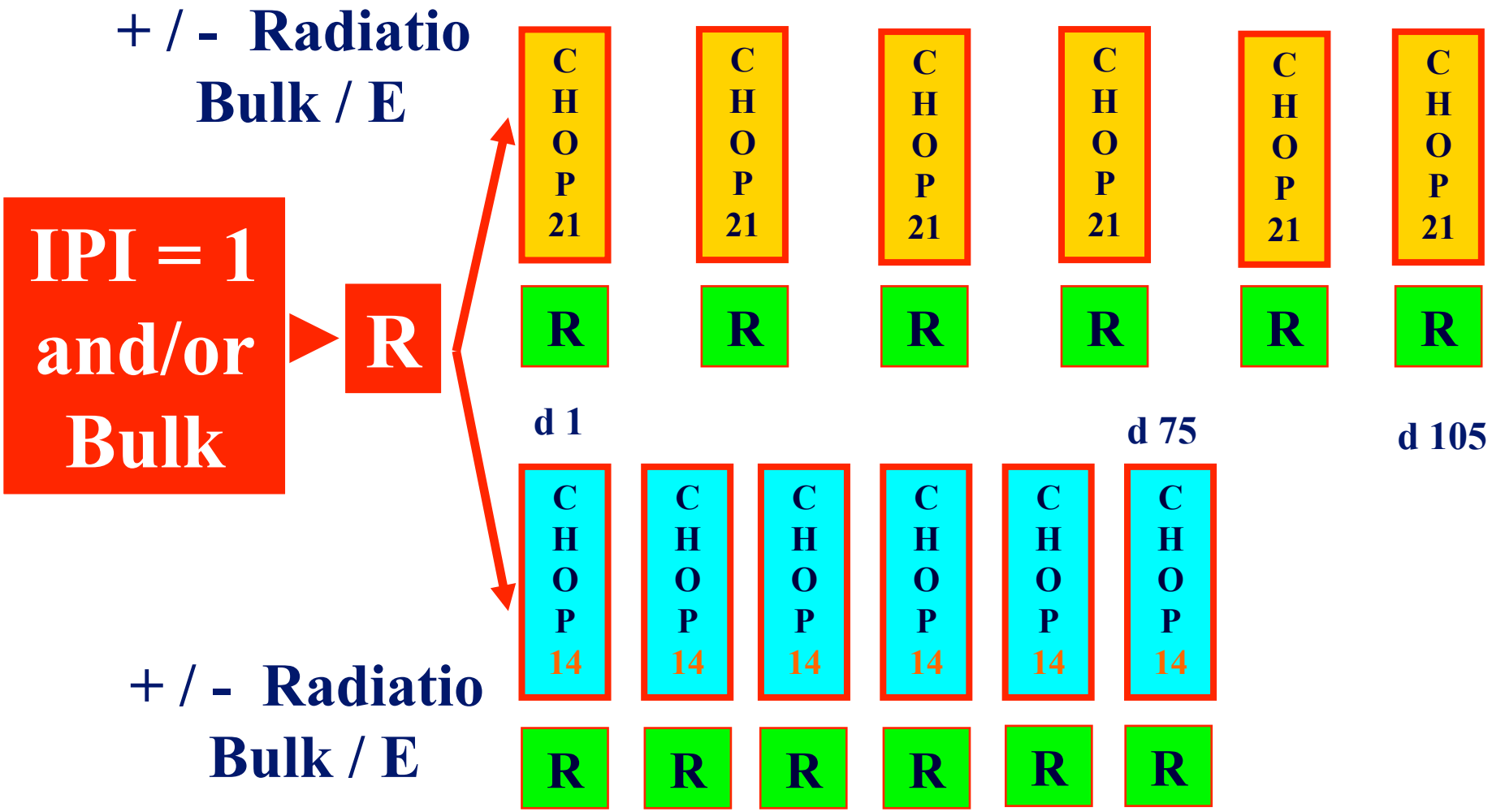
Current Risk-adapted Approaches

OS~90%
EFS~75%



post-MInT

UNFOLDER (21/14) STUDY DESIGN



RADIOTHERAPY ROLE

Radiotherapy in the Rituximab Era

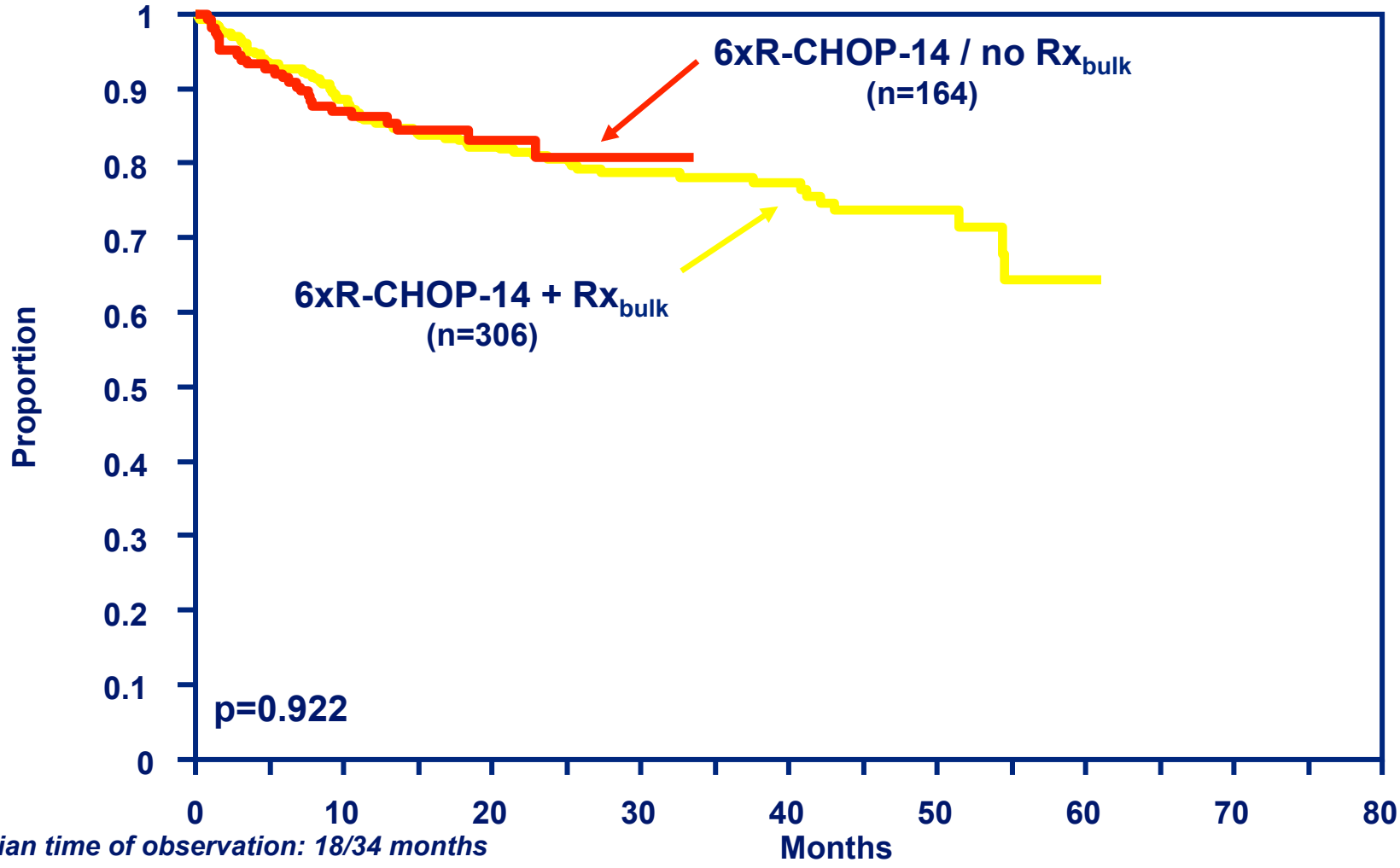
Background:

1. **RICOVER-60: Rx to bulky disease (<7.5cm) after R-CHOP-14**

2. **Impact and role of radiotherapy in this setting unknown**

Radiotherapy in the Rituximab Era

Overall Survival



Median time of observation: 18/34 months

Radiotherapy in the Rituximab Era

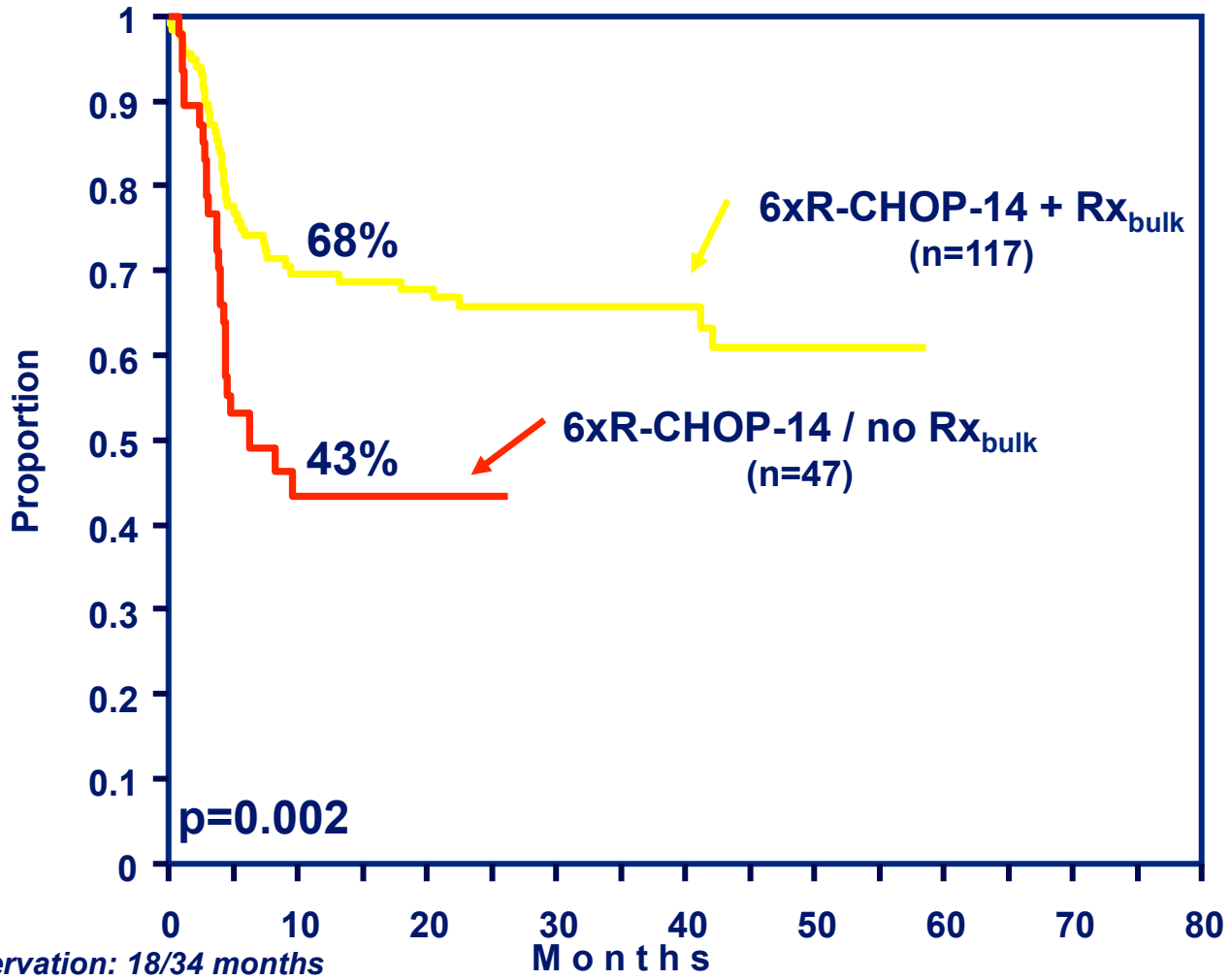
EFS: Multivariate analysis* adjusted for strata

Factor	Relative risk	p-value	95% CI
Rx vs. no Rx	1.2	0.265	(0.9; 1.7)
LDH > UNV	1.7	0.004	(1.2; 2.4)
ECOG > 1	1.6	0.023	(1.1; 2.4)
Extranodal involvement > 1	1.2	0.314	(0.8; 1.9)
Stage III/ IV	1.1	0.799	(0.7; 1.5)
Bulk yes	1.3	0.096	(1.0; 1.9)
Age > 70 years	1.6	0.007	(1.1; 2.1)

* n=470

Radiotherapy in the Rituximab Era

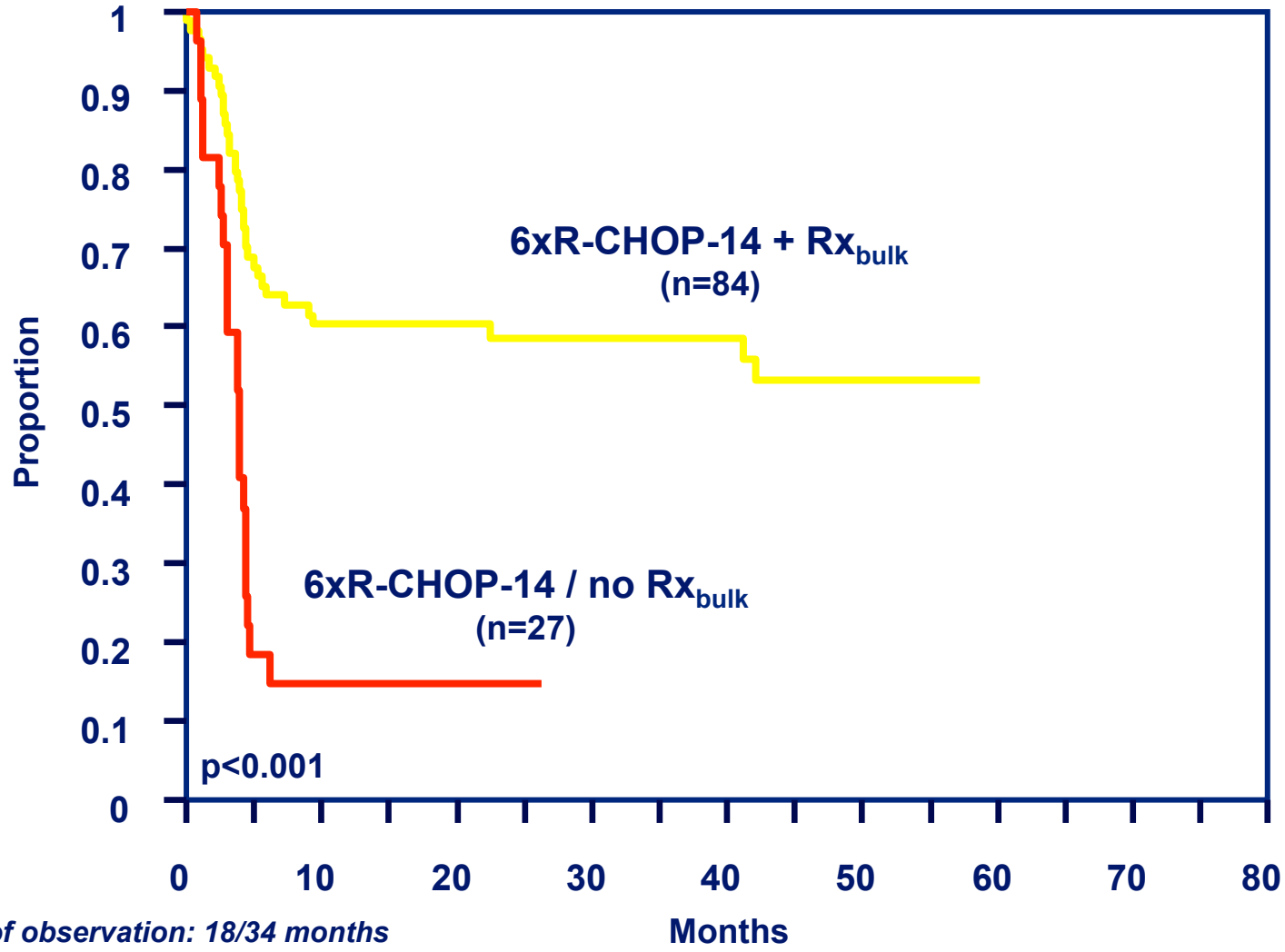
Bulky Disease: Event-free Survival



Median time of observation: 18/34 months

Radiotherapy in the Rituximab Era

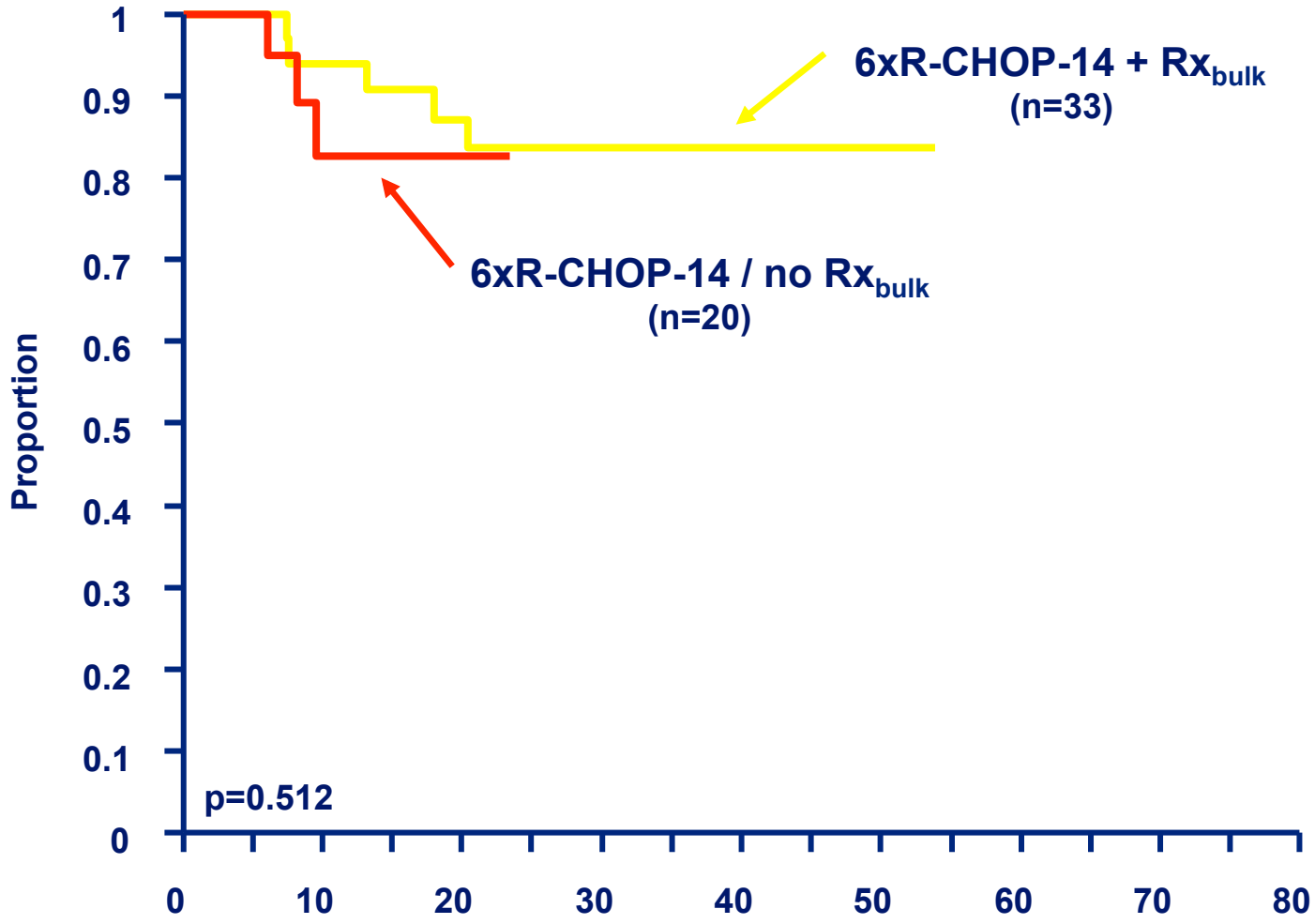
EFS of Bulky Disease after R-CHOP-14: <CR/CRu



Median time of observation: 18/34 months

Radiotherapy in the Rituximab Era

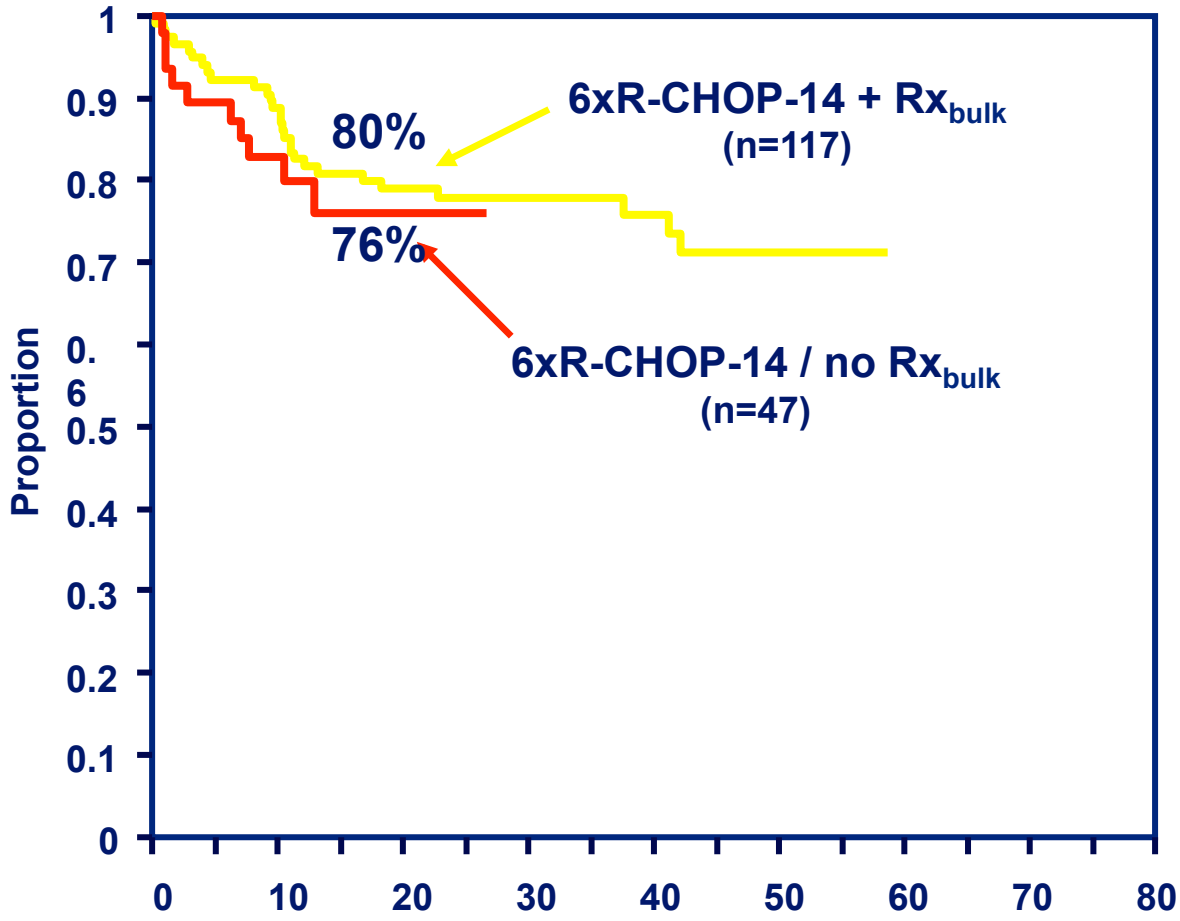
EFS of Bulky Disease in CR after R-CHOP-14



Median time of observation: 18/34 months

Radiotherapy in the Rituximab Era

Bulky Disease: Overall Survival



Median time of observation: 18/34 months

Radiotherapy in the Rituximab Era

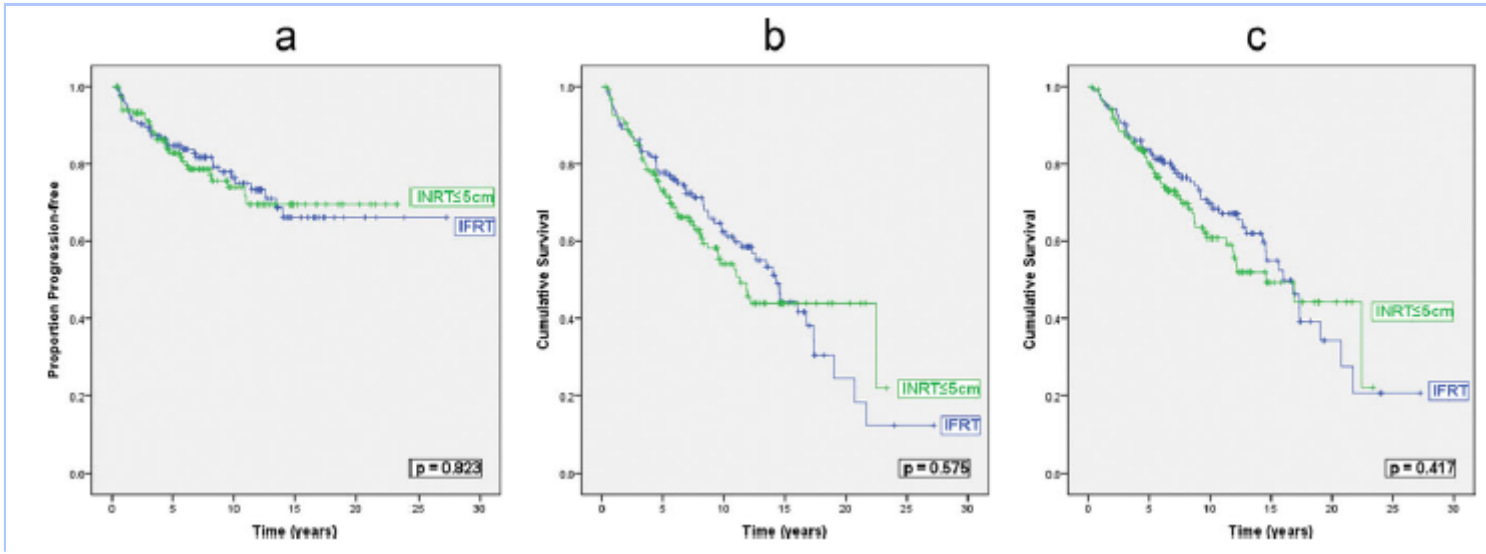
Conclusions:

- **Rx of bulk not indicated for patients in CR/ CRu after 6xR-CHOP-14**
- **Rx to bulk appears to be beneficial for patients in PR after 6xR-CHOP-14**

Limited-Stage Diffuse Large B-Cell Lymphoma Treated With Abbreviated Systemic Therapy and Consolidation Radiotherapy

Involved-Field Versus Involved-Node Radiotherapy

Belinda A. Campbell, MBBS[1,2,3]; Joseph M. Connors, MD[2]; Randy D. Gascoyne, MD[2,4]; W. James Morris, MD[3]; Tom Pickles, MD[3]; and Laurie H. Sehn, MD[2]



In conclusion, IFRT can be safely replaced by INRT≤5 cm in limited-stage DLBCL treated with abbreviated systemic therapy and consolidation radiotherapy.

Cancer September 1, 2012

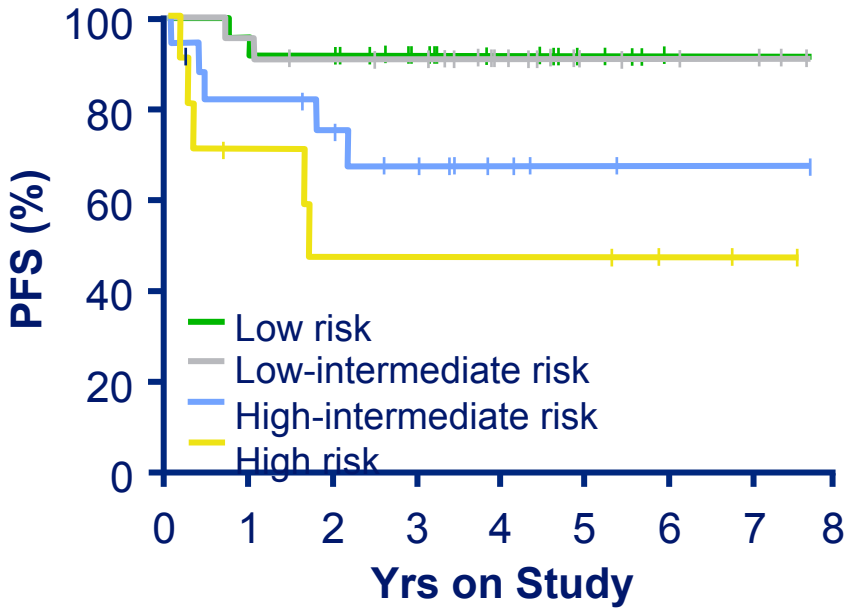
OTHER OR NEW APPROACHES

R-EPOCH Regimen

- Given every 21 days for 4-6 cycles
- Dose-adjusted regimen consisting of
  - Rituximab 375 mg/m^2 on Day 1
  - Etoposide 65 mg/m^2 continuous IV on Days 2-4
  - Prednisone 60 mg/m^2 PO on Days 1-14
  - Vincristine 0.5 mg continuous IV on Days 2-4
  - Cyclophosphamide 750 mg/m^2 IV on Day 5
  - Doxorubicin 15 mg/m^2 continuous IV on Days 2-4

Wilson WH, et al. J Clin Oncol. 2008;26:2717-2724.

Phase II Study of Dose-Adjusted EPOCH-R in DLBCL (CALGB 50103): PFS by IPI Score

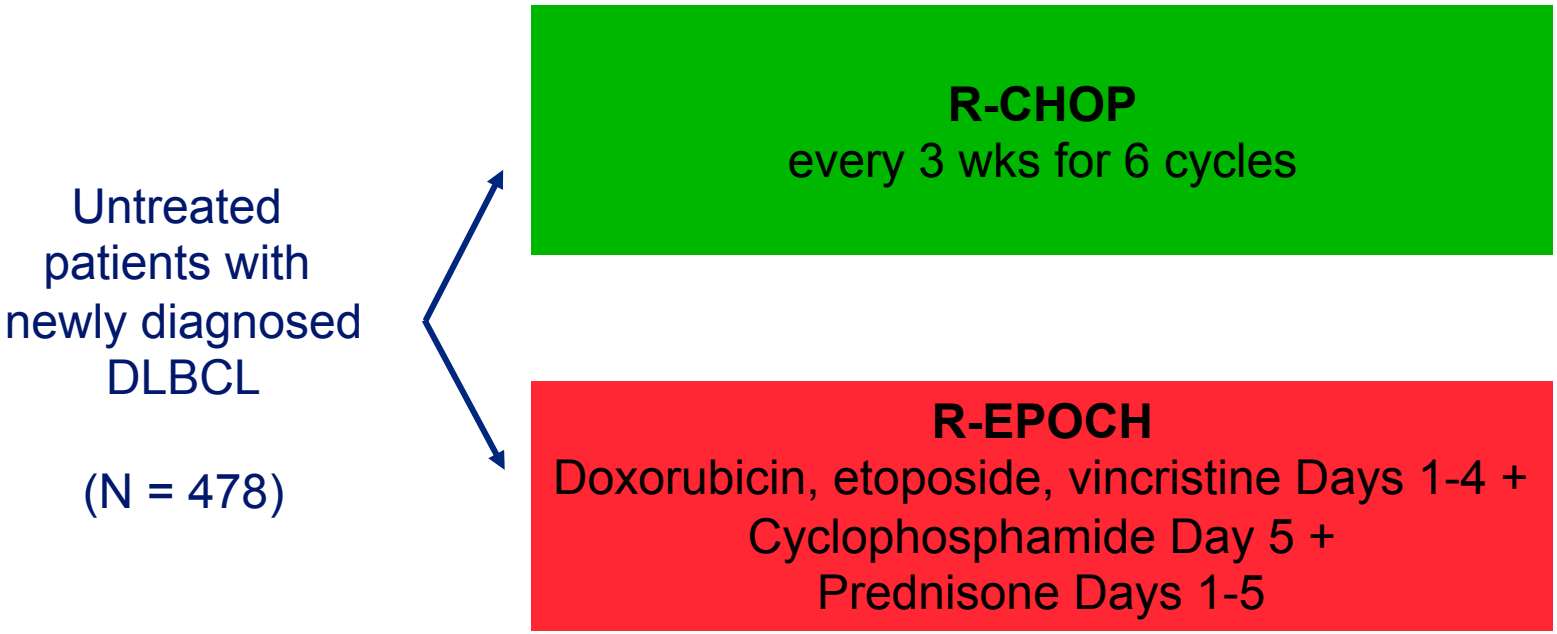


- **5-yr PFS: 79%**
  - **Low risk IPI: 91%**
  - **Low-int risk IPI: 90%**
  - **High-int risk IPI: 67%**
  - **High risk IPI: 47%**
- **IPI score significantly associated with PFS (*P* = .007)**

- Median potential follow-up: 54 mos

Wilson WH, et al. J Clin Oncol. 2008;26:2717-2724.

CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL



- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling for pathological diagnosis, prospective validation of FDG-PET

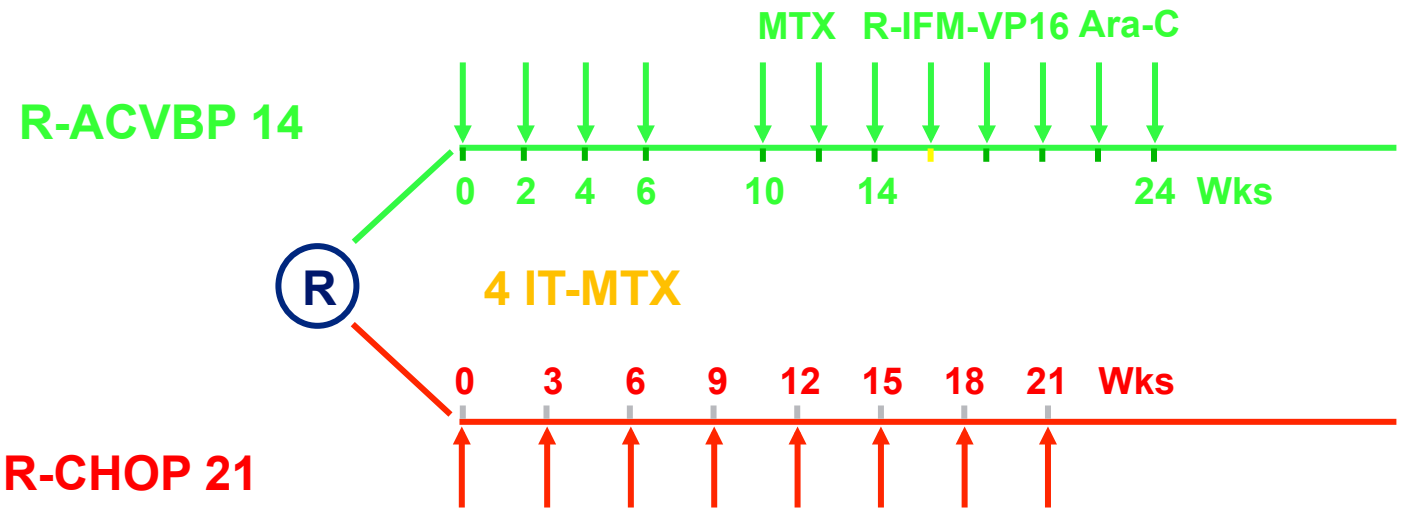
ClinicalTrials.gov. NCT00118209.

Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial

Christian Récher, Bertrand Coiffier, Corinne Haioun, Thierry Jo Molina, Christophe Fermé, Olivier Casasnovas, Catherine Thiéblemont, André Bosly, Guy Laurent, Franck Morschhauser, Hervé Ghesquières, Fabrice Jardin, Serge Bologna, Christophe Fruchart, Bernadette Corront, Jean Gabarre, Christophe Bonnet, Maud Janvier, Danielle Canioni, Jean-Philippe Jais, Gilles Salles, Hervé Tilly, for the Groupe d'Etude des Lymphomes de l'Adulte

Compared with standard R-CHOP, intensified immunochemotherapy with R-ACVBP significantly improves survival of patients aged 18-59 years with diffuse large B-cell lymphoma with low-intermediate risk according to the International Prognostic Index. Haematological toxic effects of the intensive regimen were raised but manageable.

Improved Efficacy With R-ACVBP vs R-CHOP in Younger DLBCL with low risk IPI: GELA LNH 03-2B study



- Patients aged 18-59 yrs
- IPI score= 1
- No radiotherapy in either treatment arm
- Primary endpoint: EFS
- Secondary endpoints: response rate at end of therapy, PFS, FDS (CR/CRu patients only), OS, CNS relapse rate, toxicity

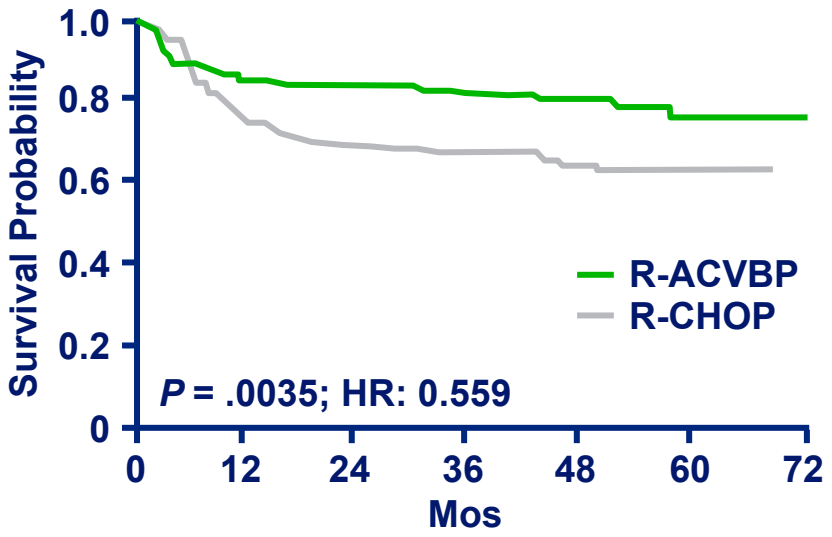
Improved Efficacy With R-ACVBP vs R-CHOP in Younger DLBCL with low risk IPI: GELA LNH 03-2B study

Outcome % 3yrs	R-ACVBP (196 pts)	R-CHOP (183 pts)	p-value
ORR	92	88	ns
CR/ CRu	84	80	ns
EFS	**81**	**67**	**.0035**
PFS	**87**	**73**	**.0015**
DFS	**91**	**80**	**.0019**
OS	**92**	**84**	**.0071**

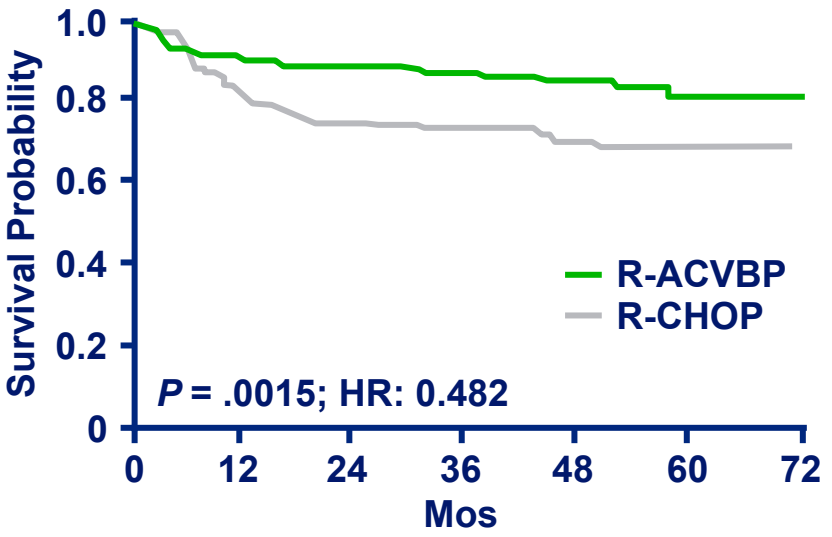
Recher et al, Lancet 2011; 378: 1858-1867

LNH 03-2B Study: Results

3-Yr EFS



3-Yr PFS



Hematologic toxicities, mucositis, and neurologic toxicity more frequent in the R-ACVBP vs R-CHOP-21

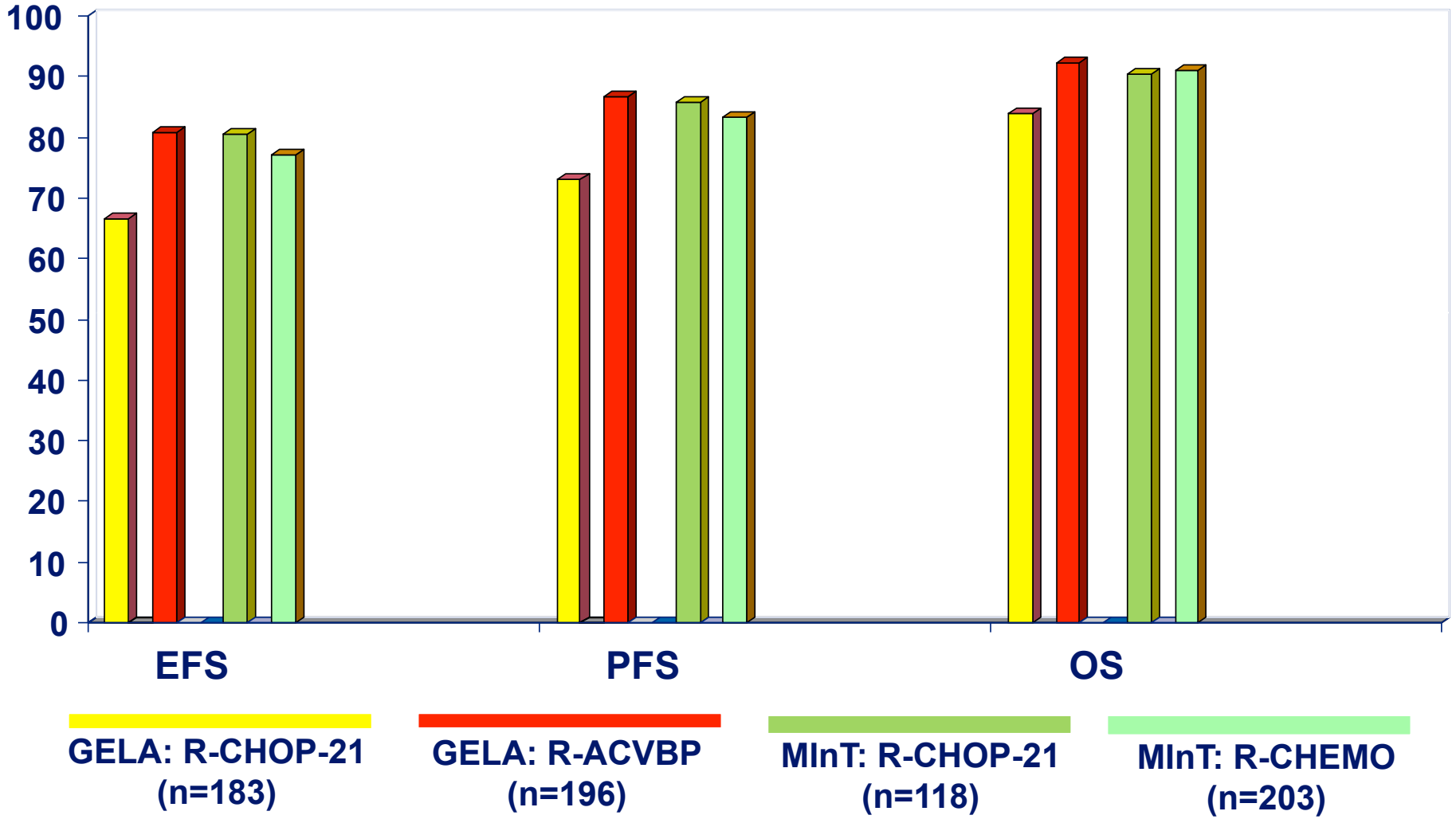
R-ACVBP	196	20% (40)	80% (156)	NA (NA)
R-CHOP	183	34% (63)	66% (120)	NA (NA)

R-ACVBP	196	14% (28)	86% (168)	NA (NA)
R-CHOP	183	28% (51)	72% (132)	NA (NA)

Recher et al, Lancet 2011; 378: 1858-1867

LNH 03-2B vs. MInT$_{aaIPI=1}$

3-Year Results



LNH 03-2B vs. MInTaaIPI=1

Unfavourable Group (IPI=1)

$8 \times \text{R-CHOP-21}_{\text{GELA}}^{*} < 6 \times \text{R-CHOP-21}_{\text{MInT}}^{**}$

$\text{R-ACVBP}_{\text{GELA}}^{*} = 6 \times \text{R-CHOP-21}_{\text{MInT}}^{**}$

Does Radiotherapy make a difference?

* No Radiotherapy

** Radiotherapy to bulky disease

Phase III study of ACVBP versus ACVBP plus rituximab for patients with localized low-risk diffuse large B-cell lymphoma (LNH03-1B)

N. Ketterer[1*], B. Coiffier[2], C. Thieblemont[3], C. Fermé[4], J. Brière[5], O. Casasnovas[6], S. Bologna[7], B. Christian[8], T. Connerotte[9], C. Récher[10], D. Bordessoule[11], C. Fruchart[12], R. Delarue[13], C. Bonnet[14], F. Morschhauser[15], B. Anglaret[16], C. Soussain[17], B. Fabiani[18], H. Tilly[19] & C. Haioun[20]

99% aaIPI: 0
2% bulky at diagnosis
> 60% stage I

Radiotherapy was not allowed

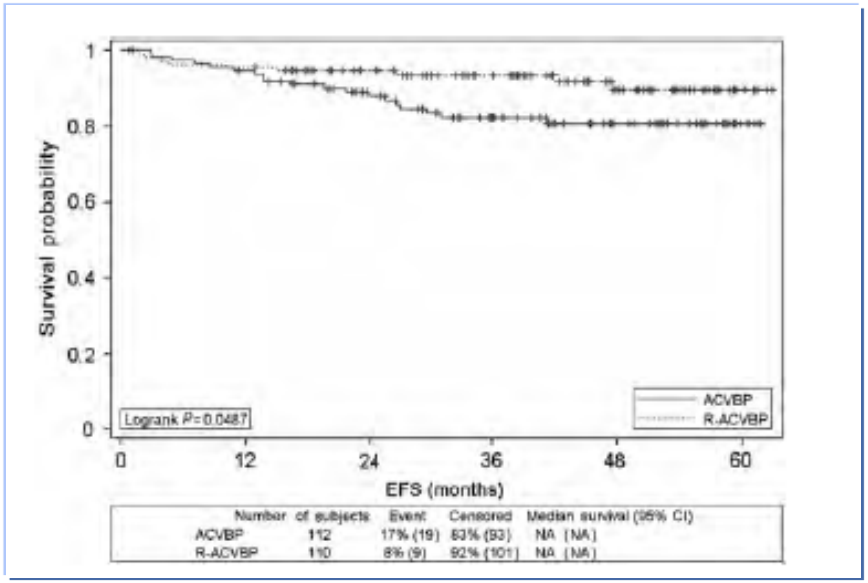
Annals of Oncology 24: 1032–1037, 2013

Table 2. Response to treatment[a]

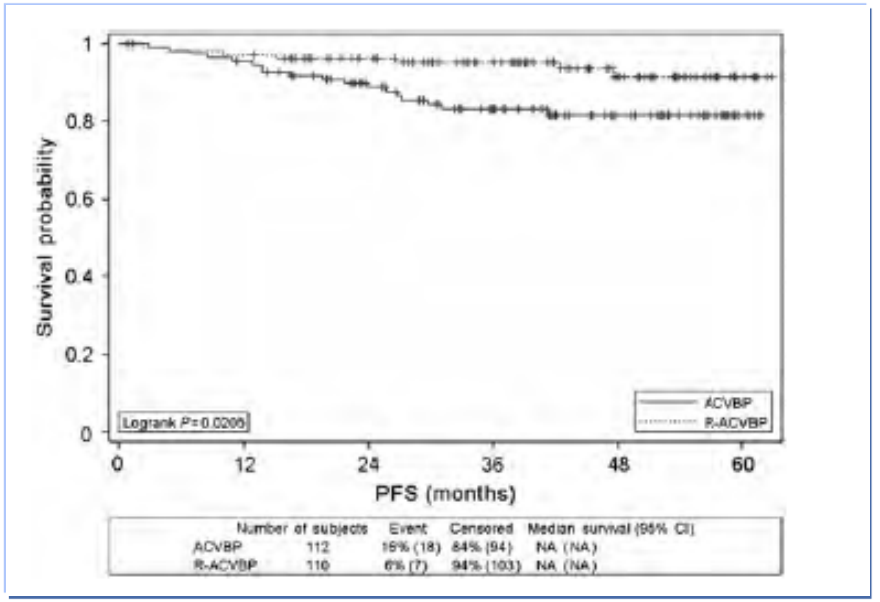
Characteristics	ACVBP ($n = 112$)		R-ACVBP ($n = 110$)	
	Number of patients	Percentage	Number of patients	Percentage
CR or CRu	105	94	107	97
PR	2	2	0	0
Primary failure	3	3	1	1
Death	0	0	1	1
Not evaluated	2	2	1	1

[a]Response was assessed 1 month after the completion of the treatment in 212 assessable patients.

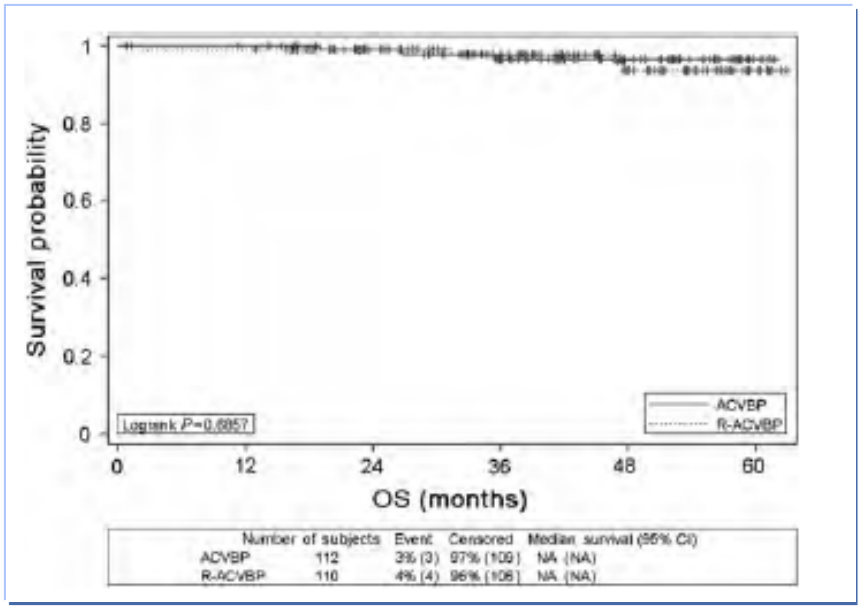
EFS


Survival probability
1
0.8
0.6
0.4
0.2
0
Logrank P=0.0487
ACVBP
R-ACVBP
0
12
24
36
48
60
EFS (months)
Number of subjects Event Censored Median survival (95% CI)
ACVBP 112 17% (19) 83% (93) NA (NA)
R-ACVBP 110 8% (9) 92% (101) NA (NA)

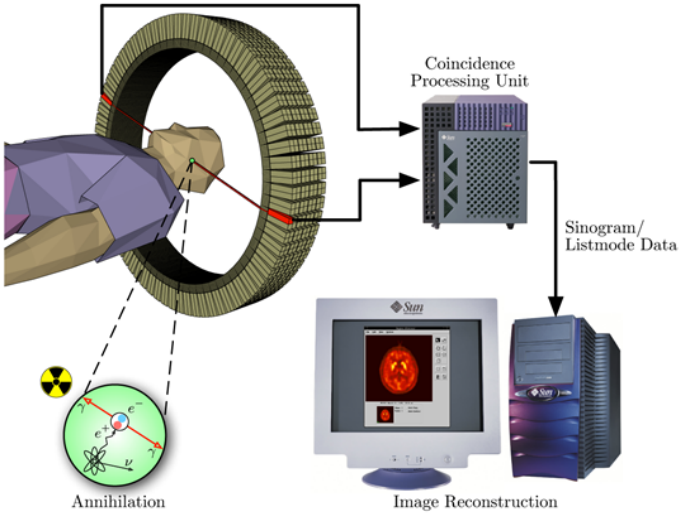
PFS

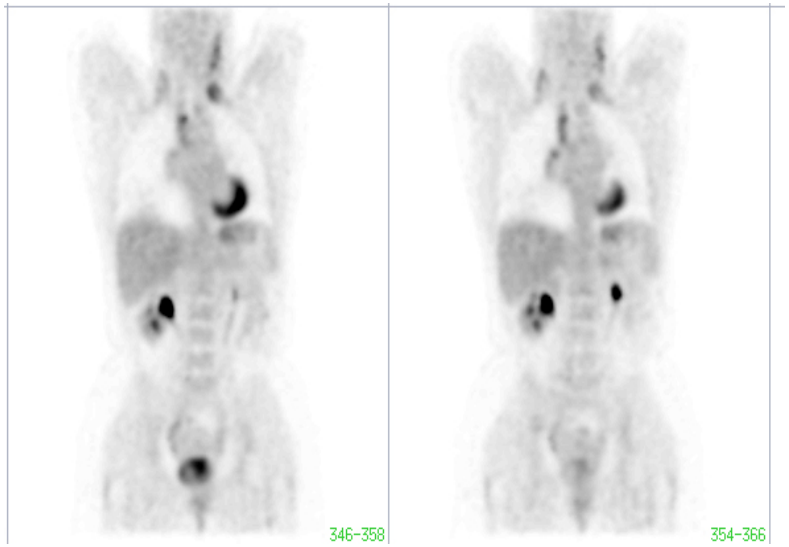

Survival probability
1
0.8
0.6
0.4
0.2
0
Logrank P=0.0206
ACVBP
R-ACVBP
0
12
24
36
48
60
PFS (months)
Number of subjects Event Censored Median survival (95% CI)
ACVBP 112 16% (18) 84% (94) NA (NA)
R-ACVBP 110 6% (7) 94% (103) NA (NA)

OS


Survival probability
1
0.8
0.6
0.4
0.2
0
Logrank P=0.6957
ACVBP
R-ACVBP
0
12
24
36
48
60
OS (months)
Number of subjects Event Censored Median survival (95% CI)
ACVBP 112 3% (3) 97% (109) NA (NA)
R-ACVBP 110 4% (4) 96% (106) NA (NA)

Role of PET to monitor response to therapy in aggressive lymphomas?

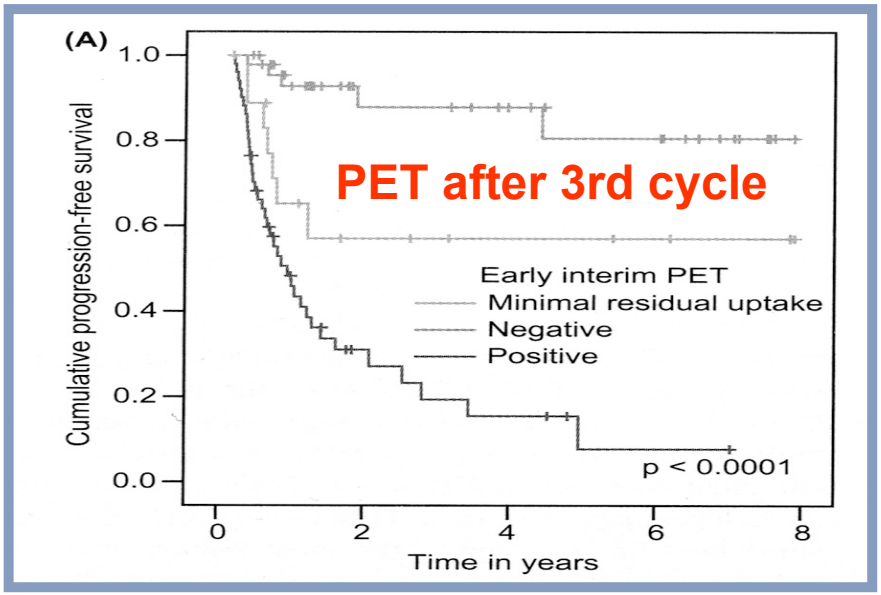




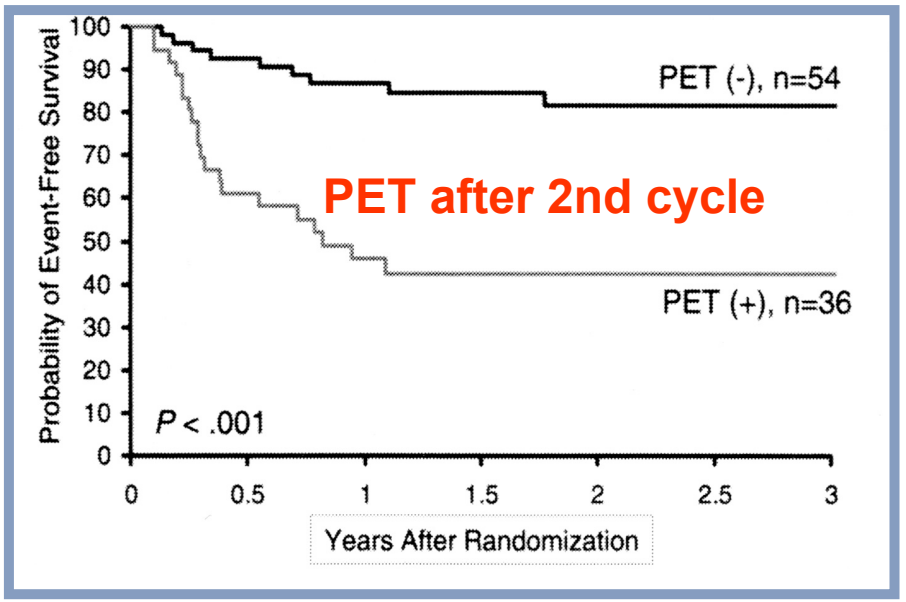
PET at the end of treatment

Interim PET response

Early clinical trials of Interim PET in aggressive lymphoma



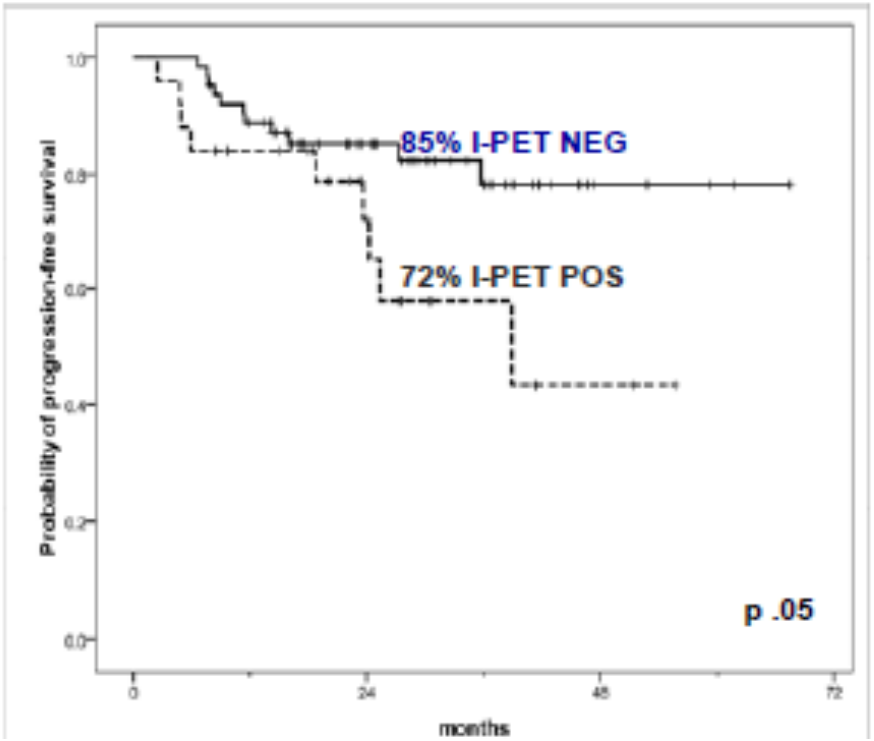
Mikhaeel et al, Ann Oncol 16: 1514, 2005

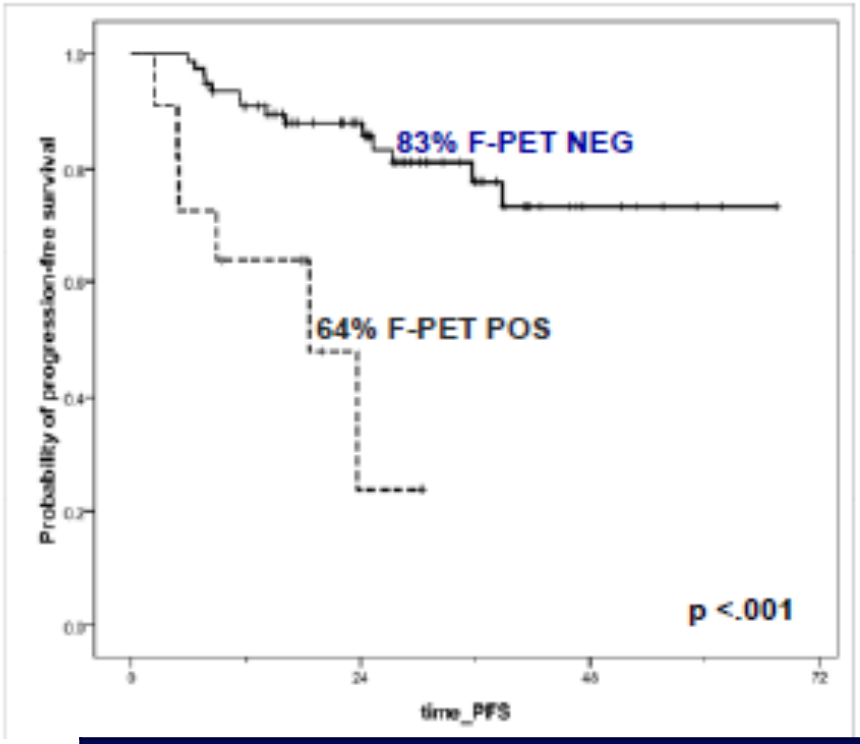


Haioun et al, Blood 106: 1376, 2005

CONTRA interim PET in DLBCL

Median FU 26,2 months; 2-ys PFS by Interim-PET and Final PET





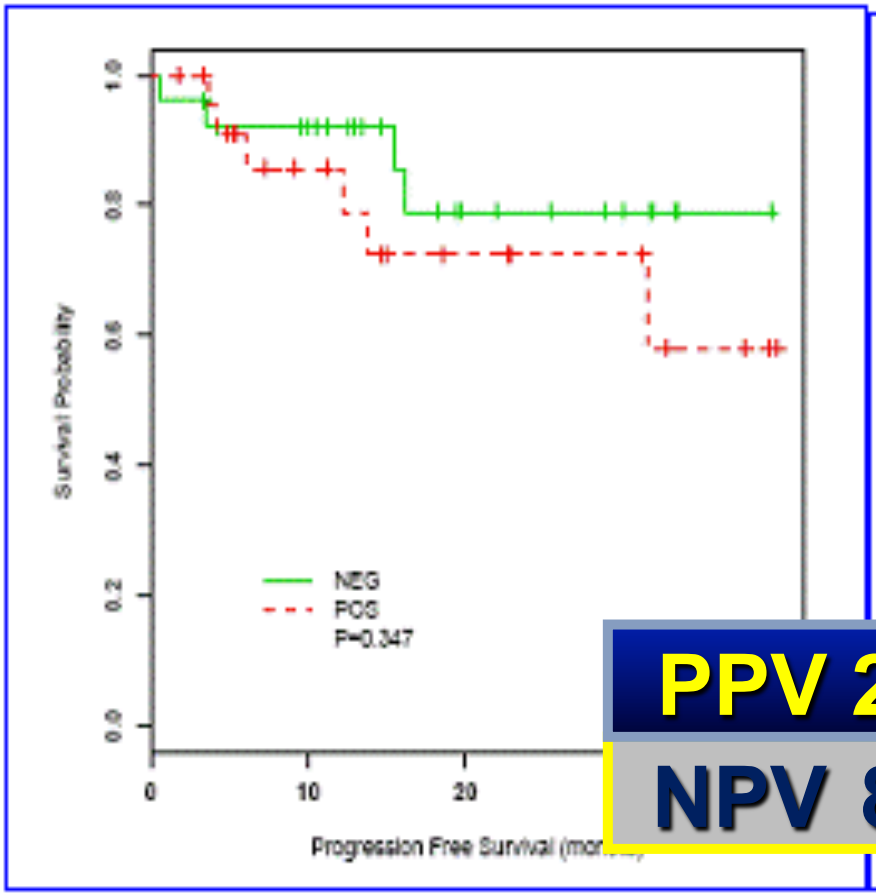
UNIVARIATE COX' s MODEL ANALYSIS FOR PFS			
I-PET (Pos vs Neg)	2.45	1.01-5.93	0.047
F-PET (Pos vs Neg)	5.97	2.19-16.28	<0.001
Others: LDH> normal, >1 extranodal sites, BM+, IH-H IPI risk were predictors of lower PFS rates			

BIVARIATE COX' s MODEL ANALYSIS FOR PFS			
I-PET (Pos vs Neg)	1.27	0.40-4.03	0.691
F-PET (Pos vs Neg)	5.03	1.37-18.43	0.015

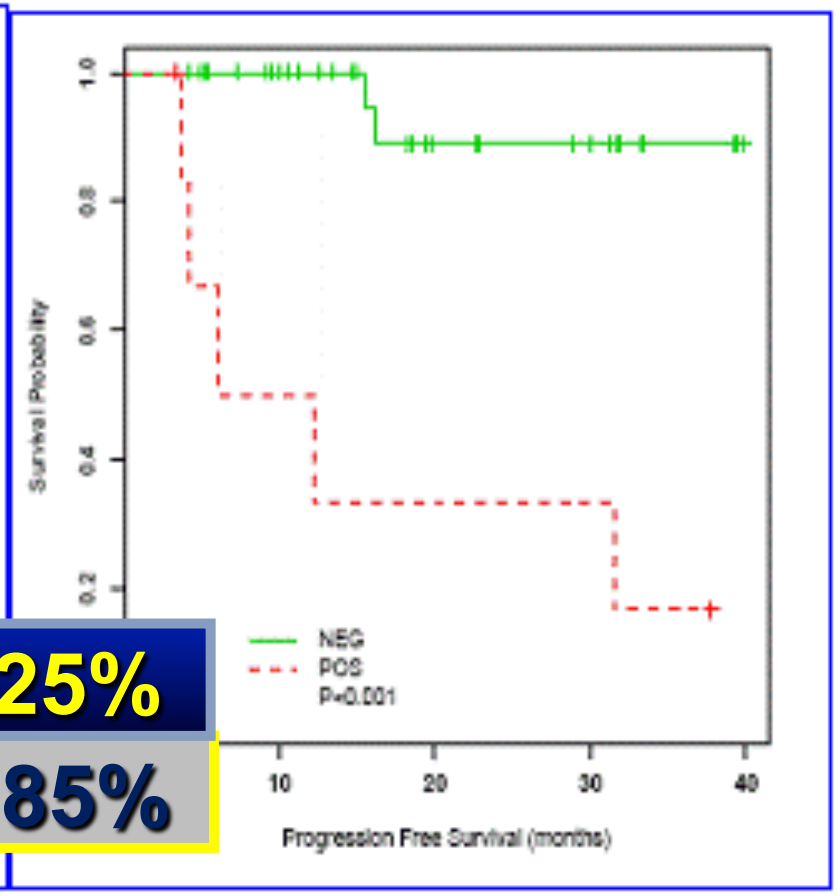
Pregno P et al, Blood 2012 .

Interim evaluation of 18-FDG-PET in DLBCL

FDG-PET/TC after cycle 2



FDG-PET/TC end of therapy



PPV 25%

NPV 85%

Cashen A et al, ASH 2008

PET – Lugano consensus meeting

- **Pretreatment PET** — **recommended**
- **Interim PET** — **not- recommended**
- **Final PET** — **recommended**
- **PET surveillance** — **not recommended**
- **Treatment modificaton** — **not recommended**

ICML Lugano 2011

DLCL10

R-CHOP-14 or R-CHOP21 with PET-oriented radiotherapy consolidation in patients with DLBCL less favourable IPI=0-1

R-CHOP-14 and consolidation radiotherapy PET oriented on patients with DLBCL IPI=0-1 less favourable outcome (according MInT)

- **Principal Investigators** — M. Balzarotti, M.G Cabras
- **Responsible for PET protocol** — L. Rigacci
- **Responsible for Radiotherapy** — U. Ricardi
- **Trial Statistician and Data Management :** — G Ciccone

Radiotherapy on PET+ residual area

196 pts
56%IPI 0-2
44%IPI 3-5

↓

RCHOP –21
x 6-8 courses
curative intent

↓

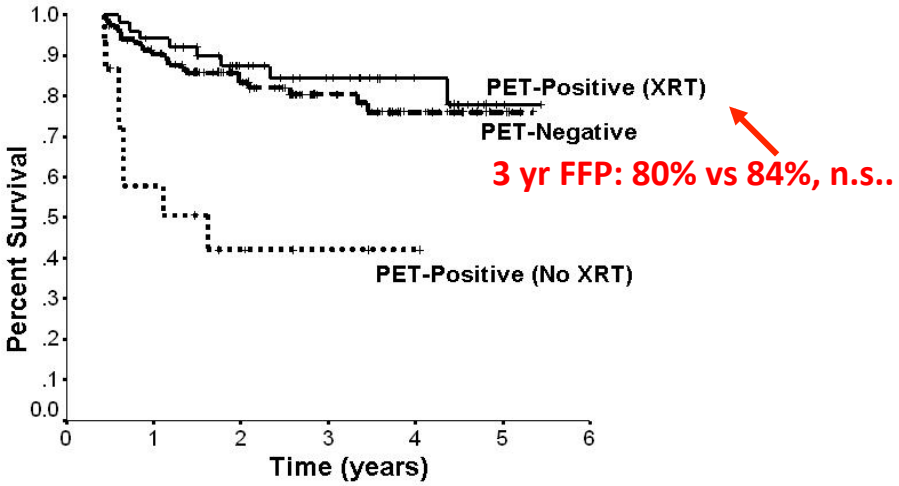
CT abnormalities
≥ 2 cm

↓

PET → NEG (62%): observation (regardless of initial bulk)

PET → POS (34%) : RT if feasible

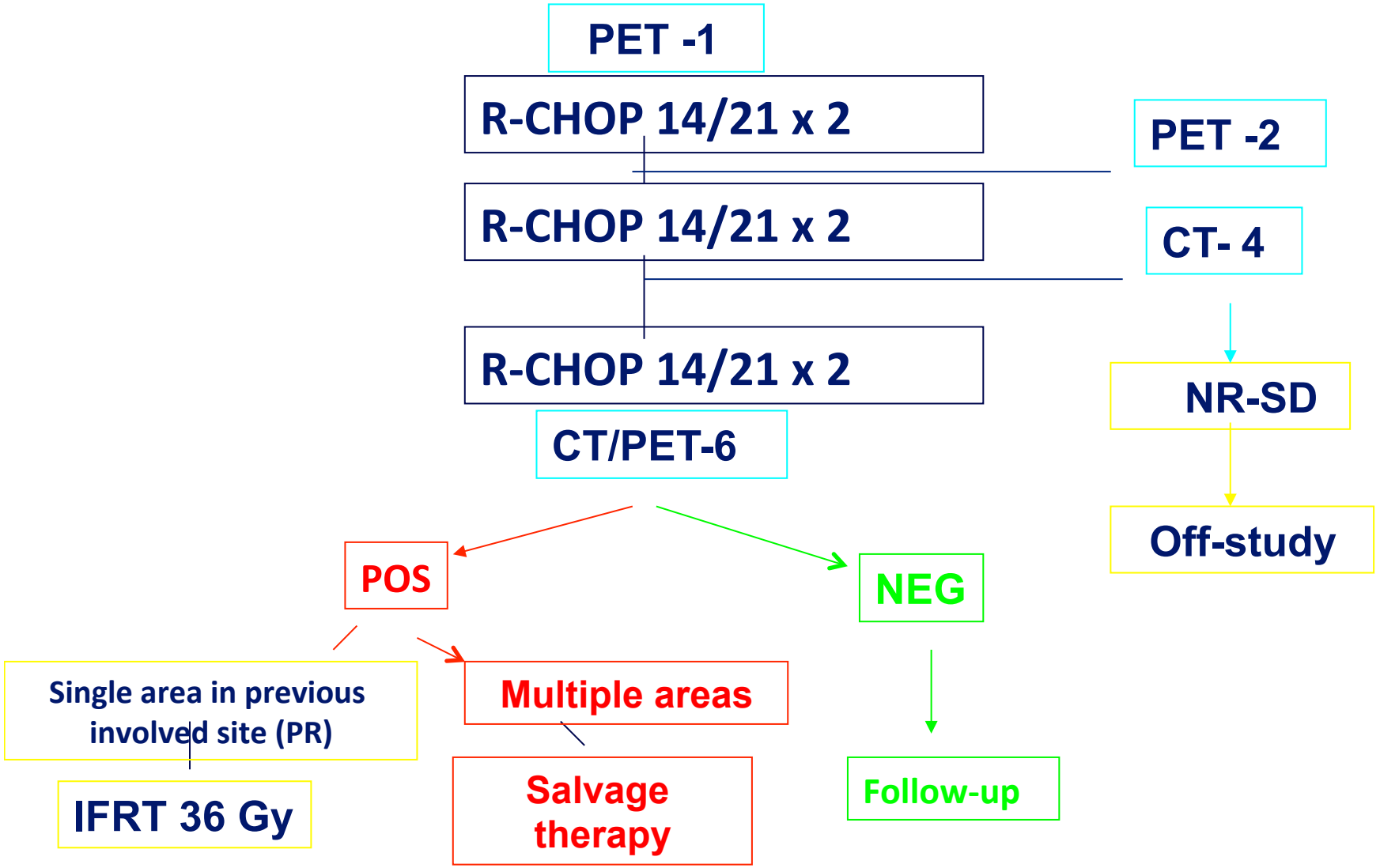
PFS in Advanced-Stage DLBCL According to Post-Treatment PET Scan Result and Consolidative Radiation



Sehn, ASH 2010

DLCL 10 IPI= 0-1+/- Bulk, age < 70 yrs

(less favourable according MInT)



Statistical analysis and endpoints

- **Phase II multicentric study**

- **Primary Endpoint:**
- **2 years PFS**
- **Secondary Endpoints:**
- **Efficacy of IFRT on PET+ lymphnodes**
- **ORR,RC,RP after 4 and 6 cycles**
- **Predictive role of PET**

DLCL10 IPI 0-1

Inclusion criteria

Age 18-70 years
Histology: DLBCL, FL IIIb, DLBCL T-cell rich
aaIPI = 1 +/-bulk or aaIPI = 0 with bulk (> 7,5 cm)
Usual criteria for observational studies
Anti-HCV+ without viral replication
Anti-HBc+, HBsAg-, Anti-HBs+/- (occult carriers)
Histological confirmation of the diagnosis

Exclusion criteria

-PMBLCL, PCNSL,PTL
- Heart failure
- hepatic or renal insufficiency not related to lymphoma
- Infection with HIV
- Active hepatitis B or C

DLBCL10

- Active Centers 28
- Enrolling patients Centers 17
- Enrolled patients at february 2016: 70

PET REVIEWED	PET NEGATIVE	PET POSITIVE
55	42	13

The mean and median review time was 3,8 days and 0,7 days, respectively

Therapy of DLBCL: key messages

- **Young low risk very favorable pts:**
  R-CHOP21, time to test CHT reduction

- **Young low risk less favorable pts:**
  R-CHOP 21, no benifit from CHT intensification (R-CHOP14) or addition of more drugs (etoposide)

Therapy of DLBCL: key messages

- **PET at end of therapy:**
  could guide the choice of radiotherapy

- **Radiotherapy:**
  The role of radiotherapy is still controversial. Probably an INRT will replace IFRT


GRAZIE