New Approaches in the Treatment of Follicular NHL: The Rituximab story

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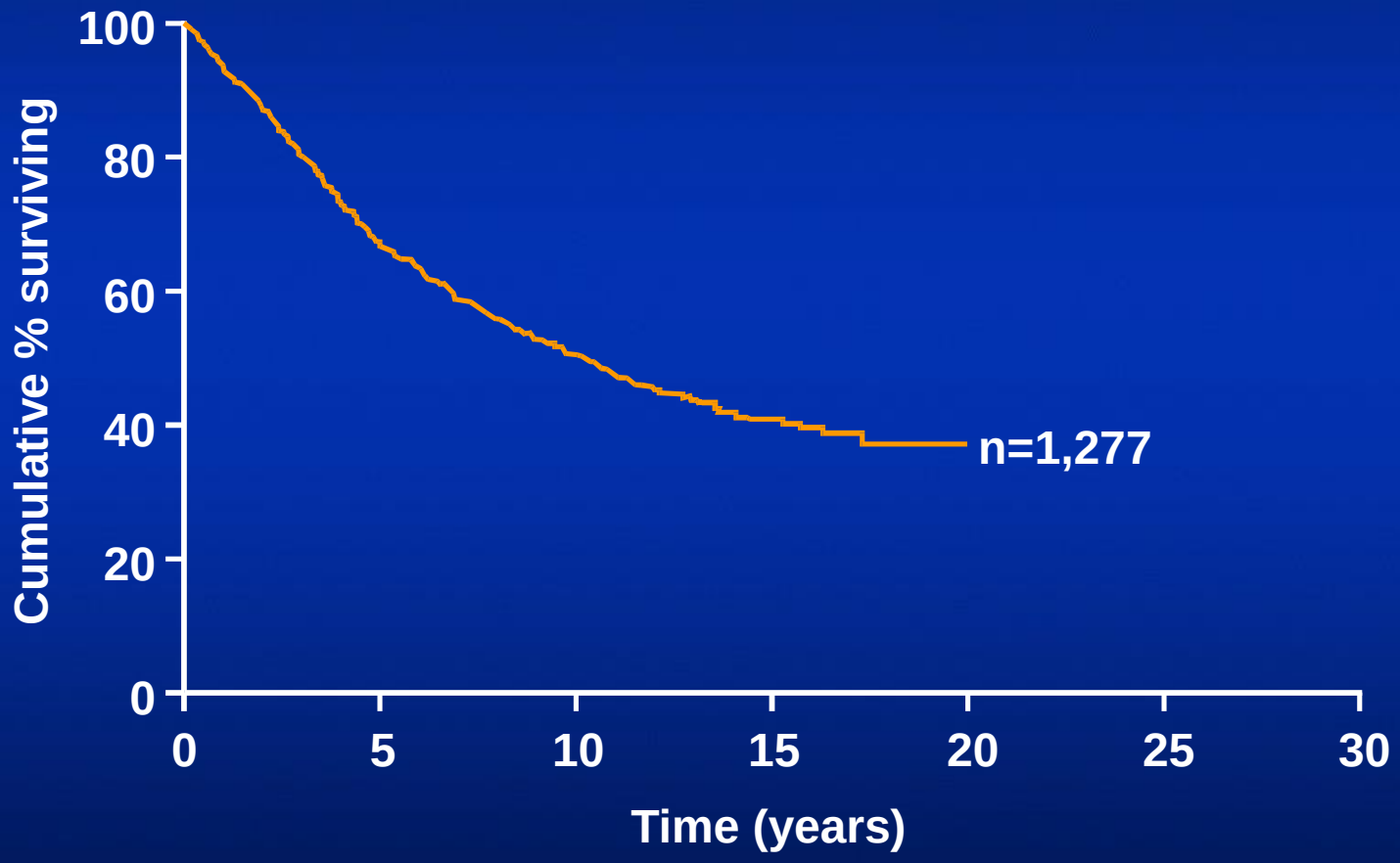
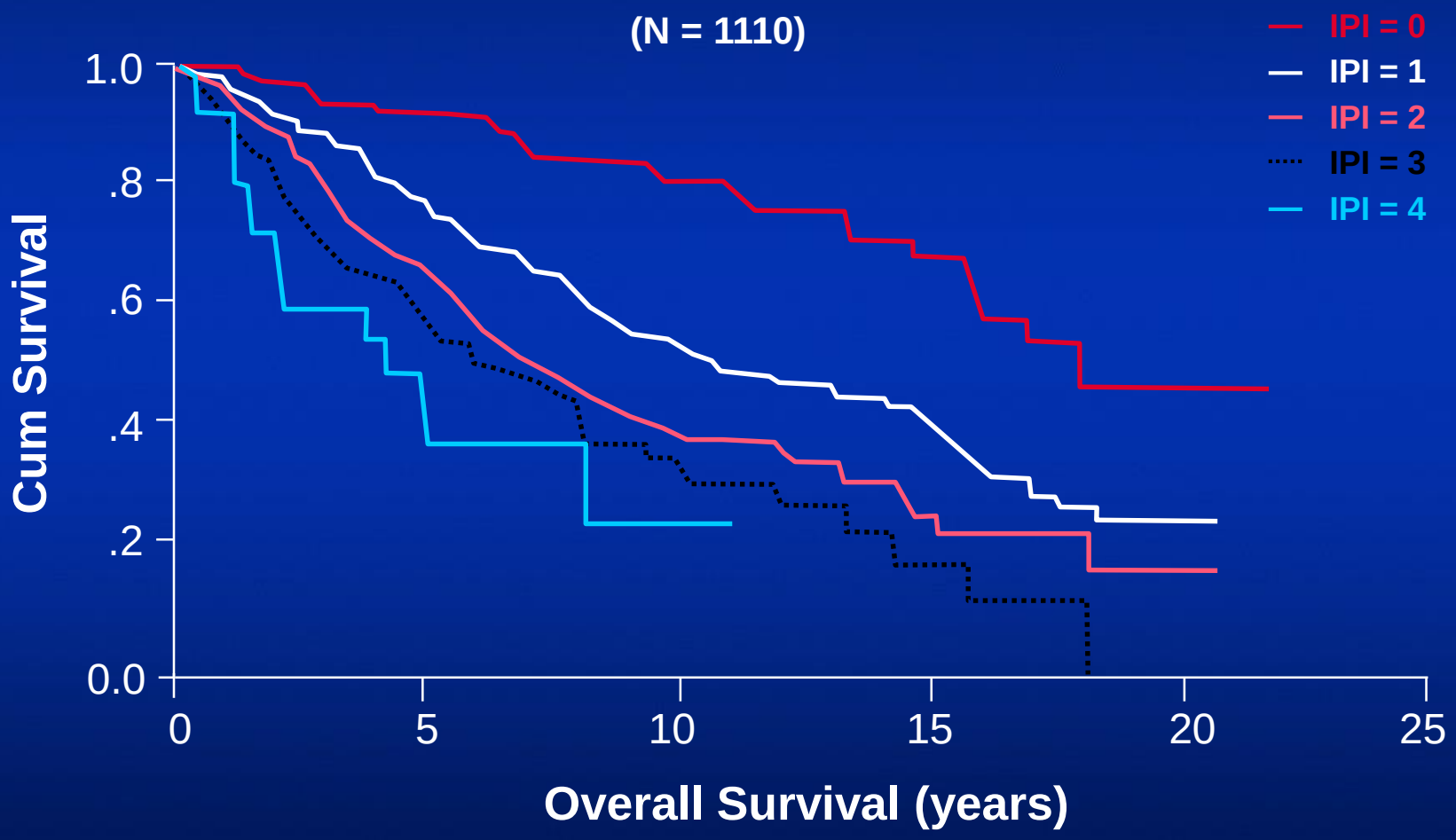
December 2008

BNLI cumulative survival follicular lymphoma



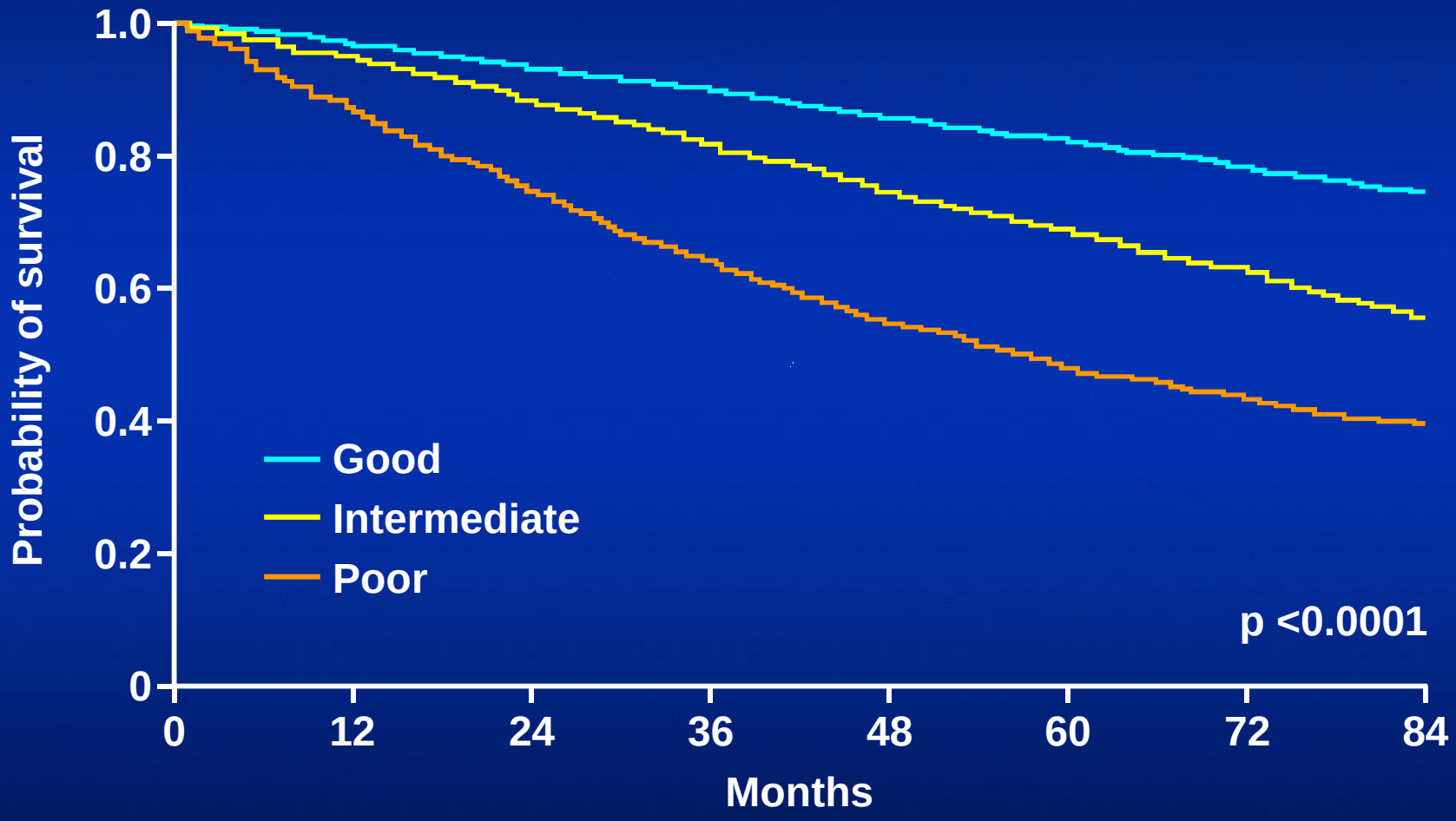
Follicular Lymphoma: Survival by IPI Index



The Follicular Lymphoma International Prognostic Index (FLIPI)

Risk group	No. of factors	Patients (%) (n=1,795)	Overall survival		Relative risk
			5-year (%)	10-year (%)	
Good	0–1	36	91	71	1
Intermediate	2	37	78	51	2.3
Poor	≥3	27	53	36	4.3

Overall survival according to FLIPI

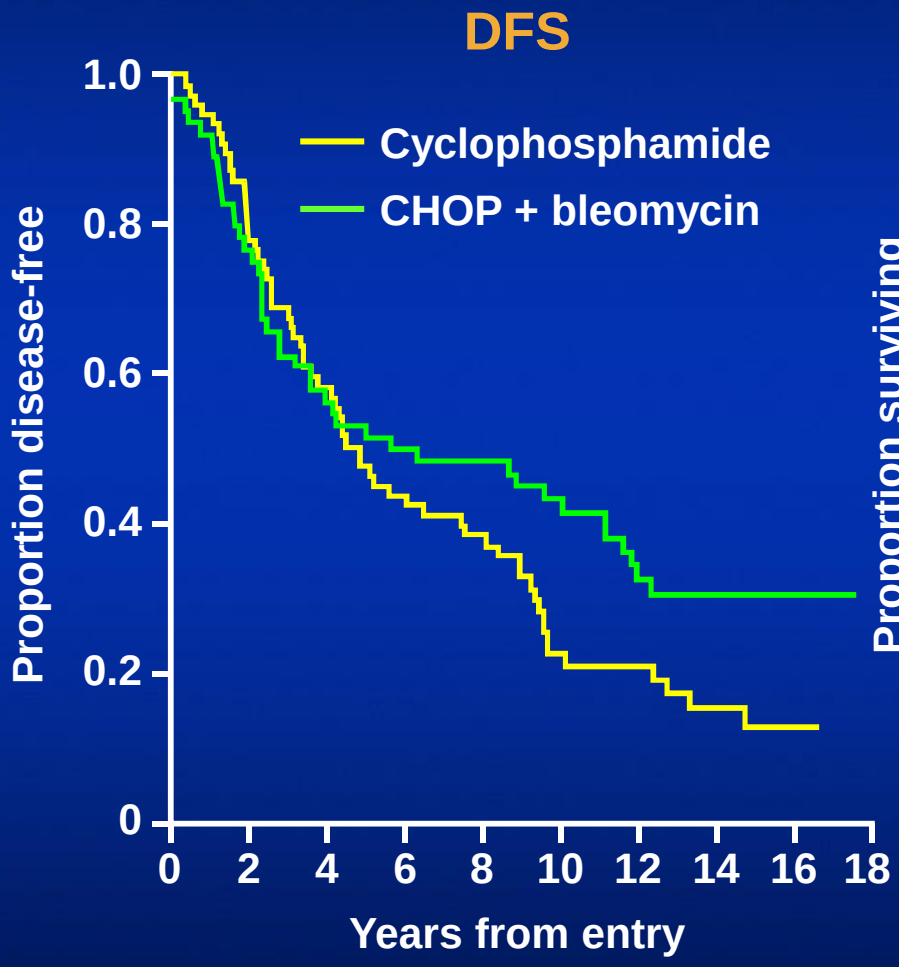


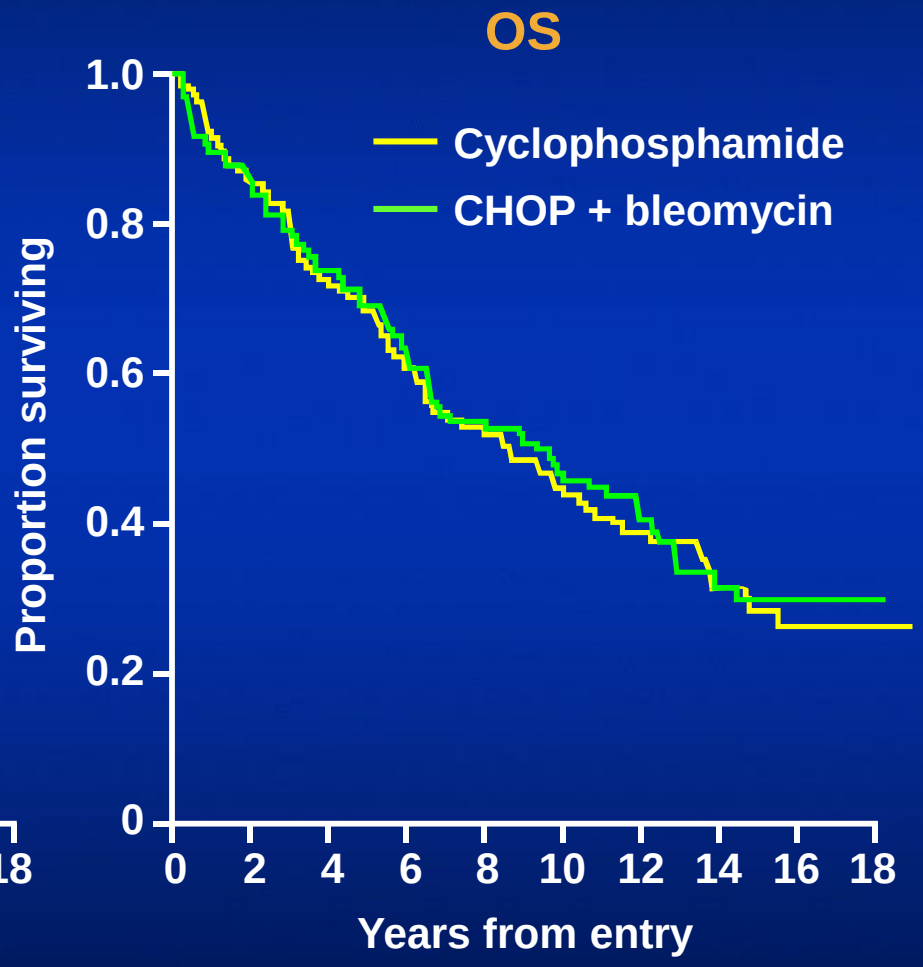
Ch/P versus CHOP in symptomatic indolent NHL

- 259 patients advanced stage, untreated, symptomatic
- ORR: Ch/P 36% versus CHOP 60% ($p < 0.01$)
- 5-year survival = 41% versus 44% (p=NS)
- Median survival = 46 versus 52 m (p=NS)

Kimby E, et al. Ann Oncol 1994;5(Suppl.2):67–71

In FL more aggressive treatment has no impact on survival





Peterson BA, et al. J Clin Oncol 2003;21:5–15

Higher Risk Indolent Lymphoma

? Advantage to Any Therapeutic Approach

Smalley et al. *N Engl J Med 1992*; *Leukemia 2001*

High risk features:

I-COPA > COPA

Solal-Celigny et al. *J Clin Oncol 1998*

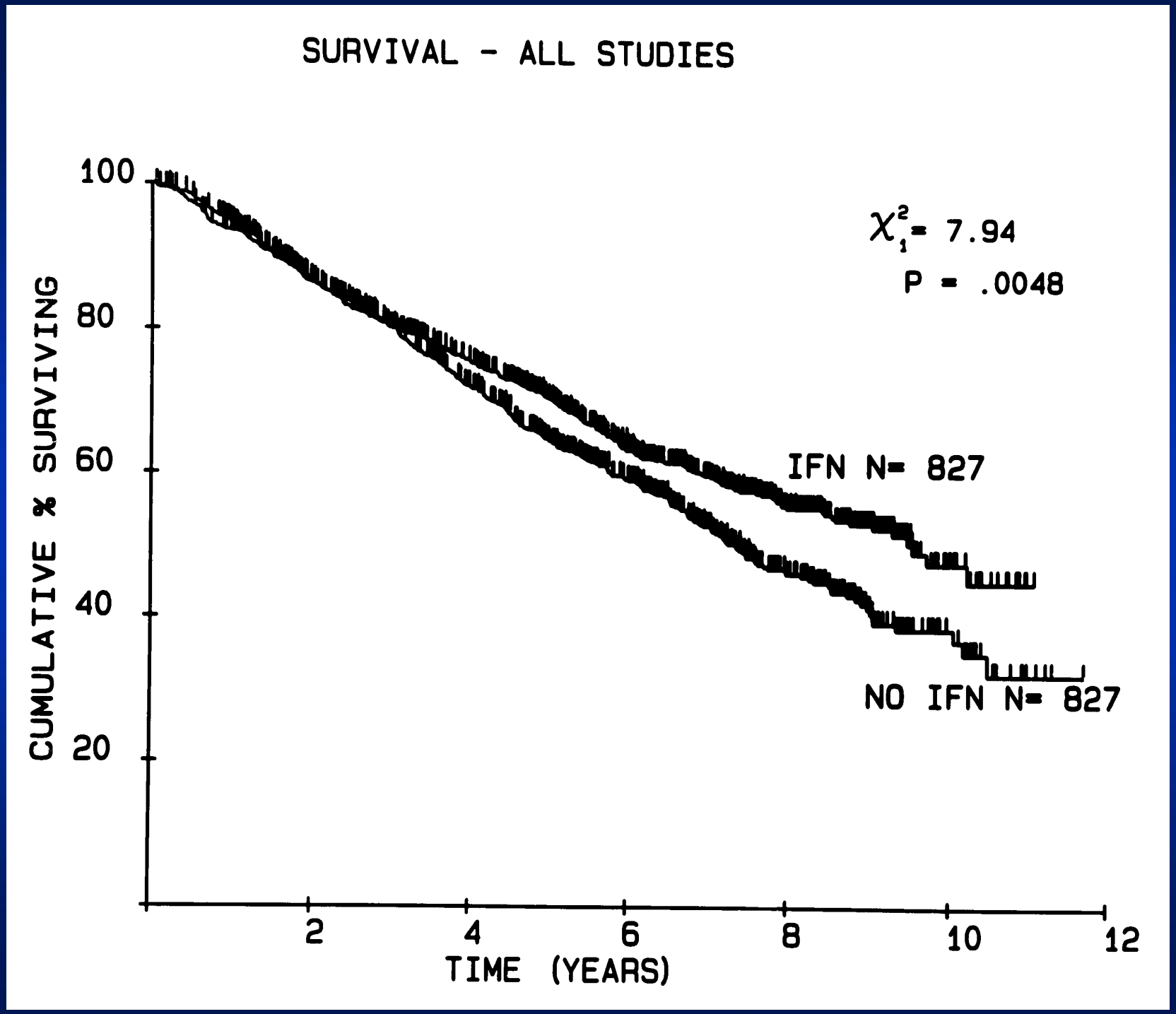
High tumor burden

CHVP + IFN > CHVP

Coiffier et al. *Ann Oncol 1999*

Age > 60, high tumor burden

CHVP + IFN > fludarabine

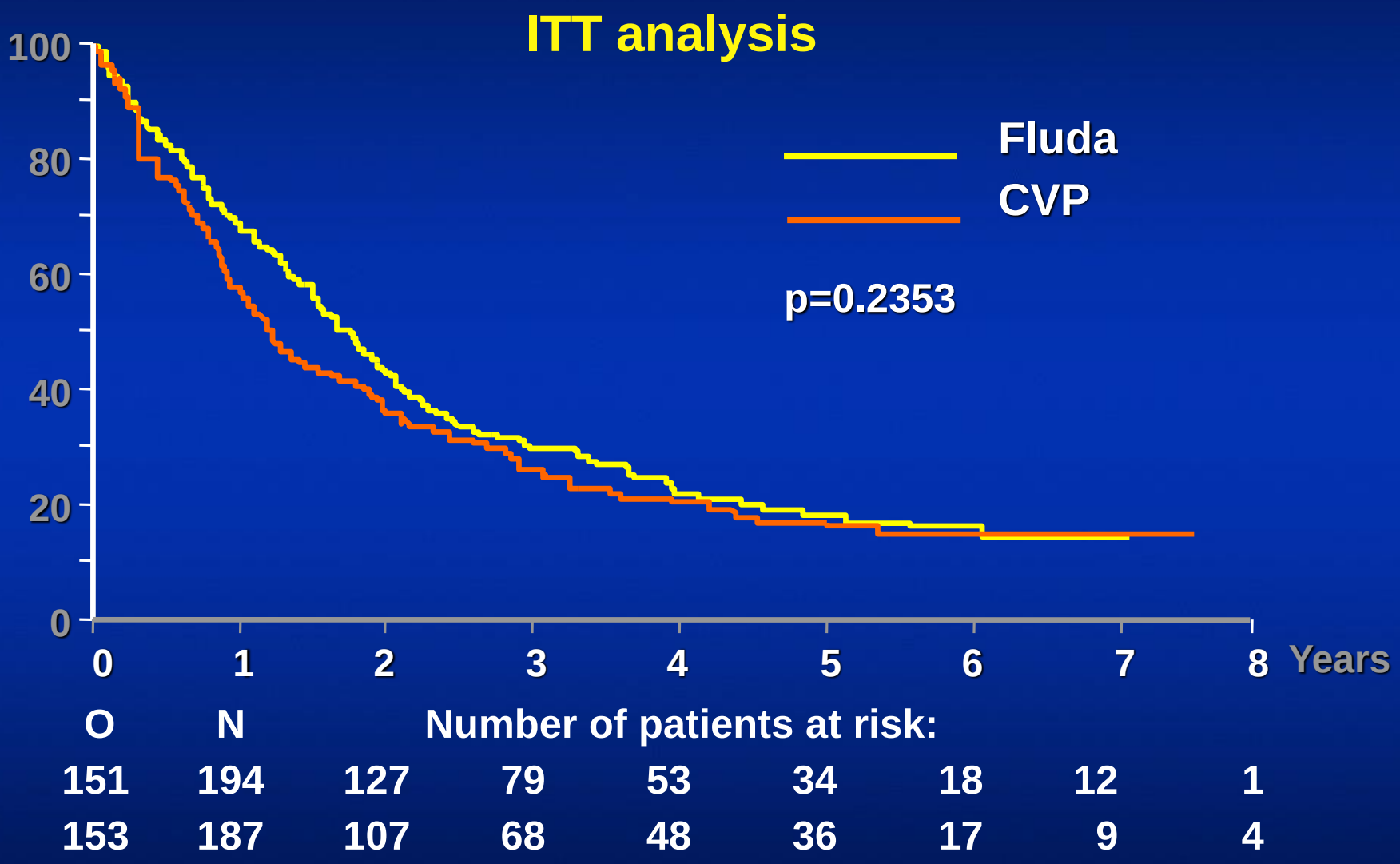

SURVIVAL - ALL STUDIES
100
80
60
40
20
CUMULATIVE % SURVIVING
χ^2_1= 7.94
P = .0048
IFN N= 827
NO IFN N= 827
2
4
6
8
10
12
TIME (YEARS)

FLUDARABINE compared to CVP in newly diagnosed patients with stage III/IV low Grade NHL
Final analysis of a prospective, randomized phase III intergroup study in 381 patients

R.E Marcus A. Hagenbeek, H. Eghbali, S. Monfardini, E. Resegotti, PJ Hoskin, C. de Wolf-Peeters, K. McLennan, E. Staab-Renner, A. Schott, I. Teodorovic, A. Negrouk, M. van Glabbeke and DC Linch

EORTC Lymphoma Group
British National Lymphoma Investigation (BNLI)
Dutch Association for Hemato-Oncology (HOVON)

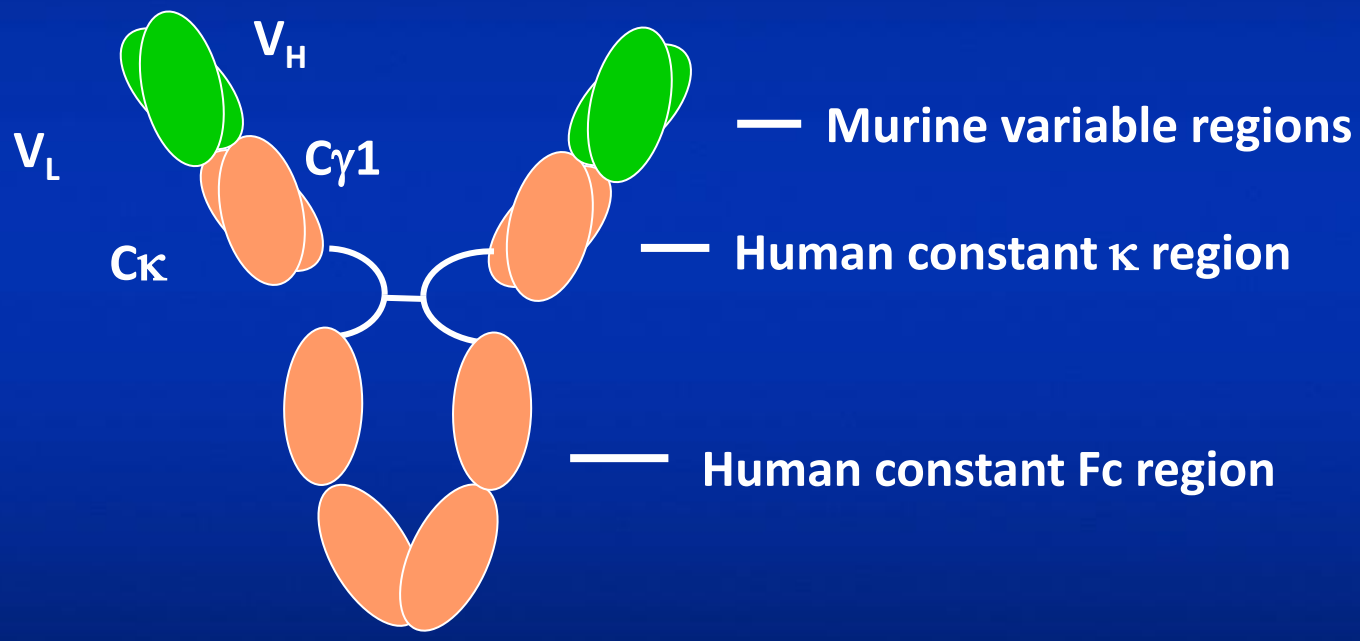
PROGRESSION FREE SURVIVAL



O	N	Number of patients at risk:						
151	194	127	79	53	34	18	12	1
153	187	107	68	48	36	17	9	4

The Structure of Rituximab

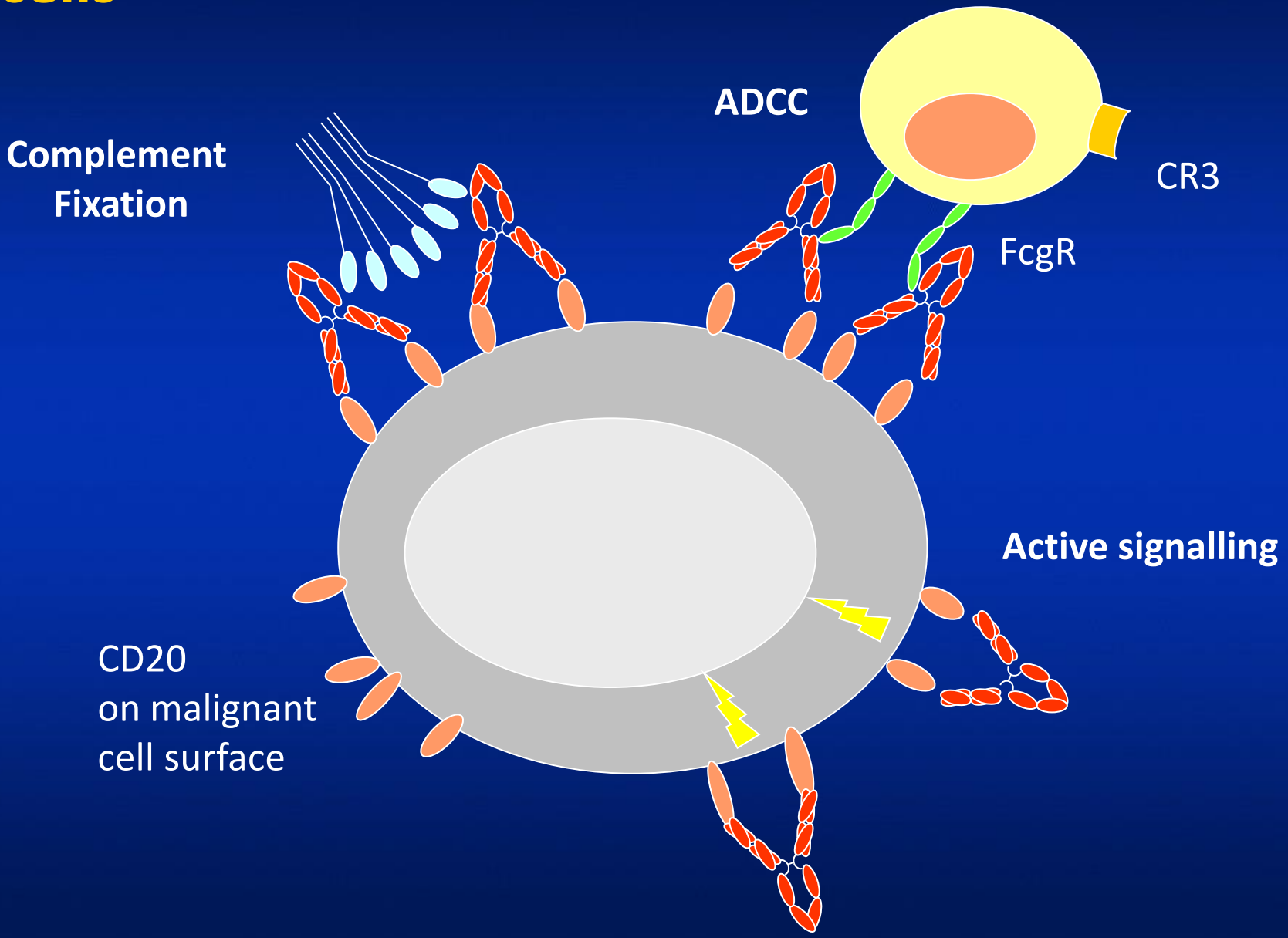
Chimeric anti-human CD20 monoclonal antibody



Variable region: murine IgG1 kappa anti-CD20

Constant region: human IgG1 heavy chain and kappa light chain

Potential Effects of anti-CD20 on Tumour cells



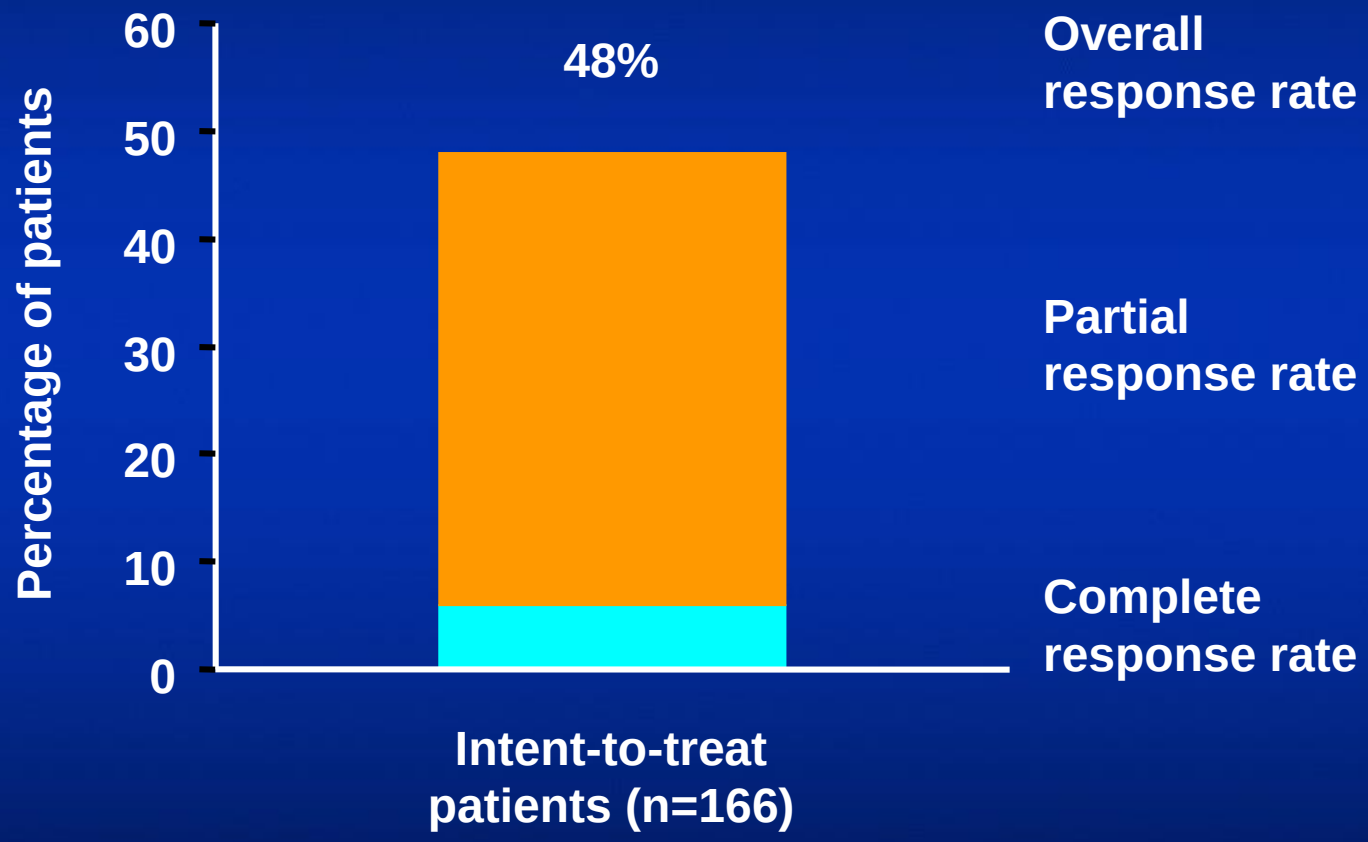
Rituximab monotherapy
" Pivotal Trial"

Multicenter, open-label, single-arm study in outpatients

- 166 patients low-grade or follicular, CD20+, B-cell NHL (IWF A–D)
- All had either relapsed or failed previous therapy
  - *2 mean prior courses of chemotherapy*
- Rituximab was infused once weekly at 375mg/m^2 for 4 doses (days 1, 8, 15, and 22)
- Independent panel convened to confirm response

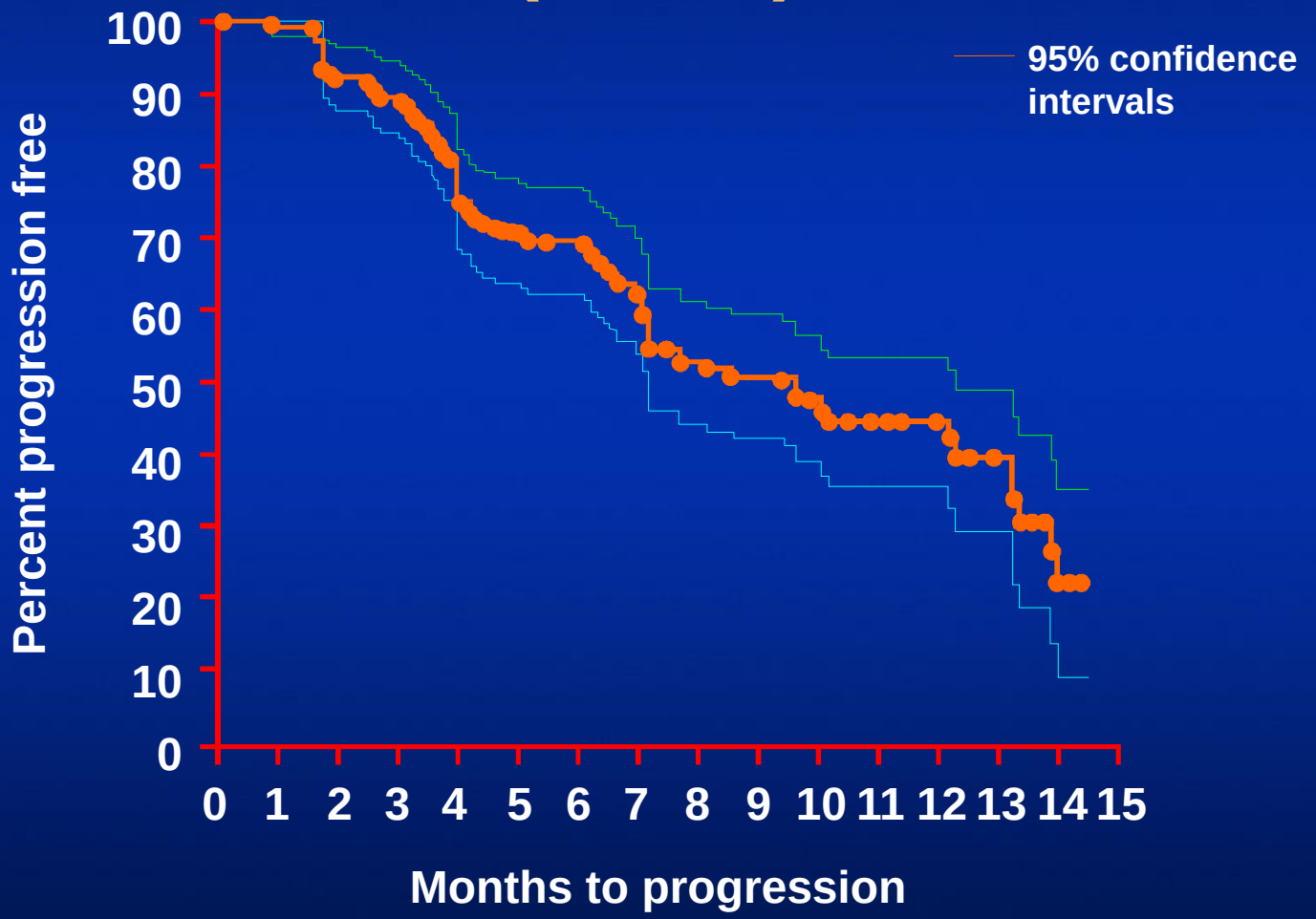
McLaughlin P et al. J Clin Oncol 1998;16:2825–33

Pivotal trial: overall response rate



McLaughlin P et al. J Clin Oncol 1998;16:2825–33
Data on file, IDEC Pharmaceuticals Corporation

Pivotal trial: time to disease progression for evaluable patients (n=151)



Rituxan for Previously Untreated Indolent NHL : Colombat et al

No. of patients		**50**
Age	**Median**	**52**
	(range)	**(32-75)**
Follicular NHL (grade)	**I**	**44%**
	II	**48%**
	III	**6%**
	Other	**2%**
Stage	**I-II**	**8%**
	III-IV	**92%**
Extranodal sites	**0-1**	**82%**
	≥ 2	**18%**

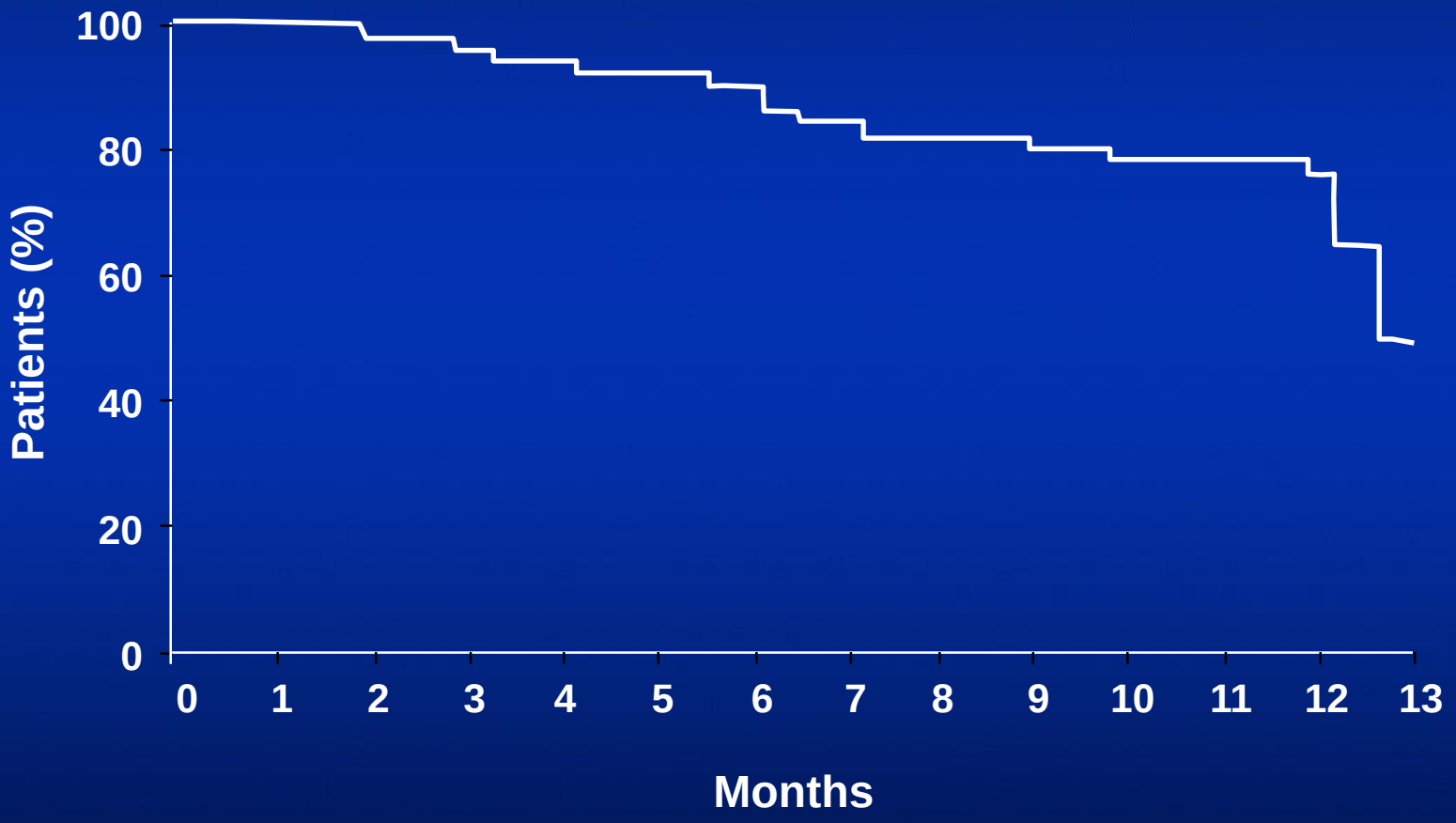
Colombat et al. *Blood.* 2001;97:101.

Rituxan® for Previously Untreated Indolent NHL: Response

	% of Patients (n = 49)*	
	1st Evaluation (~ 3 months)	2nd Evaluation (12 months)
ORR	73	80
CR/CRu	26	41
PR	47	39

Colombat et al. *Blood.* 2001;97:101.

Rituxan® for Previously Untreated Indolent NHL: TTP



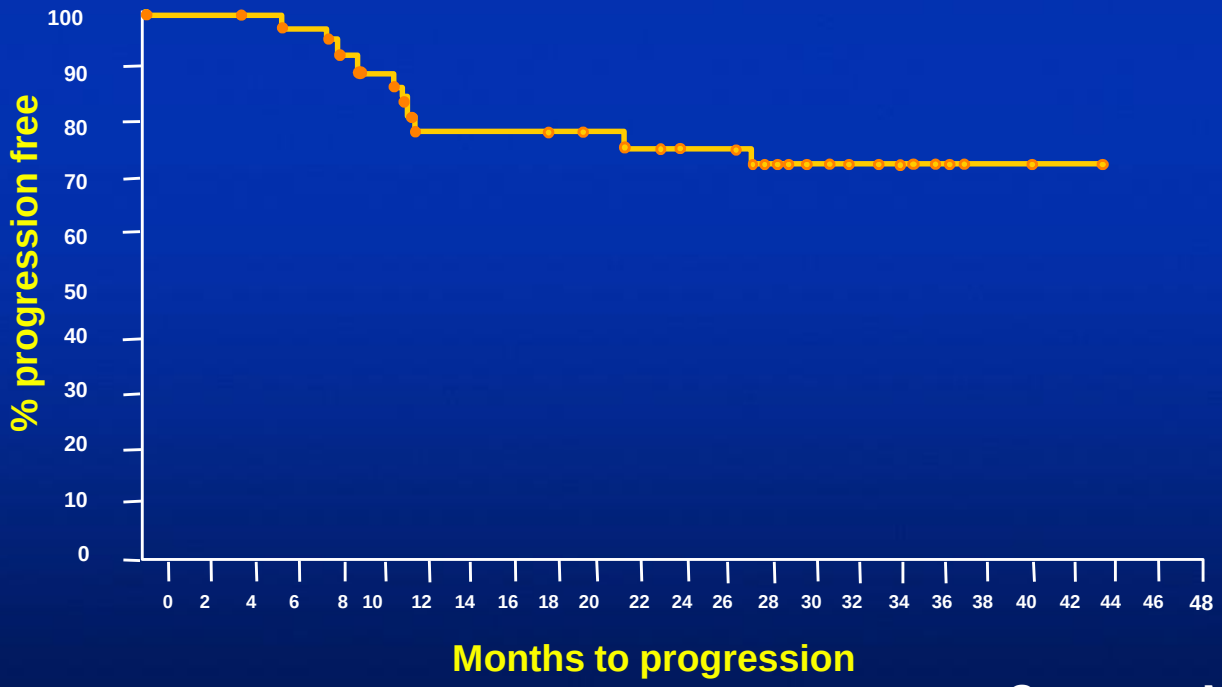
Adapted from Colombat et al. *Blood.* 2001;97:101.

Combination of CHOP plus Rituximab in Follicular Lymphoma

Rituximab (375 mg/m²)

week 1 2 5 8 11 14 17 20 21

CHOP (every 3 weeks)



Czuczman M et al. J Clin Oncol. 1999;17:268–276

Czuczman M et al. Blood. 2003; 102 Abstract 1493

M39021 - An international multicentre randomised open-label phase III trial comparing CVP chemotherapy plus rituximab with CVP alone in untreated patients with stage III/IV follicular non-Hodgkin's lymphoma

-

Final Analysis

Robert Marcus, Kevin Imrie, Andrew Belch, David Cunningham, Eduardo Flores, John Catalano, Philippe Solal-Celigny, Fritz Offner, Jan Walewski, João Raposo, Andrew Jack, Paul Smith

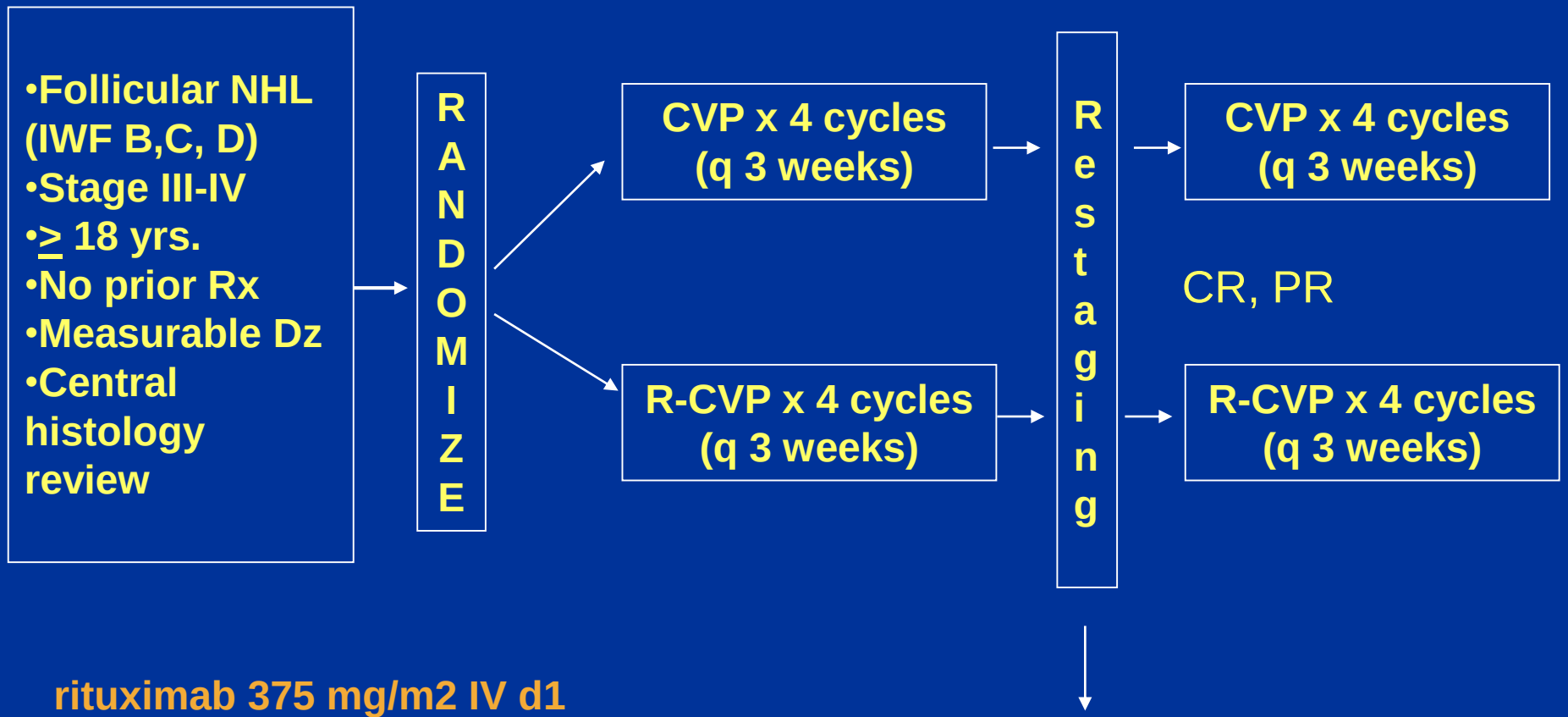
Rationale (CVP)

- Anthracycline containing regimens show high response rates with increased toxicity : no proven prolongation of TTF
- Interferon, fludarabine not generally accepted as first line therapy
- CVP remains standard first line therapy for stage III / IV follicular NHL

Rationale (rituximab)

- Rituximab effective in previously untreated stage III/IV follicular lymphoma
- Response rate and duration equivalent to standard chemotherapies
- Rituximab with chemotherapy shows high response rates with minimally increased toxicity

M39021 – Study Design



rituximab 375 mg/m2 IV d1
cyclophosphamide 750 mg/m2 IV d1
vincristine 1.4 mg/m2 IV d1
prednisone 40 mg/m2 PO d1–5

Inclusion criteria

- CD20+ follicular NHL; Ann Arbor stage III or IV (classes B, C and D)
- No previous systemic antilymphoma treatment
- WBC <25 x 10^9/L
- No CNS involvement
- Additional standard inclusion criteria

Primary endpoint

- Time to treatment failure (TTF)
- Events defined by:
  - progressive disease/relapse after response
  - death
  - institution of a new antilymphoma treatment (at any time)
  - stable disease after cycle 4

Secondary endpoints

- Overall response rate (ORR)
- Time to progression (TTP)
- Time to next lymphoma therapy (TNLT)
- Duration of response
- Disease free survival
- Overall survival

Patient characteristics

	CVP n=159	R-CVP n=162
Median Age (years)	53	52
% of patients		
Stage III–IV	99	99
Histology–Follicular NHL		
Grade 1,2	89	90
Grade 3	8	9
Elevated LDH level	26	26
B-symptoms	32	40
Bulky disease	46	39

Prognostic factors
IPI

	CVP (n=151)	R-CVP (n=151)
IPI, n (%)		
0	1 (0.7)	1 (0.7)
1	69 (45.7)	72 (47.7)
2	57 (37.7)	57 (37.7)
3	21 (13.9)	19 (12.6)
4	3 (2.0)	2 (1.3)
5	0	0
B-symptoms, n (%)	51 (32.1)	65 (40.1)

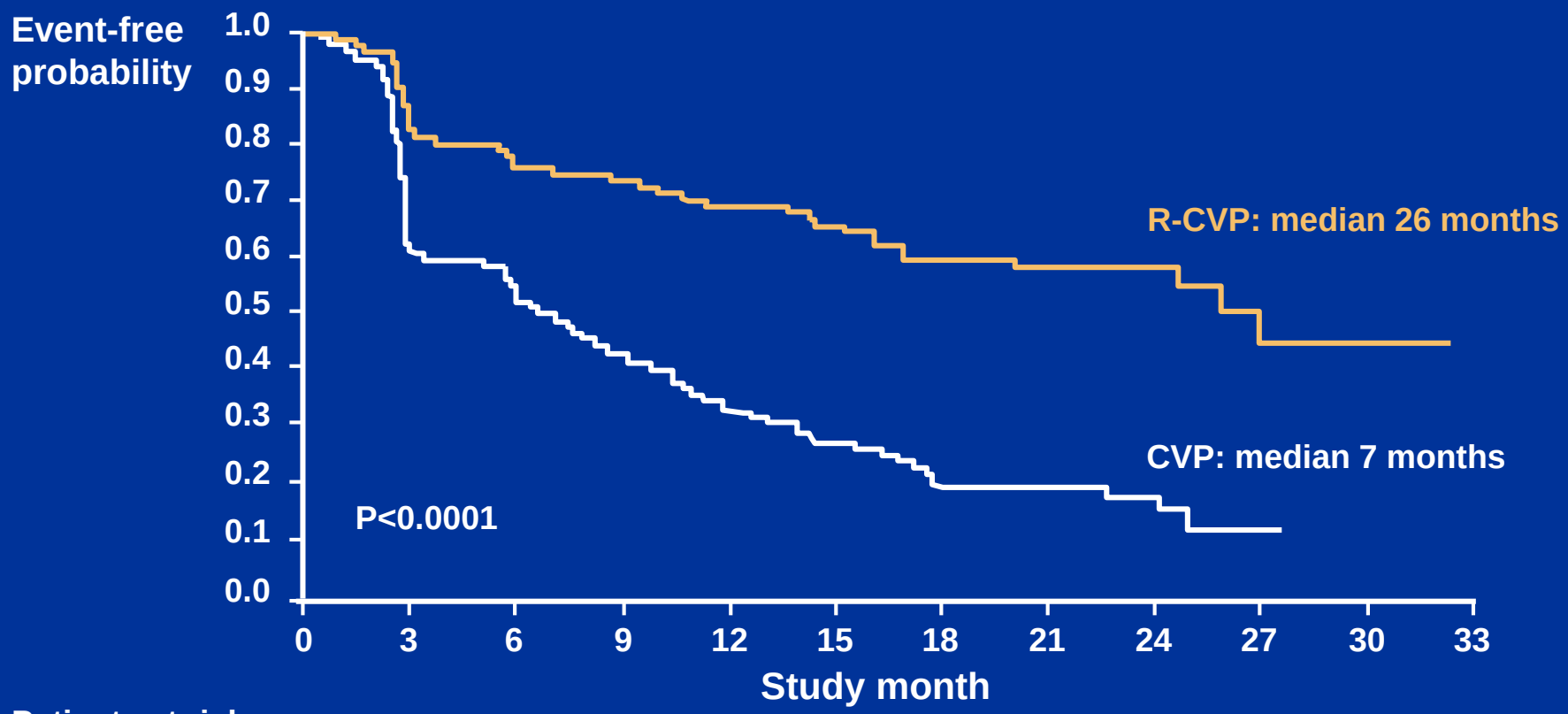
Prognostic factors
Follicular Lymphoma International Prognostic Index (FLIPI)

	CVP (n=150)	R-CVP (n=151)
FLIPI score, n (%)		
0–1 (good)	10 (6.7)	19 (12.6)
2 (intermediate)	65 (43.3)	61 (40.4)
3–5 (poor)	75 (50.0)	71 (47.0)

Response rates

Response	CVP (n=159)	R-CVP (n=162)	
ORR	57.2 %	80.9 %	*P<0.0001*
CR	7.5 %	30.2 %	
CRu	2.5 %	10.5 %	
CR/CRu	10.0 %	40.7 %	*P<0.0001*
PR	47.2 %	40.1 %	

Time to treatment failure
Final Analysis (18 months FU)



Patients at risk:

CVP	159	100	87	67	43	29	14	13	9	1	0	0
R-CVP	162	140	123	114	95	73	50	37	20	8	3	0

Follow-up in patients with stable disease after cycle four

- **CVP**
  - **42 patients had stable disease after cycle four**
    - 8 patients had no further events
    - 34 patients had an event
      - 22 new treatment
      - 9 progressive disease, 3 relapsed
- **Rituximab + CVP**
  - **21 patients had stable disease after cycle four**
    - 6 patients had no further events
    - 15 patients had an event
      - 8 new treatment
      - 4 progressive disease, 3 relapsed

Patients in stable disease at cycle four

- **CVP**
  - **26 patients (62%) continued**
    - 19 completed eight cycles
      - 9 achieved a response
      - 7 remained in stable disease
      - 3 progressed
- **Rituximab + CVP**
  - **17 patients (81%) continued**
    - 12 patients completed eight cycles
      - 7 achieved a response
      - 3 remained in stable disease
      - 2 progressed

Time to treatment failure: type of first event

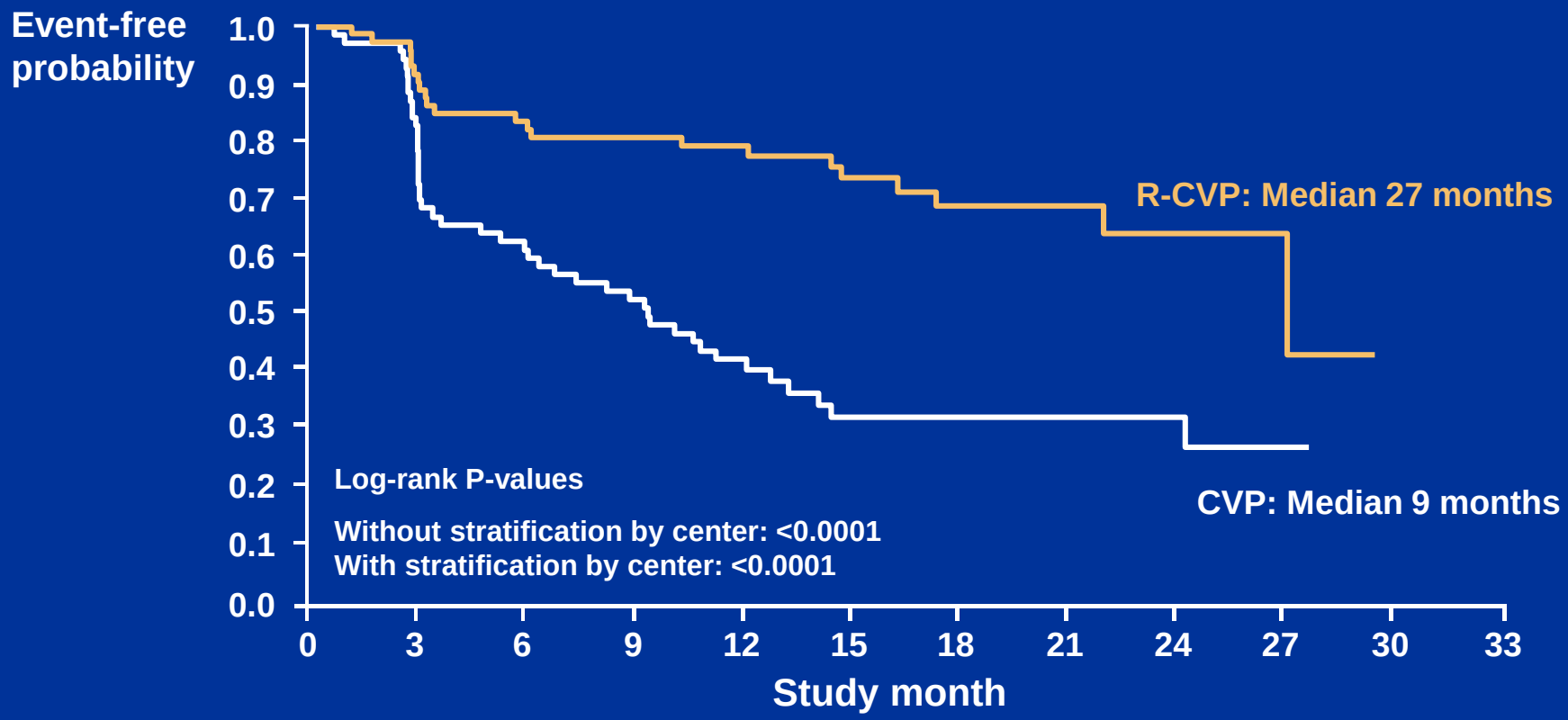
	No. of patients (%)	
	CVP (n=159)	R-CVP (n=162)
Patients with event	124 (78.0)	65 (40.1)
Event		
Relapse after response	51 (32.1)	31 (19.1)
Stable disease after cycle four	42 (26.4)	21 (13.0)
Progressive disease	15 (9.4)	9 (5.6)
Institution of a new treatment regimen	14.8 (8.8)	4 (2.5)
Death from any cause	2 (1.3)	0

Second-line therapy

- **CVP**
  - **94 started new treatment**
    - 13 received rituximab monotherapy
    - 13 received rituximab and chemotherapy
- **Rituximab + CVP**
  - **44 started new treatment**
    - 2 had rituximab-containing regimens

(Kaplan-Meier plots by intent to treat)

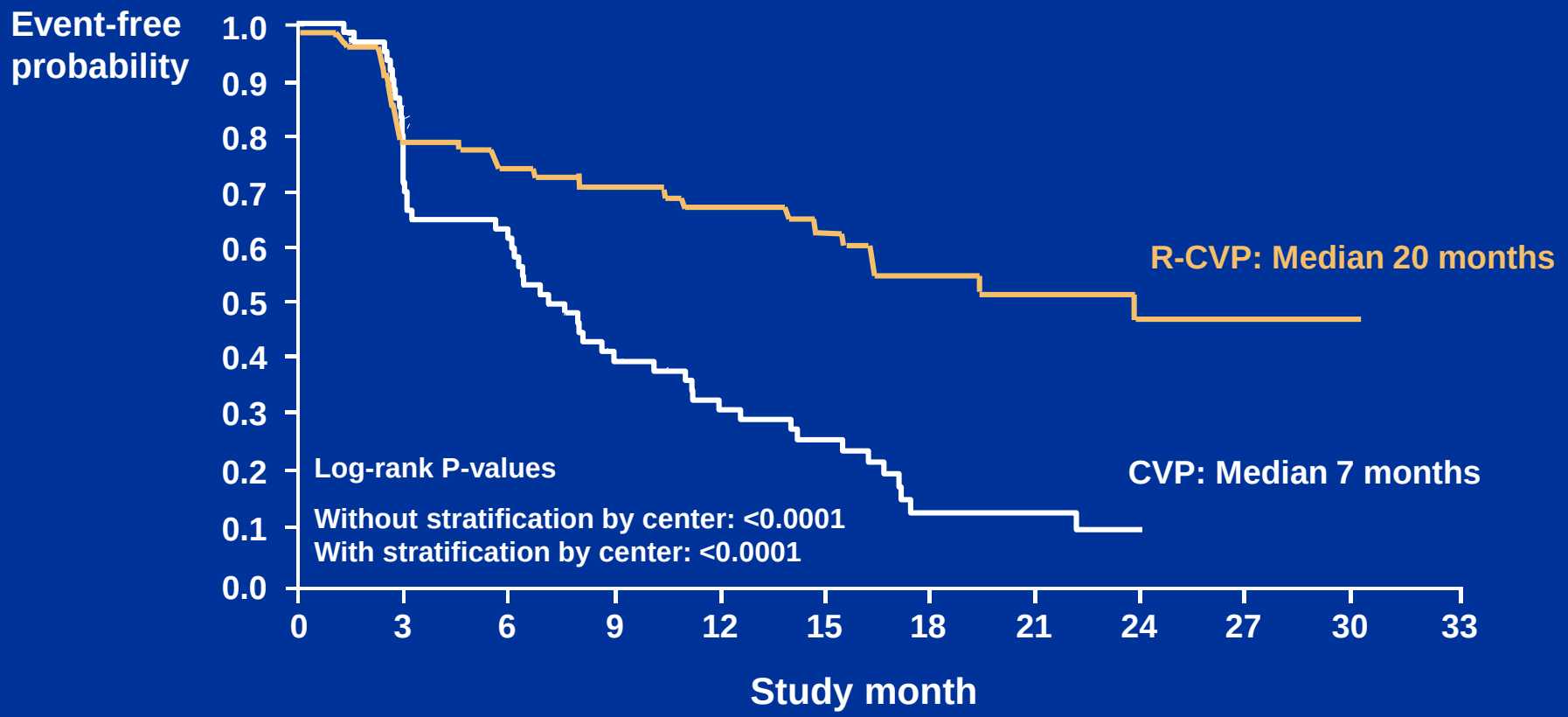
Time to treatment failure by baseline IPI score — good prognosis (IPI 1) Final Analysis



Patients at risk:

CVP	69	47	41	35	21	14	8	8	6	1	0	0
R-CVP	72	64	58	56	46	35	25	18	5	2	0	0

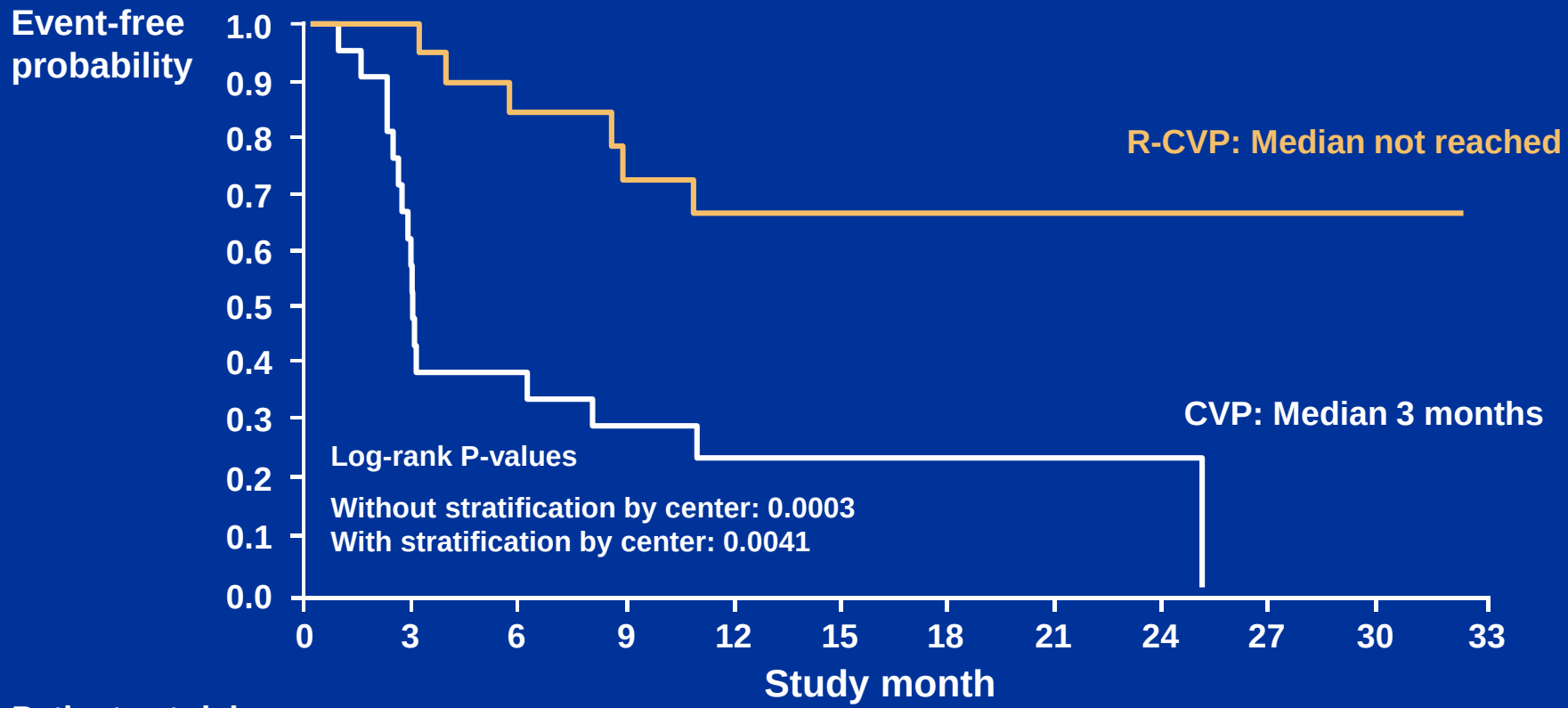
Time to treatment failure by baseline IPI score — intermediate prognosis (IPI 2) Final Analysis



Patients at risk:

CVP	57	37	31	21	18	11	4	3	2	0	0	0
R-CVP	57	46	40	37	32	27	16	13	11	3	1	0

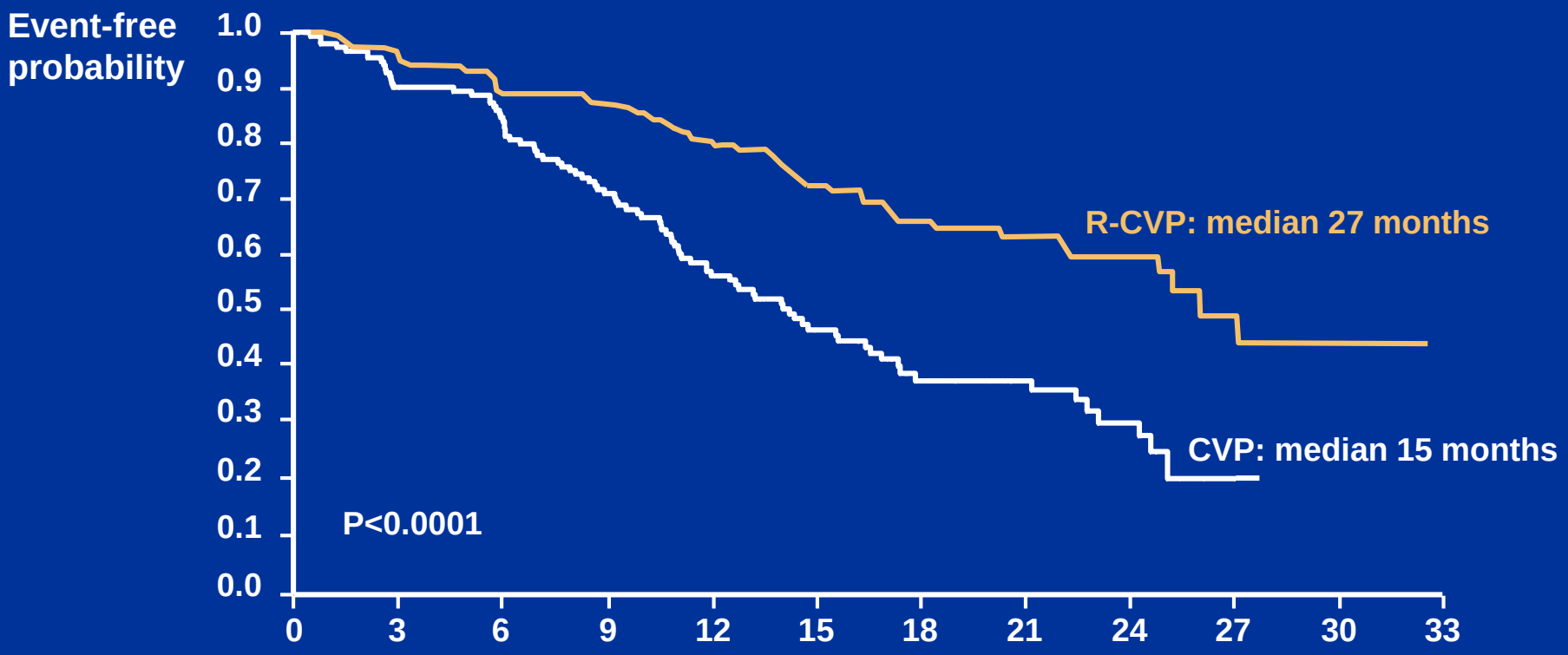
Time to treatment failure by baseline IPI score — poor prognosis (IPI 3,4) Final Analysis



Patients at risk:

CVP	21	8	8	5	3	2	2	2	1	0	0	0
R-CVP	19	19	16	12	10	7	5	4	3	3	2	0

Time to progression, relapse or death
Final Analysis (18 months FU)

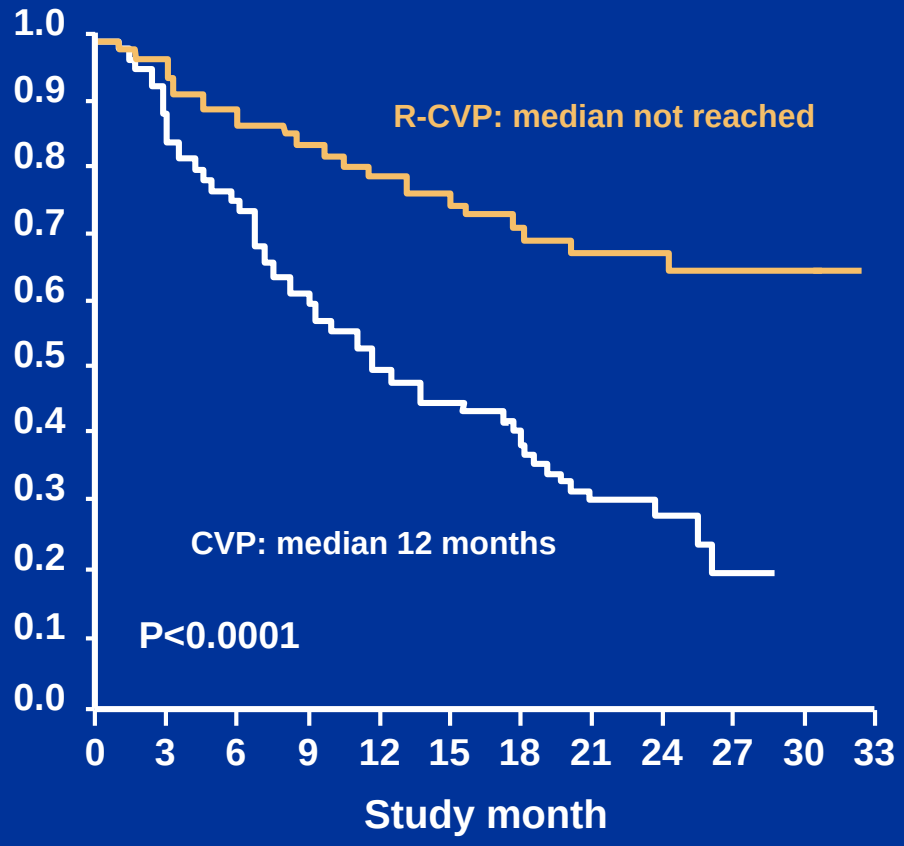


Patients at risk:

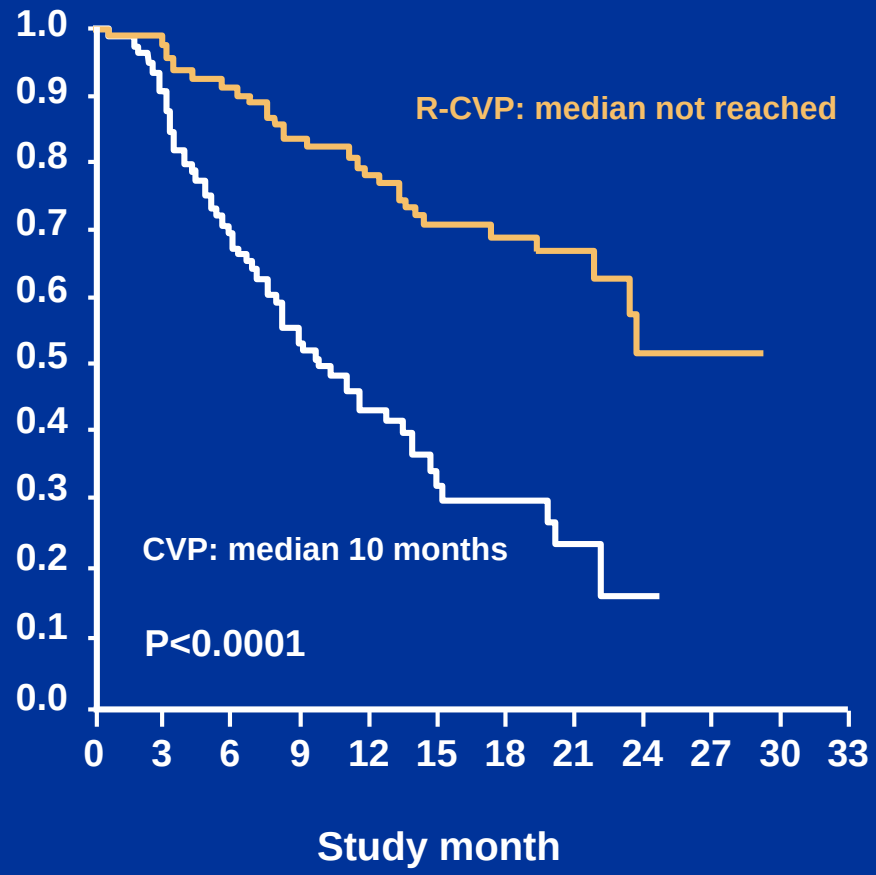
CVP	159	140	130	106	75	49	31	24	16	2	0	0
R-CVP	162	156	143	134	110	83	60	44	25	9	3	0

Time to next antilymphoma treatment and duration of response Final Analysis (18 months FU)

Time to next antilymphoma treatment or death



Duration of response



Adverse events occurring within 24 hours of infusion

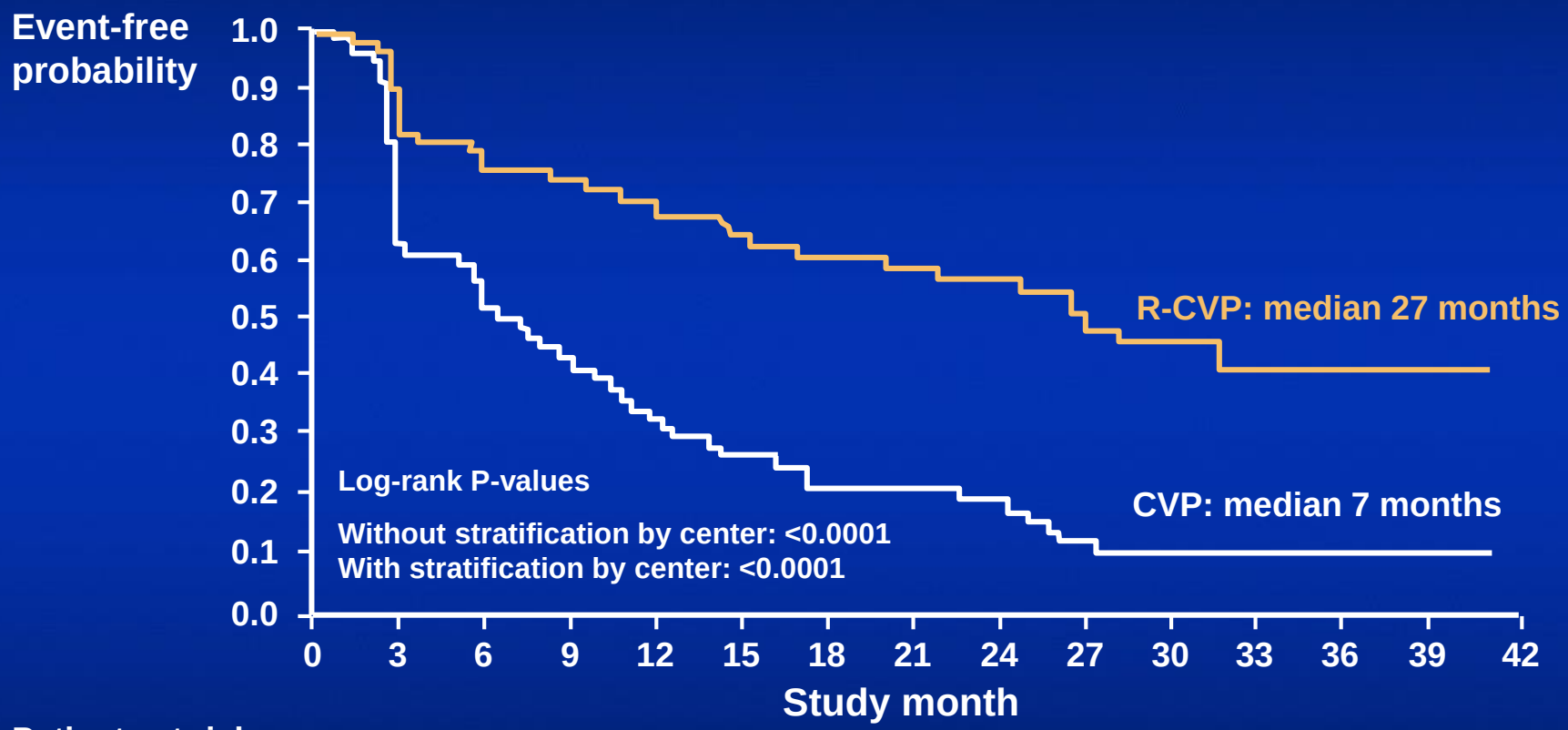
	CVP (n=159)	R-CVP (n=162)
Patients with at least one AE within 24 hrs, n (%)	81 (51.0)	115 (71.0)
Patients with a grade 3 or 4 rituximab-related IRR, n (%)		14 (8.6)
Patients prematurely withdrawn owing to rituximab-related IRR, n (%)		2 (1.3)

No fatal infusion-related reaction occurred in the R-CVP arm

Haematology adverse events (worst values grade 3–4) and infections

	CVP (n=159)	R-CVP (n=162)
No. of patients (%)		
Haemoglobin	3 (1.9)	1 (0.6)
Neutrophils	23 (14.5)	39 (24.1)
Platelets	0	2 (1.2)
Leucocytes	14 (8.8)	19 (11.7)
Infections	7 (4.4)	7 (4.3)

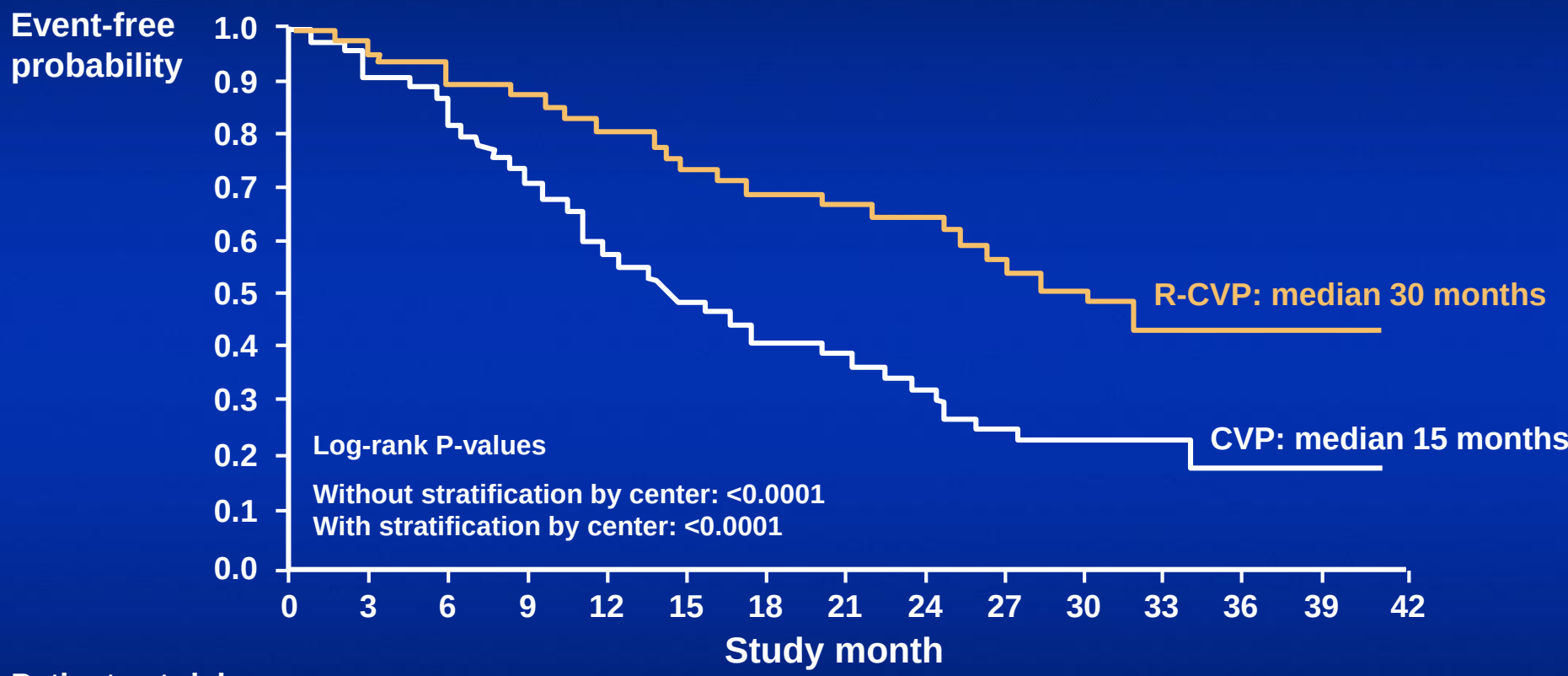
R-CVP vs CVP
TTF (Median FU 25 months)



Patients at risk:

CVP	159	100	87	69	52	43	29	24	20	6	3	3	1	0	0
R-CVP	162	140	123	119	113	104	90	70	52	36	24	11	4	2	0

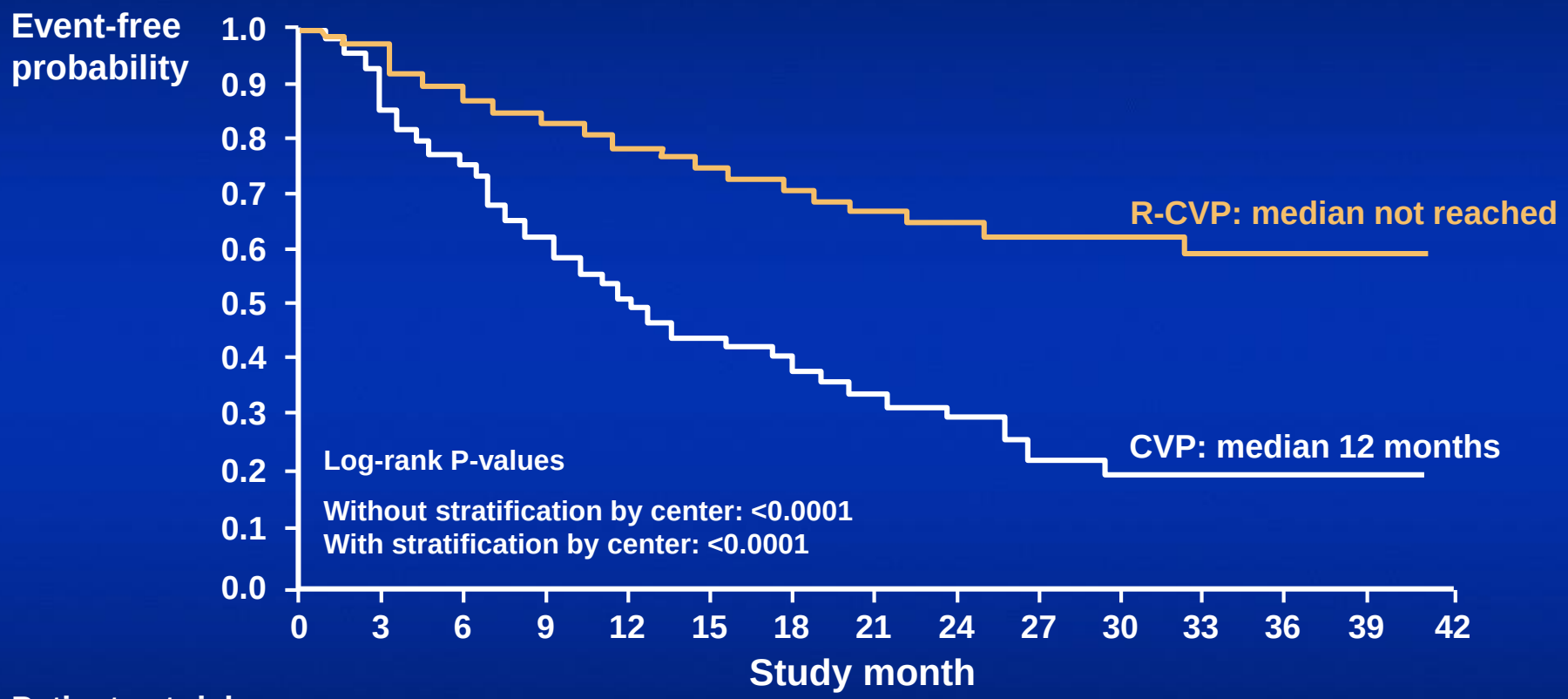
R-CVP vs CVP
TTP (Median FU 25 months)



Patients at risk:

CVP	159	140	130	110	89	74	56	44	35	17	7	5	1	0	0
R-CVP	162	156	144	140	131	118	103	80	60	41	26	11	4	2	0

R-CVP vs CVP
Time to next Therapy (Median FU 25 months)



Patients at risk:

CVP	159	135	119	98	81	70	56	42	33	16	8	4	1	0	0
R-CVP	162	156	141	135	129	120	104	79	62	48	34	16	8	2	0

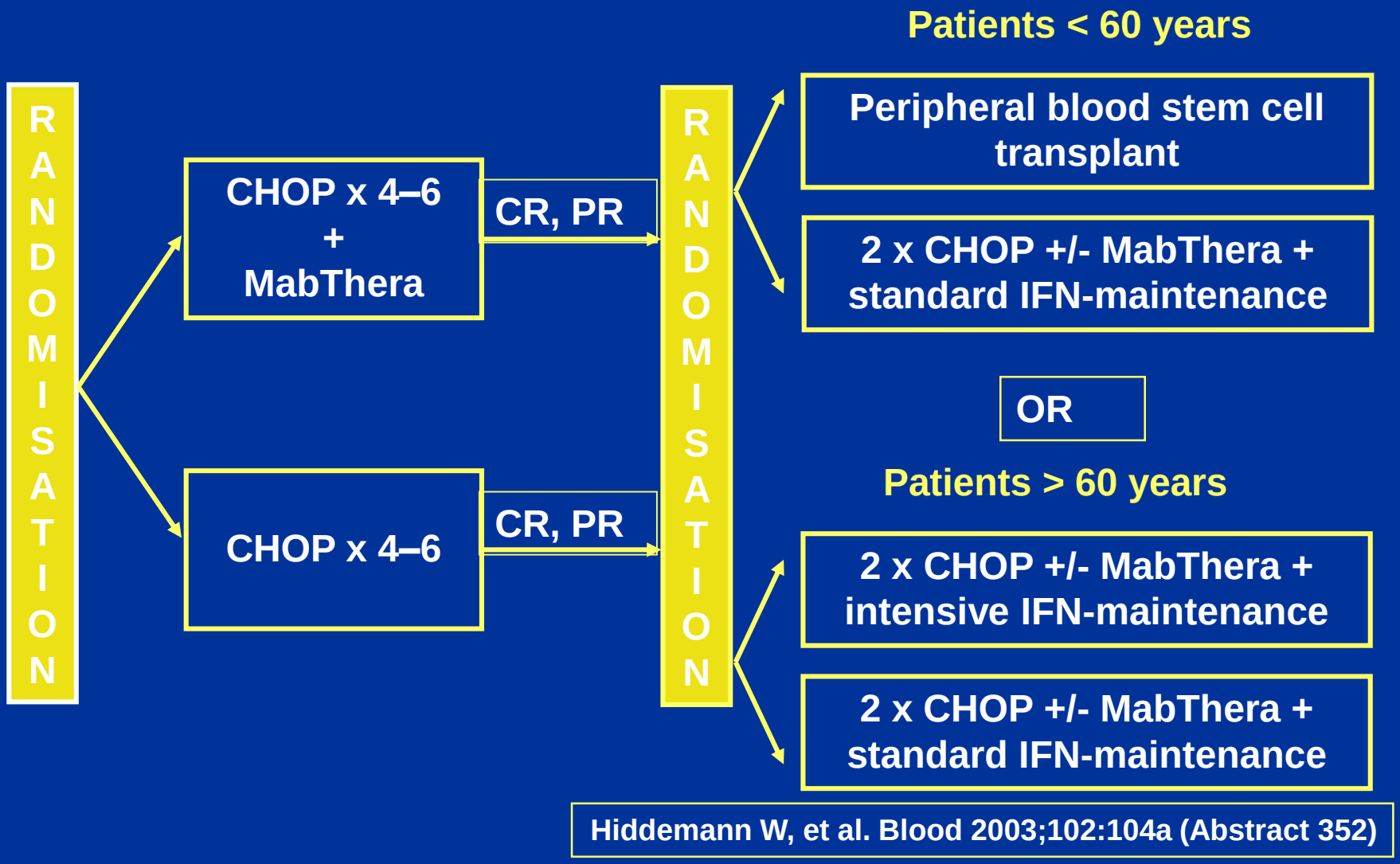
R-CVP *vs* CVP
Summary of results (25 mo FU)

	CVP (n=159)	R-CVP (n=162)	p-value
Overall Response	57 %	81 %	0.0001
Time to Treatment Failure	7 mo	27 mo	<0.0001
Time to Progression	15 mo	30 mo	<0.0001
Time to new antilymphoma treatment	12 mo	N.R.	<0.0001

Conclusions

- The addition of Rituximab to each of 8 courses of CVP demonstrates major improvement in all clinical endpoints
- R-CVP is an effective, short and very low toxicity regimen
- R-CVP shows superior efficacy to any other chemotherapy regimen published in a large scale clinical trial

CHOP ± MabThera in previously untreated follicular lymphoma: protocol



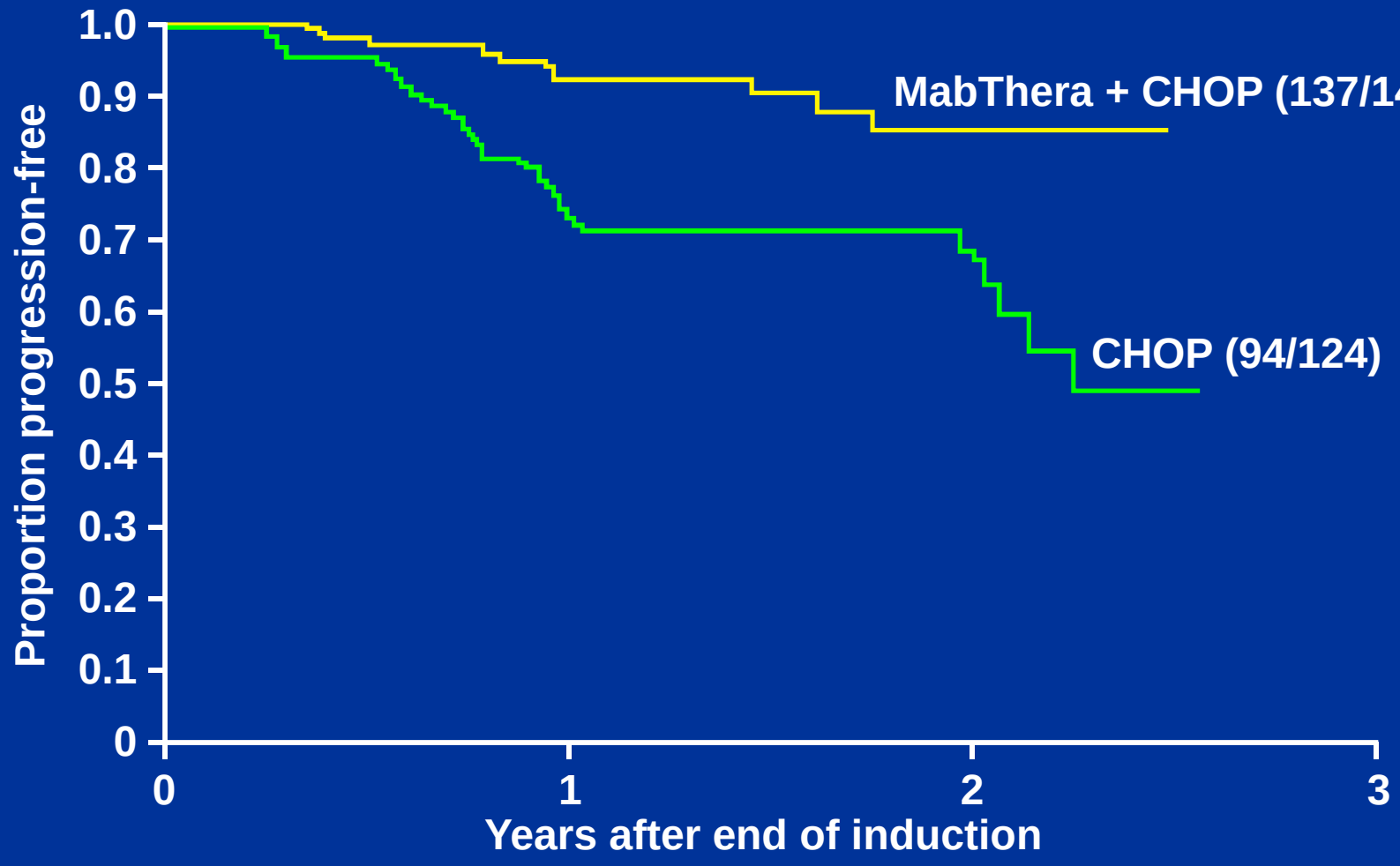
Hiddemann W, et al. Blood 2003;102:104a (Abstract 352)

CHOP ± MabThera in previously untreated follicular lymphoma: results

	CHOP (%) (n=187)	MabThera + CHOP (%) (n=201)
ORR	93	97
CR	17	21
PR	75	76
MR	2	1
SD	2	1
PD	3	1
Excluded	1	1

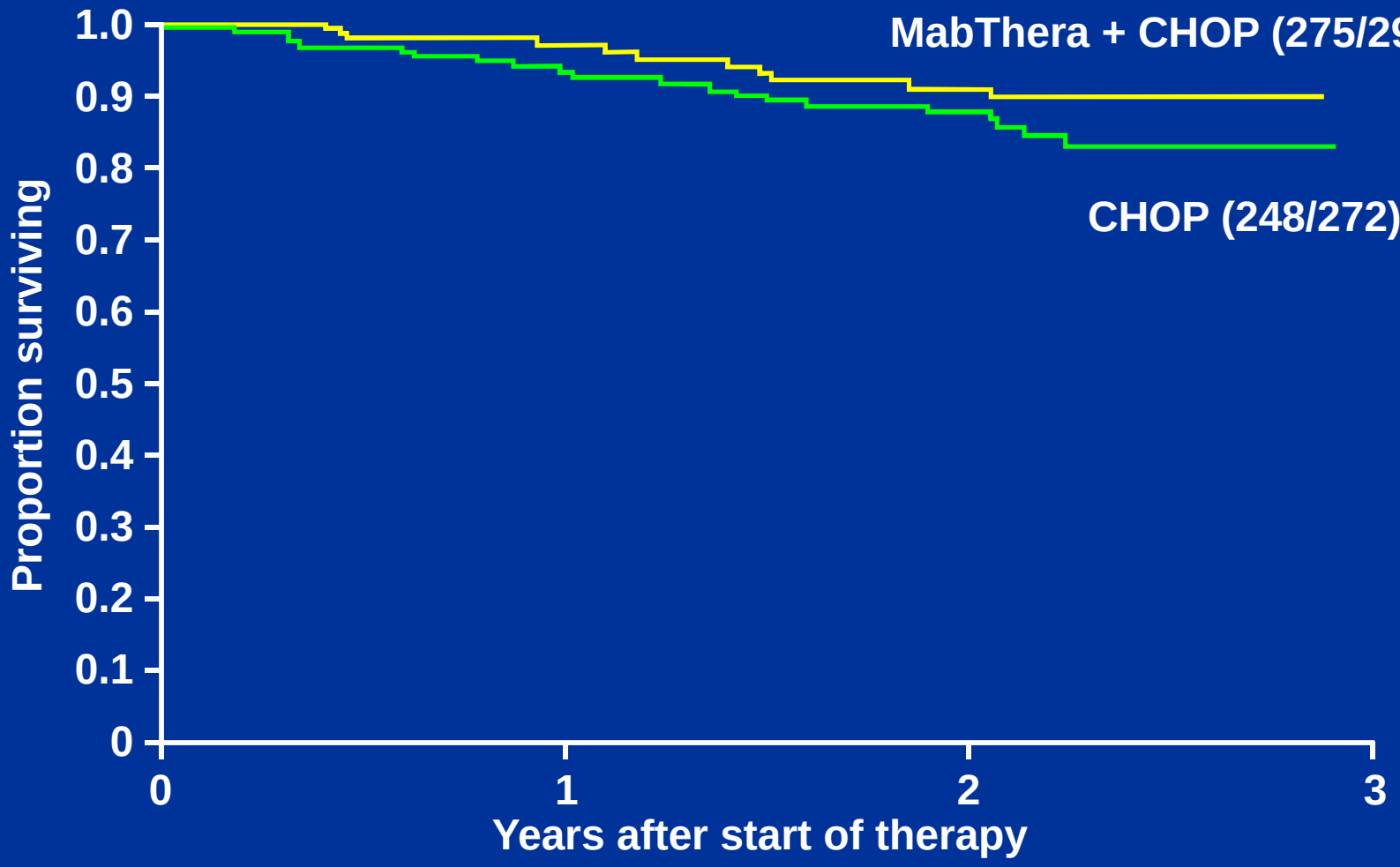
Hiddemann W, et al. Blood 2003;102:104a (Abstract 352)

CHOP ± MabThera in previously untreated follicular lymphoma: progression-free survival



Hiddemann W, et al. Blood 2003;102:104a (Abstract 352)

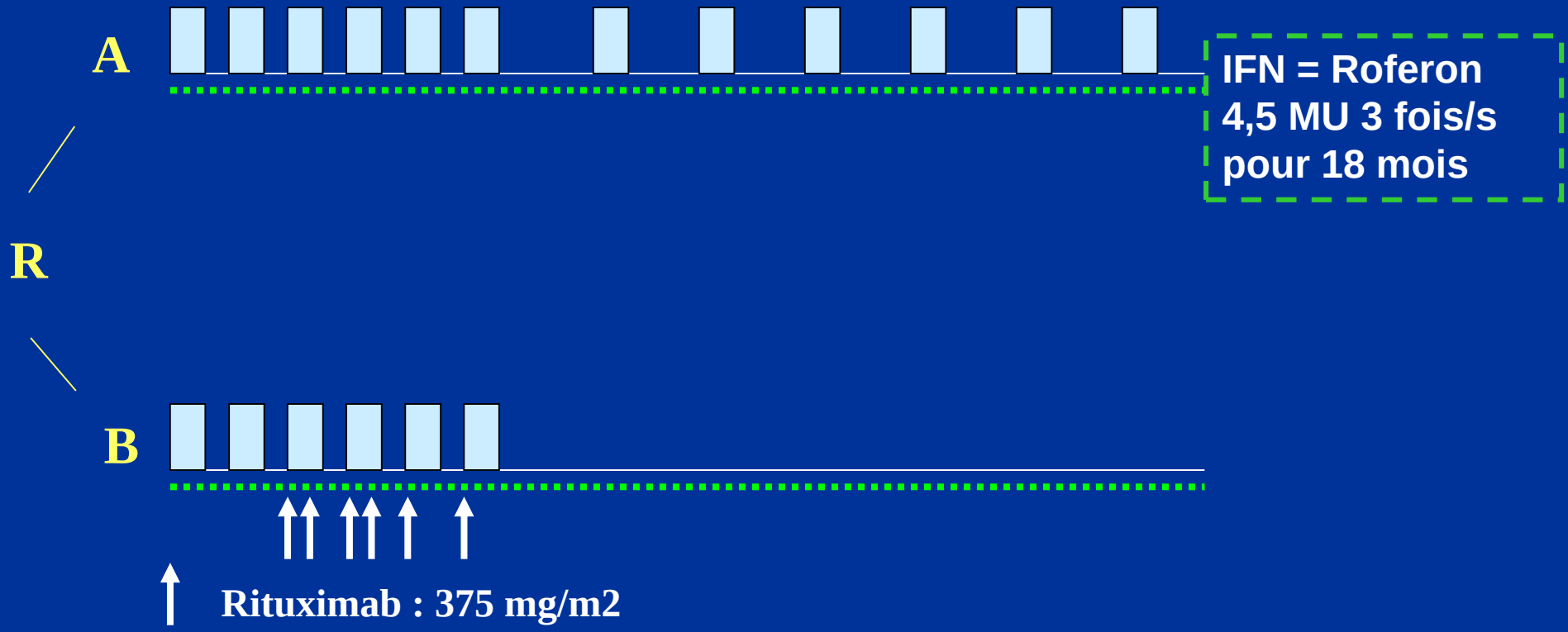
CHOP ± MabThera in previously untreated follicular lymphoma: overall survival



Hiddemann W, et al. Blood 2003;102:104a (Abstract 352)

Protocole FL-2000

CHVP : Cyclo 600 mg/m², Adria 25 mg/m², VP16 100 mg/m² ,
Pred. 40 mg/m² x 5

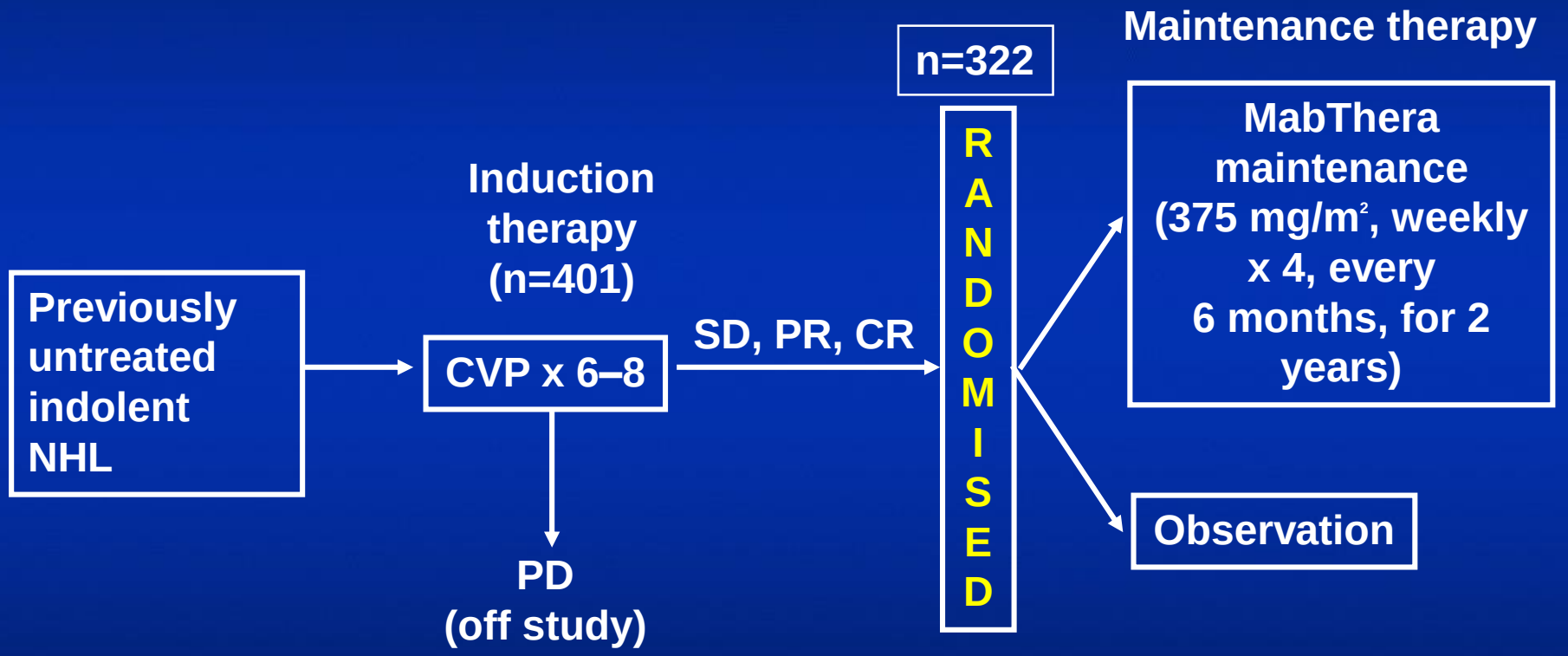


Patients de 18 à 75 ans inclus

CVP ± MabThera maintenance therapy in previously untreated indolent NHL (E1496): eligibility

- Low-grade (WF) histology: A, B, C
- Stage III–IV
- Previously untreated
- Age ≥18 years, ECOG 0–1
- Adequate organ function
- Prospective assessment of tumour burden

CVP ± MabThera maintenance therapy in previously untreated indolent NHL (E1496): study design



CVP ± MabThera maintenance therapy in previously untreated indolent NHL (E1496): Results

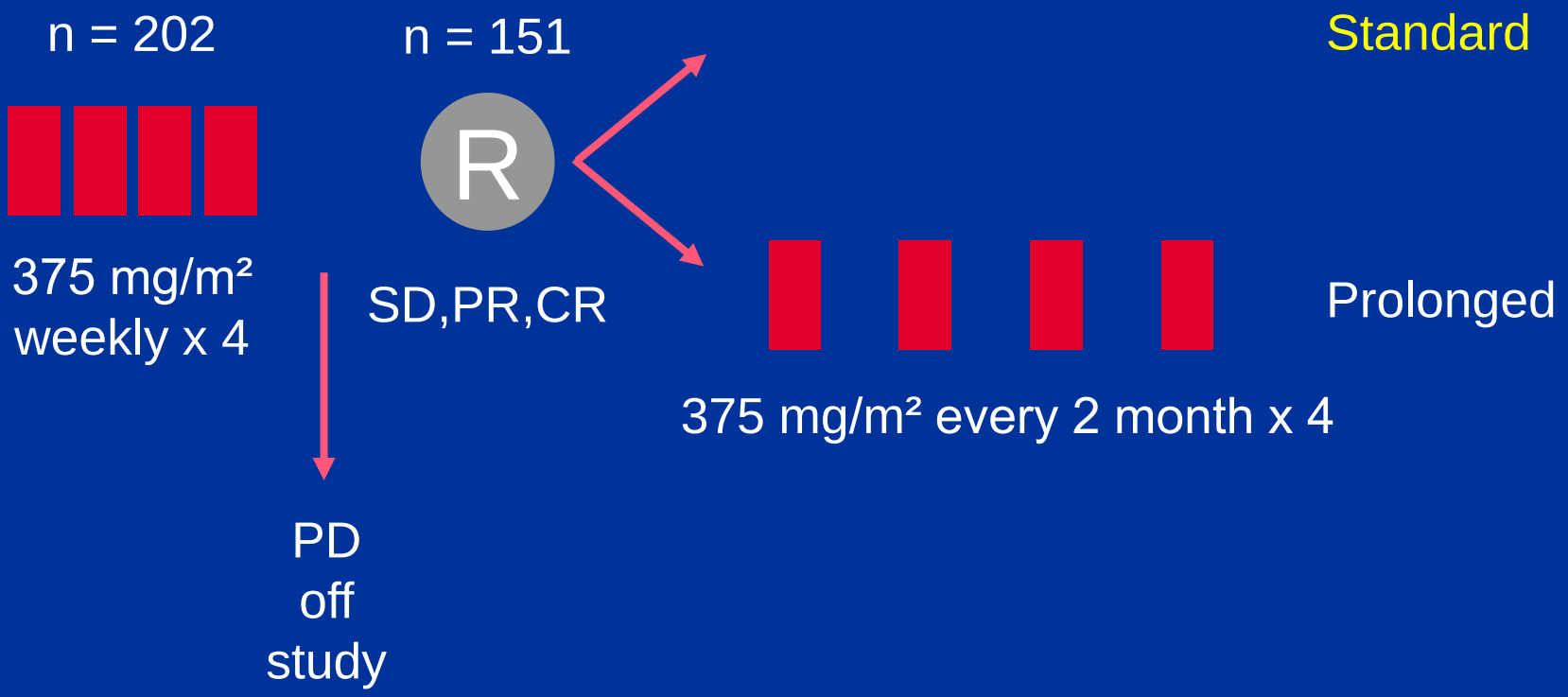
	MabThera (n=154)	Observation (n=149)
Estimated 2-year PFS (%)	74	42
Estimated 4-year PFS (%)	58	34
Estimated 2-year OS (%)	95	91

Median 1.2 years follow-up

CVP ± MabThera maintenance therapy in previously untreated indolent NHL (E1496): conclusions

- Maintenance MabThera significantly prolongs PFS after CVP chemotherapy in patients with advanced indolent NHL
- The impact of superior PFS on survival will be determined after longer follow-up

SAKK Study design



Characteristics of the patients

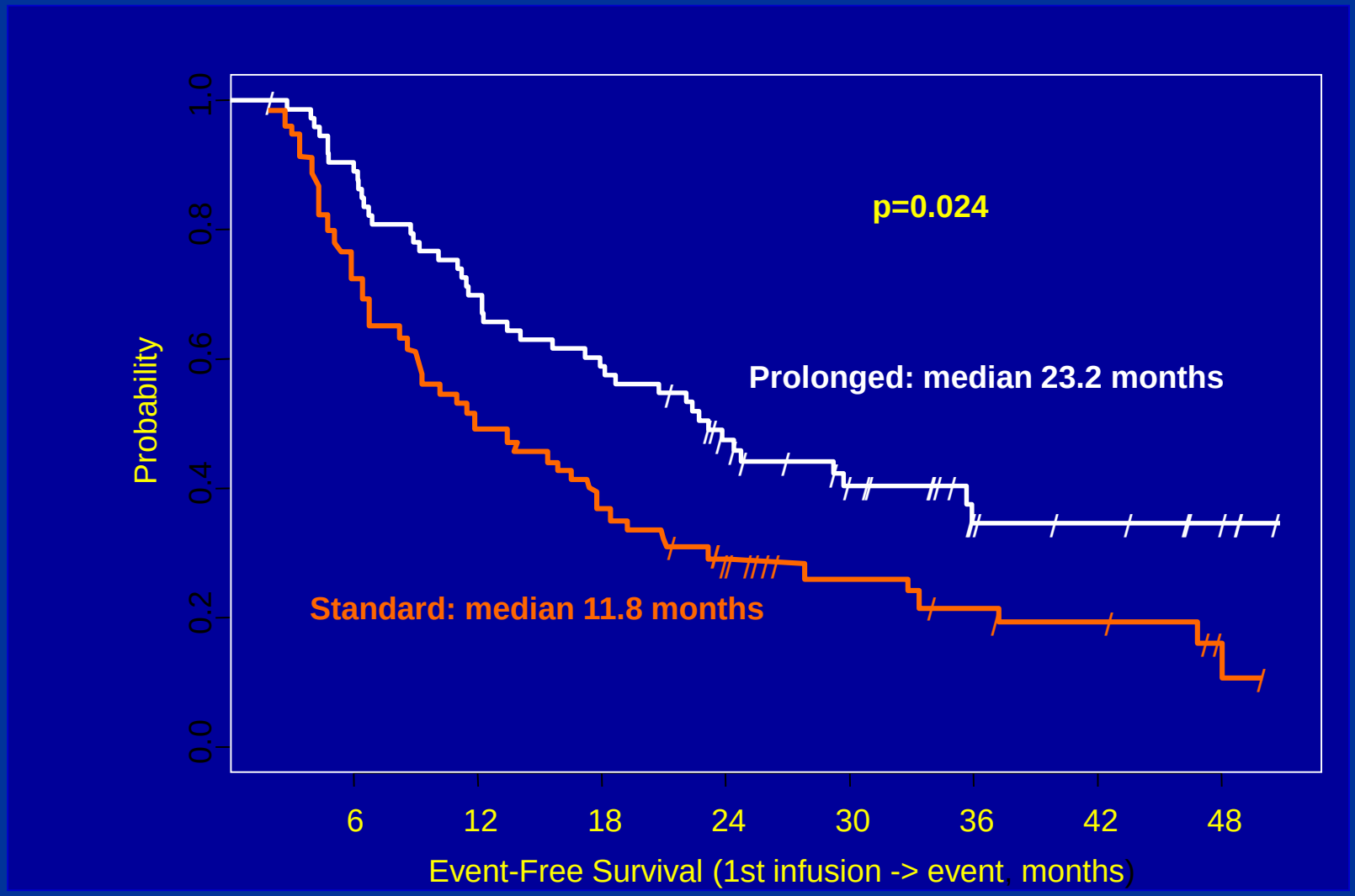
	Standard	Prolonged
Median age	57	56
PS 0-I	99 %	95 %
Stage III-IV	79 %	85 %
Involved BM	51 %	48 %
Elevated LDH	28 %	27 %
Previous chemotherapy	67 %	66 %

Induction phase

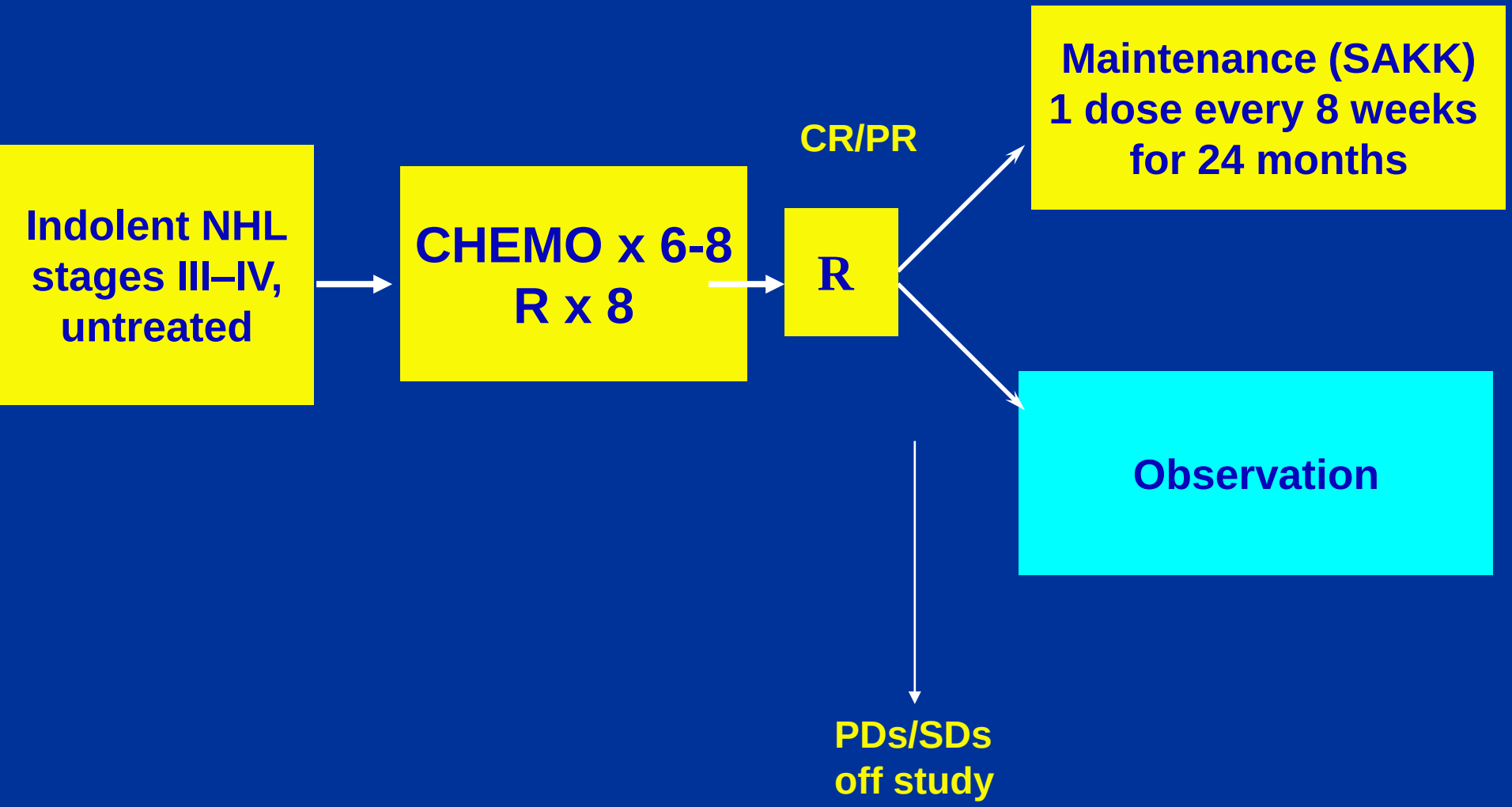
Entered n = 202
Evaluable n = 186

Response at week 10-12		**PR**	**CR**	**RR**
Chemo-naive	**(n = 58)**	**57 %**	**9 %**	**66 %**
Pre-treated	**(n = 128)**	**38 %**	**8 %**	**46 %**

Effect on event free survival



PRIMA Study : Final Design



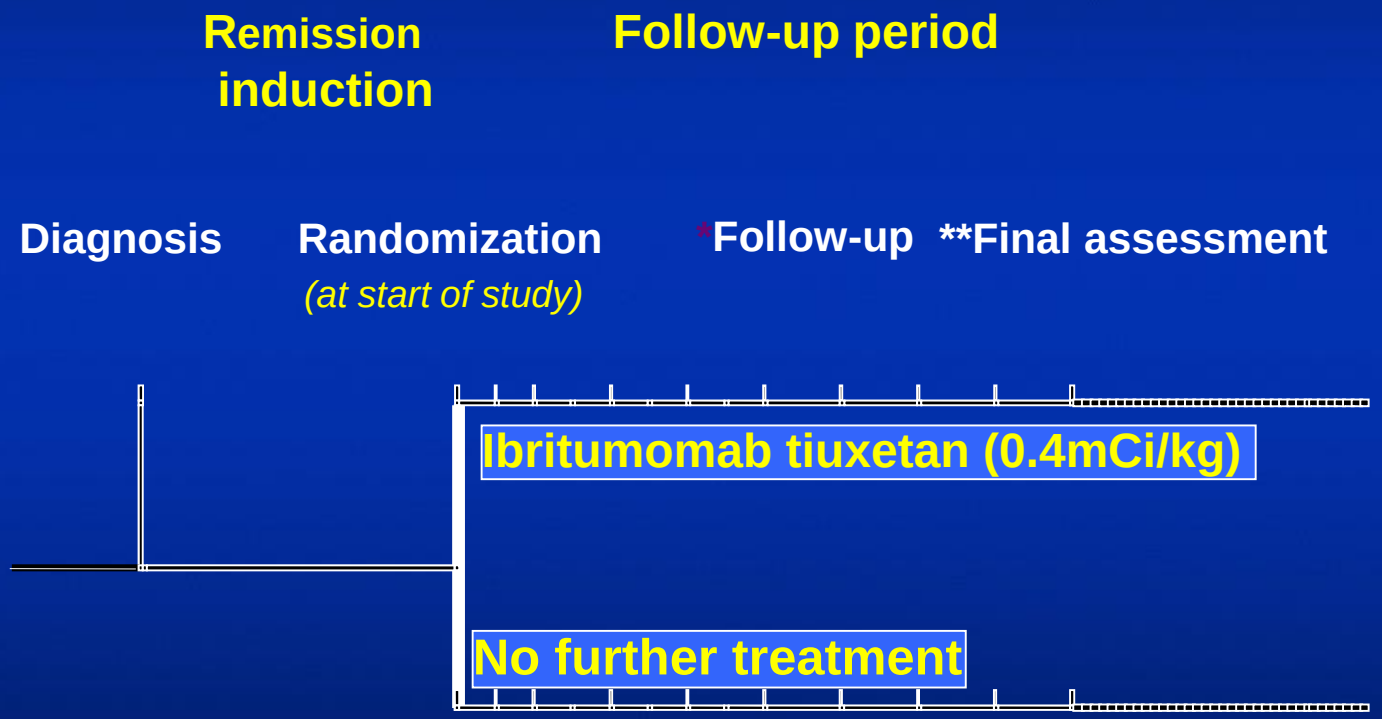
CHOP followed by Tositumab
(SWOG) Press et al. Blood 2003

Table 3. Responses to therapy

Response	After CHOP, n (%)	After CHOP + tositumomab/iodine I 131 tositumomab,* n (%)
Complete remission	24 (27)	49 (54)
Complete remission, unconfirmed	11 (12)	11 (12)
Partial remission	44 (49)	21 (23)
Stable disease	2 (2)	2 (2)*
Not evaluable†	9 (10)	7 (8)
Total	90 (100)	90 (100)

*Patients who did not achieve a PR, CRu, or CR with CHOP were not eligible to receive tositumomab/iodine I 131 tositumomab.

Ibritumomab tiuxetan vs no further treatment
in previously untreated patients with stage III or IV follicular NHL



*every 3 months for the 6 months and every 6 months thereafter
**2 years after randomization of last patient

Future directions

- Is R-CVP now standard therapy for follicular lymphoma?
- Will more intensive induction treatment yield superior ORR and DR?
- What is the role of maintenance therapy?
- Is there a role for early PBSCT in the antibody era?

High grade data

- If required for discussion

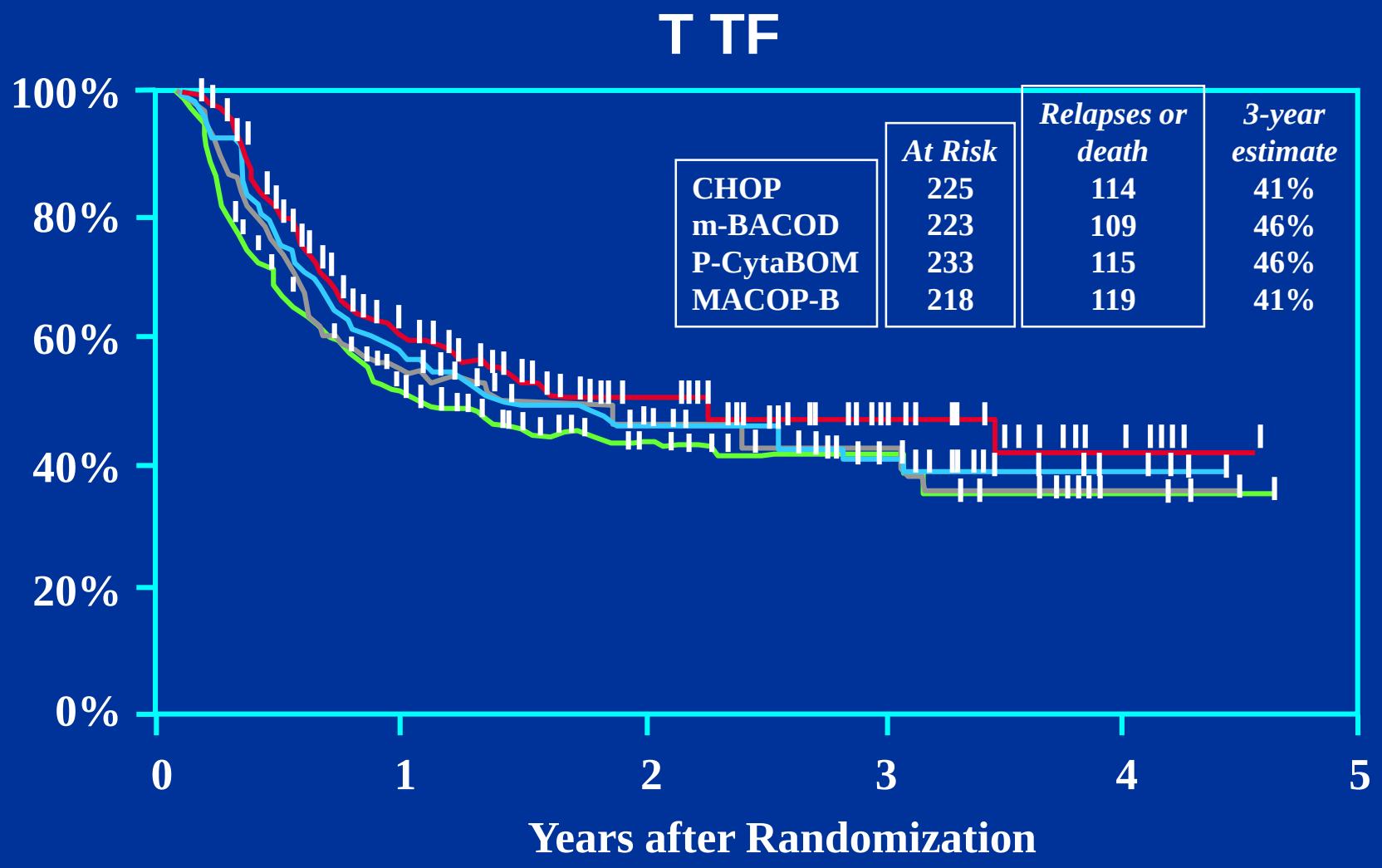
Role of Rituximab in High Grade NHL

- Two presented/published randomised trials
- Third study [MinT] to be presented at ASCO ’04
- Canadian population based “change in practice”
- NCI R-EPOCH data

Why new therapy in High Grade NHL

- Old treatments fail
- No proof that dose escalation valuable in first CR
- No advances in therapy since 1976!

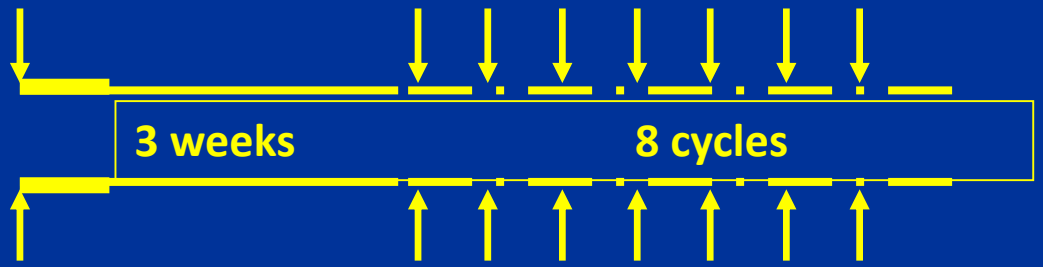
National High Priority Lymphoma Study:



Fisher et al. N Engl J Med. 1993;328:1002.

LNH-98.5: CHOP compared with CHOP plus Rituximab

Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/d x 5 d

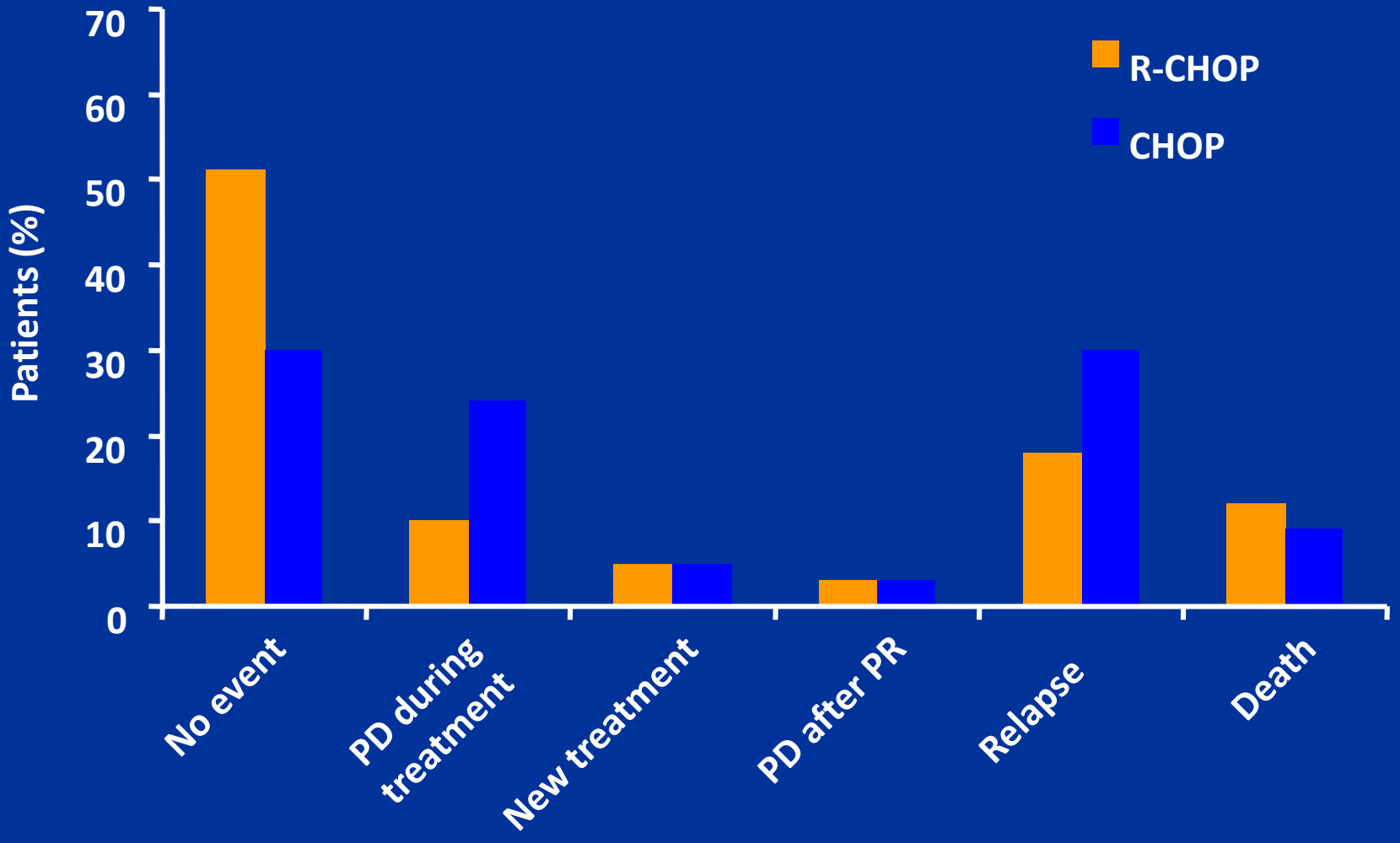


CHOP

Rituximab 375 mg/m²

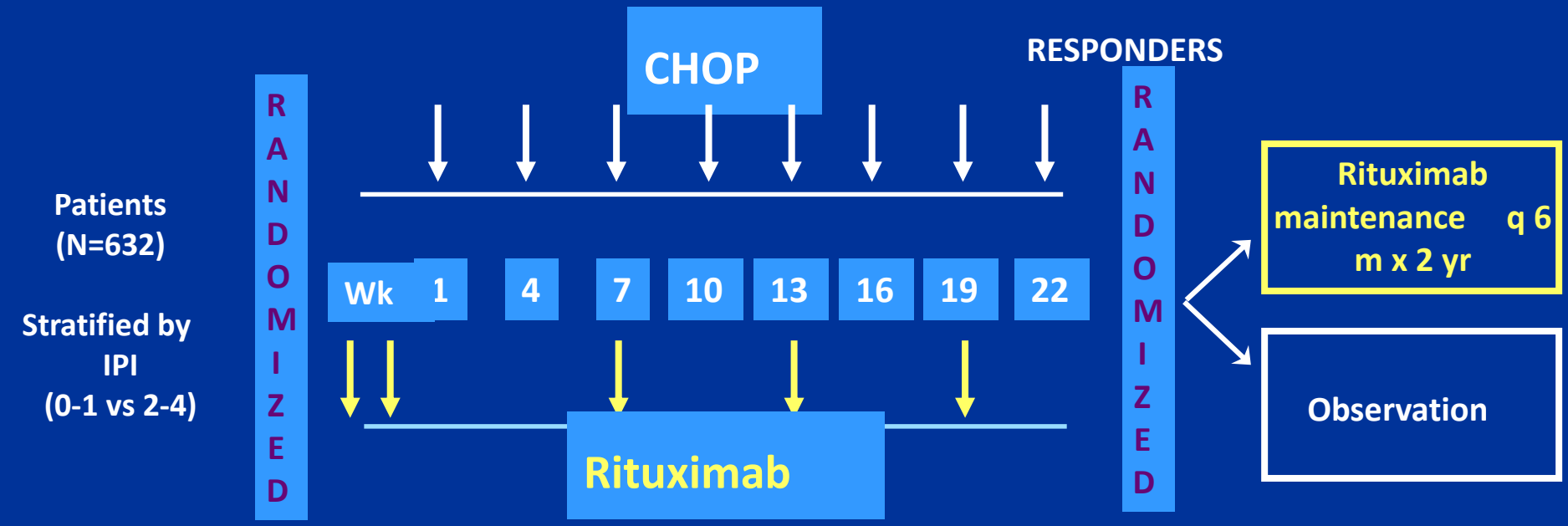
- Patients 60-80 years old with untreated DLCL
- Primary endpoint: event-free survival
  - events: progression, relapse, new alternative treatment, death from any cause
- Intent-to-treat analysis
- 399 patients with a median follow-up of 2 years

GELA 98.5 trial: Events after 4-year median follow-up



p=0.001

E4494 intergroup phase III trial: CHOP v R-CHOP +/- MR



E4494 intergroup phase III trial: CHOP v R-CHOP +/- MR

Response Prior to 2nd Randomization

	R-CHOP	CHOP
CR/PR	78	77
Stable	12	15
PD	1	3
Inevaluable	9	5

Introduction Of Combined CHOP-Rituximab Therapy Dramatically Improved Outcome Of Diffuse Large B-Cell (DLBC) Lymphoma In British Columbia (BC)

Laurie H Sehn, Jane Donaldson, Mukesh Chhanabhai, Catherine Fitzgerald, Nicol MacPherson, Susan O'Reilly, John Spinelli, Kenneth Wilson, Randy D Gascoyne, and Joseph M Connors

Study Aim and Design

- On March 1st, 2001, the BC Cancer Agency implemented a new policy recommending CHOP+Rituximab for all patients with advanced stage DLBC in BC

- Population based retrospective analysis over a 3 year interval (Sept 1/99-Aug31/02)

- Compare outcomes

  18 months prior to rituximab policy (Pre-Ritux)

  versus

  18 months following rituximab policy (Post-Ritux)

Inclusion/Exclusion Criteria

Inclusion Criteria

- Age > 16 years
- Biopsy proven newly diagnosed DLBC
- Clinically advanced stage disease
  - **Stage III/IV**
  - **Stage I/II with B-symptoms or bulky disease or contraindication to radiation**
  - **Testicular DLBC any stage**
- Received CHOP-like chemotherapy with curative intent

Exclusion Criteria

- HIV positive
- CNS involvement
- Evidence of transformation
- Never treated or treated with palliative intent

Clinical Characteristics

	Pre-Ritux N =142	Post- Ritux N=152
Median Age (y)	63	63
Male Sex (%)	58	60
PS > 1 (%)	49	40
High LDH (%)	67	61
>1 EN Site (%)	36	33
Stage III/IV (%)	70	65
Bulky Disease (>10cm)	44	40
IPI (%)		
Low	21	27
Low-Intermed	23	24
High-Intermed	24	26
High	32	23

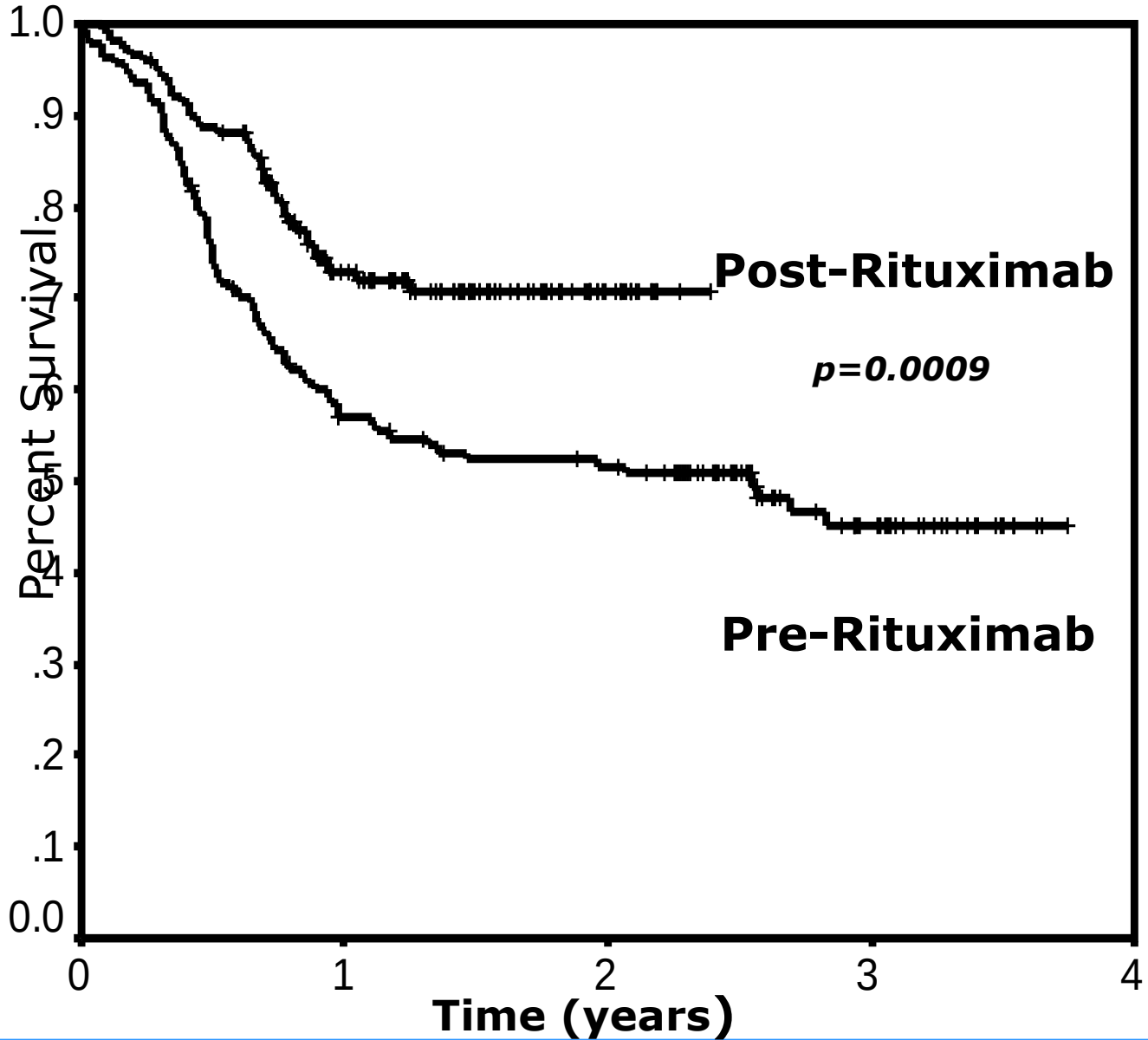
Therapy

- All patients received a CHOP-like chemotherapy regimen
- Rituximab was administered at a dose of 375 mg/m^2 with each cycle of CHOP, between 24 to 72 hours after CHOP infusion
- Rituximab was received by 9% of the Pre-Ritux group and 85% of the Post-Ritux group
- More patients in the Pre-Ritux group received radiation therapy than in the Post-Ritux group (25% *v* 15%, p=0.04)

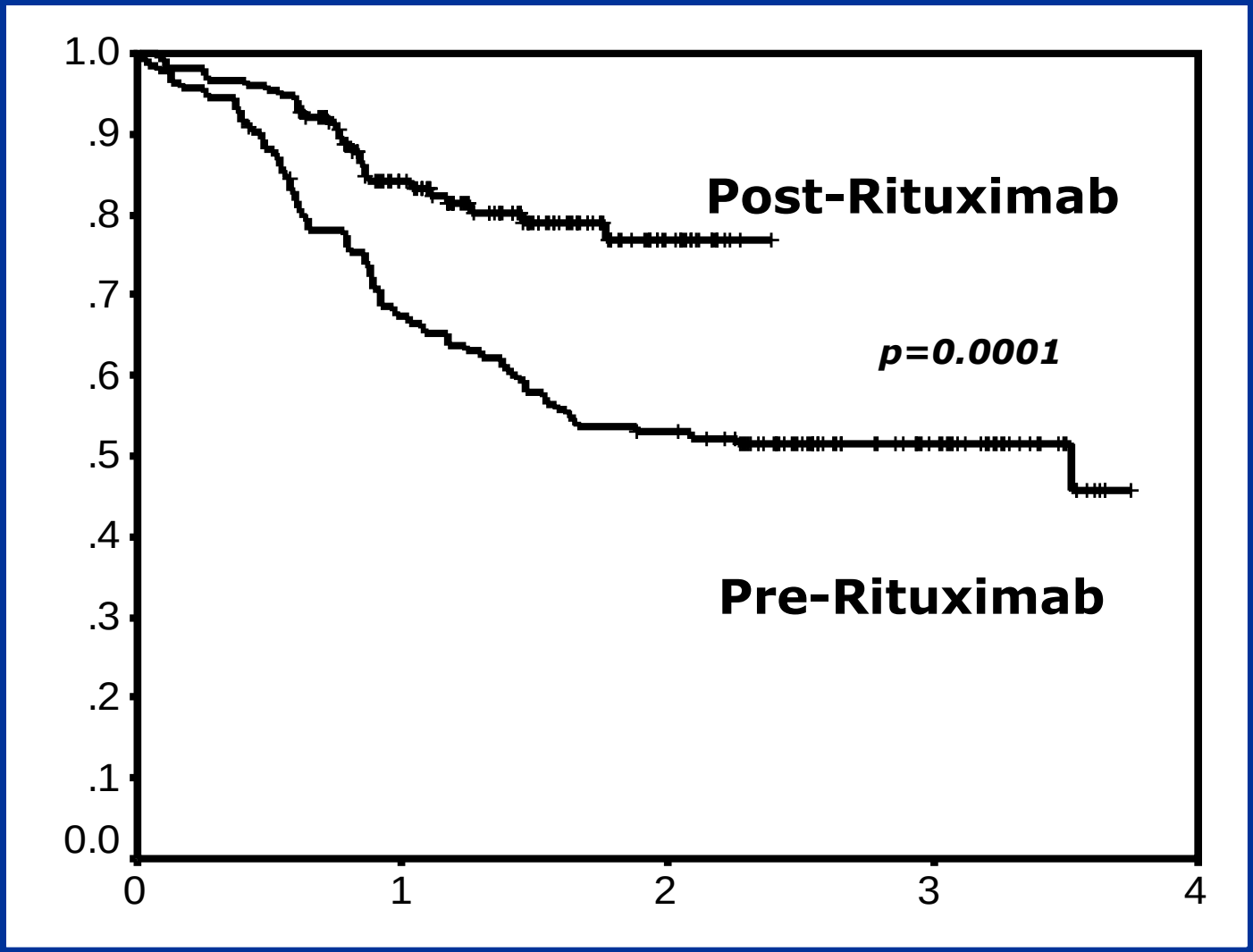
RESULTS
All Patients N=294

	Pre-Ritux	Post-Ritux	p-value
Median f/u (mos) (range)	34 (5-45)	17 (7-29)	
2-year PFS (%	52	72	0.0009
2-year OS (%)	53	77	0.0001

Progression-Free Survival by Treatment Era: All Patients (N=294)

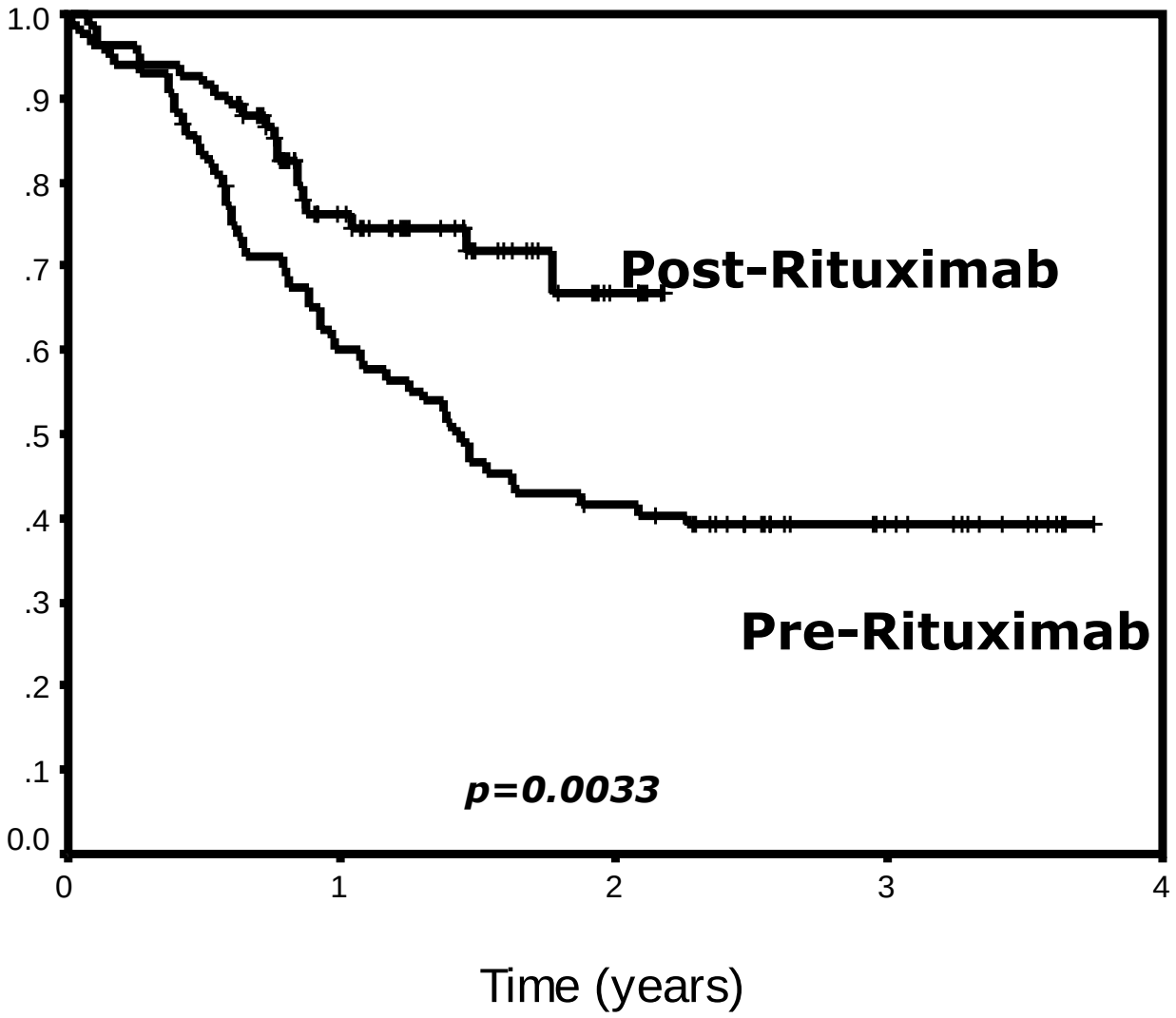


Overall Survival by Treatment Era
All Patients (N=294)



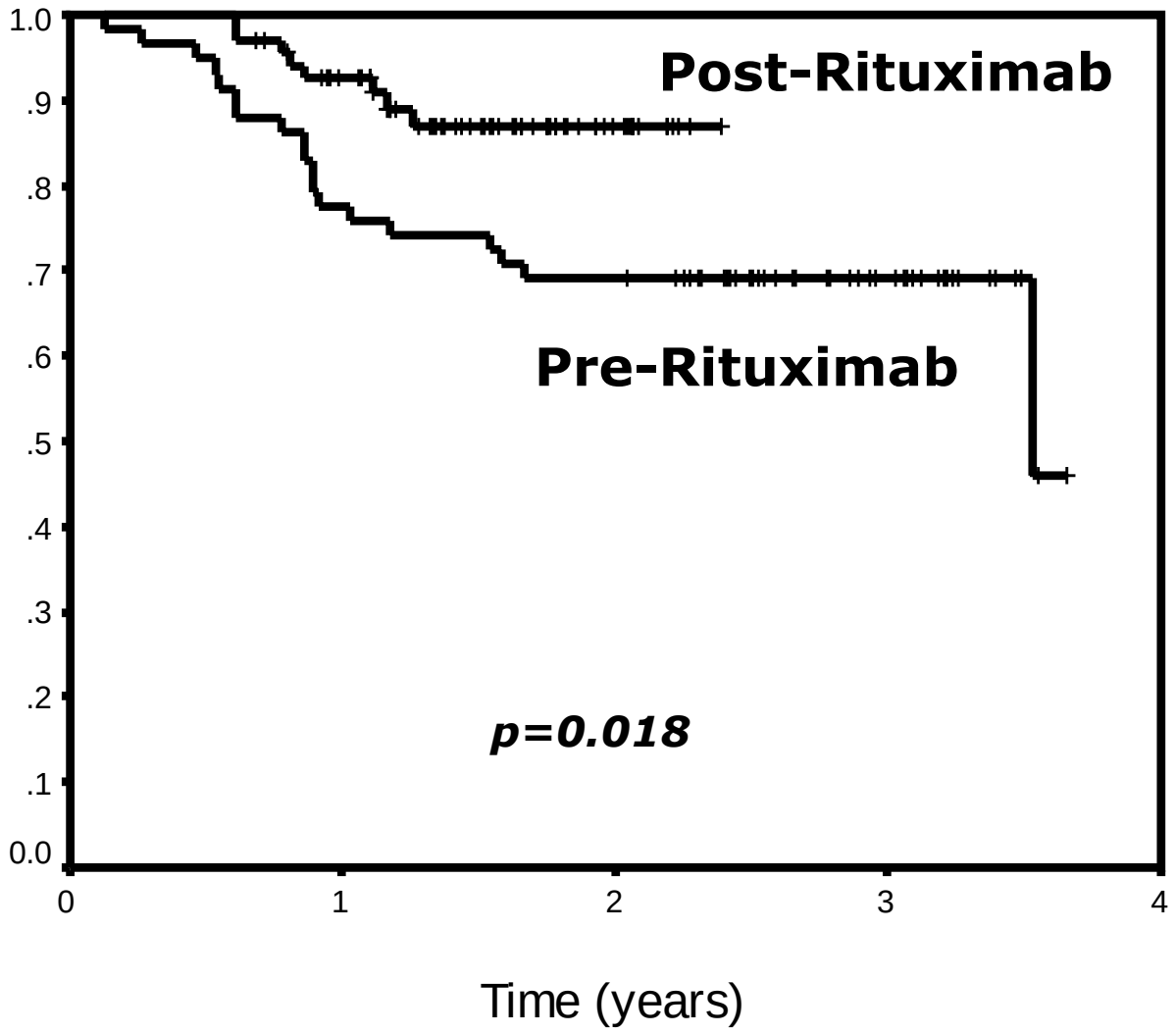
Overall Survival by Treatment Era

Elderly Patients (Age ≥60 y) N=167



Overall Survival by Treatment Era

Young Patients (Age <60 y) N=127



Conclusions

- **Addition of rituximab to CHOP chemotherapy has resulted in a dramatic improvement in outcome for advanced stage DLBC in BC**
- **Addition of rituximab resulted in a 50% reduction in the risk of dying at 2 years**
- **Improvement in outcome was seen in all age groups, but was greatest for the elderly population**

Other approaches to improvements in outcome in High Grade NHL

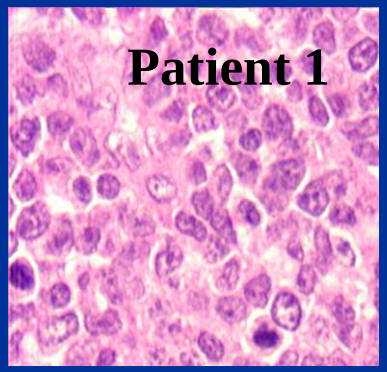
- **Dose adjustment/escalation**
- **Tailor treatment to individual tolerance**
- **Assess role of Rituximab with dose escalation**

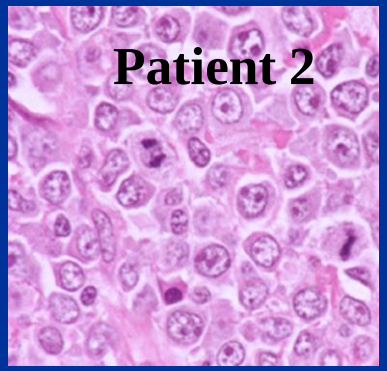
(Courtesy Wyndham Wilson NCI,Bethesda)

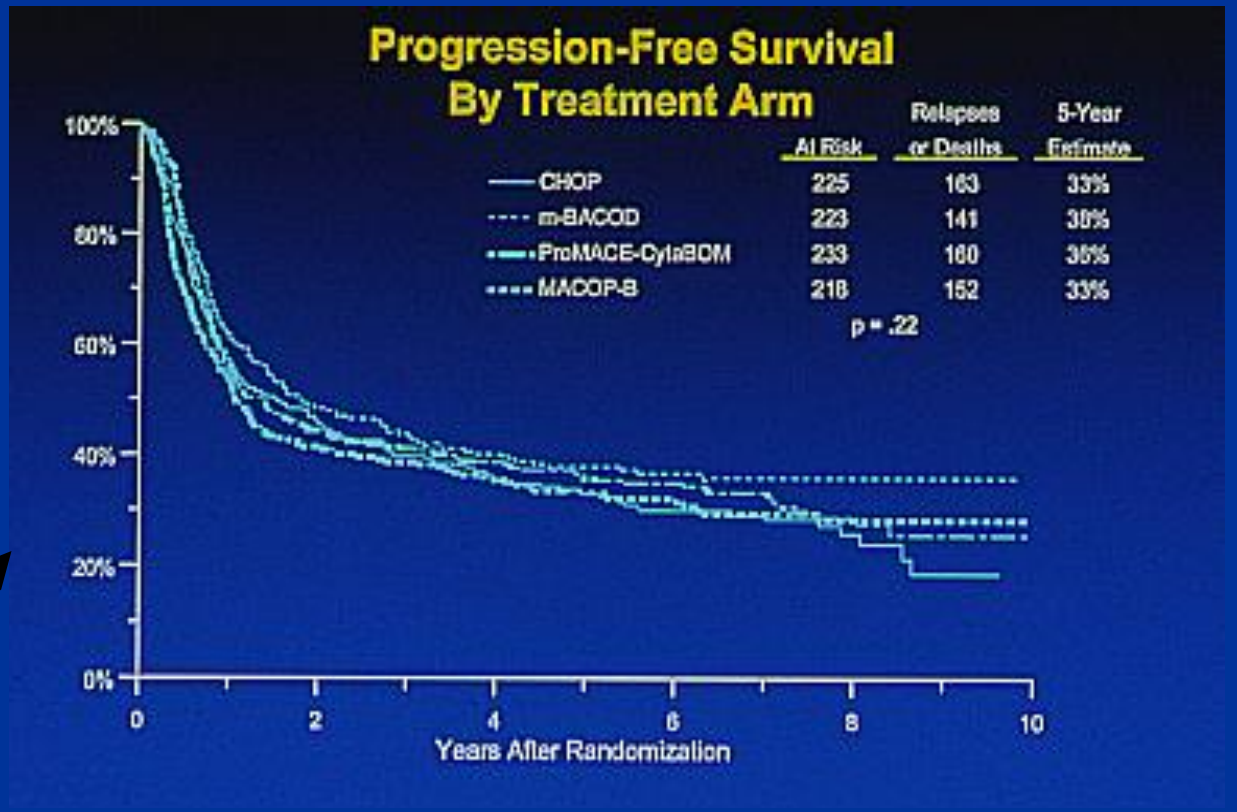
Diffuse Large B-cell Lymphoma

- **CHOP Still the Standard After 30 Years**
- **One Diagnosis-Multiple Diseases?**

SWOG Randomized Trial



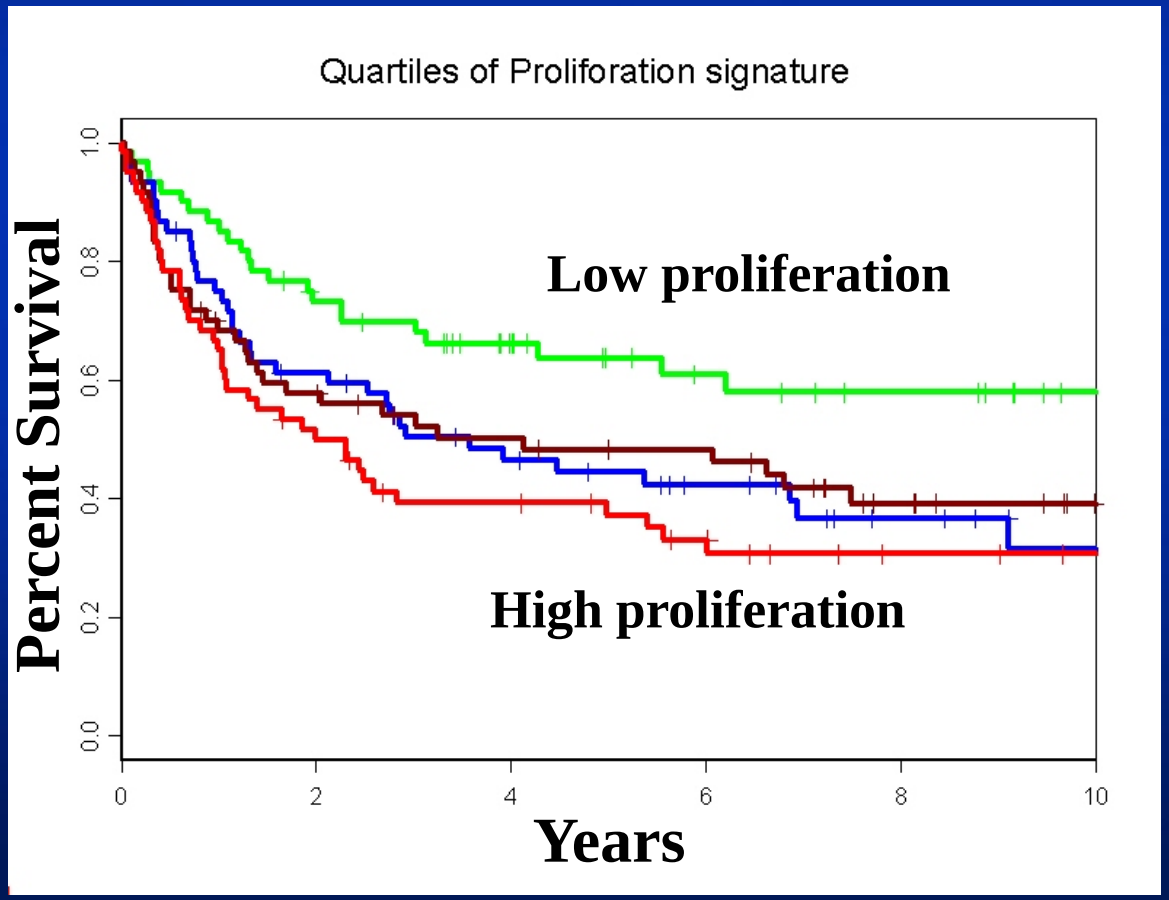




Background

- **High tumor proliferation signature by microarray predicts treatment failure with CHOP in DLBCL**

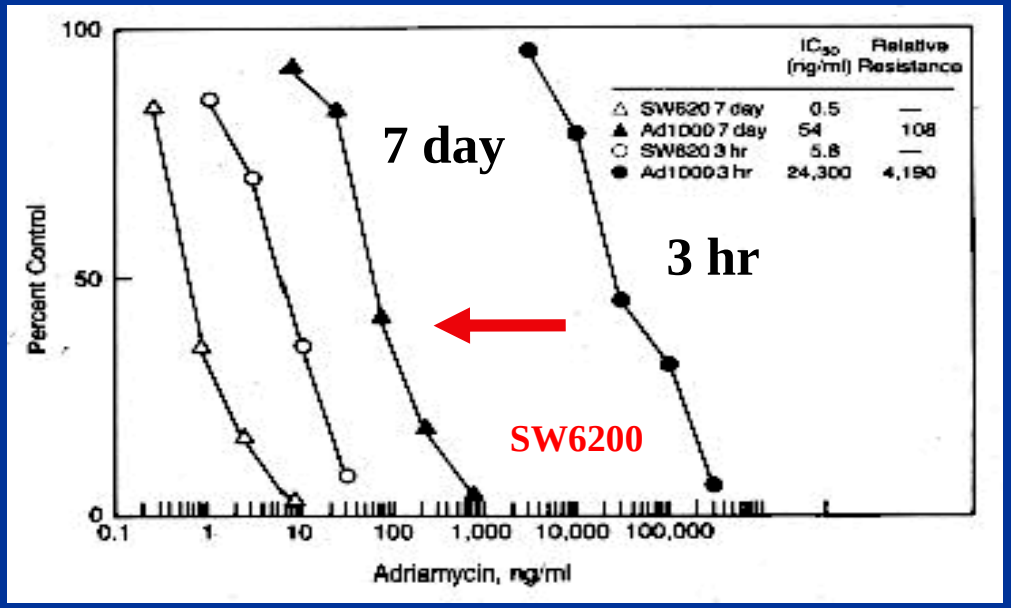
Microarray Analysis of 274 untreated DLBCL



Hypothesis

- **Drug schedule increases tumor drug sensitivity and may overcome effects of high proliferation**

Doxorubicin



- Schedule dependent drugs
  - Doxorubicin
  - Etoposide
  - Vincristine

Dose-Adjusted EPOCH

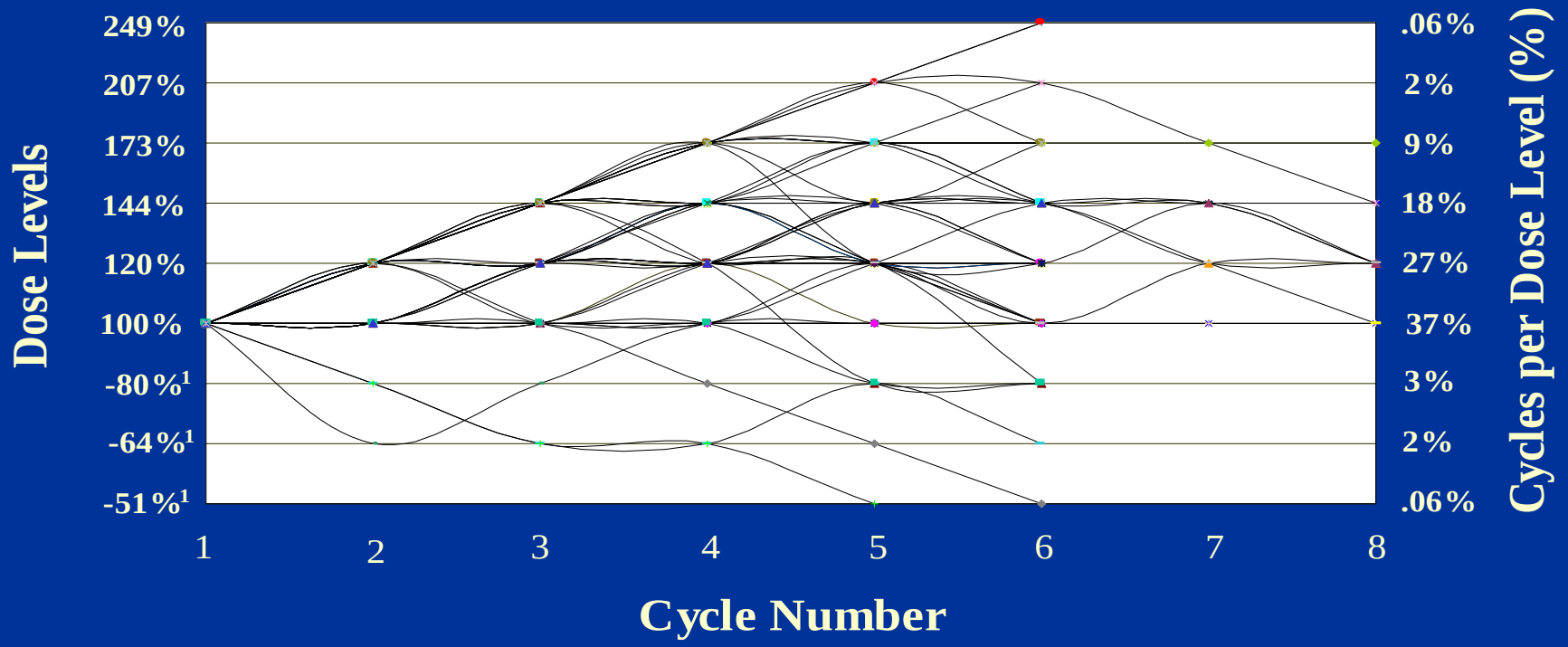
	Dose mg/m^2/day	Treatment Days	
Infusional Agents			
Etoposide	50		
Vincristine	0.4	Days 1,2, 3, 4	
Doxorubicin	10		
Bolus Agents			
Prednisone	60 BID	Days 1, 2, 3, 4, 5	Cycle 21 Days for 6-8 cycles
Cyclophosphamide	750	Day 5	
Biologic Agents			
Filgrastim	5 (μg/kg)	Days 6 → ANC recovery	

Pharmacodynamic Dose Adjustment

- To reach effective threshold concentrations, drug doses are normalized to the neutrophil nadir
- Dose-adjustment for etoposide, cyclophosphamide doxorubicin based on twice weekly CBC:
  - Nadir ANC > 500/ul: ↑ 20%
  - Nadir ANC < 500/ul 1-2 measurements: No change
  - Nadir ANC < 500/ul > 2 measurements: ↓ 20%

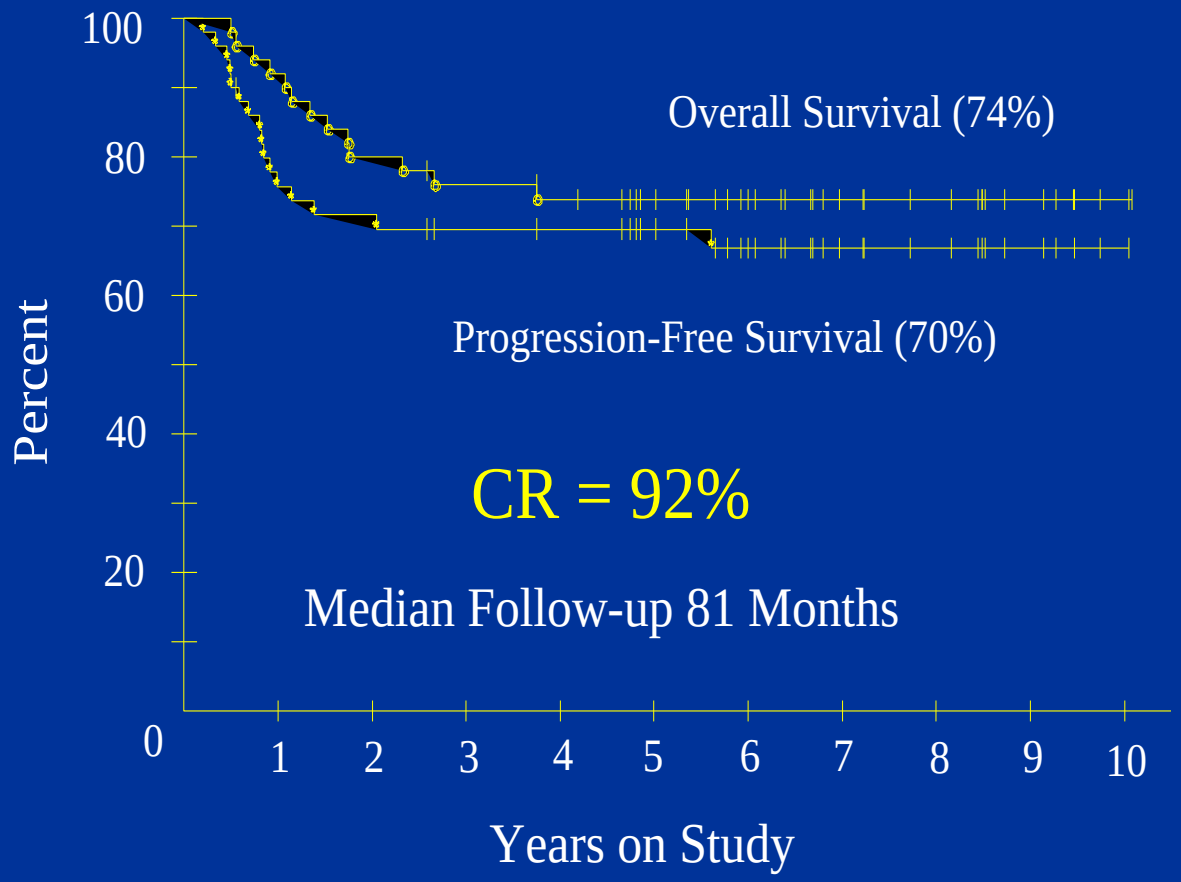
Role of Dose Adjustment

Dose-Adjustment Map



DA-EPOCH
Progression-Free and Overall Survival

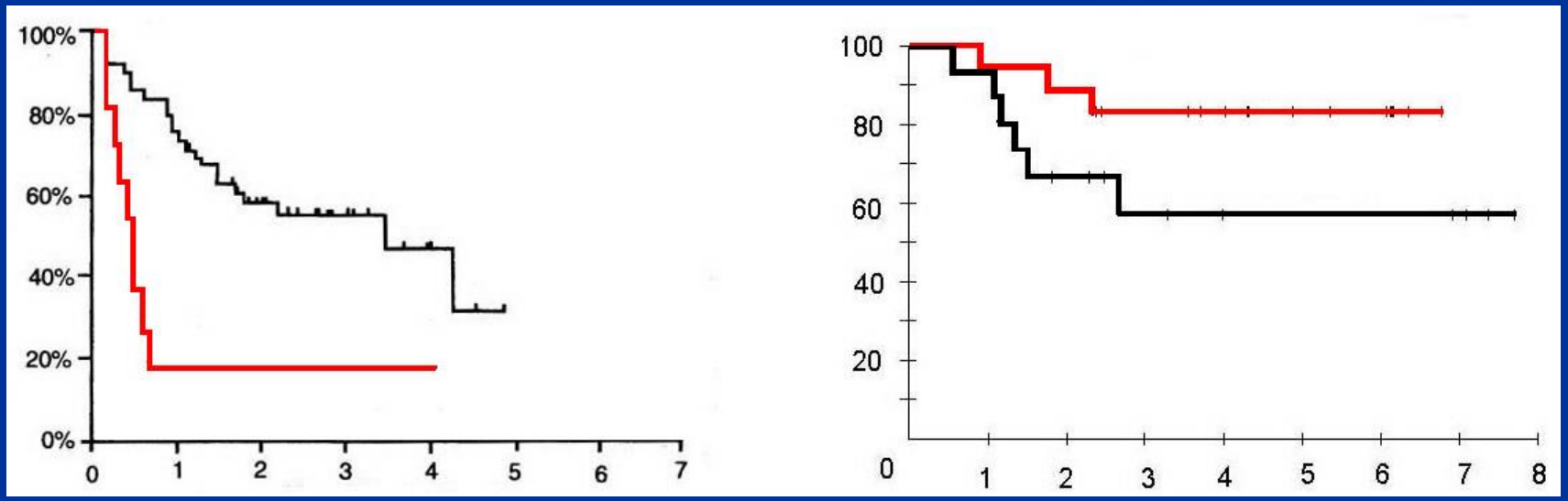
- 50 untreated DLBCL received DA-EPOCH



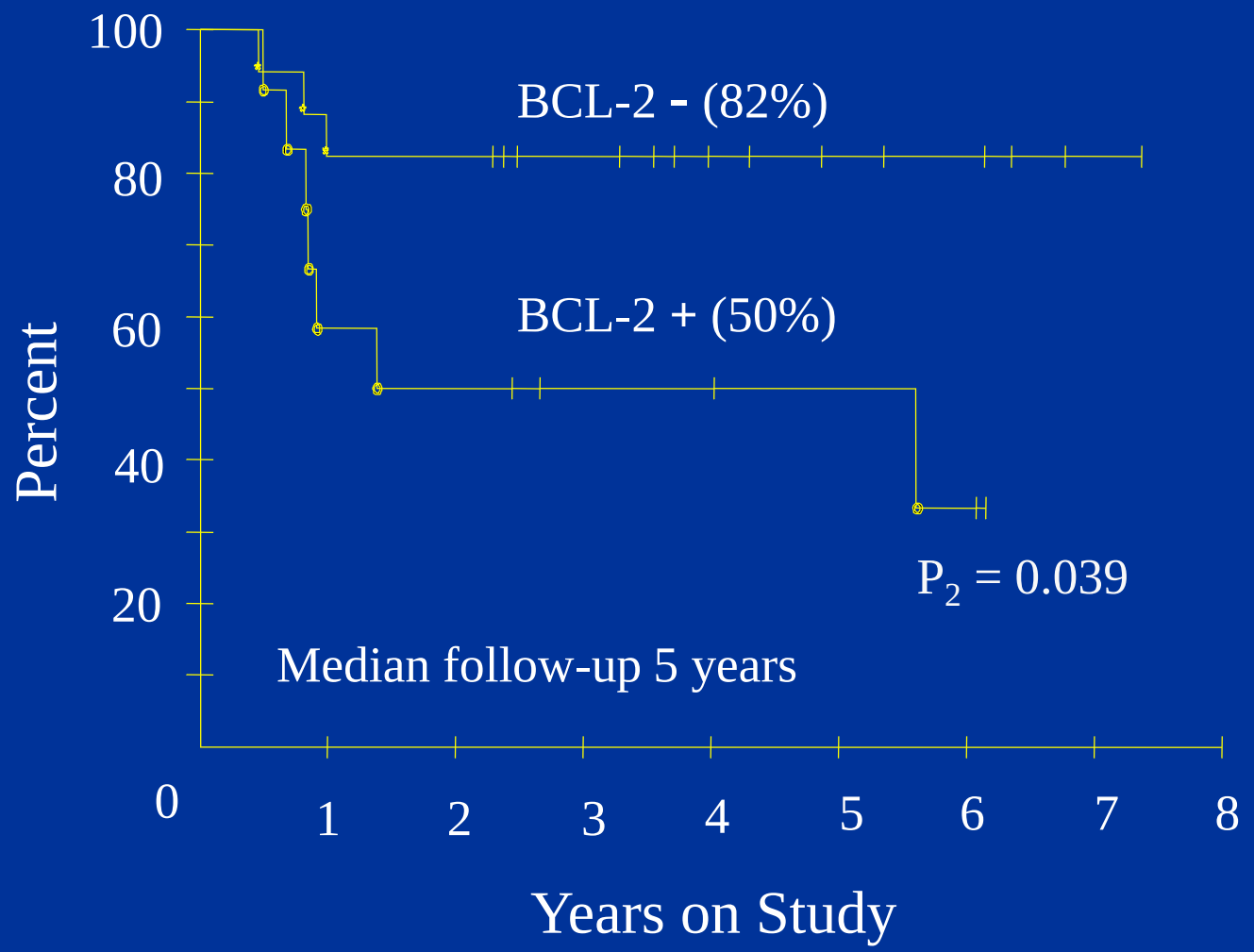
Outcome Following CHOP and DA-EPOCH May Be Dictated by Different Biological Variables

Effect of Tumor Proliferation Index with CHOP Chemotherapy

Effect of Tumor Proliferation Index with EPOCH Chemotherapy

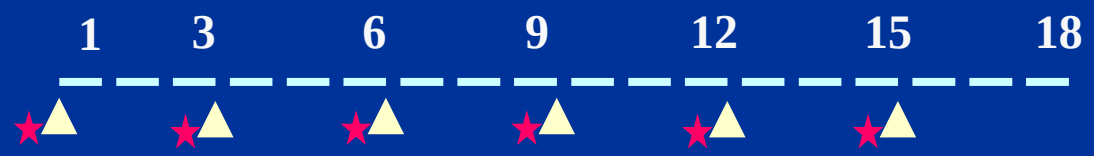


BCL-2 Expression Associated with DA-EPOCH in DLBCL



DA-EPOCH-R in Untreated DLBCL

- **Hypothesis**
  - **Rituximab down regulates BCL-2 in vitro**
  - **Rituximab may reverse BCL-2 associated resistance**
- **EPOCH-R schedule**



DA-EPOCH: ▲ Rituximab: ★

Patient Characteristics

	Nos. Pts	(Percent)
Enrolled Patients	**69**	
Age: median (range)	**49 (12-85)**	
Male sex	**42**	**(61%)**
International Prognostic Index		
• **Low Risk (0-2 factors)**	**43**	**(62%)**
• **High Risk (3-5 factors)**	**26**	**(38%)**

Toxicity

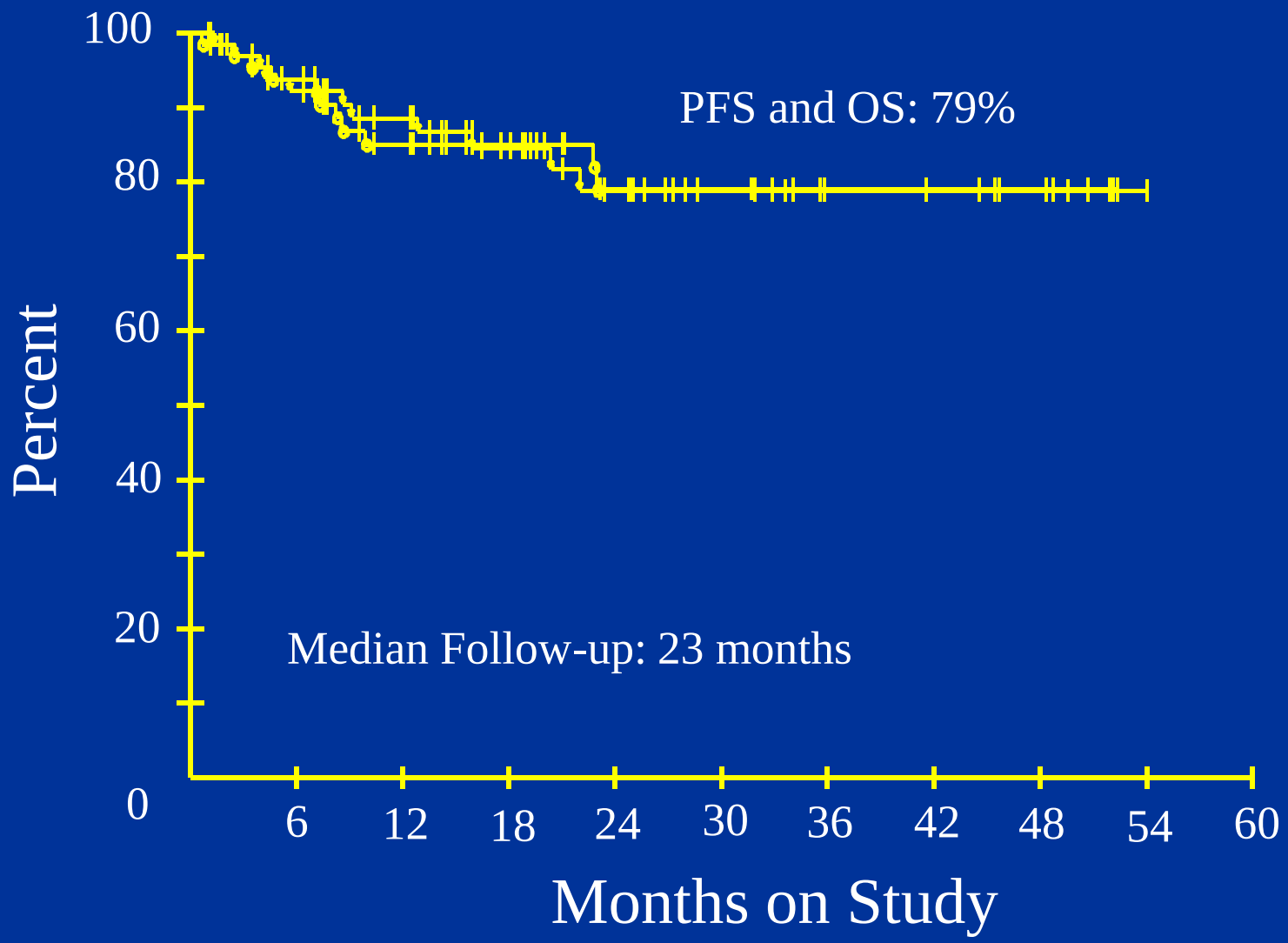
Toxicity	Percent
Platelets < 25,000/uL[1]	9%
ANC < 500/uL[1]	60%
Fever/Neutropenia[1]	16%
> Grade 2 GI Toxicity[1]	4%
> Grade 2 Neurological[2]	11%
Treatment related deaths[2]	3%

[1]Based on 380 total cycles
[2]Based on 69 total patients

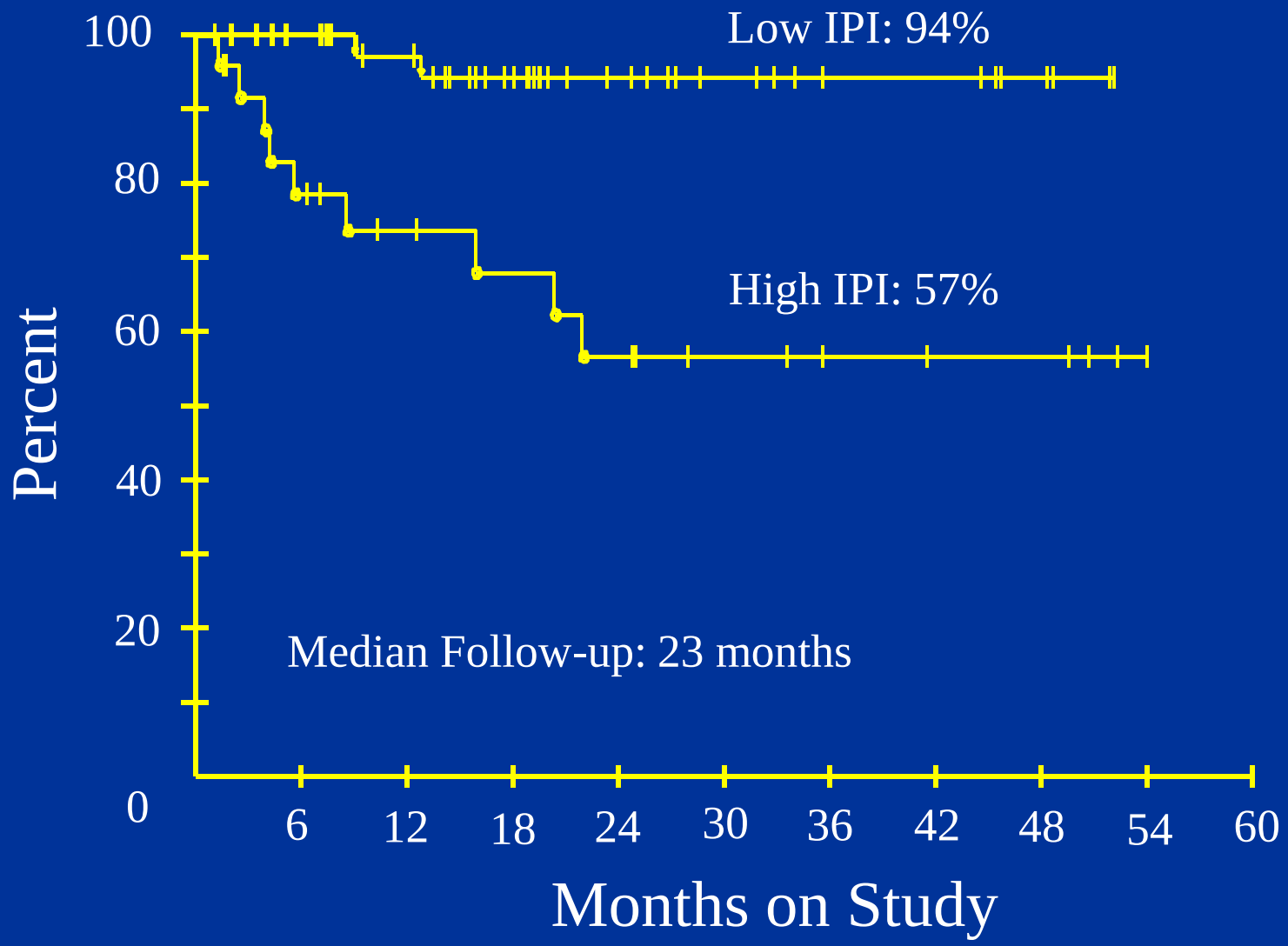
Response

	Nos.	CR	PD	Total RR
All Patients (4 TE; 1 NE)	**64**	**92% (95% CI:83-97)**	**5%**	**95%**
Low Risk IPI	**42**	**100% (95% CI:92-100)**	**0%**	**100%**
High Risk IPI	**22**	**77% (95% CI:55-92)**	**9%**	**86%**

Progression-Free and Overall Survival

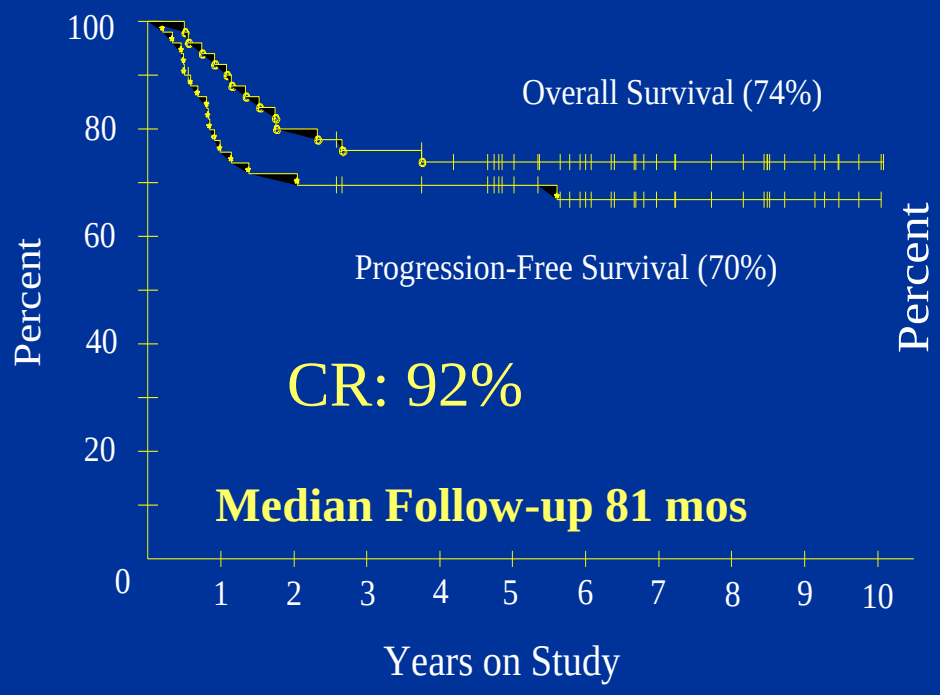


Progression-Free Survival
Low v High IPI

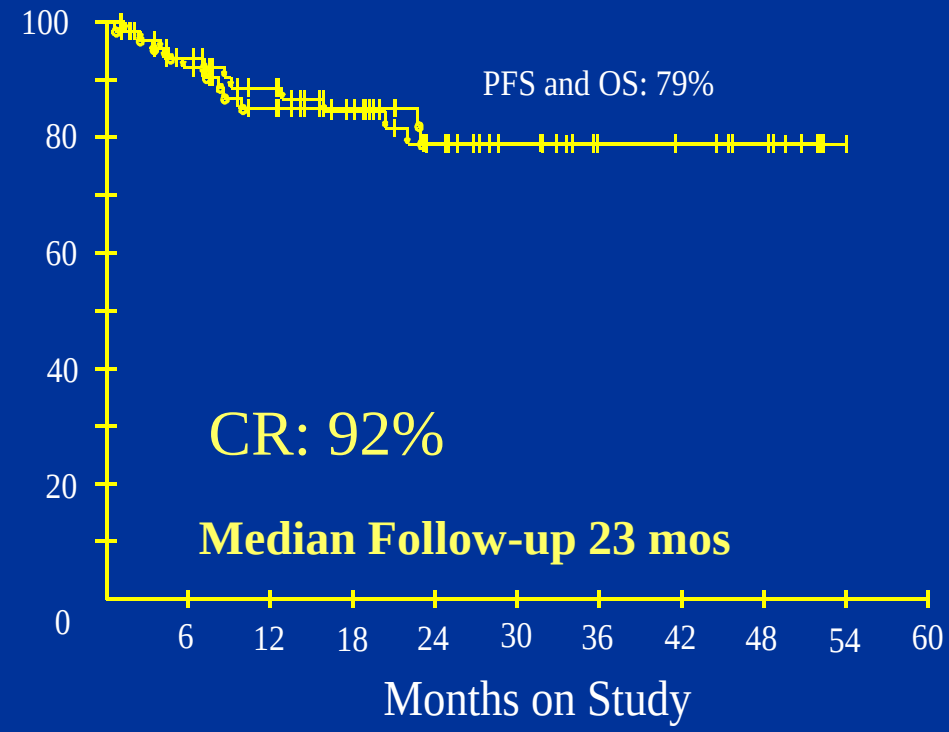


PFS and OS of
DA-EPOCH v DA-EPOCH-R

DA-EPOCH

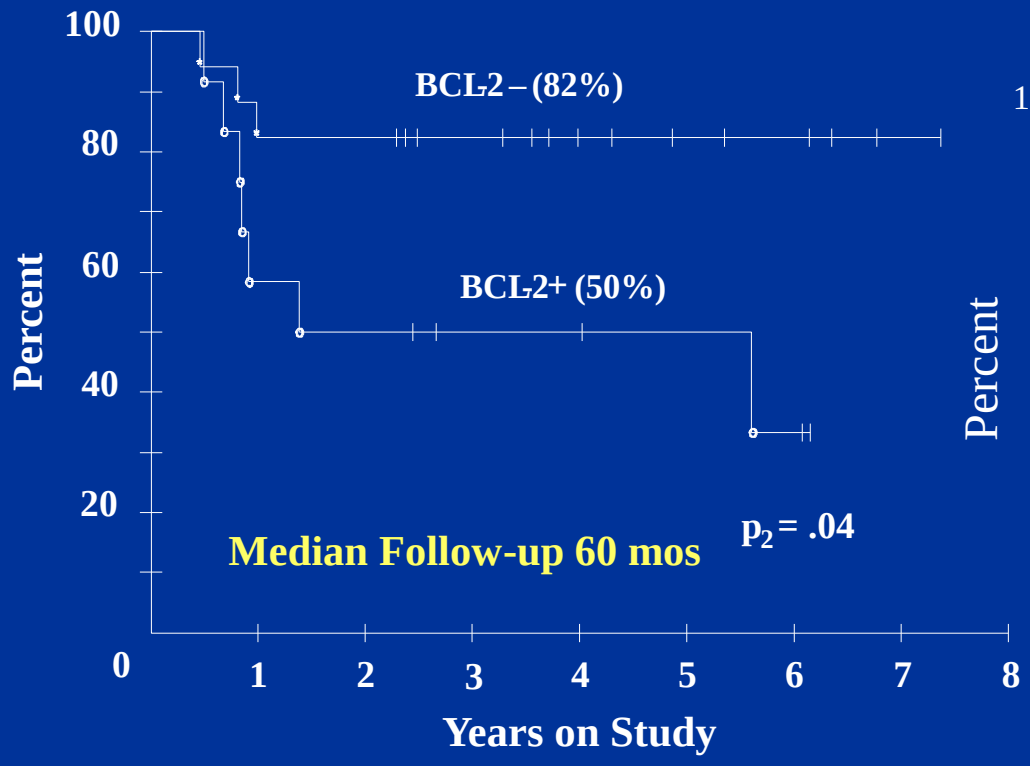


DA-EPOCH-R

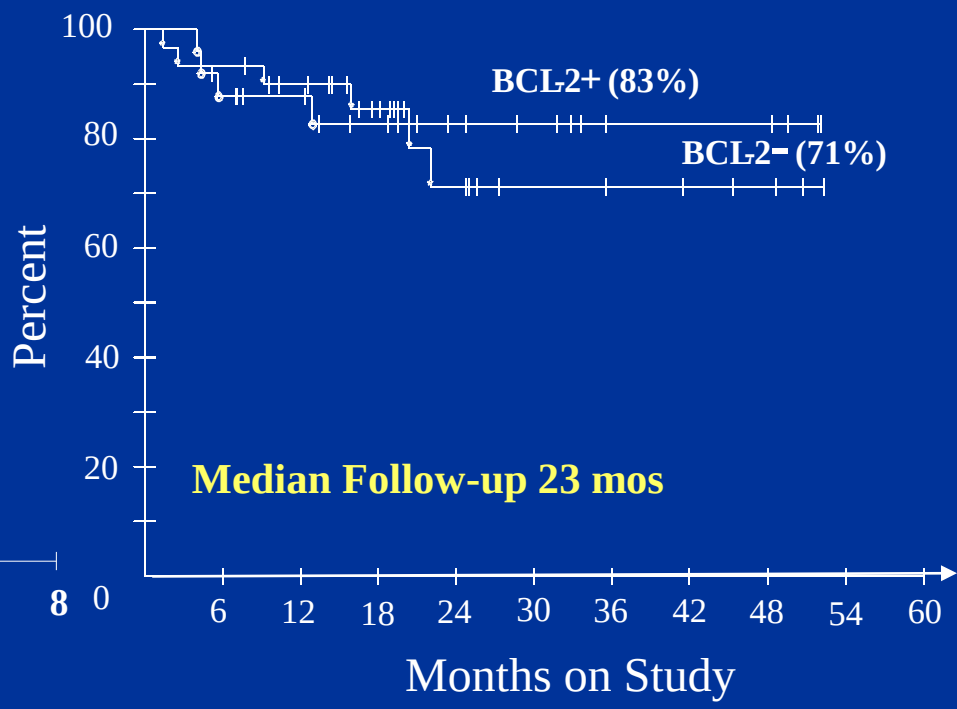


Effect of BCL-2 Expression on Progression-Free Survival

DA-EPOCH

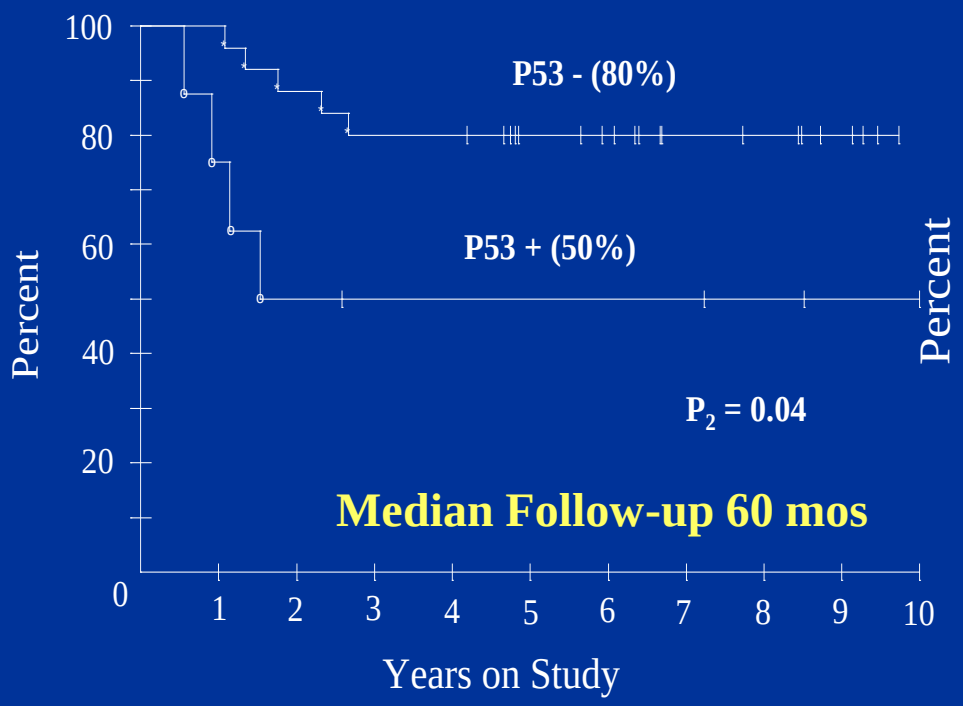


DA-EPOCH-R

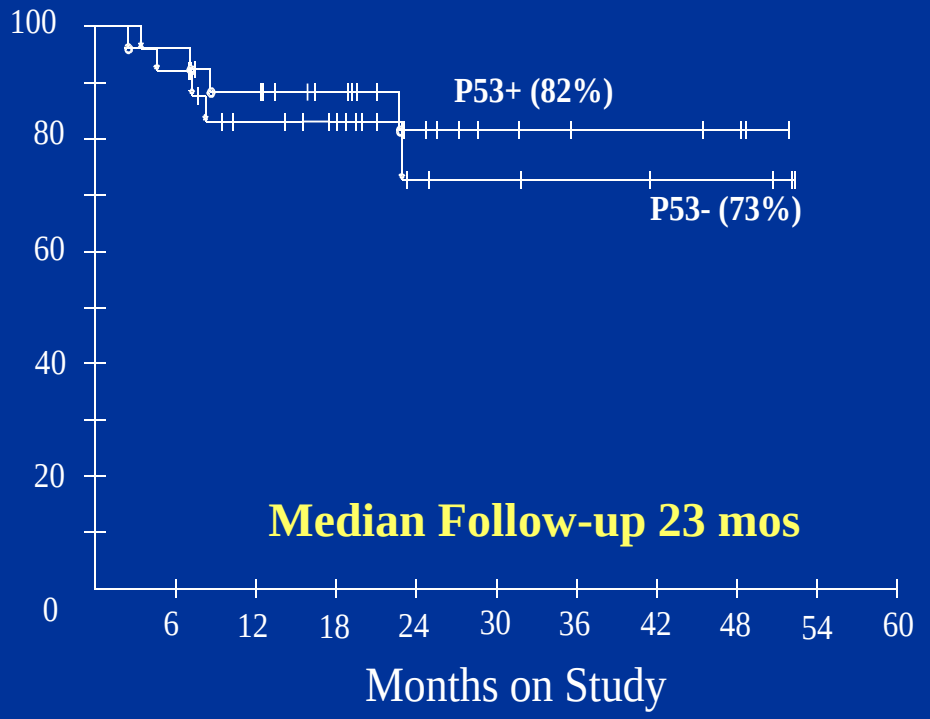


Effect of P53 Expression on Overall Survival

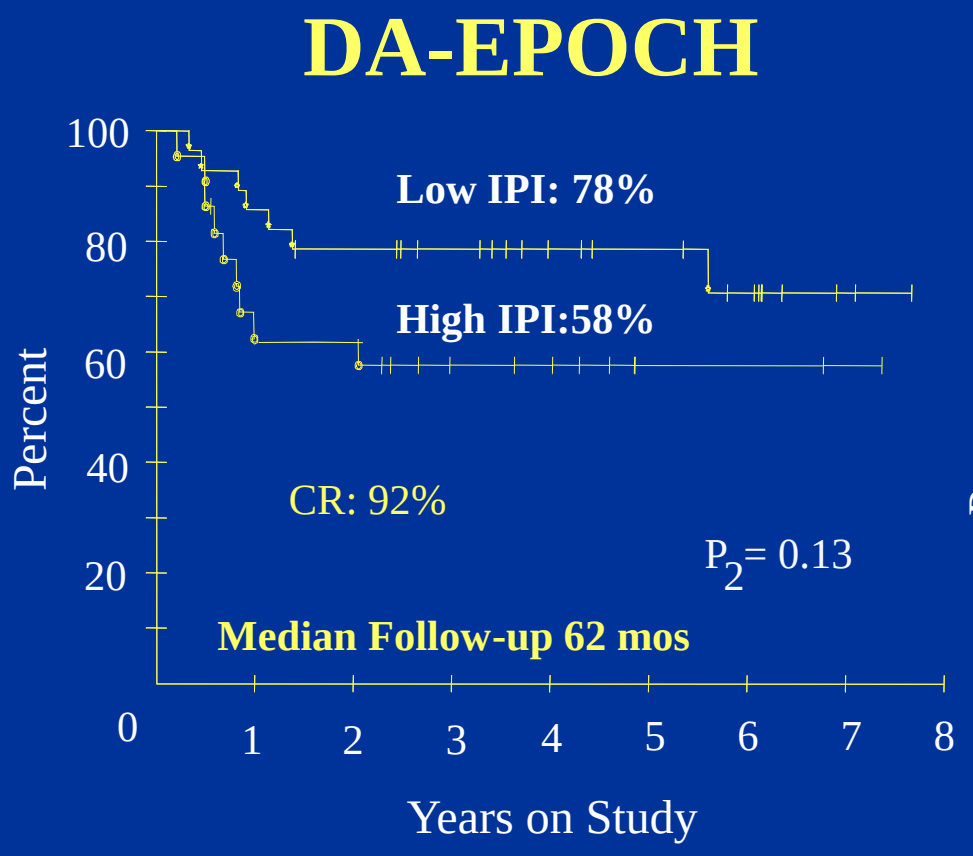
DA-EPOCH

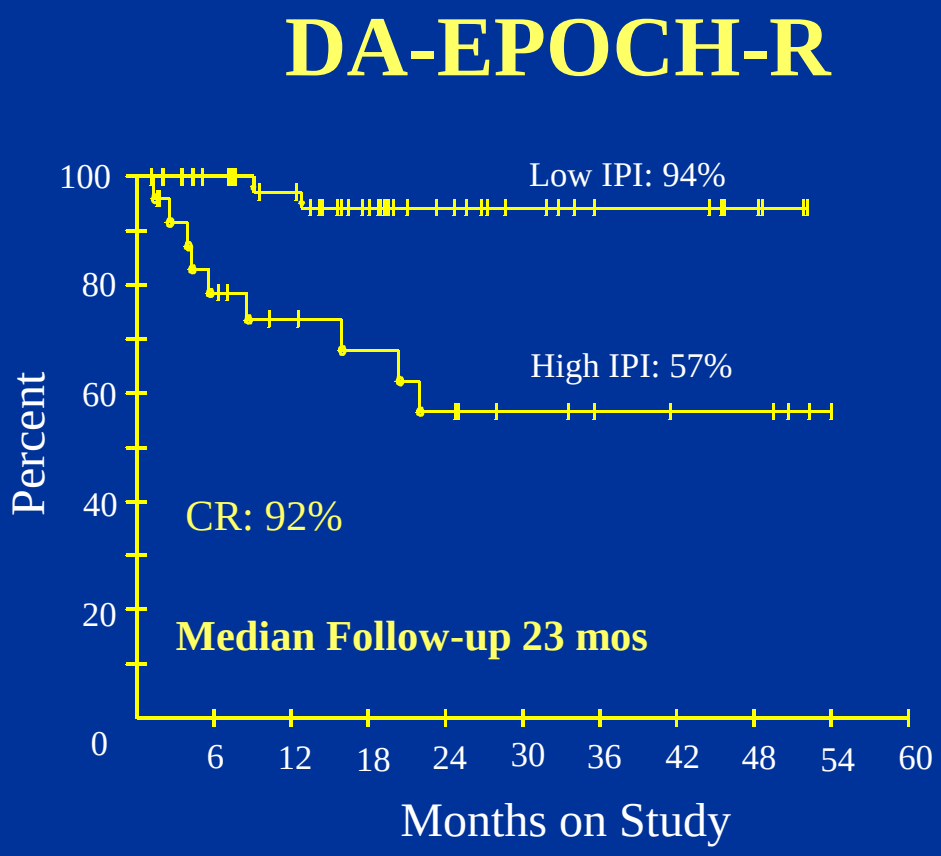


DA-EPOCH-R

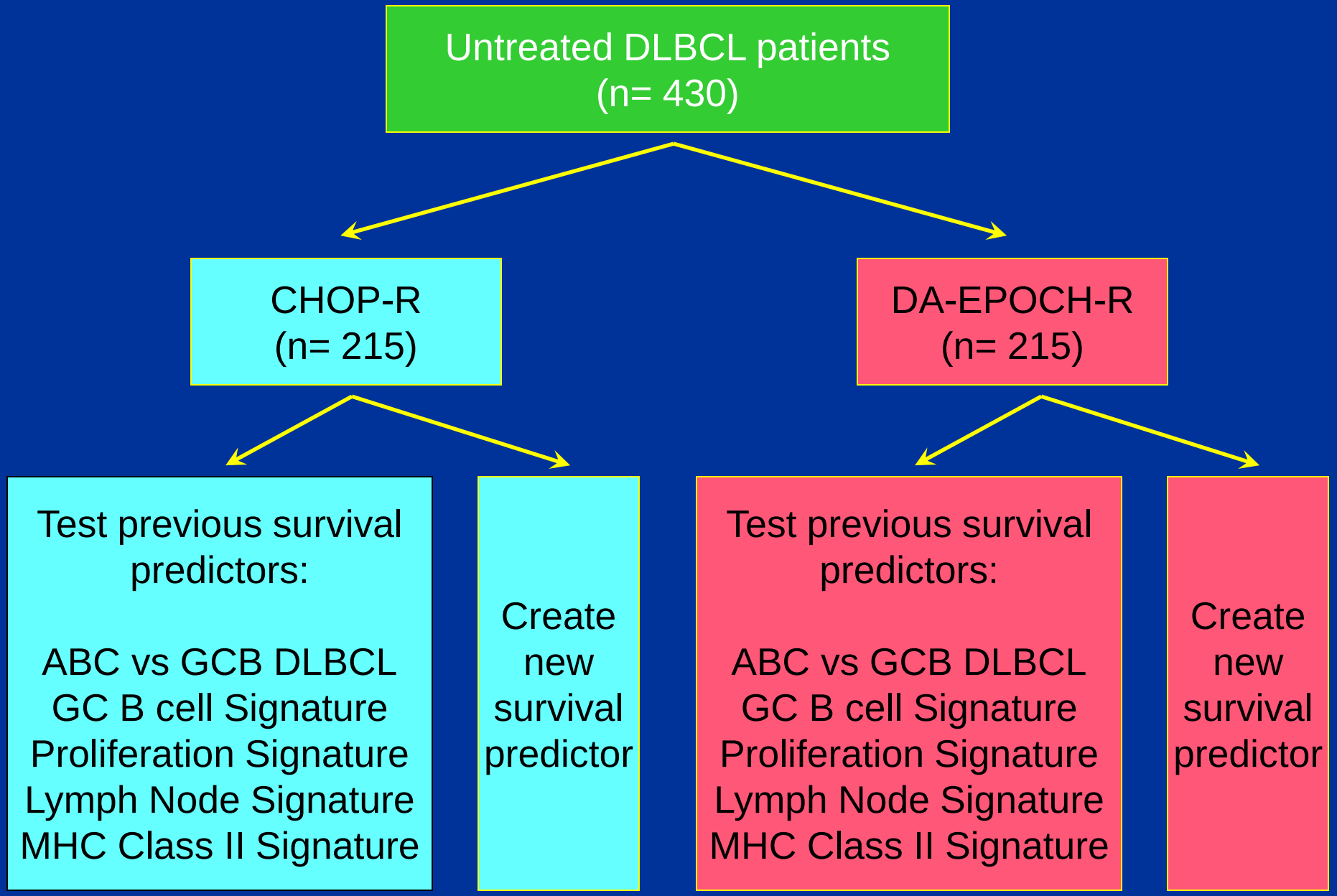


PFS of Low and High IPI in
DA-EPOCH v DA-EPOCH-R





NCI Phase III R-CHOP v DA-EPOCH-R



Conclusions

- The addition of Rituximab to chemotherapy increases EFS and OS in high grade NHL
- This effect is most marked in low IPI and bcl2+ patients
- 30-40% of patients will still die from their disease
- Future directions:
  - Dose adjusted/escalated therapy
  - New agents ?Bortezimib
  - Role for RIT