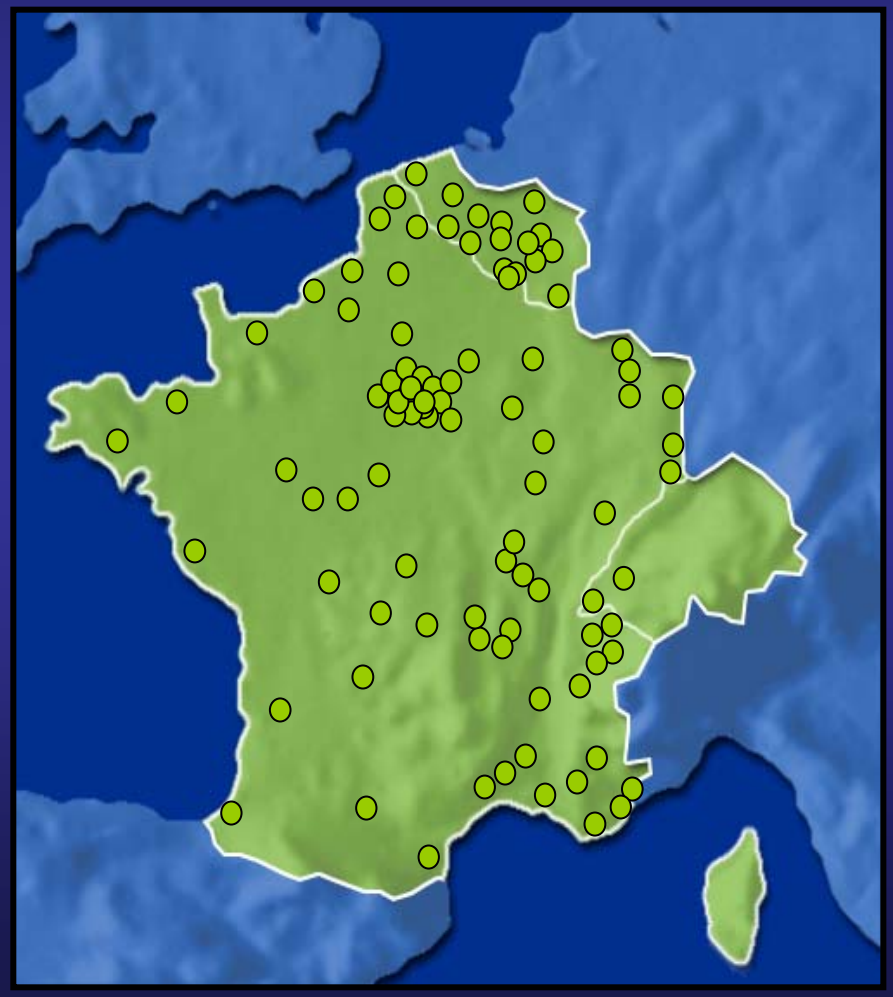
Non-Hodgkin Lymphomas

- Update on Aggressive NHL
  - CHOP-R (GELA)
  - MINT
  - Dose dense CHOP
  - Dose dense CHOP-R (RICOVER trial)
  - Rituximab maintenance in DLCL
  - Salvage GROC protocol

- Update on Indolent NHL
  - Prognostic Factors
  - Summary of MD Anderson 25 years experience
  - Role of Rituximab maintenance
  - New drugs for indolent NHL
  - Rituximab toxicity
- Role of PET Scan in NHL
- Rituximab in benign hematologic disorders

Aggressive NHL

Groupe d'Etude des Lymphomes de l'Adulte



- >130 centers in France, Belgium, and Switzerland
- 86 centers entered patients in this study
- Central pathology review on all cases

GELA

LNH-98.5

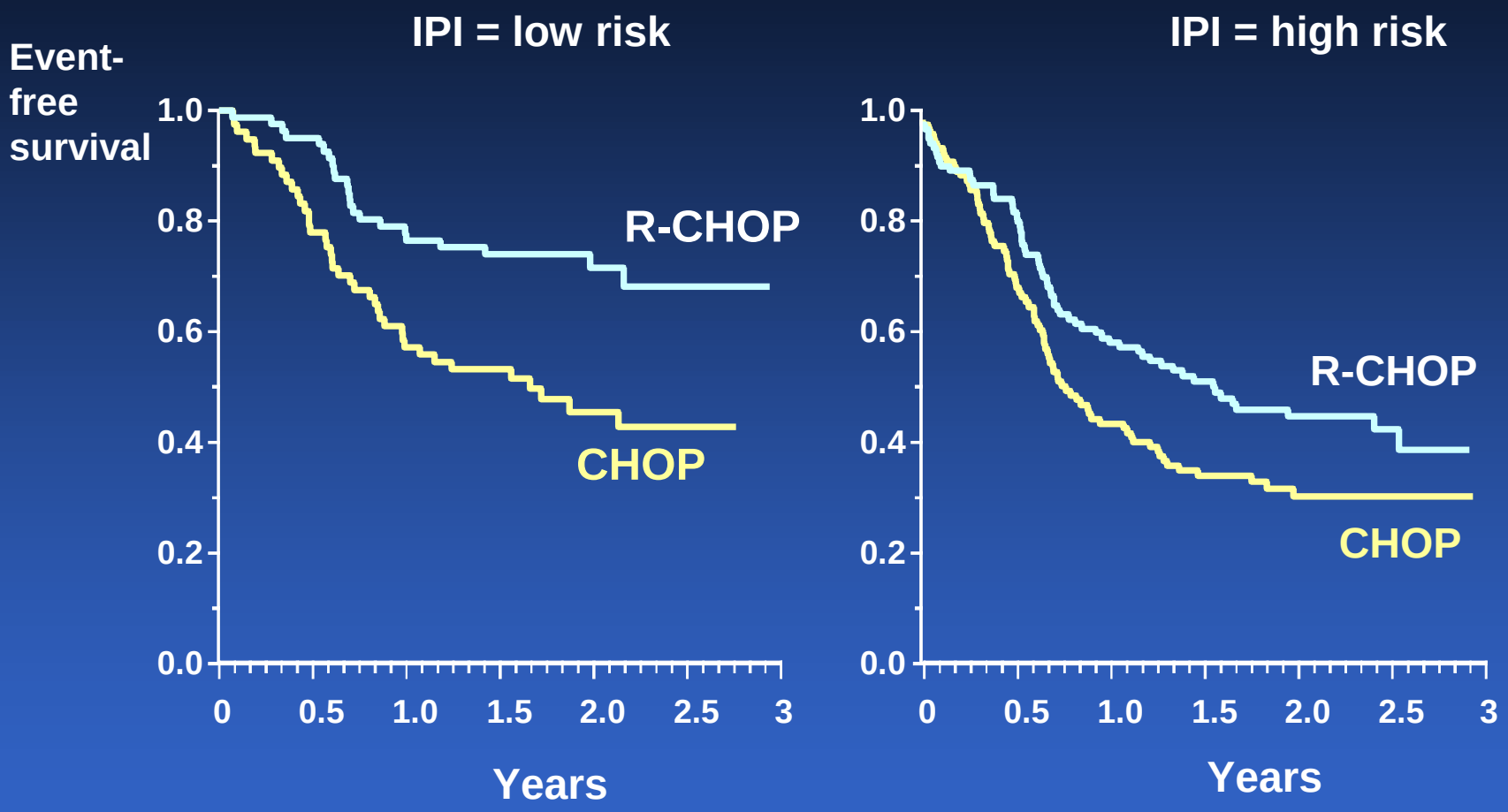
CHOP compared with CHOP plus Rituximab

Standard CHOP	Cyclophosphamide	750 mg/m²	Day 1
	Doxorubicin	50 mg/m²	Day 1
	Vincristine	1.4 mg/m²	Day 1
	Prednisone	40 mg/m²	x 5 days
R-CHOP	CHOP	as above	Day 1
	Rituximab	375 mg/m²	Day 1

Every 3 weeks for 8 cycles

GELA

CHOP vs CHOP-R in Patients over 60: Event-free survival according to IPI



Patients were stratified on IPI before randomization

Coiffier et al. NEJM 346:235-242, 2002

GELA Study Results Apply Only to Patients >60 Years Old

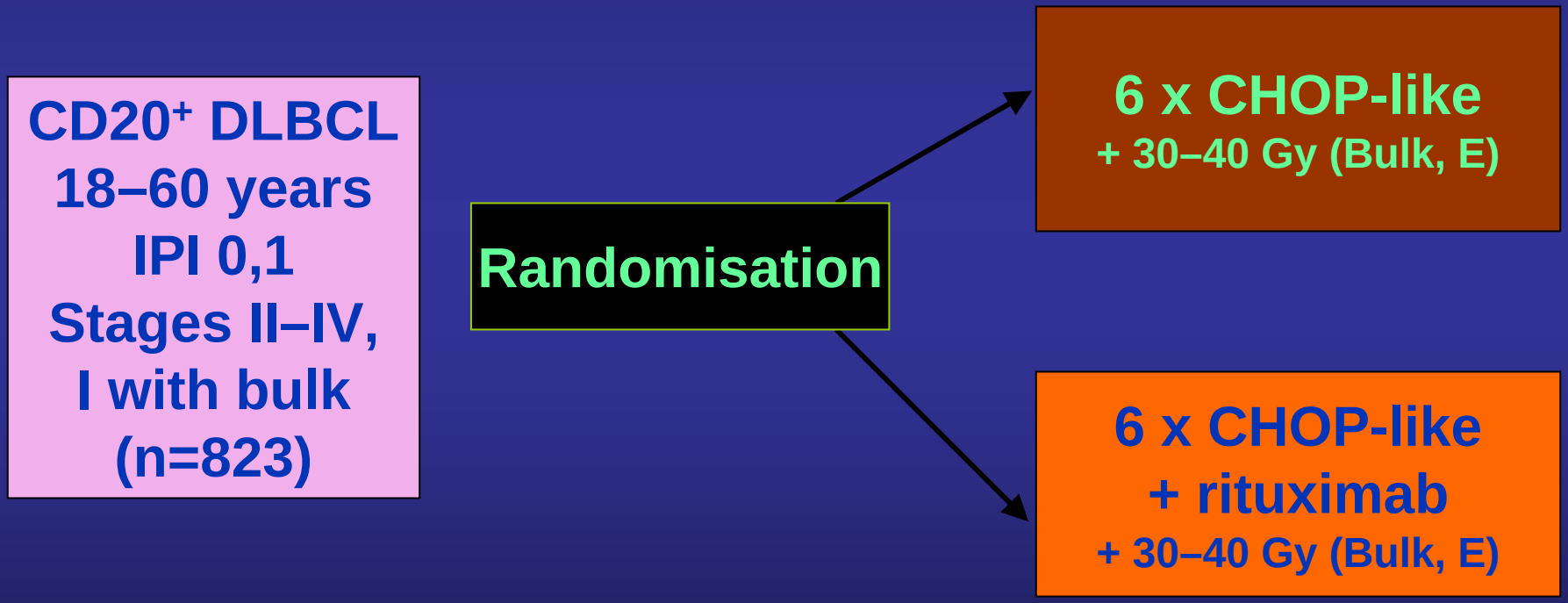
[157] First Analysis of the Completed Mabthera International (MInT) Trial in Young Patients with Low-Risk Diffuse Large B-Cell Lymphoma (DLBCL): Addition of Rituximab to a CHOP-Like Regimen Significantly Improves Outcome of All Patients with the Identification of a Very Favorable Subgroup with IPI=O and No Bulky Disease. Session Type: Oral Session

Michael Pfreundschuh, *Lorenz Truemper, Devinder Gill, Anders Osterborg, Ruth Pettengell, Marek Trneny, Kevin Imrie, Jan Walewski, Pier-Luigi Zinzani, Markus Loeffler . Med. Klinik I, Saarland University Medical School, Homburg, Germany; Universitaet Goettingen, Goettingen, Germany; Princess Alexandra Hospital, Brisbane, Australia; Karolinska Hospital, Stockholm, Sweden; St. George Hospital, London, United Kingdom; Charles University, Prague, Czech Republic; Sunnybrook Cancer Center, Toronto, Canada; Sklodowska-Curie Institute, Warsaw, Poland; Istituto di Ematologia, Bologna, Italy; Leipzig University, Leipzig, Germany*

157] First Analysis of the Completed Mabthera International (MInT) Trial in Young Patients with Low-Risk Diffuse Large B-Cell Lymphoma (DLBCL)

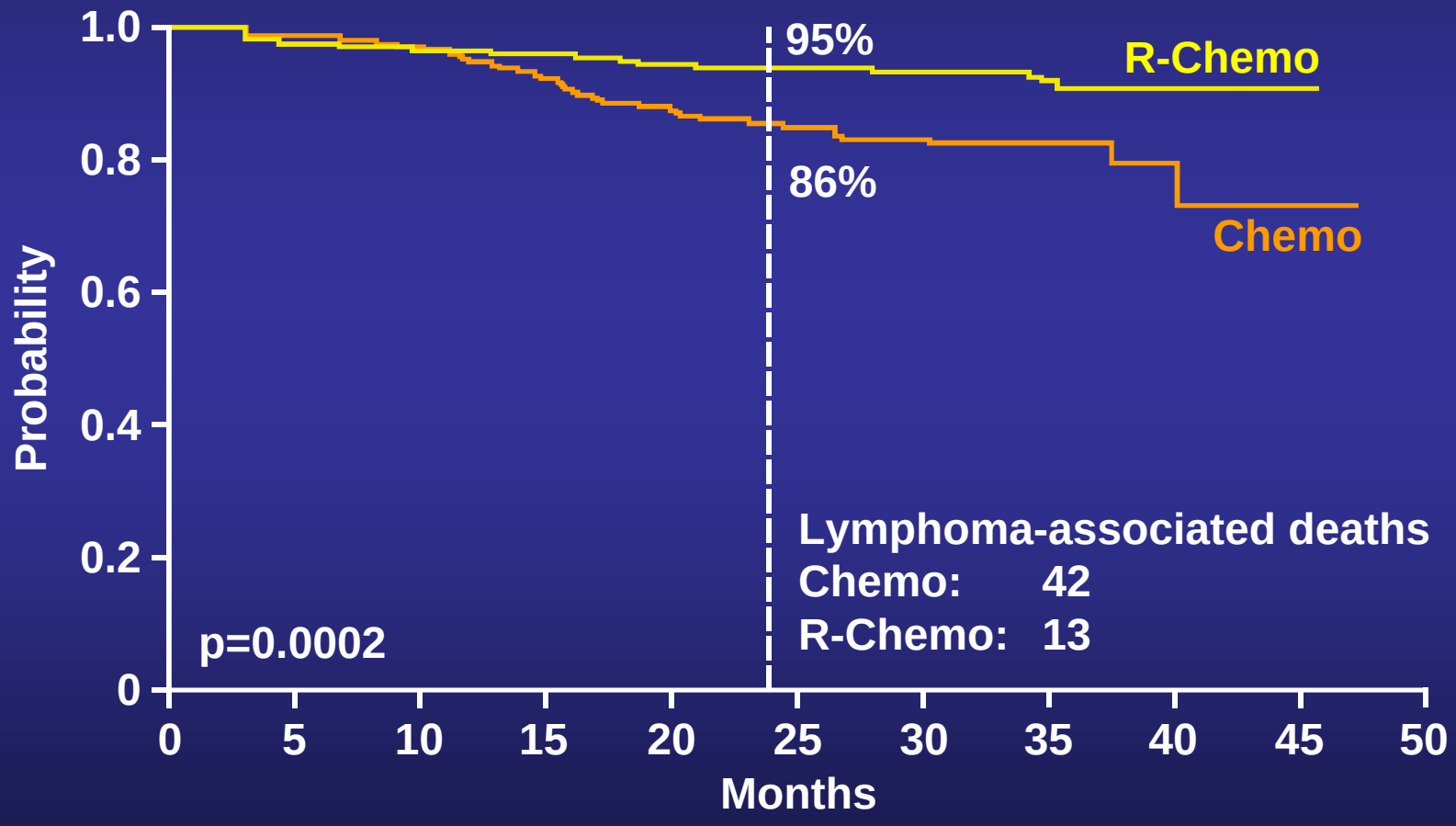
- **Background: Rituximab has been shown to improve outcome in elderly patients with DLBCL (Coiffier et al., NEJM, 2002), but there is only limited data for young low-risk patients**
- **Patients: 823 cases with $CD20^+$ DLBCL with IPI 0 or 1, stages II-IV and bulky stage I.**
- **Therapy: Randomized to either 6 cycles of a CHOP-like regime or the same chemotherapy plus rituximab 375 mg/m^2 given on days 1, 22, 43, 64, 85, and 106.**

Chemotherapy ± rituximab in younger patients with DLBCL (MInT): trial design



Pfreundschuh M, et al. Proc Am Soc Clin Oncol 2005;23:567s (Abstract 6529)

MInT: overall survival

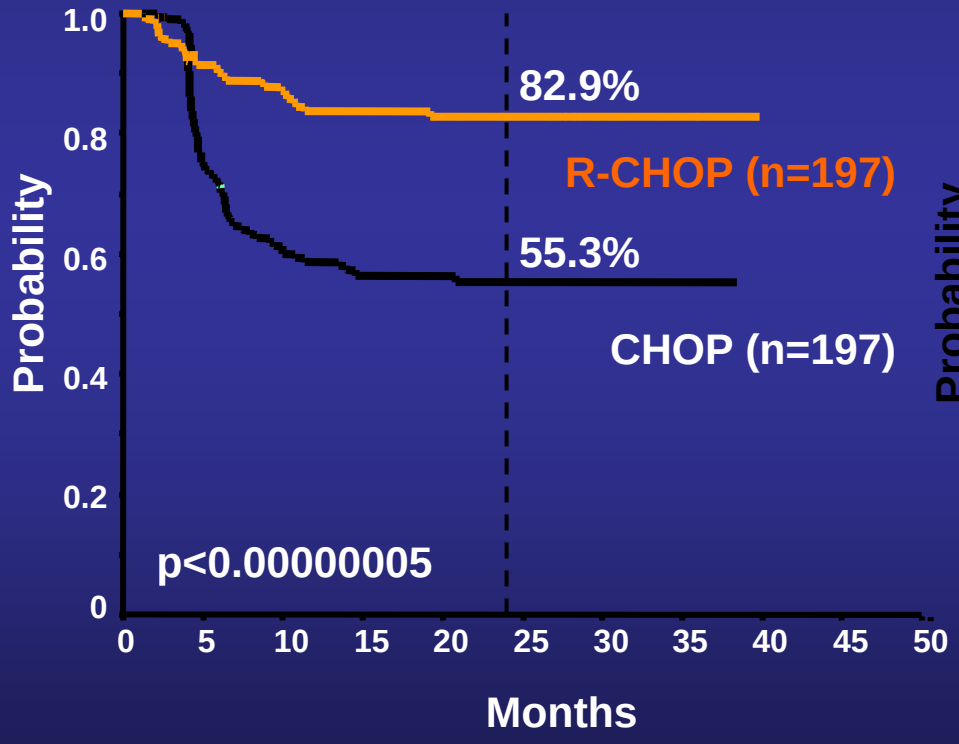


Median observation time: 23 months

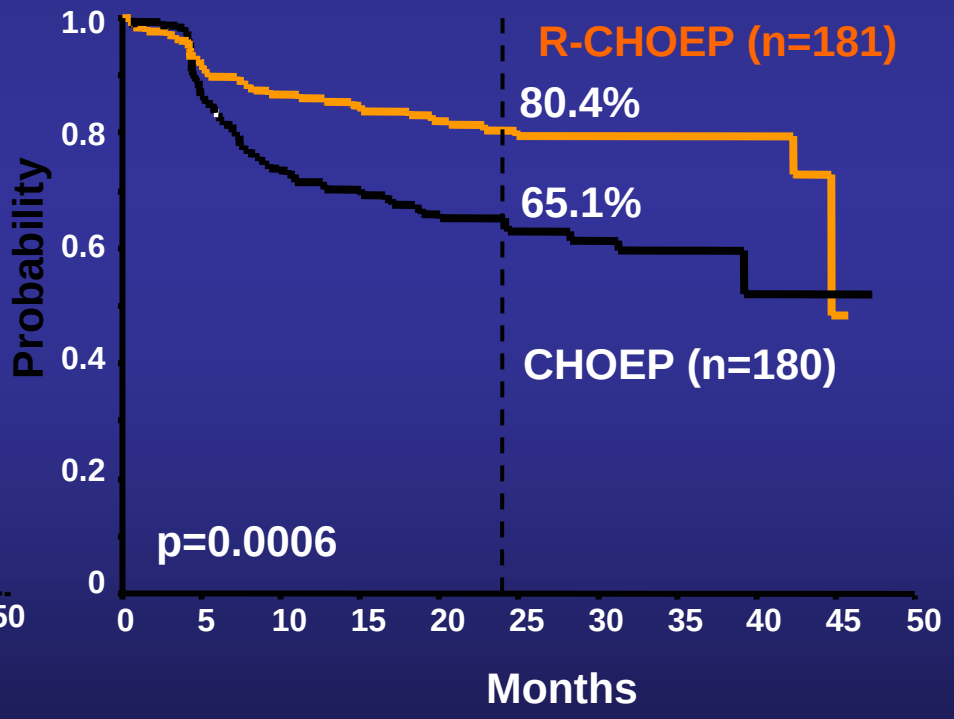
Pfreundschuh M, et al. Proc Am Soc Clin Oncol 2005;23:567s (Abstract 6529)

MInT: Time to Treatment Failure

R-CHOP vs CHOP



R-CHOEP vs CHOEP



Pfreundschuh M, et al. Proc Am Soc Clin Oncol 2005;23:567s (Abstract 6529)

Tumors with high proliferative fraction (i.e. high Ki-67) tend to grow in between courses of chemotherapy

Principle:

Intervals Between Courses of Chemotherapy Should be as Short as Possible.

The importance of dose density in management of aggressive lymphoma was proven in a study that tested accelerated CHOP given every 14 days with G-CSF

Two-weekly vs 3-weekly CHOP chemotherapy Pfreundschuh, et al. *Blood.* 2002;100:774a (abstr 3060).

- 689 patients ages 61 to 75 years randomized to:
  - 6 cycles of either
    - CHOP-21 no G-CSF
    - CHOP-14 + G-CSF
    - CHOEP-21 (CHOP plus etoposide) no G-CSF
    - CHOEP-14 (CHOP plus etoposide) + G-CSF
- Patients in the 2-weekly regimens received G-CSF.
- Radiotherapy (36 Gy) to sites of initial bulky disease and extranodal disease.

CHOP-14, CHOP-21, CHOEP-14, and CHOEP-21 for DLBCL

	Complete Response Rates					
Regimen	**PT**	**ALL**		**LDH-NL**		**LDH>NL**
Patients	728	728		392		336
CHOP-14	179	77	0.005	85	NS	68
CHOEP-14	180	74		79		68
CHOP-21	189	63		79		45
CHOEP-21	180	72		82		60

CHOP-14, CHOP-21, CHOEP-14, and CHOEP-21 for DLBCL

- Time to Treatment Failure (4-year)
  - CHOP-14= 47% vs. CHOP-21=39%
- Overall Survival (4-year)
  - CHOP-14= 59% vs. CHOP-21= 45%

CHOP-14, CHOP-21, CHOEP-14, and CHOEP-21 for DLBCL

- Toxicity of CHOP-14 and CHOP-21 was similar
  - Less neutropenia with CHOP-14
- CHOEP-21 and in particular CHOEP-14 were more toxic.
- Due to its favorable efficacy and toxicity profile, CHOP-14 should be considered the new standard chemotherapy regimen for patients ages 60 or older with aggressive lymphoma.

Is Dose Dense CHOP as Good as Dose Dense R-CHOP?

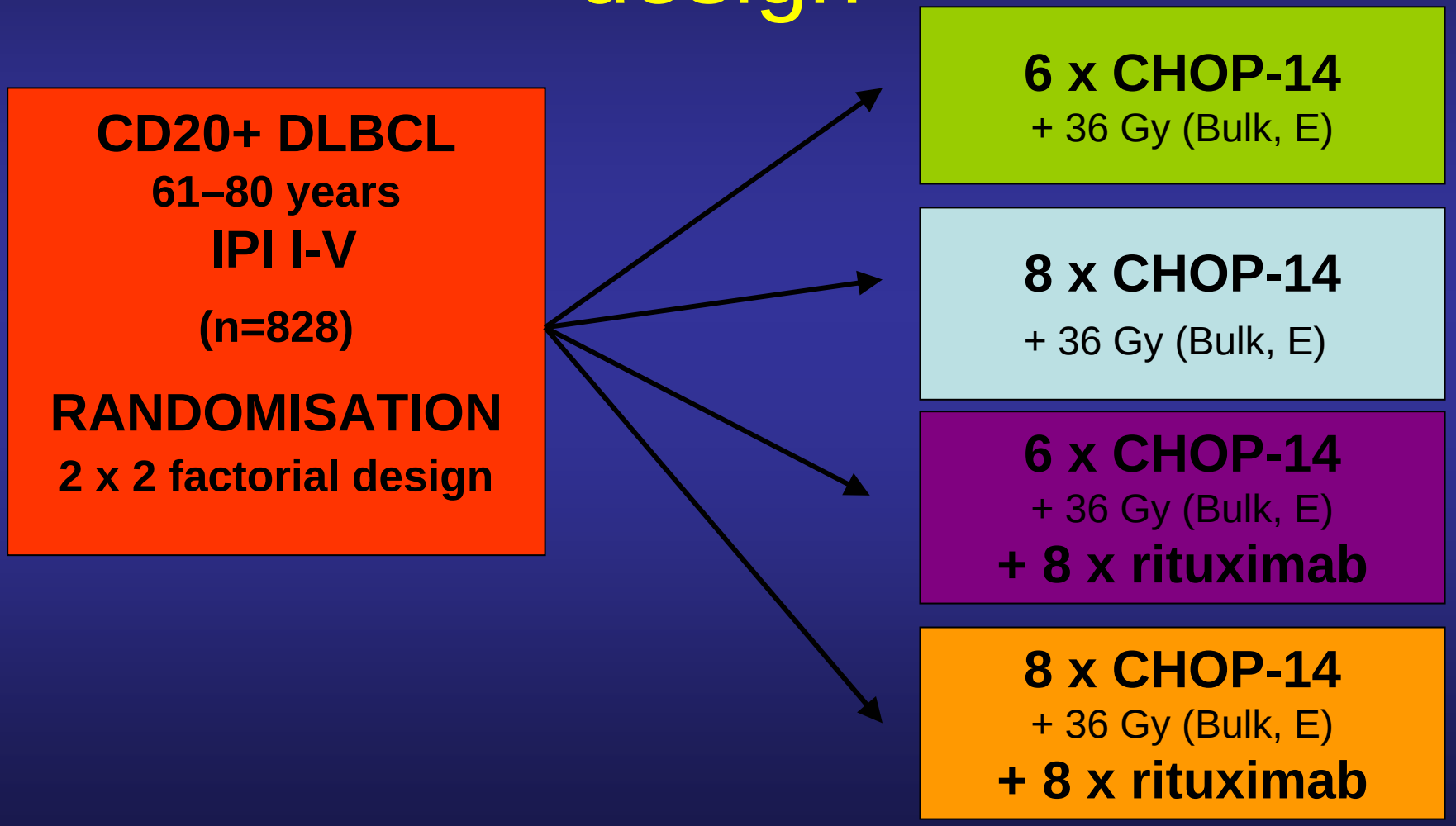
OR

Do We Still Need Rituximab If We Use Dose Dense CHOP?

Another Question

- **What is the ideal number of CHOP chemotherapy courses: 6 or 8?**

Dose-intensified chemotherapy ± Rituximab (RICOVER 60): trial design

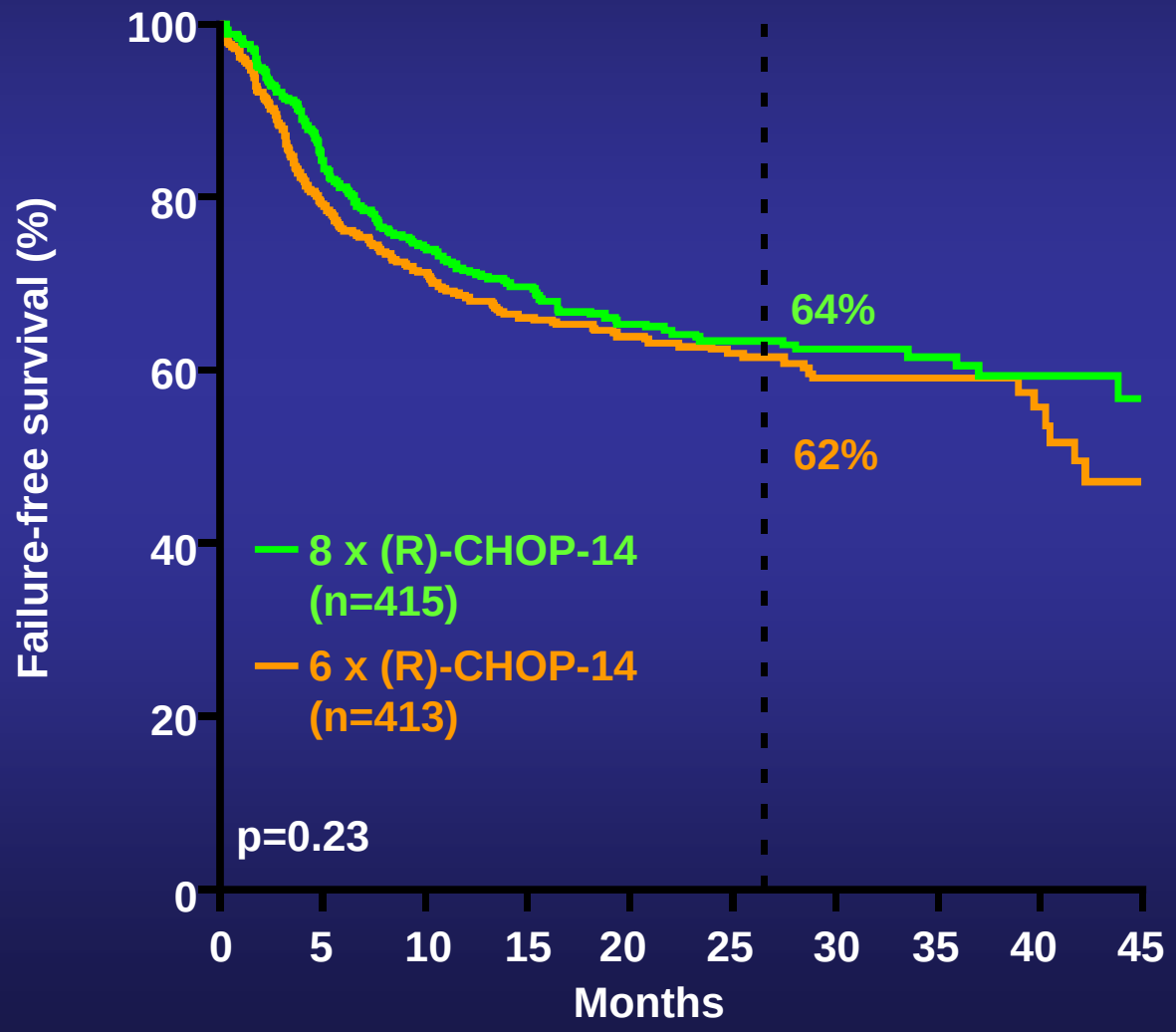


Pfreundschuh M, et al. Blood 2005;106 (Abstract 13)

German High Grade NHL Group Study
Abstract #13 (Oral)

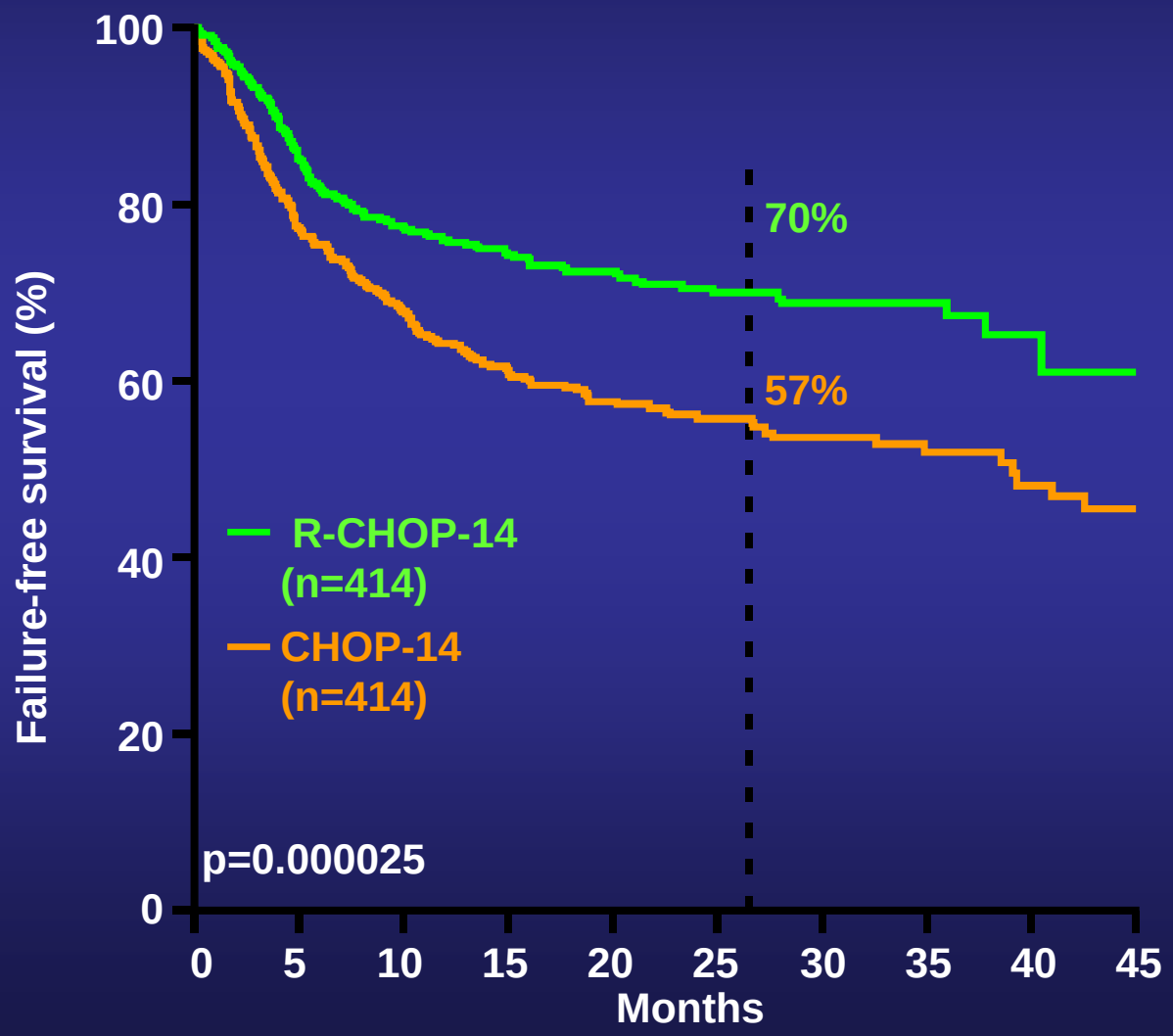
- Eligibility: stage I-IV pts with DLCL-B > 60 y/o
- Median age 68 y/o
- Median follow-up 26 mos.
- 1,330 randomized to 4 arms

RICOVER 60: time to treatment failure – 6 cycles vs 8 cycles



Pfreundschuh M, et al. Blood 2005;106 (Abstract 13)

RICOVER 60: Failure Free Survival: CHOP-14 vs R-CHOP-14



Pfreundschuh M, et al. Blood 2005;106 (Abstract 13)

German High Grade NHL Group CHOP q. 14 days with or without Rituximab (RICOVER-60 Trial)

Abstract #13

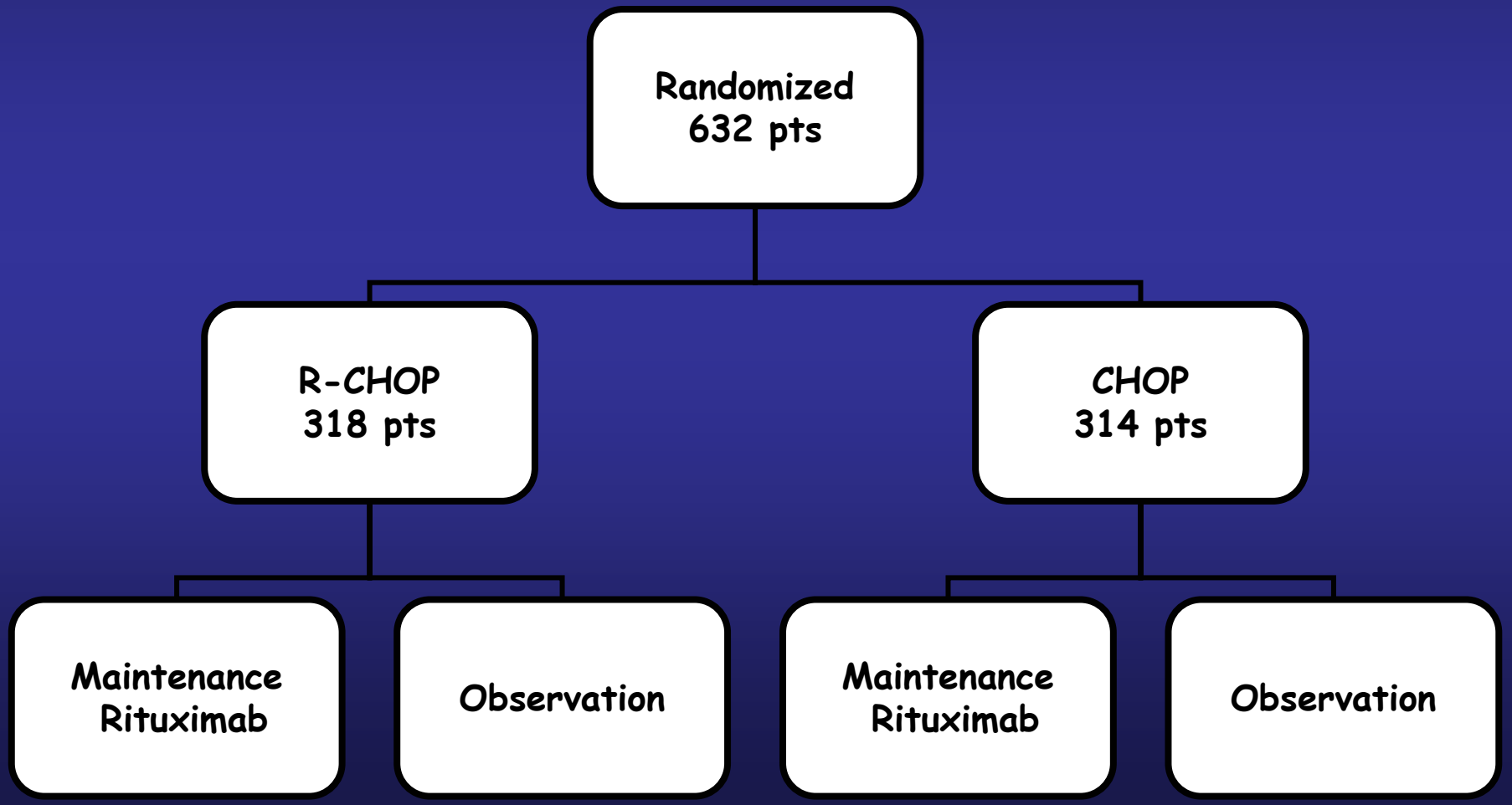
Treatment Arm	TTF	OS
CHOP x8	58%	n.a.
CHOP-R x8	70%	n.a.
CHOP x6	53%	72%
CHOP-R x6	70%*	78%**

P<.05

** P= N.S.

What is the Role of Rituximab Maintenance in Diffuse Large Cell NHL?

Phase III Trial of Rituximab-CHOP vs CHOP with a Second Randomization to Maintenance Rituximab vs. Observation in Patients 60 Years or Older with DLBCL (Haberman et al, ASH Abstract # 8, 2003)



Phase III Trial of Rituximab-CHOP vs CHOP with a Second Randomization to Maintenance Rituximab vs. Observation in Patients ≥ 60 Years with DLBCL (Abstract #8 ASH 2003)

- On the R-CHOP arm, the second randomization to Rituximab maintenance vs observation was not associated with an improved outcome.
- Study was not designed to compare CHOP vs R-CHOP
- Weighted (non-planned) analysis showed CHOP-R vs. CHOP better TTF (p=0.02) and OS (p=0.03)
- Addition of Rituximab either to induction or maintenance arms increased TTF

New Salvage Regimen: GROC

Gemcitabine, Oxaliplatin, Rituximab Salvage Regimen for Aggressive NHL: Comparison of Two Studies

Institution	N	CR	PR	FFS	% 1^0 Refractory
Puerto Rico	19	42%	37%	34% (at 1 yr)	47%
France	46	50%	33%	53% (at 2 yrs)	13%

Indolent NHL

blood JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Blood, 1 September 2004, Vol. 104, No. 5, pp. 1258-1265.

CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Follicular Lymphoma International Prognostic Index

Philippe Solal-Céligny, Pascal Roy, Philippe Colombat, Josephine White, Jim O. Armitage, Reyes Arranz-Saez, Wing Y. Au, Monica Bellei, Pauline Brice, Dolores Caballero, Bertrand Coiffier, Eulogio Conde-Garcia, Chantal Doyen, Massimo Federico, Richard I. Fisher, Javier F. Garcia-Conde, Cesare Guglielmi, Anton Hagenbeek, Corinne Haïoun, Michael LeBlanc, Andrew T. Lister, Armando Lopez-Guillermo, Peter McLaughlin, Noël Milpied, Pierre Morel, Nicolas Mounier, Stephen J. Proctor, Ama Rohatiner, Paul Smith, Pierre Soubeyran, Hervé Tilly, Umberto Vitolo, Pier-Luigi Zinzani, Emanuele Zucca, and Emili Montserrat

The prognosis of follicular lymphomas (FL) is heterogeneous and numerous treatments may be proposed. A validated prognostic index (PI) would help in evaluating and choosing these treatments. Characteristics at diagnosis were collected from 4167 patients with FL diagnosed between 1985 and 1992. Univariate and multivariate analyses were used to propose a PI. This index was then tested on 919 patients. Five adverse prognostic factors were selected: age (> 60 years vs ≤ 60 years), Ann Arbor stage (III-IV vs I-II), hemoglobin level (< 120 g/L vs ≥ 120 g/L), number of nodal areas (> 4 vs ≤ 4), and serum LDH level (above normal vs normal or below). Three risk groups were defined: low risk (0-1 adverse factor, 36% of patients), intermediate risk (2 factors, 37% of patients, hazard ratio [HR] of 2.3), and poor risk (≥ 3 adverse factors, 27% of patients, HR = 4.3). This Follicular Lymphoma International Prognostic Index (FLIPI) appeared more discriminant than the International Prognostic Index proposed for aggressive non-Hodgkin lymphomas. Results were very similar in the confirmation group. The FLIPI may be used for improving treatment choices, comparing clinical trials, and designing studies to evaluate new treatments. (Blood. 2004;104:1258-1265)

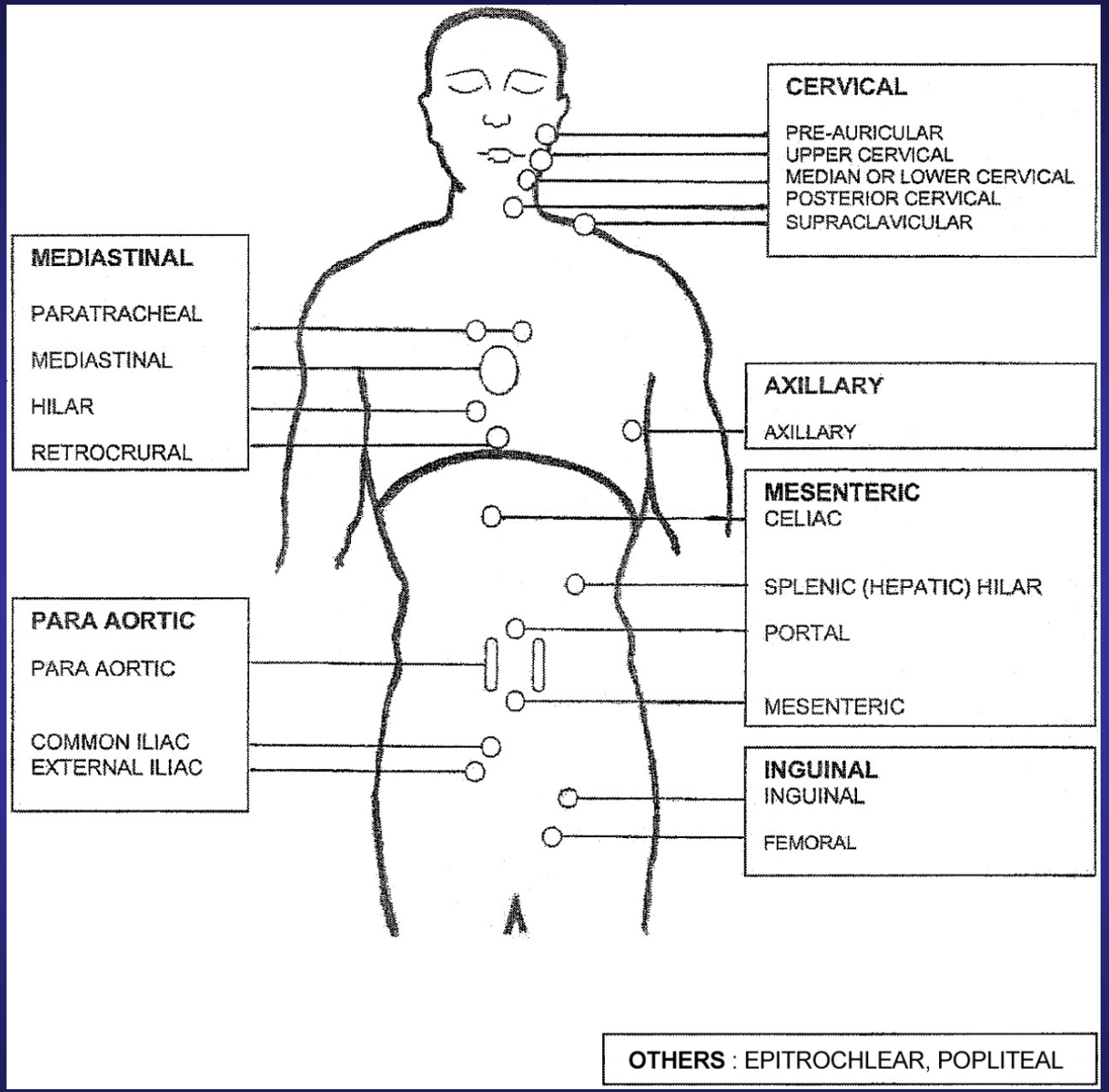
Introduction

Follicular lymphomas (FLs) account for one third of non- presence of bulky tumor(s),[6,8] increased serum lactate dehydroge-

FLIPI Indolent NHL score

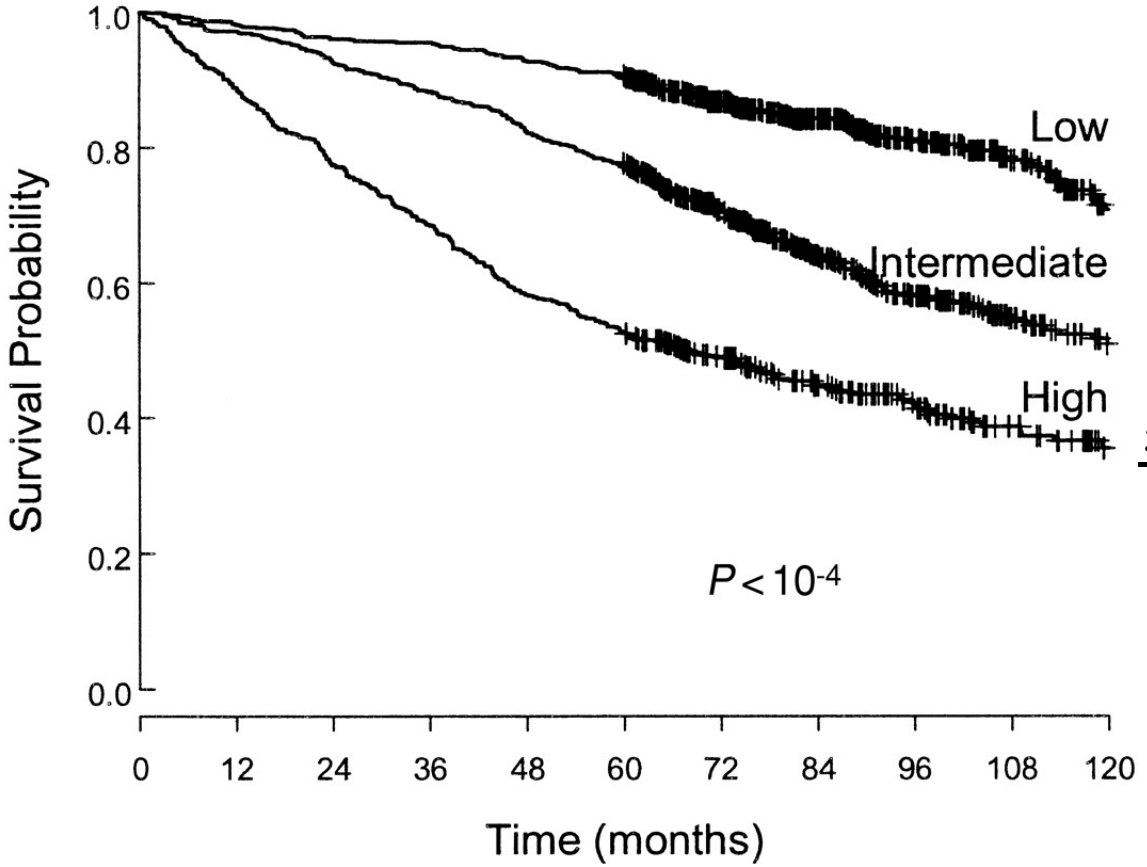
- **"No LASH"**
  - nodal areas >4
  - LDH high
  - Age >60
  - Stage 3-4
  - Hgb<12

Mannikin used for counting the number of involved areas



Solal-Celigny, P. et al. Blood 2004;104:1258-1265

Survival according to risk group as defined by FLIPI



0-1 Factors

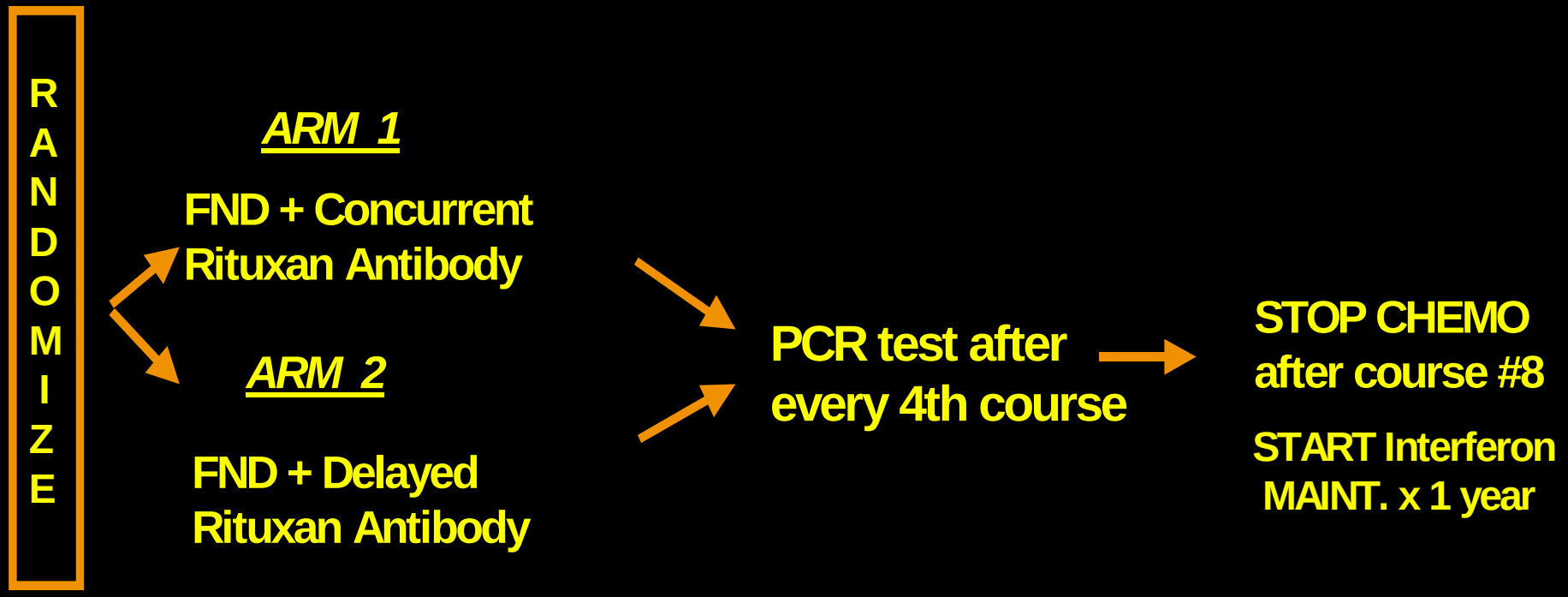
2 Factors

≥3 Factors

No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

Rituxan Has Been Shown To Synergize With Fludarabine

MD ANDERSON FRONT LINE STUDY FOR INDOLENT STAGE IV LYMPHOMAS



R-FND vs FND → R: Role of Chemo-Immunotherapy Sequence

Regimen	R + FND (concurrent) N = 82	FND → R (sequential) N = 78
NHL subsets (%)		
Follicular lymphoma	70%	69%
SLL	30%	30%
ORR %	100%	96%
(CR %)	(88%)	(85%)
Survival at 3 years	96%	94%
FFS (% at 3 years)		
All Pts	76%	60%
Follicular only	84% (*P* = 0.01)	59%
Molecular response (%)		
with follicular lymphoma	89% (*P* < 0.01)	60%
at 6 months	89% (*P* = 0.01)	68%
at 12 months		

McLaughlin P et al. *Proc Am Soc Clin Oncol*. 2003;22:564. Abstract 2269.

New Treatments Have Altered the Unfavorable Natural History of Indolent Lymphomas

VOLUME 24 · NUMBER 10 · APRIL 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Improvement of Overall and Failure-Free Survival in Stage IV Follicular Lymphoma: 25 Years of Treatment Experience at The University of Texas M.D. Anderson Cancer Center

Qi Liu, Luis Fayad, Fernando Cabanillas, Fredrick B. Hagemeister, Gregory D. Ayers, Mark Hess, Jorge Romaguera, M. Alma Rodriguez, Apostolia M. Tsimberidou, Srdan Verstovsek, Anas Younes, Barbara Pro, Ming-Sheng Lee, Ana Ayala, and Peter McLaughlin

From the Departments of Lymphoma/Myeloma, Biostatistics and Applied Mathematics, and Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted July 19, 2005; accepted January 24, 2006.

Supported by National Cancer Institute Core Grant CA16672 awarded to The University of Texas M.D. Anderson Cancer Center, and Schering-Plough Corp, Integrated Therapeutics Group Inc, Genentech Inc, Biogen IDEC Pharmaceuticals, Berlex Corporation, Burroughs Wellcome Co.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Peter McLaughlin, MD, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 429, Houston, TX 77030; e-mail: pmclaughl@mdanderson.org.

0732-183X/06/2410-1582/$20.00

DOI: 10.1200/JCO.2005.03.2695

ABSTRACT

Purpose
Advanced-stage follicular lymphoma is considered incurable. The pace of improvements in treatment has been slow. This article analyzes five sequential cohorts of patients with stage IV follicular lymphoma treated between 1972 and 2002.

Methods
Five consecutive studies (two were randomized trials) involving 590 patients were analyzed for overall survival (OS), failure-free survival (FFS), and survival after first relapse. A proportional hazards analysis, and subset analyses using the follicular lymphoma international prognostic index (FLIPI) score were performed. Treatment regimens included: cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin (CHOP-Bleo); CHOP-Bleo followed by interferon alfa (IFN-α); a rotation of three regimens (alternating triple therapy), followed by IFN-α; fludarabine, mitoxantrone, dexamethasone (FND) followed by IFN-α; and FND plus delayed versus concurrent rituximab followed by IFN-α.

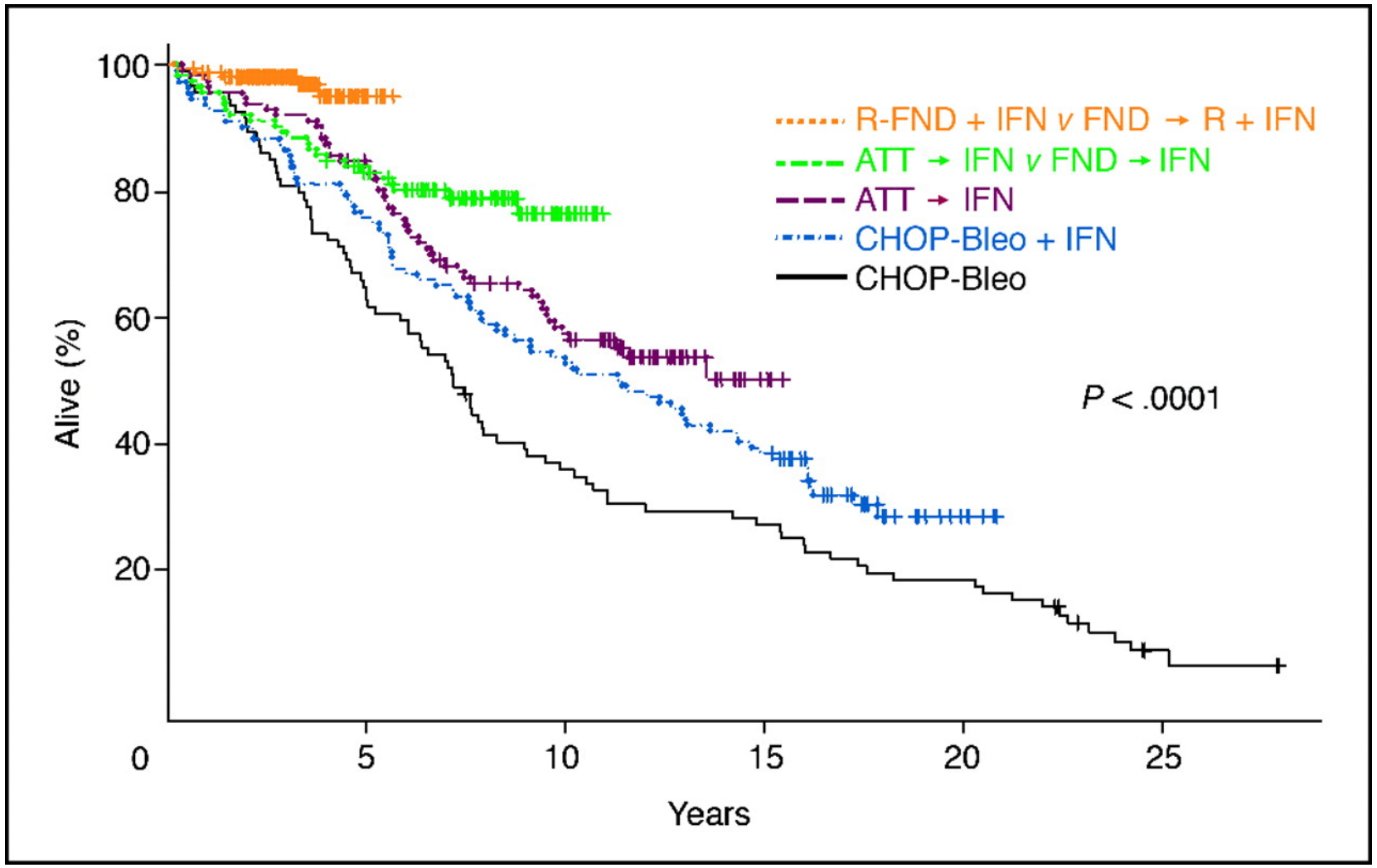
Results
Improvements in 5-year OS (from 64% to 95%) and FFS (from 29% to 60%) indicate steady progress, perhaps partly due to more effective salvage therapies, but the FFS data also indicate improved front-line therapies; these observations held true after controlling for differences in prognostic factors among the cohorts. The FLIPI model adds rigor to and facilitates comparisons among the different cohorts. An unexpected finding in this study was a trend toward an apparent FFS plateau.

Conclusion
Evolving therapy, including the incorporation of biologic agents, has led to stepwise significant outcome improvements for patients with advanced-stage follicular lymphoma. The apparent plateau in the FFS curve, starting approximately 8 to 10 years from the beginning of treatment, raises the issue of the potential curability of these patients.

J Clin Oncol 24:1582-1589. © 2006 by American Society of Clinical Oncology

[redacted] oboma ultimately suffer relapse. Some data suggest

25 Years Experience Indolent NHL at MD Anderson
Overall survival according to treatment regimen



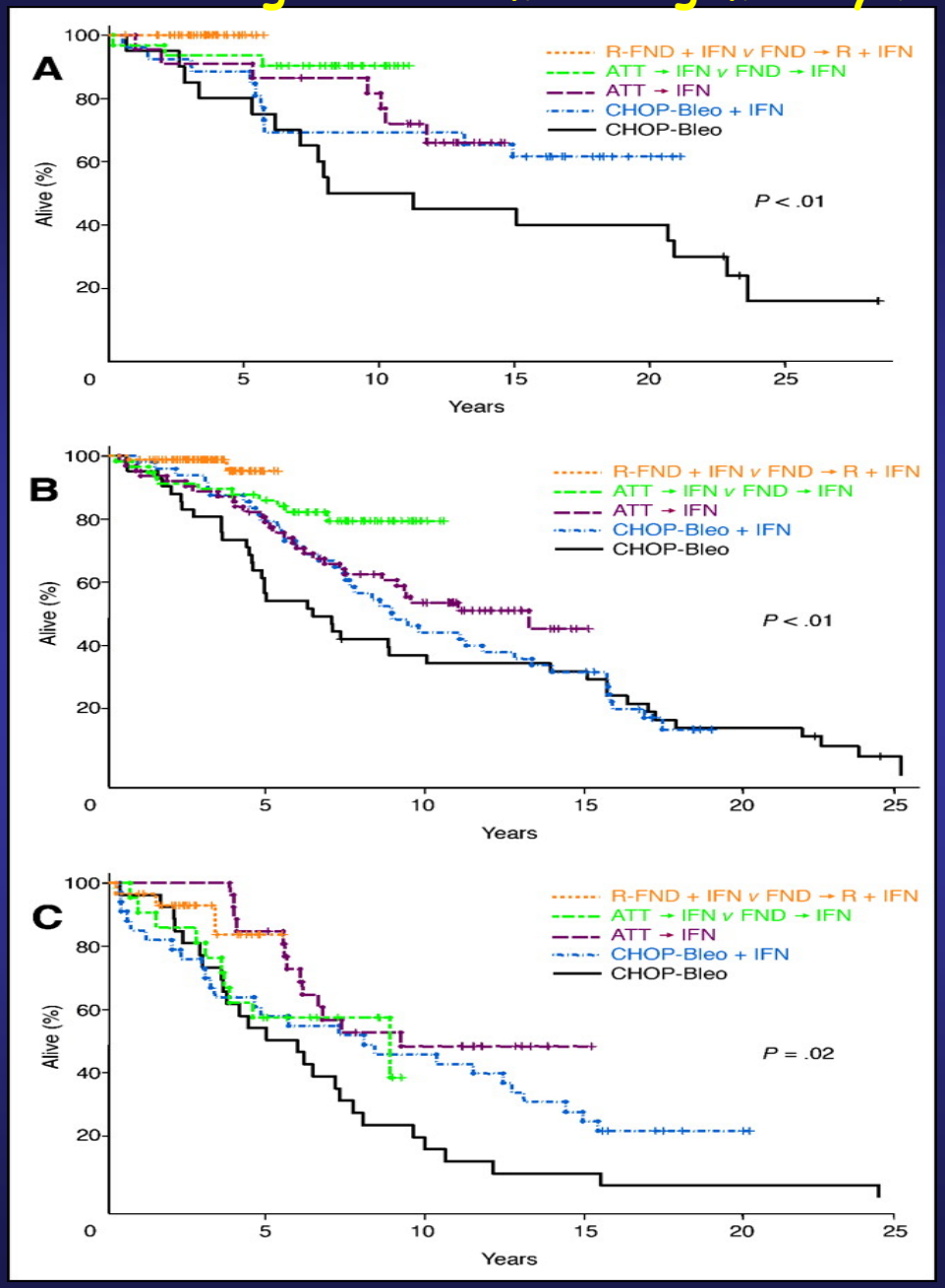
Liu, Q. et al. J Clin Oncol; 24:1582-1589 2006

Overall survival according to treatment regimen by FLIPI score

FLIPI 1-2

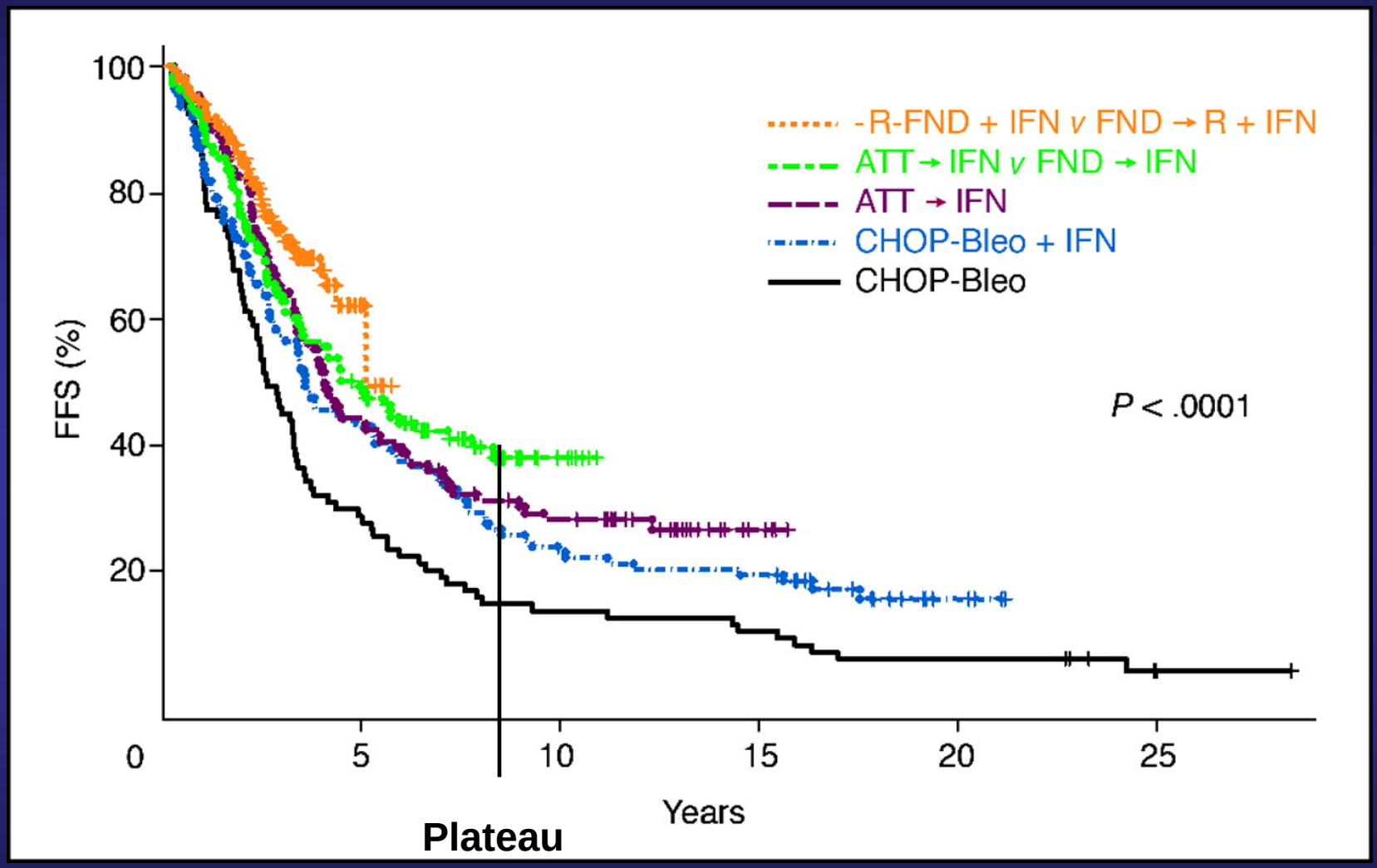
FLIPI 3

FLIPI 4-5



25 Years Experience Indolent NHL at MD Anderson

Failure-free survival according to treatment regimen



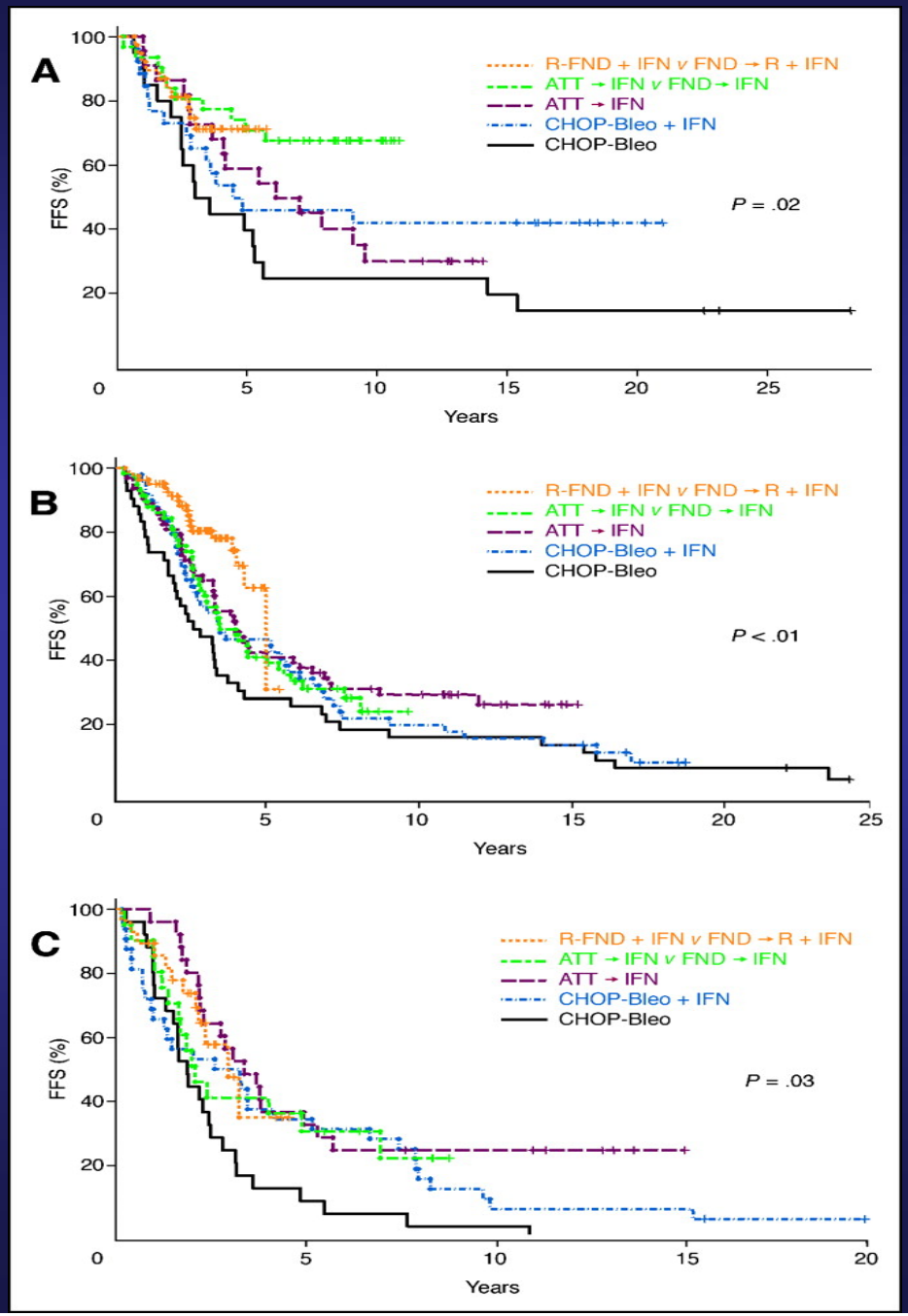
Liu, Q. et al. J Clin Oncol; 24:1582-1589 2006

Failure-free survival according to treatment regimen by FLIPI score

FLIPI 1-2

FLIPI 3

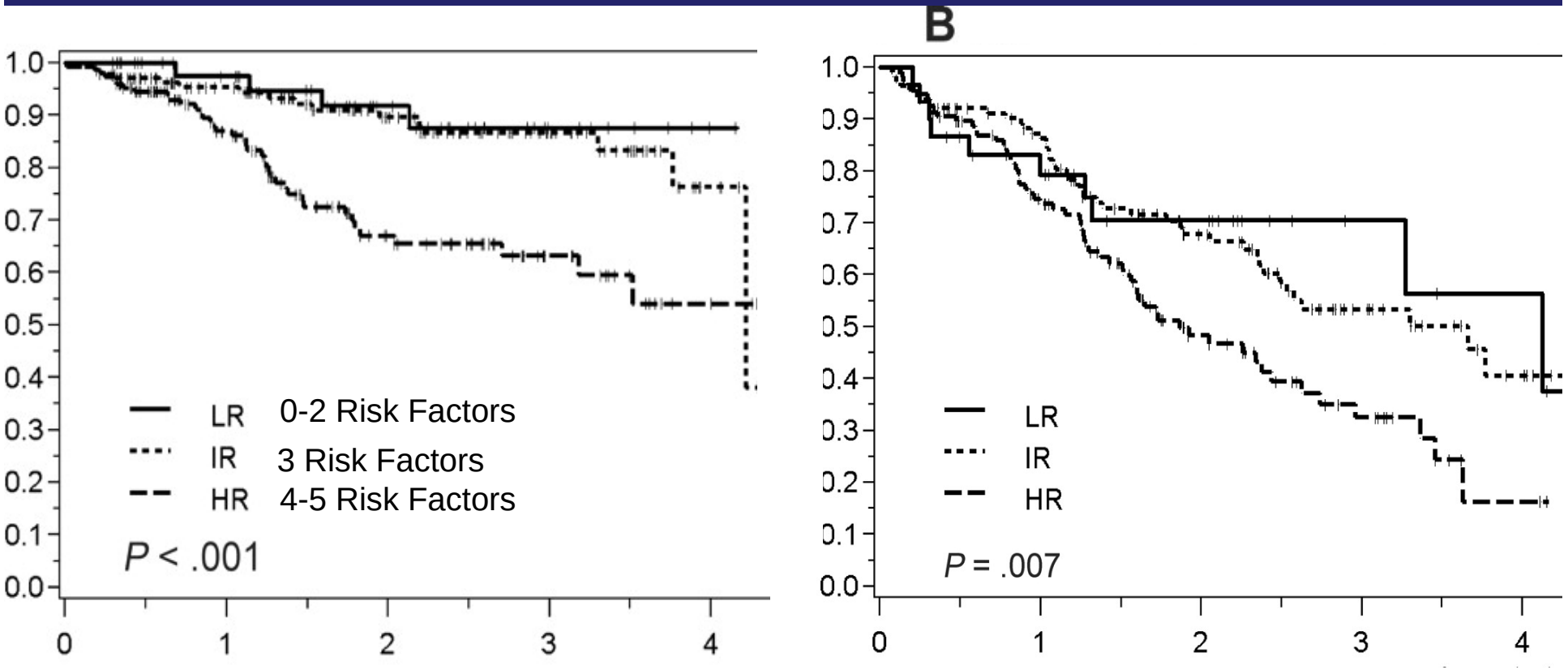
FLIPI 4-5



Other Studies that Support the Concept of an Improvement in the Natural History of Indolent NHL

Overal Survival According to FLIPI Score and Therapy with or without Rituximab

CHOP-Rituximab **CHOP**



Buske, C. et al. Blood 2006;108:1504-1508

[583] New Treatment Options Have Changed the Natural History of Follicular Lymphoma.

Session Type: Oral Session

Richard I. Fisher et al

SWOG

[583] New Treatment Options Have Changed the Natural History of Follicular Lymphoma.

Overall Survival by Treatment Strategy

TREATMENT	N	DEATH	4-YR OS
CHOP	356	226	69%
ProMACE	425	189	79%
CHOP + Rituxan	179	18	91%

[583] New Treatment Options Have Changed the Natural History of Follicular Lymphoma.

Progression-Free Survival by Treatment Strategy

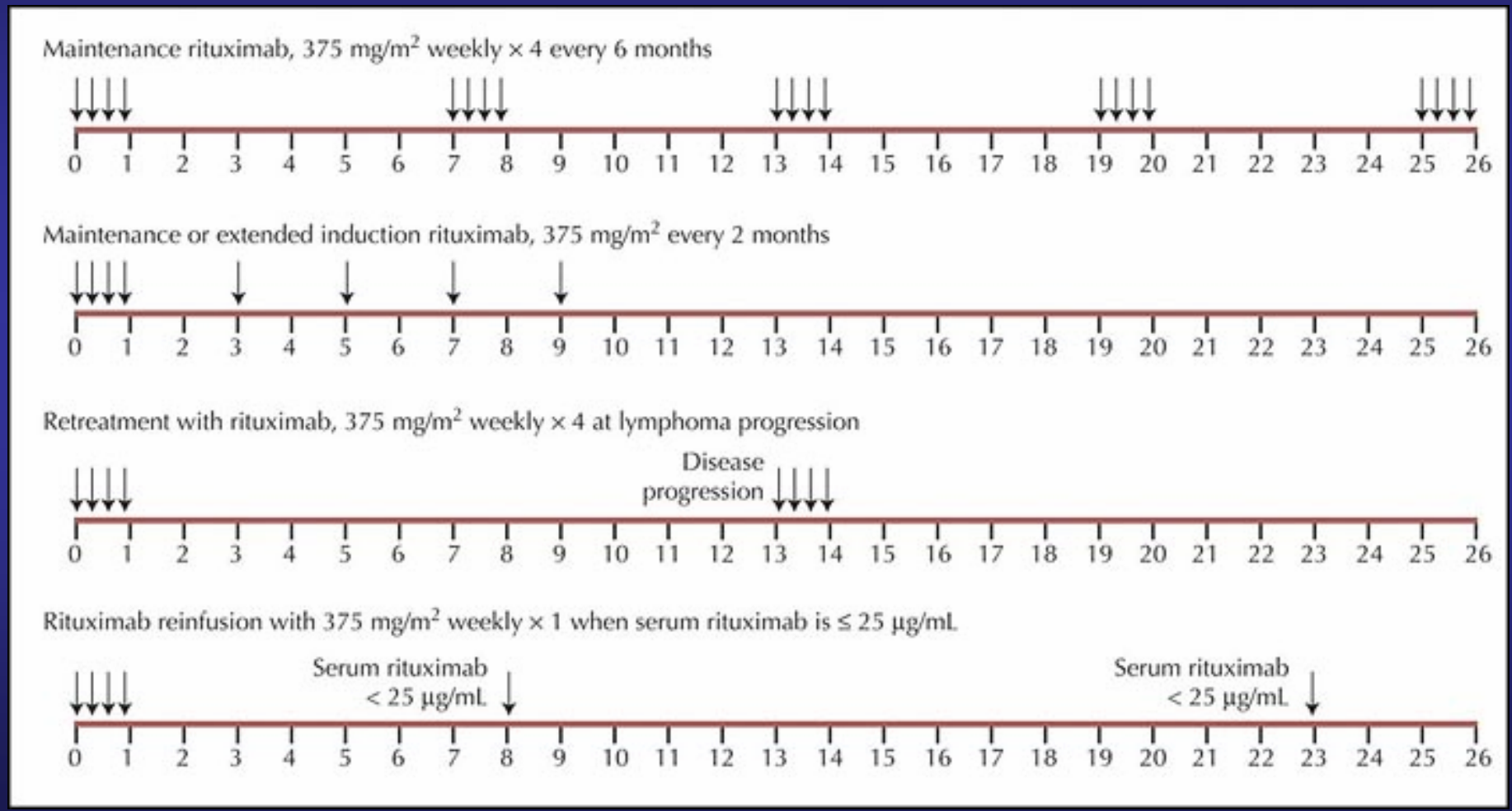
TREATMENT	N	DEATH/PRO-GRESSION	4-YR PFS
CHOP	356	257	46%
ProMACE	425	290	48%
CHOP + Rituxan	179	75	61%

Rituxan Maintenance

Background

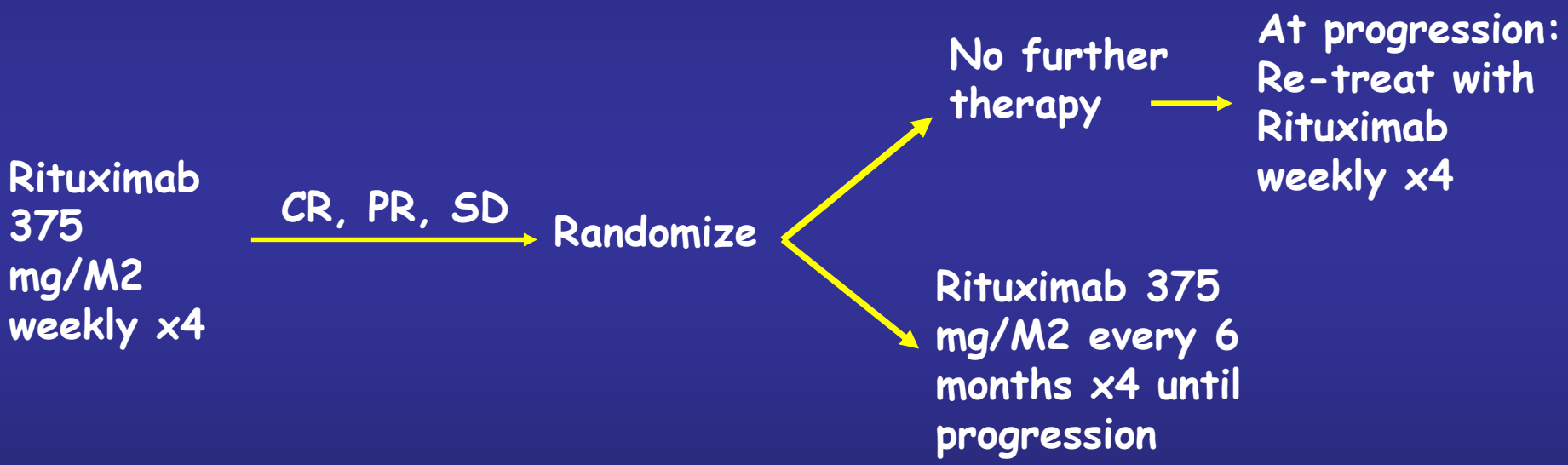
- There is no scientific rationale for using Rituximab 375 mg/M^2 weekly x 4.
- A steady state serum concentration is not reached after the 4th dose
  - After the 4th dose, the maximum concentration is higher than in previous doses
  - In a study by Piro et al using 8 weekly doses, a steady state was reached after the 6th dose and the duration of response was longer than on the 4 weekly doses study.
- Responders to Rituximab show a higher serum concentration of the drug than non-responders
  - This suggests that some patients might require either a higher dose or a more prolonged exposure
- The half-life of Rituximab after the 4th dose is very long: 206 hours
  - Some patients can have delayed response which suggests that prolonged exposure might be advantageous

Strategies to Maximize Rituximab Effectiveness



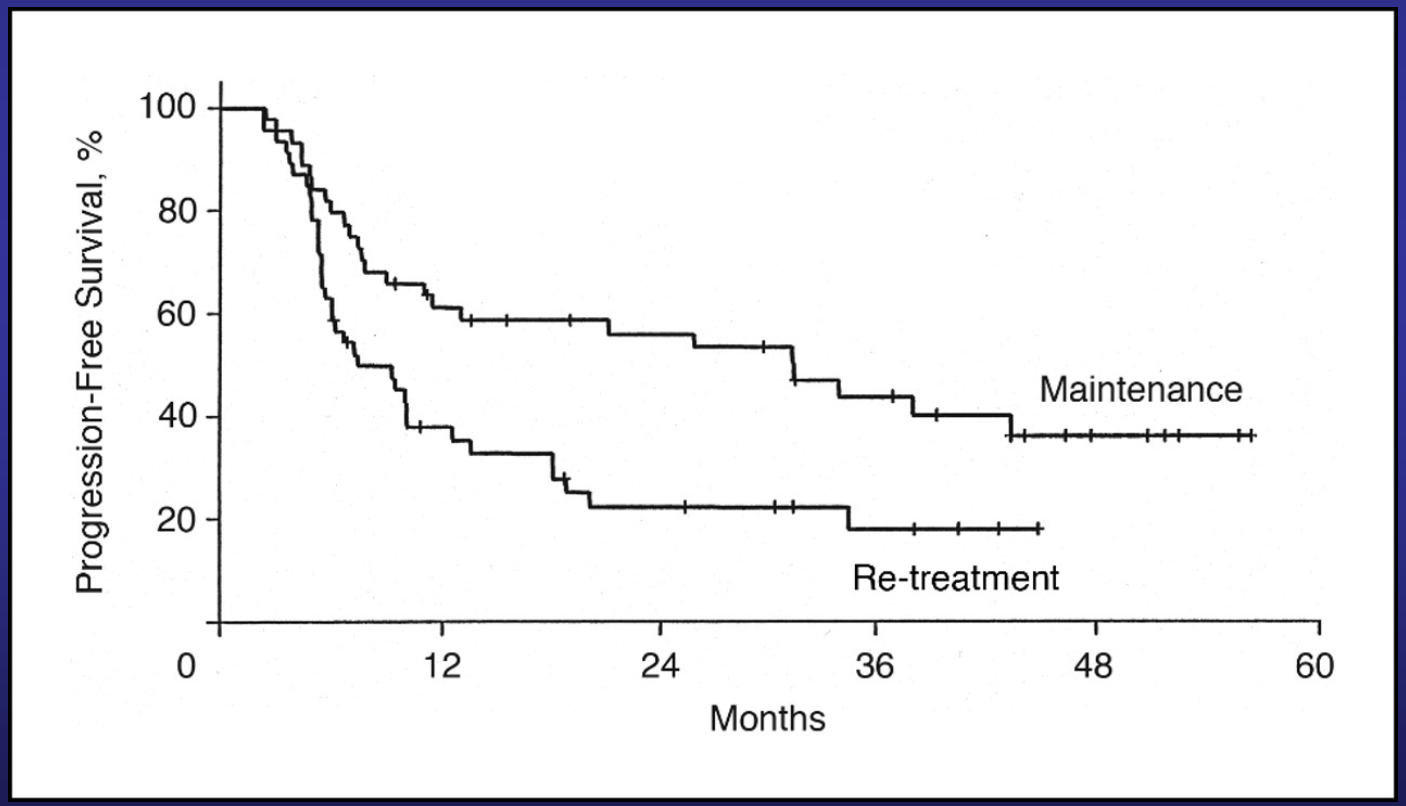
Randomized Study of Maintenance Therapy Versus Re-Treatment at Progression in Patients With Indolent NHL

Hainsworth et al: JCO Vol 23, No 6 (February 20), 2005: pp. 1088-1095



Randomized Study of Maintenance Therapy Versus Re-Treatment at Progression in Patients With Indolent NHL

Hainsworth et al: JCO Vol 23, No 6 (February 20), 2005: pp. 1088-1095

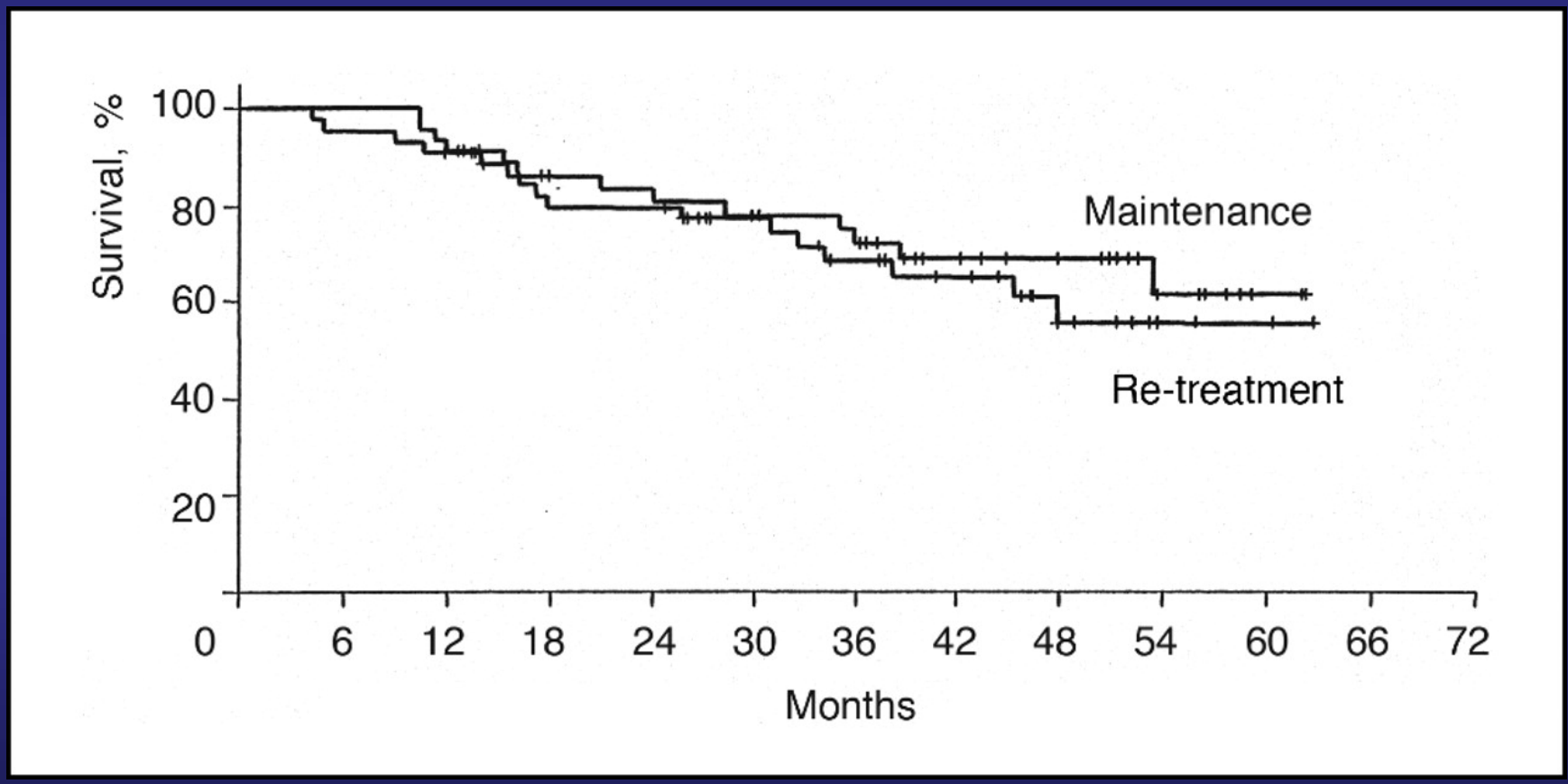


Hainsworth, J. D. et al. J Clin Oncol; 23:1088-1095 2005

Overall Survival

Randomized Study of Maintenance Therapy Versus Re-Treatment …

Hainsworth et al: JCO Vol 23, No 6 (February 20), 2005: pp. 1088-1095

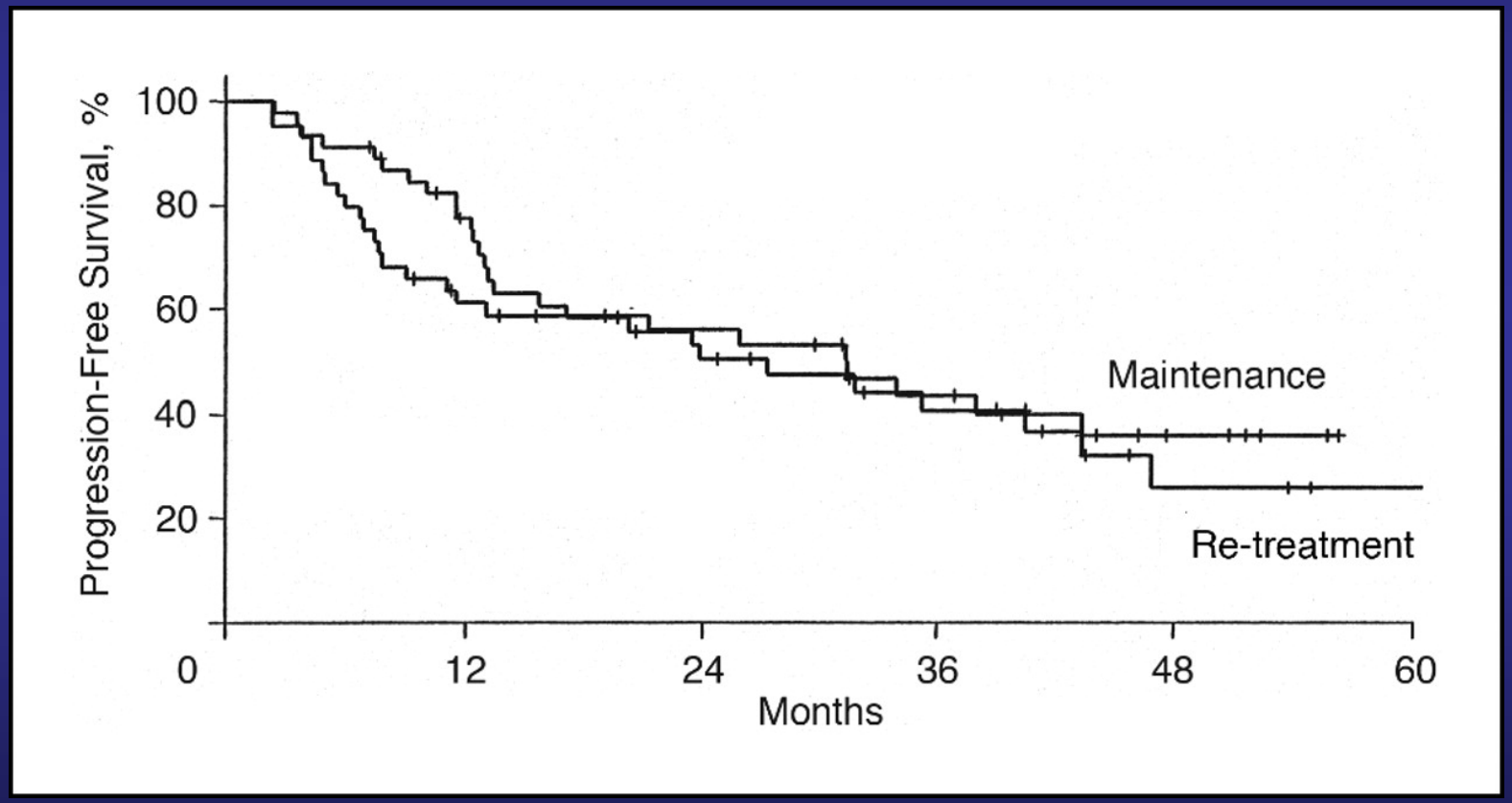


Hainsworth, J. D. et al. J Clin Oncol; 23:1088-1095 2005

Actuarial duration of rituximab benefit

Randomized Study of Maintenance Therapy Versus Re-Treatment …

Hainsworth et al: JCO Vol 23, No 6 (February 20), 2005: pp. 1088-1095

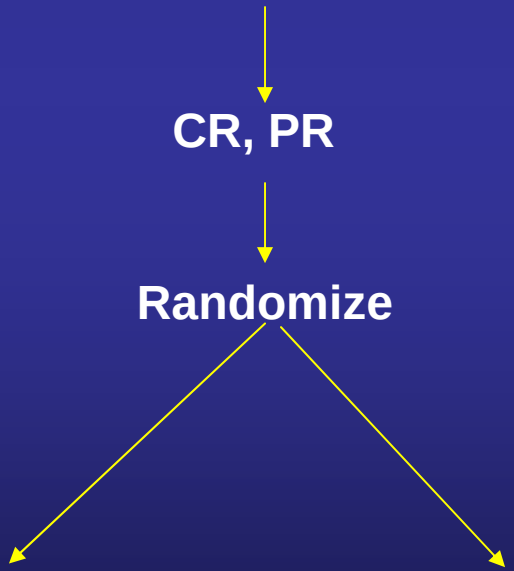


Hainsworth, J. D. et al. J Clin Oncol; 23:1088-1095 2005

Rituximab maintenance improves progression free and overall survival after combined immunochemotherapy (R-FCM)… Dreyling et al Abstr #7502 ASCO 2006

Study design

R-FCM (Rituximab, Fludara, CTX, Mitoxantrone) x 4



Rituximab maintenance improves progression free and overall survival after combined immunochemotherapy (R-FCM)… Dreyling et al Abstr#7502 ASCO 2006

- Eligibility: Relapsed/refractory follicular and mantle cell NHL
- N=138
- PFS: Maintenance arm=not reached yet vs 17 months for observation (P=.001)
- 3 yr survival: Maintenance arm=82% vs observation 55% (P=.056)
- Differences seen both in follicular and MCL

The New Paradigm:

Indolent NHL is a slow-growing disease which is as curable as diffuse large cell lymphoma.

It is characterized by a continuous relapse rate for the first 8 years with a subsequent plateau in the Failure Free Survival Curve at 40%.

New Drugs for Indolent NHL

Abstract 932
Bendamustine (Treanda)Plus Rituximab ….
Robinson et al
Background

- Novel DNA alkylator active against several alkylator resistant cell lines.
  - Lacks cross resistance with many other drugs, suggesting unique mechanism of action
  - Induces durable DNA damage, different from other alkylators
  - Causes apoptosis independent “mitotic catastrophe” in cancer cells resistant to apoptosis
- European and USA studies show activity against indolent NHL, CLL, myeloma

Abstract 932
Bendamustine (Treanda)Plus Rituximab ….
Robinson et al
Results

- 67 pts entered, 57 currently evaluable:
  - 60% follicular, 16% Mantle, 15% SLL, 3% LPL, 3% MZL
  - Median age 60 y/o
  - Median # of relapses=1
- Treatment with Rituxan 375 mg/M2 day 1 Bendamustine 90 mg/M2 days 2 and 3 q. 28 days
- Demographics:
  - 37% had received Rituxan

Abstract 932
Bendamustine (Treanda)Plus Rituximab ….
Robinson et al
Response Rate

Type of Response	Response Rate
CR, CRu	33%
PR	54%
Overall (CR+PR)	87%

Abstract 932

Bendamustine (Treanda)Plus Rituximab ….

Robinson et al

Hematologic Toxicity

Event	Grade 3-4
Neutropenic Fever	0
Neutropenia	29%
Thrombopenia	16%
Anemia	16%
Alopecia	0

Abstract #7556 ASCO 2006
Patterson et al
Dana Farber Cancer Center

Sildenafil **(Viagra)** suppresses disease progression in patients with Waldenstrom's Macroglobulinemia…

With Some Nice Side Effects!

BUT……


VIAGRA
WARNING:
This product can
produce unexpected
effects in animals


That's odd. This bottle of Viagra was full two days ago.

Rituximab Toxicity

Abstract #2445

High Incidence of Non-Neutropenic Infections Induced by Rituximab Plus Chemotherapy and Associated with Hypogammaglobulinemia: A Frequently Unrecognized and Easily Treatable Complication.

Fernando Cabanillas, MD, Orestes Pavia, MD and Ezequiel Rivera, MD. Cancer Center, Auxilio Mutuo Hospital,

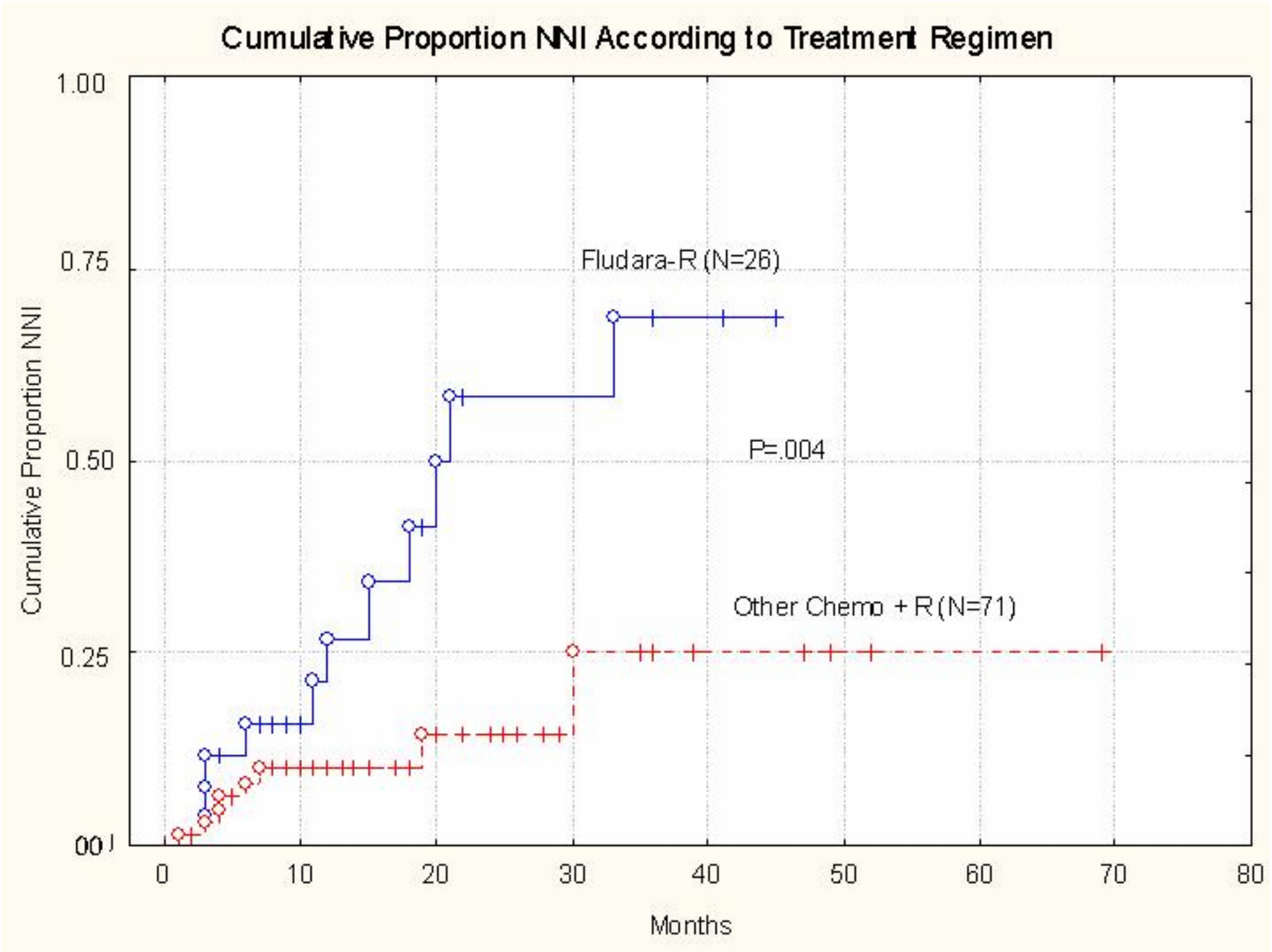
San Juan, Puerto Rico, 00918

Background

- Rituximab as a single agent *not* associated with high incidence of infections or hypogammaglobulinemia.

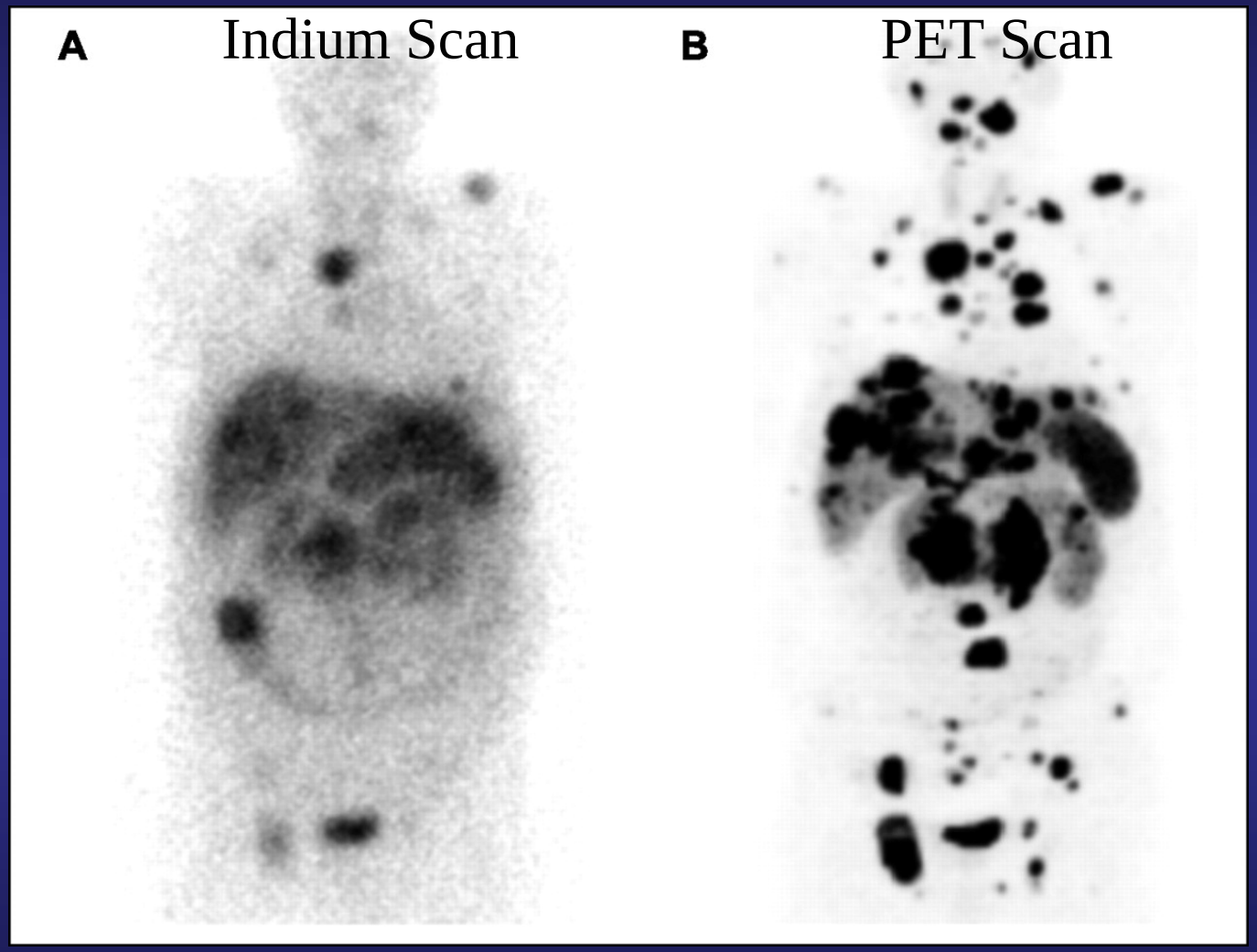
- Clinical experience with combination chemotherapy plus Rituximab suggested a high incidence of upper respiratory tract infections associated with hypogammaglobulinemia.

- This prompted us to explore further the incidence, clinical features and types of drugs associated with this problem


Cumulative Proportion NNI According to Treatment Regimen
1.00
0.75
0.50
0.25
00
Cumulative Proportion NNI
Fludara-R (N=26)
P=.004
Other Chemo + R (N=71)
0
10
20
30
40
50
60
70
80
Months

What is the Role of PET Scan in Lymphoma?

Comparison of Indium-111 (111In) -labeled octreotide and positron emission tomography (PET) with the octreotide analog fluorine-18 (18F) -labeled FP-Gluc-TOCA



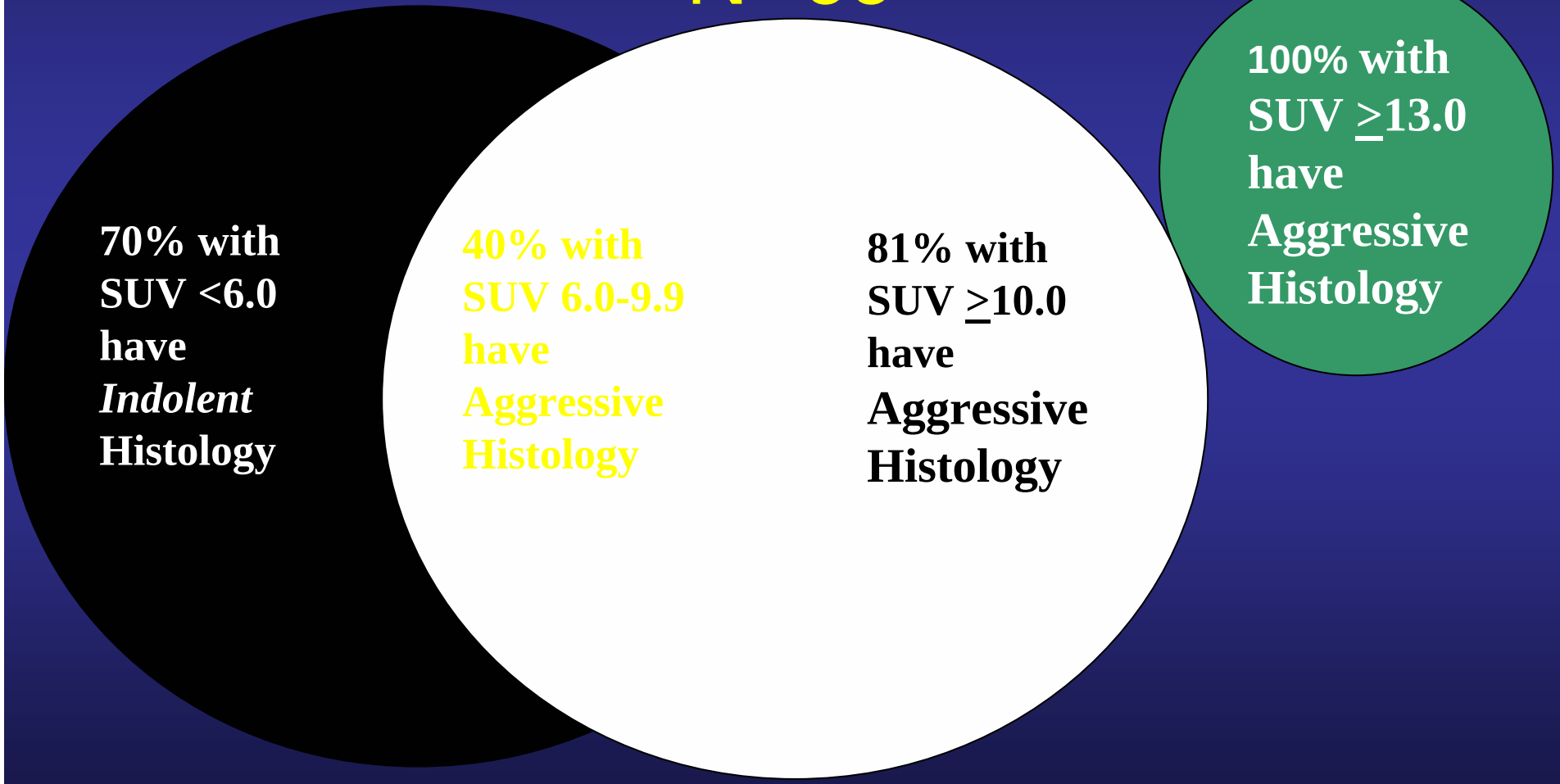
Weber, W. A. J Clin Oncol; 24:3282-3292 2006

What clinical implications do Standardized Uptake Value (SUV) results have?

What is the Meaning of FDG PET Scan SUV Measurements in NHL?

- The amount of uptake in ^{18}F FDG-PET scan can be measured by SUV (Standard Uptake Value)
- High SUVs (>6) in PET scan correlate with a higher histological grade
  - NHLs with high Ki-67 proliferative index or with high S phase show high SUVs
- The few false negatives with PET are usually with very low-grade NHL such as MALT

Correlation of SUV_{max} with Histologic Grade NHL N=69



Schoder et al. J Clin Oncol 2005; 23: 4643-4651

Widely Divergent SUVs in a Patient with NHL Could Indicate Divergent Histologies

PET Scan Post Therapy as a Prognostic Factor

PET Predicts Prognosis After 1 Cycle of Chemotherapy in Aggressive Lymphoma and Hodgkin's Disease

Lale Kostakoglu, MD[1], Morton Coleman, MD[2], John P. Leonard, MD[2]

Journal of Nuclear Medicine Vol. 43 No. 8 1018-1027

Puerto Rico Chemotherapy Consortium

Evaluation of the Prognostic Value of PET Using 18 F-FDG Uptake 7 Days after the Initiation of Chemotherapy for Malignant Lymphomas

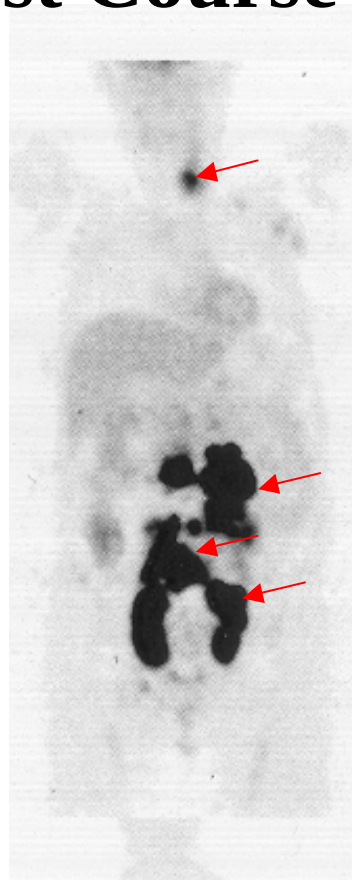
PET Scan Project CCAM

- Objectives
  - To determine if results of an early PET scan correlate well with the PET results after the 3rd course of chemotherapy.
  - To define quantitavely what is a negative PET scan.
  - To determine if PET scans done very early during treatment (i.e. 1 week after 1st chemotherapy) already show improvement
  - To generate pilot data which can provide some correlation with early negativization of PET and duration of response to chemotherapy
- Eligibility
  - Aggressive histology NHL
  - Previously treated and untreated
- Design
  - Baseline pre-treatment PET scan
  - Follow up PET scans at:
    - 1 week post course 1
    - Post course 3

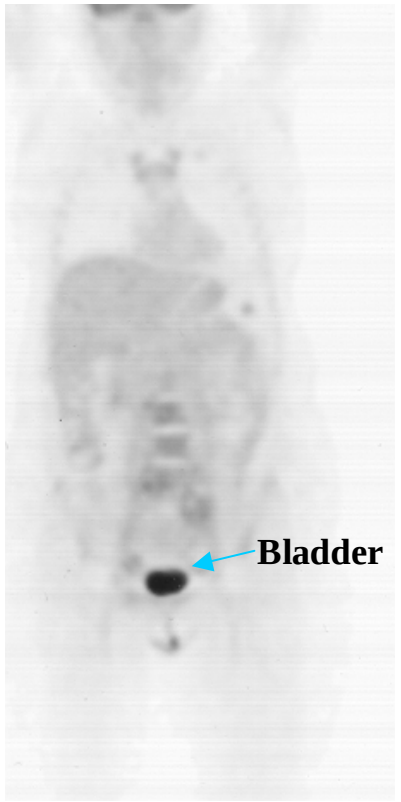
PET Scan Project CCAM

- Entered: 35
- Evaluable: 33
- Diagnosis
  - 28 DLCL-B
  - 4 Follicular grade 3
  - 1 High grade B cell NHL
- Prognostic Features
  - 10 Previously treated
  - 18 MD Anderson Tumor Score $\geq$3
  - 23 IPI > 1

Baseline PET Scan and 1 Week After First Course of Chemotherapy



Baseline PET



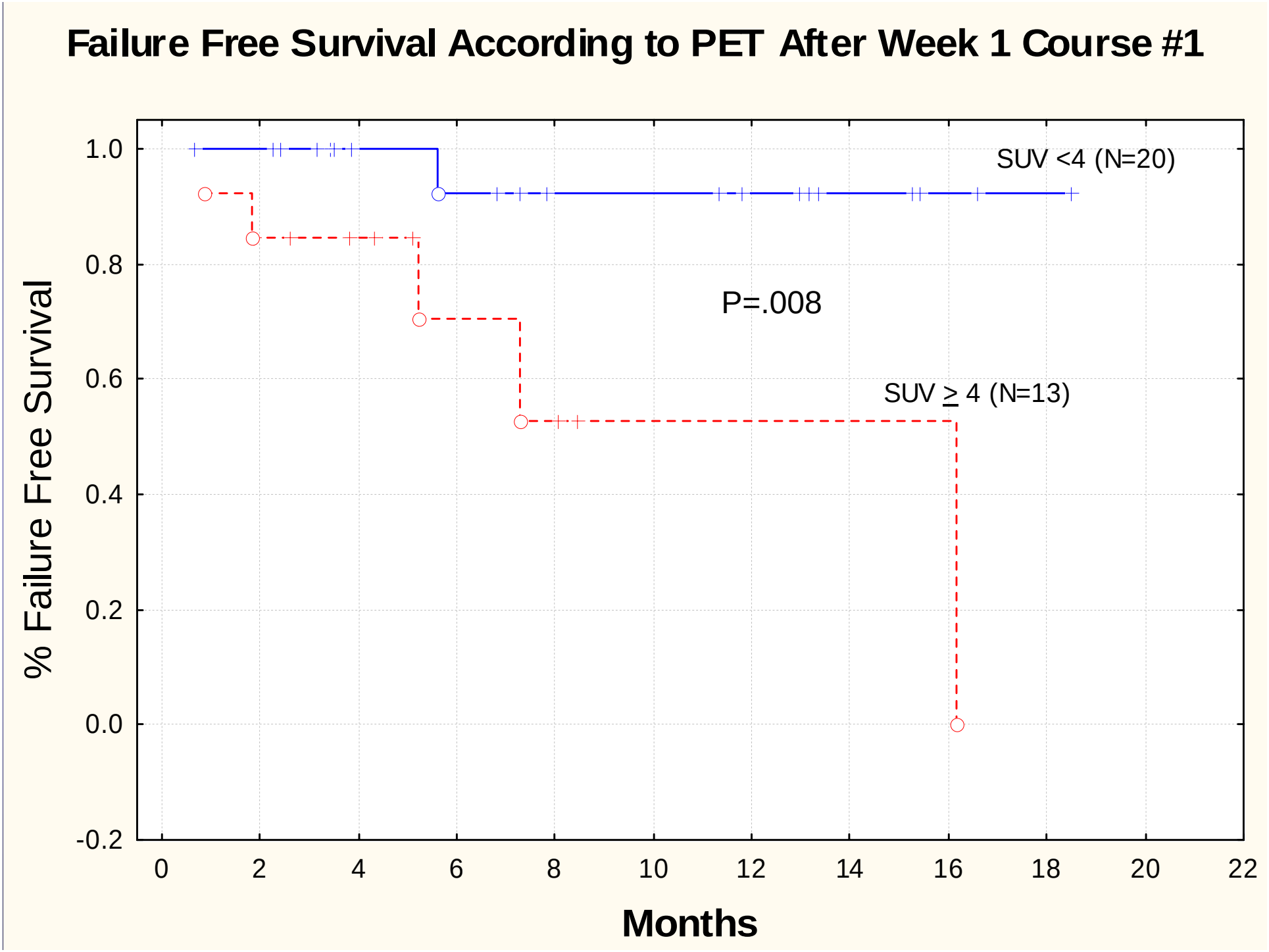
PET: One week post-chemo #1

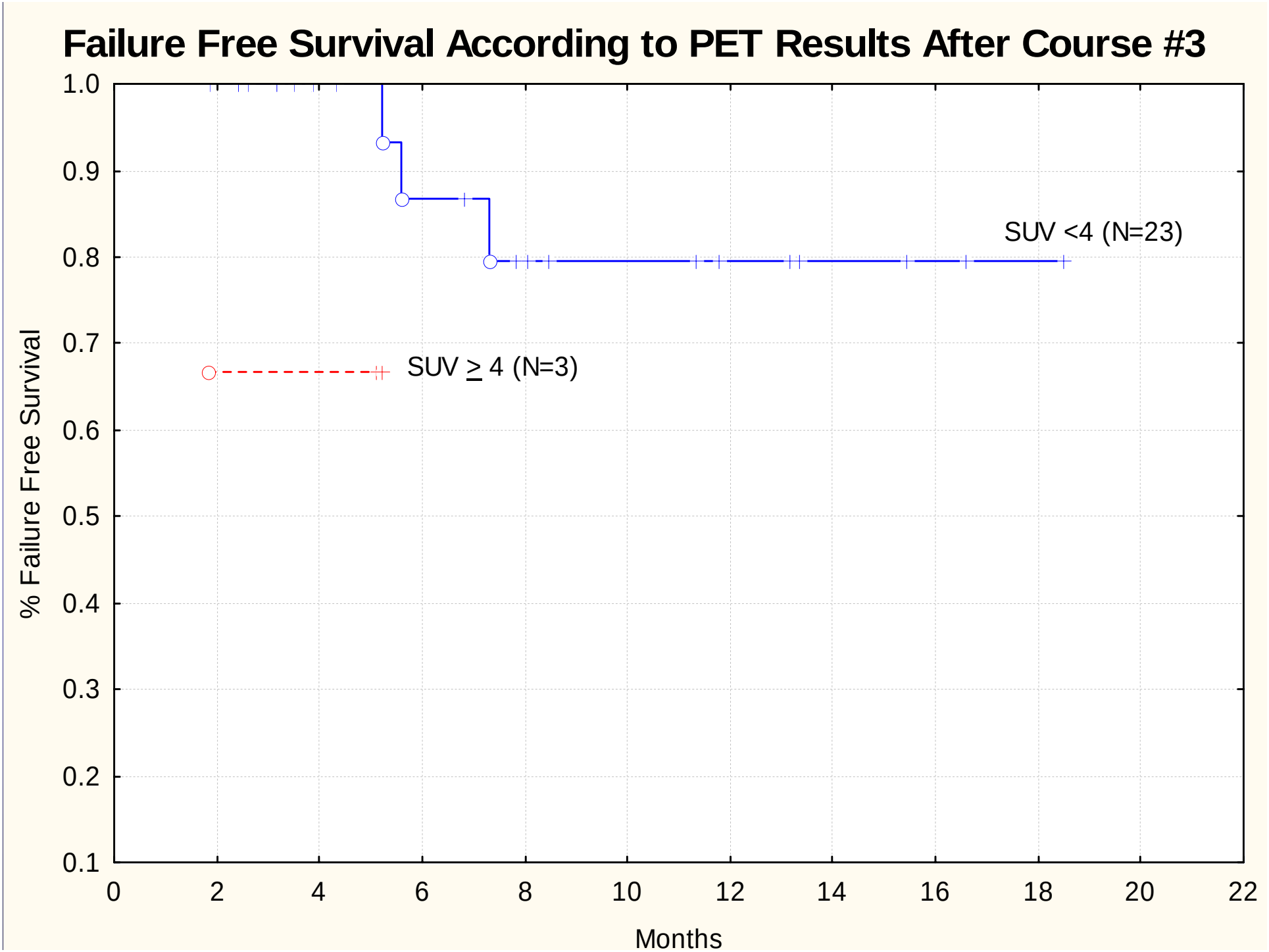
PET Scan Project CCAM

- Parameters analyzed
  - Average baseline SUV
  - Average SUV post 1 week course 1
  - Average SUV post course 3
  - Maximum baseline SUV
  - Maximum SUV post 1 week course 1
  - Maximum SUV post course 3

Correlation of Week 1 PET with Course 3 PET

W1PET SUVmax	N	C3 PET SUVmax <4.0	C3 PET SUVmax≥4.0
<4.0	15 (58%)	15	0
≥4.0	11 (42%)	8	3


Failure Free Survival According to PET After Week 1 Course #1
% Failure Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0
2
4
6
8
10
12
14
16
18
20
22
Months
SUV <4 (N=20)
P=.008
SUV ≥ 4 (N=13)


Failure Free Survival According to PET Results After Course #3
% Failure Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2
4
6
8
10
12
14
16
18
20
22
Months
SUV <4 (N=23)
SUV ≥ 4 (N=3)

Conclusions

- Striking improvements in PET are seen as early as 1 week after chemotherapy.
- The result of the W1 PET anticipates correctly 18/26 (69%) of C3 PET results.
- An SUVmax <4.0 on the W1 PET correlates well with relapse rate and is associated with a significantly superior FFS.
  - Thus an SUV cut-off of <4.0 at W1 PET can be used to define mCR and should be confirmed in an independent set of patients.
- W1 PET appears superior to C3 PET in predicting clinical outcome (more sensitive and specific).

Rituximab
Other Uses

The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura

Nichola Cooper,[1] Roberto Stasi,[2] Susanna Cunningham-Rundles,[1] Michael A. Feuerstein,[1] John P. Leonard,[1] Sergio Amadori[3] and James B. Bussel[1]

[1]*Division of Hematology/Oncology, Departments of Pediatrics and Medicine, New York Presbyterian Hospital – Weill Medical College of Cornell University, New York, NY, USA,* [2]*Department of Medical Sciences, Regina Apostolorum Hospital, Albano Laziale, and* [3]*University of Rome 'Tor Vergata', Rome, Italy*

 British Journal of Haematology, **125,** 232–239

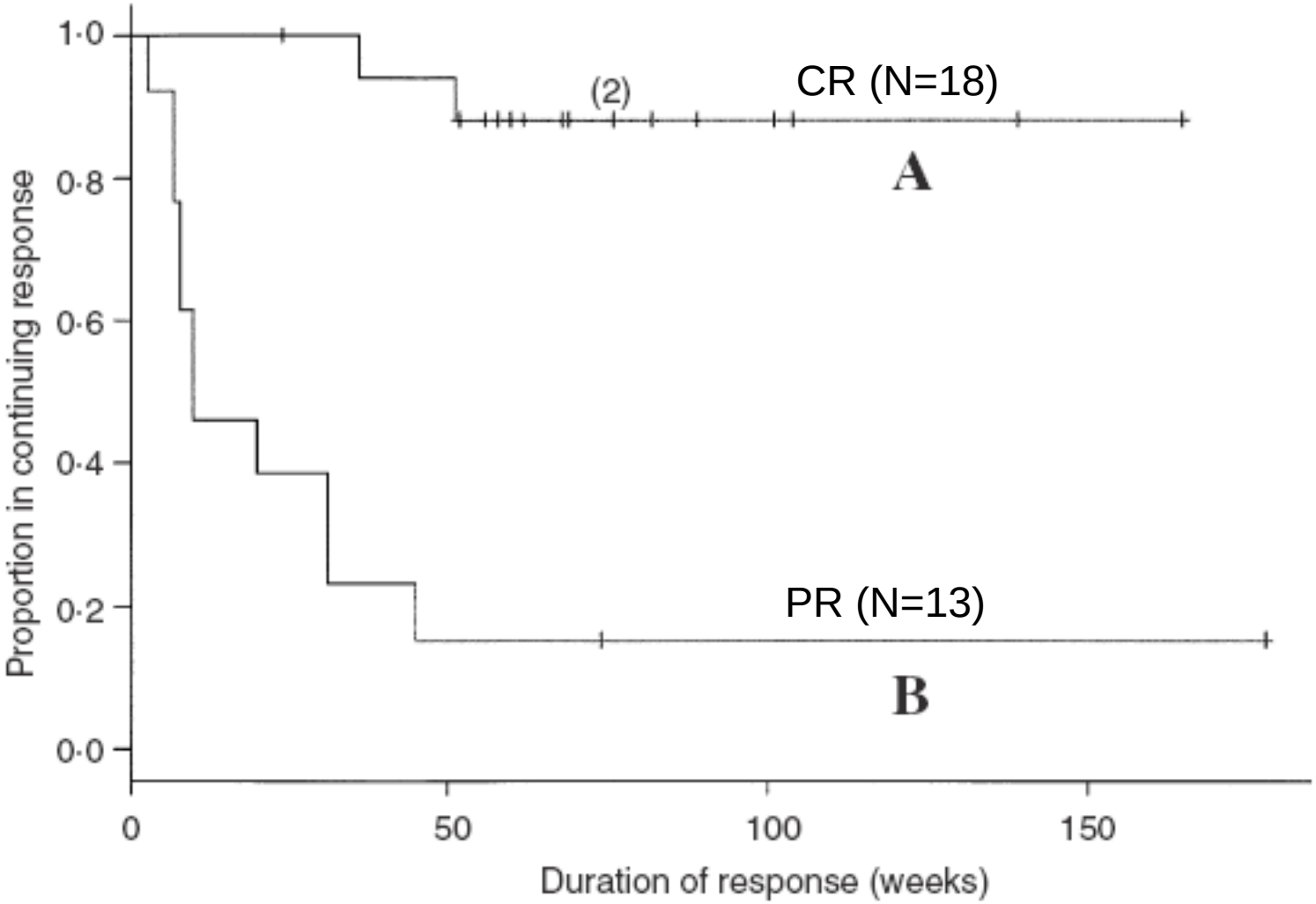
Received 5 September 2003; accepted for publication 16 December 2003

Correspondence: Nichola Cooper MRCP, Department of Haematology, Camelia Botna Laboratories, Level 2, Great Ormond Street

Summary

Because of its B-cell depleting effect, rituximab has entered clinical trials several autoimmune conditions. This study assesses the efficacy and safety rituximab in 57 adults with chronic immune thrombocytopenic purpu (ITP). All patients had platelet counts $<30 \times 10^9$/l, all had received two more previous ITP treatments and 31 had undergone splenectomy. Patie received rituximab 375 mg/m^2 weekly for 4 weeks. Thirty-one patients (54 responded, achieving a platelet count $>50 \times 10^9$/l: 18 achieved a compl response (CR: platelet count $>150 \times 10^9$/l) and 13 a partial response (l platelet count $50–150 \times 10^9$/l). Twenty-nine responses occurred wit 8 weeks of the first infusion. Sixteen of 18 CR patients (28% overa including eight who had failed splenectomy, continued in CR after a med of 72·5 weeks; 15 of 16 are >1 year from the first infusion. Only two of maintained a PR. Thirty-three patients experienced grade 1–2 adverse eve and one a grade 3 event, but they all completed treatment. Circulating B c fell to $<0{\cdot}03 \times 10^9$/l. No changes in immunoglobulin levels or infecti complications were seen. In summary, rituximab was well tolerated with immediate complications and induced a lasting, substantial response in 3

Duration of Response to Rituximab According to Quality of Response



Results of Rituximab in Chronic ITP

Prior Splenectomy	N	Initial CR	Initial PR	Long Term CR	Long Term PR	Resp. duration (weeks)
No	26	9 (35%)	7 (27%)			
Yes	31	9 (29%)	6 (19%)			
Total	57	18 (32%)	13 (23%)	16 (28%)	2 (4%)	73

Cooper: Br J Haematol 125 232, 2004

Splenectomized patients

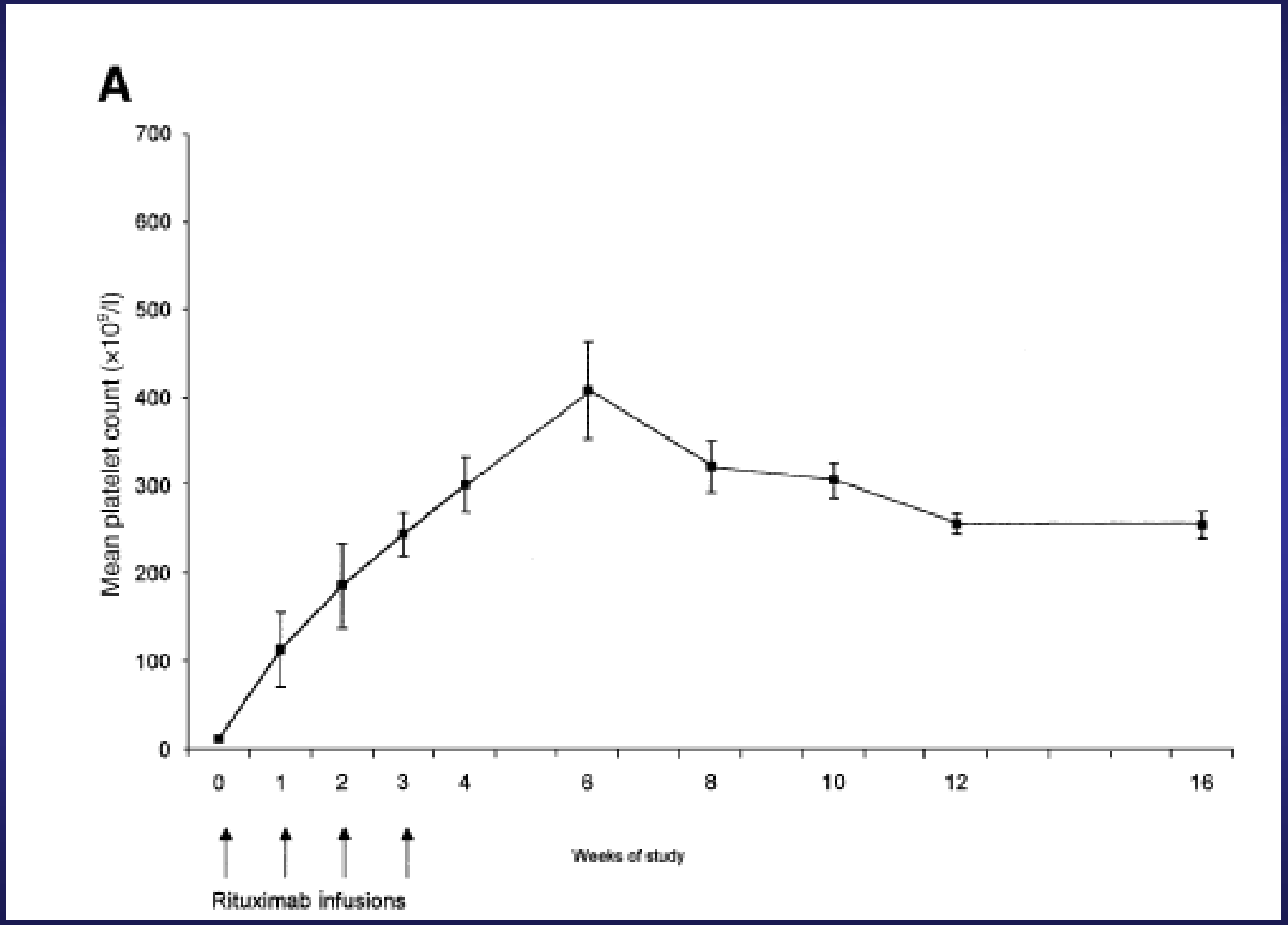
The 31 splenectomized patients had all received multiple treatments without lasting effect: seven had received two previous treatments (IVIG and steroids) in addition to splenectomy, six had received three treatments, and 18 had received four or more previous treatments.

Subsequent analyses combine the two groups.

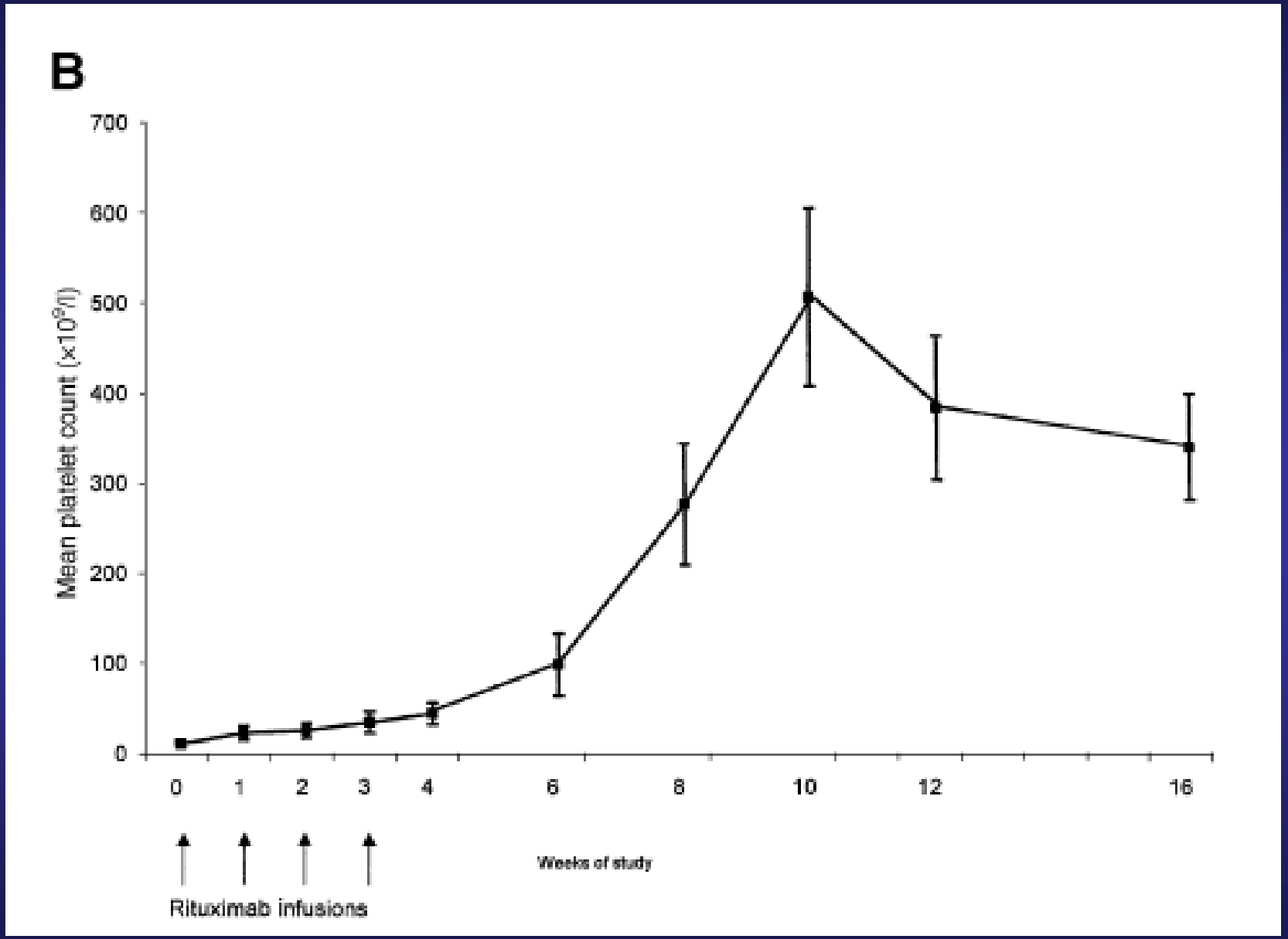
Platelet response. Thirty-one of 57 patients (54%) responded to rituximab in achieving platelet counts $>50 \times 10^9$/l with 18 CRs (platelet counts $>150 \times 10^9$/l) and 13 PRs (platelet counts $50–150 \times 10^9$/l).

Timing of platelet response. Twenty-nine of the 31 responders (94%) had a platelet increase to $>50 \times 10^9$/l within 8 weeks of the initial infusion. The median time to achieve this count was 3·5 weeks (range 1–19 weeks).

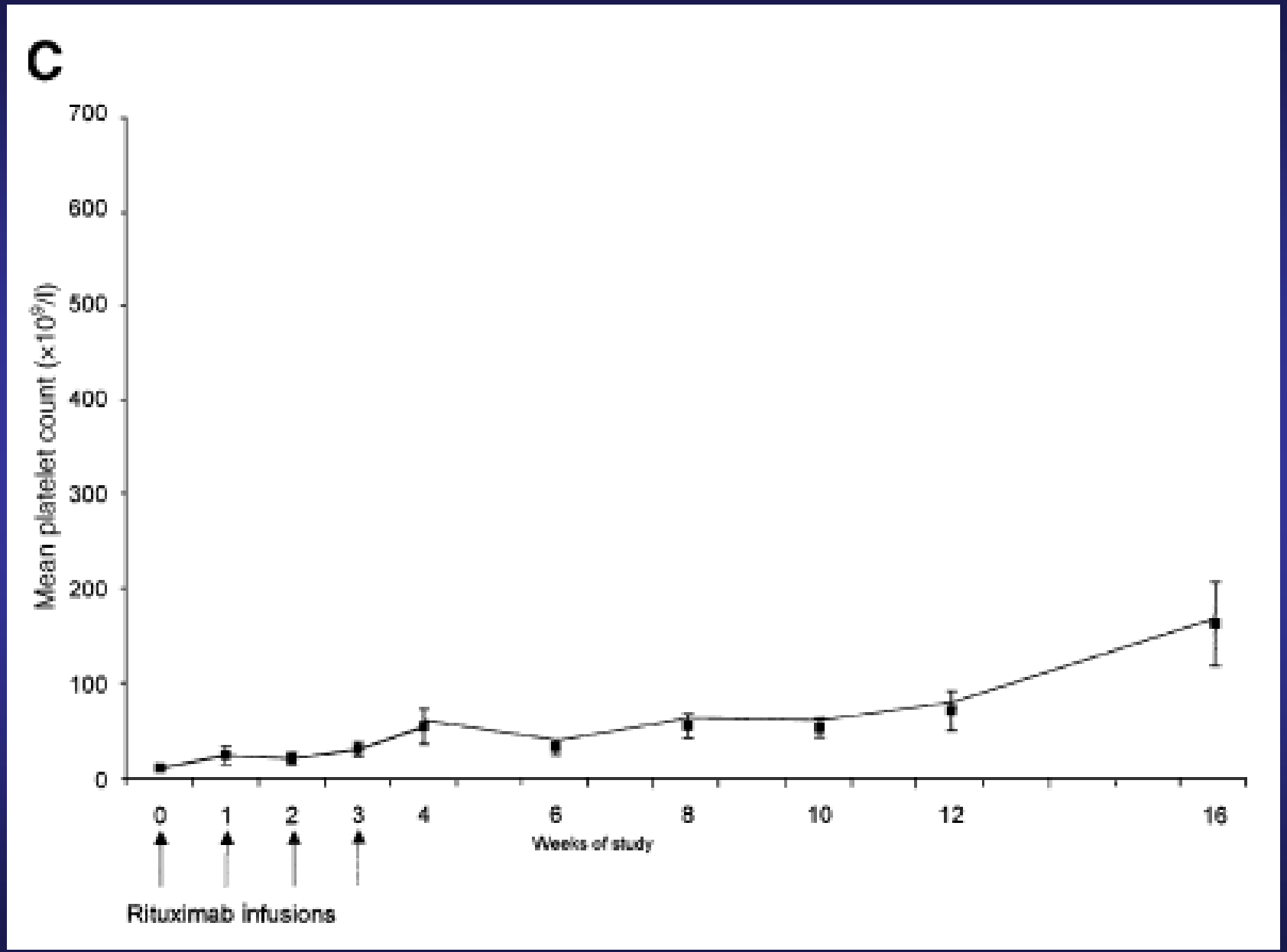
Example of a Quick Response to Rituximab



Example of a Gradual Response to Rituximab



Example of a Slow Response to Rituximab



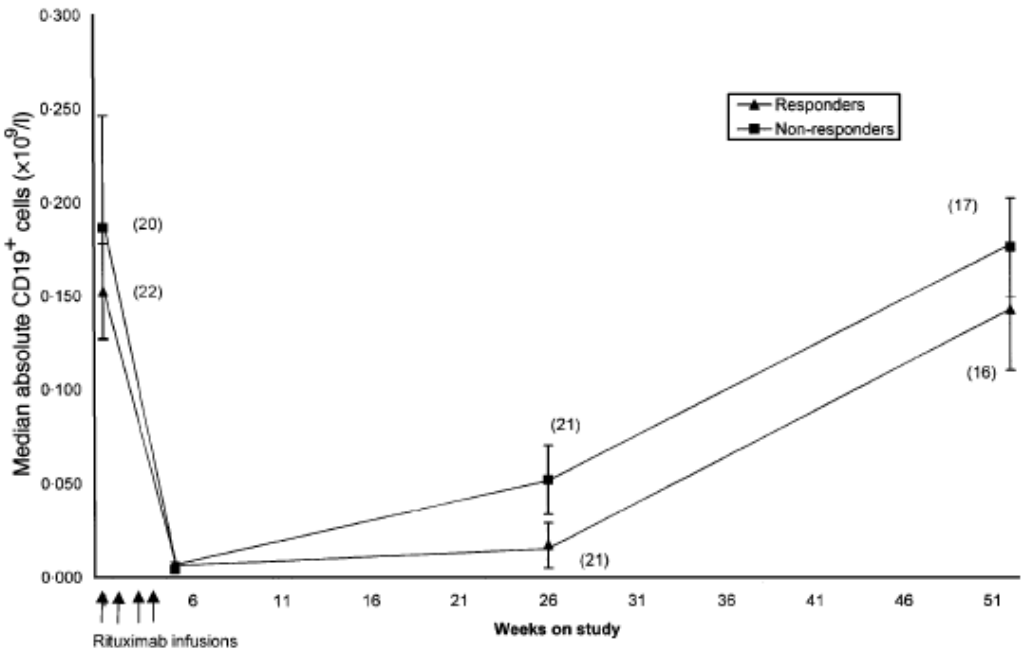


Fig 5. B-cell depletion and return with rituximab. The *x*-axis is the number of weeks from the first rituximab infusion with data indicated at weeks 1 (pre), 5, 26 and 52. The *y*-axis shows the median number of $CD19^+$ B cells ($\times 10^9$/l). This figure shows the median absolute number of $CD19^+$ B cells ($\times 10^9$/l) in partial and complete responders (triangles) *versus* non-responders (squares). The number of patients at each of the time points is indicated within parentheses. B cells were substantially reduced to undetectable levels by week 5 of treatment in essentially all patients. There was a significantly higher absolute number of B cells in non-responders than in complete and partial responders at 26 weeks from the initial infusion. This suggests that the degree of B-cell depletion may be important to the degree of response.

Thrombotic Thrombocytopenic Purpura

POORLY RESPONSIVE OR RESISTANT TTP

- 10- 20% of patients will have a transient, incomplete, or no response to plasma therapy.
  - It is not possible to identify these patients in advance.
- Those who either do not respond to plasma exchange, develop worsening disease in spite of continuing plasma exchange plus steroids, or have relapsing disease, may benefit from more intensive immunosuppressive treatment.
- A number of case reports have indicated success employing rituximab, with or without cyclophosphamide, with decrease or disappearance of the inhibitor to the VWf-cleaving protease.

The End