OMICS International
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April 18-20, 2016 Dubai,UAE



Rituximab maintenance in follicular lymphoma

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Agenda

- The biological and clinical rationale for R maintenance in FL
- The data from randomised clinical trials (RCT)
- Controversies surrounding R maintenance strategy in FL

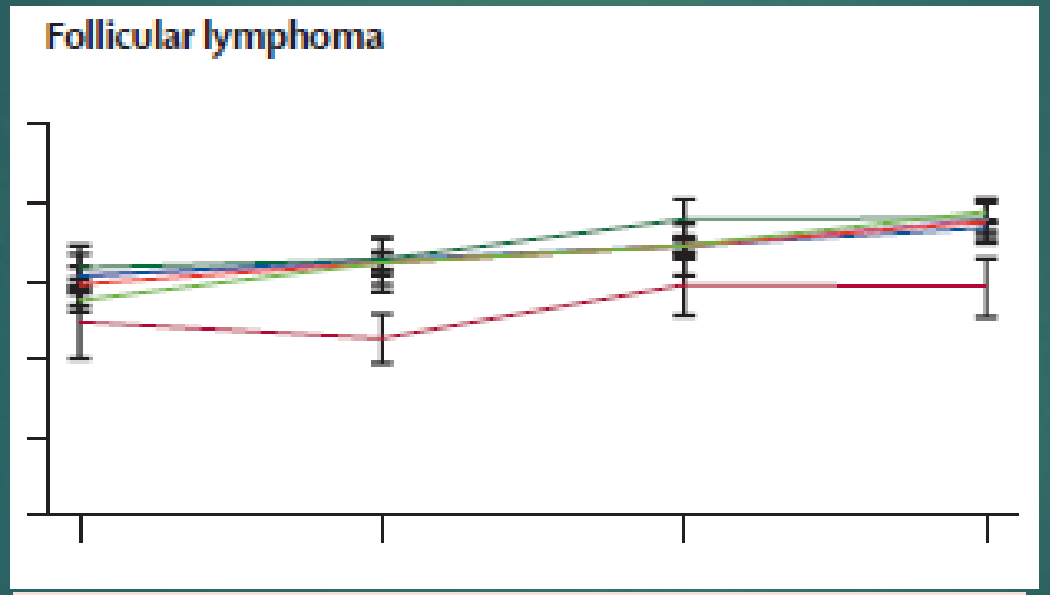
FL outcomes in modern day hematology:

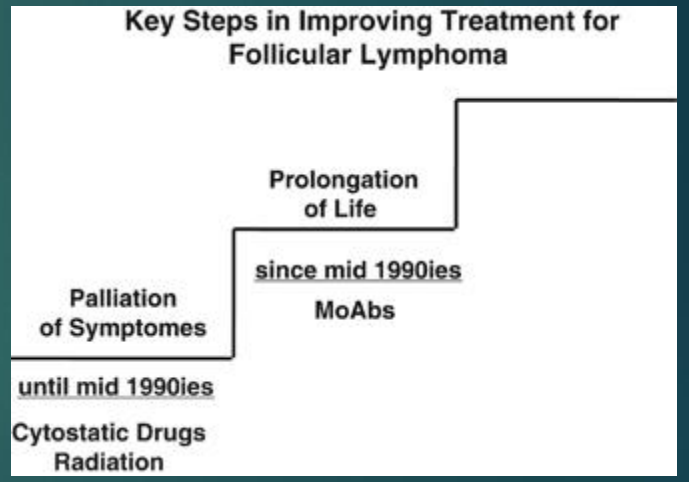
Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study

Milena Sant, Pamela Minicozzi, Morgane Mounier, Lesley A Anderson, Hermann Brenner, Bernd Holleczek, Rafael Marcos-Gragera, Marc Maynadié, Alain Monnereau, Gemma Osca-Gelis, Otto Visser, Roberta De Angelis, the EUROCARE-5 Working Group*

Lancet Oncol 2014; 15: 931–42

5-year OS rate





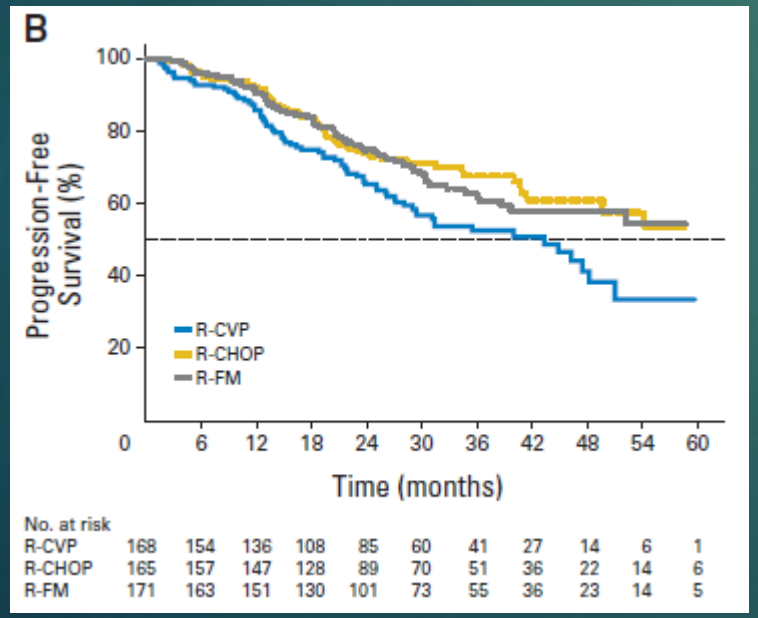
Outcomes have dramatically improved but the cure is elusive…

VOLUME 31 · NUMBER 12 · APRIL 20 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Follicular Lymphoma: Results of the FOLL05 Trial Conducted by the Fondazione Italiana Linfomi

Massimo Federico, Stefano Luminari, Alessandra Dondi, Alessandra Tucci, Umberto Vitolo, Luigi Rigacci, Francesco Di Raimondo, Angelo Michele Carella, Alessandro Pulsoni, Francesco Merli, Luca Arcaini, Francesco Angrilli, Caterina Stelitano, Gianluca Gaidano, Matteo Dell'Olio, Luigi Marcheselli, Vito Franco, Sara Galimberti, Stefano Sacchi, and Maura Brugiatelli



Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Durk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)

Lancet 2013; 381: 1203–10

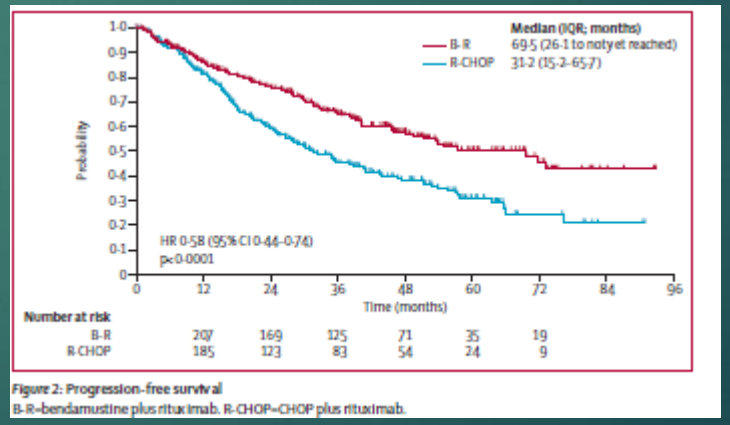


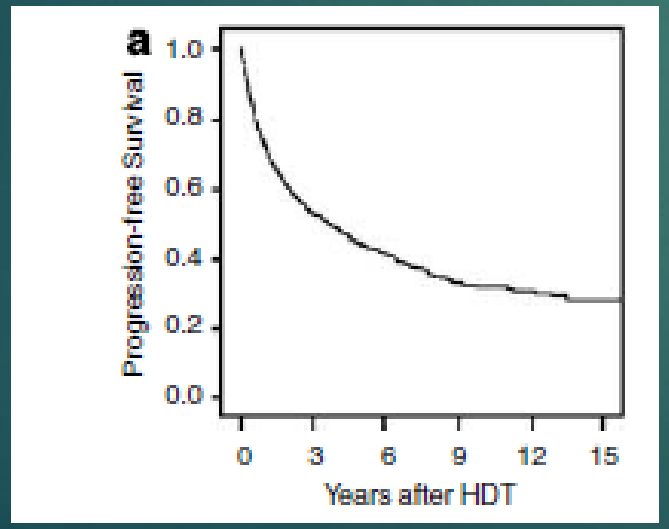
Figure 2: Progression-free survival
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

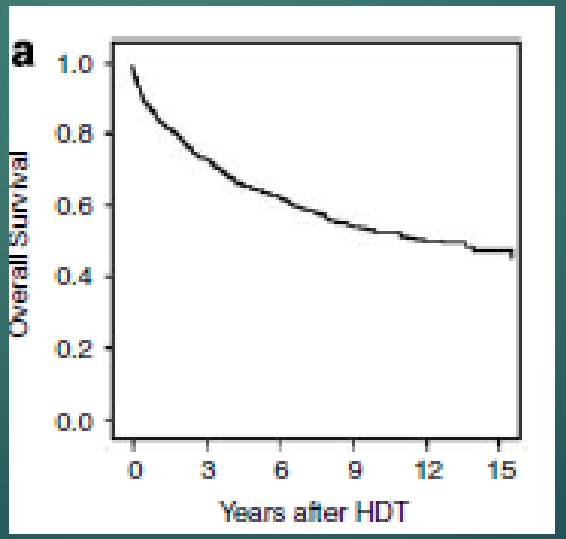
Yet, even with our strongest weapon (ASCT), the plateau has not been reached...

Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study

S Montoto[1], C Canals[2], AZS Rohatiner[1], G Taghipour[3], A Sureda[2], N Schmitz[4], C Gisselbrecht[5], L Fouillard[6], N Milpied[7], C Haioun[8], S Slavin[9], E Conde[10], C Fruchart[11], A Ferrant[12], V Leblond[13], H Tilly[14], TA Lister[1] and AH Goldstone[15], for the EBMT Lymphoma Working Party

Leukemia (2007) 21, 2324–2331





So, should our goal be postponing relapse? And how?



So, lets go back in time...pivotal study of R in FL!

Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program

By Peter McLaughlin, Antonio J. Grillo-López, Brian K. Link, Ronald Levy, Myron S. Czuczman, Michael E. Williams, Meyer R. Heyman, Isabelle Bence-Bruckler, Christine A. White, Fernando Cabanillas, Vinay Jain, Anthony D. Ho, John Lister, Ken Wey, David Shen, and Brian K. Dallaire

J Clin Oncol 16:2825-2833. © 1998

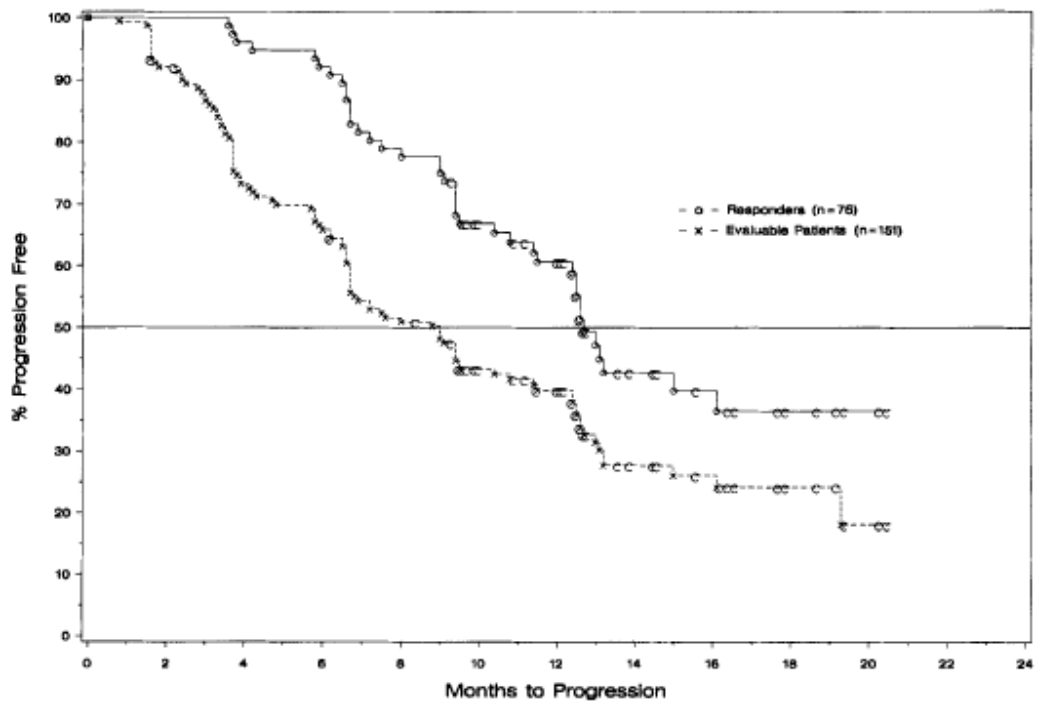


Fig 1. Time to progression (TTP) for all 151 assessable patients and TTP for 76 responders (CR or PR). Kaplan-Meier projected overall median TTP is 9.0 months (95% confidence interval [CI], 6.7 to 11.4); projected TTP for responders is 12.5 months (95% CI, 11.0 to 16.0).

What distinguished responders from non-responders?

Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program

By Peter McLaughlin, Antonio J. Grillo-López, Brian K. Link, Ronald Levy, Myron S. Czuczman, Michael E. Williams, Meyer R. Heyman, Isabelle Bence-Bruckler, Christine A. White, Fernando Cabanillas, Vinay Jain, Anthony D. Ho, John Lister, Ken Wey, David Shen, and Brian K. Dallaire

J Clin Oncol 16:2825-2833. © 1998

Table 4. Serum Antibody Concentrations Preinfusion and Postinfusion for Responders and Nonresponders

Infusion	Patient Response	No. of Patients	Preinfusion Concentration (μg/mL)	P	Postinfusion Concentration (μg/mL)	P
1	Responders	65	0.0	—	249.8	.468
	Nonresponders	72	0.0		229.5	
2	Responders	70	71.3	.006	324.4	.302
	Nonresponders	77	57.9		308.4	
3	Responders	70	128.3	.161	398.5	.850
	Nonresponders	73	120.0		382.6	
4	Responders	67	205.6	.007	502.8	.010
	Nonresponders	74	163.5		412.4	

NOTE. Serum concentrations of IDEC-C2B8 were higher in responding patients. Serum antibody levels were also higher for responders at 1, 4, and 13 weeks postinfusion (data not shown).

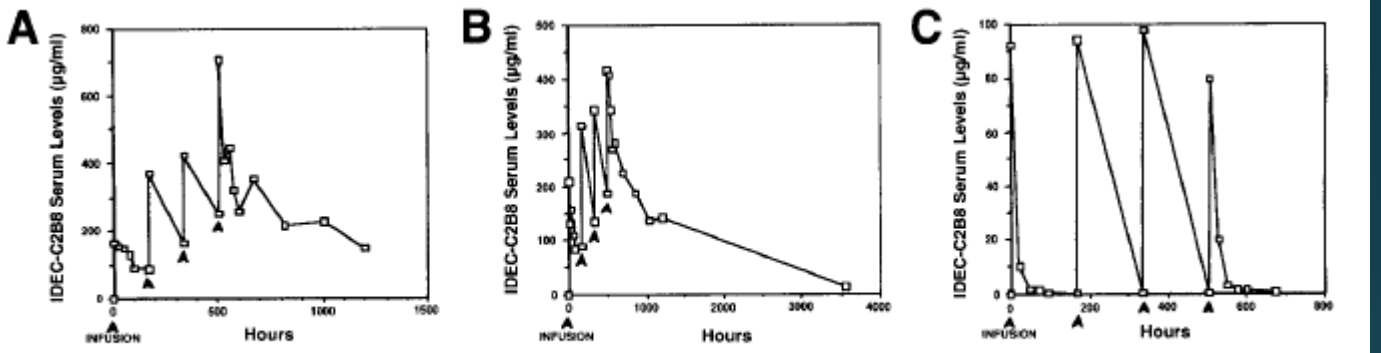


Fig 4. Patients with (A) CR or (B) PR show accumulation of antibody, whereas (C) nonresponder shows rapid clearance.

Which led to hypothesis that prolonged exposure to R may influence the outcomes…

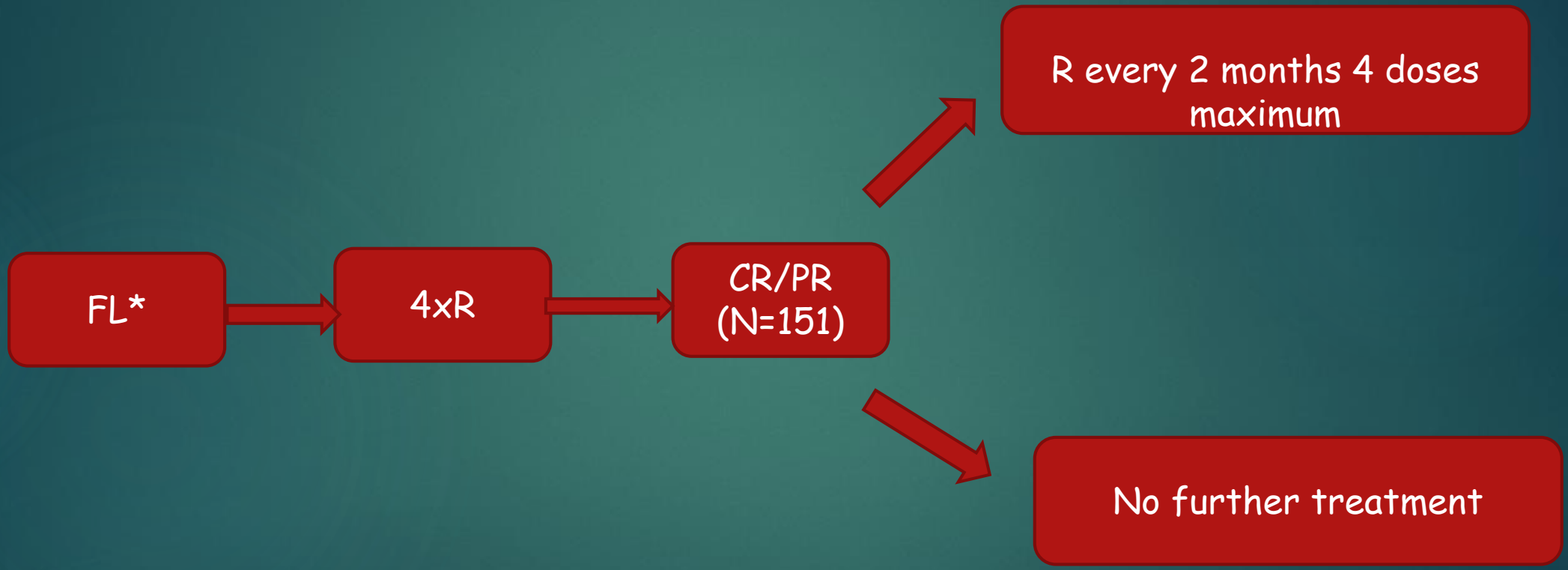


The design of first RCT!

Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule

Michele Ghielmini, Shu-Fang Hsu Schmitz, Sergio B. Cogliatti, Gabriella Pichert, Jörg Hummerjohann, Ursula Waltzer, Martin F. Fey, Daniel C. Betticher, Giovanni Martinelli, Fedro Peccatori, Urs Hess, Emanuele Zucca, Roger Stupp, Tibor Kovacsovics, Claudine Helg, Andreas Lohri, Mario Bargetzi, Daniel Vorobiof, and Thomas Cerny, for the Swiss Group for Clinical Cancer Research (SAKK)

BLOOD, 15 JUNE 2004 • VOLUME 103, NUMBER 12



Both newly diagnosed and R/R FL

Results:

Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule

Michele Ghielmini, Shu-Fang Hsu Schmitz, Sergio B. Cogliatti, Gabriella Pichert, Jörg Hummerjohann, Ursula Waltzer, Martin F. Fey, Daniel C. Betticher, Giovanni Martinelli, Fedro Peccatori, Urs Hess, Emanuele Zucca, Roger Stupp, Tibor Kovacsovics, Claudine Helg, Andreas Lohri, Mario Bargetzi, Daniel Vorobiof, and Thomas Cerny, for the Swiss Group for Clinical Cancer Research (SAKK)

BLOOD, 15 JUNE 2004 • VOLUME 103, NUMBER 12

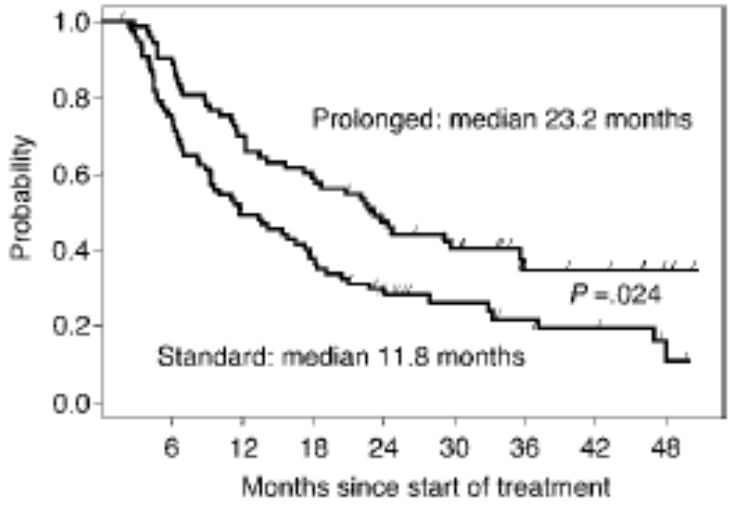


Figure 3. EFS of all randomized patients according to study arm. The curves are parallel, suggesting that the gain acquired during the 9 months of prolonged treatment is maintained over time.

The strategy of prolonged R exposure in FL is feasible !

Yet, this trial did not reflect routine clinical practice using chemotherapy as backbone of treating FL!

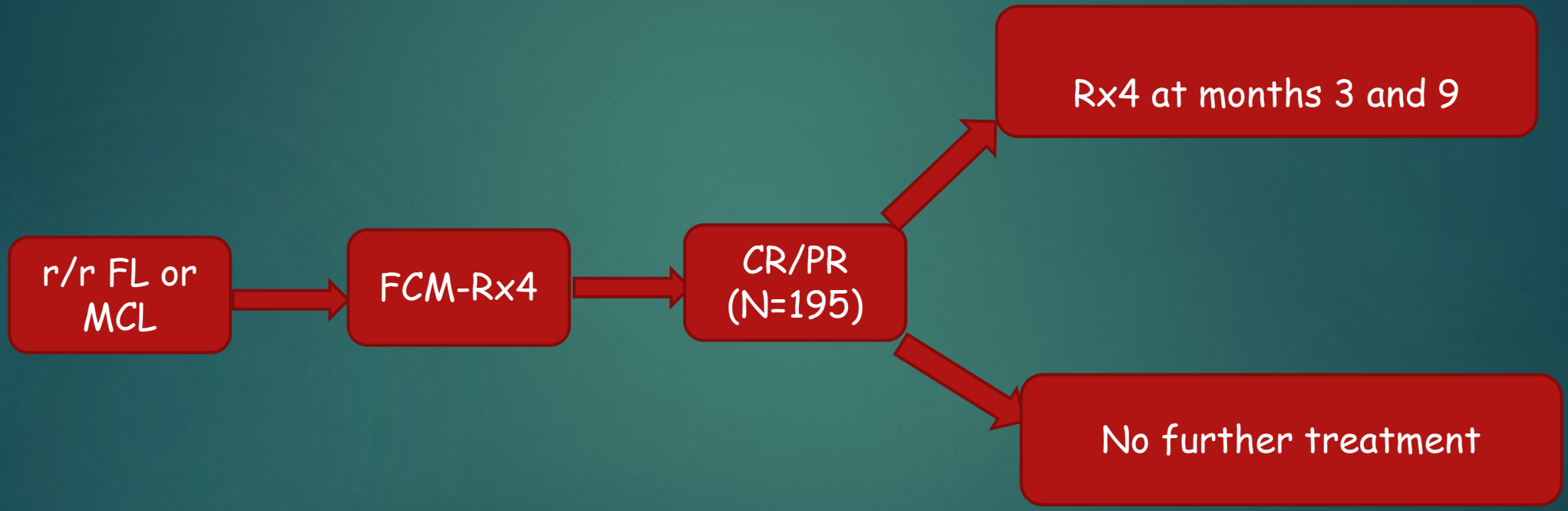


R maintenance following R-reinduction in r/r FL:

Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG)

Roswitha Forstpointner, Michael Unterhalt, Martin Dreyling, Hans-Peter Böck, Roland Repp, Hannes Wandt, Christiane Pott, John F. Seymour, Bernd Metzner, Annette Hänel, Tanja Lehmann, Frank Hartmann, Hermann Einsele, and Wolfgang Hiddemann

BLOOD, 15 DECEMBER 2006 • VOLUME 108, NUMBER 13



Again, the results were favorable!!

Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG)

Roswitha Forstpointner, Michael Unterhalt, Martin Dreyling, Hans-Peter Böck, Roland Repp, Hannes Wandt, Christiane Pott, John F. Seymour, Bernd Metzner, Annette Hänel, Tanja Lehmann, Frank Hartmann, Hermann Einsele, and Wolfgang Hiddemann

BLOOD, 15 DECEMBER 2006 • VOLUME 108, NUMBER 13

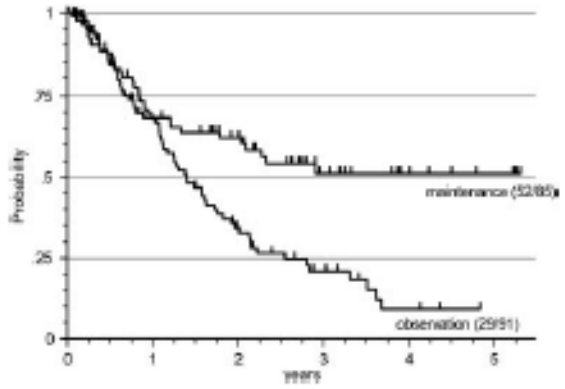


Figure 1. Response duration for R maintenance and observation. A significantly longer response duration was observed for the total group of patients on the R-maintenance arm ($P < .001$) with the median not being reached in this evaluation, compared with an estimated median of 17 months for patients receiving no further treatment.

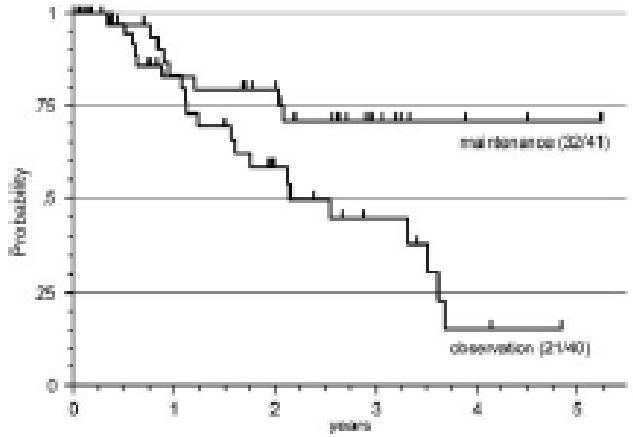


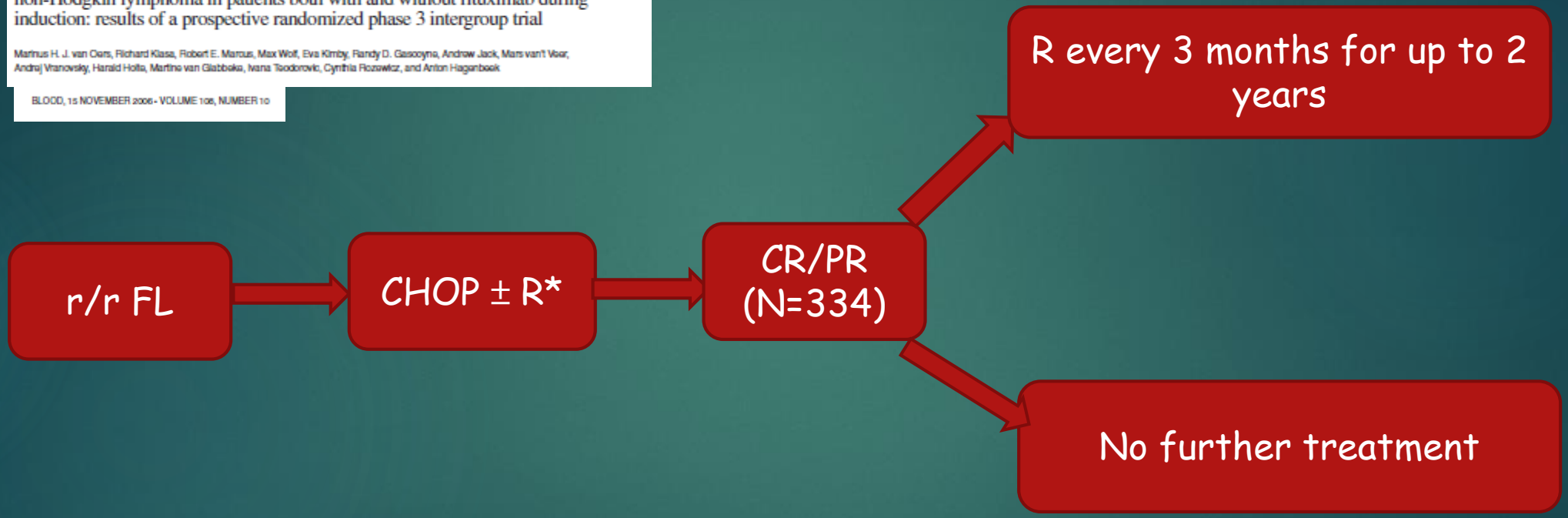
Figure 2. Response duration after R-FCM in patients with FL. A significant prolongation of response duration by R-maintenance compared with observation only was observed ($P = .035$), with the median not being reached in this evaluation, compared with an estimated median of 26 months.

Yet, we had to wait for RCTs with larger sample; the design:

Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial

Marinus H. J. van Oers, Richard Klasa, Robert E. Marcus, Max Wolf, Eva Kimby, Randy D. Gascoyne, Andrew Jack, Mars van't Veer, Andrej Vranovsky, Harald Holte, Martino van Glabbeke, Ivana Teodorovic, Cynthia Rozewicz, and Anton Hagenbeek

BLOOD, 15 NOVEMBER 2006 - VOLUME 108, NUMBER 10



*first randomization based on R use in reinduction

Outcomes were better regardless of reinduction regimen!

Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial

Marinus H. J. van Oers, Richard Klasa, Robert E. Marcus, Max Wolf, Eva Kimby, Randy D. Gascoyne, Andrew Jack, Mars van't Veer, Andrej Vranovsky, Harald Holte, Martine van Glabbeke, Ivana Teodorovic, Cynthia Rozewicz, and Anton Hagenbeek

BLOOD, 15 NOVEMBER 2006 • VOLUME 108, NUMBER 10

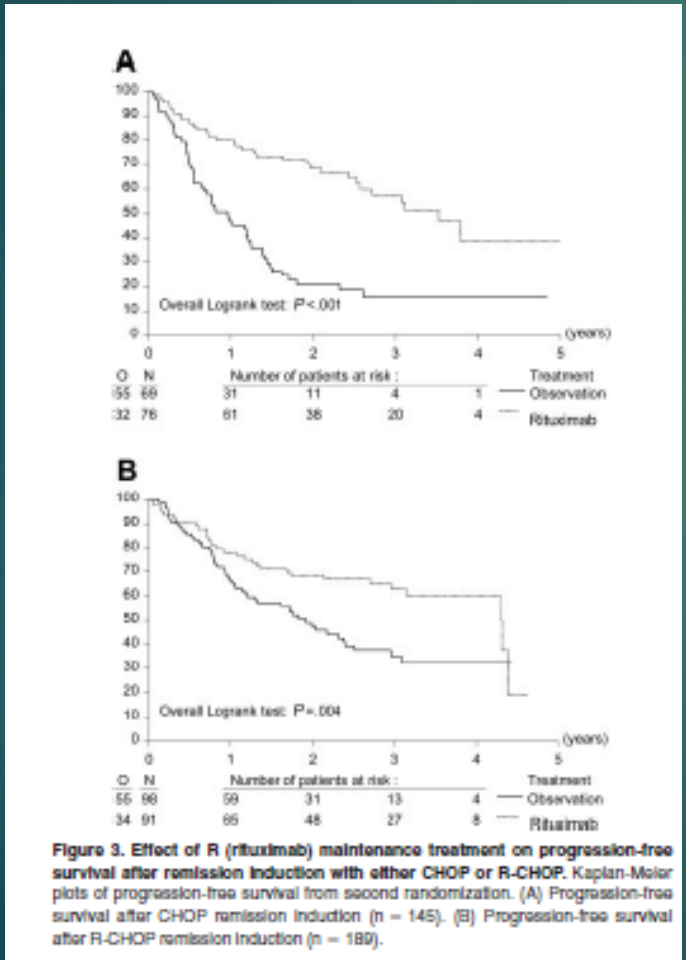
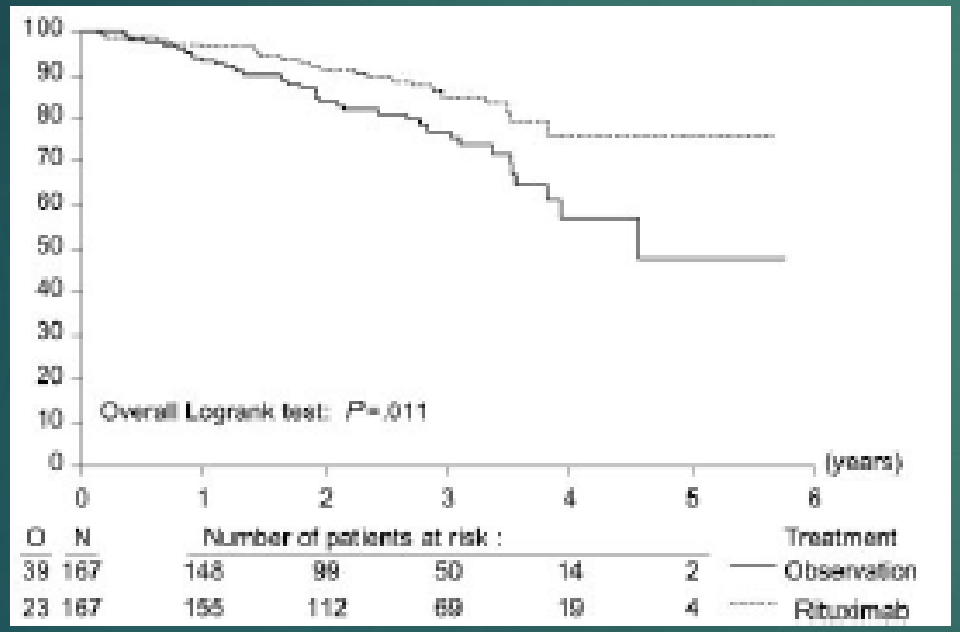


Figure 3. Effect of R (rituximab) maintenance treatment on progression-free survival after remission induction with either CHOP or R-CHOP. Kaplan-Meier plots of progression-free survival from second randomization. (A) Progression-free survival after CHOP remission induction (n = 145). (B) Progression-free survival after R-CHOP remission induction (n = 189).

42.2 vs. 11.6 months

51.8 vs. 23 months

R maintenance has shown OS benefit in this setting!



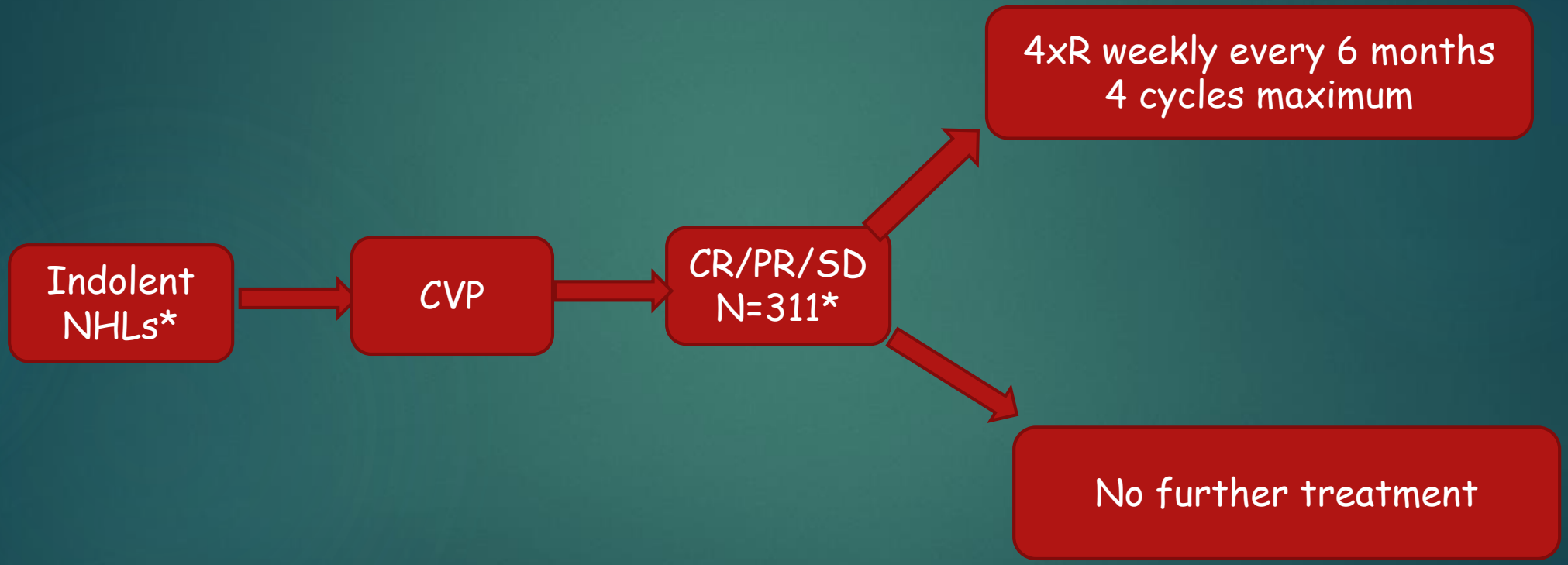
3-year OS rate 85.1% vs 77.1%

So, R maintenance has established its role in relapse setting of FL, but..

What about first line?
It seems as an attractive option!

Design of ECOG trial:

Eastern Cooperative Oncology Group



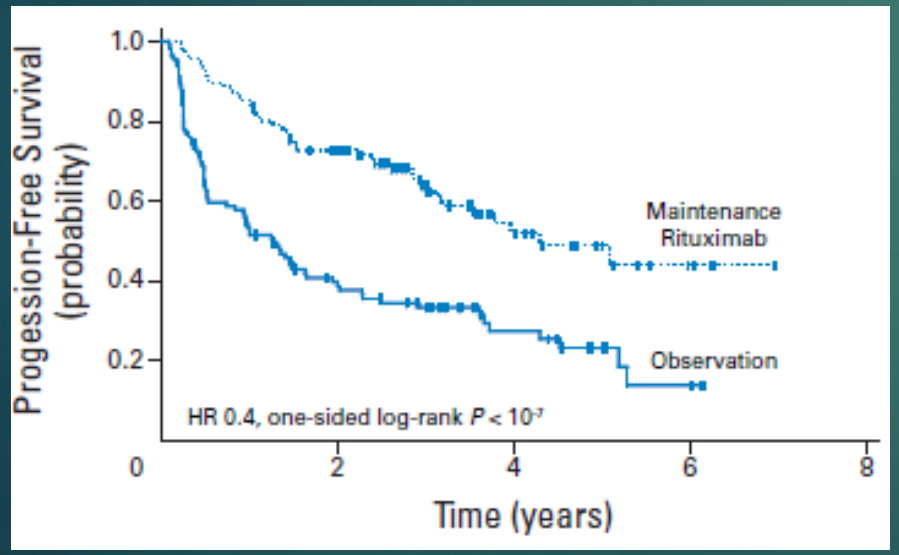
In this setting R maintenance remained beneficial in terms of PFS:

Data for FL

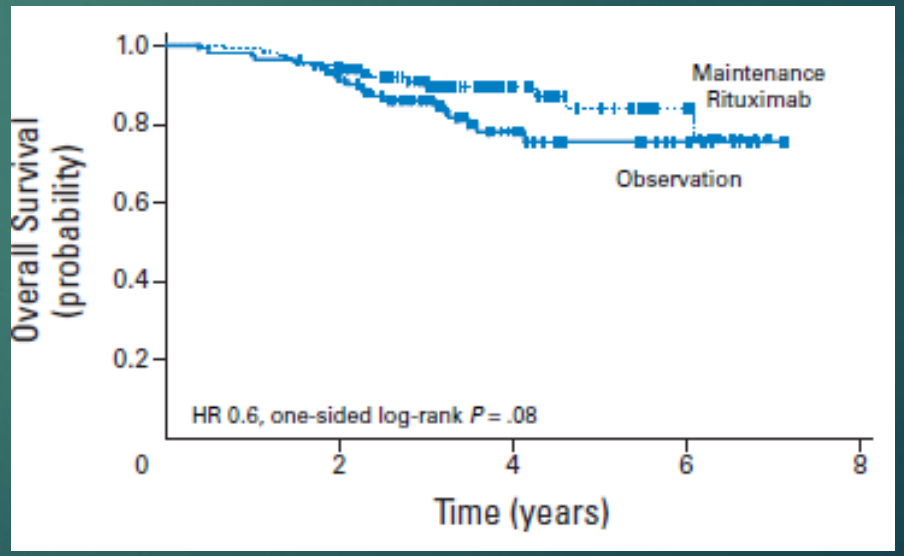
VOLUME 27 · NUMBER 10 · APRIL 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG1496 Study

Howard Hochster, Edie Weller, Randy D. Gascoyne, Thomas M. Habermann, Leo I. Gordon, Theresa Ryan, Lijun Zhang, Natalia Colocci, Stanley Frankel, and Sandra J. Horning

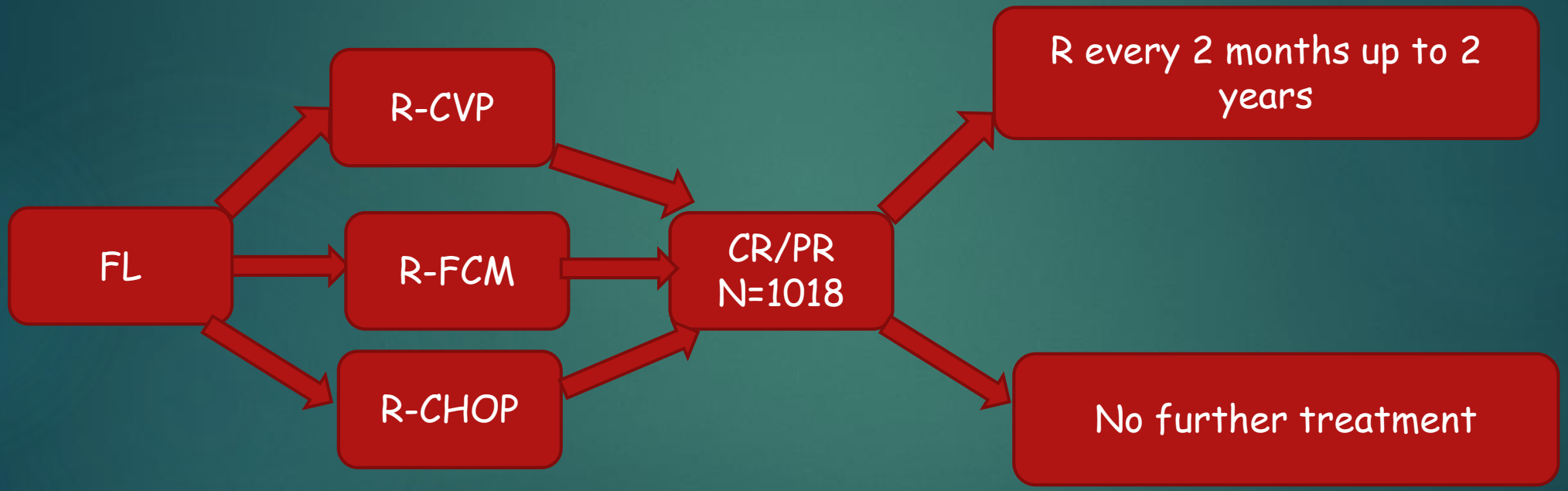


4.3 vs. 1.3 years



3-year OS rate 91% vs. 86% NS

Yet we need the data on maintenance in the era of R based induction regimens: PRIMA design!

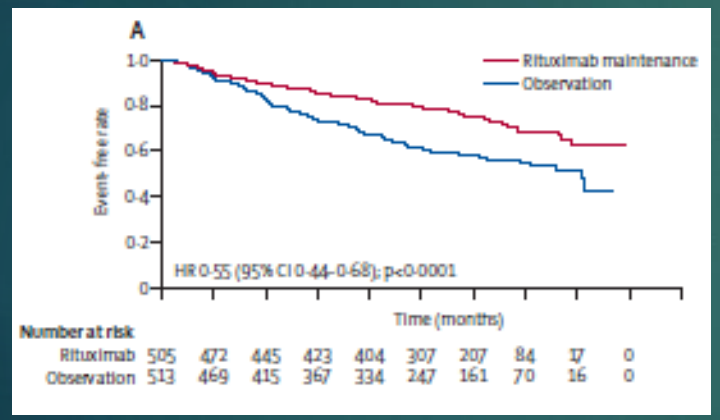


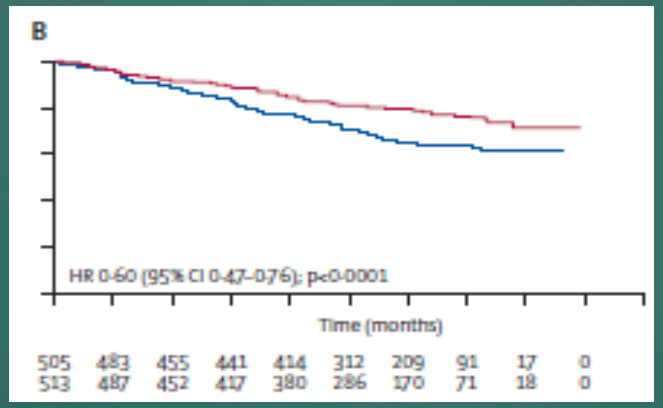
Results after 3 years follow up:

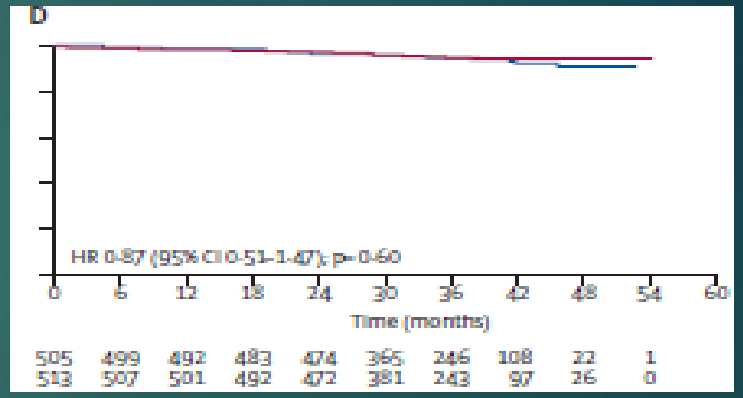
Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Møller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly

Lancet 2010; 377: 42–51







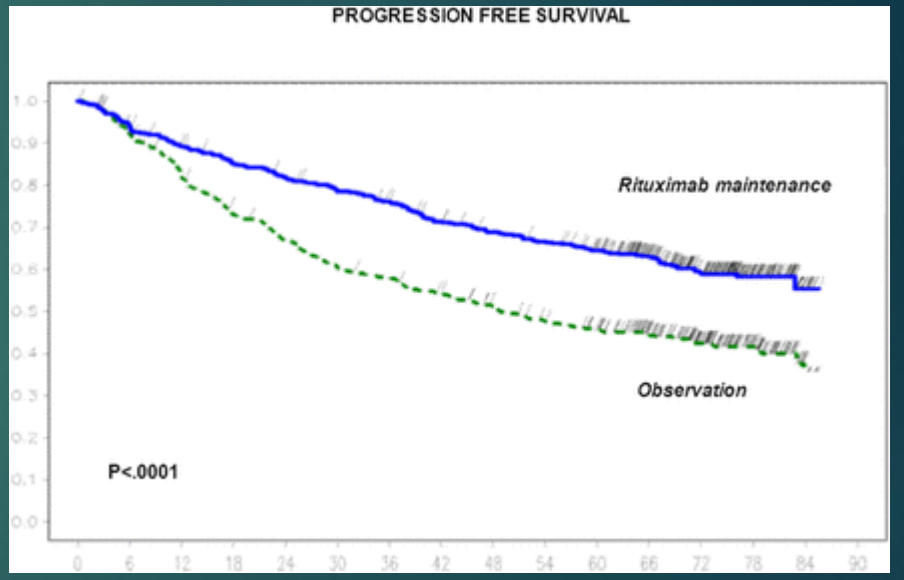
PFS

Time to next treatment

OS NS

Long-term follow-up of PRIMA:

- Salles et al., 2013
- Median follow-up 6 years
- 6-year PFS rate 59.2% vs. 42.7%, p<0.0001
- 6-year OS rate 87.4% vs.88.7%, p=NS
- Reduction of risk for next antilymphoma treatment
- Reduction of risk for chemotherapy



So, R maintenance in first line setting was endorsed by regulatory agencies!



ESMO and NCCN position:

NCCN National Comprehensive Cancer Network®

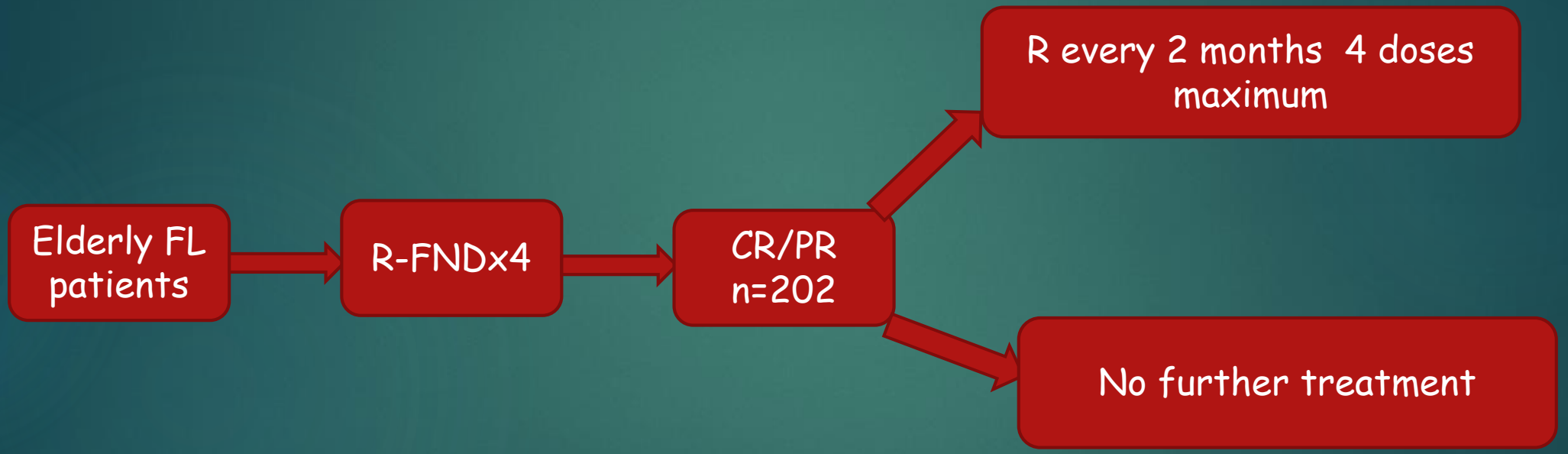
Grade 1 for first line or relapsed setting



I B for first line and
IA for relapsed setting

But, everything is not as clear as it seems: Italian experience!?





Results were disappointing?

VOLUME 31 · NUMBER 27 · SEPTEMBER 20 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Rituximab Maintenance Compared With Observation After Brief First-Line R-FND Chemoimmunotherapy With Rituximab Consolidation in Patients Age Older Than 60 Years With Advanced Follicular Lymphoma: A Phase III Randomized Study by the Fondazione Italiana Linfomi

Umberto Vitolo, Marco Ladetto, Carola Boccomini, Luca Baldini, Federico De Angelis, Alessandra Tucci, Barbara Botto, Annalisa Chiappella, Annalisa Chiarenza, Antonello Pinto, Amalia De Renzo, Francesco Zaja, Claudia Castellino, Alessia Bari, Isabel Alvarez De Celis, Andrea Evangelista, Guido Parvis, Enrica Gamba, Chiara Lobetti-Bodoni, Giovannino Ciccone, and Giuseppe Rossi

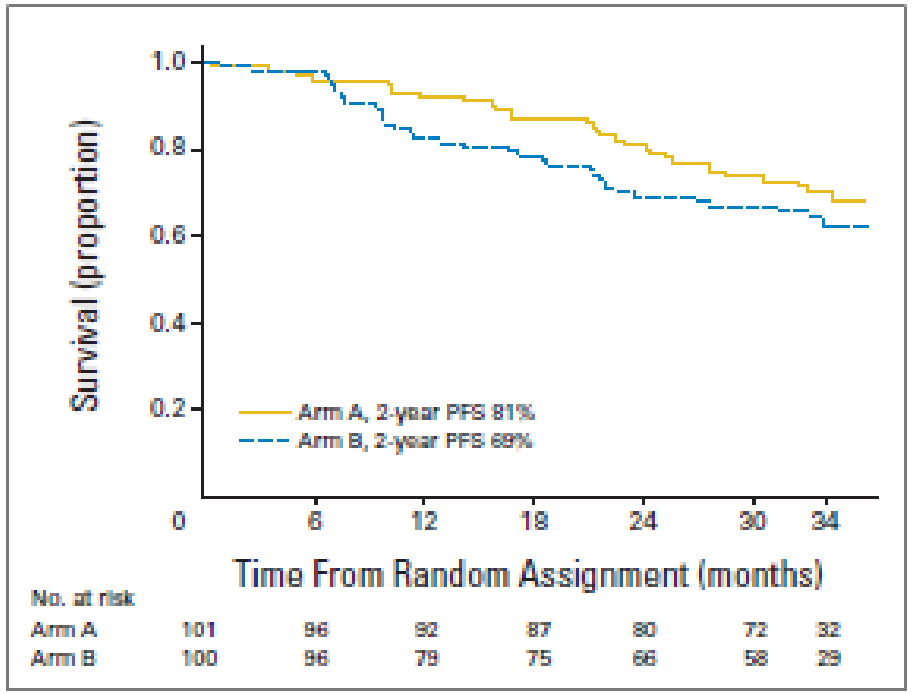
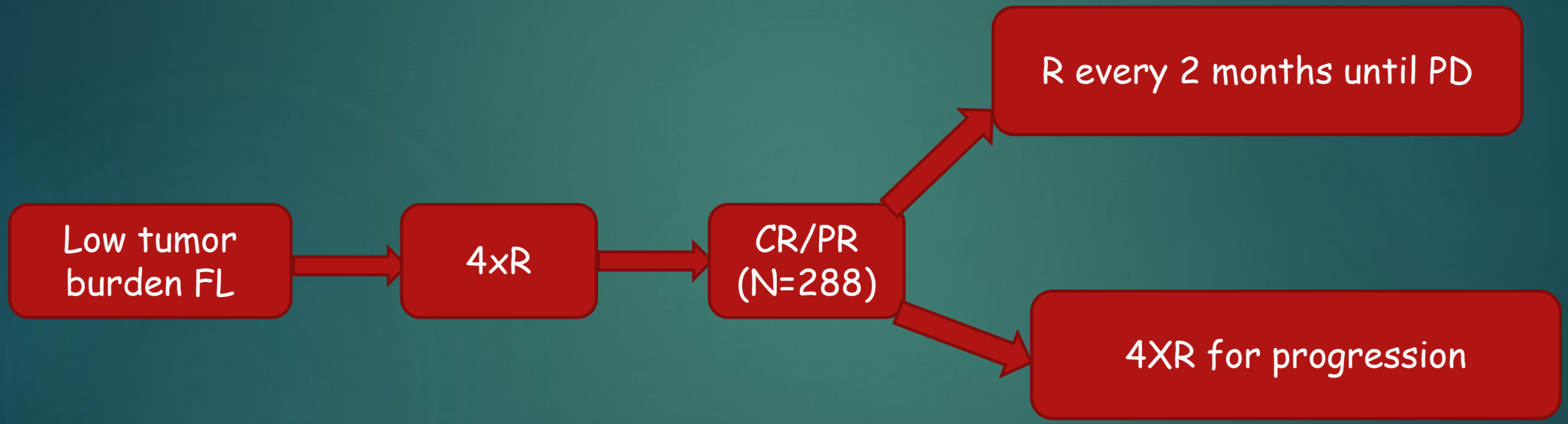


Fig 3. Effect of rituximab maintenance treatment on progression-free survival (PFS). Kaplan-Meier plot of PFS after rituximab maintenance (arm A; n = 101) or observation (arm B; n = 101). Median follow-up period: 34 months from randomization. Stratified hazard ratio of 0.74 (95% CI, 0.45 to 1.21; $P = .226$).

Different induction regimen?

Relatively low exposure to R?

Yet, maintenance strategy was challenged by retreatment option…RESORT design!



Both strategies were shown to be equally feasible!

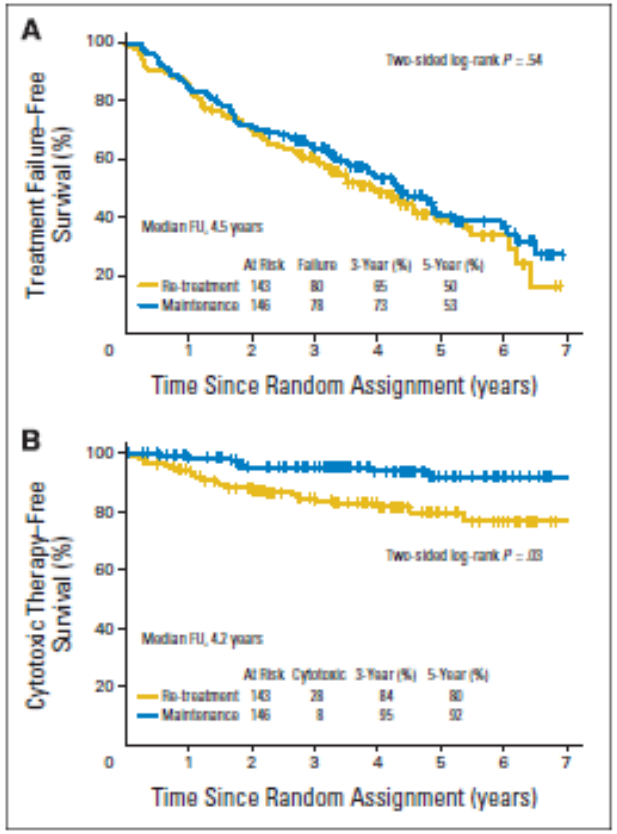


Fig 3. Time to (A) treatment failure and (B) first cytotoxic therapy in 289 patients with follicular lymphoma randomly assigned to re-treatment rituximab or maintenance rituximab. FU, follow-up.

4.3 vs. 3.9 years

VOLUME 32 · NUMBER 28 · OCTOBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Rituximab Extended Schedule or Re-Treatment Trial for Low–Tumor Burden Follicular Lymphoma: Eastern Cooperative Oncology Group Protocol E4402

Brad S. Kahl, Fangxin Hong, Michael E. Williams, Randy D. Gascoyne, Lynne I. Wagner, John C. Krauss, Thomas M. Habermann, Lode J. Swinnen, Stephen J. Schuster, Christopher G. Peterson, Mark D. Sborov, S. Eric Martin, Matthias Weiss, W. Christopher Ehmann, and Sandra J. Horning

In summary, the RESORT trial demonstrates that single-agent rituximab, administered in an RR strategy, is as efficacious as MR in low–tumor burden FL. There was no advantage for MR in TTF or HRQOL. There was a small advantage for MR in time to first cytotoxic therapy, but significantly more rituximab was required to achieve this benefit. This trial has implications for both research and practice. With regard to research, it would be highly interesting to determine if an RR strategy could produce outcomes comparable to those of an MR strategy, when applied after rituximab plus chemotherapy in high–tumor burden FL.[21] Given the widespread use of MR, the resource use implications are large. With regard to practice, RESORT indicates that if opting for single-agent rituximab as initial therapy for low–tumor burden FL, a strategy of re-treatment at disease progression is recommended over a strategy of continuous maintenance therapy.

But the extrapolation to high burden FL is impossible: Gilles Salles, 2015 NYC

The major differences between PRIMA and RESORT

	RESORT	PRIMA
Tumor burden	Low	High
Chemotherapy	No	Yes
Depth of response after induction	+	+++
Median F-up	4 years	6 years
Treatment at progression	Rituximab, then chemo	chemo (80%)



So, as we see, there are some questions using maintenance strategy in FL treatment in 2016:

- Toxicity?
- OS benefit?
- Quality of life?
- Cost?
- To retreat or maintain?
- New drugs?

Do we harm our patients by "overtreatment"? Toxicity issue!

Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Møller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly

Lancet 2010; 377: 42–51

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

Data are number (%). NA=not applicable. *Safety during maintenance was assessed for patients who undertook at least one visit (rituximab treatment or observation) after randomisation. All adverse events, defined as any adverse change from the patient's baseline condition, whether considered related to treatment or not, were collected and graded according to the Common Terminology Criteria for Adverse Events 3.0 grading system.[28] All grade 3 and 4 events plus grade 2 infections were recorded in detail during maintenance or observation and 6 months thereafter. †Other events leading to treatment discontinuation were pyrexia, fulminant hepatitis, hypersensitivity, post-procedural fistula, and lung disorder (one case each).

Table 2: Grade 3 and 4 adverse events* experienced by 2% or more of patients and adverse events leading to treatment discontinuation, after randomisation to rituximab maintenance or observation

	Baseline (randomisation)		After 1 year		End of maintenance phase	
	Maintenance	Observation	Maintenance	Observation	Maintenance	Observation
IgA						
n	131	125	118	89	111	61
g/L	1·33 (0·63)	1·57 (3·55)	1·26 (0·58)	1·40 (0·88)	1·25 (0·50)	1·55 (0·91)
IgG						
n	131	125	118	89	100	60
g/L	7·87 (2·26)	7·76 (2·13)	7·73 (2·12)	8·22 (2·22)	7·48 (2·13)	8·31 (2·32)
IgM						
n	127	121	113	89	110	61
g/L	0·64 (0·52)	0·59 (0·55)	0·55 (0·39)	0·55 (0·31)	0·51 (0·39)	0·58 (0·25)

Immunoglobulin concentrations are given as mean (SD). Serum concentrations of immunoglobulins were assessed only in a subset of patients in one participating country.

Table 3: Serum concentrations of immunoglobulins at randomisation, after 1 year of maintenance, and at the end of the maintenance phase

No additional safety signal in longer follow-up, Salles et al., 2013

Real world data (N=545)

Maintenance with rituximab is safe and not associated with severe or uncommon infections in patients with follicular lymphoma: results from the phase IIIb MAXIMA study

Mathias Witzens-Harig · Robin Foá · Alice Di Rocco · Guy van Hazel · Dalton F. A. Chamone · Jacob M. Rowe · Luca Arcaini · Irina Poddubnaya · Anthony D. Ho · Valentina Ivanova · Andrej Vranovsky · Dan Thurley · Stephan Oertel

Ann Hematol (2014) 93:1717–1724

Table 3 Most common AEs and IRRs

Event	Overall, *N* = 534						Treatment-related	
	Any grade		Grade 3		Grade 4		Any grade	
	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*
All hematologic AEs[a]	35 (6.6)	51	11 (2.1)	13	7 (1.3)	8	8 (1.5)	11
Neutropenia	18 (3.4)	26	8 (1.5)	9	5 (0.9)	5	5 (0.9)	8
Leukopenia	6 (1.1)	9	1 (0.2)	1	0 (0.0)	0	1 (0.2)	1
Febrile neutropenia	3 (0.6)	4	1 (0.2)	1	3 (0.6)	3	1 (0.2)	1
All infections and infestations	193 (36.1)	422	21 (3.9)	27	2 (0.4)	2	23 (4.3)	36
Nasopharyngitis	38 (7.1)	58	0 (0.0)	0	0 (0.0)	0	1 (0.2)	1
Bronchitis	25 (4.7)	28	0 (0.0)	0	0 (0.0)	0	2 (0.4)	2
Sinusitis	23 (4.3)	31	2 (0.4)	2	0 (0.0)	0	5 (0.9)	6
Any IRR	31 (5.8)	50	2 (0.4)	3	1 (0.2)	1	NA	
Hypotension	5 (0.9)	5	0 (0.0)	0	0 (0.0)	0	NA	
Hypertension	3 (0.6)	3	0 (0.0)	0	0 (0.0)	0	NA	
Pyrexia	3 (0.6)	3	0 (0.0)	0	0 (0.0)	0	NA	
Headache	3 (0.6)	4	1 (0.2)	1	0 (0.0)	0	NA	
Erythema	3 (0.6)	4	0 (0.0)	0	0 (0.0)	0	NA	

AEs adverse events, *IRR* infusion-related reaction, *NA* not applicable, *SAE* serious adverse event

[a] Total AEs, SAEs, and treatment-related AEs include one episode of immune thrombocytopenia that resulted in the death of the patient

R maintenance is feasible and not associated with severe AEs

The fact: first line R maintenance does not provide OS benefit!?

Rituximab Maintenance for the Treatment of Patients With Follicular Lymphoma: An Updated Systematic Review and Meta-analysis of Randomized Trials

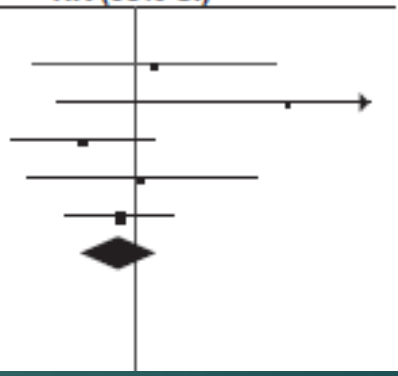
Liat Vidal, Anat Gafter-Gvili, Gilles Salles, Martin H. Dreyling, Michele Ghielmini, Shu-Fang Hsu Schmitz, Ruth Pettengell, Mathias Witzens-Harig, Ofer Shpilberg

J Natl Cancer Inst 2011;103:1799–1806

Study or Subgroup	log[HR]	SE	Weight	HR (95% CI)
Maintenance in first remission				
Ardeshna 2010	0.19	0.61	2.7%	1.21 (0.37 to 4.00)
Hochster 2007	1.5067	1.155	0.8%	4.51 (0.47 to 43.40)
Hochster 2009	-0.51	0.3537	8.1%	0.60 (0.30 to 1.20)
Martinelli 2010	0.073	0.5775	3.0%	1.08 (0.35 to 3.34)
Salles 2010	-0.14	0.27	13.8%	0.87 (0.51 to 1.48)
Subtotal (95% CI)			**28.4%**	**0.86 (0.60 to 1.25)**

Heterogeneity: $Chi^2 = 3.55$, $df = 4$ ($P = .47$); $I^2 = 0\%$

Test for overall effect: $Z = 0.78$ ($P = .44$)



But, let me ask you when was the last time we saw OS benefit in FL first line setting?

VOLUME 26 · NUMBER 28 · OCTOBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma

Robert Marcus, Kevin Imrie, Philippe Solal-Celigny, John V. Catalano, Anna Dmoszynska, João C. Raposo, Fritz C. Offner, José Gomez-Codina, Andrew Belch, David Cunningham, Elisabeth Wassner-Fritsch, and George Stein

Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group

Wolfgang Hiddemann, Michael Kneba, Martin Dreyling, Norbert Schmitz, Eva Lengfelder, Rudolf Schmits, Marcel Reiser, Bernd Metzner, Harriet Harder, Susanna Hegewisch-Becker, Thomas Fischer, Martin Kropff, Hans-Edgar Rieis, Mathias Freund, Bernhard Wörmann, Roland Fuchs, Manfred Planker, Jörg Schimka, Hartmut Elmermacher, Lorenz Trümper, Ali Aldaoud, Reza Parwaresch, and Michael Unterhalt

BLOOD, 1 DECEMBER 2005 · VOLUME 106, NUMBER 12

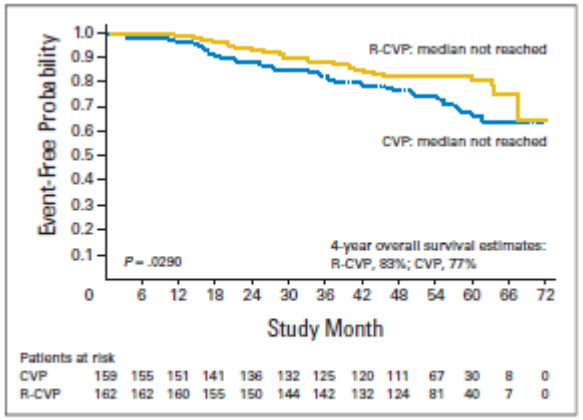


Fig 2. Overall survival in patients assigned to chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP) or with CVP plus rituximab (R-CVP).

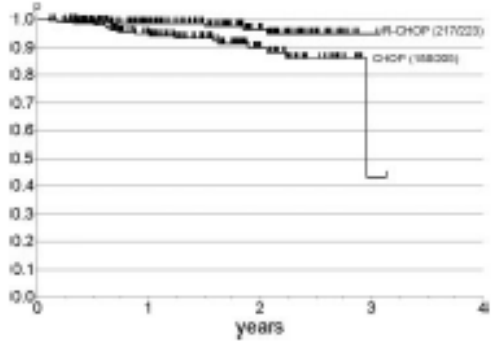


Figure 3. OS after start of therapy for CHOP and R-CHOP. Median OS has not been reached in either group. After 3 years, 6 patients in the R-CHOP arm have died compared with 17 patients in the CHOP arm ($P = .016$).

Does PFS correlate with OS in indolent histologies?

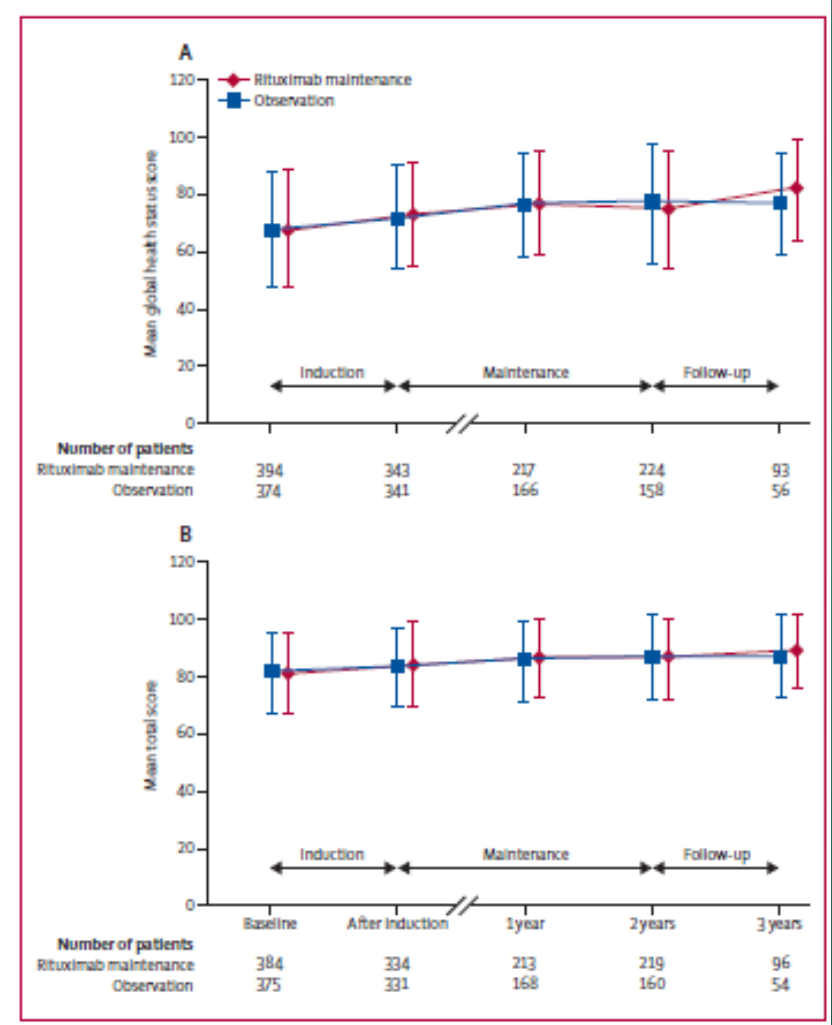
Identification of potential surrogate end points in randomized clinical trials of aggressive and indolent non-Hodgkin's lymphoma: correlation of complete response, time-to-event and overall survival end points

L. Lee[1], L. Wang[2] & M. Crump[1*]

Annals of Oncology 22: 1392–1403, 2011

	Aggressive			Indolent		
	Nonparametric Spearman rank coefficient	95% CI	*P*-value	Nonparametric Spearman rank coefficient	95% CI	*P*-value
CR and 3-year time-to-event and OS end points						
CR and 3-year EFS	0.88	0.57–0.97	0.0003	0.86	0.35 to 0.97	0.0059
CR and 3-year PFS	0.63	0.21–0.84	0.005	0.41	−0.52 to 0.88	0.35
CR and 3-year PFS/EFS	0.70	0.42–0.86	<0.0001	0.77	0.41–0.92	0.0007
CR and 3-year OS	0.58	0.29–0.77	0.004	0.41	−0.1 to 0.74	0.098
Potential surrogate end points and 5-year OS						
CR and 5-year OS	0.50	0.23–0.74	0.01	0.21	−0.34 to 0.5	0.44
3-year EFS or PFS and 5-year OS	0.90	0.73–0.96	<0.0001	0.26	−0.38 to 0.72	0.41

What about QoL?



Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Møller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly

Lancet 2010; 377: 42–51

QoL didn't differ among the groups but the patients, who progressed, were censored

What is true impact of progression on QoL?

The impact of follicular lymphoma on health-related quality of life

R. Pettengell[1]*, C. Donatti[2], P. Hoskin[3], C. Poynton[4], P. J. Kettle[5], B. Hancock[6], S. Johnson[7], M. J. S. Dver[8]. S. Rule[9]. M. Walker[10] & D. Wild[2]

Annals of Oncology 19: 570–576, 2008

Thus, it is the patient's disease status that had the greatest impact on these scores. It is arguable that prolonging a patient's *status quo* as disease free (i.e. prolonging the time to treatment failure is beneficial either by more intense induction or by maintenance treatment) is important in terms of improving HRQoL.

Relapsed patients had the worst QoL scores

What about costs?

PharmacoEconomics (2013) 31:403–413
DOI 10.1007/s40273-013-0043-8

REVIEW ARTICLE

Rituximab for the First-Line Maintenance Treatment of Follicular Non-Hodgkin's Lymphoma

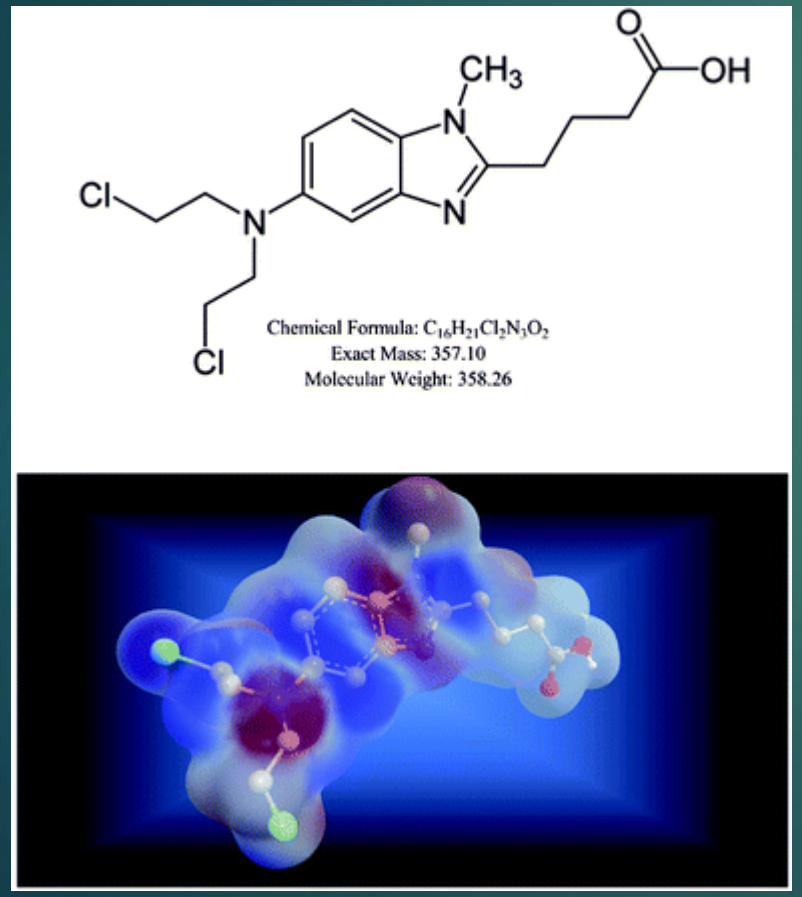
A NICE Single Technology Appraisal

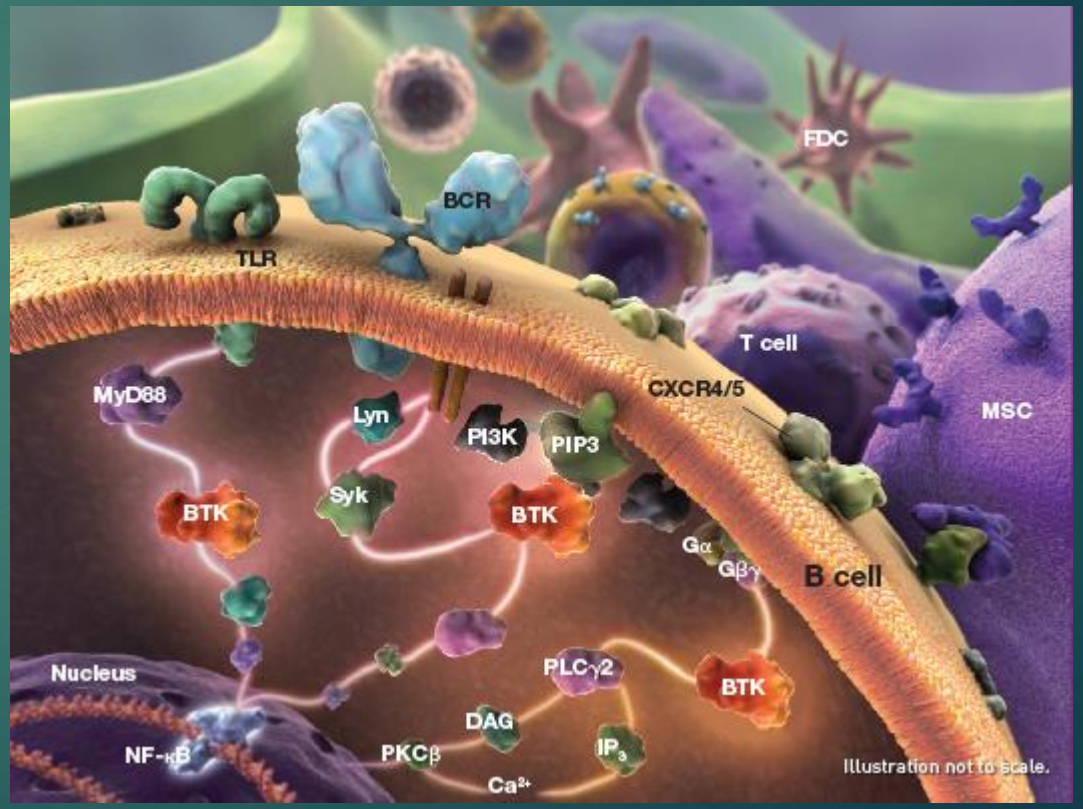
Janette Greenhalgh · Adrian Bagust · Angela Boland · Michaela Blundell · James Oyee · Sophie Beale · Yenal Dundar · Juliet Hockenhull · Chris Proudlove · Patrick Chu

In its final deliberations, the AC noted that the manufacturer's ICERS for RTX maintenance therapy compared with observation were less than £30,000 per QALY gained for most scenarios and the ERG ICERs ranged from £24,600 to £35,000 per QALY gained (depending on the conversion rate of PFS to OS). The AC also noted that the model did not include the utility associated with delaying CTX, and that if it were included it would decrease the ICER to an estimate that would be considered as a cost-effective use of NHS resources. The AC therefore recommended the use of RTX in this indication.

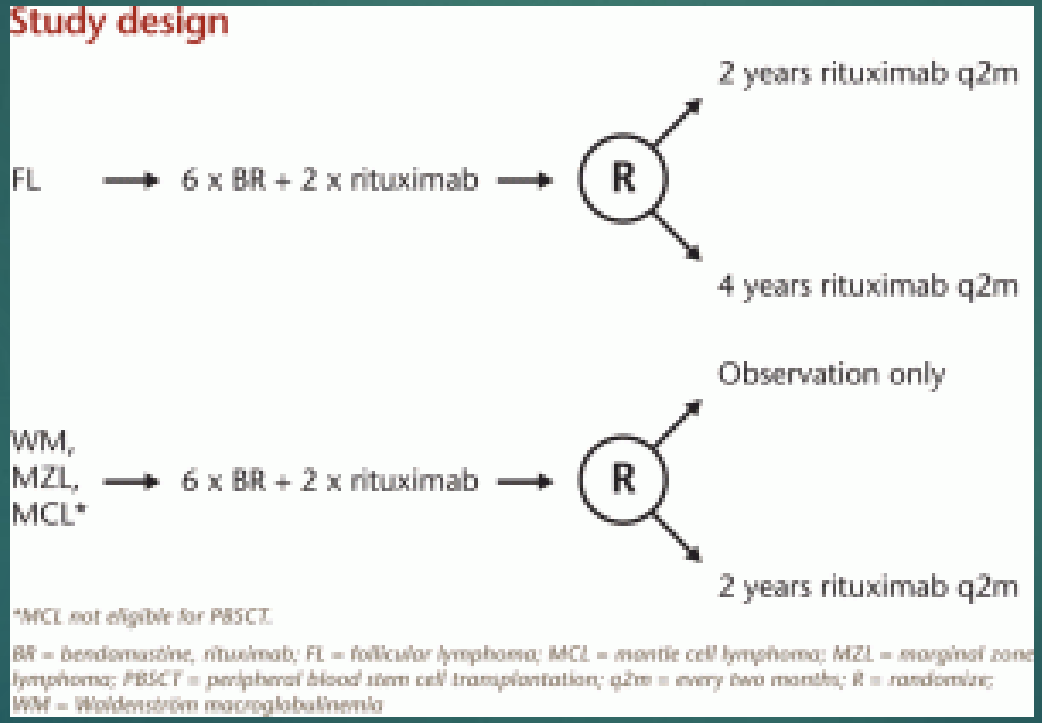


Yet, the greatest "threat" comes from new drugs….





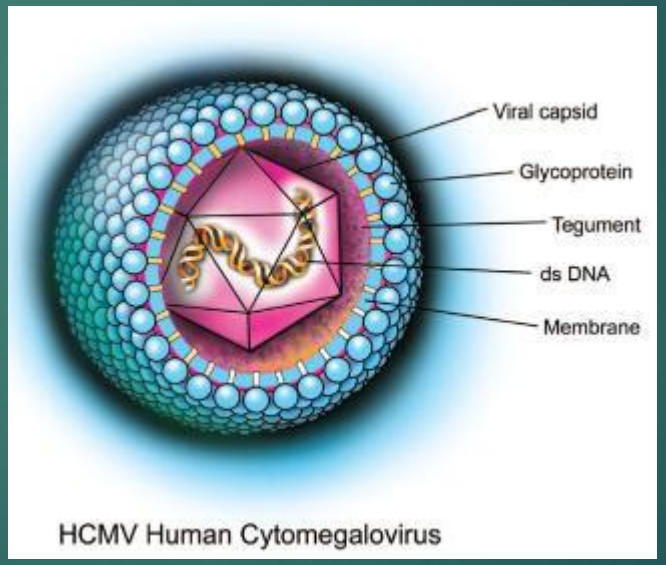
Concerning bendamustine, MAINTAIN trial is ongoing…



We expect to see results in 2017!

And with BCR pathway inhibitors we have experienced a setback…





Other inhibitors in phase I/II trials

Key points:

- R maintenance in first line setting prolongs PFS in high tumor burden FL
- R maintenance in second line setting prolongs OS in high tumor burden FL ineligible for ASCT
- R maintenance has manageable toxicity profile
- R maintenance doesn't interfere with QoL
- R maintenance is cost-effective
- so, the answer is…

Yes, R maintenance is a standard of care of high tumor burden FL in 2016!

HOW TO MANAGE...

How we manage follicular lymphoma

W Hiddemann[1] and BD Cheson[2]

Leukemia (2014) **28**, 1388–1395;

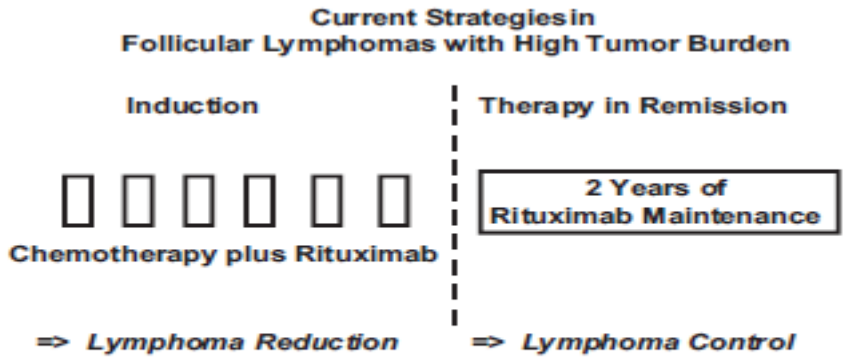


Figure 2. The current strategy of therapy in follicular lymphomas with a high tumour burden comprises initial immunochemotherapy for achieving a complete or partial remission, followed by 2 years of rituximab maintenance.