5 Minute JournalClub

Key ASH Presentations

Issue 1, 2012

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CME Information

LEARNING OBJECTIVES

- Evaluate the efficacy and toxicity outcomes of maintenance rituximab versus rituximab re-treatment upon disease progression, and incorporate this information into your personal treatment algorithm for patients with low tumor burden follicular lymphoma.
- Assess the efficacy of maintenance rituximab in disease settings in non-Hodgkin lymphoma for which standard treatment is not well established, including for elderly patients with advanced follicular lymphoma.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES

The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Results of E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma

Kahl BS et al.

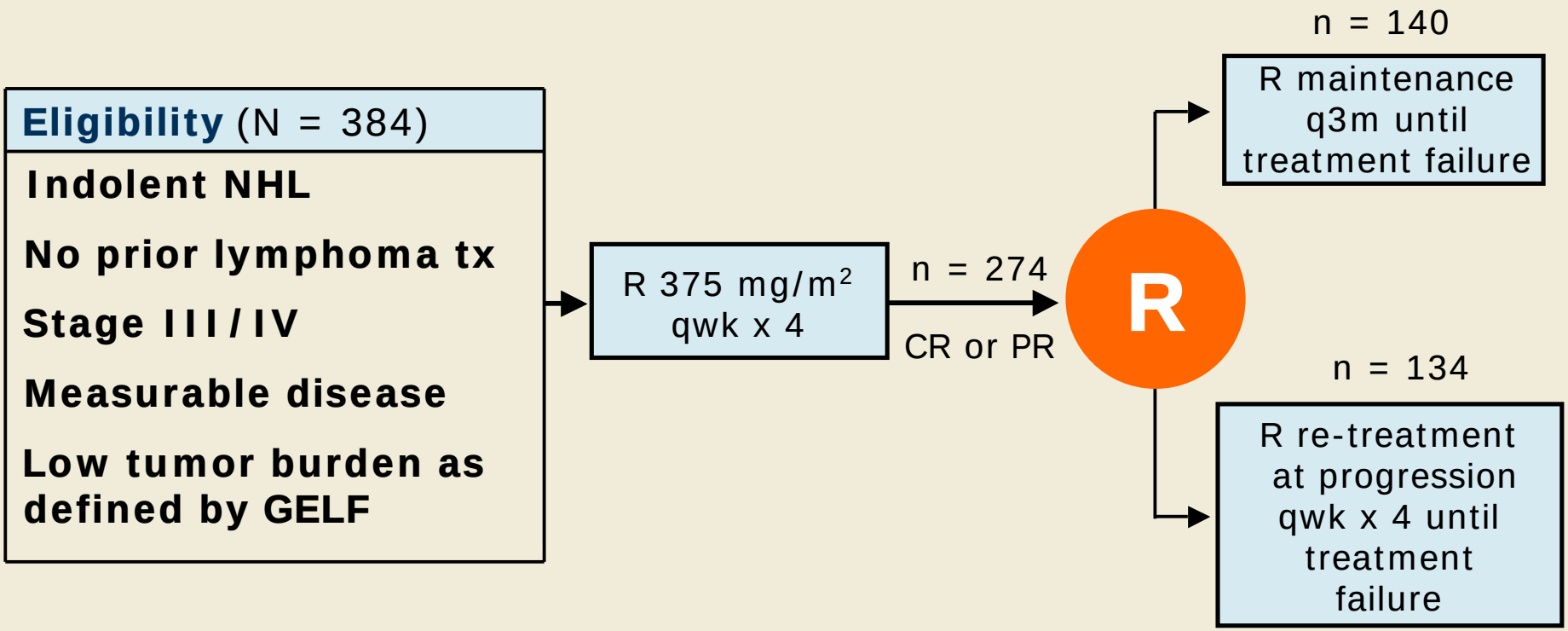
Proc ASH 2011;Abstract LBA-6.

Background

- Optimal treatment of low tumor burden (LTB) follicular lymphoma (FL) and the role of rituximab (R) in the management of this disease are uncertain.
- Previous data with watch-and-wait approaches are associated with an average of 3 years to initiation of chemotherapy.
- **Hypothesis:**
  - Rituximab could delay the need for chemotherapy.
  - Maintenance rituximab (MR) would provide superior disease control compared to rituximab re-treatment (RR) at progression.

Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

E4402 Phase III Study Schema

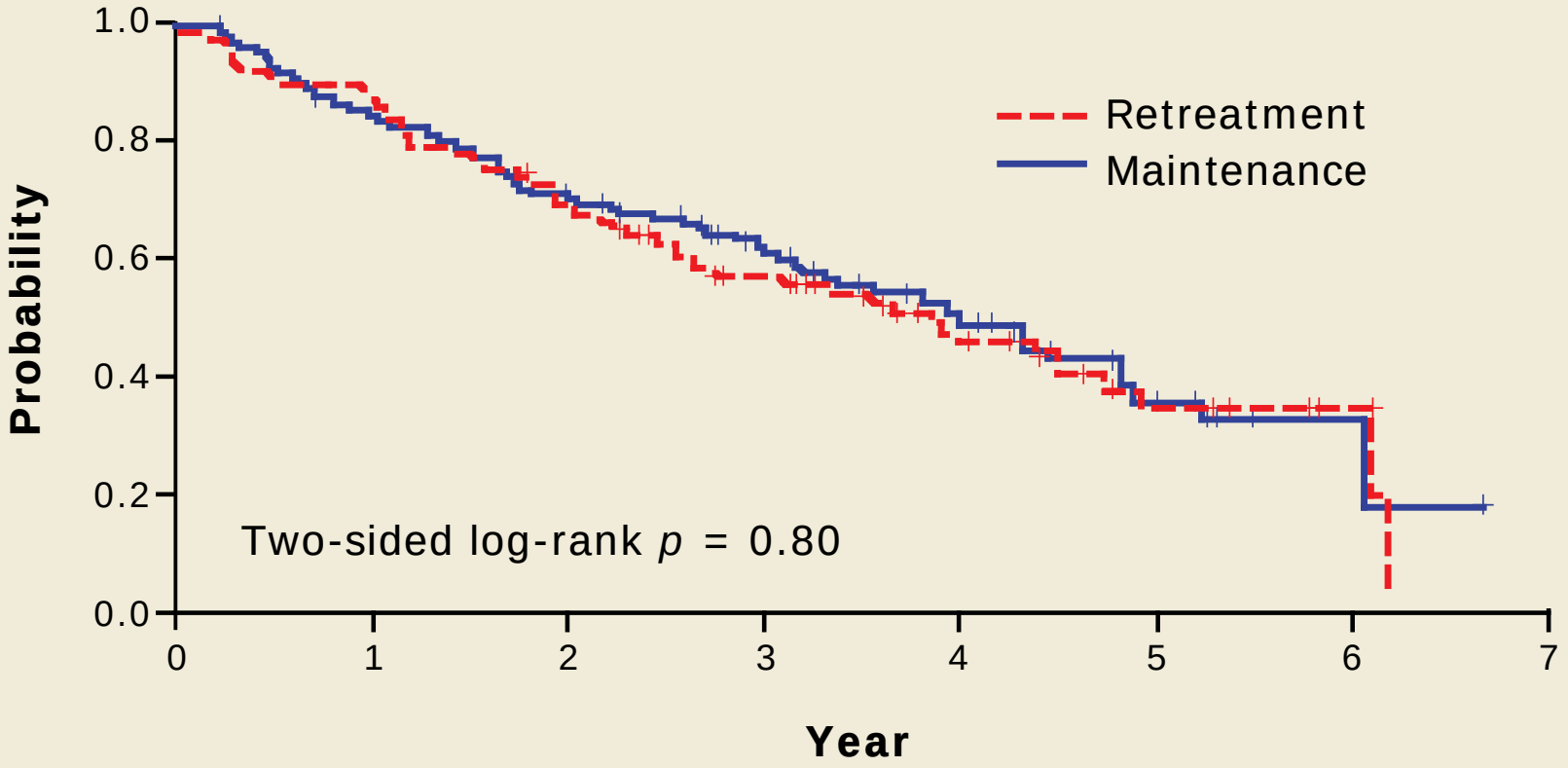


Primary Endpoint: Time to treatment failure (TTTF)

Secondary Endpoints: Time to first cytotoxic therapy (TTCT), quality of life (QOL) and safety

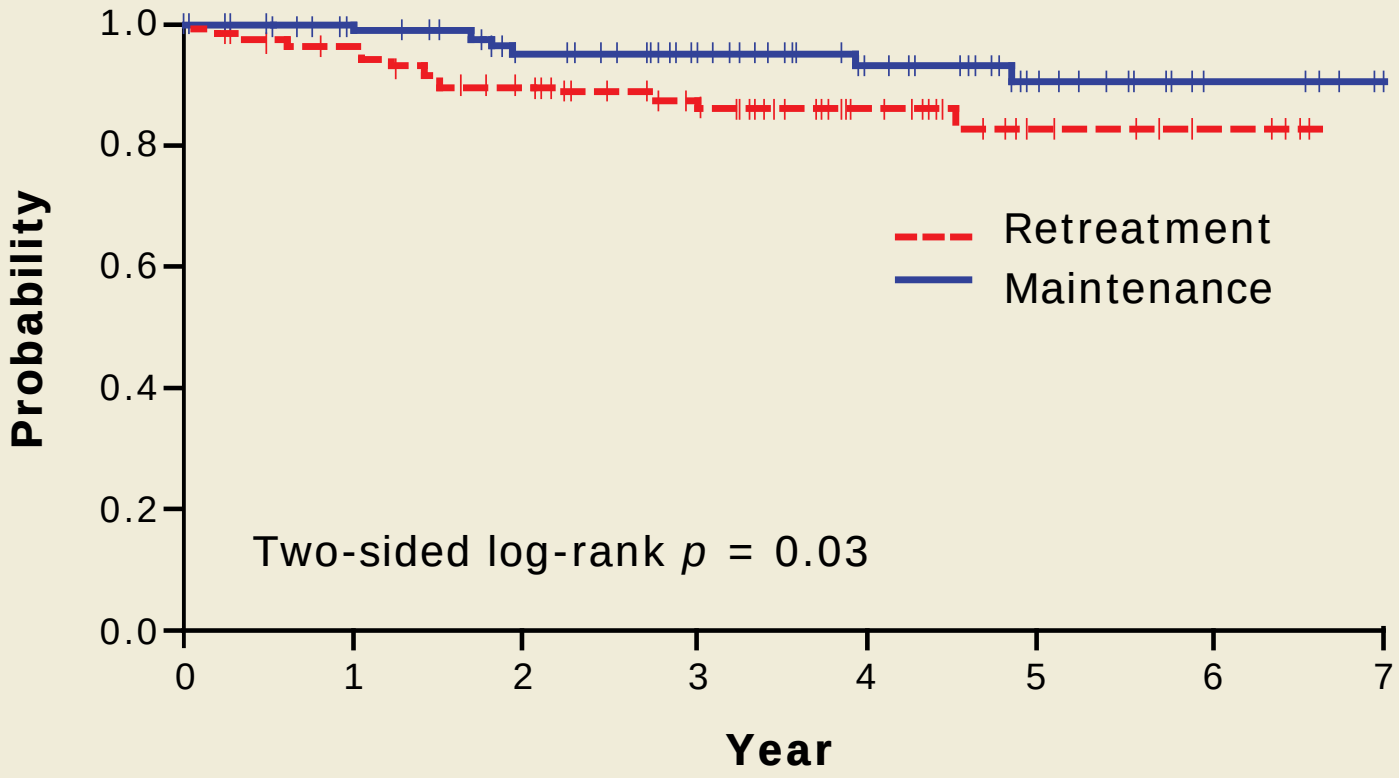
Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Time to Treatment Failure



With permission from Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Time to First Cytotoxic Therapy



With permission from Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Select Adverse Events (AE)

Grade 3/4 AE	RR	MR
Neutrophils	2	—
Fever w/o neutropenia	—	1
Infection	—	1
Fatigue	1	3
LV dysfunction	—	1
Hypertension	1	1

Other adverse events included secondary malignancies, n = 9, 7; progressive multifocal leukoencephalopathy, n = 0, 1; deaths, n = 10, 12

Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Author Conclusions

- In previously untreated, low tumor burden FL, RR was as effective as MR for time to treatment failure.
- The TTCT was delayed in both arms compared to conventional controls. MR was superior to RR for TTCT but is 3.5 times more costly.
- No benefit in QOL or anxiety with MR at 12 months (data not shown).
- These data suggest that RR produces outcomes comparable to MR and may be a recommended strategy for this patient population.

Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Investigator Commentary: RESORT Trial — Rituximab Maintenance versus Re-treatment Upon Disease Progression in FL

The major finding in the RESORT trial was that patients with low tumor burden FL fare just as well if you put them on rituximab maintenance as if you re-treat the disease when it comes back. The delay to chemotherapy was a little longer in the group that received rituximab maintenance. This was at the cost of a lot more rituximab, a much bigger expense and the concern of administering a drug that potentially has side effects. If I decide to administer rituximab alone I do it for 4 weeks.

Interview with Stephanie A Gregory, MD, January 11, 2012

I don't take a totally negative view of the study. Some elderly patients could be treated with 4 doses of rituximab without the need for chemotherapy. I've always used the "watch and wait" strategy, but now, based on the RESORT data, I may move away from that approach. Since ASH I've administered rituximab to a patient who could have been monitored. I use the SAKK regimen, with 8 total doses of rituximab. I would administer 4 weekly doses and then 1 dose every 2 months times 4.

Interview with Craig Moskowitz, MD, January 11, 2012

Brief Chemoimmunotherapy R-FND with Rituximab Consolidation Followed by Randomization between Rituximab Maintenance vs Observation as First Line Treatment in Elderly Patients with Advanced Follicular Lymphoma (FL): Final Results of a Prospective Randomized Trial by Italian Lymphoma Foundation (FIL)

Vitolo U et al.

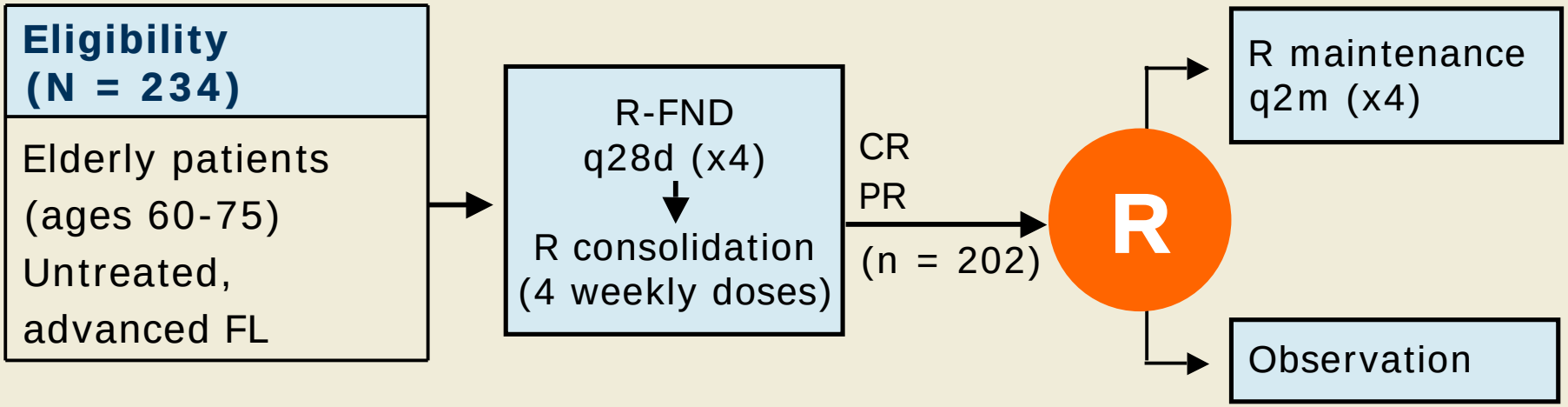
Proc ASH 2011;Abstract 777.

Background

- Management of FL in elderly patients is challenging, and the efficacy and safety of standard regimens in this group of patients is unclear.
- Rituximab maintenance was shown to improve the survival of patients with FL (*J Natl Cancer Inst* 2009;101:248).
- **Current Study Aim:** To determine the efficacy and safety of rituximab maintenance versus observation in elderly patients who respond to brief chemoimmunotherapy with 4 courses of R-FND and 4 doses of rituximab as consolidation.

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Study Schema



R-FND = rituximab, fludarabine, mitoxantrone, dexamethasone

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Baseline Characteristics (Abstract Only)

Characteristic	
Median age	66 yrs
Stage of disease • Stage II • Stage III • Stage IV	 14% 21% 65%
Bone marrow involvement	55%
FLIPI score • Low • Intermediate • High	 11% 34% 55%

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Response to Therapy (Abstract Only)

After R-FND + R consolidation	(n = 202)	*p*-value
Overall response rate	86%	
Two-year overall survival	93%	NR
Two-year progression-free survival (PFS)	77%	
Two-year PFS after R maintenance/observation		
R maintenance	80%	0.225
Observation	68%	
Two-year PFS by FLIPI score		
Low/intermediate risk	87%	<0.0001
High risk	70%	

Median follow-up = 33 mo
NR = not reported; NS = not statistically significant

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Adverse Events (AEs) (Abstract Only)

During rituximab maintenance/observation phase	
AEs (Grade 3/4)	**n**
Neutropenia	15
Cardiac events	8
Infections	4
Secondary malignancies	11

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Author Conclusions

- Elderly patients with follicular lymphoma, including those with high-risk FLIPI scores, treated with short-term R-FND and rituximab consolidation can achieve a high CR rate and favorable 2-year PFS.
- Patients receiving R maintenance achieved a promising 2-year PFS of 80%, although there was no statistically significant difference compared to observation.
  - This finding may be due to short follow-up or to the short course of rituximab maintenance or both.

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Investigator Commentary: Brief R-FND with Rituximab Consolidation Followed by Rituximab Maintenance versus Observation as First-Line Therapy for Elderly Patients with FL

This study reported no difference between rituximab maintenance and observation. The authors suggest this could be due to the short follow-up or to the short course of rituximab maintenance.

Only 4 doses of R maintenance were administered — 1 dose every 2 months — instead of continuing for 2 years. The results from this study amount to an outlier and do not fit with data from other studies.

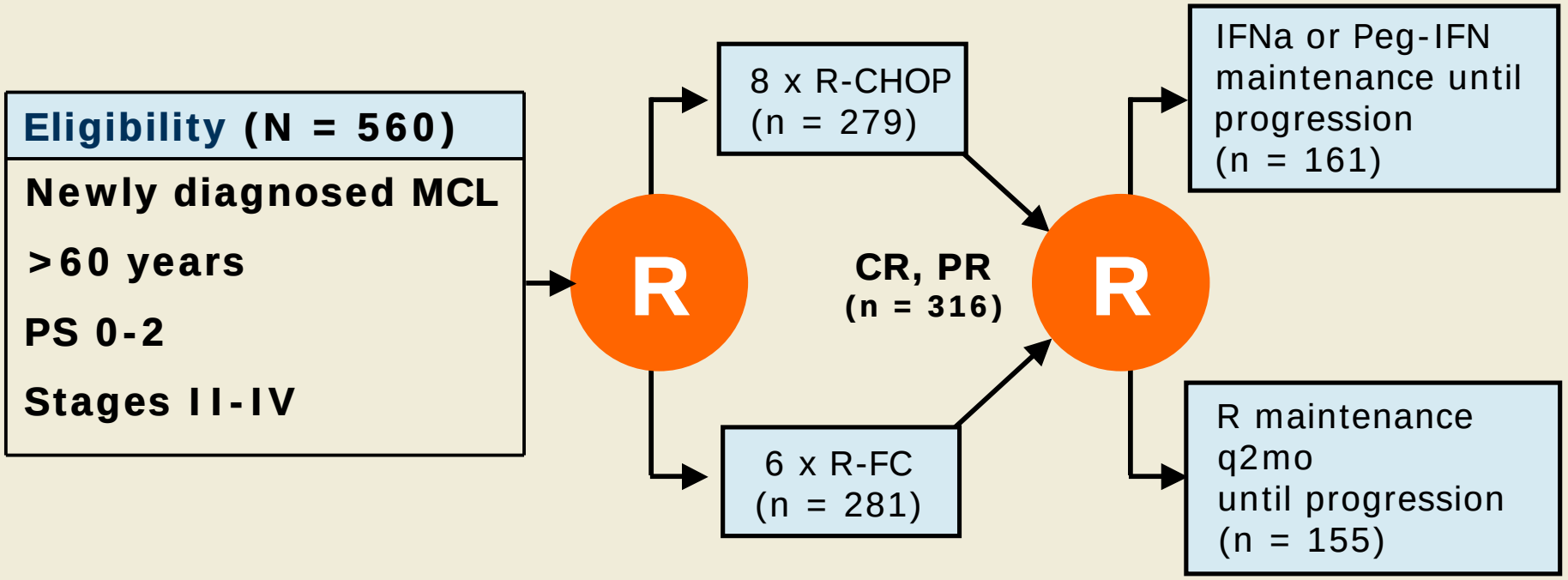
Interview with Stephanie A Gregory, MD, January 11, 2012

R-CHOP vs R-FC Followed by Maintenance with Rituximab vs Interferon-Alfa in Elderly Patients with Mantle Cell Lymphoma

Kluin-Nelemans HC et al.

Proc ASH 2011;Abstract 439.

Study Schema



R = rituximab; CR = complete response; PR = partial response

Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

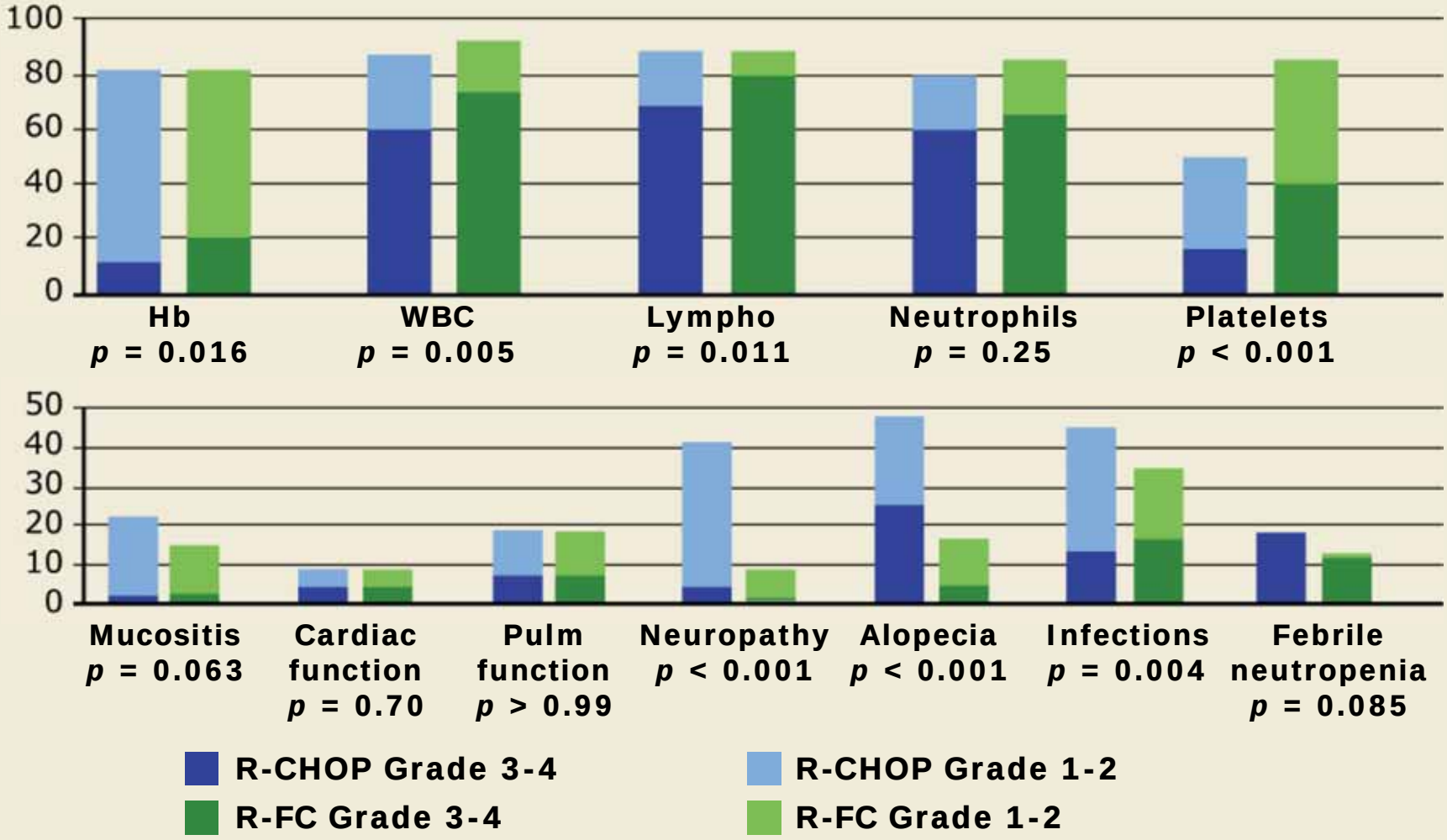
Efficacy of R-CHOP vs R-FC Induction

	R-CHOP (n = 232)	R-FC (n = 243)	*p*-value
Overall response rate	87%	78%	0.0508
CR/CRu	50%	53%	
PR	37%	25%	
PD	5%	14%	
Median time to treatment failure	28 mo	26 mo	0.52
Median overall survival	77 mo	43 mo	0.0023

Median follow-up 36 months

Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

R-CHOP vs R-FC Toxicity



With permission from Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

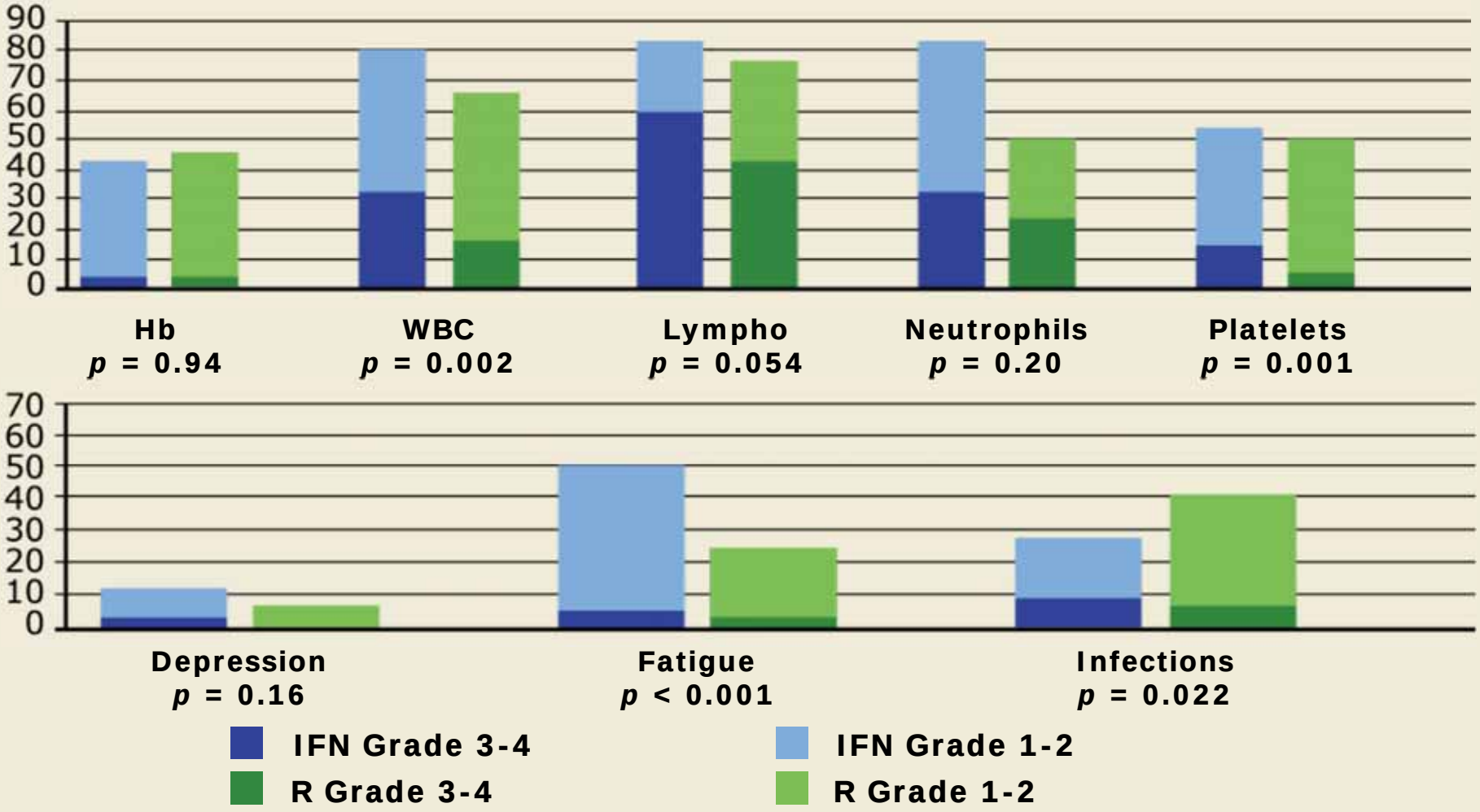
Efficacy of Rituximab vs IFN Maintenance

	Rituximab maintenance (n = 139)	IFN maintenance (n = 128)	Hazard ratio	*p*-value
Remission duration	77 mo	26 mo	0.54	0.0005
Four-year overall survival	77%	65%	—	0.15
Four-year overall survival related to induction regimen				
After R-CHOP	87%	61%	—	0.0058
After R-FC	70%	70%	—	0.5

Median follow-up 36 months

Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

Toxicity of IFN and Rituximab



With permission from Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

Author Conclusions

- Induction therapy with R-CHOP versus R-FC favors R-CHOP with more overall responses and less toxicity.
- Rituximab maintenance doubles the remission duration in patients responding to initial therapy.
- Patients pretreated with R-CHOP and maintained on rituximab have a 4-year overall survival of 87%.
- Long-term rituximab has low toxicity.
- R-CHOP followed by maintenance rituximab should become the gold standard to which new induction regimens are compared.

Kluin-Nelemans HC et al. *Proc ASH* 2011;Abstract 439.

Investigator Commentary: R-CHOP versus R-FC Followed by Maintenance with Rituximab versus IFN in Elderly Patients with Mantle-Cell Lymphoma (MCL)

Treatment of MCL in elderly patients is a challenge. This study reported that R-CHOP followed by rituximab maintenance is much better than R-FC followed by maintenance with rituximab or IFN. This was an older study — IFN is not being used any more.

R-CHOP followed by rituximab maintenance should be the treatment approach for elderly patients with MCL. For older patients with MCL who do not receive transplants, I do administer rituximab maintenance.

Interview with Stephanie A Gregory, MD, January 11, 2012

Rituximab Maintenance in Patients with Chronic Lymphocytic Leukemia (CLL) After Upfront Treatment with Rituximab plus Fludarabine, Cyclophosphamide, and Mitoxantrone (R-FCM): Final Results of a Multicenter Phase II Trial on Behalf of the Spanish CLL Study Group (GELLC)

Bosch F et al.

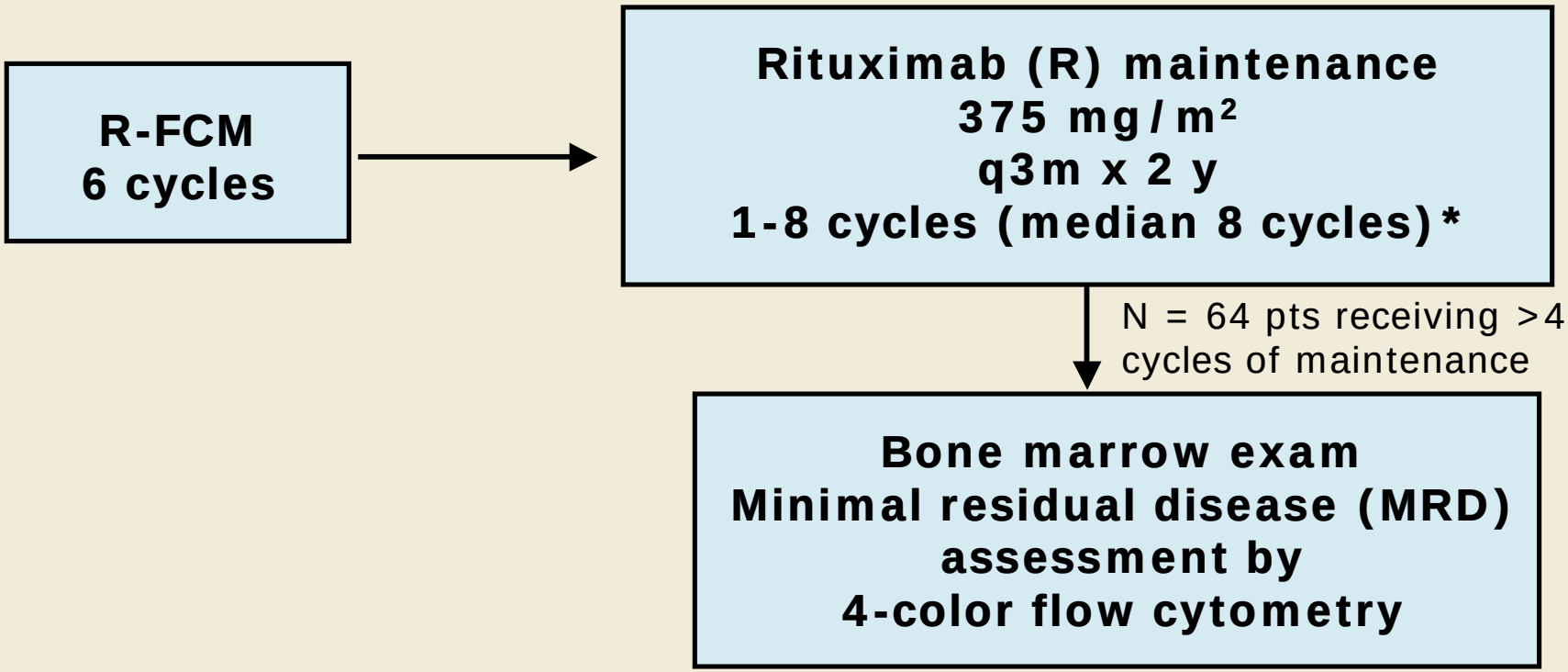
Proc ASH 2011;Abstract 293.

Background

- Rituximab, a chimeric antibody against CD20, has been shown to improve clinical outcome in patients with B-cell CLL when used as consolidation and maintenance therapy (*Cancer* 2008;112:119).
- The effectiveness of rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) in the treatment of CLL has been studied in a Phase II trial with 2 treatment phases, induction and maintenance (*JCO* 2009;27:4578).
- This study, the second part of the Phase II trial, investigates the effects of rituximab maintenance in patients who achieved a CR or PR after R-FCM treatment.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Study Schema



* 76% of patients completed entire planned treatment.
Treatment was considered to have failed in patients who received ≤4 cycles of R due to toxicity.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Adverse Events (Abstract Only)

Adverse event (AE)	%
Neutropenia (% of cycles)	31.3%
Thrombocytopenia (% of cycles)	4.6%
Anemia (% of cycles)	1.2%
AE after R maintenance	
Low Ig levels (% of patients) • Low IgA • Low IgG • Low IgM	 45% 37% 66%
Infectious episodes (% of cycles) • With Grade 3/4 neutropenia • With Grade 1/2 neutropenia	 19.5% 3%
Deaths (% of patients)	3%*

* Two deaths, 1 due to multifocal leukoencephalopathy, 1 due to hemophagocytic syndrome

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Response to R Maintenance (Abstract Only)

Response to R maintenance					
		CR MRD(-)	CR MRD(+)*	PR	Failure
Response to R-FCM (N = 64)	CR MRD(-) (n = 35)	22 (34.4%)	9 (14.1%)	—	4 (6.3%)
	CR MRD(+) (n = 21)	2 (3.1%)	15 (23.4%)	2 (3.1%)	2 (3.1%)
	PR (n = 8)	2 (3.1%)	2 (3.1%)	3 (4.7%)	1 (1.6%)

* Median time to conversion from MRD(-) to MRD(+) after R maintenance vs after R-FCM: 45.4 mo vs 16.4 mo (p = 0.011)

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Time to Next Treatment (Abstract Only)

Response	Time to next treatment	*p*-value
CR MRD(+) after R-FCM	44.1 mo	0.049
CR MRD(+) after R maintenance	54.5 mo	
PR after R-FCM	6.5 mo	0.001
PR after R maintenance	54.4 mo	

Three-year progression-free survival = 94%

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Author Conclusions

- Rituximab maintenance after R-FCM in patients with CLL is feasible and might improve outcome, particularly for patients who do not attain a MRD(-) CR after initial up-front therapy.
- Toxicity in patients receiving R maintenance is not negligible.
- Ongoing studies should clarify the role of R maintenance in the management of CLL.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

Investigator Commentary: Rituximab Maintenance in Patients with CLL After Up-Front Treatment with R-FCM

This study suggests that the addition of R maintanence to R-FCM induction therapy results in an improvement in progression-free survival. Use of this regimen has not caught on in the United States. Studies are evaluating alternate maintenance therapies such as lenalidomide. Rituximab does not work as well in CLL as it does in follicular lymphoma because of the lower expression of CD20.

Interview with Stephanie A Gregory, MD, January 11, 2012

These data are preliminary and not compelling. The study endpoint, minimal residual disease (MRD), was a purely surrogate endpoint. The data are hypothesis generating, and a group of patients may exist for whom getting to MRD negativity is important. No profound clinical benefit was demonstrated, and more toxicity occurred than would be expected. I do not believe that R maintenance should be considered in CLL.

Interview with Jonathan W Friedberg, MD, MMSc, January 11, 2012

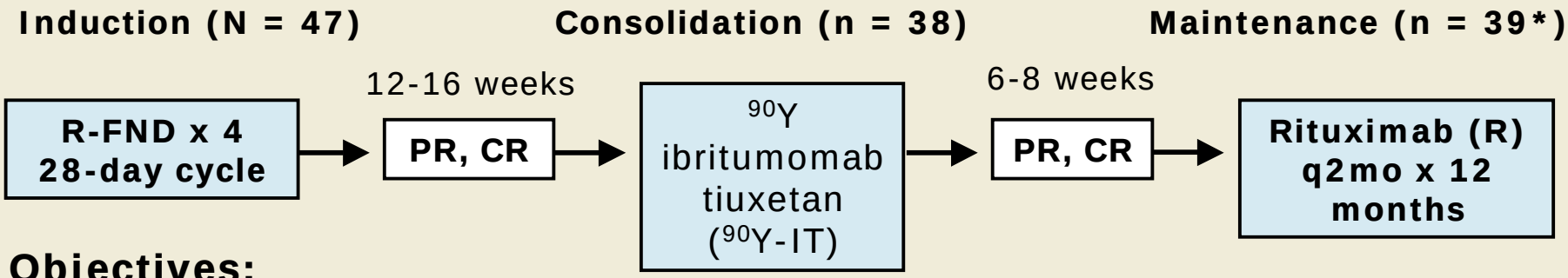
Phase II Study with R-FND Followed by 90-Y Ibritumomab Tiuxetan Radioimmunotherapy and Rituximab Maintenance for Untreated High-Risk Follicular Lymphoma

Fowler NH et al.

Proc ASH 2011;Abstract 99.

Study Schema

Eligibility
Untreated Stage III-IV FL, Grades 1-3
High-risk FLIPI score (≥3)
Performance score ≤2
Adequate renal, hepatic, hematologic function
No evidence of active infection



Objectives:

Primary: Progression-free survival

Secondary: Overall survival, response, safety, molecular response

* Two patients did not receive ^{90}Y-IT but received R maintenance.

Fowler NH et al. *Proc ASH* 2011;Abstract 99.

Response Following Treatment (Intent-to-Treat Analysis N = 47)

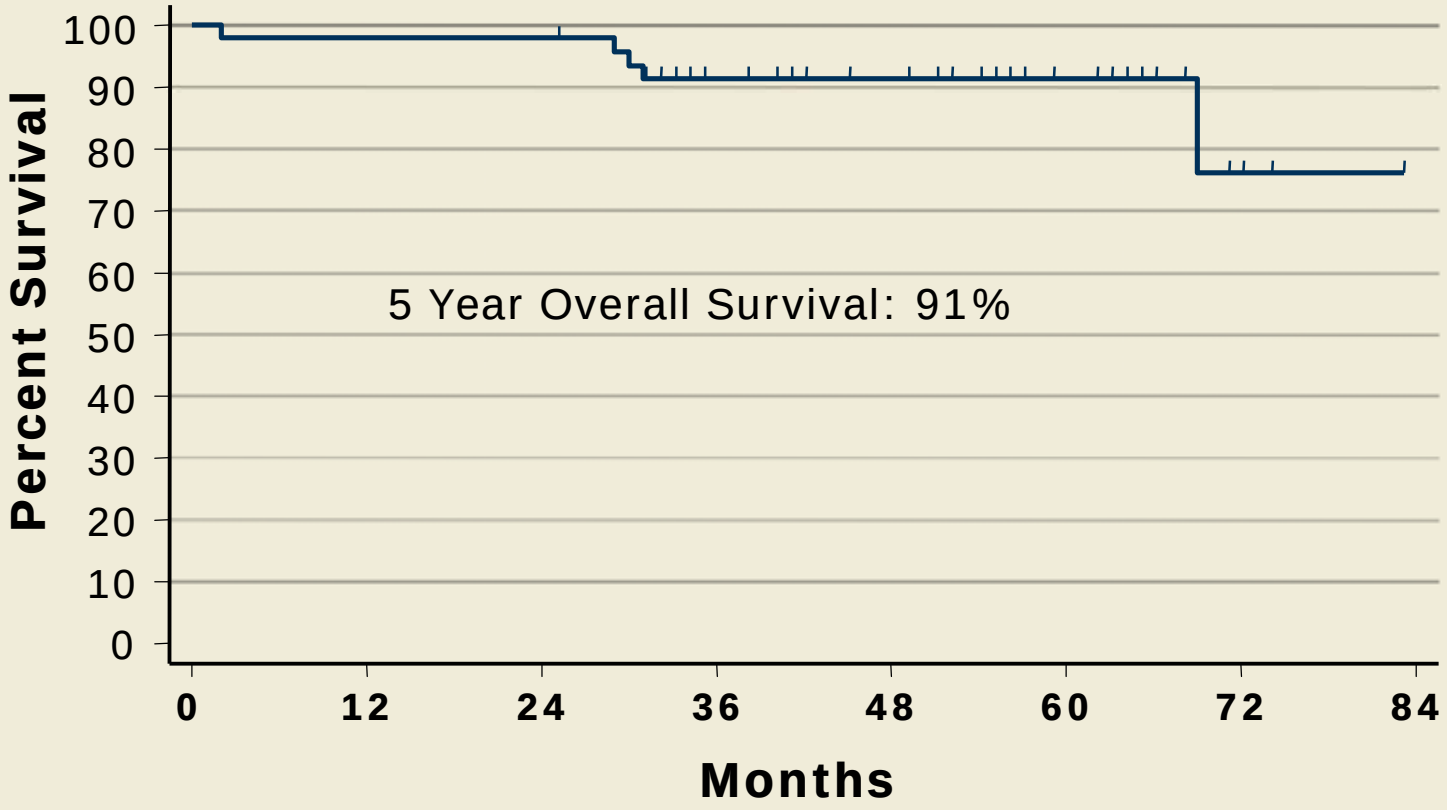
Response	R-FND induction	^{90}Y-IT consolidation	R maintenance
Treated N (%)	47 (100)	38 (81)	39 (83)*
ORR	46 (98)	45 (95)	41 (87)
PD	0	1 (2)	5 (11)†
Not evaluable	1 (death)	1	1

- 3 out of 6 patients converted from PR to CR following ^{90}Y-IT consolidation.
- Complete response rate in patients receiving ^{90}Y-IT consolidation: 95%

* Two patients did not receive ^{90}Y-IT but received R maintenance.
† One patient with PD refused R maintenance.

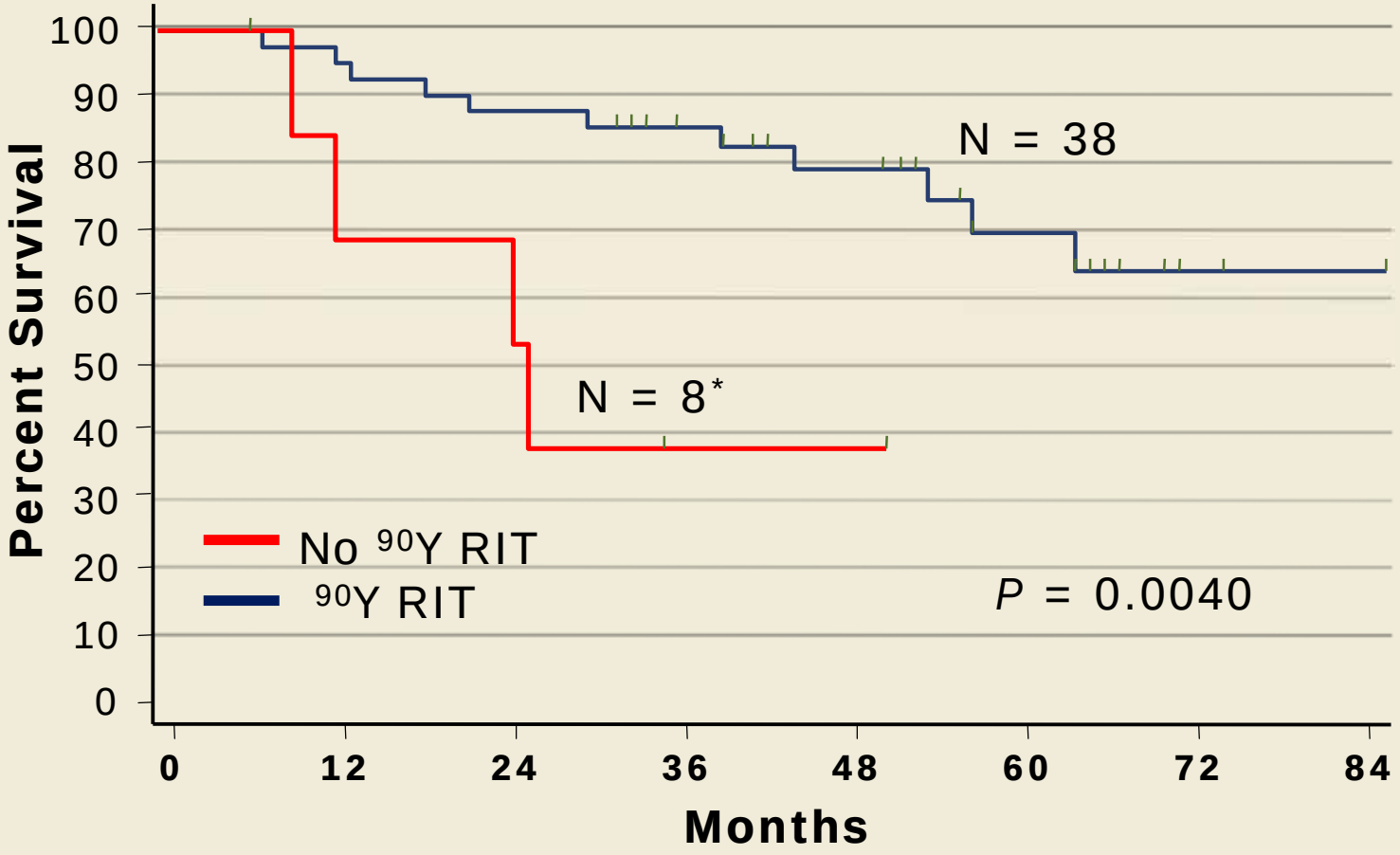
Fowler NH et al. *Proc ASH* 2011;Abstract 99.

Overall Survival



With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

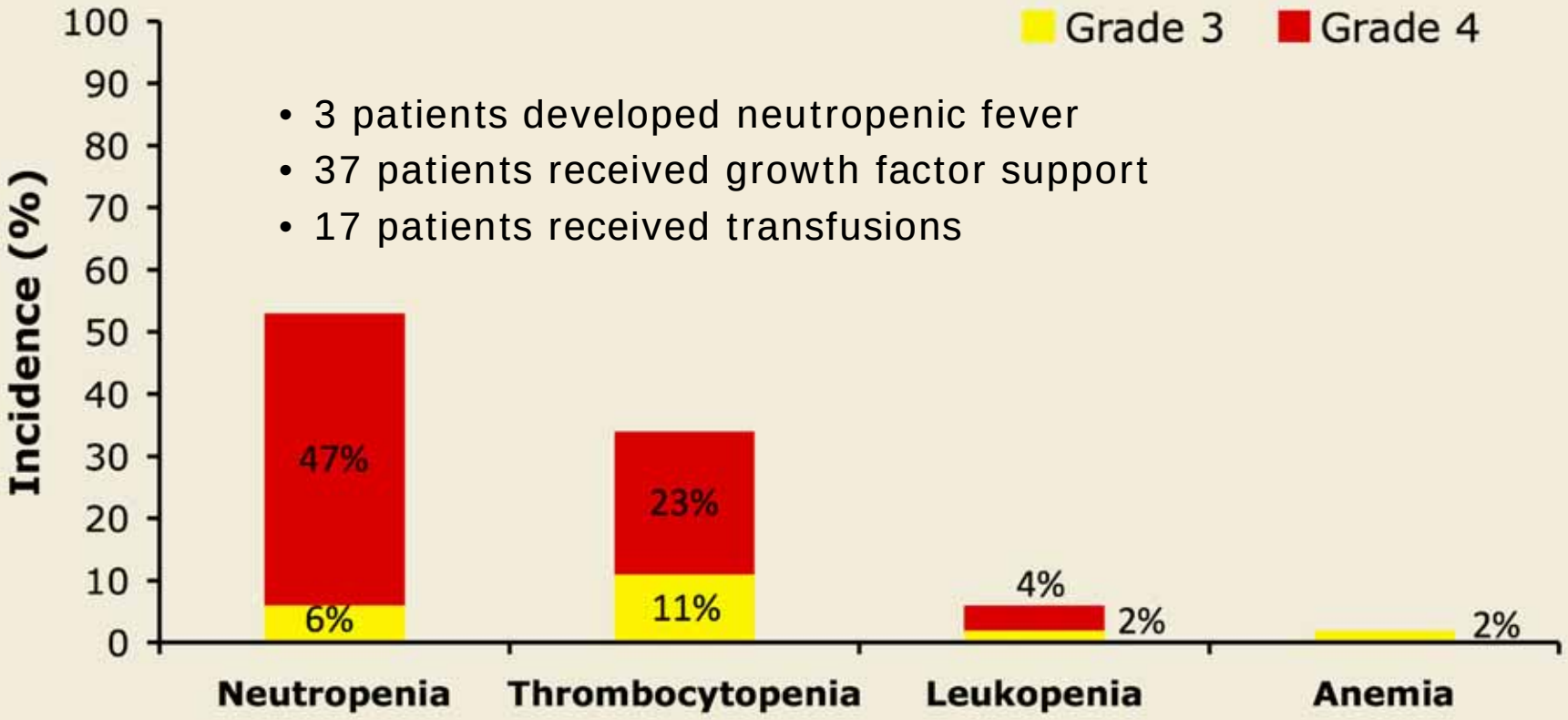
Failure-Free Survival (FFS) with Radioimmunotherapy



* One patient excluded due to unrelated death during cycle 1

With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

Grade 3 or 4 Hematologic Toxicity and Secondary Malignancies



Secondary malignancies: MDS (3, 1 case in patient who did not receive 90Y-RIT), breast (1), DCIS (1), papillary thyroid (1)

With permission from Fowler NH et al. *Proc ASH* 2011;Abstract 99.

Author Conclusions

- R-FND followed by ^{90}Y ibritumomab tiuxetan and rituximab maintenance results in high OS and FFS in high-risk FLIPI patients.
- High levels of molecular response were observed with the combination (data not shown).
- Although there are notable toxicities (eg, MDS), the benefits of this combination are substantial in this high-risk subset of patients.

Fowler NH et al. *Proc ASH* 2011;Abstract 99.

Investigator Commentary: R-FND Followed by Radioimmunotherapy and R Maintenance

This is one of the first studies that evaluated rituximab/chemotherapy followed by radioimmunotherapy (RIT) and rituximab maintenance. We need larger studies to evaluate rituximab/chemotherapy followed by RIT consolidation and rituximab maintenance, or a trial of rituximab/chemotherapy randomly assigning patients to either RIT or rituximab maintenance.

The high incidence of MDS was surprising. Another group at ASH showed that RIT increases the risk of transformation to a more aggressive lymphoma in patients with follicular lymphoma treated with a fludarabine regimen. I conducted a small Phase II trial of 20 patients who received R-FND, then RIT consolidation and R maintenance and have 3 cases of MDS. We have to be careful about fludarabine and RIT. There is a worry, but it's not significant enough to stop one from administering RIT. I like to point out Mark Kaminski's data with front-line treatment with RIT in 76 patients with follicular lymphoma. He has had 1 case of MDS, and the study is now in its eighth year of follow-up.

Interview with Stephanie A Gregory, MD, January 11, 2012