5 Minute Journal Club

Key ASH Presentations

Issue 2, 2011

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CME Information

LEARNING OBJECTIVES

- Counsel patients with asymptomatic nonbulky follicular lymphoma about the benefits and risks of observation versus immediate initiation of rituximab.
- Recall the activity and safety of lenalidomide combined with rituximab in the treatment of relapsed or refractory CLL.
- Describe the impact of lenalidomide consolidation on quality of CLL response following induction chemoimmunotherapy.
- Educate patients receiving fludarabine-based induction therapy, with or without cyclophosphamide, about the risk of secondary myeloid neoplasia.
- Consider long-term safety events in the selection of initial treatment for CLL.
- Describe the emerging body of evidence with the combination of bortezomib and rituximab in follicular lymphoma.
- Compare and contrast the incremental benefit of bortezomib when added to rituximab for patients with relapsed follicular lymphoma who have high- versus low-risk disease.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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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:

Bruce D Cheson, MD
Professor of Medicine; Head of Hematology; Director of Hematology Research
Georgetown University Hospital, Lombardi Comprehensive Cancer Center
Washington, DC

Advisory Committee: Allos Therapeutics, Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium — The Takeda Oncology Company; *Consulting Agreement:* Millennium — The Takeda Oncology Company.

An Intergroup Randomised Trial of Rituximab versus a Watch & Wait Approach in Patients with Advanced Stage, Asymptomatic, Non-bulky Follicular Lymphoma

Ardeshna KM et al.

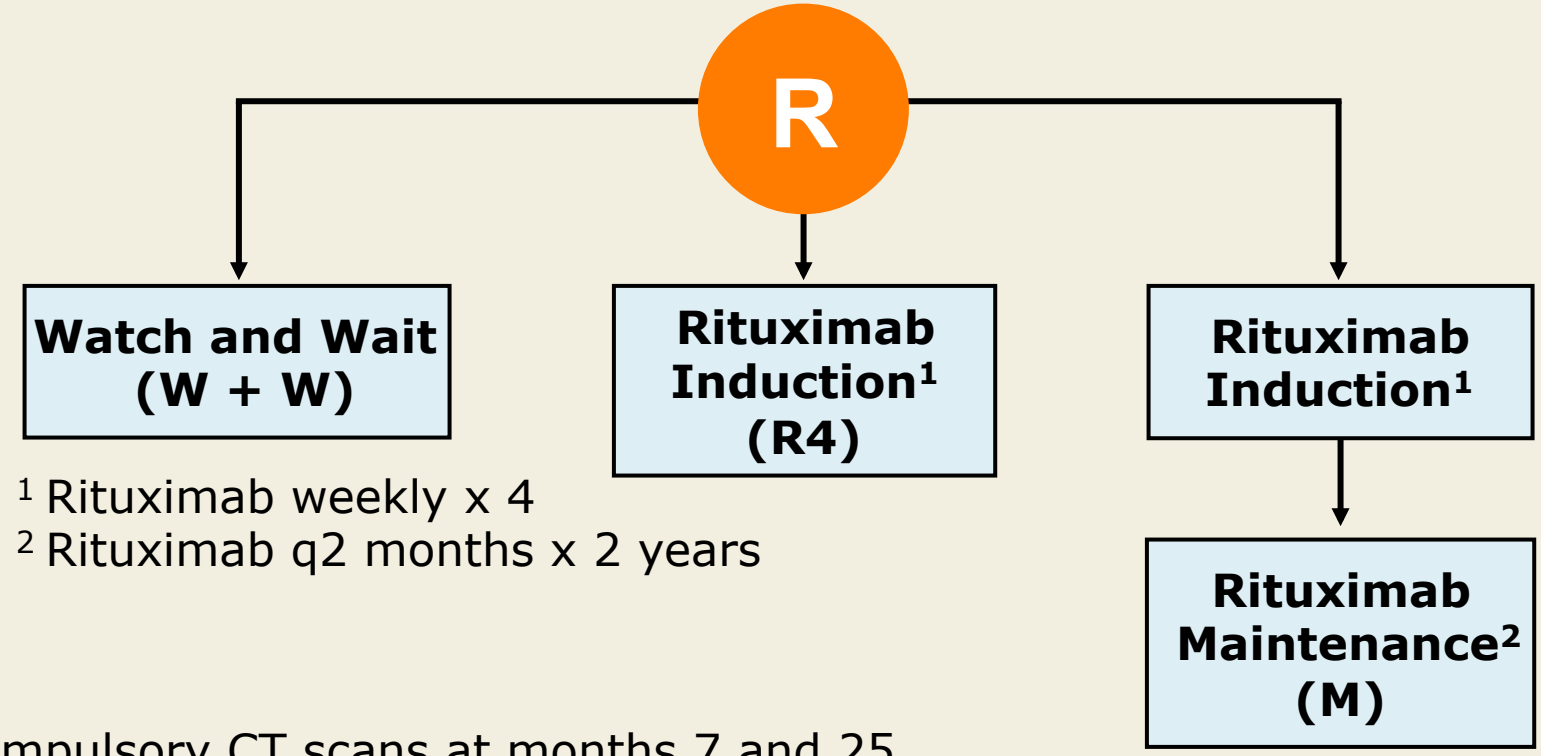
Proc ASH 2010;Abstract 6.

Eligibility

- Follicular lymphoma Grade 1, 2, 3a
- Stage II, III, IV
- Asymptomatic (no B symptoms or pruritus)
- Entry within 3 months of biopsy with no prior therapy
- Low tumor burden
  - Normal LDH
  - Largest nodal or extranodal mass <7 cm
  - No more than 3 nodal sites with diameter >3 cm
  - Spleen enlargement ≤16 cm by CT
  - Hb >10 g/dL, neutrophils >5 x 10^9/L, platelets >100 x 10^9/L
  - No significant serous effusions by CT
  - Less than 5 x 10^9/L circulating tumor cells

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

Study Schema



[1] Rituximab weekly x 4
[2] Rituximab q2 months x 2 years

Compulsory CT scans at months 7 and 25

CT scans at month 13 only if clinical CR

Bone marrow evaluation for histology and MRD only if CT shows CR at months 7, 13 and 25

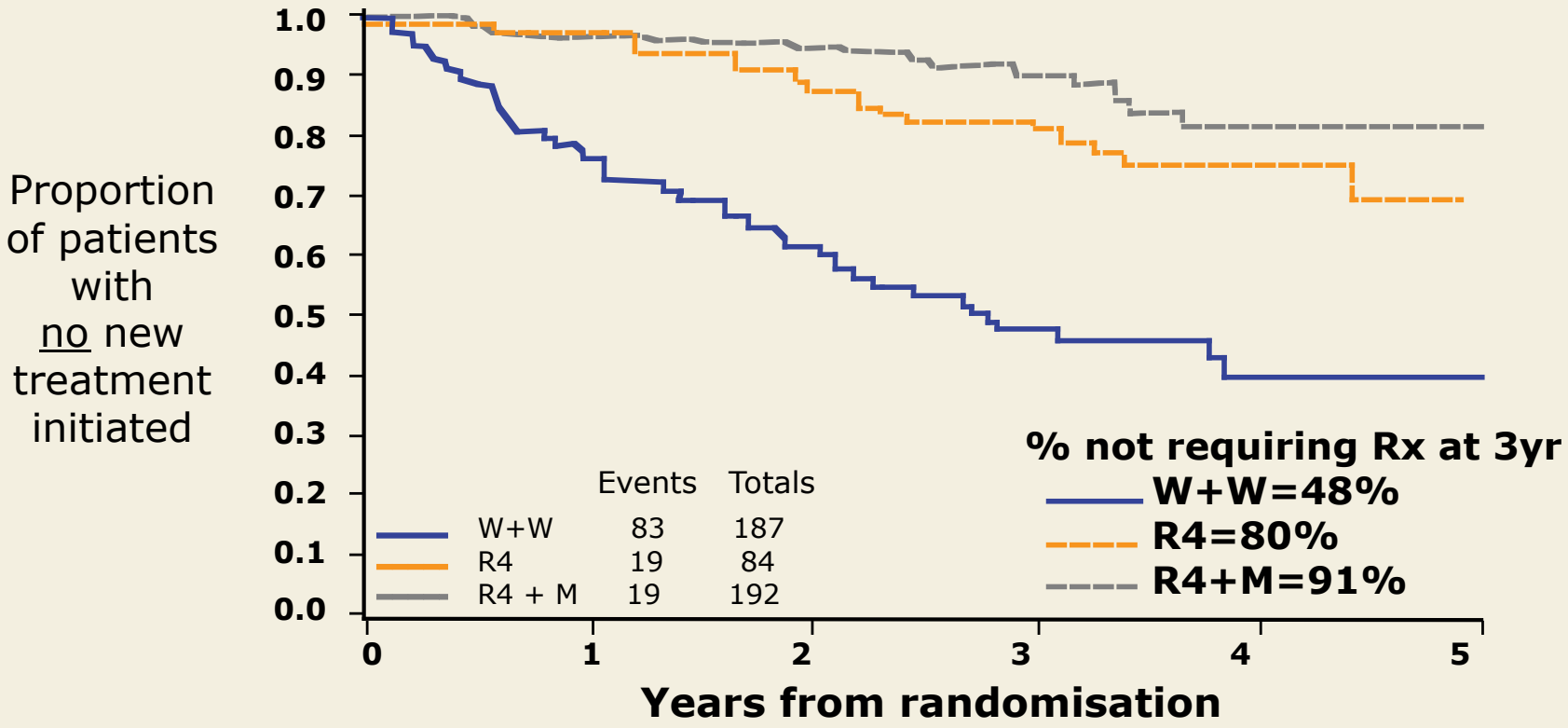
Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

Endpoints

- Primary
  - Time to initiation of new therapy (TTINT)
    - New therapy = chemotherapy or radiotherapy
- Secondary
  - Progression-free survival (PFS)
  - Overall survival
  - Response at 25 months
  - Frequency of spontaneous clinical remissions

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

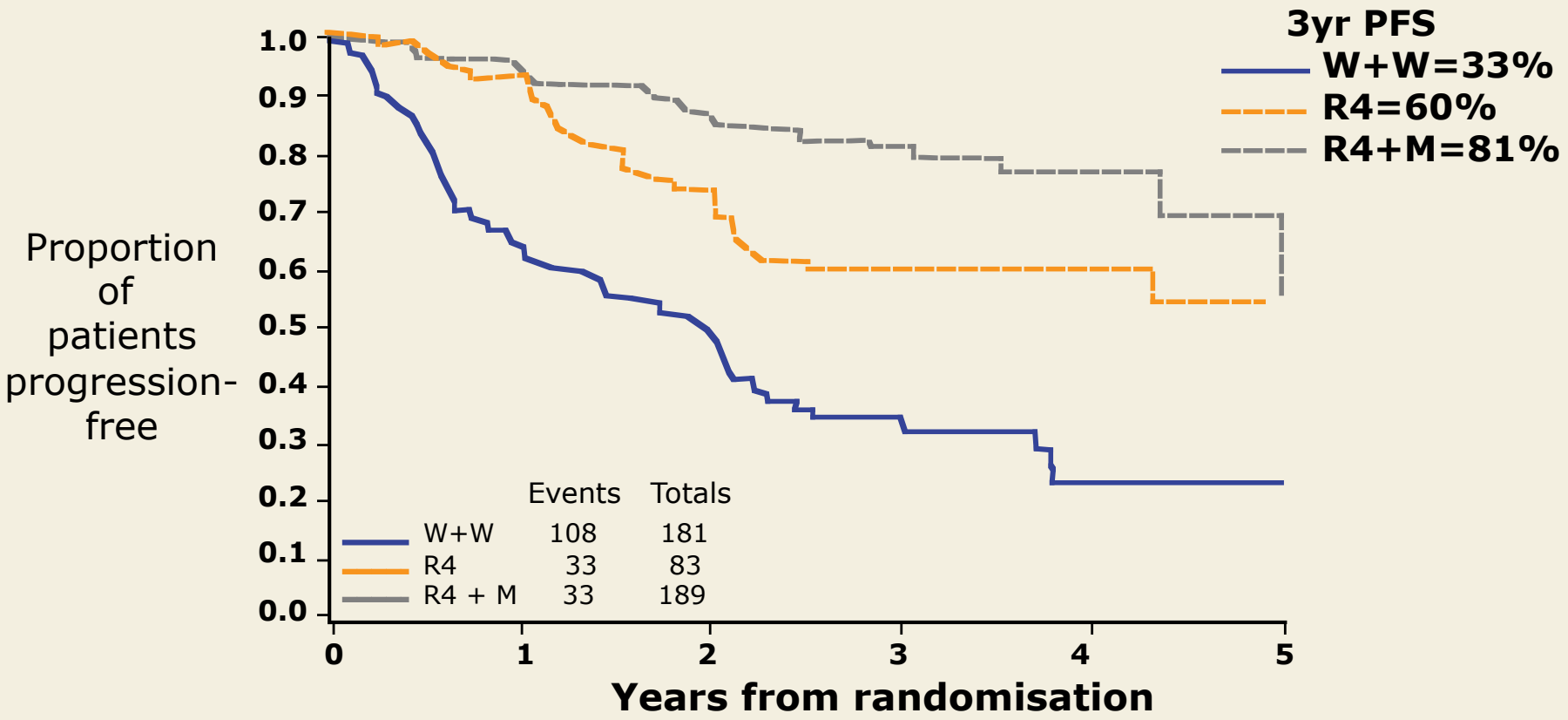
Time to Initiation of New Therapy



HR (R4 vs W+W) = 0.37, 95% CI = 0.25, 0.56, p <0.001
HR (R4 + M vs W+W) = 0.20, 95% CI = 0.13, 0.29, p <0.001
HR (R4 + M vs Rituximab) = 0.57, 95% CI = 0.29, 1.12, p =0.10

With permission from Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

Progression-Free Survival



HR (R4 vs W+W) = 0.46, 95% CI = 0.33, 0.65, p<0.001
HR (R4 + M vs W+W) = 0.21, 95% CI = 0.15, 0.29, p<0.001
HR (R4 + M vs Rituximab) = 0.43, 95% CI = 0.24, 0.72, p=0.001

With permission from Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

Conclusions

- Rituximab significantly improves TTINT and PFS in patients with asymptomatic FL when compared with watchful waiting.
- It is currently unclear if overall survival may be impacted by initial rituximab treatment of asymptomatic FL (data not shown).
- Need to determine the effect of prior rituximab on
  - Response to first new treatment
  - Response duration of first new treatment
  - Time to second new treatment

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

Investigator Commentary: Rituximab versus Watch and Wait for Stage II to IV, Asymptomatic, Nonbulky FL

The time to initiation of a new therapy and progression-free survival were significantly longer in the two rituximab-containing arms compared to observation alone. On the surface, it would suggest that this study provides support for early intervention with rituximab in this patient population. However, rituximab is associated with expense, inconvenience and possible side effects. Moreover, no data indicated that survival was prolonged by early intervention.

This is important because several trials suggest that if rituximab is used later, it might be just as effective as if it had been used earlier. So whether or not this early intervention will be beneficial in the long run remains to be seen, because we also don't know how patients will respond to their next line of treatment. In the patients observed with a watch-and-wait approach, the next line of treatment will be systemic treatment. In the other arm, the second line of treatment will be a second systemic therapy. We don't know how they will fare in the long run with this form of early intervention, and it should not be assumed that this is now the standard approach.

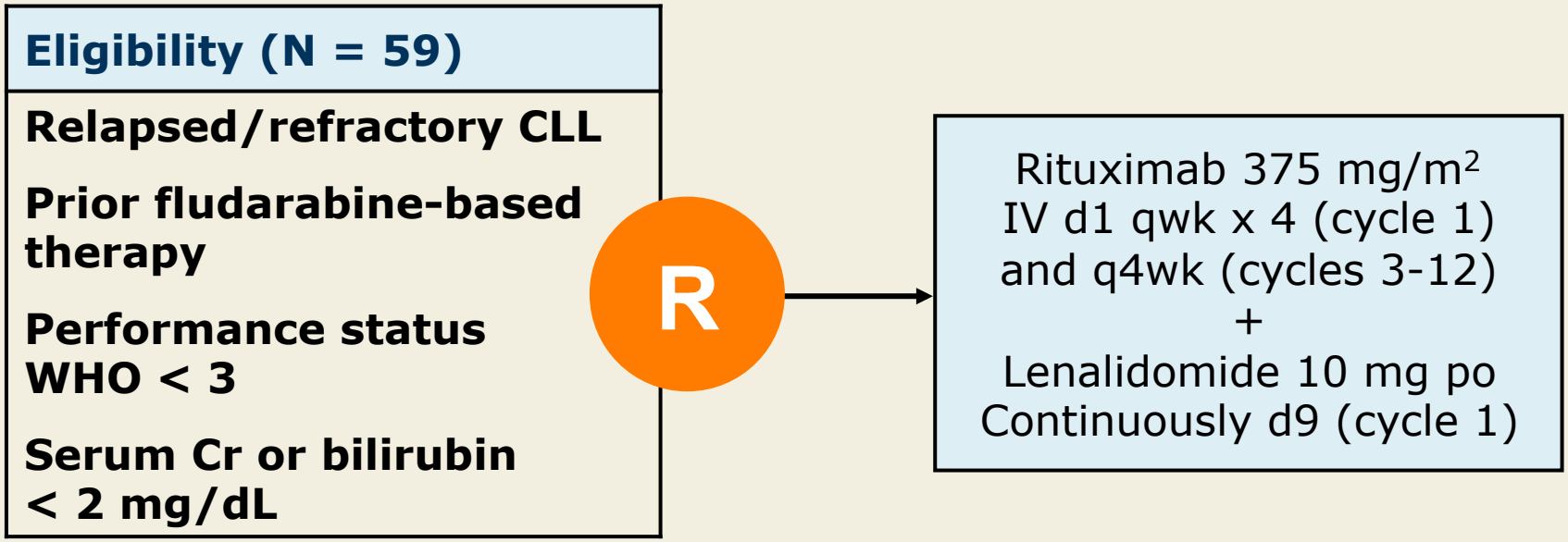
Interview with Bruce D Cheson, MD, December 23, 2010

The Combination of Lenalidomide and Rituximab Induces Complete and Partial Responses in Patients with Relapsed and Refractory Chronic Lymphocytic Leukemia (CLL)

Ferrajoli A et al.

Proc ASH 2010;Abstract 1395.

Phase II Study Schema



Allopurinol 300 mg qd x 1-2 weeks as tumor lysis prophylaxis. Cycles were 28 days.

Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

Efficacy and Adverse Events

All patients are evaluable for response and clinical outcome (N = 59)

Overall Response Rate (ORR)	Complete Response (CR)	CR with Incomplete Hematological Recovery (CRi)	Nodular Partial Remission (nPR)	Partial Response (PR)
64%	8%	5%	12%	39%

Neutropenia	Thrombocytopenia	Anemia	Infections
68%	22%	10%	31%

Grade 3 Tumor Lysis Syndrome	1.7%
Grade 1-2 Tumor Flare Reactions	37.3%

Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

Conclusions

- Lenalidomide/rituximab in relapsed or refractory CLL has promising response rates and appears to be better than single-agent lenalidomide (*Blood* 2008;111(11):5291; *J Clin Oncol* 2006;23(34):5343).

- The combination of lenalidomide and rituximab in relapsed-refractory CLL is well tolerated, with the most common toxicity being myelosuppression.

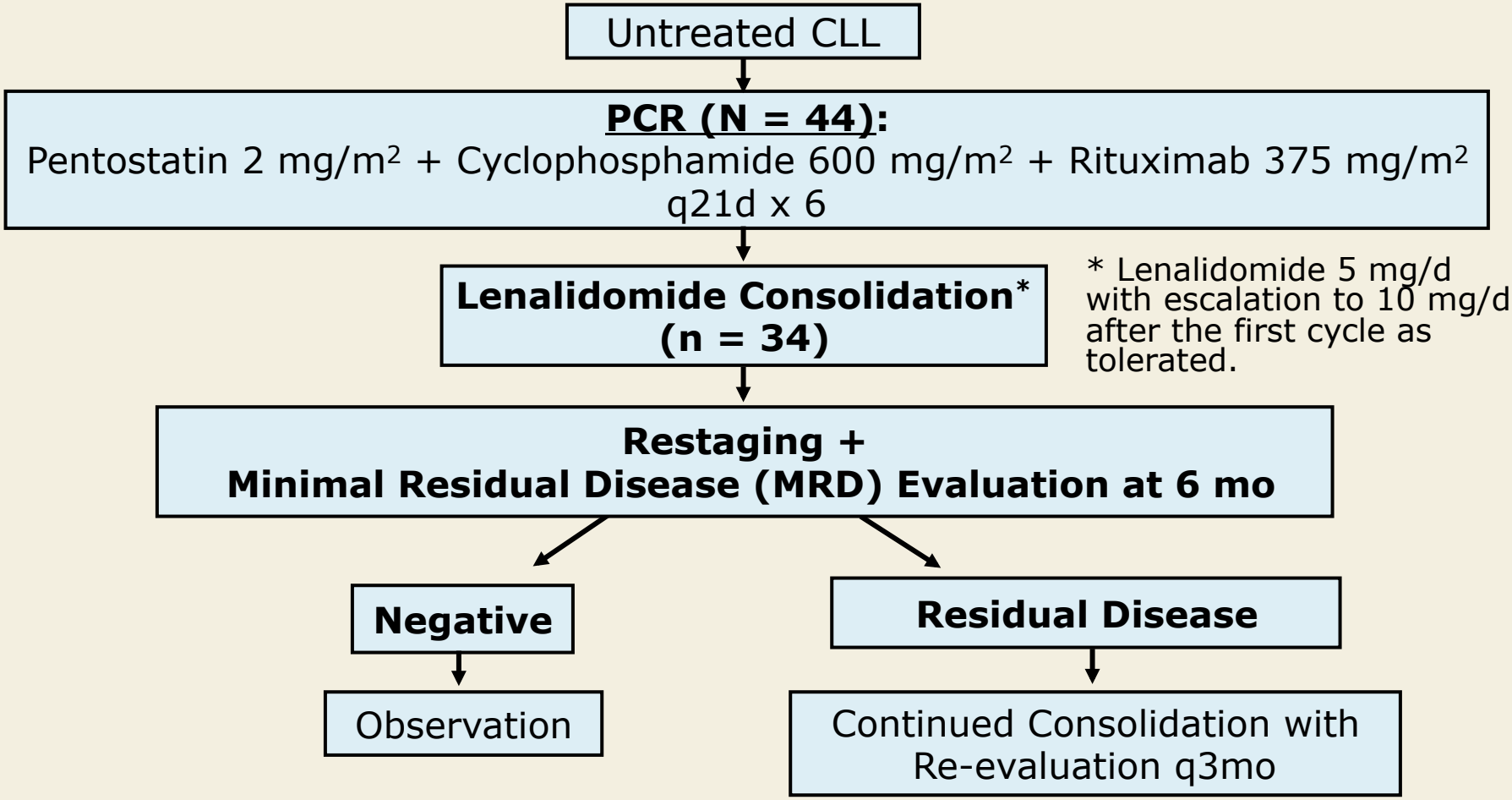
Ferrajoli A et al. *Proc ASH* 2010;Abstract 1395.

Lenalidomide Consolidation After First-Line Chemoimmunotherapy for Patients with Previously Untreated CLL

Shanafelt T et al.

Proc ASH 2010;Abstract 1379.

Study Schema



Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

Efficacy Results

PCR Induction (N = 44)

Overall Response Rate	95%
CR/CRi/CCR	38%
PR/nPR	57%

12 patients with CR/CRi underwent evaluation for MRD assessment after PCR induction

MRD-Negative, n (%)	7 (58%)

Lenalidomide Consolidation (n = 34)

Improvement in Quality of Response	21%
MRD+ to MRD-, n (%)	3 (8.8%)

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

Select Adverse Events with Lenalidomide Consolidation

Safety Evaluable (n = 34)

Adverse Event	Grade 3	Grade 4
Neutropenia	41%	21%
Thrombocytopenia	9%	0%
Rash	6%	0%

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

Conclusions

- Lenalidomide consolidation improves the quality of response in patients with CLL receiving first-line induction.
- Lenalidomide consolidation appears to be feasible with an acceptable adverse event profile.
- Longer follow-up is necessary in order to determine the clinical benefit with this strategy.

Shanafelt T et al. *Proc ASH* 2010;Abstract 1379.

Investigator Commentary: Evaluation of Lenalidomide in CLL

Lenalidomide is active in relapsed and refractory CLL, with response rates ranging from 30 to 45 percent. Some of the complications associated with lenalidomide in this context are unique, including tumor lysis syndrome and tumor flare response. Rituximab alone has modest activity in the relapsed setting. Nevertheless, it seems to make other drugs work better. So Ferrajoli and the MD Anderson group combined lenalidomide and rituximab in patients with relapsed and refractory CLL and demonstrated an overall response rate of 64 percent, including eight percent complete responses, which is better than might be expected from either drug alone. However, this should not be considered a standard regimen and further evaluation is warranted in both the relapsed and up-front settings.

Another way to consider using lenalidomide is as consolidation after chemoimmunotherapy in patients with previously untreated CLL. In the study by Shanafelt et al, patients received a pentostatin-based regimen (PCR) followed by lenalidomide consolidation. Only 7/34 patients experienced improvement in the quality of response, and a significant proportion of patients experienced at least Grade 3 hematologic toxicity.

Interview with Bruce D Cheson, MD, December 23, 2010

Increased Incidence of Therapy-Related Myeloid Neoplasia (t-MN) After Initial Therapy for CLL with Fludarabine-Cyclophosphamide (FC) vs Fludarabine (F): Long-Term Follow-Up of US Intergroup Study E2997

Smith MR et al.

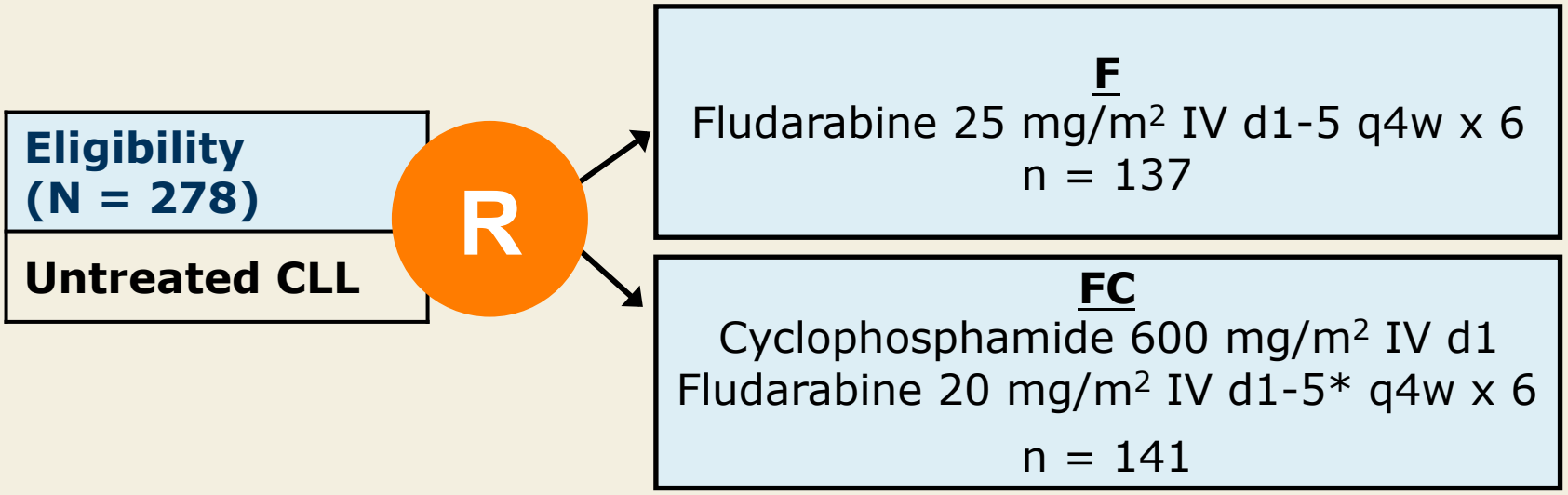
Proc ASH 2010;Abstract 924.

Background

- Therapy-related myeloid neoplasia (t-MN) is a serious, long-term consequence of conventional chemotherapy, such as alkylating agents, topoisomerase-II inhibitors, and antimetabolites.
- Combination fludarabine and cyclophosphamide, when compared to fludarabine alone, led to higher complete and overall response rates and longer progression-free survival in Phase III E2997 trial (*J Clin Oncol* 2007;25(7): 793).
- Combination therapy also caused more myelosuppression, which could lead to greater long-term effects on myeloid hematopoietic function, including t-MN.
- A follow-up of study E2997, examining the incidence of t-MN, is presented here.

Smith MR et al. *Proc ASH* 2010;Abstract 924.

Trial Schema



* Received filgrastim 5 mcg/kg and antiviral prophylaxis

- All patients received allopurinol (cycle 1) and PCP prophylaxis.
- All patients were assessed for t-MN by required reporting of these events.
- Baseline genetic and molecular features of CLL were available for 235 patients (122 on FC and 113 on F).

Smith MR et al. *Proc ASH* 2010;Abstract 924.

Patient Characteristics

Characteristic	Patients (N = 278)
Median follow-up	6.4 years
Cases of t-MN, n (%)	
Total	13 (4.7%)
After FC (N = 141)	9 (6.4%)
After F (N = 137)	4 (2.9%)
Rate of t-MN at 7 years	
After FC (N = 141)	8.2%
After F (N = 137)	4.6%
Median time from initial therapy to t-MN diagnosis	5 years

Smith MR et al. *Proc ASH* 2010;Abstract 924.

Characteristics of Patients with t-MN

Characteristics	FC (n = 9)	F (n = 4)
Additional therapy prior to t-MN		
No	7	1
Yes	2	3
IgV_H gene status		
Mutated	7	1
Unmutated	0	3
Data not available	2	0

Smith MR et al. *Proc ASH* 2010;Abstract 924.

Conclusions

- Higher incidence of t-MN was observed after combination therapy with FC than after single-agent F.
- t-MN after FC occurred most often without additional therapy and in IgV_H-mutated CLL, which is associated with a more favorable outcome.
- The increased incidence of t-MN after FC, usually in the absence of additional treatment, suggests that FC is more leukemogenic than F alone.
- This finding emphasizes a need for longer follow-up of toxicity and survival before concluding that combination FC is preferable to single-agent F as the chemotherapy backbone for initial therapy of both low- and high-risk CLL.

Smith MR et al. *Proc ASH* 2010;Abstract 924.

Investigator Commentary: Incidence of Therapy-Related Myeloid Neoplasia with FC vs F as Initial Therapy for CLL

Several different therapies are effective for the initial treatment of CLL, including fludarabine/rituximab (FR), fludarabine/cyclophosphamide/rituximab (FCR) and bendamustine-based therapy. However, it is unclear which is the optimal regimen.

FCR versus FR is currently being compared in a large Intergroup trial. One of the concerns of using alkylating agents in patients with CLL is the potential for increased secondary diseases, such as myeloid neoplasia. In this study from the Eastern Cooperative Oncology Group, they found a slight increase in the number of patients who developed therapy-related myeloid neoplasia with FC versus fludarabine alone. The numbers were small, and longer follow-up is needed to determine whether the impression that FC is more leukemogenic is valid, because FCR is widely used as the initial treatment for CLL.

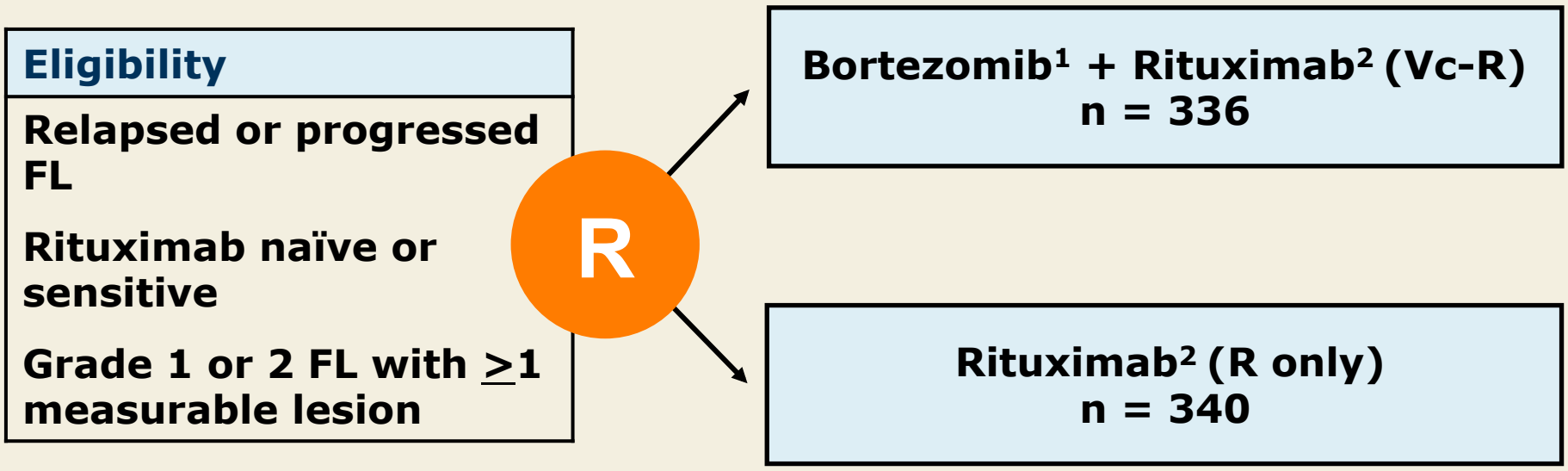
Interview with Bruce D Cheson, MD, December 23, 2010

A Phase III Trial Comparing Bortezomib plus Rituximab with Rituximab Alone in Patients with Relapsed, Rituximab-Naïve or -Sensitive, Follicular Lymphoma

Coiffier B et al.

Proc ASH 2010;Abstract 857.

Study Schema



[1] Bortezomib 1.6 mg/m^2 d1, 8, 15, 22 q5wk x 5 cycles

[2] Rituximab 375 mg/m^2 d1, 8, 15, 22 in cycle 1 and d1 only in cycles 2-5

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Efficacy Endpoints

	Vc-R (n = 315)	R Only (n = 324)	Odds Ratio	*p*-value
Overall Response	63%	49%	0.569	<0.001
Durable Response (>6 months)	50%	38%	0.608	0.002
Complete Response	25%	18%	0.665	0.035
	Vc-R (n = 336)	**R Only (n = 340)**	**Hazard Ratio**	***p*-value**
Progression-Free Survival (PFS)	12.8 mo	11.0 mo	0.822	0.039
Time to next treatment	23.0 mo	17.7 mo	0.802	0.027

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Progression-Free Survival in High-Risk Follicular Lymphoma

	Vc-R	R Only	Hazard Ratio	*p*-value
Median PFS (FLIPI ≥ 3) (n = 139; 140)	11.4 months	7.9 months	0.707	0.0133
Median PFS (High Tumor Burden by GELF) (n = 185; 179)	11.3 months	8.4 months	0.751	0.0186

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Select Adverse Events

	Vc-R (n = 334)	R Only (n = 339)
Diarrhea		
All Grades	52%	8%
Grade ≥3	7%	0%
Neutropenia		
All Grades	17%	7%
Grade ≥3	11%	4%
Peripheral Sensory Neuropathy		
All Grades	16%	1%
Grade ≥3	3%	0%
Febrile Neutropenia (Grade ≥3)	1%	1%

Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Conclusions

- Addition of weekly bortezomib to rituximab therapy in patients with relapsed FL is associated with statistically significant improvements in:
  - PFS (primary endpoint)
  - Response rate
  - Time to next antilymphoma treatment
- Patients at high risk in the bortezomib–rituximab arm had significantly longer PFS than patients treated with rituximab alone.
- Increase in side effects did not affect feasibility of treatment or quality of life (data not shown).

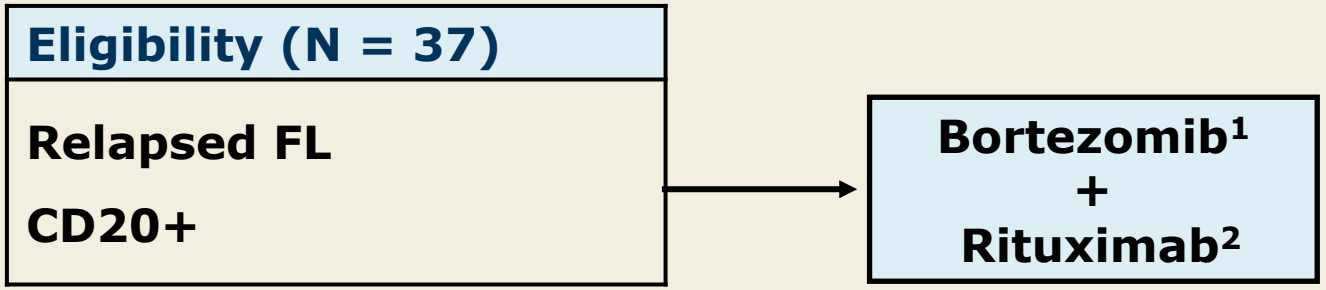
Coiffier B et al. *Proc ASH* 2010;Abstract 857.

Phase II Study of Bortezomib plus Rituximab in Relapsed Follicular Lymphomas

Sacchi S et al.

Proc ASH 2010;Abstract 1801.

Study Schema



[1] Bortezomib 1.3 mg/m^2 d1, 4, 8, 11 q21d x 6 cycles

[2] Rituximab 375 mg/m^2 d1 in cycles 3-6, and q21d x 2 additional doses

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

Efficacy and Safety Results

Response Evaluable (n = 33)

Overall Response	Complete Response	Partial Response
58%	49%	9%

Safety Evaluable (n = 33)

Neuropathy		Neutropenia		Infections	
Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
30%	15%	6%	3%	15%	3%

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

Conclusions

- Bortezomib and rituximab combination in relapsed follicular lymphoma has a promising percentage of responses.
- Longer follow-up is needed to evaluate response duration and survival.
- Toxicity with the combination of bortezomib and rituximab in relapsed FL is acceptable.

Sacchi S et al. *Proc ASH* 2010;Abstract 1801.

Investigator Commentary: Bortezomib with Rituximab for Relapsed FL

Coiffier and colleagues demonstrated a higher overall response rate, complete response rate and time to disease progression with the combination arm in a large number of patients. Unfortunately, it was a negative study, because they did not meet their goal of a 33 percent improvement in progression-free survival. It remains to be seen whether this regimen will be adopted by practicing clinicians, because it is associated with considerably more toxicity, particularly peripheral neuropathy.

The study reported by Sacchi evaluated the same regimen of bortezomib/rituximab, but it was not a randomized trial and it included a smaller number of patients. Approximately 50 percent of the patients achieved a complete response, with an overall response rate of 58 percent. Other regimens, such as bendamustine/rituximab, for this patient population are associated with a considerably higher response rate and might be considered a preferable therapy.

Interview with Bruce D Cheson, MD, December 23, 2010