

Phase II Study of Lenalidomide and Rituximab As Salvage Therapy for Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia

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Published online ahead of print at www.jco.org on December 26, 2012.

Presented in part at the 53rd Annual Meeting of the American Society of Hematology, San Diego, CA, December 10-13, 2011, and the 52nd Annual Meeting of the American Society of Hematology, Orlando, FL, December 4-7, 2010.

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

Clinical trial information: NCT00759603.

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0732-183X/13/3105-584/\$20.00

DOI: 10.1200/JCO.2012.42.8623

A B S T R A C T

Purpose

Lenalidomide is an immunomodulatory drug active as salvage therapy for chronic lymphocytic leukemia (CLL). We combined lenalidomide with rituximab to improve response rates in patients with relapsed or refractory CLL.

Patients and Methods

Fifty-nine adult patients (age 42 to 82 years) with relapsed or refractory CLL were enrolled onto a phase II study of lenalidomide and rituximab. Patients had received prior fludarabine-based therapy or chemoimmunotherapy. Rituximab (375 mg/m² intravenously) was administered weekly during cycle one and on day 1 of cycles three to 12. Lenalidomide was started on day 9 of cycle one at 10 mg orally and administered daily continuously. Each cycle was 28 days. Rituximab was administered for 12 cycles; lenalidomide could continue indefinitely if patients benefitted clinically.

Results

The overall response rate was 66%, including 12% complete responses and 12% nodular partial remissions. Time to treatment failure was 17.4 months. Median overall survival has not been reached; estimated survival at 36 months is 71%. The most common grade 3 or 4 toxicity was neutropenia (73% of patients). Fourteen patients (24%) experienced a grade 3 to 4 infection or febrile episode. There was one episode of grade 3 tumor lysis; one patient experienced renal failure during the first cycle of therapy, and one venous thromboembolic event occurred during the study.

Conclusion

The combination of lenalidomide and rituximab is active in patients with recurrent CLL and warrants further investigation.

J Clin Oncol 31:584-591. © 2012 by American Society of Clinical Oncology

INTRODUCTION

The introduction of fludarabine-based chemoimmunotherapy as first-line therapy for chronic lymphocytic leukemia (CLL) has led to significant improvement in response duration and overall survival (OS).^{1,2} Chemotherapy combinations including fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine are effective in relapsed patients³⁻⁷; however, patients who have repeated relapses or short response duration after standard chemoimmunotherapy have limited salvage therapy options.⁸

Although monoclonal antibodies such as alemtuzumab and ofatumumab are effective and approved for patients with relapsed and refractory CLL, as monotherapy, these agents are associated with median progression-free survival (PFS) of gen-

erally less than 1 year.⁹⁻¹² Development of therapies with novel mechanisms of action may increase the options available to this therapeutically challenging population.

Lenalidomide is an immunomodulatory drug with activity in multiple myeloma. Lenalidomide enhances T-cell and natural killer (NK) –cell cytolytic activity in vitro and in vivo.¹³ In CLL, lenalidomide alters the tumor microenvironment by modulating cytokine production by dendritic cells as well as modifying expression of costimulatory molecules by T cells, potentially repairing defective humoral immunity¹⁴⁻¹⁸ and defective T-cell to B-cell synapse formation characteristic of CLL.^{19,20}

Phase II clinical trials have shown that lenalidomide is active in relapsed and refractory CLL. Using a starting dose of 25 mg on a schedule of 21 of 28 days, lenalidomide induced responses in patients

with CLL but was associated with tumor lysis syndrome (TLS) and tumor flare reaction (TFR).²¹ After reducing the starting dose to 5 mg with dose escalation, Chanan-Khan et al²¹ demonstrated this regimen to be safe and effective. Severe tumor lysis or other toxicity has also been noted by other groups with higher starting doses and rapid dose escalation of lenalidomide.^{22,23} Our group confirmed the activity and safety of lenalidomide monotherapy administered continuously at a starting dose of 10 mg escalated up to 25 mg per day in heavily pretreated patients with CLL.²⁴

There is synergistic activity between rituximab and lenalidomide against CLL and non-Hodgkin lymphoma cells in vitro. Lenalidomide enhances rituximab-mediated antibody-dependent NK- and T-cell cytotoxicity via improved B-cell synapse formation and upregulation of costimulatory molecules.¹⁶ In non-Hodgkin lymphoma, lenalidomide was shown to enhance NK- and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ cells.¹³ We hypothesized that rituximab administered before lenalidomide could also act as a debulking agent and reduce the rate and severity of TFR. We therefore investigated the activity of the combination of lenalidomide and rituximab in patients with relapsed or refractory CLL.

PATIENTS AND METHODS

This study protocol was approved by The University of Texas MD Anderson Cancer Center institutional review board and registered at clinicaltrials.gov (NCT00759603). Informed consent was obtained in accordance with institutional guidelines and the Declaration of Helsinki.

Patients with relapsed or refractory CLL were enrolled onto a phase II study of lenalidomide and rituximab at the MD Anderson Cancer Center between September 2008 and September 2009. All patients were at least 18 years of age. Patients had a diagnosis of CLL and active disease with indication for therapy in accordance with the 1996 National Cancer Institute working group criteria.^{25,26} All patients had received prior purine analog-based therapy, except one patient (age 82 years), who had received R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone). Patients were required to have Eastern Cooperative Oncology Group/WHO performance status ≤ 2 and adequate renal (serum creatinine ≤ 2 mg/dL) and hepatic (serum bilirubin ≤ 2 mg/dL) function. Patients with another malignancy within 3 years of study entry were excluded, with the exception of patients with localized skin, breast, or prostate cancer likely to be cured. Patients with active hepatitis B or C virus, HIV positivity, or a history of tuberculosis and patients with a history of deep venous thrombosis or pulmonary embolism within 6 months of study entry were excluded.

Pretreatment Evaluation

Before initiation of therapy, all patients were assessed by history, physical examination, and peripheral blood studies, including blood count, serum chemistry, thyroid-stimulating hormone, and β_2 -microglobulin (B2M). Bone marrow aspiration and biopsy were performed before therapy for immunophenotype by flow cytometry for clonality, CD38 and ZAP-70 expression by flow, and immunoglobulin heavy chain variable region (*IGHV*) gene mutation analysis.²⁷ Genomic abnormalities were detected by fluorescent in situ hybridization (FISH) using standard CLL probes on bone marrow samples (Vysis CLL FISH Probe Kit; Abbott Molecular, Des Plaines, IL). Fludarabine refractoriness was defined as no response or progression within 6 months of the latest fludarabine-containing regimen.

Drug Administration

Rituximab (375 mg/m²) was administered intravenously on days 1, 8, 15, and 22 during cycle one and once every 4 weeks on day 1 for cycles three to 12. Lenalidomide was started on day 9 of cycle one at 10 mg per day and administered continuously. Each cycle of treatment was 28 days. Treatment duration

was planned for 12 cycles, although patients could continue lenalidomide indefinitely beyond 12 cycles if there was a significant clinical benefit, such as ongoing partial (PR) or complete response (CR). Allopurinol was administered for the first 14 days of cycle one. Growth factor support was permissible at the investigator's discretion as per American Society of Clinical Oncology guidelines.²⁸ No antibacterial, antiviral, deep venous thrombosis, or tumor flare prophylaxis was mandated.

Dose Adjustment

Lenalidomide dosing could be adjusted for sustained (≥ 7 days) grade 3 to 4 neutropenia or thrombocytopenia. Dose reductions were recommended for grade 3 rash, allergic reaction, or neuropathy. Lenalidomide was discontinued for grade 4 nonhematologic toxicity. Lenalidomide was held for serious (grade ≥ 3) nonhematologic toxicity and could be reinitiated without time limitation at a lower dose level after resolution of toxicity to grade ≤ 2 . Dose reduction steps are summarized in Appendix Table A1 (online only).

Response Evaluation

Response was evaluated after three, six, and 12 cycles and every six cycles thereafter. Clinical response was defined as best response obtained with therapy, assessed according to 1996 National Cancer Institute working group²⁵ criteria, including bone marrow aspirate and biopsy evaluation with three-color flow cytometry performed at each assessment. Computed tomography (CT) scans were not required for response assessment but were used if clinically indicated.

Study End Points and Statistical Analysis

The primary end point of this study was overall response rate (ORR) assessed on an intent-to-treat basis. The effects of pretreatment characteristics were compared using Fisher's exact test (two tailed). Differences were considered significant if $P < .05$. Additional study objectives included time to treatment failure (TTF), defined as time from the start of therapy to death, progression of disease, or initiation of next therapy, and OS. TTF and OS were calculated using Kaplan-Meier estimates including all patients in the study, and survival estimates were compared among subgroups of patients using the log-rank test. All analyses were performed using SPSS (version 19.0; SPSS, Chicago, IL). Treatment-related toxicity was assessed using Common Terminology Criteria for Adverse Events (version 3.0).

RESULTS

Patient Characteristics

The median age of 59 patients enrolled onto this study was 62 years (range, 42 to 82 years); 47% had Rai stage III to IV CLL. The median number of prior treatments received was two (range, one to nine). Other pretreatment characteristics are listed in Table 1. Fifty-eight patients (98%) had received prior rituximab, 58 patients (98%) had received prior fludarabine, including 55 patients (93%) who had received at least one prior purine analog-based chemoimmunotherapy combination (Appendix Table A2, online only). Twelve patients (20%) were refractory to their last fludarabine-containing therapy.

Efficacy

The ORR was 66%, including seven CRs (12%), seven nodular PRs (12%), and 25 PRs (42%). Two patients (3%) had flow cytometry-negative CRs. Response assessment was confirmed by CT in 12 patients (20%). A majority of patients had achieved an objective response (PR or better) by three cycles of therapy (Table 2), whereas all CRs were observed to occur after 12 or more cycles of therapy (Appendix Fig A1, online only).

The ORR was 53% for patients with chromosome 17p deletion and did not differ significantly from patients without 17p deletion

Table 1. Patient Pretreatment Characteristics

Characteristic	No.	%
Age, years		
Median	62	
Range	42-83	
Hemoglobin, g/dL		
Median	12.2	
Range	8.8-15.8	
Platelets, ×10 ⁹ /L		
Median	129	
Range	22-338	
WBC, ×10 ⁹ /L		
Median	40.7	
Range	2.5-190	
Lymphocytes, ×10 ⁹ /L		
Median	34.4	
Range	0.4-188	
ANC, ×10 ⁹ /L		
Median	3.0	
Range	0.1-28.2	
< 1.5	20	34
≥ 1.5	39	66
β ₂ -microglobulin, mg/L		
Median	3.5	
Range	1.5-9.0	
No. of prior treatments		
Median	2	
Range	1-9	
1	22	37
2	13	22
≥ 3	24	41
Rai stage		
0	7	12
I-II	24	41
III-IV	28	47
Sex		
Female	13	22
Male	46	78
CD38 flow, % (ND = 2)*		
≥ 30	31	53
< 30	26	44
IGHV mutation status (ND = 2)		
Mutated	14	24
Unmutated	43	73
FISH bone marrow (ND = 1)		
13q deletion	9	15
Negative	11	19
Trisomy 12	7	12
11q deletion	16	27
17p deletion†	15	25
Fludarabine		
Not refractory	47	80
Refractory	12	20

Abbreviations: ANC, absolute neutrophil count; FISH, fluorescent in situ hybridization; IGHV, immunoglobulin variable heavy chain; ND, not done.
 *CD38 expression by flow cytometry on CD19-positive lymphocytes in bone marrow aspirate.
 †Twelve of 15 patients had > 20% p53-deleted cells (range, 10.5% to 93%).

(ORR, 70%; *P* = .35). Response to treatment was correlated with prior response to fludarabine, with an ORR of 70% among patients not refractory to their last fludarabine-containing regimen compared with 33% among patients refractory to fludarabine (*P* = .041). We also

Table 2. Response at Each Assessment Point and Best Response to Lenalidomide and Rituximab by Intent to Treat (n = 59)

NCI-WG Response	Three Cycles		Six Cycles		12 Cycles		Best Response*	
	No.	%	No.	%	No.	%	No.	%
CR	0	0	0	0	4	7	7	12
Nodular PR	5	8	8	14	8	14	7	12
PR	27	46	27	46	22	37	25	42
ORR	32	54	35	59	34	58	39	66

Abbreviations: CR, complete response; NCI-WG, National Cancer Institute Working Group criteria for response; ORR, overall response rate; PR, partial response.
 *Best response could occur beyond 12 cycles of therapy.

noted a nonsignificant trend toward lower ORR in patients with bulky adenopathy (≥ 5 cm) compared with patients without bulky adenopathy (ORR, 40% v 67%, respectively; *P* = .07). There were no other statistically significant associations between biologic pretreatment characteristics and ORR (Table 3).

Forty-five patients (76%) have discontinued therapy (Appendix Table A3, online only); 42 patients (71%) had disease progression,

Table 3. ORR According to Pretreatment Characteristics

Characteristic	No.	ORR (%)	<i>P</i>
All patients	59	66	
Age, years			1.00
< 65	34	65	
≥ 65	25	68	
Rai stage			.18
I-II	31	71	
III-IV	28	54	
Maximum lymph node size, cm			.07
< 5	49	67	
≥ 5	10	40	
β ₂ -microglobulin, mg/L			.16
< 4.0	34	74	
≥ 4.0	24	54	
FISH hierarchy (n = 58)			
13q deletion	9	67	
Negative	11	55	
Trisomy 12	7	71	
11q deletion	16	69	
17p deletion	15	53	.35*
CD38, % (n = 57)			.57
< 30	19	73	
≥ 30	20	65	
IGHV mutation status (n = 57)			.34
Mutated	14	79	
Unmutated	43	60	
No. of prior treatments			.16
1-2	35	74	
≥ 3	24	54	
Fludarabine			.041
Not refractory	47	70	
Refractory	12	33	

Abbreviations: FISH, fluorescent in situ hybridization; IGHV, immunoglobulin variable heavy chain; ORR, overall response rate.
 *17p deletion versus no 17p deletion.

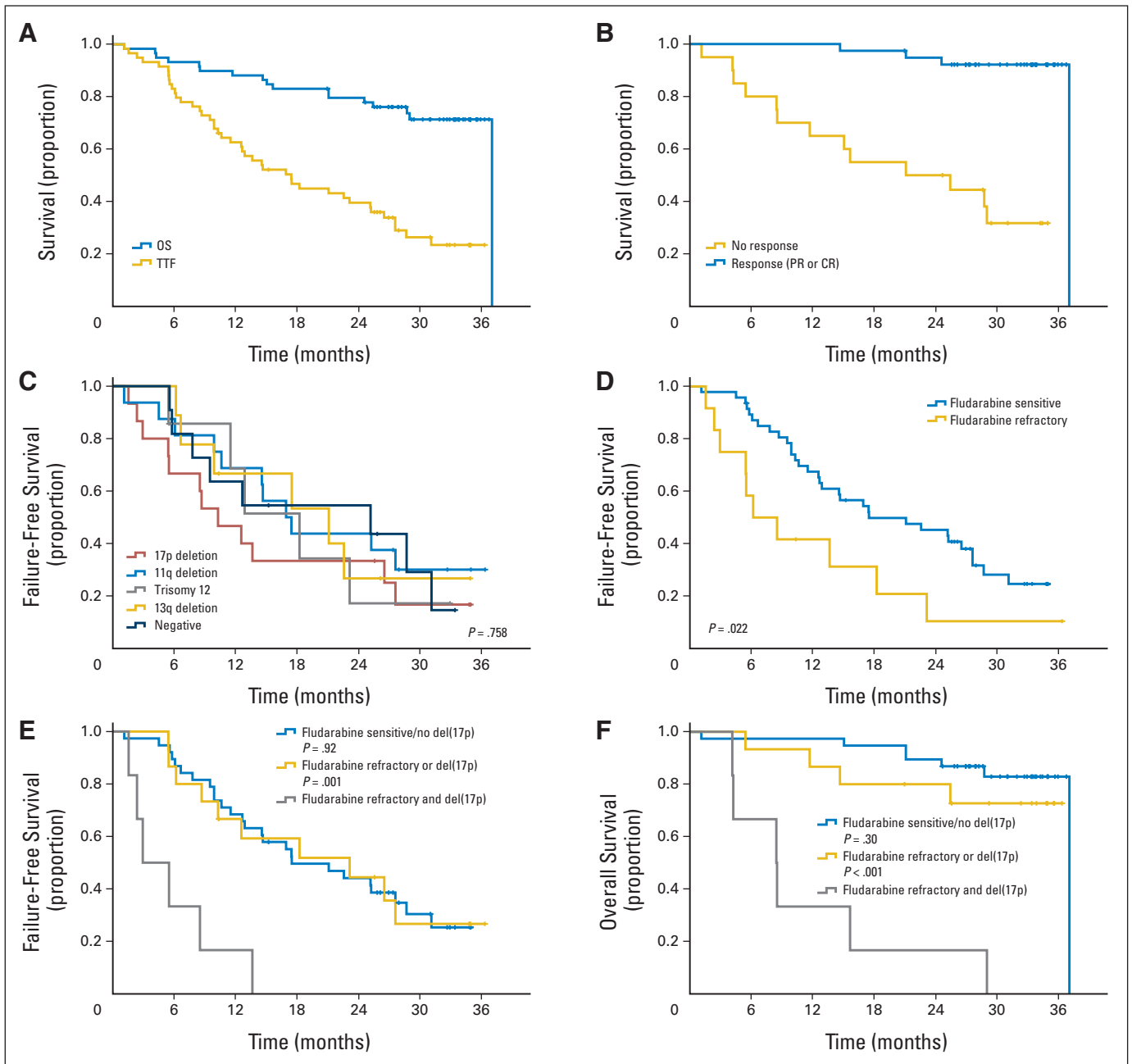


Fig 1. Kaplan-Meier overall (OS) and failure-free survival curves for all study patients. (A) OS and time to treatment failure (TTF) for all patients receiving lenalidomide and rituximab (n = 59), with median 33 months of follow-up. (B) OS for responding patients (complete [CR] or partial response [PR], n = 39) compared with nonresponders (stable or progressive disease, n = 20). (C) TTF according to pretreatment fluorescent in situ hybridization by Döhner cytogenetic hierarchy. (D) TTF by refractoriness to fludarabine. (E) TTF by cytogenetic risk group and prior fludarabine response; patients with 17p deletion and refractory to last fludarabine therapy (n = 6) are compared with patients with only one of these high-risk features (ie, fludarabine refractory or del(17p), n = 15) and patients without these high-risk features (n = 38). (F) OS by cytogenetic risk group and prior fludarabine response comparing the same patient subgroups as in (E); patients who were fludarabine refractory but had no 17p deletion and patients who had 17p deletions but were not refractory to fludarabine had TTF and OS similar to those in patients with neither of these high-risk features; patients who had 17p deletions and were also refractory to fludarabine had significantly shorter TTF and OS compared with all other patients.

required another CLL therapy, or died. The median TTF for all patients was 17.4 months (95% CI, 11.9 to 23.0 months; Fig 1A). The median time to progression for responding patients was 27.6 months (95% CI, 24.6 to 30.6 months). Four (10%) of 39 patients who achieved a response to treatment have died (Fig 1B), three patients after progression of disease and one patient 15 months after the development of del(5q) myelodysplastic syndrome.

We analyzed the impact of biologic prognostic markers on TTF. Elderly patients or patients with advanced Rai stage, bulky lymphadenopathy, high B2M, or unmutated *IGHV* genes did not experience shorter TTF (data not shown). Although limited by small subgroup size, patients with 17p deletion by FISH did not seem to have significantly shorter TTF than patients in other cytogenetic risk groups (Fig 1C). Response to prior therapy correlated with TTF. Patients who

were refractory to their last fludarabine-containing regimen had significantly shorter TTF than those sensitive to fludarabine (Fig 1D). In particular, the combination of fludarabine refractoriness and del(17p) was associated with significantly shorter TTF and OS compared with all other patients, whereas patients with only one of these high-risk characteristics had similar TTF or OS compared with patients without these high-risk characteristics (Figs 1E, 1F).

OS

There have been 17 deaths after a median follow-up for surviving patients of 32.8 months (range, 21.0 to 36.8 months). The median OS for all patients has not been reached (Fig 1A), and the estimated proportion of patients alive at 36 months is 71% (95% CI, 59% to 83%). Four deaths occurred during treatment, including one death after complications of an ischemic stroke, one death after an exacerbation of chronic obstructive pulmonary disease, one death in a patient with Richter's transformation, and one death resulting from an unknown cause. Another two patients died within 6 months of therapy discontinuation, including one patient after subsequent therapy for Richter's transformation and one patient with *Pneumocystis jirovecii* pneumonia while receiving immunosuppressive therapy for autoimmune hemolytic anemia. The remaining patients died after progression of disease (10 patients) or myelodysplastic syndrome (one patient) a median of 15 months (range, 7 to 24 months) after cessation of treatment with lenalidomide and rituximab.

Toxicity

A total of 1,054 cycles were administered, with a median of 15 cycles of treatment per patient. Hematologic toxicity is summarized in Table 4. Neutropenia was the most common grade 3 or 4 hematologic toxicity experienced at least once by 73% of patients and during 32% of treatment cycles. Twenty-five patients (42%) required granulocyte colony-stimulating factor for neutropenia, and 19 patients (32%) required interruption of therapy lasting a median of 10 days (range, 4 to 31 days). Grade 3 or 4 anemia and

thrombocytopenia were less common, occurring during 10% and 3% of treatment cycles, respectively.

Nine patients (15%) experienced a grade 3 or 4 infectious episode, and eight patients experienced a febrile episode, mostly neutropenic fever (Table 4). Most episodes were lower respiratory tract infections, including pneumonia or bronchitis (six episodes), febrile neutropenia without a documented source (six episodes), or fever without a documented source (three episodes).

Other grade 3 or 4 nonhematologic toxicity was uncommon (Table 5), with the exception of grade 3 fatigue reported by eight patients (14%). One patient experienced grade 3 TLS at the start of therapy; another developed a TFR complicated by grade 4 hypercalcemia, acute renal failure, and myocardial ischemia during the first cycle of therapy and discontinued treatment. Other toxicities (grade 3) included one thromboembolic event and one patient with cardiac arrhythmia. Other events observed in one patient only are listed in Table 5. Grade 1 or 2 TFR was observed in 27% of patients. Other grade 1 or 2 toxicities included fatigue, diarrhea, sensory neuropathy, and rash, as previously described with lenalidomide monotherapy.^{21,23,24,29}

There were five patients with Richter's transformation, either during or after completion of therapy, a median of 8 months (range, 2 to 13 months) after initiation of study. Three of these patients were heavily pretreated and had 17p deletion by FISH at the start of study, one patient was enrolled with bulky adenopathy after four prior regimens including an allogeneic stem-cell transplantation, and one patient had trisomy 12 by FISH with a complex karyotype. We noted four second malignancies during the study: one melanoma in situ, one squamous cell carcinoma of the skin, one patient with recurrence of a head and neck cancer, and one patient with del(5q) myelodysplastic syndrome.

DISCUSSION

This phase II study is the first to our knowledge to demonstrate the effectiveness of lenalidomide combined with rituximab in patients

Table 4. Hematologic and Infectious Toxicity

Toxicity	Grade 3-4				Grade 4 Only		
	Patients		No. of Episodes	% of Cycles	Patients		
	No.	%			No.	%	% of Cycles
Hematologic							
Neutropenia	43	73		17	30	51	9.0
Thrombocytopenia	20	34		7.4	9	15	2.1
Anemia	9	15		3.0	1	1.7	0.2
Infection*							
Pneumonia/bronchitis	6	10	6				
Urinary tract	1	2	1				
Other infection†	2	3	2				
Any infectious event‡	9	15	9				
Fever							
Neutropenic fever	6	10	6				
Febrile, non-neutropenic	2	3	3				
Any febrile or infectious event§	14	24	18				

*All infectious toxicity was grade \leq 3.

†Other infection: orodental (n = 1), wound (n = 1).

‡Total of pneumonia/bronchitis, urinary tract, and other infections.

§Total of neutropenic and non-neutropenic febrile events and infectious events.

Table 5. Other Nonhematologic/Noninfectious Toxicity

Toxicity*	Grade 1-2		Grade 3-4	
	No.	%	No.	%
Renal failure†	0	0	1	1.7
Acute myocardial infarction†	0	0	1	1.7
Tumor lysis syndrome	0	0	1	1.7
Pain (abdomen)	0	0	1	1.7
Venous thrombosis	0	0	1	1.7
Weakness	0	0	1	1.7
Fatigue	24	41	8	14
Diarrhea	21	36	1	1.7
Tumor flare	16	27	0	0
Sensory neuropathy	14	24	0	0
Rash	13	22	0	0
Constipation	11	20	1	1.7
Nausea	10	19	0	0
Neurologic (other)	10	17	0	0
Arthralgia	9	17	1	1.7
Anorexia	9	15	0	0
Metabolic or laboratory	9	15	0	0
Hyperglycemia	8	15	0	0
Pruritus	8	14	0	0
Elevated serum creatinine	7	14	0	0
GI pain	7	12	0	0
Hypomagnesemia	7	12	0	0
Hyperbilirubinemia	6	12	1	1.7
Dyspnea	6	10	0	0
Peripheral edema	6	10	0	0
Heartburn	6	10	0	0
Headache	6	10	0	0

*Toxicity listed if any grade 3 or 4, or grade 1 or 2 in $\geq 10\%$ of patients.

†One patient developed grade 4 acute renal failure after tumor flare reaction complicated by acute myocardial infarction; all other nonhematologic toxicities were grade ≤ 3 .

with relapsed or refractory CLL. The majority of responders remained on lenalidomide therapy until failure of therapy or lack of tolerance. Studies of lenalidomide monotherapy in more heavily pretreated patients with CLL have reported ORRs of 32% to 47%.^{21,24} Although we cannot directly compare outcomes with the monotherapy studies, the ORR of 66% and sustained responses observed suggest a benefit with the addition of rituximab.

The outcomes in this study are comparable to those of commonly used salvage therapies. In a phase II study of FCR as salvage therapy, patients who had received prior fludarabine and alkylating-agent therapy experienced 73% ORR, with median PFS of 19 months.³ The combination of bendamustine and rituximab (BR) is also effective in relapsed and refractory CLL.^{4,5,7} The ORR after BR was 59%, the CR rate was 9%, and median PFS was 14.7 months.⁷ Most of our patients had received prior FCR-like therapy; therefore, the combination of lenalidomide and rituximab could be considered in patients for whom standard initial and salvage chemoimmunotherapy has failed.

Patients in this study are not comparable to high-risk fludarabine-refractory or bulky-refractory patients enrolled onto studies of alemtuzumab^{9,11} or ofatumumab¹⁰; however, a significant proportion of patients demonstrated high-risk characteristics such as B2M > 4 mg/L, unmutated *IGHV* genes, high-risk cytogenetic abnormalities, and prior exposure to chemoimmunotherapy or allogeneic

stem-cell transplantation. Adequate responses and response duration were noted in these patients.

Patients with relapsed CLL with 17p deletions represent a particularly high-risk group of patients with limited response to chemotherapy. We noted responses in eight of the 15 patients with del(17p) treated with lenalidomide and rituximab, although del(17p) patients who were also refractory to fludarabine had poor responses to therapy. Two objective responses to lenalidomide monotherapy have been reported among 14 patients (15%) in two studies of patients with relapsed CLL with del(17p).^{24,30} After BR, only one of 14 patients with del(17p) had an objective response.⁷ Monoclonal antibody therapy including alemtuzumab or ofatumumab are effective in refractory patients and patients with del(17p) but have generally been associated with median PFS < 12 months in high-risk patients.^{9-11,31-35} Subgroup analysis was not a primary objective of this study, and although interesting, our results should be interpreted with caution and require confirmation by larger clinical trials with a focus on high-risk CLL populations.

In comparison with the estimated survival of 71% at 3 years in this study, patients treated with FCR as salvage therapy in our center had an approximate survival of 62% at 3 years.³ The estimated median survival was 33.9 months for patients treated with BR. In the current study, the majority of patients had received prior FCR-like therapy, and treatment with lenalidomide and rituximab offered an effective alternative for patients who had relapsed after fludarabine-containing chemoimmunotherapy.³⁶ The survival rate in this study is encouraging and supports further prospective comparison of this combination with commonly used salvage regimens.

Early lenalidomide monotherapy studies in relapsed and refractory CLL demonstrated episodes of severe toxicity, including TLS and TFR.^{21,22,37} These complications were associated with high lenalidomide starting doses (25 mg) on a schedule of 21 of 28 days. Although the optimal starting dose of lenalidomide has not been clearly established, we attempted to reduce the incidence of TLS and TFR by starting therapy at the low dose of 10 mg on a continuous schedule because we previously established this dose could be safely administered in patients with CLL.²⁴ In addition, we administered rituximab before lenalidomide, aiming to reduce the severity of TFR. With this schedule, we observed one episode of grade 3 TLS, and one patient experienced a grade 4 episode of hypercalcemia and renal failure after a TFR at initiation of lenalidomide therapy. Although our dosing schedule seems safe for administration in this setting, appropriate precautions should be taken against TLS, including antihyperuricemic medication and adequate hydration as per standard recommendations.³⁸ On the basis of phase I data demonstrating safe escalation of lenalidomide to 20 mg,³⁹ a phase III study to establish the optimal starting doses of lenalidomide (5, 10, or 15 mg) is currently ongoing.⁴⁰

Although clinical responses to therapy occurred early in this treatment regimen, patients who continued to receive lenalidomide therapy demonstrated improvement in quality of response. All complete remissions in this study occurred at or beyond 12 cycles of therapy. The majority of patients with continued responses remained on lenalidomide therapy indefinitely. One of the challenges with continued lenalidomide therapy is persistence of grade 1 to 2 toxicities, leading to patient discontinuation of treatment. These include GI symptoms, fatigue, sensory neuropathy, and neutropenia. Therefore, approaches including patient education and supportive care are important to improve tolerance of long-term treatment with lenalidomide.⁴¹

We monitored the occurrence of other malignancies in this study in view of the recent reports of other malignancies after lenalidomide administration in patients with multiple myeloma.⁴² Of the four patients who developed nonhematologic malignancies, two had a history of malignancy. Increased rates of other malignancies have been well described in patients with CLL.^{43,44} Because of the size of our study, we are not able to make conclusive statements about the role of lenalidomide in second malignancies. The potential association between lenalidomide and other malignancies should be explored further in larger studies using this therapy.

In our experience, the combination of lenalidomide and rituximab has a role in the treatment of patients with relapsed CLL. With an ORR of 66%, the combination is comparable to currently employed chemotherapy combinations. At a starting dose of 10 mg daily administered continuously, we noted few grade 3 or 4 nonhematologic adverse events. Continued therapy led to durable and some complete remissions. Given these results, we plan to further evaluate the activity of this combination as initial therapy for patients unfit for chemoimmunotherapy and as a partner for novel agents.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Michael J. Keating, Celgene (C); William G. Wierda, Celgene (C), Genentech (C); Susan M. O'Brien, Celgene (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** Alessandra Ferrajoli, Celgene, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

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