The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma

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Given the significant activity and tolerability of bendamustine, rituximab, and bortezomib in patients with relapsed indolent and mantle cell non-Hodgkin lymphoma, and laboratory studies suggesting synergistic activity, we conducted a multicenter phase 2 study of the bendamustine/bortezomib/rituximab combination. Patients with relapsed or refractory indolent and mantle cell lymphoma with adequate organ function were treated with bendamustine 90 mg/m^2 days 1 and 4; rituximab 375 mg/m^2 day 1, and bortezomib 1.3 mg/m^2 days 1, 4, 8, 11. Six 28-day cycles were planned. Thirty patients (7 with mantle cell lymphoma) were enrolled and treated. Eight patients experienced serious adverse events, including one event of grade 5 sepsis. Common nonhematologic adverse events were generally grade 1 or grade 2 and included nausea (50%), neuropathy (47%), fatigue (47%), constipation (40%), and fever (40%). Of 29 patients evaluable for efficacy, 24 (83%) achieved an objective response (including 15 with complete response). With median follow-up of 24 months, 2-year progression-free survival is 47% (95% confidence interval, 25%-69%). On the basis of these promising results, the US cooperative groups have initiated randomized trials to evaluate this regimen in follicular and mantle cell lymphoma. This trial was registered at www.clinicaltrials.gov as #NCT00547534. (*Blood*. 2011;117(10): 2807-2812)

Introduction

As a result of improvements in both therapy and supportive care, the survival of patients with both follicular and mantle cell non-Hodgkin lymphoma (NHL) has improved significantly over the past decade.[1-3] Routine incorporation of the monoclonal antibody rituximab into therapeutic algorithms for these diseases has had a major effect on progression-free survival (PFS).[4,5] For selected patients, autologous and allogeneic transplantations offer the potential for substantial long-term benefit.[6,7] However, for most patients, these diseases remain incurable, and novel, well-tolerated therapeutic strategies are needed.

Bendamustine is a novel alkylating agent approved for the treatment of rituximab-refractory indolent lymphoma.[8,9] Two modern studies have evaluated the combination of bendamustine and rituximab in patients with relapsed indolent and mantle cell lymphoma, and both have shown response rates exceeding 90% and remission durations exceeding 2 years.[10,11] Preliminary results from a German randomized trial that compared bendamustine/rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone/rituximab in patients with newly diagnosed indolent and mantle cell lymphoma suggest the bendamustine/rituximab regimen confers lower toxicity with improved PFS.[12]

Bortezomib is a first-in-class proteasome inhibitor approved as a single agent for the treatment of relapsed mantle cell lymphoma, based largely on a multicenter phase 2 trial showing a response rate of 33% and median response duration of 9 months.[13] Bortezomib has also been studied in combination with rituximab for treatment of follicular lymphoma, with promising results and reasonable tolerability.[14] Bortezomib can also be safely combined with chemotherapy, given a nonoverlapping toxicity profile.[15]

Given the significant activity and tolerability of the bendamustine/rituximab regimen and of bortezomib in patients with relapsed indolent and mantle cell NHL, and laboratory studies suggesting synergy between chemotherapy agents and bortezomib, we conducted a multicenter phase 2 study of the bendamustine/bortezomib/rituximab combination. Our findings show a high response rate and reasonable tolerability in a heavily pretreated and refractory patient population, suggesting that this regimen may potentially improve outcomes in various clinical settings.

Methods

Study design and objectives

This multicenter trial was initiated at the University of Rochester, Weill Cornell Medical Center, and the University of Nebraska in October 2007. The primary endpoint was to determine the PFS after treatment of the bendamustine/bortezomib/rituximab combination. Secondary endpoints included safety, objective response rate, and laboratory correlative studies. The protocol was approved by the institutional review board at each site, and written consent was obtained from all patients before enrollment. The

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study was registered before enrolling patients (ClinicalTrials.gov NCT00547534).

Eligibility

Patients older than 18 years of age were eligible if they had a diagnosis (World Health Organization classification) of follicular NHL grade 1-3, marginal zone NHL, small lymphocytic NHL (with circulating lymphocyte count $< 5.0 \times 10^9$/L [5000/mm^3]), lymphoplasmacytic lymphoma, and mantle cell lymphoma; all pathology, particularly most recent slides, had to be confirmed by a hematopathology expert at the enrolling institution. Patients must have received ≥ 1 prior chemotherapy regimens for NHL and have measurable disease or an indication to receive additional therapy. Baseline laboratory parameters included absolute neutrophil count $> 1.0 \times 10^9$/L (1000 cells/mm^3), platelet count $> 74.0 \times 10^9$/L (74 000 cells/mm^3), and adequate renal (creatinine clearance > 0.25 ml/s/m^2 [> 30 ml/min]) and hepatic function. Patients were excluded if they had grade 2 (National Cancer Institute Common Terminology Criteria Version 3) or higher peripheral neuropathy, symptomatic heart failure, or active conduction system abnormalities. Patients were excluded if they had received prior bendamustine, had a prior autologous transplantation or radioimmunotherapy within the previous 4 months, or had received an allogeneic transplant. Patients receiving a prior bortezomib-containing regimen were eligible as long as the time to progression after bortezomib was > 6 months. Patients with other malignancies requiring treatment, a history of central nervous system lymphoma, prior solid organ transplantation, or HIV positive were excluded.

Treatment

Baseline evaluation included a history and physical examination, radiographic imaging (positron emission tomographic [PET] and computed tomographic scans), routine laboratory studies, and an electrocardiogram. A baseline bone marrow evaluation was required within 8 weeks before enrollment. Treatment cycles were 28 days in length, and 6 cycles of therapy were planned. Bendamustine (supplied by Cephalon) was infused at a dose of 90 mg/m^2 intravenously over 30-60 minutes on days 1 and 4. Rituximab was administered in a standard fashion on day 1 at 375 mg/m^2. Bortezomib (supplied by Millennium Pharmaceuticals) was administered at 1.3 mg/m^2 intravenous push on days 1, 4, 8, and 11. On day 1, bortezomib was given before rituximab, and bendamustine was administered last. On day 4, bortezomib was given before bendamustine. All dosing was determined by patient body surface area as calculated from actual weight; there was no adjustment for obese patients.

If the patient experienced febrile neutropenia, grade 4 neutropenia or thrombocytopenia, or $\geq$ grade 3 nonhematologic toxicity, treatment was held until toxicity resolved to $\leq$ grade 1. On day 1 of each cycle, treatment was held until granulocyte count $> 1.0 \times 10^9$/L (1000/mm^3) and platelet count was $> 75.0 \times 10^9$/L (75 000/mm^3). Patients who experienced bortezomib-related neuropathic pain or peripheral sensory neuropathy were managed with dose reductions summarized as follows: grade 1 pain or grade 2 neuropathy, decrease dose to 1.0 mg/m^2; grade 2 pain or grade 3 neuropathy, hold bortezomib until resolution and resume at dose of 0.7 mg/m^2. Bortezomib was discontinued for grade 4 neuropathy.

Antiemetic therapy, including steroid premedication, was according to institutional guidelines, and growth factors, including filgrastim and pegfilgrastim, were allowed according to institutional guidelines. No antibiotic or antiviral prophylaxis was given. Treatment was discontinued in patients showing progressive disease, unacceptable toxicity, or at the discretion of the patient or investigator.

Criteria for response and toxicity

Assessment of response was performed by the investigator after 3 cycles of treatment with the use of the same imaging techniques used for baseline measurements. Received dose intensity was calculated according to the methods described by Hryniuk and Goodyear.[16] Response was defined with the International Workshop NHL criteria.[17] Common Terminology Criteria Version 3.0 was used to grade toxicities.

PFS was calculated from the first dose of study drug to the first documentation of disease progression, death regardless of cause, or change in therapy because of disease progression, whichever occurred first. Patients who were alive and progression free at the time of final data analysis were censored at the time of their last assessment. If disease progression did not occur by the end of treatment, patients were evaluated every 3 months until progression with physical examination, laboratory studies, and conventional computed tomographic imaging, up to a maximum of 2 years.

Correlative laboratory studies

To confirm additive activity of bendamustine and bortezomib in vitro, we evaluated the combination in Granta and NCEB mantle cell lines. Two independent experiments were performed; 3×10^5 cells/mL were seeded in triplicate with or without bendamustine (10 μg/mL) or bortezomib (7.5 nM) or both. Forty-eight hours later surviving cells were harvested and counted on a hemactyometer with the use of Trypan blue to identify viable cells.

To determine mechanism of the combination within the clinical trial, p65/RelA activation was monitored in peripheral blood mononuclear cells obtained before initiation of therapy, 2 hours after the first dose of bortezomib, and immediately before the third dose of bortezomib (cycle 1, day 8). For each time point, 15 mL of blood was obtained and run on a standard Ficoll-Hypaque (Histopaque) gradient to isolate the white cell layer. These cells were collected, washed, pelleted, and frozen at −80°C. An enzyme-linked immunoabsorbent assay–based kit was used to monitor p65/RelA activation. DNA binding was measured with a Nuclear Extract Kit and TransAM NF-κB (nuclear factor-κB) p65 Chemi Kit (Active Motif) as previously reported.[18] When sufficient material was available, assays were performed in triplicate; in all cases variability between replicate determinations was $< 5\%$. Values were expressed as the change in p65/RelA activity/DNA binding compared with pretreatment controls, set as a value of 1.0.

We also evaluated baseline tumor necrosis factor (TNF) levels as a potential surrogate marker from serum with the use of a commercial reference laboratory (ARUP Laboratories).

Statistical analysis

For the primary objective, an intent-to-treat analysis was performed. At 2 years, with 30 patients enrolled, this study had 90% power to show an improvement in PFS from 50% (in historical controls of bendamustine/rituximab[10,11]) to 75%, using the Kaplan-Meier estimator. Safety analyses were descriptive in nature. A 2-sample t test was used to compare pretreatment p65/RelA activation levels in peripheral blood mononuclear cells at baseline with values obtained after therapy.

Results

Patient characteristics

Between October 2007 and March 2009, 31 patients were enrolled. One patient was determined to be ineligible and did not receive any therapy. Baseline clinical characteristics and prior therapies are detailed in Table 1. Of the 31 patients enrolled, 74% were men, and median age was 64 years. Follicular Lymphoma International Prognostic Index scores[19] at enrollment for patients with follicular lymphoma included 2 low risk, 5 intermediate risk, and 9 high risk. Most patients presented with advanced stage disease (80% stage III/IV) and were asymptomatic at baseline (7 patients with documented B symptoms). Two patients were previously treated with bortezomib. The median number of prior regimens was 4, and 10 (33%) were rituximab refractory.

Treatment

Nineteen patients (61%) received a full 6 cycles of therapy. Among these 19 patients, the median received dose intensity for the

Table 1. Baseline demographic and clinical patient characteristics

Characteristic	No. of patients	%
Total enrolled	31	
Sex		
Male	23	74
Female	8	26
Median age, y (range)	64 (44-84)	
Race/ethnicity		
White, non-Hispanic	27	87
White, Hispanic	2	7
Black, non-Hispanic	1	3
American Indian or Alaskan Native, non-Hispanic	1	3
Histology		
Follicular lymphoma	16	52
Follicular NHL grade 1	7	23
Follicular NHL grade 2	3	10
Follicular NHL grade 3	5	16
Follicular, NOS	1	3
Marginal zone	3	10
Small lymphocytic lymphoma	3	10
Mantle cell lymphoma	7	23
Lymphoplasmacytic lymphoma	2	6
FLIPI risk group (n = 16)		
Low risk (0-1 risk factors)	2	13
Intermediate risk (2 risk factors)	5	31
High risk (≥ 3 risk factors)	9	56
B symptoms at baseline	7	23
Baseline stage		
I	1	4
II	5	16
III	14	45
IV	11	35
Prior therapy		
CHOP (+/- R)	19	63
Purine analog chemotherapy (fludarabine +/- R)	6	20
ASCT	6	20
Radioimmunotherapy	9	30
Bortezomib	2	7
Median no. of prior regimens	4	
Rituximab refractory	10	33*

NOS indicates not otherwise specified; FLIPI, Follicular Lymphoma International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; and ASCT, autologous stem cell transplantation.

*Thirty-three percent of the 30 patients who had received prior rituximab therapy.

regimen components was 96% for rituximab, 93% for bendamustine, and 79% for bortezomib. Thirty patients received ≥ 1 cycle of therapy, 25 patients (81%) received ≥ 4 cycles of therapy, and 29 patients were evaluable for response. Reasons for early termination included progressive disease (n = 4) and toxicity (n = 7, including nausea and vomiting, febrile neutropenia, back pain, abscess, pancytopenia, and herpes zoster reactivation, and 1 grade 5 sepsis). Early termination of therapy was not associated with prior fludarabine, prior autologous stem cell transplantation, or prior radioimmunotherapy.

Safety

Eight patients (26%) experienced serious adverse events, including 1 patient with grade 4 liver and renal failure, and grade 5 sepsis; grade 3 peripheral neuropathy (n = 2), fatigue (n = 2), hypotension (n = 2), herpes zoster reactivation (n = 2), and dehydration (n = 2), as detailed in Table 2. Hematologic toxicity included 5 patients with grade 3 thrombocytopenia, 5 patients with grade 3 or 4 neutropenia, and 2 patients who developed febrile neutropenia. Hematopoietic growth factor support with filgrastim or pegfilgrastim was administered to 8 patients; 7 after grade 3 or 4 neutropenia. Common nonhematologic adverse events, occurring in ≥ 10% of treated patients, are detailed in Table 3. The most common nonhematologic toxicities included nausea (50%), peripheral neuropathy (47%), fatigue (47%), constipation (40%), fever (40%), and diarrhea (27%). Ten patients experienced painful neuropathy; 5 after cycle 1, 2 after cycle 2, 2 after cycle 3, and 1 after cycle 4. Of note, 4 patients had reactivation of herpes zoster.

Table 2. Nonhematologic serious adverse events (all grade 4 and 5 toxicities, and grade 3 toxicities occurring in ≥ 2 patients)

	Grade				
Event	3	4	5	Total	Patients, %*
Sepsis, n			1	1	3.3
Liver failure, n		1		1	3.3
Renal failure, n		1		1	3.3
Peripheral neuropathy, n	2			2	6.7
Fatigue, n	2			2	6.7
Hypotension, n	2			2	6.7
Herpes zoster, n	2			2	6.7
Dehydration, n	2			2	6.7

*Percentage of patients who started treatment (n = 30).

Efficacy

Of the 29 patients evaluable for treatment response, 24 (83%; 95% confidence interval [CI], 65%-92%) achieved a partial response (PR; n = 9) or complete response (CR; n = 15) to therapy. Of the 15 patients in CR, 7 had PET imaging; in only one case did the PET scan convert a PR to a CR. Two additional patients maintained stable disease at the posttreatment restaging. Among the 19 patients who received all 6 cycles of therapy, 18 (95%; 95% CI, 75%-99%) achieved a PR or CR to therapy. By histologic subtype, the overall response rate (proportion of patients achieving a CR or PR) was 93% (95% CI, 69%-99%) in follicular lymphoma and 71% (95% CI, 36%-92%) in mantle cell lymphoma. Tumor response for each

Table 3. Common nonhematologic adverse events (occurring in ≥ 10% of patients)

	Grade						
Event	1	2	3	4	5	Total	Patients, %*
Nausea, n	10	4	1			15	50.0
Peripheral neuropathy, n	6	6	2			14	46.7
Fatigue, n	5	7	2			14	46.7
Constipation, n	4	7	1			12	40.0
Fever, n	6	6				12	40.0
Diarrhea, n	3	4	1			8	26.7
Cough, n	6	1				7	23.3
Hypotension, n	1	3	2			6	20.0
Rigors/chills, n	4	1				5	16.7
Leg pain, n	2	3				5	16.7
Herpes zoster, n	2		2			4	13.3
Back pain, n	1	2	1			4	13.3
Allergic reaction, n	1	3				4	13.3
Headache, n		4				4	13.3
Pruritus, n	3					3	10.0
Anorexia, n	1	2				3	10.0
Dizziness, n	2	1				3	10.0
Rash, n	3					3	10.0
Shortness of breath, n	2	1				3	10.0
Stomach pain, n	1	2				3	10.0

*Percentage of patients who started treatment (n = 30).

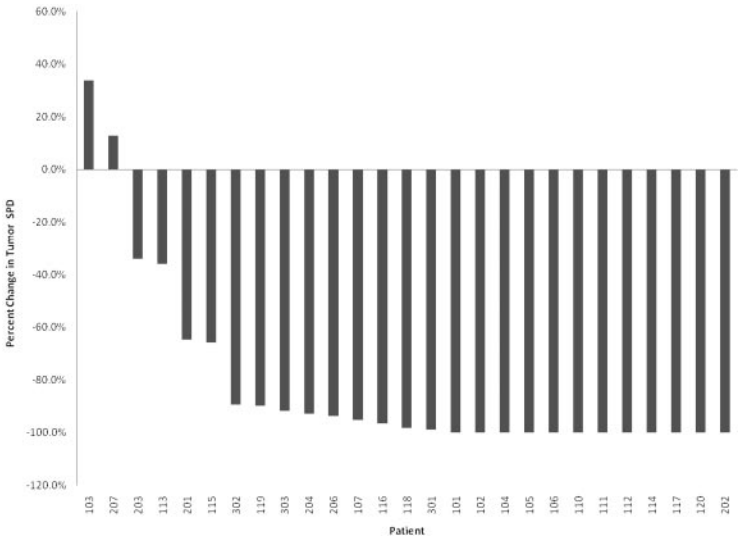

Figure 1. Waterfall plot of best response after therapy. Three of the treated patients (n = 30) are not included because of rapid clinical progression without additional imaging (n = 2) and 1 death before restaging evaluation.

patient is outlined in Figure 1. Of note, rituximab-refractory patients (no response or progression within 6 months of rituximab-containing regimen) had a similar response rate to the overall group (75%; $P = .5$).

As of September 30, 2010, the median follow-up of the patients still alive was 27 months (range, 20-36 months). To date, 13 of the 29 evaluable patients have relapsed, and 7 of those 13 patients have died. The 2-year PFS among these 29 evaluable patients is 47% (Figure 2). Among the 24 patients who responded to therapy, the 2-year PFS is 53% (95% CI, 27%-79%).

In vitro study

In the Granta line, treatment with the combination of bendamustine and bortezomib resulted in 4% cell survival, relative to untreated cells, at 48 hours. Notably, this was significantly better than with either single-agent bendamustine (20% cell survival relative to untreated cells) or single-agent bortezomib (20% cell survival relative to untreated cells). In the NCEB mantle cell line, the observed effect of the bendamustine and bortezomib combination is less dramatic, with 31% cell survival (relative to untreated cells), compared with 66% and 32% cell survival after treatment with single-agent bendamustine and bortezomib, respectively.

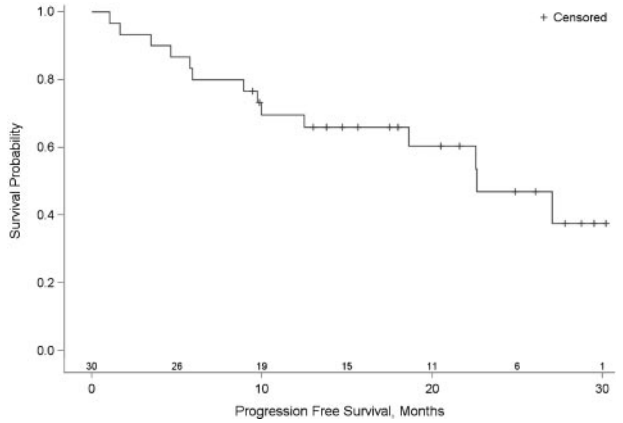

Figure 2. Progression-free survival. Kaplan-Meier estimate progression-free survival, with number at risk, for (A) all treated patients (n = 30), (B) patients with follicular lymphoma (n = 15), and (C) patients with mantle cell lymphoma (n = 7).

Laboratory correlates

Assessment of p65/RelA activation, as a surrogate for NF-κ B activation, in peripheral blood was assessed in 5 patients. Variability in p65/RelA activation was observed at the 2-hour interval, with 3 patient samples displaying increased activation, 1 sample showing a decline, and 1 sample displaying no change. However, in all samples but 1 sample at day 8, there was pronounced decline in activity, with reductions as high as 80%. Cells from 3 of the 4 responding patients studied displayed substantial declines in p65/RelA activation.

TNF levels at baseline were studied in 13 patients and were not detectable in 12 patients. In all patients studied, TNF was not detected after 3 cycles of therapy.

Discussion

In this multicenter trial, the combination of bendamustine, bortezomib, and rituximab was highly effective in both indolent and mantle cell NHL histologies. Our patient population was heavily pretreated, with 20% of patients having received prior autologous stem cell transplant, and 30% of patients having received prior radioimmunotherapy. Moreover, one-third of our patients were refractory to rituximab before study entry, a group of patients who were excluded from the prior studies of the bendamustine/rituximab regimen,[10,11] and 9 of 16 patients with follicular lymphoma had high-risk Follicular Lymphoma International Prognostic Index scores. Despite this significant prior therapy, patients tolerated our combination well, with most patients completing 6 cycles of therapy and 80% of patients completing 4 cycles of therapy. Prior studies of single-agent bendamustine at higher doses and more intensive schedules had higher toxicity with only a minority of patients completing 6 cycles of therapy, largely because of cumulative hematologic toxicity.[8] An International Consensus panel has suggested that a bendamustine dose of 90 mg/m^2 on days 1 and 2 (28-day cycle) is optimal for patients with relapsed indolent lymphoma when bendamustine is combined with rituximab.[20] Our choice to give bendamustine on days 1 and 4 was for patient convenience, and we chose to administer bortezomib first to facilitate the planned correlative studies. Given minimal grade 4 hematotoxicity in our trial, our dose and schedule of bendamustine appear to be an appropriate option when used in this

combination. A trial in follicular lymphoma combining bortezomib with bendamustine and rituximab also determined a bendamustine dose of 90 mg/m^2 to be optimal.[21]

Neuropathy is the main limiting toxicity of bortezomib. Recent studies in follicular lymphoma have suggested that neuropathy may be decreased when bortezomib is given on a weekly schedule rather than on the conventional schedule (days 1, 4, 8, and 11).[14] We chose the conventional schedule for this trial because of data suggesting that response rates and clinical activity in lymphoma are highest with the conventional schedule when bortezomib is used as a single agent.[22] A series of 12 patients treated with weekly bortezomib and bendamustine (no rituximab) had results inferior to those observed in our study.[23] In our study, only 17% of patients had grade 3 or 4 neuropathy, which reversed on dose adjustment of bortezomib. The importance of the bortezomib schedule in the setting of a chemotherapy combination is not known and will require further study in future clinical trials.

We also observed 13% of patients develop reactivation of varicella zoster virus. This has been reported in other studies that incorporated bortezomib in the relapsed setting of multiple myeloma.[24] Our patients were not treated with antiviral prophylaxis, but, given data suggesting efficacy of this approach in patients with multiple myeloma treated with bortezomib,[25,26] we would suggest that antiviral prophylaxis be used for future combination studies, including bendamustine and bortezomib.

Our limited in vitro study suggests additive activity when bortezomib is combined with bendamustine. The mechanism of how bortezomib augments chemotherapy in this setting is not known. Bortezomib can inhibit NF-κB through blocking IκB degradation. A recently published study in diffuse large B-cell lymphoma suggests that bortezomib can enhance chemotherapy in patients with activated B-cell type diffuse large B-cell lymphoma, which is dependent on NF-κB.[27] We performed correlative studies to determine the feasibility of monitoring NF-κB activation, reflected by p65/RelA DNA binding, in a surrogate target tissue (normal peripheral blood mononuclear cells) before and after administration of bortezomib. The small sample size and high response rate of the regimen make it difficult to draw definitive conclusions about possible correlation between changes in p65/RelA activation and clinical outcome. Recent studies suggest that bortezomib can trigger NF-κB activation under some conditions, consistent with our limited findings.[28] Because of the ease of studying peripheral blood mononuclear cells for these pharmacodynamic studies, we suggest it may be of value to explore NF-κB activation with this technique in future trials.

In indolent and mantle cell lymphoma, patients with a high pretreatment TNF-α level have been shown to have a poor prognosis, and a previous study of bortezomib suggested that decreasing TNF-α levels over time was a correlative marker of response in a small number of patients with mantle cell lymphoma.[29] In our larger study, most patients had undetectable TNF-α levels at baseline, rendering a correlation of this cytokine with tumor response noninformative.

An important issue in our study is to what degree bortezomib contributed to these promising efficacy results. We did not meet our ambitious endpoint of 25% 2-year PFS improvement compared with historical studies of bendamustine and rituximab. However, unlike the prior studies of the bendamustine/rituximab combination, our patient population was more heavily pretreated and included rituximab-refractory patients. The prior studies were limited to either rituximab-naive[11] or rituximab-sensitive patients.[10] Moreover, our high response rate and promising PFS results were preserved even in patients who had prior autologous transplantation. However, randomized trials will be required to determine how important bortezomib is in this combination, and whether increased toxicity associated with bortezomib is warranted. The bendamustine and rituximab combination has substantial promise in the therapy of both indolent and mantle cell lymphoma[30] and may evolve to become a standard to which other treatments are compared.[12] On the basis of our promising results and the similar results of a another trial of bendamustine, bortezomib, and rituximab limited to follicular lymphoma,[21] the US cooperative groups are planning to study the bendamustine, bortezomib, rituximab combination in a randomized fashion, in both follicular and mantle cell lymphoma as part of upfront therapy. In addition, a randomized trial in relapsed indolent and mantle cell lymphoma in Germany is planned that will compare the bendamustine, bortezomib, and rituximab combination with bendamustine and rituximab without bortezomib.

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Authorship

Contribution: J.W.F., J.M.V., J.P.L., J.L.K., and S.G. developed manuscript concept and design; N.K.P., S.B., and J.L.K. provided administrative support; J.W.F., J.M.V., F.Y., S.H.B., L.R., J.L., R.I.F., J.O.A., and J.P.L. provided study materials or patients; N.K.P., S.B., J.L.K., and D.P. collected and/or assembled the data; J.W.F., J.L.K., D.P., R.I.F., and S.G. interpreted/analyzed the data; J.W.F., J.M.V., J.L.K., D.P., N.K.P., and J.P.L. contributed to the writing of the manuscript. All authors approved the final manuscript.

Conflict-of-interest disclosure: J.W.F. is a consultant and serves in an advisory role for Genentech Inc and Cephalon. R.I.F. is a consultant and serves in an advisory role for Allos Therapeutics, Cytokinetics, GlaxoSmithKline, Roche, Mundipharma, Seattle Genetics, and Millenium. The remaining authors declare no competing financial interests.

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