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Phase I Trial of Weekly and Twice-Weekly Bortezomib with Rituximab, Cyclophosphamide, and Prednisone in Relapsed or Refractory non-Hodgkin Lymphoma

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Abstract

Purpose—To determine the safety and efficacy of substituting weekly or twice weekly bortezomib for vincristine in the R-CVP regimen (rituximab, cyclophosphamide, vincristine, prednisone) in patients with relapsed/refractory indolent and mantle cell lymphoma.

Experimental Design—Of the 57 patients in this phase 1 trial, 55 participated in 1 of 2 dosing schedules that included rituximab (375 mg/m^2) and cyclophosphamide (750 mg/m^2 or 1000 mg/m^2) administered on day 1 of each 21-day cycle, and prednisone (100 mg orally) days 2–6. In the once-weekly schedule, bortezomib was administered on days 2 and 8; on the twice-weekly

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Conflict of Interest disclosure: John Gerecitano (unpaid), Owen A. O'Connor and Andrew D. Zelenetz have served as advisors to Millennium Pharmaceuticals; Andrew D. Zelenetz have served as an advisor to Genentech and Roche Pharmaceuticals; John Gerecitano and Paul Hamlin have served on a speaker's bureau for Genentech and Biogen-Idec; Carol Portlock, Craig H. Moskowitz, Ariela Noy, David Straus, Philip Schulman, Otilia Dumitrescu, Debra Sarasohn, Jennifer Pappanicholaou, Alexia Iasonos, Zhigang Zhang, Qianxing Mo, Endri Horanlli and Celeste N. Rojas declare no competing financial interests.

schedule, bortezomib was given on days 2, 5, 9, and 12. Bortezomib and cyclophosphamide were alternately escalated. A separate cohort of 10 patients in the twice-weekly schedule received concurrent pegfilgrastim on day 2.

Results—Both schedules of rituximab, cyclophosphamide, bortezomib and prednisone (R-CBorP) were well tolerated. Most toxicities across all dose levels and cycles were grade 1 or 2. The overall response rates (ORR) for patients on the weekly (n=13) and twice-weekly (n=33) schedules were 46% (23% complete response/complete response unconfirmed [CR/CrU]) and 64% (36% CR/CRu), respectively. Concurrent pegfilgrastim did not increase hematologic toxicities in this regimen. A randomized phase II study is under way to further compare toxicity and efficacy of the 2 dosing schedules.

Conclusions—R-CBorP is a safe and effective regimen in patients with relapsed/refractory indolent and mantle cell lymphomas. Most toxicities were grade one or two, and a promising response rate was seen in this phase 1 study.

INTRODUCTION

Indolent and mantle cell lymphomas (MCL) represent approximately 40% of newly diagnosed non-Hodgkin lymphomas (NHL) in the United States. Although these malignancies are responsive to chemotherapy, cures are rare. The relatively recent integration of immunotherapies and other new agents into treatment paradigms for these diseases may be changing the natural history of follicular and mantle cell lymphoma (1–3). The indolent lymphomas, which include Follicular Lymphoma (FL), Marginal Zone Lymphoma (MZL) and Small Lymphocytic Lymphoma (SLL) typically follow a slow-growing course marked by frequent remissions to chemotherapy, but inevitable relapses (4). In the age of immunochemotherapy, the course of these indolent lymphomas can span decades, during which time patients will typically undergo several courses of immuno- and chemotherapy. In contrast to the indolent lymphomas, the course of MCL tends to be much more aggressive, and the life span of patients afflicted with this disease is shorter. Current treatments for MCL range from conservative “watch and wait” approaches to induction chemotherapy (R-CHOP, HyperCVAD-R, Maxi-CHOP-R) followed by peripheral blood stem cell transplant (5–7). Despite a diversity of treatment options, these diseases remains incurable. Well-tolerated treatment regimens that are non-cross resistant with conventional treatment options are needed to extend and improve the quality of life in patients with these incurable lymphomas.

Bortezomib is the first proteasome inhibitor approved by the US Food and Drug Administration. It was originally approved for the treatment of relapsed or refractory multiple myeloma. Several phase II trials (8–10) reported marked activity in a number of NHL subtypes, including MCL, FL and MZL. Following the promising results of four single-arm phase 2 studies reporting similar response rates in patients with relapsed or refractory MCL, the multicenter PINNACLE study established an overall response rate (ORR) of 31%, with a median duration of response of 9.2 months in 141 patients with MCL. (11, 12) These findings led to approval of bortezomib for second line treatment of MCL. Bortezomib was well tolerated in these patients, who experienced similar symptoms of neuropathy and thrombocytopenia seen in the earlier studies.

Because of the agent's impressive single-agent activity, and preclinical data suggesting synergy with conventional agents (13), we sought to evaluate the safety and efficacy of substituting bortezomib for vincristine in the conventional R-CVP regimen. Given the lack of robust data in support of vincristine's activity in this setting, we hypothesized that this substitution could improve the activity of the regimen without increasing neuropathy. Because of the differential risk of neuropathy seen in prior reports of the weekly and twice-weekly schedules of bortezomib (14, 15), we explored both schedules in this phase 1 study to allow for a direct comparison of toxicity. We also scheduled bortezomib after the alkylating agent, based on preclinical data suggesting that this order may increase activity of the combination. Finally, because of the emergent neutropenia observed, we explored the effects of concurrent pegfilgrastim on the hematologic toxicity profile.

PATIENTS AND METHODS

Demographics

Adult patients (≥18 years of age) with histologically confirmed chronic lymphocytic leukemia/B-cell small lymphocytic lymphoma (CLL/SLL); MZL; FL; Waldenström's macroglobulinemia; transformed FL; and MCL were eligible (Table 1). All patients had assessable disease, and must have had at least 1 prior treatment regimen, with no more than three prior cytotoxic chemotherapy regimens, and ≤1 prior radioimmunotherapy (RIT) regimen. Patients with prior stem cell transplantation were included (with preparative cytoreduction and high-dose therapy counted as 1 prior cytotoxic regimen). Patients could not have received any therapeutic monoclonal antibodies within three months of enrollment unless progression of disease (POD) was documented in the interim. A washout period of four weeks after prior cytotoxic chemotherapy (six weeks for BCNU or mitomycin C), and 12-weeks after last treatment with RIT was required.

All patients were required to have a Karnofsky performance status (KPS) > 50%, with adequate organ and marrow function as defined by: absolute neutrophil count (ANC) > 1000/μL on day 1 of each cycle (or >500/μL if known involvement of bone marrow), platelets (Plt) > 50,000/μL, total bilirubin < 1.5 times the institutional upper limit of normal (ULN) (or < 5 mg/dl for patients with Gilbert disease), AST and ALT < 2.5 times the institutional ULN (< 4 times ULN for patients with hepatic involvement), and creatinine < 1.5 times the institutional ULN or creatinine clearance ≥ 50%. Patients were not enrolled if they had brain or meningeal metastases, uncontrolled intercurrent illness, baseline neuropathy grade ≥ 2, or were HIV positive by serology. All patients signed IRB-reviewed informed consent for participation in the clinical trial. Patients were included in the safety/toxicity analysis if they received at least one dose of bortezomib, and in the efficacy analysis if they received at least two cycles of planned therapy.

Treatment

A 3 + 3 design with cohort expansions and alternate dose escalation was adopted. Two dosing schedules were explored. The first three patients on a weekly schedule were given 1.3 mg/m^2 bortezomib and 750 mg/m^2 of cyclophosphamide (with a constant dose of rituximab and prednisone). The last patient in each cohort was followed for one complete cycle (21

days) before enrollment of the next cohort. We alternately escalated bortezomib (B) and cyclophosphamide (C) (Table 2). Following safe dose escalation to cohort 4, the twice-weekly schedule was initiated. Cohorts 7 and 8 received prophylactic filgrastim. The maximum tolerated dose (MTD) was prospectively defined as the dose at which < 30% of patients experienced a dose-limiting toxicity. Patients who did not receive at least one dose of bortezomib were replaced in the cohort.

After four 21-day cycles, a restaging computed tomography (CT) scan was evaluated using International Working Group criteria (16). Patients with stable disease (SD) or partial remission (PR) received four additional cycles of treatment for a total of eight. Patients in complete remission/complete remission unconfirmed (CR/CRu) received two additional cycles of treatment, for a total of six. Patients experiencing progression of disease (POD) were removed from protocol. A comprehensive metabolic panel (CMP) and complete blood count (CBC) were assessed for each patient on day one of each cycle, and additional CBCs were assessed on all bortezomib administration days.

Toxicities were defined according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0. Dose-limiting toxicity (DLT) was defined as any of the following occurring during cycle one of treatment: (1) grade 4 neutropenia (ANC < 500 cells/mm^3) for ≥ seven consecutive days or febrile neutropenia (fever > 38.5° C with an ANC < 1000 cells/mm^3); (2) grade 4 thrombocytopenia (Plt <25,000) with a bleeding episode requiring transfusions, or lasting for seven consecutive days, Plt <10,000 x one day; (3) neurosensory toxicity of grade two with pain or grade > 2; (4) grade ≥ 3 nausea and/or vomiting despite adequate/maximal medical intervention and/or prophylaxis; (5) any grade ≥ 3 nonhematologic toxicity (except grade three injection site reaction, alopecia, fatigue); (6) re-treatment delay of > three weeks.

Pegfilgrastim Safety Cohort Expansion

A separate cohort of ten patients (Cohort 9) was enrolled to assess the safety of pegfilgrastim (PegG) administered simultaneously with bortezomib on day two of the twice-weekly regimen. Enrollment criteria were not changed. Patients in this cohort were treated identically to patients in Cohort 7 (i.e., with a fixed dose of bortezomib 1.3 mg/m^2 and cyclophosphamide 1000 mg/m^2), except that filgrastim was replaced by PegG (6 μg subcutaneously) on day two after bortezomib. Serial CBCs were followed as above.

Supportive Care and Follow-up

Filgrastim was allowed for patients on the weekly schedule according to American Society of Clinical Oncology (ASCO) guidelines. Erythropoietin was allowed for anemia. Antiemetic treatment and precautions for rituximab and cyclophosphamide followed institutional guidelines. Additional intravenous normal saline during each injection of bortezomib was allowed. All patients received prophylactic acyclovir (17) and sulfamethoxazole/trimethoprim (or other suitable PCP prophylaxis in patients with allergies to sulfa drugs) during and for three months following treatment.

All patients had a restaging computed tomography scan (CT) three to four weeks after the end of treatment. Repeat CT scans were required at least every four months thereafter for

two years. A pretreatment bone marrow biopsy and aspirate were required; this was repeated only as required to document CR.

Statistical Analysis

A competing risks analysis was used to analyze progression free survival, where progression is the event of interest and death caused by other reasons is regarded as the competing risk. R (http://cran.r-project.org/) package 'cmprsk' was used for the competing risks analysis.

To assess the safety of pegfilgrastim support administered concurrently with the first dose of bortezomib in the twice-weekly schedule, hematologic toxicities and absolute values for total white blood cell count, hemoglobin, ANC, and platelets were compared between Cohorts 7 and 9, using data from the first four treatment cycles. The Wilcoxon rank-sum test was used to compare the highest grades of all hematologic toxicities. Ordinary least-squares regression was used for each patient and each type of measurement to compute the slope of the fitted line for each laboratory trend. The slopes of plotted values for hemoglobin, ANC, and platelets were then compared between groups using the Wilcoxon rank-sum test.

RESULTS

Fifty-seven patients were enrolled in this phase I trial, 16 on the weekly schedule (Cohorts 1–4) and 41 on the twice-weekly schedule (Cohorts 5–9). The median number of prior treatments (including cytotoxic and non-cytotoxic therapies) was four for the weekly group and two for the twice-weekly group, with ≥ 90% of each group having had prior exposure to rituximab and over three-fourths of each group having been treated with prior anthracycline-containing regimens (Table 1). Only 2 patients (one in each treatment group) had received rituximab as their sole treatment prior to enrollment.

Toxicity

One patient (Cohort 4) who developed pancytopenia immediately after his first dose of cyclophosphamide and rituximab before receiving a dose of bortezomib was replaced, and one patient in Cohort 8 who experienced a grade 3 reaction to rituximab was removed from study before other drugs were given. Hence, 55 patients received at least one dose of bortezomib and are included in the safety analysis.

Both treatment schedules were well tolerated. Nine patients on the weekly schedule (60%) did not complete the full course of planned therapy (i.e., 6–8 cycles): five due to doctor or patient choice for lack of desired response, one after patient choice once CR was achieved, one because of clinical POD, and two because of adverse events deemed to be unrelated to the treatment (one patient had a non-resolving lung nodule later found to represent a primary lung malignancy, and another patient withdrew to have elective surgical repair of a pre-existing prolapsed rectum). Fourteen patients on the twice-weekly schedule (35%) failed to complete planned therapy: one chose to withdraw for lack of response, nine had adverse events (one pneumonia during a treatment delay, during which hospitalization the patient decided to withdraw from the trial and seek home hospice care, seven sensory neuropathy, one two-week delay due to grade 3 thrombocytopenia), and four chose to withdraw for

clinical POD. Toxicities are presented corrected for baseline. The most common toxicities in both treatment schedules were grade 1–2 (Tables 3, 4).

One episode of grade 3 diarrhea was observed in Cohort 2 (weekly bortezomib, 1.6 mg/m^2 + cyclophosphamide 750 mg/m^2), and this cohort was expanded to six patients. Since no further DLTs were seen, enrollment continued to the preplanned maximum administered dose levels for the weekly schedule. In Cohort 6 (twice-weekly bortezomib, 1.3 mg/m^2 + cyclophosphamide 750 mg/m^2), a neutropenic fever caused the initial cohort to be expanded to six patients. A second neutropenic fever was observed, and the protocol was modified to include prophylactic filgrastim administration at 380 mg on days 3, 4, 6, 7, 8, 10, and 11 in all subsequent patients (Table 2). For safety, six patients were enrolled in the first cohort of filgrastim-supported twice-weekly dosing (Cohort 7). This cohort was expanded to 12 patients when 1 person experienced both grade 4 thrombocytopenia lasting seven consecutive days and grade 4 peripheral neuropathy. No additional DLTs were seen in this cohort, and dose escalation continued to the 8th cohort without additional DLTs. A maximum tolerated dose (MTD) was therefore not reached in either dosing schedule.

Grade 3–4 clinical toxicities are shown in Table 4. Although the overall rate of neuropathy was similar between the treatment schedules, two instances of severe neuropathy (1 grade 3, 1 grade 4) were seen in the twice-weekly group. Patients were followed until resolution or stabilization of neuropathic symptoms. Of the patients who developed neuropathy, 83% in the weekly group experienced resolution after a median of 0.7 months, and 58% in the twice-weekly group after a median of four months. Patients reported a variable level of relief with clinical interventions (18). Peripheral neuropathy leading to hospitalization occurred in two patients in the twice-weekly group (both at the 1.3 mg/m^2 bortezomib dose level). One patient developed grade 3 neuropathy after four cycles of treatment, and recovered to a grade 1 neuropathy after 3.3 months; the other patient developed grade 4 neuropathy after one cycle of treatment, and remained at grade 4 until her death from progression 26 months after completion of treatment.

Hematologic toxicities for patients in the PegG-supported group (Cohort 9) were similar to those of patients treated with non-overlapping filgrastim (Cohort 7). The Wilcoxon rank-sum test failed to show a significant difference in rate of highest overall hematologic toxicity between the two groups (P = 0.64), with similar results obtained for each subtype of toxicity (anemia P = 1, neutropenia P = 0.45, thrombocytopenia P = 0.71). The trend of each hematologic value, as characterized by the best-fit slope across four cycles, was also not significantly different between the two groups (ANC P = 0.47, hemoglobin P = 0.08), with the exception of a significant but mild decline in platelets (P = 0.007) in the PegG group (Cohort 9).

Efficacy

Patients were considered evaluable for response if they received at least two cycles of the intended treatment. The overall response rate (ORR) in the combined 46 evaluable patients for the entire study was 59% (47% by intention to treat [ITT]), with an ORR of 46% (38% ITT) and 64% (51% ITT) in the weekly and twice-weekly schedules, respectively. Thirteen of the 15 patients in the weekly group were evaluable for response (Table 5). Responses

were seen in six patients (46%), with three CR/CRu (23%) and three PR (23%). Thirty-three of the 40 patients in the twice-weekly group were evaluable for response, and responses were seen in 21 patients (64%), with 12 CR/CRu (36%) and 9 PR (27%). Fifty patients were evaluable for the competing risk survival analysis, among which 34 patients progressed, 7 patients died, and 9 patients were censored. There was no statistically significant difference between the twice-weekly and weekly treatment groups for the cumulative incidence functions (p=0.83). The median time to progression for all patients treated was 13 months. The median time to progression for the weekly and twice-weekly treated patients was 9 and 14 months, respectively. By diagnosis, responses were seen in 14 of 23 patients (61%) with FL, six of ten patients (60%) with MCL, five of six patients (83%) with MZL, one of two patients (50%) with SLL, and zero of four (0%) patients with transformed indolent lymphoma (two of these were classified as transformed based on clinical/radiographic characteristics but not histologically proven to represent transformed histology). The one patient with grade 3b FL achieved a PR that lasted 5.3 months. Responses were seen in 13 of 22 patients (59%) who responded to their prior treatment, and 13 of 21 patients (62%) deemed to be refractory to their last prior treatment. Of the 41 patients who had received prior treatment with an anthracycline-based regimen, responses were seen in 22 (53.6%). Of the 41 patients who had received either R-CVP or R-CHOP at some point prior to enrollment, responses were seen in 20 (48.8%). Many of these patients had received R-CVP or R-CHOP early in the course of their disease, and the median time between the end of R-CVP or R-CHOP and R-CBorP was 28 months (range 1–172). Four patients in the weekly R-CBorP treatment group (2 with MCL, 2 with FL) had received prior bortezomib at a dose of 1.5 mg/m^2 twice weekly. One patient (with MCL) had an initial PR to bortezomib, but SD with a 2nd course upon relapse. The other 3 patients did not respond to single agent bortezomib (2 SD, 1 POD). With RCBorP, two of these patients responded (1 CR in the MCL patient with an initial response to single agent bortezomib, 1 PR), and two had SD. Three patients in the twice-weekly R-CBorP group (all with FL) had prior bortezomib at a dose of 1.8 mg/m^2 weekly. All three were refractory to the single agent (2 SD, 1 POD). With R-CBorP, 2 of these patients achieved PR, and one had SD.

DISCUSSION

We set out to exploit the preclinical synergy and non-overlapping activity of bortezomib by incorporating it into the popular and effective R-CVP regimen. Two similar combination regimens in which bortezomib was added to R-CVP(19) or R-CHOP(20) have recently been reported in abstract form. In those reports, neuropathy was not significantly more severe than expected with either Vinca alkaloids or bortezomib alone. However, both trials enrolled untreated patients who had not been previously exposed to potentially neurotoxic chemotherapeutic agents. Since the single-agent activity of vincristine is not well established in this setting, we chose to replace vincristine with bortezomib, instead of simply adding bortezomib to the regimen. In order to best characterize the toxicity profile of this regimen, a conservative 3 + 3 design and alternate dose escalation was adopted. Given recent reports suggesting similar efficacy and greater tolerability of bortezomib given on a weekly schedule with rituximab (15), we compared two dosing schedules in the combination regimen. Although this design required greater patient resources, it allowed for a thorough

analysis of potential adverse events, and the larger patient numbers provided substantial estimates of efficacy.

The R-CBorP regimen was well tolerated, with relatively few grade 3 or 4 toxicities. Only one DLT requiring cohort expansion (a grade 3 diarrhea in cohort 2) was seen in patients treated with weekly bortezomib. Dose escalation proceeded without further cohort expansion to the highest pre-determined doses of bortezomib and cyclophosphamide. The most concerning hematologic toxicity in the twice-weekly group was neutropenia. Because 2 of 6 patients experienced this toxicity in the 6^{th} cohort, the effective MTD of this regimen without growth-factor support is 1.3 mg/m^2 bortezomib and 750 mg/m^2 cyclophosphamide. Given the fact that neutropenia was the only DLT to emerge up to that point on the twice weekly schedule, it was thought that growth factor support might allow for maximization of therapeutic potential without putting patients at significant risk. Such support is routinely used to allow for chemotherapy intensification in lymphomas, and the investigators believed that it would be safe and would not compromise the study to add growth factor support to this regimen. Although the use of filgrastim and pegfilgrastim did not significantly change the overall incidence of neutropenia measured during treatment, there were no further neutropenia-related DLTs noted after growth factor support was instituted, and its use allowed for dose escalation to all pre-planned dose levels. Of note, thrombocytopenia was not severe, even in this population including several heavily pretreated patients, who were allowed to enroll with liberal pre-treatment (>50,000) and pre-dosing (>25,000 on bortezomib days) platelet requirements. Of the non-hematologic toxicities, the most clinically concerning was neuropathy. The incidence of mild neuropathy (grade 1–2) was 40% and 60% in the weekly and twice-weekly bortezomib groups, respectively. Two instances of severe (grade 3–4) neuropathy were seen in the twice weekly group, while none were seen in the weekly group. Interestingly, neuropathy resolved in a greater proportion of patients over a shorter period of time in the weekly group than in the twice-weekly group. These findings are similar to those reported in a recent phase II study employing two schedules of bortezomib with rituximab (15), and support prior observations of resolution after discontinuing bortezomib (21).

Shortly after we added filgrastim support to the twice-weekly regimen, it was shown that patients with multiple myeloma treated with overlapping doses of filgrastim and bortezomib did not appear to exhibit any detrimental effects on stem cells (22). We therefore sought to demonstrate the safety of administering PegG support simultaneously with bortezomib. Serial CBCs failed to show significantly greater hematologic toxicities in this group compared with a prior cohort of patients treated with non-overlapping short-acting filgrastim, and none of the ten patients in the overlapping PegG cohort experienced a DLT. To augment the safety analysis, the trend of each hematologic data point over four cycles was compared between these two groups, and the only significant finding was a slightly greater decline in platelets over time in the PegG group. PegG is therefore safe and effective in patients being treated with overlapping doses of bortezomib.

The ORR in evaluable patients of 46% (weekly) and 64% (twice-weekly) with an overall time to progression of 13 months is encouraging. A greater number of patients received the twice-weekly schedule of treatment, due to toxicities leading to more cohort expansions for

this schedule. Given the difference in patient numbers, the greater number of patients treated at the highest dosing levels in the twice-weekly group, and higher number of prior treatments (including greater prior use of bortezomib) seen by chance in patients in the weekly group, (Table 1) response rates and survival cannot be directly compared in this phase 1 study. Of patients whose disease was refractory to their last prior treatment, 62% achieved a response, with responses seen even in patients treated previously with components of the current regimen (some of whom were refractory to those treatments). These results support the idea that a combination of these agents can overcome resistance to common treatment regimens – even if those regimens have contained similar agents. Data are beginning to emerge that demonstrate safe and effective combinations of bortezomib with other active agents in these diseases, as well (23, 24).

CONCLUSIONS

R-CBorP appears to be safe and effective in treating indolent and mantle cell lymphomas, and exhibits activity in heavily pretreated patients with prior exposure to similar agents. Overlapping growth factor support to prevent neutropenia is safe and effective with this regimen. Although our prior experience with single-agent bortezomib suggests that a weekly schedule of administration is inferior to a twice-weekly schedule (14), the current combination regimen is designed to exploit preclinical synergies seen between the agents, and it may not be possible to extrapolate single agent activity to multiagent regimens where such synergies may exist. In a recent study comparing weekly with twice-weekly bortezomib in combination with rituximab, both schedules yield similar clinical outcomes (25). As discussed above, we cannot make definitive comparisons between the efficacy of the two treatment schedules studied in this phase 1trial, and there may be significant differences in toxicity profile. We have therefore proceeded to a randomized phase II study to compare toxicity and efficacy between the two regimens described in this report.

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STATEMENT OF TRANSLATIONAL RELEVANCE

This Phase 1 study has built upon preclinical data demonstrating the synergies between bortezomib and rituximab, and bortezomib and cyclophosphamide. In order to assess how these drugs can be most safely combined in the clinic, a sequential phase 1 trial was conducted. This trial determined the suggested Phase 2 doses for two different treatment schedules of bortezomib combined with cyclophosphamide, rituximab and prednisone. The promising toxicity profile and efficacy seen in both arms of this study have led us to bring this regimen forward into a phase 2 trial. A multicenter, randomized phase 2 trial has recently been initiated in order to better characterize the efficacy of this regimen in a larger population of lymphoma patients, and to determine which schedule of this regimen is the least toxic and most efficacious. We plan to ultimately compare this regimen directly with the R-CVP regimen, to determine which is superior in this patient population. The results of this project have the potential to alter the treatment recommendations for a substantial number of patients with non-Hodgkin Lymphoma.

Table 1

Patient Demographics (N=55)

	Weekly (n=15)		Twice Weekly (n=40)		Combined (N=55)	
Characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**
Median age	66	61	64			
Male	6	(40)	19	(48)	25	(45)
Histology						
FL (grade 1–3a)	5	(36)	19	(48)	24	(45)
FL (grade 3b)	1	(7)	0	(0)	1	(2)
MCL	3	(20)	8	(20)	11	(20)
MZL	2	(13)	6	(15)	8	(16)
SLL	1	(7)	3	(8)	4	(7)
Transformed FL *	3	(20)	4	(10)	7	(11)
Bulky Disease at Baseline	5	(33) **	21	(57) **	26	(50) **
Prior Therapies						
Anthracycline combination	12	(80)	32	(80)	44	(80)
Alkylator combination	13	(87)	37	(93)	50	(91)
Auto PBSCT	3	(20)	7	(18)	10	(18)
Bortezomib	4	(27)	3	(8)	7	(13)
Platinum based	4	(27)	13	(33)	17	(31)
Purine-analog based	3	(20)	5	(13)	8	(15)
Refractory to prior therapy †	8	(53)	16	(40)	24	(44)
RIT	4	(27)	9	(23)	13	(24)
Rituximab	14	(93)	36	(90)	50	(91)
Median No. of treatments	4	2	2			
Median PFS (mos) to last prior treatment ***	7.9	13.6	11.5			

Abbreviations: MCL, mantle cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma SLL, small lymphocytic lymphoma, PBSCT, peripheral blood stem cell transplantation; RIT, radioimmunotherapy; PFS, progression-free survival

[*] Transformation was based on clinical/radiologic characteristics in 2 patients, and histologic confirmation in the other.

[†] Patients were deemed refractory to their prior therapy if they failed to respond, or if they progressed within 6 months of treatment

[**] Bulky disease was defined as any site of involvement measuring ≥ 5 cm in greatest diameter. Only those patients with baseline documentation of measurable disease (n = 14 in the weekly group, n = 37 in the twice-weekly group) were included.

[***] The number of patients evaluable for PFS from last prior treatment was 15 in the weekly group, 37 in the twice-weekly group, and 52 in the combined group (i.e. dates of last prior treatment and progression after that treatment were not available for 3 patients in the twice-weekly group).

Table 2

Bortezomib and Cyclophosphamide Dose Escalation Schedule (21-Day Cycle)[a]

Cohort	Bortezomib (mg/m^2)	Cyclophosphamide (mg/m^2)	# Pts	DLT
Weekly Schedule[b]				
1	1.3	750	3	
2	1.6	750	6	Gr3 diarrhea
3	1.6	1000	3	
4	1.8	1000	4	1 pt replaced[†]
Twice-Weekly Schedule [c]				
5	1.0	750	3	
6	1.3	750	6	2 Gr3 ntpf[*]
7 [d]	1.3	1000	12	1 pt:Gr4 plts/Gr4 neurop[#]
8 [d]	1.5	1000	4	1 pt replaced[†]
9[e]	1.3[e]	1000[e]	10	

[a]With fixed dose of rituximab (375 mg/m^2 day 1) and prednisone (100 mg daily, days 2–6)

[b]Bortezomib administered days 2 and 8.

[c]Bortezomib administered days 2, 5, 9 and 12.

[d]With prophylactic filgrastim days 3, 4, 6, 7, 8,10, 11

[e]With pegfilgrastim day 2

[*]ntpf = neutropenic fever

[#]neurop = sensory neuropathy

[†]2 patients were replaced because they did not receive at least one dose of bortezomib

Table 3

Hematologic Toxicities*

	Weekly								Twice-Weekly							
Toxicity	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**(%)**	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**(%)**
Anemia	8	(53)	6	(40)					23	(58)	6	(15)	3	(8)		
Leukopenia	6	(40)	2	(13)	7	(47)	1	(7)	10	(25)	7	(18)	8	(20)	3	(8)
Lymphopenia					8	(53)	3	(20)	4	(10)			24	(60)	5	(13)
Neutropenia			4	(27)	5	(33)	3	(20)	1	(3)	3	(8)	4	(10)	11	(28)
Thrombocytopenia	6	(40)			3	(20)	2	(13)	20	(50)	8	(20)	4	(10)	3	(8)

*All toxicities are corrected for baseline

Table 4

Nonhematologic Toxicities* Above Baseline (Grade 1 and 2 toxicities occurring in ≥ 10% and all grade 3 and 4 toxicities are shown)

	Weekly								Twice-Weekly							
Toxicity	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**%**	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**(%)**
Albumin, low	6	(40)	2	(13)					12	(30)						
Alk phos	5	(33)							19	(48)						
Allerg rhinitis	3	(20)							2	(5)	1	(3)				
ALT	8	(53)	2	(13)					15	(38)	1	(3)				
Anxiety	2	(13)								(0)						
AST	9	(60)							15	(38)						
Bilirubin	1	(7)	2	(13)					3	(8)	2	(5)	1	(3)		
Bruising	2	(13)							4	(10)						
Calcium, low	5	(33)	3	(20)						(0)						
Constipation	6	(40)	4	(27)					11	(28)	15	(38)				
Cough	13	(87)							10	(25)						
Creatinine	5	(33)							11	(28)	1	(3)				
Dehydration					1	(7)										
Diarrhea	6	(40)	3	(20)	1	(7)			14	(35)	5	(13)				
Dizziness	2	(13)								(0)						
Dry Mouth									4	(10)						
Dyspnea	8	(53)							12	(30)	5	(13)				
Edema	7	(47)							4	(10)						

	Weekly								Twice-Weekly							
Toxicity	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**%**	**Grade 1**	**(%)**	**Grade 2**	**(%)**	**Grade 3**	**(%)**	**Grade 4**	**(%)**
Fatigue	7	(47)	6	(40)					19	(48)	8	(20)	3	(8)		
Febrile neutropenia					1	(7)				(0)			2	(5)		
Fever	9	(60)	2	(13)					6	(15)	2	(5)	1	(3)		
Glucose, high	9	(60)	4	(27)					18	(45)	2	(5)				
Glucose, low	4	(27)	1	(7)	1	(7)			7	(18)	1	(3)				
Hypoxia													1	(3)		
Incontinence, anal					1	(7)										
Infection					2	(13)							1	(3)		
Insomnia	2	(13)							6	(15)						
Magnesium, low	2	(13)	1	(7)					3	(8)	1	(3)				
Nausea	8	(53)	2	(13)					10	(25)	6	(15)				
Neuropathy: sensory	4	(26)	2	(13)					15	(38)	9	(23)	1	(3)	1	(3)
Phosphate, low			4	(27)	3	(20)				(0)	6	(15)	1	(3)		
Potassium, high									7	(18)	3	(8)				
Potassium, low	2	(13)			2	(13)			4	(10)			1	(3)		
Pruritus	2	(13)	1	(7)					4	(10)						
Rash	2	(13)	1	(7)					3	(8)	3	(8)				
Rigors/chills	5	(33)							4	(10)						
Sodium, high	7	(47)							14	(35)						
Sodium, low	5	(33)							9	(23)						

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Toxicity	Weekly						Twice-Weekly					
	Grade 1	(%)	Grade 2	(%)	Grade 3	(%)	Grade 4	%	Grade 1	(%)	Grade 2	(%)	Grade 3	(%)	Grade 4	(%)
Sweating	2	(13)							1	(3)						
Urinary frequency	2	(13)							3	(8)						
Vomiting	3	(20)	1	(7)					4	(10)	2	(5)				

*All toxicities are corrected for baseline

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Table 5

Overall Response in Evaluable Patients (N = 46)

Response Evaluation	POD No. (%)	SD No. (%)	PR No. (%)	CR/CRu No. (%)	ORR No. (%)	ITT ORR No. (%)
Weekly (n = 13)	1 (8)	6 (46)	3 (23)	3 (23)	6 (46)	6 (38)
Twice wkly (n=33)	3 (9)	9 (27)	9 (27)	12 (36)	21 (64)	21 (51)
By Histology						
FL Gr 1-3a (n = 23)	1 (4)	8 (35)	7 (30)	7 (30)	14 (61)	14 (58)
FL Gr 3b (n = 1)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)
MCL (n = 10)	1 (10)	3 (30)	1 (10)	5 (50)	6 (60)	6 (50)
MZL (n = 6)	0 (0)	1 (17)	3 (50)	2 (33)	5 (83)	5 (56)
SLL (n = 2)	1 (50)	0 (0)	0 (0)	1 (50)	1 (50)	1 (25)
Transformed (n = 4)	2 (50)	2 (50)	0 (0)	0 (0)	0 (0)	0 (0)
By Response to Last Prior Therapy						
Refractory[†] (n = 23)	1 (5)	7 (33)	10 (48)	3 (14)	13 (62)	13 (52)
Responsive (n = 24)	3(14)	7 (32)	2 (9)	10 (45)	12 (55)	12 (48)

Abbreviations: POD, progression of disease; SD, stable disease; PR, partial response; CR/CRu, complete response/complete response unconfirmed; ORR, objective response rate; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; wkly = weekly, Gr = grade ITT ORR = Intention to Treat ORR including all patients enrolled (n = 16 weekly, 41 twice-weekly)

[†]Patients were deemed refractory to their prior therapy if they failed to respond, or if they progressed within 6 months of treatment