Bortezomib for the Treatment of Mantle Cell Lymphoma

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Abstract **Purpose:** To describe the Food and Drug Administration review and marketing approval considerations for bortezomib (Velcade) for the treatment of patients with mantle cell lymphoma.
Experimental Design: Food and Drug Administration reviewed a multicenter study of bortezomib in 155 patients with progressive mantle cell lymphoma after at least one prior therapy.
Results: Seventy-seven percent were stage IV, and 75% had one or more extranodal sites of disease. Prior therapy included an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. Median age was 65 years. All received bortezomib 1.3 mg/m^2 i.v. on days 1, 4, 8, and 11 of each 3-week cycle. The primary end point was response. Response and progression were determined by independent review of serial computed tomography scans using International Lymphoma Workshop Response Criteria. The overall response rate was 31%, including complete response (CR) plus CR unconfirmed (CRu) plus partial response; median response duration was 9.3 months. The CR plus CRu response rate was 8% with a median duration of 15.4 months. Adverse events were similar to those observed previously for bortezomib. The most commonly reported treatment-emergent adverse events were asthenia (72%), peripheral neuropathies (55%), constipation (50%), diarrhea (47%), nausea (44%), and anorexia (39%). The most common adverse event leading to discontinuation was neuropathy.
Conclusions: Bortezomib received regular approval for the treatment of patients with mantle cell lymphoma in relapse after prior therapy.

On December 8, 2006, bortezomib (Velcade for injection) received marketing approval by the U.S. Food and Drug Administration (FDA) for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy for their disease. This drug approval is the first for the specific indication of mantle cell lymphoma, a subtype of non-Hodgkin's lymphoma characterized by unique pathologic, cytogenetic, and clinical features (1).

Bortezomib, a modified dipeptidyl boronic acid derived from leucine and phenylalanine, is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome, a large protein complex that degrades most intracellular proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins. Inhibition of the 26S proteasome prevents this targeted proteolysis, which then may alter multiple signaling cascades within the cell.

Bortezomib had received accelerated approval in 2003 for multiple myeloma after two prior therapies and in 2005 received regular approval for the treatment of multiple myeloma after one prior therapy (2). The sponsor, Millennium Pharmaceuticals, Inc., in conjunction with Johnson and Johnson Research and Pharmaceutical Development, met with FDA during the design of this registration study and during the conduct and analysis phases to assure agreement on the study design, end points, adjudication plan for assessing the end points, and the analysis plan intended to show efficacy and safety necessary for drug approval. The regular marketing approval for mantle cell lymphoma (after prior therapy) was based on the results of the FDA review of the sponsor's single, multicenter study. This report summarizes the FDA analysis and basis for approval.

Materials and Methods

The sponsor conducted a single-arm, single-agent prospective study of bortezomib in 155 patients with relapsed, progressive mantle cell lymphoma following one or two prior therapies among 35 centers in North America and Europe. The initial proposal was for a single-arm phase 2 study to assess time-to-progression, overall response rate, and response duration for previously treated mantle cell lymphoma patients. The sample size initially was chosen to provide 80% power, using a two-sided α of 0.05, to show a 50% improvement in time to progression when compared with a historical control group. The

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primary analysis population was all patients who received at least one dose of drug. FDA cautioned that interpreting time-to-progression in a single-arm study would be problematic due to variables such as patient selection, natural history, and evolving concurrent therapies and supportive measures. The sponsor agreed prospectively that the primary end point for the supplemental New Drug Application submission was overall response rate, as defined by the 1999 International Lymphoma Workshop Response Criteria (IWRC; ref. 3) to include the proportion of patients achieving complete response (CR) plus CR unconfirmed (CRu) plus partial response (PR). In accord with these 1999 criteria, no positron emission tomography or isotope scans were used for disease assessment. Duration of response was calculated from the date of initial documentation of first response to the date of progressive disease.

Tumor assessments for the primary end point were determined by serial tumor measurements from computed tomography (CT) scans. The sponsor selected an independent radiology review contractor and developed a protocol for the process of blinded scan review. The sponsor also developed an algorithm to apply the IWRC consistently.

Response, as defined by the IWRC, is a composite requiring assessment of all of the following: CT scan results, disease-related symptom assessment, physical examination of nonscanned areas, disease-related biochemistry (e.g., lactate dehydrogenase), and bone marrow evaluation (if positive at baseline). CR requires not only the complete disappearance of disease but also disappearance of all disease-related symptoms. CRu denotes patients who fulfill the CR criteria except for a residual lymph node mass (and >75% shrinkage) or indeterminate bone marrow. PR required a ≥50% decrease in the sum of the perpendicular diameters of the six largest dominant nodes or nodal masses.

Protocol eligibility required a pathologic diagnosis of mantle cell lymphoma, including expression of cyclin D1 or evidence of t(11;14) by cytogenetics, fluorescence *in situ* hybridization, or PCR; an independent pathology review was also planned to verify the pathology findings. In addition to adequate performance status (Karnofsky score, ≥50%), patients were required to have measurable (or evaluable) disease with documented relapse or progression following first- or second-line treatment including an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. No prior bortezomib therapy, recent radiation, or recent radioisotope therapy was allowed.

All patients received bortezomib 1.3 mg/m^2 i.v. bolus on days 1, 4, 8, and 11 every 21 days for up to 12 months. Prophylactic use of leukocyte growth factors was proscribed. Tumor assessments by CT and clinical examinations were done every 6 weeks through week 18 and then every 12 weeks. Dose adjustments and interruptions followed the schedule in the FDA-approved label.[1]

Results

Among the 155 mantle cell lymphoma patients who were enrolled and received at least one dose of bortezomib, 89% were confirmed as fulfilling diagnostic criteria for mantle cell lymphoma by independent pathology review. This high level of pathology concordance was expected and is deemed satisfactory. The median time from original diagnosis of mantle cell lymphoma to the start of bortezomib was 2.3 years, the median patient age was 65 years, 77% were stage IV, and 55% had positive bone marrows at entry.

With regard to prior therapy, all patients had received at least one prior regimen, and 91% had received all three agents: anthracycline, cyclophosphamide, and rituximab. In addition, 37% had received prior high-intensity chemotherapy including hyper-CVAD, ICE, ESHAP, or DHAP with or without stem cell transplant. Baseline patient and disease characteristics are summarized in Tables 1 and 2.

FDA reviewed the sponsor's data and independently analyzed response and progression. The response rate was determined using the entire enrolled population (155 patients) rather than some other response-evaluable subgroup as the denominator. The results were calculated using the algorithm-determined response and duration of response in all patients except for one patient in whom only clinical tumor measurements (palpable neck lymph nodes) were available. Protocol deviations and violations were judged as minor and not likely to have altered the results. Several study sites were audited for comparison of the source documents with the data recorded in the case report forms. No substantive deficiencies were found.

The efficacy findings are summarized in Table 3. The overall response rate was 31% (48 of 155) and the 95% confidence interval (95% CI) was 24%, 39%. The median duration of response was 9.3 months (95% CI, 5.4, 13.8). For the CR plus CRu responder group, the response rate was 8% (12 of 155; 95% CI, 4%, 13%); the median duration of response was 15.4 months (95% CI, 13.4, 15.4). [The 95% CI upper bound is equal to the median duration of response for the CR plus CRu responders (n = 12) because of the high percentage of censoring (8 of the 12 responders did not experience disease progression or death)]. Only four events of progression or death were observed in CR plus CRu responders at 45, 143, 409, and 470 days since their first response.

Adverse events were generally similar to those previously described in myeloma studies and are described in the product label. Adverse events resulting in drug discontinuation occurred in 30% of the patients and were consistent with prior Velcade experience. The most common adverse event associated with drug discontinuation was neuropathy.

Discussion

The study population seems representative of a population of patients with mantle cell lymphoma treated with optimal

Table 1. Baseline demographic characteristics in 155 mantle cell lymphoma patients

	***N* = 155**
Age (y)	
Mean (SD)	64.9 (9.3)
Median	65.0
Minimum, maximum	42, 89
Sex, *n* (%)	
Male	125 (81)
Female	30 (19)
Race, *n* (%)	
White	142 (92)
Black	6 (4)
Hispanic	4 (3)
Asian or Pacific Islander	3 (2)
KPS, *n* (%)	
<50	0
50-60	7 (5)
70-80	37 (24)
90-100	109 (71)
Missing	2

Abbreviation: KPS, Karnofsky performance score.

[1] http://www.fda.gov/cder/foi/label/2006/021991lbl.pdf

Table 2. Baseline disease characteristics in 155 mantle cell lymphoma patients

Prognostic factor	*N* = 155
Time since initial diagnosis to first dose (y)	
Mean (SD)	2.7 (1.9)
Median	2.3
Minimum, maximum	0.2, 11.2
Diagnosed <3 y before first dose, *n* (%)	103 (66)
Diagnosed ≥3 y before first dose, *n* (%)	52 (34)
MCL stage at screening, *n* (%)/*n* (%)	
Stage I/II	5 (3)/7 (5)
Stage III/IV	24 (15)/119 (77)
IPI score	
0-1	34 (23)
2	48 (33)
3	48 (33)
4-5	17 (12)
Missing	8
LDH, *n* (%)/*n* (%)	
Normal/elevated	95 (64)/54 (36)
Missing	6
No. involved extranodal sites, *n* (%)/*n* (%)	
0/1	38 (25)/64 (41)
2/≥3	32 (21)/21 (14)
Bone marrow evaluation (biopsy and/or aspirate)	
Positive results	84 (55)
Negative/indeterminate	70 (45)
No. prior lines of therapy	
1/2	84 (54)/ 65 (42)
≥3	6 (4)
Received prior regimen containing the following agents	
Anthracycline/mitoxantrone	152 (98)
Alkylating agents	150 (97)
Rituximab	149 (96)
Received at least 2 of the above 3	155 (100)
Received all of the above 3	141 (91)
Received prior high-intensity therapy*	58 (37)
Received prior high-intensity therapy as last prior regimen*	47 (30)

Abbreviations: MCL, mantle cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase.
*High-intensity prior regimen defined as hyper-CVAD, R-hyper-CVAD, ICE/ESHAP/DHAP with or without rituximab, and stem cell transplant.

front-line combination chemotherapy and without available therapy of likely benefit. The study patients are probably healthier and slightly younger than a community-based patient sample; this is expected by the study design and referral center nature of the study sites. In this group, with median age 65 years, 77% stage IV, 75% with extranodal disease sites, and 37% with prior "high-intensity" therapy, such as stem cell transplant or hyper-CVAD, historical experience indicates that few patients would be expected to obtain benefit from further therapies.

In designing this study, the sponsor sought to apply the IWRC lymphoma response and progression consensus criteria literally using an algorithm. During the initial prospective validation of the algorithm, some criteria proved to be too sensitive, and some modifications of the IWRC definitions were necessary to achieve concurrence with clinical findings. For example, serial measurements of small lymph nodes (<1 cm) could vary sufficiently between CT assessments to suggest progression mathematically (a 50% increment from nadir), although there was no evidence clinically that progression was occurring.

Minor modifications to the IWRC definitions were made. The lymph node dimensions had to exceed 1.0 cm to be considered measurable by CT, and the minimum increment in dimension had to be at least 0.5 cm to qualify for assessment of change. For PR, response assessment criteria were changed to allow inclusion of sites of dominant extranodal disease (still requiring a 50% or greater decrease in the sum of the perpendicular diameters of measurable sites of disease) because extranodal disease is common in mantle cell lymphoma. The sponsor presented these findings, and FDA concurred with the changes. These changes may be of interest to others using the IWRC measurement procedures for response and progression.

For this group, single-agent bortezomib therapy resulted in a 31% overall response rate with a median duration of response of 9.2 months. For the 12 CR plus CRu patients, the response rate was 8%, the median duration of response for this group was 15.4 months, and the Kaplan-Meier estimate of 1-year survival was 100%. No unexpected frequency or severity of adverse events was observed.

This experience in a different population, patients with mantle cell lymphoma, provided further safety information for bortezomib beyond the myeloma experience. Interstitial lung disease, which has been reported rarely in myeloma patients (4, 5), was not observed during this study. Fluid retention syndromes, including pleural effusion, ascites, edema, congestive heart failure, and respiratory distress, have occurred at low frequency and are described in the current product label. Ongoing clinical attention to hydration status is important for the safe use of bortezomib because adverse events have included both dehydration and fluid retention syndromes.

The sponsor's study is the primary basis for the approval action. During the conduct of this study, several other clinical investigations were reported (6–8). Although the additional studies were not formally reviewed for this supplemental New Drug Application, the findings are from multiple independent sources and seem consistent with the Millennium results.

Mantle cell lymphoma is recognized as an uncommon and distinct category of lymphoma based on several unique characteristics, including pathology, cytogenetics, biomarkers (including immunohistochemistry), and clinical behavior. Despite high initial response rates, most patients with mantle cell lymphoma relapse and median survival from diagnosis is 3 to 4 years. For a well-characterized population of relapsed or refractory mantle cell lymphoma patients such as those enrolled here, FDA agreed that alternative therapy of general benefit is not available. A randomized study in a population

Table 3. FDA response analysis in 155 mantle cell lymphoma patients

Response analyses (*N* = 155)	*n* (%)	95% CI
Overall response rate (CR + CRu + PR)	48 (31)	(24, 39)
CR (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
PR	36 (23)	(17, 31)
Duration of response, median (mo)		
CR + CRu + PR (*n* = 48)	9.3	(5.4, 13.8)
CR + CRu (*n* = 12)	15.4	(13.4, 15.4)
PR (*n* = 36)	6.1	(4.2, 9.3)

receiving second-line therapy for mantle cell lymphoma is challenging to conduct considering the low frequency of the disease, extensive yet varied prior therapy, comorbidities in an older age population, and usual rapid progression of recurrent mantle cell lymphoma. When a disease process is known to proceed rapidly in the absence of effective therapy, a response end point of sufficient magnitude and duration for a single-agent treatment may be clinically meaningful and sufficient evidence for an approval.

In this setting, a single-arm, single-agent study showing a clinically meaningful response rate, with durability, with evidence of response in visceral sites, with adherence to a generally recognized set of criteria defining the response and progression criteria, and with verification by independent blinded review of the tumor assessment end point, could show substantial evidence of efficacy and safety for bortezomib. In addition, safety could consist of evidence that the adverse events, toxicity, and dose adjustments of bortezomib remained broadly similar to the findings already established in myeloma. Where alternative therapy is available and perceived to be of benefit, an active control comparator arm should be chosen, and the design should show superiority on an end point reflecting the treatment effect on the entire study population (such as time-to-progression or progression-free survival). For this reason, such time-to-event end points are more informative than the evaluation of a responder subgroup, assuming that the criteria defining progression are explicit and amenable to careful measurement.

FDA reviewed the patients' on-study characteristics, the study conduct, the response and progression determinations by the investigators and the independent reviewers, and the tolerance to bortezomib treatment. The bortezomib responses are convincing for their durability and for their reduction of the disease burden on the responding patients (e.g., adenopathy and hepatosplenomegaly), and they were verified by independent blinded radiologic review of serial CT scans. Toxicity is similar to that observed in the myeloma setting, is already well described in the existing label, and is familiar to hematology-oncology physicians. FDA judged the results sufficient to conclude that clinical benefit was shown in this advanced disease state. Quality clinical science with compelling evidence allows the FDA to act promptly. Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions, and contraindications, is available online.[1]

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