CLINICAL UPDATE

Brand Name	bortezomib
Generic Name	bortezomib
Drug Manufacturer	Hospira, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New strength

FDA APPROVAL DATE

May 2, 2022

LAUNCH DATE

May 16, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 5 - New Formulation or New Manufacturer, New Drug Application (NDA): 209191

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Bortezomib for Injection is a proteasome inhibitor indicated for:

- Treatment of adult patients with multiple myeloma.
- Treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy.

MECHANISMS OF ACTION

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma.

DOSAGE FORM(S) AND STRENGTH(S)

For injection: 1 mg or 2.5 mg of bortezomib as a lyophilized powder in a single-dose vial for reconstitution and withdrawal of the appropriate individual patient dose.

DOSE & ADMINISTRATION

The recommended starting dose of Bortezomib for Injection is 1.3 mg/m^2. Bortezomib for Injection is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL.

Dosage in Previously Untreated Multiple Myeloma-

Bortezomib for Injection is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles as shown in Table 1.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice Weekly Bortezomib for Injection (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib for Injection (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly Bortezomib for Injection (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Bortezomib for Injection (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Dose Modification Guidelines for Bortezomib for Injection When Given in Combination with Melphalan and Prednisone

Prior to initiating any cycle of therapy with Bortezomib for Injection in combination with melphalan and prednisone:

- Platelet count should be at least 70 x 10^9 /L and the absolute neutrophil count (ANC) should be at least 1 x 10^9 /L.
- Non-hematological toxicities should have resolved to Grade 1 or baseline.

Table 2: Dose Modifications During Cycles of Combination Bortezomib for Injection, Melphalan and Prednisone Therapy

Toxicity	**Dose modification or delay**
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle.	Consider reduction of the melphalan dose by 25% in the next cycle

If platelet count is not above 30 x 10^9/L or ANC is not above 0.75 x 10^9/L on a Bortezomib for Injection dosing day (other than Day 1)	Withhold Bortezomib for Injection dose
If several Bortezomib for Injection doses in consecutive cycles are withheld due to toxicity	Reduce Bortezomib for Injection dose by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher non-hematological toxicities	Withhold Bortezomib for Injection therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, Bortezomib for Injection may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For Bortezomib for Injection-related neuropathic pain and/or peripheral neuropathy, hold or modify Bortezomib for Injection.

Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Bortezomib for Injection (1.3 mg/m2 /dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib for Injection may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib for Injection.

Patients with multiple myeloma who have previously responded to treatment with Bortezomib for Injection (either alone or in combination) and who have relapsed at least six months after their prior Bortezomib for Injection therapy may be started on Bortezomib for Injection at the last tolerated dose. Retreated patients are administered Bortezomib for Injection twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Bortezomib for Injection. Bortezomib for Injection may be administered either as a single agent or in combination with dexamethasone.

EFFICACY

Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma- A prospective, international, randomized (1:1), open-label clinical study (NCT00111319) of 682 patients was conducted to determine whether bortezomib administered intravenously (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of nine cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Antiviral prophylaxis was recommended for patients on the bortezomib study arm.

The median age of the patients in the study was 71 years (48;91), 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80 (60;100). Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/L (64;165), and a median platelet count of 221,500/microliter (33,000;587,000).

Efficacy results for the trial are presented in Table 3. At a pre-specified interim analysis (with median follow-up of 16.3 months), the combination of bortezomib, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was

halted, and patients receiving melphalan and prednisone were offered bortezomib in addition. A later, pre-specified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the bortezomib, melphalan and prednisone treatment arm despite subsequent therapies including bortezomib based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the bortezomib, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

Table 3: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	Bortezomib, Melphalan and Prednisone (n=344)	Melphalan and Prednisone (n=338)
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median [a] (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio [b]	0.54	
(95% CI) p-value [c]	(0.42, 0.70) 0.000002	
Progression-Free Survival		
Events n (%)	135 (39)	190 (56)
Median [a] (months)	18.3	14.0
(95% CI)	(16.6,21.7)	(11.1, 15.0)
Hazard ratio [b]	0.61	
(95% CI) p-value [c]	(0.49, 0.76) 0.00001	
Response Rate		
CR[d] n (%)	102 (30)	12 (4)
PR[d] n (%)	136(40)	103(30)
nCR n (%)	5 (1)	0
CR + PR[d] n (%)	238 (69)	115 (34)
p-value[e]	$<10^{-10}$	
Overall Survival at Median Follow-Up of 36.7 Months		
Events (deaths) n (%)	109 (32)	148 (44)
Median [a] (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio [b]	0.65	
(95% CI) p-value [c]	(0.51, 0.84) 0.00084	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis. a. Kaplan-Meier estimate, b. Hazard ratio estimate is based on a Cox proportional-hazard

model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than one indicates an advantage for bortezomib, melphalan and prednisone, c. p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region, d. EBMT criteria, e. p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors.

Randomized, Clinical Study in Relapsed Multiple Myeloma of Bortezomib vs Dexamethasone- A prospective Phase 3, international, randomized (1:1), stratified, open-label clinical study (NCT00048230) enrolling 669 patients was designed to determine whether bortezomib resulted in improvement in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline Grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/µL. A total of 627 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had previously received (one previous line vs more than one line of therapy), time of progression relative to prior treatment (progression during or within six months of stopping their most recent therapy vs relapse > 6 months after receiving their most recent therapy), and screening beta2-microglobulin levels (≤ 2.5 mg/L vs > 2.5 mg/L).

Baseline patient and disease characteristics are summarized in Table 4.

Table 4: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

Patient Characteristics	**Bortezomib (N=333)**	**Dexamethasone (N=336)**
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median $beta_2$-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%

Prior experimental or other types of therapy	3%	2%

Patients in the bortezomib treatment group were to receive 8, three-week treatment cycles followed by 3, five-week treatment cycles of bortezomib. Patients achieving a CR were treated for four cycles beyond first evidence of CR. Within each three-week treatment cycle, bortezomib 1.3 mg/m^2 /dose alone was administered by intravenous bolus twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten-day rest period (Days 12 to 21). Within each five-week treatment cycle, bortezomib 1.3 mg/m^2 /dose alone was administered by intravenous bolus once weekly for four weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35).

Patients in the dexamethasone treatment group were to receive 4, five-week treatment cycles followed by 5, four-week treatment cycles. Within each five-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15-day rest period (Days 21 to 35). Within each four-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered bortezomib at a standard dose and schedule on a companion study. Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted, and all patients randomized to dexamethasone were offered bortezomib, regardless of disease status.

In the bortezomib arm, 34% of patients received at least one bortezomib dose in all eight of the three-week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number of bortezomib doses during the study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all four of the five-week treatment cycles of therapy, and 6% received at least one dose in all nine cycles.

The time to event analyses and response rates from the relapsed multiple myeloma study are presented in Table 5. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF-). Partial response (PR) requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least two occasions for a minimum of at least six weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF+).

Table 5: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study

Efficacy Endpoint	**All Patients**		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**	
	Bortezomib	**Dex**	**Bortezomib**	**Dex**	**Bortezomib**	**Dex**
	(n=333)	**(n=336)**	**(n=132)**	**(n=119)**	**(n=200)**	**(n=217)**
Time to Progression Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio [b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value [c]	<0.0001		0.0019		<0.0001	
Overall Survival Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio [b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value [c,d]	<0.05		<0.05		<0.05	

Response Rate Population[e] n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR [f] n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR [f] n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR [f,g] n(%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR [f] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value [h]	<0.0001		0.0035		<0.0001	

[a] Kaplan-Meier estimate [b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than one indicates an advantage for bortezomib

[c] p-value based on the stratified log-rank test including randomization stratification factors [d] Precise p-value cannot be rendered [e] Response population includes patients who had measurable disease at baseline and received at least one dose of study drug [f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category [g] In two patients, the IF was unknown

[h]p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

Randomized, Open-Label Clinical Study of Bortezomib Subcutaneous vs Intravenous in Relapsed Multiple Myeloma- An open-label, randomized, Phase 3 non-inferiority study (NCT00722566) compared the efficacy and safety of the subcutaneous administration of bortezomib vs the intravenous administration. This study included 222 bortezomib naïve patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of bortezomib by either the subcutaneous (n=148) or intravenous (n=74) route for eight cycles. Patients who did not obtain an optimal response (less than Complete Response (CR)) to therapy with bortezomib alone after four cycles were allowed to receive oral dexamethasone 20 mg daily on the day of and after bortezomib administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade ≥ 2 peripheral neuropathy or neuropathic pain, or platelet counts < 50,000/µL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (one previous line vs more than one line of therapy), and international staging system (ISS) stage (incorporating beta2-microglobulin and albumin levels; Stages I, II, or III).

The baseline demographic and other characteristics of the two treatment groups are summarized as follows: the median age of the patient population was approximately 64 years of age (range: 38 to 88 years), primarily male (subcutaneous: 50%, intravenous: 64%); the primary type of myeloma is IgG (subcutaneous: 65% IgG, 26% IgA, 8% light chain; intravenous: 72% IgG, 19% IgA, 8% light chain), ISS staging I/II/III (%) was 27, 41, 32 for both subcutaneous and intravenous, Karnofsky performance status score was ≤ 70% in 22% of subcutaneous and 16% of intravenous, creatinine clearance was 67.5 mL/min in subcutaneous and 73 mL/min in intravenous, the median years from diagnosis was 2.68 and 2.93 in subcutaneous and intravenous respectively and the proportion of patients with more than one prior line of therapy was 38% in subcutaneous and 35% in intravenous.

This study met its primary (non-inferiority) objective that single agent subcutaneous bortezomib retains at least 60% of the overall response rate after four cycles relative to single agent intravenous bortezomib. The results are provided in Table 6.

Table 6: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of Bortezomib Subcutaneous vs Intravenous		
	Subcutaneous Bortezomib	**Intravenous Bortezomib**
Intent to Treat Population	**(n=148)**	**(n=74)**

Primary Endpoint		
Response Rate at 4 Cycles		
ORR (CR + PR) n (%)	63 (43)	31 (42)
Ratio of Response Rates (95% CI)	1.01 (0.73, 1.40)	
CR n (%)	11 (7)	6 (8)
PR n (%)	52 (35)	25 (34)
nCR n (%)	9 (6)	4 (5)
Secondary Endpoints		
Response Rate at 8 Cycles		
ORR (CR + PR)	78 (53)	38 (51)
CR n (%)	17 (11)	9 (12)
PR n (%)	61 (41)	29 (39)
nCR n (%)	14 (9)	7 (9)
Median Time to Progression, months	10.4	9.4
Median Progression-Free Survival, months	10.2	8.0
1-year Overall Survival (%) [a]	72.6	76.7

[a]Median duration of follow-up is 11.8 months

A Randomized, Phase 2 Dose-Response Study in Relapsed Multiple Myeloma- An open-label, multicenter study randomized 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy to receive bortezomib 1 mg/m^2 or 1.3 mg/m^2 intravenous bolus twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten-day rest period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma and first dose of bortezomib on this trial was two years, and patients had received a median of one prior line of treatment (median of three prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

A Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma- Patients from the two Phase 2 studies, who in the investigators' opinion would experience additional clinical benefit, continued to receive bortezomib beyond eight cycles on an extension study. Sixty-three (63) patients from the Phase 2 multiple myeloma studies were enrolled and received a median of seven additional cycles of bortezomib therapy for a total median of 14 cycles (range: 7 to 32). The overall median dosing intensity was the same in both the parent protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard three-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged bortezomib treatment.

A Single-Arm Trial of Retreatment in Relapsed Multiple Myeloma- A single-arm, open-label trial (NCT00431769) was conducted to determine the efficacy and safety of retreatment with bortezomib. One hundred and thirty patients (≥18 years of age) with multiple myeloma who previously had at least partial response on a bortezomib-containing regimen (median of two prior lines of therapy [range: 1 to 7]) were retreated upon progression with bortezomib administered intravenously. Patients were excluded from trial participation if they had peripheral neuropathy or neuropathic pain of Grade ≥2. At least six months after prior bortezomib therapy, bortezomib was restarted at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤ 1.0 mg/m^2 (n=37) and given on Days 1, 4, 8 and 11 every three weeks for maximum of eight cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with bortezomib to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of bortezomib retreatment cycles.

The primary endpoint was best confirmed response to retreatment as assessed by European Group for Blood and Marrow Transplantation (EBMT) criteria. Fifty of the 130 patients achieved a best confirmed response of Partial Response or better for an overall response rate of 38.5% (95% CI: 30.1, 47.4). One patient achieved a Complete Response and 49 achieved Partial Response. In the 50 responding patients, the median duration of response was 6.5 months, and the range was 0.6 to 19.3 months.

Mantle Cell Lymphoma in Adult Patients Who Have Received at Least 1 Prior Therapy

A Phase 2 Single-Arm Clinical Study in Relapsed Mantle Cell Lymphoma after Prior Therapy- The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study (NCT00063713) of 155 patients with progressive disease who had received at least one prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were Stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty-seven percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of bortezomib 1.3 mg/m^2 /dose was administered twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for four cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity.

Responses to bortezomib are shown in Table 7. Response rates to bortezomib were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was four; in responding patients the median number of cycles was eight. The median time to response was 40 days (range: 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 7: Response Outcomes in a Phase 2 Relapsed Mantle Cell Lymphoma Study

Response Analyses (N=155)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
Duration of Response	**Median**	**95% CI**
CR + CRu + PR (N=48)	9.3 months	(5.4, 13.8)
CR + CRu (N=12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)