

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI). Refer to the AHFS Level of Evidence Rating System for additional information about interpretation of both the Evidence Rating and the Grade of Recommendation.

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
Bortezomib as front-line therapy for newly diagnosed multiple myeloma ineligible for stem cell transplant (SCT) <sup>a</sup>	<p><b>VMP (also referred to as VcMP)</b>  <i>Cycles 1-4</i>            Bortezomib 1.3 mg/m<sup>2</sup> IV (days 1, 4, 8, 11, 22, 25, 29, and 32)            Melphalan: 9 mg/m<sup>2</sup> po (days 1-4)            Prednisone: 60 mg/m<sup>2</sup> po (days 1-4)  <i>Cycles 5-9</i>            Bortezomib 1.3 mg/m<sup>2</sup> IV (days 1, 8, 22, and 29)            Melphalan: 9 mg/m<sup>2</sup> po (days 1-4)            Prednisone: 60 mg/m<sup>2</sup> po (days 1-4)</p> <p>Cycles repeated every 6 weeks for a total of 9 courses</p>	High quality; TTP and OS	Reasonable choice as front-line therapy for standard and high-risk multiple myeloma patients not eligible for stem-cell transplant. (Accepted)	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008
Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing an stem cell transplant (SCT)	<p><b>VD</b>            Bortezomib: 1.3 mg/m<sup>2</sup> IV (days 1, 4, 8, and 11)            Dexamethasone: 40 mg po (days 1-4 during cycle 1-4; days 9-12 with cycle 1-2 only)</p> <p>Cycle repeated every 21 days x 4 courses</p>	Moderate quality; PFS and OS	Reasonable choice as front-line, induction therapy for standard and high-risk patients undergoing an autologous stem-cell transplant. (Accepted)	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008
Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing an stem cell transplant (SCT)	<p><b>VTD</b>            Bortezomib: 1.3 mg/m<sup>2</sup> IV (days 1, 4, 8, and 11)            Dexamethasone: 40 mg po (days 1, 2, 4, 5, 8, 9, 11, and 12)            Thalidomide: 200 mg po (days 1-21)</p> <p>Cycle repeated every 21 days x 3 courses</p>	Moderate quality; ORR	Not fully established	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008

<sup>a</sup> Bortezomib, in combination with melphalan and prednisone, was FDA approved for previously untreated multiple myeloma patients, on June 20, 2008.

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing an stem-cell transplant (SCT)	<b>PAD</b> Bortezomib with doxorubicin and dexamethasone. Dosage regimen <i>not</i> fully established. See clinical trial summary for regimen studied	Moderate quality; PFS, TTRT and OS	Not fully established	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008
Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing an stem-cell transplant (SCT)	<b>CyBorD</b> Bortezomib 1.3 mg/m <sup>2</sup> IV (days 1, 4, 8, and 11) Cyclophosphamide 300 mg/m <sup>2</sup> po (days 1, 8, 15, and 22) Dexamethasone 40 mg po (days 1-4, 9-12 and 17-20)  Cycle repeated every 28 days x 4 courses	Moderate quality; ORR	Not fully established	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008
Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing an stem-cell transplant (SCT)	<b>BCD (with BTD)</b> Bortezomib 1.3 mg/m <sup>2</sup> IV (days 1, 4, 8, and 11) Cyclophosphamide 300 mg/m <sup>2</sup> IV (days 1 and 8) Dexamethasone 40 mg po (days 1, 2, 4, 5, 8, 9, and 12) Cycle repeated every 21 days x 3 courses <i>followed by</i> Bortezomib 1.3 mg/m <sup>2</sup> IV (days 1, 4, 8, and 11) Thalidomide 100 mg po (days 1-21) Dexamethasone 40 mg po (days 1, 4, 8, and 11)  Cycle repeated every 21 days x 3 courses	Moderate quality; ORR	Not fully established	One committee member disclosed consultant and speaker's bureau activities with Celgene. Because of their expertise, this member participated in the review but was excluded from the final vote.	June 2008

## ***Clinical Trial Summary:***

### **Bortezomib as first-line therapy for newly diagnosed multiple myeloma patients ineligible for stem-cell transplant (SCT)**

#### **Bortezomib-melphalan-prednisone (VMP)<sup>1</sup>**

- VMP, when compared with melphalan-prednisone (MP) in a phase III randomized trial (n=682), resulted in an improved complete response (CR) rate (30 versus 4%, respectively) defined by immunofixation negativity using the European Bone Marrow Transplant (EBMT) response criteria.
- The time-to-progression (TTP) and overall survival (OS) at 2 years were superior with VMP compared with the MP regimen (TTP: 24 months versus 17 months; OS at 2 years: 82.6 versus 70% for the VMP and MP regimens, respectively).
- No significant differences in complete + ≥ partial response rates (CR + ≥ PR) in patients with varying renal function; creatinine clearance (CrCl) less than 60 mLs/min (CR and ≥ PR rates: 35 and 81%, respectively) or greater than 60 mL/min (CR and ≥ PR rates: 34 and 82%)
- Improved 2-year survival for patients for all ages in the VMP arm compared with MP, with similar survival rates for patients < 75 years of age (84%) and ≥ 75 years of age (79%).
- Similar CR and PR rates reported for high-risk patients [i.e., t(4;14), t(14;16) and chromosome 17 deletion] receiving VMP compared with standard risk patients (CR: 35 versus 32%, respectively; PR: 81 versus 82%, respectively. TTP reported as 23 months (standard risk) versus 20 months (high risk).
- Multivariate analysis showed trend towards improvement in TTP for patients with advanced-stage disease ( $\beta_2$ -microglobulin [ $\beta_2$ M] level > 5.5 mg/L and International Staging System [ISS] Stage III) for VMP compared with MP.
- A higher incidence of gastrointestinal side effects and grade III peripheral neuropathy were reported with the VMP regimen compared with MP; however, the reported cases of peripheral neuropathy were either resolved or improved in 75% of the patients in a median of 64 days.
- This study was stopped prematurely at the request of the Independent Data Monitoring Committee (IDMC) because of improved study endpoints for the VMP arm (i.e., TTP and OS).

### **Bortezomib as induction therapy for newly diagnosed multiple myeloma patients undergoing a stem-cell transplant (SCT).**

#### **Bortezomib-dexamethasone (VD)<sup>2</sup>**

- Bortezomib-dexamethasone, compared with vincristine-doxorubicin-dexamethasone (VAD) as an induction regimen, with or without DCEP (dexamethasone-cyclophosphamide-etoposide-cisplatin) consolidation, in a phase III randomized trial (n= 482), resulted in statistically significant improved responses as defined by complete/near complete responses (CR/nCR) and greater than a very good partial response (≥ VGPR), both post-induction and post-transplant (postinduction: CR/nCR: 21.3 versus 8.3%; ≥VGPR: 46.7 versus 18.6%; posttransplant: CR/nCR: 35 versus 23.6%; ≥VGPR: 61.7 versus 41.7%, for the VD and VAD regimens, respectively).
- Higher post induction-responses (CR/nCR) were reported with VD in patients with advanced-stage disease (e.g.,  $\beta_2$ M level > 3.0 mg/dL) compared with VAD (18.3 versus 7.9%, respectively); higher responses also reported with the VD regimen for patients with a chromosome 13 deletion (25.7 versus 9.6%, respectively). A higher percentage of patients, based on ≥VGPR response rates, were able to undergo an ASCT following induction with VD compared with VAD (71.8 versus 51%, respectively).

**Bortezomib-dexamethasone (VD) (cont)**

- A higher incidence of hematologic toxicity (i.e. anemia and neutropenia), thrombosis, and infections reported with VAD compared with VD (heme: 33 versus 17%, respectively; venous thromboembolism [VTE]: 8 versus 4%, respectively); however, the incidence of herpes zoster infections (2 versus 8%, respectively), rash (10 versus 5%, respectively), and grade III/IV peripheral neuropathy (6 versus 1.3%, respectively) was higher with VD than with VAD.
- Both the progression-free (PFS) and OS at 1 year were similar for both treatment groups (PFS: 93 versus 90%; OS: 97 versus 95%, for the VD and VAD regimens, respectively).

**Bortezomib-thalidomide-dexamethasone (VTD)<sup>3</sup>**

- Bortezomib-thalidomide-dexamethasone (VTD), compared with thalidomide-dexamethasone (TD) as an induction regimen, both followed by a melphalan (MEL) conditioning regimen in a phase III randomized study (n = 256), was associated with improved post-induction responses (CR/nCR: 36 versus 9%, respectively; VGPR: 60 versus 27%, respectively) and improved post-transplant responses (CR/nCR: 57 versus 28%, respectively;  $\geq$  VGPR: 77 versus 54%, respectively).
- Higher postinduction CR/nCR response rates reported with VTD compared with TD in patients with high-risk cytogenetics ([t(4;14) translocation: 47 versus 43%; chromosome 13 deletion: 4 versus 8%, for VTD and TD, respectively).
- Higher incidence of skin rashes and peripheral neuropathy (PN) with the VTD regimen (rash: 6.5 versus 1%; PN: 7 versus 2%); a higher incidence of deep venous thrombosis (DVT) was reported with the TD regimen (6.5 versus 3%).
- No survival data has been reported as part of this interim analysis.

**Bortezomib-liposomal doxorubicin-dexamethasone (VDD)<sup>4</sup>**

- Interim analysis of a phase II study (n=64) with VDD followed by a reduced-dose melphalan (MEL) conditioning regimen in elderly patients (median age 67 years of age), revealed a  $\geq$ VGPR rate of 60% post-induction with an increased  $\geq$ VGPR rate (80%) post transplant.
- Grade III hematological complications reported in 15-18% of patients; the incidence of infections was 11%. PN reported as 18%, DVT 7%, and early deaths <5%. Compared with VAD (as a historical control), a higher incidence of grade III/IV hematologic, PN, infections, DVT, and early deaths reported with the VDD regimen.
- Similar  $\geq$  VGPR rates across all age groups and in both standard and high-risk patients; however, a non-significant benefit was observed in patients  $\geq$ 70 years of age and those with the chromosome 13 deletion. A non-significant decline in VGPR rates was reported in patients with advanced-stage disease ( $\beta_2$ M level >3.5 mg/dL) and those with the t(4;14) translocation.
- The event-free survival (EFS) and OS at 2 years (following VDD-MEL) are both reported as 91%, including a similar EFS rate for patients with the chromosome 13 deletion; however, the EFS rate was lower in patients  $\geq$ 70 years of age (p= < 0.05).

**Bortezomib (PS-341)-doxorubicin-dexamethasone (PAD)<sup>5</sup>**

- A phase I/II dose-seeking study (n=41) evaluating different doses of both bortezomib and doxorubicin as induction therapy prior to ASCT evaluated the following regimens:
  - **PAD1**- bortezomib dose of 1.3 mg/m<sup>2</sup> with a dose-escalated doxorubicin regimen (0, 4.5 and 9 mg/m<sup>2</sup>)
  - **PAD2**- bortezomib dose of 1 mg/m<sup>2</sup> with a fixed doxorubicin dose of 9 mg/m<sup>2</sup>
- Preliminary results revealed higher, but non-significant, post-induction and post-transplant response rates (CR/nCR and VGPR) with the PAD1 cohort compared with PAD2: CR/nCR postinduction and posttransplant: 29 and 58%, respectively (PAD1) versus 16 and 42 %, respectively (PAD2); VGPR postinduction and posttransplant: 62 and 81%, respectively (PAD1) versus 42 and 53%, respectively (PAD2).

### **Bortezomib (PS-341)-doxorubicin-dexamethasone (PAD) (cont)**

- Survival responses (e.g., PFS, time-to-retreatment (TTRT), and OS at 1 and 2 years) were not statistically different between groups, but trended in favor of the PAD1 group. (PFS: 29 versus 24 months; TTRT: 36 versus 29 months, for the PAD1 and PAD2 cohorts, respectively. The OS at 1 year was 100 and 95%; the OS at 2 year was 95 and 73%, for the PAD1 and PAD2 cohorts, respectively).
- Significant increase in grade I/II sensory and painful PN reported in the PAD1 versus PAD 2 cohort (43 versus 9%, respectively); lower overall incidence of toxicities reported for the PAD2 cohort. Grade III/IV toxicities reported with the PAD2 regimen included elevated transaminases (15%), psychiatric (10%), and hematologic or infectious complications (10% and 5%, respectively).
- Plans are to compare PAD (using the 1.3 mg/m<sup>2</sup> dose) with the VAD regimen in the randomized phase III HOVON trial.

### **Cyclophosphamide-bortezomib-dexamethasone (CyBorD) <sup>6</sup>**

- Preliminary results from a phase II study (n=33) evaluating CyBorD revealed a CR/nCR response rate of 64% and ≥ VGPR rate of 85% after 4 cycles, with a rapid decline in serum M-protein levels by 66 and 83% after cycle 1 and 2, respectively.
- Grade III toxicities included hematologic 29% (neutropenia 20 and thrombocytopenia 9%), hyperglycemia 17%, and PN 5%; overall, 69% of patients experienced grade I-II PN.
- Compared with the historical control regimen, lenalidomide-dexamethasone, CyBorD has been reported to produce a more frequent, a more rapid, and a more deeper response, characterized by a reduction in serum M-protein levels.<sup>7</sup>

### **Bortezomib-cyclophosphamide-dexamethasone (BCD) <sup>8</sup>**

- Preliminary results from a phase II study (n=30) evaluating VCD (or BCD) followed by 3 cycles of VTD revealed a ≥VGPR response rate of 61% post induction.
- Grade II PN reported overall as 35% (20% with bortezomib; 15% after starting thalidomide); 15% of patients required discontinuance from bortezomib or thalidomide. Grade II toxicities related to either cyclophosphamide (e.g., neutropenia, pneumonia) or dexamethasone (hyperglycemia and insomnia) were reported as 12 and 15%, respectively.

### **Discussion:**

#### ***Bortezomib as first-line therapy for newly diagnosed, multiple myeloma patients ineligible for stem-cell transplant (SCT)***

The use of VMP in multiple myeloma patients not eligible for SCT is considered a reasonable choice for both standard-risk and high-risk patients of all ages based on the improved survival compared with patients receiving MP in the VISTA<sup>b</sup> trial. Additionally, VMP, compared with the MP regimen, was shown to be effective in patients with varying degrees of renal function. Unlike thalidomide or lenalidomide, bortezomib does not require a dose adjustment for impaired renal function. Therefore, this regimen may be considered a preferred regimen for patients who present with renal insufficiency. The overall 2-year survival rate reported for all patients receiving VMP on the VISTA trial (mean 71 years of age) is 83%;<sup>1</sup> whereas, the reported mean overall survival for patients treated with the melphalan-prednisone-thalidomide (MPT) regimen was approximately 85% in two studies comparing MPT to MP, based on Kaplan-Meier survival estimates.<sup>9,10</sup> A high 2-year survival rate (i.e., 79%) has been maintained for patients ≥75 years of age enrolled on the VISTA study.<sup>1</sup> Data from another study (IFM 01/01 trial), comparing MPT with MP exclusively in patients ≥75 years of age, have revealed an estimated survival of 45.3 months for patients receiving the MPT regimen, based on a median follow up of 24 months.<sup>11</sup> Approximately 30% of the patients enrolled in the VISTA trial were ≥75 years of age; yet, the survival and response data for this subset of patients were not statistically different from the overall survival and responses reported for all patients in this trial, including patients with poor risk cytogenetics. Although data are not available from the IFM 01/01 study regarding response or survival rates for the subgroup of patients with poor risk features, the same investigators performed a post hoc analysis of responses in a previous study comparing MPT with MP (i.e., the IFM 99-06 trial). The analysis indicated that the MPT regimen overcame

<sup>b</sup> VISTA: Velcade as initial standard therapy in multiple myeloma: Assessment with melphalan and prednisone

the negative prognostic effects in patients with a poor-risk cytogenetics (i.e., chromosome 13 deletion). However, these specific data have not yet been published.

Therefore, based on the available data, VMP may be considered a preferred regimen for elderly (i.e.,  $\geq 75$  years of age) patients with adverse prognostic or high risk features, but risk/benefit considerations should be evaluated against the higher incidence of hematologic toxicity seen with VMP in the VISTA<sup>1</sup> study compared with MPT as reported in the IFM 01/01 trial<sup>11</sup> (40 versus 23%, respectively) versus a higher incidence of both PN and DVT with MPT (PN: 20 versus 13% ; DVT: 6 versus 1%, respectively), as well as the high treatment discontinuance rate (42%) reported with the MPT regimen in patients  $\geq 75$  years of age.<sup>11</sup>

### ***Bortezomib as first-line induction therapy for newly diagnosed, multiple myeloma patients undergoing an stem-cell transplant (SCT)***

**VD:** VD is considered a reasonable choice as an induction regimen based on improved response rates seen both postinduction and posttransplant compared with the VAD regimen, and based on improved hematologic and VTE-related toxicities; however, the incidence of neurologic complications is higher with VD than with VAD (PN all grades: 35 versus 23%; grade III/IV PN: 6 versus 1.3%, respectively). Higher responses postinduction have been reported in patients with advanced-stage disease (elevated  $\beta_2$ M levels) and in patients with the chromosome 13 deletion. Despite the improved posttransplant response rates reported with VD, a survival benefit (i.e., TTP or OS) at 1 year has not been shown when compared with VAD; additional data are needed to correlate the high posttransplant responses with the impact on survival beyond one year. However, VD may be considered a preferred regimen in patients with poor prognostic features, such as an elevated  $\beta_2$ M level or chromosome 13 deletion.

**VTD:** The VTD regimen, when compared with TD, has resulted in improved responses post-induction and has shown a trend towards higher CR/nCR response rates after transplant. Higher postinduction responses (CR/nCR) have been reported in patients with high risk cytogenetics [i.e., t(4;14) translocation and chromosome 13 deletion] compared with patients receiving TD, suggesting a high activity of VTD in patients with high-risk features. However, the role of VTD, in either standard or poor risk patients, is not fully established given the lack of survival data.

**VDD:** VDD, followed by reduced-dose melphalan in a cohort of elderly patients (mean age 67 years of age) in preparation for a stem-cell transplant (SCT), revealed a  $\geq$ VGPR response rate of 60% post-induction with an increase to 80% posttransplant. Compared with VAD, VDD is associated with a higher incidence of both hematologic and infectious complications, as well as a higher incidence of peripheral neuropathy. Survival rates are similar for VDD + reduced-dose melphalan at 2 years compared with the historical control regimen (e.g., VAD + reduced-dose melphalan): 2 year survival: 91 and 89% for VDD-MEL and VAD-MEL, respectively. Similar EFS rates have been reported for both standard and high-risk patients (e.g., chromosome 13 deletion), suggesting high activity of this combination in patients with poor-risk features; however, the EFS rate is lower for patients  $> 70$  years of age. Additional data are needed to establish the survival benefit and tolerability of VDD in comparison with other “triplet” regimens as induction therapy, especially in elderly patients undergoing an ASCT.

**PAD:** The PAD regimen has been studied using various doses of both doxorubicin and bortezomib. Plans are to compare the PAD regimen with the VAD regimen as part of a phase III trial to determine the optimal dosing regimen, tolerability, response, and survival rate.

**CyBorD:** Higher responses ( $\geq$ VGPR and declines in M-protein levels) have been reported in a small number of patients receiving CyBorD compared with the historical control regimen, lenalidomide-dexamethasone. However, a high frequency (37%) of hematologic complications has been reported with this regimen. Additional survival, toxicity, and transplant data, derived from a randomized study are needed to establish the role of the CyBorD regimen.

**BCD:** BCD, administered as an induction regimen followed by BTD, has produced  $\geq$ VGPR response rates of 61% postinduction, which is higher than responses rates reported with the VD regimen (39%<sup>7</sup> and 47%<sup>2</sup> in two separate studies). Additional survival and transplant response data are needed to establish the role of this regimen.

### **Summary:**

Many factors (including toxicity-related issues) must be considered when selecting either a transplant-induction regimen or a regimen for an elderly patient with multiple myeloma. However, bortezomib-based regimens may be considered preferred regimens for patients with a contraindication to receiving VTE prophylaxis, which is a requirement for both thalidomide and lenalidomide-based regimens. Many of the newer bortezomib-containing doublet and the triplet regimens have been evaluated previously in patients with relapsed/refractory disease, but these combinations have demonstrated considerable activity in newly diagnosed multiple myeloma, including in patients with poor or high risk features. Additional data obtained from ongoing and future randomized trials will further define the response rates and overall tolerability, as well as establish the survival benefit for these various regimens, both in the transplant and non-transplant setting.

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