

AHFS Final Determination of Medical Acceptance: Off-label Use of Bortezomib in Combination with Doxorubicin and Dexamethasone as Induction Therapy for Newly Diagnosed Multiple Myeloma in Transplant-eligible Patients

Drug/Drug Combination: Bortezomib in combination with doxorubicin and dexamethasone

Off-label Use: Induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients

Criteria Used in Selection of Off-label Use for Review:

• Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in January 2009. At the time of the original review, the use of bortezomib in combination with doxorubicin (conventional or liposomal) and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients undergoing a stem-cell transplant (SCT) was not fully established.

Bortezomib in Combination with Conventional Doxorubicin and Dexamethasone:

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Progression-free survival

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions):

Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 in combination with conventional doxorubicin hydrochloride 9 mg/m² IV per day on days 1–4 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 4-week cycle for 3 cycles (*HOVON-65/GMMG-HD4* [reference 10023])

Bortezomib in Combination with Liposomal Doxorubicin and Dexamethasone:

Strength of Evidence: Level 3 (Low strength/quality)

Strength of Study End Point(s): Complete response plus near-complete response

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions):

Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 and liposomal doxorubicin hydrochloride 30 mg/m² IV on day 4 of each 3-week cycle for 6 cycles along with dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycle 1 and then 20 mg orally daily during cycles 2–6 (*Jakubowiak et al [reference 10024]*)

Grade of Recommendation: Not fully established:

Bortezomib 1 mg/m² IV, liposomal doxorubicin hydrochloride 5 mg/m² IV, and dexamethasone phosphate 40 mg IV on days 1, 4, 8, and 11 of each 4-week cycle until maximum response is achieved plus 2 additional cycles or a maximum of 8 cycles (*Berenson et al [reference 10026]*)

Narrative Summary:

Bortezomib, Dexamethasone, and Doxorubicin (or Pegylated Liposomal Doxorubicin):

Efficacy and safety of bortezomib in combination with dexamethasone and conventional doxorubicin[†] (bortezomib-doxorubicin-dexamethasone) as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients[†] have been studied in an open-label, randomized phase 3 study (HOVON-65/GMMG-HD4).^{10005, 10023}

In the HOVON-65/GMMG-HD4 study, 827 patients with newly diagnosed multiple myeloma were randomized to receive conventional doxorubicin and dexamethasone in combination with either bortezomib or vincristine as an induction regimen.¹⁰⁰²³ Patients receiving the bortezomib-doxorubicin-dexamethasone induction regimen received bortezomib 1.3 mg/m² as an IV injection on days 1, 4, 8, and 11 along with doxorubicin hydrochloride 9 mg/m² IV per day on days 1–4 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during each 28-day cycle for 3 cycles.¹⁰⁰²³ Those receiving the vincristine-doxorubicin-dexamethasone induction regimen received vincristine sulfate 0.4 mg and doxorubicin hydrochloride 9 mg/m² IV per day on days 1–4, 9–12, and 17–20 during each 28-day cycle for 3 cycles.¹⁰⁰²³ Those receiving the vincristine-doxorubicin-dexamethasone induction regimen received vincristine sulfate 0.4 mg and doxorubicin hydrochloride 9 mg/m² IV per day on days 1–4 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 during each 28-day cycle for 3 cycles.¹⁰⁰²³ Patients who received bortezomib-doxorubicin-dexamethasone induction therapy received 2 years of maintenance therapy with bortezomib (1.3 mg/m² every 2 weeks) following stem cell transplantation, while those who received vincristine-doxorubicin-dexamethasone induction therapy received thalidomide (50 mg daily) as maintenance therapy.¹⁰⁰²³ The median age of patients enrolled in the study was 57 years; 87% had World Health Organization (WHO) performance status of 0 or 1, and 23% had International Staging System (ISS) stage III disease.¹⁰⁰²³ Among patients for whom cytogenetic tests were performed, 43, 14, or 11% had del(13q), t(4;14) translocation, or del(17p13) chromosomal abnormalities, respectively.¹⁰⁰²³

The primary measure of efficacy in the HOVON-65/GMMG-HD4 study was progression-free survival.¹⁰⁰²³ Tumor responses were assessed using European Group for Blood and Marrow Transplantation (EBMT) response criteria.¹⁰⁰²³ At a median follow-up of 41 months, patients who received bortezomibdoxorubicin-dexamethasone had prolonged progression-free survival (35 versus 28 months; hazard ratio: 0.75) and higher postinduction (11 versus 5%) and posttransplant (31 versus 15%) complete plus near-complete response rates compared with those who received vincristine-doxorubicin-dexamethasone.¹⁰⁰²³ Median overall survival had not been reached at a median follow-up of 66 months; however, no significant difference in 5-year overall survival was observed between the groups.¹⁰⁰²³ Subgroup analyses based on presence of renal insufficiency or high-risk cytogenetic features (i.e., del(13q14), t(4;14), del(17p13) chromosomal abnormalities) suggested prolonged progression-free and overall survival with bortezomib-doxorubicin-dexamethasone compared with vincristine-doxorubicin-dexamethasone induction therapy in patients with serum creatinine concentrations exceeding 2 mg/dL and in those with del(17p13) chromosomal abnormality, as well as an overall survival benefit for bortezomib-doxorubicin-dexamethasone compared with vincristine-doxorubicindexamethasone in patients with del(13g14) chromosomal abnormality.¹⁰⁰²³ Herpes zoster (2 versus 0%) and grade 3 or 4 thrombocytopenia (10 versus 5%), GI toxicity (11 versus 7%), and peripheral neuropathy (24 versus 10%) occurred more frequently in patients receiving bortezomib-doxorubicin-dexamethasone compared with those receiving vincristine-doxorubicin-dexamethasone.¹⁰⁰²³

Use of bortezomib and dexamethasone also has been studied in combination with pegylated liposomal

doxorubicin† (bortezomib-pegylated liposomal doxorubicin-dexamethasone) as induction therapy for previously untreated multiple myeloma† in 2 open-label, noncomparative phase 2 studies.^{10004, 10024, 10025, 10026}

In the first study, 40 patients with newly diagnosed multiple myeloma received bortezomib 1.3 mg/m² as an IV injection on days 1, 4, 8, and 11 along with pegylated liposomal doxorubicin hydrochloride 30 mg/m² IV on day 4 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycle 1.¹⁰⁰²⁴ During cycles 2–6, the same dosages of bortezomib and pegylated liposomal doxorubicin were administered, but the dexamethasone dosage was 20 mg orally daily.¹⁰⁰²⁴ Treatment cycles were repeated every 3 weeks for a total of 6 cycles.¹⁰⁰²⁴ Overall response rate and complete plus near-complete response rate were 85 and 38%, respectively, following 6 cycles of induction therapy with bortezomib-pegylated liposomal doxorubicin-dexamethasone.¹⁰⁰²⁴ Among patients who underwent stem cell transplantation, the complete plus near-complete response rate increased to 57% following transplantation, but the overall response rate did not improve substantially.¹⁰⁰²⁴ At a median follow-up of 45.1 months, median progression-free survival had not been reached; however, among patients who underwent stem cell transplantation, actuarial 2- and 4-year progression-free survival rates were 93 and 65%, respectively, and actuarial 2- and 4-year overall survival rates were 97 and 67%, respectively.¹⁰⁰²⁵ Grade 1 or 2 peripheral neuropathy, fatigue, palmar-plantar erythrodysesthesia (hand-foot syndrome), and constipation occurred in 90, 88, 75, and 70% of patients, respectively.¹⁰⁰²⁴

Because bortezomib and pegylated liposomal doxorubicin frequently cause adverse effects, another phase 2 study evaluated a modified bortezomib-pegylated liposomal doxorubicin-dexamethasone regimen in 35 patients with previously untreated multiple myeloma.¹⁰⁰²⁶ Patients received bortezomib 1 mg/m² as an IV injection, pegylated liposomal doxorubicin hydrochloride 5 mg/m² IV, and dexamethasone phosphate 40 mg IV on days 1, 4, 8, and 11 of each 28-day cycle for a maximum of 8 cycles.¹⁰⁰²⁶ Overall response rate was 86%; complete response was achieved in 20% of patients.¹⁰⁰²⁶ At a median follow-up of 17.7 months, median time to progression, duration of response, and overall survival had not been reached.¹⁰⁰²⁶ Constipation, fatigue, peripheral neuropathy, insomnia, and nausea occurred in 51, 46, 34, 29, and 26%, respectively, of patients.¹⁰⁰²⁶

Based on current evidence,^{10023, 10024, 10025} use of bortezomib in combination with doxorubicin (or pegylated liposomal doxorubicin) and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients may be considered a reasonable choice (accepted; with possible conditions); however, in the absence of longer follow-up data, use of a modified bortezomib-pegylated liposomal doxorubicin-dexamethasone regimen (i.e., reduced dosages of bortezomib and pegylated liposomal doxorubicin),¹⁰⁰²⁶ is not fully established because of unclear risk/benefit and/or inadequate experience. Factors that should be considered when selecting a combination chemotherapy regimen for use as induction therapy include performance status and preexisting conditions (e.g., peripheral neuropathy).

Dosage:

Bortezomib has been used in several regimens in combination with doxorubicin (or pegylated liposomal doxorubicin) and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients.^{10023, 10024, 10026}

When bortezomib has been used in combination with doxorubicin and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients, bortezomib 1.3 mg/m² has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with doxorubicin hydrochloride 9 mg/m² IV per day on days 1–4 and dexamethasone 40 mg orally on days 1–4, 9–12, and 17–20 of each 28-day cycle for 3 cycles.¹⁰⁰²³

Bortezomib 1.3 mg/m² also has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with pegylated liposomal doxorubicin hydrochloride 30 mg/m² IV on day 4 and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycle 1.¹⁰⁰²⁴ During cycles 2–6, the same dosages of bortezomib and pegylated liposomal doxorubicin were administered along with dexamethasone 20 mg orally daily.¹⁰⁰²⁴ Treatment cycles were repeated every 3 weeks for a total of 6 cycles.¹⁰⁰²⁴

A modified regimen using reduced dosages of bortezomib and pegylated liposomal doxorubicin¹⁰⁰²⁶ is not fully established.

References:

- 10004. Palumbo A, Avonto I, Patriarca F et al. Bortezomib, pegylatedlyposomal-doxorubicin and dexamethasone followed by melphalan 100 mg/m² in elderly new diagnosed patients: an interim analysis. *Blood.* 2007; 110: Abstract 448 (presented at the 49th annual ASH meeting. Atlanta, GA: 2007 Dec 10).
- 10005. Popat R, Oakervee H, Hallam S et al. Bortezomib, doxorubicin, and dexamethasone (PAD) front line treatment of multiple myeloma: updated results after long term follow up. *Br J Haematol.* 2008; 141:512-6.
- 10023. Sonneveld P, Schmidt-Wolf IG, van der Holt B et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol. 2012; 30:2946-55.
- 10024. Jakubowiak AJ, Kendall T, Al-Zoubi A et al. Phase II trial of combination therapy with bortezomib, pegylated liposomal doxorubicin, and dexamethasone in patients with newly diagnosed myeloma. *J Clin Oncol.* 2009; 27:5015-22.
- 10025. Dytfeld D, Griffith KA, Friedman J et al. Superior overall survival of patients with myeloma achieving very good partial response or better to initial treatment with bortezomib, pegylated liposomal doxorubicin, and dexamethasone, predicted after two cycles by a free light chain- and M-protein-based model: extended follow-up of a phase II trial. *Leuk Lymphoma*. 2011; 52:1271-80.
- 10026. Berenson JR, Yellin O, Chen CS et al. A modified regimen of pegylated liposomal doxorubicin, bortezomib and dexamethasone (DVD) is effective and well tolerated for previously untreated multiple myeloma patients. *Br J Haematol.* 2011; 155:580-7.

Oncology Expert Committee Voting Results:

Bortezomib in Combination with Conventional Doxorubicin and Dexamethasone:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); progression-free survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, treatment option): 5 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Bortezomib in Combination with Liposomal Doxorubicin and Dexamethasone:

Proposed Level of Evidence: Level 3 (Low strength/quality); complete response plus near-complete response

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 and liposomal doxorubicin hydrochloride 30 mg/m² IV on day 4 of each 3-week cycle for 6 cycles along with dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycle 1 and then 20 mg orally once daily during cycles 2–6 (Jakubowiak et al [reference 10024]):

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 2 votes

Not fully established (Unclear risk/benefit or equivocal): 1 vote

Not recommended (Unaccepted): 0 votes

Bortezomib 1 mg/m² IV, liposomal doxorubicin hydrochloride 5 mg/m² IV, and dexamethasone phosphate 40 mg IV on days 1, 4, 8, and 11 of each 4-week cycle until maximum response is achieved plus 2 additional cycles or a maximum of 8 cycles (Berenson et al [reference 10026]):

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 2 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Based on current evidence,^{10023, 10024, 10025} use of bortezomib in combination with doxorubicin (or pegylated liposomal doxorubicin) and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients may be considered a reasonable choice (accepted; with possible conditions); however, in the absence of longer follow-up data, use of a modified bortezomib-pegylated liposomal doxorubicin-dexamethasone regimen (i.e., reduced dosages of bortezomib and pegylated liposomal doxorubicin)¹⁰⁰²⁶ is not fully established because of unclear risk/benefit and/or inadequate experience. Factors that should be considered when selecting a combination chemotherapy regimen for use as induction therapy include performance status and preexisting conditions (e.g., peripheral neuropathy).

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Bortezomib in Combination with Conventional Doxorubicin and Dexamethasone:

Reviewer #4: [Specific patient population] Risk evaluation in patients with peripheral neuropathy.

Reviewer #5: [Grade of recommendation] Based on phase 3 noninferiority trial comparing VCD to PAD (Mai et al. *Leukemia*. 2015; 28:1721-8), PAD was more toxic with similar efficacy.

Bortezomib in Combination with Liposomal Doxorubicin and Dexamethasone:

Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 and liposomal doxorubicin hydrochloride 30 mg/m² IV on day 4 of each 3-week cycle for 6 cycles along with dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 during cycle 1 and then 20 mg orally once daily during cycles 2–6 (Jakubowiak et al [reference 10024]):

Reviewer #2: [Specific patient population] Per exclusion criteria.

Bortezomib 1 mg/m² IV, liposomal doxorubicin hydrochloride 5 mg/m² IV, and dexamethasone phosphate 40 mg IV on days 1, 4, 8, and 11 of each 4-week cycle until maximum response is achieved plus 2 additional cycles or a maximum of 8 cycles (Berenson et al [reference 10026]):

None submitted.

Comments on Draft Narrative Summary:

Reviewer #5: Regarding narrative on reference 10026, consider showing the specific CR [complete response] rate reported since it is numerically much lower than the CR/nCR [complete response/near-complete response] rate in 10024 reference (as direct comparison of pegylated doxorubicin).

Comments on Proposed Consensus Recommendation:

Reviewer #4: Recommend clarification of dosing schedule with [bortezomib in combination with liposomal doxorubicin and dexamethasone] regimen.

Reviewer #4: Do we need to say daily x 4 instead of days 1–4?

Participants:

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AHFS Oncology Expert Committee Members (reviewing and voting): Mandy Gatesman, Pharm.D., BCOP; LeAnne Kennedy, Pharm.D., BCOP; LeAnn Norris, Pharm.D., BCOP; Rowena Schwartz, Pharm.D., BCOP; Ron Walters, M.D., MBA, MHA, MS

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this offlabel oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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