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

Drug/Drug Combination: Bortezomib in combination with thalidomide 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 thalidomide and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients undergoing a stem-cell transplant (SCT) was not fully established.

Strength of Evidence: Level 1 (High 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/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally daily (after initial dosage escalation during cycle 1 with 100 mg orally on days 1–14 followed by 200 mg orally daily thereafter) and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles *(GIMEMA [reference 10013])*

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally daily (after initial dosage escalation during cycle 1 with 50 mg orally on days 1–14 followed by 100 mg orally on days 15–28) and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 4-week cycle for 6 cycles *(PETHEMA/GEM [reference 10014])*

Bortezomib 1.3 mg/m^2 by subcutaneous injection on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles *(IFM2013-04 [reference 10027])*

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles *(Ludwig et al [reference 10016])*

Grade of Recommendation: Not fully established:

Bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 and thalidomide 100 mg orally daily during each 3-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4 and 9–12 during cycles 1 and 2 and then 40 mg orally on days 1–4 during cycles 3 and 4; bortezomib dose may be increased to 1.3 mg/m^2 and thalidomide dosage may be increased to 200 mg orally daily during cycles 3 and 4 for inadequate response (less than partial response) after 2 cycles *(Moreau et al [reference 10015])*

Narrative Summary:

Bortezomib, Dexamethasone, and Thalidomide:

Efficacy and safety of bortezomib in combination with thalidomide and dexamethasone† (bortezomib-thalidomide-dexamethasone) as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients† have been studied in several phase 3, open-label, randomized studies.[10013, 10014, 10015, 10027]

The GIMEMA and PETHEMA/GEM studies compared bortezomib-thalidomide-dexamethasone with the combination of thalidomide and dexamethasone (thalidomide-dexamethasone).[10013, 10014] In the GIMEMA study, 480 patients were randomized to receive bortezomib-thalidomide-dexamethasone or thalidomide-dexamethasone; both induction regimens were followed by tandem autologous stem cell transplantation and consolidation therapy with the same drug combination used for induction therapy.[10013] Patients receiving bortezomib-thalidomide-dexamethasone induction therapy received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 along with thalidomide 200 mg orally daily (after initial dose escalation during cycle 1) and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.[10013] Those receiving thalidomide-dexamethasone induction therapy received the same dosage of thalidomide; however, dexamethasone 40 mg was administered orally on days 1–4 and 9–12 of each 21-day cycle.[10013] Both regimens were continued for a total of 3 cycles.[10013] In the PETHEMA/GEM study, 386 patients were randomized to receive bortezomib-thalidomide-dexamethasone, thalidomide-dexamethasone, or alternating cycles of vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) and vincristine, carmustine, doxorubicin, and dexamethasone (VBAD) followed by bortezomib as induction therapy.[10014] Patients receiving bortezomib-thalidomide-dexamethasone received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 along with thalidomide 200 mg orally daily (after initial dose escalation during cycle 1) and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 4-week cycle for 6 cycles.[10014] Patients receiving thalidomide-dexamethasone received the same dosages of thalidomide and dexamethasone.[10014] Those receiving VBMCP/VBAD received each regimen in alternating cycles for 4 cycles followed by two 3-week cycles of bortezomib 1.3 mg/m^2 administered as an IV injection on days 1, 4, 8, and 11.[10014, 10017] In the GIMEMA study, the primary measure of efficacy was postinduction complete plus near-complete response rate.[10013] In the PETHEMA/GEM study, the primary measures of efficacy were postinduction and posttransplant complete response rates.[10014] In both studies, responses were assessed according to European Group for Blood and Marrow Transplantation (EBMT) response criteria.[10013, 10014] In both studies, a higher postinduction response rate and prolonged progression-free survival were observed in patients who received bortezomib-thalidomide-dexamethasone compared with those who received the comparator regimens; however, addition of bortezomib to thalidomide and dexamethasone induction therapy did not provide an overall survival benefit in either study.[10013,10014]

In the GIMEMA study, postinduction complete plus near-complete response rate was 31% in patients receiving bortezomib-thalidomide-dexamethasone compared with 11% in those receiving thalidomide-dexamethasone; improved responses also were observed with bortezomib-thalidomide-dexamethasone following first (52 versus 31%) and second (55 versus 41%) autologous stem cell transplants and subsequent

consolidation therapy (62 versus 45%).[10013] The median time to best complete or near-complete response was shorter in patients receiving bortezomib-thalidomide-dexamethasone compared with those receiving thalidomide-dexamethasone (9 versus 14 months).[10013] At a median follow-up of 36 months, progression-free survival was prolonged in patients who received bortezomib-thalidomide-dexamethasone compared with those who received thalidomide-dexamethasone (hazard ratio 0.63); however, no difference in estimated 3-year overall survival (86 versus 84%, respectively) was observed between the groups.[10013] Subgroup analysis based on poor prognostic factors (i.e., older than 60 years of age, advanced disease stage, elevated serum LDH concentration, high infiltration of bone marrow plasma cells, del(13q), t(4;14) translocation with or without del(17p) chromosomal abnormality) suggested that the progression-free survival benefit of bortezomib-thalidomide-dexamethasone was consistent across these subgroups; however, because the proportion of patients with the del(17p) chromosomal abnormality was substantially smaller than the proportion of patients with other high-risk cytogenetic abnormalities, the effect of bortezomib-thalidomide-dexamethasone on progression-free survival in patients with the del(17p) chromosomal abnormality was not evaluated.[10013]

In the PETHEMA/GEM study, the complete response rate (35 versus 14%) was higher following induction therapy with bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone; improved complete response rates also were maintained following autologous stem cell transplantation (46 versus 24%).[10014] Among patients evaluated for high-risk cytogenetic features, 21% had high-risk features (i.e., t(4;14), t(14;16), and/or del(17p) chromosomal abnormalites); 64 or 31% of these patients had t(4;14) or del(17p) chromosomal abnormalities, respectively.[10014] Among the patients with high-risk cytogenetic features, complete response rate was substantially higher in patients who received bortezomib-thalidomide-dexamethasone compared with those who received thalidomide-dexamethasone (35 versus 0%); complete responses were achieved in 38 or 58% of patients receiving bortezomib-thalidomide-dexamethasone who had t(4;14) or del(17p) chromosomal abnormalities, respectively, compared with 0% of patients receiving thalidomide-dexamethasone who had either chromosomal abnormality.[10014] At a median follow-up of 35.2 months, median progression-free survival was prolonged in patients who received bortezomib-thalidomide-dexamethasone compared with those who received thalidomide-dexamethasone (56.2 versus 28.2 months); however, no difference in estimated 4-year overall survival (74 versus 65%, respectively) was observed between the treatment groups.[10014]

In both the GIMEMA and PETHEMA/GEM studies, grade 3 or 4 peripheral neuropathy occurred more frequently in patients receiving bortezomib-thalidomide-dexamethasone (10 and 14%, respectively) compared with those receiving thalidomide-dexamethasone (2 and 5%, respectively).[10013, 10014]

In the third study (IFM2013-04), 340 patients were randomized to receive bortezomib by subcutaneous injection in combination with thalidomide and dexamethasone or in combination with cyclophosphamide and dexamethasone.[10027] Patients receiving bortezomib-thalidomide-dexamethasone received bortezomib 1.3 mg/m^2 by subcutaneous injection on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle.[10027] Those receiving bortezomib-cyclophosphamide-dexamethasone received the same dosages of bortezomib and dexamethasone along with cyclophosphamide 500 mg/m^2 orally on days 1, 8, and 15 of each 3-week cycle.[10027] Both induction regimens were continued for a total of 4 cycles.[10027] The median age of patients enrolled in the study was approximately 60 years; 22% had International Staging System (ISS) stage III disease, and 18% had t(4;14) translocation and/or del(17p) chromosomal abnormalities.[10027] The primary measure of efficacy was the rate of very good partial response or better, as assessed according to the International Myeloma Working Group Uniform Response criteria, following induction therapy.[10027] Overall response rate (92.3 versus 83.4%) and the rate of

very good partial response or better (66.3 versus 56.2%) based on intent-to-treat analysis were higher following induction therapy with bortezomib-thalidomide-dexamethasone compared with bortezomib-cyclophosphamide-dexamethasone; however, no significant difference in complete response rate was observed between the treatment groups.[10027] Grade 2 or greater peripheral neuropathy (21.9 versus 12.9%) occurred more frequently in patients receiving bortezomib-thalidomide-dexamethasone, while grade 3 or 4 neutropenia (33.1 versus 18.9%), thrombocytopenia (10.6 versus 4.7%), and anemia (9.5 versus 4.1%) occurred more frequently in patients receiving bortezomib-cyclophosphamide-dexamethasone.[10027]

Because peripheral neuropathy occurs frequently with bortezomib- and thalidomide-based induction regimens, a modified bortezomib-thalidomide-dexamethasone induction regimen was compared with bortezomib-dexamethasone in another phase 3 study in 199 patients.[10015] Patients receiving bortezomib-dexamethasone received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 of each 3-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4 and 9–12 during cycles 1 and 2 and then on days 1–4 during cycles 3 and 4.[10015] Patients receiving the modified bortezomib-thalidomide-dexamethasone regimen received the same dosage of dexamethasone along with bortezomib 1 mg/m^2 as an IV injection on days 1, 4, 8, and 11 and thalidomide 100 mg orally daily during each 3-week cycle for 4 cycles.[10015] In patients with an inadequate (less than partial) response after 2 cycles of the modified bortezomib-thalidomide-dexamethasone regimen (7% of patients receiving the regimen), the dose of bortezomib was increased to 1.3 mg/m^2 and the dosage of thalidomide was increased to 200 mg daily during subsequent cycles.[10015] The median age of patients enrolled in the study was approximately 58 years; 22% had ISS stage III disease and, among those with cytogenetic test results, 20% had t(4;14) translocation or del(17p) chromosomal abnormalities.[10015] The primary measure of efficacy was complete response rate, as assessed according to the International Myeloma Working Group Uniform Response criteria, following induction therapy.[10015] The rate of very good partial response or better following induction therapy was higher with bortezomib-thalidomide-dexamethasone compared with bortezomib-dexamethasone (49 versus 36%); however, postinduction complete response (13 and 12%, respectively) and overall response (88 and 81%, respectively) rates were similar for both treatment groups.[10015] At a median follow-up of 32 months, median progression-free survival was similar in patients who received bortezomib-thalidomide-dexamethasone compared with those who received bortezomib-dexamethasone (26 versus 30 months, respectively).[10015] Peripheral neuropathy occurred more frequently in patients receiving bortezomib-dexamethasone compared with those receiving bortezomib-thalidomide-dexamethasone (70 versus 53%).[10015]

Use of bortezomib in combination with thalidomide and dexamethasone also was investigated in an open-label, noncomparative phase 2 study in 98 patients randomized to receive bortezomib-thalidomide-dexamethasone with or without cyclophosphamide.[10016, 10020] Patients receiving bortezomib-thalidomide-dexamethasone received bortezomib 1.3 mg/m^2 as an IV injection on days 1, 4, 8, and 11 along with thalidomide 100 mg orally daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 21-day cycle.[10016] Patients receiving bortezomib-thalidomide-dexamethasone-cyclophosphamide received the same dosages of bortezomib, thalidomide, and dexamethasone along with cyclophosphamide 400 mg/m^2 IV on days 1 and 8 of each 21-day cycle.[10016] Both induction regimens were continued for a total of 4 cycles.[10016] Postinduction rates of overall response and complete plus near-complete response were 100 and 51%, respectively, in patients receiving bortezomib-thalidomide-dexamethasone and 94 and 43%, respectively, in those receiving bortezomib-thalidomide-dexamethasone-cyclophosphamide.[10016] At a median follow-up of 64.8 months, median progression-free survival was 56.3 months with bortezomib-thalidomide-dexamethasone and 36.3 months with bortezomib-thalidomide-dexamethasone-cyclophosphamide; the difference was not statistically significant and was largely related to an imbalance between treatment groups in the number of

patients receiving subsequent therapy for relapsed disease prior to meeting the specified criteria for disease progression.[10020] A trend toward improved quality of life (assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 [EORTC QLQ-C30] and EuroQoL EQ-5D health status questionnaire) was observed following the first posttransplantation follow-up visit in patients who received bortezomib-thalidomide-dexamethasone compared with those who received bortezomib-thalidomide-dexamethasone-cyclophosphamide.[10016]

Use of bortezomib-thalidomide-dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients has improved postinduction response rates and prolonged progression-free survival in several randomized controlled studies;[10013, 10014, 10016, 10027] however, the same benefits were not observed in a study evaluating a modified bortezomib-thalidomide-dexamethasone regimen (i.e., reduced bortezomib and thalidomide dosages).[10015] Therefore, the role of a modified bortezomib-thalidomide-dexamethasone regimen using reduced dosages of bortezomib and thalidomide[10015] is unclear. In addition, in the absence of studies including adequate numbers of patients with the del(17p) chromosomal abnormality, attempts to identify whether these patients might derive clinical benefit (e.g., prolonged progression-free survival) from bortezomib-thalidomide-dexamethasone induction therapy are speculative; additional studies are needed to identify subgroups of patients with high-risk cytogenetic features who might benefit from such therapy. The AHFS Oncology Expert Committee concluded that use of bortezomib in combination with thalidomide 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, use of a modified bortezomib-thalidomide-dexamethasone regimen using reduced dosages of bortezomib and thalidomide[10015] 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 for newly diagnosed multiple myeloma in transplant-eligible patients include performance status and preexisting conditions (e.g., peripheral neuropathy).

Dosage:

Bortezomib has been used in several regimens in combination with thalidomide and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients.[10013, 10014, 10016, 10027]

When bortezomib has been used in combination with thalidomide and dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients, bortezomib 1.3 mg/m^2 has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 and thalidomide 200 mg orally daily (after initial dosage escalation during cycle 1 with 100 mg orally on days 1–14 followed by 200 mg orally daily thereafter).[10013] Treatment cycles were repeated every 21 days for 3 cycles.[10013]

Bortezomib 1.3 mg/m^2 also has been administered by IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with dexamethasone 40 mg orally on days 1–4 and 9–12 and thalidomide 200 mg orally daily (after initial dosage escalation during cycle 1 with 50 mg orally on days 1–14 followed by 100 mg orally on days 15–28).[10014] Treatment cycles were repeated every 4 weeks for 6 cycles.[10014]

Bortezomib 1.3 mg/m^2 also has been administered by subcutaneous or IV injection twice weekly for 2 weeks (days 1, 4, 8, and 11) along with dexamethasone 40 mg orally on days 1–4 and 9–12 and thalidomide 100 mg orally daily.[10016, 10027] Treatment cycles were repeated every 3 weeks for 4 cycles.[10016, 10027]

A modified regimen using reduced dosages of bortezomib and thalidomide[10015] is not fully established.

References:

10013. Cavo M, Tacchetti P, Patriarca F et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet.* 2010; 376:2075-85.

10014. Rosiñol L, Oriol A, Teruel AI et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood.* 2012; 120:1589-96.

10015. Moreau P, Avet-Loiseau H, Facon T et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood*. 2011; 118:5752-8; quiz 5982.

10016. Ludwig H, Viterbo L, Greil R et al. Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. *J Clin Oncol*. 2013; 31:247-55.

10017. GEM05 for patients with multiple myeloma under 65 years (GEM05MENOS65). From ClinicalTrials.gov registry. Accessed 2016 Nov 18.

10020. Ludwig H, Greil R, Masszi T et al. Bortezomib, thalidomide and dexamethasone, with or without cyclophosphamide, for patients with previously untreated multiple myeloma: 5-year follow-up. *Br J Haematol*. 2015; 171:344-54.

10027. Moreau P, Hulin C, Macro M et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016; 127:2569-74.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); complete response plus near-complete response

Concur with rating: 4 votes

Do not concur with rating: 1 vote

Grade of Recommendation:

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally once daily (after initial dosage escalation during cycle 1) and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles (GIMEMA [reference 10013]):

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

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

Not recommended (Unaccepted): 0 votes

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally once daily (after initial dosage escalation during cycle 1) and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 4-week cycle for 6 cycles (PETHEMA/GEM [reference 10014]):

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

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

Not recommended (Unaccepted): 0 votes

Bortezomib 1.3 mg/m^2 by subcutaneous injection on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles (IFM2013-04 [reference 10027]):

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 4 votes

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

Not recommended (Unaccepted): 0 votes

Bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 and thalidomide 100 mg orally once daily during each 3-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4 and 9–12 during cycles 1 and 2 and then 40 mg orally on days 1–4 during cycles 3 and 4; bortezomib dose may be increased to 1.3 mg/m^2 and thalidomide dosage may be increased to 200 mg orally once daily during cycles 3 and 4 for inadequate response (less than partial response) after 2 cycles (Moreau et al [reference 10015]):

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

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles (Ludwig et al [references 10016]):

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 4 votes

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

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Use of bortezomib-thalidomide-dexamethasone as induction therapy for newly diagnosed multiple myeloma in transplant-eligible patients has improved postinduction response rates and prolonged progression-free survival in several randomized controlled studies;[10013, 10014, 10016, 10027] however, the same benefits were not observed in a study evaluating a modified bortezomib-thalidomide-dexamethasone regimen (i.e., reduced bortezomib and thalidomide dosages).[10015] Therefore, the role of a modified bortezomib-thalidomide-dexamethasone regimen using reduced dosages of bortezomib and thalidomide[10015] is unclear. In addition, in the absence of studies including adequate numbers of patients with the del(17p) chromosomal abnormality, attempts to identify whether these patients might derive clinical benefit (e.g., prolonged progression-free survival) from bortezomib-thalidomide-dexamethasone induction therapy are speculative; additional studies are needed to identify subgroups of patients with high-risk cytogenetic features who might benefit from such therapy. The AHFS Oncology Expert Committee concluded that use of bortezomib in combination with thalidomide 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, use of a modified bortezomib-thalidomide-dexamethasone regimen using reduced dosages of bortezomib and thalidomide[10015] 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 for newly diagnosed multiple myeloma in transplant-eligible patients 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:

Reviewer #5: [Level of evidence] Level 1. Although there are potential options that are "better", the studies are consistent with level 1 rating.

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally once daily (after initial dosage escalation during cycle 1) and dexamethasone 40 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for 3 cycles (GIMEMA [reference 10013]):

Reviewer #1: [Specific patient population] Unclear if applicable to the del17p patients. Preexisting neuropathy may be a problem.

Reviewer #3: [Grade of recommendation] Reasonable choice for patients who cannot use lenalidomide as a part of a 3-drug regimen.

Reviewer #4: [Specific patient population] Age less than 65.

Reviewer #5: [Specific patient population] Add thromboprophylaxis; evaluate risk benefit in patients with grade 2 or greater peripheral neuropathy.

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 200 mg orally once daily (after initial dosage escalation during cycle 1) and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 4-week cycle for 6 cycles (PETHEMA/GEM [reference 10014]):

Reviewer #1: [Specific patient population] Unclear in del17p. Peripheral neuropathy is a problem.

Reviewer #3: [Grade of recommendation] Reasonable choice for patients who cannot use lenalidomide as a part of a 3-drug regimen.

Reviewer #5: [Specific patient population] Add thromboprophylaxis; evaluate risk benefit in patients with grade 2 or greater peripheral neuropathy.

Bortezomib 1.3 mg/m^2 by subcutaneous injection on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles (IFM2013-04 [reference 10027]):

Reviewer #1: [Specific patient population] Peripheral neuropathy concerns.

Reviewer #3: [Grade of recommendation] Reasonable choice for patients who cannot use lenalidomide as a part of a 3-drug regimen.

Reviewer #4: [Specific patient population] Induction treatment.

Reviewer #4: [Grade of recommendation] No collection of PFS [progression-free survival] or OS [overall survival] data.

Reviewer #5: [Specific patient population] Add thromboprophylaxis; evaluate risk benefit in patients with grade 2 or greater peripheral neuropathy.

Bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11 and thalidomide 100 mg orally once daily during each 3-week cycle for 4 cycles along with dexamethasone 40 mg orally on days 1–4 and 9–12 during cycles 1 and 2 and then 40 mg orally on days 1–4 during cycles 3 and 4; bortezomib dose may be increased to 1.3 mg/m^2 and thalidomide dosage may be increased to 200 mg orally once daily during cycles 3 and 4 for inadequate response (less than partial response) after 2 cycles (Moreau et al [reference 10015]):

Reviewer #1: [Specific patient population] Peripheral neuropathy concerns.

Reviewer #3: [Grade of recommendation] Lower dosing as initial therapy is what led to not fully established.

Reviewer #4: [Grade of recommendation] Concerns: 1) patients needed increased dosing of bortezomib (small percentage); 2) failed to show significant improvement in CR [complete response]; 3) more difficulties with peripheral stem cell mobilization. Positive: decreased peripheral neuropathy.

Reviewer #5: [Specific patient population] Add thromboprophylaxis; evaluate risk benefit in patients with grade 2 or greater peripheral neuropathy.

Bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11 along with thalidomide 100 mg orally once daily and dexamethasone 40 mg orally on days 1–4 and 9–12 of each 3-week cycle for 4 cycles (Ludwig et al [reference 10016]):

Reviewer #1: [Specific patient population] Peripheral neuropathy concerns.

Reviewer #4: [Specific patient population] Previously untreated transplant-eligible patients.

Reviewer #4: [Grade of recommendation] Offers better quality of life than VTDC [bortezomib, thalidomide, dexamethasone, and cyclophosphamide]; long-term follow-up persistent response.

Reviewer #5: [Specific patient population] Add thromboprophylaxis; evaluate risk benefit in patients with grade 2 or greater peripheral neuropathy.

Comments on Draft Narrative Summary:
None submitted.

Comments on Proposed Consensus Recommendation:

Reviewer #1: Subcutaneous bortezomib is equivalently efficacious as IV bortezomib with less peripheral neuropathy. There are options that have less potential neuropathy (i.e., those without thalidomide and using alternate agents). The current proposal meets level 1 rating.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Marc Earl, Pharm.D., BCOP; Christine Gegeckas, RPh, BCOP; Raymond Hohl, M.D., Ph.D.; LeAnn Norris, Pharm.D., BCPS, BCOP; Rowena Schwartz, Pharm.D., BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label 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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