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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Millennium Pharmaceuticals, Inc., I respectfully request the NCCN Multiple Myeloma Guidelines Panel to review the enclosed data on the use of VELCADE[®] (bortezomib) as induction therapy prior to stem cell transplantation (SCT), and as maintenance therapy, in patients with multiple myeloma (MM).

Specific Changes: Consider updating the NCCN guidelines with recently published and presented data from Phase 3 and Phase 2 studies of VELCADE-based induction regimens. Consider the inclusion of VELCADE as a Category 2A recommended treatment option for maintenance therapy, based upon recently published and presented data from Phase 3 studies.

FDA Clearance: The FDA has approved VELCADE for the treatment of multiple myeloma. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

Rationale: Final or updated results from five Phase 3 and two Phase 2 studies of VELCADE-based induction regimens in transplant-eligible patients have recently been published or presented, warranting updates to the NCCN guidelines and providing further support for the existing treatment recommendations:

- Final data from the IFM 2005-01 Phase 3 study demonstrating the superiority of VELCADE-dexamethasone versus VAD as induction have been published,¹ supporting the Category 1 recommendation for this regimen
- Final data from the GIMEMA MMY-3006 Phase 3 study demonstrating the superiority of VELCADE-thalidomide-dexamethasone versus thalidomide-dexamethasone as induction and consolidation have been published,² supporting the Category 1 recommendation for this regimen
 - In addition, updated data from the GEM05MENOS65³ and IFM 2007-02⁴ Phase 3 studies incorporating bortezomib-thalidomide-dexamethasone were presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, Florida, in December 2010, and the 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois, in June 2010, respectively, providing further support for the Category 1 recommendation for this regimen as induction therapy
- Updated data from the HOVON-65/GMMG-HD4 Phase 3 trial demonstrating the superiority of VELCADE-doxorubicin-dexamethasone versus VAD as induction were presented at the ASH 2010 meeting,⁵ supporting the Category 1 recommendation for this regimen
- Updated data from the EVOLUTION Phase 2 study incorporating VELCADE-cyclophosphamide-dexamethasone induction,⁶ and new data from the IFM 2008 Phase 2 study of VELCADE-lenalidomide-dexamethasone as induction and consolidation,⁷ were also presented at the ASH 2010 meeting, supporting the Category 2A and 2B recommendations for these regimens, respectively

Regarding the use of VELCADE as maintenance therapy, final or updated results from four Phase 3(b) studies have recently been published or presented, supporting the inclusion of VELCADE as a Category 2A recommended treatment option for maintenance therapy:

- Updated data from the HOVON-65/GMMG-HD4 Phase 3 study incorporating VELCADE versus thalidomide as maintenance therapy following SCT were presented at the ASH 2010 meeting, demonstrating the good tolerability of VELCADE maintenance and the induction of additional responses⁵
- Updated data from the UPFRONT Phase 3b study incorporating VELCADE maintenance following VELCADE-based induction were presented at the ASH 2010 meeting, demonstrating some increases in response rates without substantial increases in toxicity compared with induction therapy⁸
- Final data from the GEM05>65⁹ and GIMEMA MM-03-05¹⁰ Phase 3 studies incorporating VELCADE-thalidomide/prednisone as maintenance therapy following VELCADE-based induction therapy have been published, demonstrating increases in response rates during maintenance therapy and notable long-term outcomes

These findings are supported by data from two Phase 2 studies of VELCADE as maintenance post-SCT¹¹ or as post-induction maintenance in patients with high-risk disease.¹²

The following enclosures (cited references) are included for your review (copyright-paid where applicable):

1. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28(30):4621-4629.
2. 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(9758):2075-2085.
3. Rosinol L, Cibeira MT, Mateos MV, et al. A phase III PETHEMA/GEM study of induction therapy prior autologous stem cell transplantation (ASCT) in multiple myeloma: superiority of VTD (bortezomib/thalidomide/dexamethasone) over TD and VBMCP/VBAD plus bortezomib [abstract]. *Blood* 2010;116:139a-140a.
4. Moreau P, Facon T, Attal M, et al. Comparison of reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) to bortezomib plus dexamethasone (VD) as induction treatment prior to ASCT in de novo multiple myeloma (MM): Results of IFM2007-02 study. Presented at the 2010 ASCO Annual Meeting in Chicago, IL; June 4–8, 2010. Oral presentation, abstract #8014.
5. Sonneveld P, Schmidt-Wolf I, van der Holt B, et al. HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, doxorubicin, dexamethasone (PAD) vs VAD followed by high-dose melphalan (HDM) and maintenance with bortezomib or thalidomide in patients with newly diagnosed multiple myeloma (MM). Presented at the 52nd ASH Annual Meeting in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #40.
6. Kumar S, Flinn IW, Richardson PG, et al. Novel three- and four-drug combination regimens of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for previously untreated multiple myeloma: results from the multi-center, randomized, phase 2 EVOLUTION study. Presented at the 52nd ASH Annual Meeting in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #621.
7. Roussel M, Avet-Loiseau H, Moreau P, et al. Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: primary results of the IFM 2008 phase II study. Presented at the 52nd ASH Annual Meeting in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #624.
8. Niesvizky R, Flinn IW, Rifkin RM, et al. Phase 3b UPFRONT study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. Presented at the

- 52nd ASH Annual Meeting in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #619.
9. Mateos MV, Oriol A, Martinez-Lopez J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol.* 2010;11(10):934-941.
 10. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol.* 2010;28(34):5101-5109.
 11. Uy GL, Goyal SD, Fisher NM, et al. Bortezomib administered pre-auto-SCT and as maintenance therapy post transplant for multiple myeloma: a single institution phase II study. *Bone Marrow Transplant.* 2009;43(10):793-800.
 12. Dispenzieri A, Jacobus S, Vesole DH, et al. Primary therapy with single agent bortezomib as induction, maintenance and re-induction in patients with high-risk myeloma: results of the ECOG E2A02 trial. *Leukemia.* 2010;24(8):1406-1411.
- VELCADE prescribing information.

Yours sincerely

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