



Submitted by:
Oliver Rosen, MD
Vice President, Global Medical Affairs
Millennium: The Takeda Oncology Company
40 Landsdowne Street
Cambridge, MA 02139
Tel: (617) 551-7933
Email: Oliver.Rosen@MPI.com

Date of request: March 28, 2013

NCCN Guidelines Panel: Multiple Myeloma

On behalf of Millennium: The Takeda Oncology Company, I respectfully request the NCCN Multiple Myeloma Guidelines Panel to review the enclosed data on the use of VELCADE® (bortezomib) as maintenance therapy in patients with previously untreated multiple myeloma.

Specific Changes:

Inclusion of new data from studies employing bortezomib-based maintenance in the Myeloma Therapy section (MYEL-D, 1 of 2) of the NCCN Clinical Practice Guidelines (NCCN Guidelines™) in Multiple Myeloma (version V2.2013), specifically inclusion of:

- Bortezomib + thalidomide for maintenance therapy
- Bortezomib + prednisone for maintenance therapy.

In addition, inclusion of these new data and associated references are warranted within the narrative section of the Guidelines, specifically on pages MS-23–24 of version V2.2013, where the current data on bortezomib as maintenance therapy are included.

FDA Clearance: The FDA has approved VELCADE for the treatment of multiple myeloma. The US Prescribing Information describes a standard schedule and a maintenance schedule, albeit a different schedule than the studies described in this document. Data from the studies referenced below are not included in the US Prescribing Information for VELCADE.

Rationale: Data on post-transplant maintenance therapy with bortezomib-thalidomide (VT), thalidomide alone, or alfa-2b-interferon were published on August 23, 2012 in *Blood*, and updated data were presented at the 2012 Annual Meeting of the American Society of Hematology (ASH), from the Spanish GEM05MENOS65 phase III randomized trial. Results showed that:

- At the updated presentation, maintenance with VT increased the post-transplant complete response (CR) rate by 21%, compared with thalidomide or alfa-2b-interferon maintenance, which each increased the CR rate by 15%
- After a median follow-up of 34.9 months, PFS from start of maintenance was significantly longer with VT vs thalidomide vs alfa-2b-interferon ($p=0.0009$); there was no significant difference in overall survival (OS) ($p=0.47$)
- Rates of grade 3–4 thrombocytopenia were 10% vs 2% with VT vs thalidomide ($p=0.01$)
- In the VT, thalidomide, and alfa-2b-interferon arms, rates of grade 3 peripheral neuropathy (PN) were 15%, 14%, and 0, respectively.

Final data from the Spanish GEM2005MAS65 phase III randomized trial in transplant-ineligible patients were published on September 27, 2012 in *Blood*, including findings from the second randomization post-bortezomib-based induction, at which 178 patients were assigned to maintenance with VT or bortezomib-prednisone (VP). Results showed that:

- After a median of 38 months from the start of maintenance with VT or VP, the overall CR rate increased from 24% post-induction to 42% (VT: 46%, VP: 39%; difference not significant)

- Depth of response improved in 33 (19%) patients (VT: 19, VP: 14), including 10 improvements from near-CR (nCR) to CR, and 17 from partial response (PR) to nCR (n=7) or CR (n=10)
- After a median follow-up of 46 months from initial randomization to induction therapy, median PFS among all patients receiving maintenance was 35 months (VT: 39 months, VP: 32 months; p=0.1), and the 5-year OS rate was 58% (VT: 69%, VP: 50%; p=0.1)
- PFS was significantly longer in patients who achieved CR vs nCR vs PR (median 54 months vs 39 months vs 24 months, respectively; hazard ratio [HR]=1.73, p<0.0001), and this translated into a significantly higher 5-year OS rate (78% vs 59% vs 54%, respectively, HR=1.5, p<0.0001)
- 1 patient in the VT arm had grade 3–4 neutropenia
- Rates of non-hematologic grade 3–4 adverse events with VT vs VP were 17% vs 5% (p=0.009), including 9% vs 3% grade 3–4 PN.

The following enclosures are submitted in support of the above proposed changes:

- Rosiñol L 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(8):1589–96
- Rosiñol L et al. Maintenance therapy after stem-cell transplantation for multiple myeloma with bortezomib/thalidomide vs. thalidomide vs. alfa-2b interferon: final results of a phase III PETHEMA/GEM randomized trial. *Blood* 2012;120(21):abstract #334; oral presentation at the 2012 Annual Meeting of the American Society of Hematology
- Mateos M-V et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. *Blood* 2012;120(13):2581–8
- VELCADE (bortezomib) for Injection. United States prescribing information, Rev 15, issued October 2012.

Yours sincerely

Oliver Rosen, MD
Vice President, Global Medical Affairs