



Submitted by:  
Liviu Niculescu, MD  
Senior Medical Director, Global Medical Affairs  
Millennium: The Takeda Oncology Company  
40 Landsdowne Street  
Cambridge, MA 02139  
Tel: (617) 679-7000  
Email: Liviu.Niculescu@takeda.com

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**NCCN Guidelines Panel: Non-Hodgkin's Lymphomas**

On behalf of Millennium: The Takeda Oncology Company, I respectfully request the NCCN Non-Hodgkin's Lymphomas Guidelines Panel to review the enclosed new phase 3 data on the use of VELCADE® (bortezomib) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP regimen) as therapy for patients with previously untreated mantle cell lymphoma.

**Specific Changes:**

Inclusion of new phase 3 data on the use of VR-CAP in the Mantle Cell Lymphoma section (MANT-A, p1–2 of 3) of the NCCN Clinical Practice Guidelines (NCCN Guidelines™) in Non-Hodgkin's Lymphomas (version V2.2014), specifically inclusion of:

- VR-CAP as a suggested treatment regimen within the section 'Induction Therapy, Less aggressive therapy' on MANT-A, p1
- VR-CAP and the associated reference within the section 'Induction Therapy, Less aggressive therapy' on MANT-A, p2

In addition, inclusion of the new data and associated reference are warranted within the narrative section of the Guidelines, specifically on pages MS-82–83 of version V2.2014, where the current data on less aggressive first-line therapy for stage II (bulky) and stage III–IV mantle cell lymphoma are included.

**FDA Clearance:** The FDA has approved VELCADE for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. The recommended dose of VELCADE is 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 in 21-day cycles, administered either as a 3–5 second bolus intravenous injection or subcutaneous injection. Data from the study referenced below are not included in the US Prescribing Information for VELCADE. A submission to the FDA is planned shortly.

**Rationale:** Data from the primary study analysis of the LYM-3002 (NCT00722137) randomized phase 3 clinical trial of VR-CAP vs rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), in 487 previously untreated mantle cell lymphoma patients not considered for bone marrow transplantation, were presented at the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO). Results showed that:

- After a median follow-up of 40 months, the median progression-free survival (PFS, primary endpoint) per independent radiology review committee (IRC) assessment was 24.7 vs 14.4 months (hazard ratio [HR] 0.63, p<0.001) with VR-CAP vs R-CHOP.
  - This analysis was supported by sensitivity analyses, including analysis of PFS by investigator assessment
- Data for secondary efficacy endpoints with VR-CAP vs R-CHOP included:
  - Rate of bone marrow- and lactate dehydrogenase-verified complete response (CR+unconfirmed CR [CRu]) by IRC: 53% vs 42%; odds ratio [OR] 1.69, p=0.007
  - Overall response rate by IRC: 92% vs 90%; OR 1.43, p=0.275
  - Duration of response by IRC: median 36.5 vs 15.1 months

- Duration of CR+CRu by IRC: median 42.1 vs 18.0 months
- Time to progression by IRC: median 30.5 vs 16.1 months; HR 0.58, p<0.001
- Time to next anti-lymphoma therapy: median 44.5 vs 24.8 months; HR 0.50, p<0.001
- Treatment-free interval: median 40.6 vs 20.5 months; HR 0.50, p<0.001
- After a median follow-up of 40 months, with 158 (32%) events, overall survival (OS) data were not mature
  - Median OS was not reached vs 56.3 months with VR-CAP vs R-CHOP (HR 0.80, p=0.173; 4-year OS rate: 64.4% vs 53.9%)
- Grade ≥3 adverse events (AEs) were reported in 93% and 85% of patients receiving VR-CAP and R-CHOP, respectively, including:
  - Neutropenia (85% vs 67%), thrombocytopenia (57% vs 6%), leukopenia (44% vs 29%), lymphopenia (28% vs 9%), anemia (15% vs 14%), and febrile neutropenia (15% vs 14%)
  - Bleeding events of any grade were reported in 6% vs 5% of patients, including 1.7% vs 1.2% with grade ≥3 bleeding events.
- Serious AEs were reported in 38% and 30% of patients receiving VR-CAP and R-CHOP, respectively

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

- Cavalli F, et al. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma patients ineligible for bone marrow transplantation. *J Clin Oncol* 2014;32(5s):Suppl(abstract 8500); oral presentation at the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO)
- Robak T, et al. Phase 3 study of frontline rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in transplantation-unsuitable mantle cell lymphoma (MCL) patients. Oral presentation to be given at the 19<sup>th</sup> Congress of the European Hematology Association; June 12–15, 2014; Milan, Italy. Abstract S1345. Available at: <https://b-com.mci-group.com/EventProgramme/EHA19.aspx>
- VELCADE (bortezomib) for Injection. United States prescribing information, Rev 15, issued October 2012.

Yours sincerely,

Liviu Niculescu, MD  
Senior Medical Director, Global Medical Affairs