Submitted by:
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NCCN Guidelines Panel: Non-Hodgkin's Lymphomas

On behalf of Millennium Pharmaceuticals, Inc., I respectfully request the NCCN Non-Hodgkin's Lymphomas Guidelines Panel to review the enclosed data on the use of VELCADE® (bortezomib) in patients with follicular lymphoma (FL).

Specific Changes: Inclusion of VELCADE plus rituximab, with or without additional chemotherapy, within the suggested treatment regimens for 'Second-line and Subsequent Therapy' of FL (grade 1–2) in the updated NCCN Clinical Practice Guidelines for Non-Hodgkin's Lymphomas, as well as in the narrative section of the Guidelines. We believe that the available findings warrant inclusion of these regimens as a category 2A recommendation.

FDA Clearance: The FDA has not approved VELCADE for the treatment of follicular lymphoma. The FDA has approved VELCADE for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Rationale: Results from the Phase 3 LYM3001 study of weekly VELCADE plus rituximab (N=336) versus rituximab alone (N=340) in patients with rituximab-naïve or rituximab-sensitive relapsed FL were recently presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, Florida, in December 2010.[1] Study results included the following:

- The primary endpoint was progression-free survival (PFS); addition of VELCADE to rituximab was associated with an improvement in median PFS, from 11.0 to 12.8 months (HR 0.822, p=0.039)
- VELCADE-rituximab resulted in higher response rates than rituximab alone
  - overall response rate: 63% versus 49%, p<0.001
  - rate of complete response/unconfirmed complete response: 25% versus 18%, p=0.035
- Time to next anti-lymphoma treatment was also improved with bortezomib-rituximab versus rituximab (median 23.0 versus 17.7 months, p=0.027)
- Bortezomib-rituximab was associated with increased rates of adverse effects compared with rituximab, but these did not affect the feasibility of treatment, and there were no clinically relevant differences in quality of life between treatment arms
- Overall (17%) and grade ≥3 (3%) rates of peripheral neuropathy were limited with bortezomib-rituximab

These findings are supported by data from an earlier randomized phase 2 study of weekly or twice-weekly VELCADE in combination with rituximab.[2] Additionally, data from phase 2 studies of VELCADE in combination with rituximab and bendamustine,[3,4] or rituximab, cyclophosphamide, and prednisone, with or without doxorubicin,[5] have recently been

presented or published. These data support the substantial activity and tolerable safety profile of bortezomib-rituximab-based combinations in patients with relapsed/refractory FL.

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

- Coiffier B, Osmanov E, Hong X, et al. A phase 3 trial comparing bortezomib plus rituximab with rituximab alone in patients with relapsed, rituximab-naive or -sensitive, follicular lymphoma. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #857.
- De Vos S, Goy A, Dakhil SR, et al. Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma. *J Clin Oncol*. 2009;27(30):5023–5030.
- Fowler N, Kahl B, Rosen P, et al. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: encouraging activity in the phase 2 VERTICAL study. Presented at the 51st Annual Meeting of the American Society of Hematology (ASH) in New Orleans, LO; December 5–8, 2009. Oral presentation, abstract #933.
- Freidberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood* 2011;117(10):2807–2812.
- Craig M, Hanna WT, Cabanillas F, et al. Bortezomib in combination with rituximab, cyclophosphamide, and prednisone with or without doxorubicin followed by rituximab maintenance in patients with relapsed or refractory follicular lymphoma: results of a phase 2 study. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Poster presentation, abstract #2798.
- VELCADE prescribing information.

Cited references:

1. Coiffier B, Osmanov E, Hong X, et al. A phase 3 trial comparing bortezomib plus rituximab with rituximab alone in patients with relapsed, rituximab-naive or -sensitive, follicular lymphoma. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #857.
2. De Vos S, Goy A, Dakhil SR, et al. Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma. *J Clin Oncol*. 2009;27(30):5023-5030.
3. Fowler N, Kahl B, Rosen P, et al. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: encouraging activity in the phase 2 VERTICAL study. Presented at the 51st Annual Meeting of the American Society of Hematology (ASH) in New Orleans, LO; December 5–8, 2009. Oral presentation, abstract #933.
4. Freidberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood* 2011;117(10):2807–2812.
5. Craig M, Hanna WT, Cabanillas F, et al. Bortezomib in combination with rituximab, cyclophosphamide, and prednisone with or without doxorubicin followed by rituximab maintenance in patients with relapsed or refractory follicular lymphoma: results of a phase 2 study. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Poster presentation, abstract #2798.

Yours sincerely

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