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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 updated data on VELCADE[®] (bortezomib) plus melphalan and prednisone (MPB regimen) in patients with previously untreated multiple myeloma.

Specific Changes:

Inclusion of recently published data (after a median follow-up of 60.1 months from randomization) from the final analysis of the phase III VISTA trial of MPB versus melphalan-prednisone (MP) alone within the narrative section of the NCCN Clinical Practice Guidelines (NCCN Guidelines[™]) in Multiple Myeloma (version V2.2013), specifically:

- Additions to the 'Melphalan/Prednisone/Bortezomib' section on pages MS-14–15, which currently summarize data from the previous updated analysis of VISTA, reported after a median follow-up of 36.7 months
- Inclusion of the associated reference for the recently published updated data (update to Reference 98).

FDA Clearance: The FDA has approved VELCADE for the treatment of multiple myeloma. The current US Prescribing Information (Rev 15, issued October 2012) incorporates overall survival (OS) data from the final analysis of VISTA:

- "In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the VELCADE, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85)"
- "Overall survival was statistically significantly longer on the VELCADE, melphalan and prednisone arm".

Rationale: Data from the final analysis of VISTA (median follow-up 60.1 months) were fully published on February 1, 2013 in the *Journal of Clinical Oncology*. These data are substantially more mature than those currently included in the NCCN Guidelines, with an additional 2 years' median follow-up. The main findings included:

- A 31% reduced risk of death with MPB vs MP (hazard ratio [HR]=0.695, p<0.001)
- Median OS of 56.4 months vs 43.1 months with MPB vs MP, with 5-year OS rates of 46.0% vs 34.4%
- Among patients who received subsequent anti-MM therapies, survival from the start of subsequent therapy was similar for MPB vs MP (median 28.1 vs 26.8 months, HR=0.914)
- Incidence proportions of second primary malignancies following MPB vs MP were 1% vs 1% (relative risk [RR]=1.003) for hematologic malignancies, 1% vs 1% (RR=0.669) for fatal hematologic malignancies, and 5% vs 3% (RR=1.605) for solid tumors
- Exposure-adjusted incidence rates for all second primary malignancies were 0.0166 vs 0.013 per patient-year following MPB vs MP.

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

- San Miguel JF et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol* 2013;31(4):448–55
- VELCADE (bortezomib) for Injection. United States prescribing information, Rev 15, issued October 2012.

Yours sincerely

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