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### **NCCN Guidelines Panel: Melanoma**

On behalf of Merck & Co., Inc., I respectfully request the NCCN Melanoma Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Clinical Practices Guidelines in Oncology for Melanoma Version 2.2016.

#### Specific changes requested:

In section ME-E (page 26), we respectfully request that KEYTRUDA (pembrolizumab) be updated from Category 2A to Category 1 for systemic therapy for patients with metastatic or unresectable melanoma. This request is based on the current level of evidence supporting the safety and efficacy of KEYTRUDA as systemic therapy for patients with metastatic or unresectable melanoma.

#### FDA approval:

FDA approved KEYTRUDA (pembrolizumab) for the treatment of patients with unresectable or metastatic melanoma, on December 18, 2015. Please see enclosed prescribing information (PI).<sup>1</sup>

#### Rationale:

KEYTRUDA (pembrolizumab) has previously demonstrated superior overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) versus ipilimumab in the treatment of patients with unresectable or metastatic melanoma based on data from the phase III, randomized and controlled study KEYNOTE-006.<sup>2</sup>

Schachter *et al.*<sup>3</sup> presented the final OS analysis of KEYNOTE-006 at ASCO 2016 showing that median overall survival was not reached for both arms of pembrolizumab (median follow-up 23 months) compared with 16 months for ipilimumab. Pembrolizumab demonstrated superior OS over ipilimumab with a HR: 0.68 (95% CI: 0.53-0.86; p=0.00083) for pembrolizumab Q3W vs. ipilimumab and HR: 0.68 (95% CI: 0.53-0.87; p=0.00085) for pembrolizumab Q2W vs. ipilimumab; 24-month OS rate was 55% (for both pembrolizumab arms) compared with 43% for ipilimumab. The median PFS was 4.1 and 5.6 months for pembrolizumab Q3W and Q2W, respectively, compared with 2.8 months for ipilimumab. Pembrolizumab demonstrated superior PFS over ipilimumab with HR: 0.61 (95% CI: 0.50-0.75; p<0.00001) for both pembrolizumab arms vs. ipilimumab; PFS rates at 24 months were 28% and 31% for pembrolizumab Q3W and Q2W, respectively, compared with 14% for ipilimumab. Safety profile remained favorable for pembrolizumab.<sup>3</sup>

In addition to data from KEYNOTE-006, KEYNOTE-001 study follow-up (pool data analysis from all 655 patients with advanced melanoma) reported OS results with a median OS in the total population of 23 months (95% CI: 20-29), a 12-month survival rate of 66% (95% CI: 62-69) and a 24-month survival rate of 49% (95% CI: 44-53). In patients given pembrolizumab as their initial systemic cancer treatment (treatment-naïve population), median OS was 31 months (95% CI, 24 months to not reached), with 12- and 24-month OS rates of 73% (95% CI, 65-79) and 60% (95% CI, 51-68).<sup>4</sup>

Robert *et al.*<sup>5</sup> presented the 3-Year Overall Survival from KEYNOTE-001 at ASCO 2016. The 3-year OS rate with all doses of pembrolizumab was 40% in the total population with a median OS of 24.4 months (95% CI: 20.2-29.0) and

45% in treatment-naïve patients with a median OS of 32.2 months (95% CI: 27.2-NR). The median PFS was 4.9 and 5.0 months for the total and treatment-naïve populations, respectively. PFS rates at 24 and 36 months were 28% and 21% in the total population and 36% and 30% in the treatment naïve group, respectively. In the safety analysis after 32 months of median follow-up, 112 (17%) of 655 patients experienced at least 1 treatment-related grade 3 or 4 adverse event (AE) and 50 (8%) patients discontinued treatment due to a treatment-related AE. There were no drug-related deaths. Pembrolizumab continued to demonstrate safety and tolerability.<sup>5</sup>

In summary, results presented were consistent with those reported previously with anti-PD-1 monoclonal antibodies as monotherapy, with additional 2-year and 3-year OS and PFS data. Altogether, the strength of the evidence supports pembrolizumab as category 1.

The following resources are submitted to assist the committee with their review:

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Robert C *et al.* Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; 372:2521-32.
3. Schachter J *et al.* Pembrolizumab versus Ipilimumab for advanced melanoma: Final Overall Survival Analysis of KEYNOTE-006. *J Clin Oncol* 2016; 34 (suppl; abstr 9504). Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2016; Chicago, IL.
4. Ribas A *et al.* Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma. *JAMA* 2016; 315(15): 1600-1609. Doi:10.1001/jama.2016.4059
5. Robert C *et al.* 3-Year Overall Survival for patients with advanced melanoma treated with Pembrolizumab in KEYNOTE-001. *J Clin Oncol* 2016; 34 (suppl; abstr 9503). Presented at American Society of Clinical Oncology Annual Meeting; June 3-7, 2016; Chicago, IL.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,



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