April 15, 2018

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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 the NCCN Guidelines V2.2018 for Melanoma.

Specific changes requested:

We respectfully request that KEYTRUDA (pembrolizumab) be added as adjuvant treatment option for patients with resected, high-risk stage III melanoma in the NCCN guidelines for Melanoma as category 1.

FDA Approval:

KEYTRUDA (pembrolizumab) is approved for the treatment of patients with unresectable or metastatic melanoma. Please see enclosed prescribing information (PI).[1]

KEYTRUDA (pembrolizumab) is not approved as an adjuvant treatment option for patients with resected stage III melanoma.

Rationale:

A multicenter, randomized, double- blind, Phase 3 Trial of the EORTC Melanoma Group (KEYNOTE-054; NCT02362594) of Pembrolizumab versus placebo after complete resection of high-risk Stage III Melanoma was conducted in patients with histologically confirmed cutaneous melanoma metastatic to regional lymph nodes who underwent a complete regional lymphadenectomy within 13 weeks prior to starting treatment. Patients with ECOG performance > 1, autoimmune disease, uncontrolled infections, use of systemic corticosteroids, and prior systemic therapy for melanoma were excluded. Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses for (~1 year) or until disease recurrence, unacceptable toxicity, major protocol violation, or withdrawal of consent. The primary endpoint was recurrence-free survival (RFS) in the overall population and in the subgroup of patients with PD-L1-positive tumors. Secondary endpoints included distant metastasis-free survival, overall survival, safety, and health-related quality of life. 1019 patients were randomized: 514 patients were assigned to the pembrolizumab group and 505 to the placebo group. The characteristics at baseline were similar between the two groups. The overall median follow-up was 15.1 months; 14.7 months in the pembrolizumab group and 15.4 months in the placebo group. The 12-month RFS rate was 75.4% (95% CI, 71.3 to 78.9) in the pembrolizumab group and 61.0% (95% CI, 56.5 to 65.1) in the placebo group. RFS was significantly longer in the pembrolizumab group than in the placebo group [hazard ratio for recurrence or death, 0.57 (98.4% CI, 0.43 to 0.74); P<0.001]. At 18 months, the corresponding rates were 71.4% (95% CI, 66.8 to 75.4) and 53.2% (95% CI, 47.9 to 58.2). In the 853 patients with PD-L1-positive tumors (MEL score $\geq$ 2), the 12-month RFS rate was 77.1% (95% CI, 72.7 to 80.9) in the pembrolizumab group and 62.6% (95% CI, 57.7 to 67.0) in the placebo group. RFS was significantly longer for

patients with PD-L1 positive tumors in the pembrolizumab group than in the placebo group [hazard ratio for recurrence or death, 0.54 (95% CI, 0.42 to 0.69); P<0.001].

Treatment-related adverse events of any grade occurred in 396 (77.8%) patients in the pembrolizumab group and in 332 (66.1%) patients in the placebo group. Treatment-related grade 3 to 5 adverse events were reported in 14.7% of patients in the pembrolizumab group and in 3.4% of patients in the placebo group. There was one treatment-related death due to myositis in the pembrolizumab group. The trial will continue to its secondary endpoints, distant metastasis-free survival and overall survival.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.

2. Eggermont AM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S *et al*. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. New England Journal of Medicine. April 15,2018 DOI: 10.1056/NEJMoa1802357

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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