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NCCN Guidelines Panel: Melanoma

On behalf of Merck & Co., Inc., I respectfully request that the NCCN Melanoma Panel review the enclosed information on KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V1.2019 for Melanoma.

Specific changes requested:

We respectfully request the NCCN panel to consider the inclusion of KEYTRUDA in combination with low dose ipilimumab as a first-line treatment recommendation in patients with unresectable or metastatic melanoma in the appropriate sections of the guidelines, including section ME-H, based on the longer follow-up data from KEYNOTE-029 presented at SMR 2018.[3]

We also respectfully request the NCCN panel consider revising the dosing information on KEYTRUDA. In section MS-40 under "*Checkpoint Immunotherapy Treatment Administration"* (and in section MS-58, Table 20, as well as other relevant sections of the guidelines), we request to revise the recommended approved dose of Keytruda from 2mg/kg every 3 weeks to the following:

- The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.[1]

FDA approval:

KEYTRUDA (pembrolizumab) is approved for the treatment of patients with unresectable or metastatic melanoma.
Please refer to the KEYTRUDA Prescribing Information for other FDA-approved indications.[1]

Rationale:

KEYNOTE-029 (NCT02089685) is an open-label, phase 1b trial evaluating the standard-dose of pembrolizumab in combination with reduced-dose ipilimumab in patients with advanced melanoma. The primary endpoints were safety and tolerability. Secondary endpoints were an objective response assessed with RECIST V1.1 by independent central review, duration of response, progression-free survival, and overall survival. 153 patients with unresectable or metastatic melanoma were enrolled from 12 medical centers in Australia, New Zealand, and the USA. No previous therapy with an anti-PD-1, anti- programmed death ligand 1 (PD-L1), anti-programmed death ligand 2, anti-CD137, or anti-CTLA-4

antibody was a requirement. Patients were also required to have an ECOG PS of 0 or 1. Patients received pembrolizumab 2 mg/kg (IV) plus ipilimumab 1 mg/kg (IV) every 3 weeks for four doses, followed by pembrolizumab 2 mg/kg every 3 weeks for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision.[2]

As of the Oct 17, 2016 cutoff date, median follow-up was 17.0 months (IQR 14.8–18.8). There were no treatment-related deaths. Of the 153 patients, treatment-related adverse events (TRAEs) led to discontinuation of pembrolizumab and ipilimumab in 22 (14%) patients, 12 (8%) patients discontinued ipilimumab only and 14 (9%) discontinued pembrolizumab only; 92 (60%) patients developed immune-mediated adverse events (imAEs) of any grade (158 imAEs), 42 (27%) patients developed imAEs grade 3–4 (50 imAEs).The most common imAEs were hypothyroidism (n=25; 16%) and hyperthyroidism (n=17; 11%). ORR was achieved by 61% (95% CI, 53–69) of the patients, 15% with a complete response and 46% with a partial response. Estimated 1-year progression-free survival was 69% (95% CI, 60–75), and estimated 1-year overall survival was 89% (95% CI, 83–93).[2]

As of the July 17, 2018 cutoff date (34 months after last patient enrolled), median follow-up was 36.8 months (range 0.8-42.1). No treatment-related deaths occurred. Of the 153 patients, TRAEs led to discontinuation of pembrolizumab and ipilimumab in 50 (33%) patients, 13 (8%) patients discontinued ipilimumab only and 16 (10%) discontinued pembrolizumab after completing ipilimumab; 147 (96%) patients had TRAE of any grade, with Grade 3-4 occurring in 72 (47%) patients. ImAEs and infusion reactions of any grade occurred in 61% of patients, with grade 3-4 observed in 26% of patients (Grade 3: 25%; Grade 4: 1%). ORR was observed in 62% (95% CI, 54-70) of patients, 27% with a complete response and 35% with a partial response. From prior cutoff date of Oct 17, 2016 to current cutoff date, the percentage of patients with a complete response increased from 15% to 27%. Duration of response rate was 93% at 1 year, 87% at 2 years, and 84% at 3 years based on Kaplan-Meier estimates. Progression-free survival rates (by RECIST v1.1, central review) were 68% at 1 year, 61% at 2 years, and 59% at 3 years. Overall survival rates were 88% at 1 year, 79% at 2 years, and 73% at 3 years.[3]

Based on the longer follow up of the KN-029 study, the data demonstrate robust and durable antitumor activity based on the increased number of patients achieving a complete response, the durability of ongoing responses, and the PFS and OS estimates. The combination was tolerable and showed a manageable safety profile. The totality of these data supports our request for the inclusion of pembrolizumab + low dose ipilimumab as first-line treatment in patients with advanced melanoma.[2,3]

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Long, GV, Atkinson V, Cebon, JS et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. The Lancet Oncology, Volume 18, Issue 9 , 1202 - 1210 DOI: https://doi.org/10.1016/S1470-2045(17)30428-X
3. Long, GV, Atkinson V, Cebon JS et al. Long-Term Follow-Up of Standard Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in 153 Patients with Advanced Melanoma: KEYNOTE-029 1B. Presented at Society for Melanoma Research (SMR); October 24-27, 2018; Manchester, England.

Thank you for considering this request. Should you need additional information, please do not hesitate to contact me.

Sincerely,

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