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NCCN Guidelines Panel: Melanoma Panel

NCCN Melanoma Panel: On behalf of Merck & Co., Inc., I respectfully request the NCCN Melanoma Panel to review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to unresectable or metastatic melanoma.

Specific Changes: We respectfully request the inclusion of pembrolizumab in combination with dabrafenib and trametinib as a treatment option for patients with unresectable or metastatic melanoma with *BRAF* V600-activating mutation in the appropriate sections of the NCCN Cutaneous Melanoma Guidelines v3.2020, including page ME-I (1 of 7).

FDA Clearance: KEYTRUDA is not indicated as a combination therapy with dabrafenib and trametinib for the treatment of patients with advanced melanoma.
KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
Please refer to the KEYTRUDA prescribing information for other FDA-approved indications.[1]

Rationale: **Ferrucci et al**. presented updated results from part 3 of the KEYNOTE-022 randomized, double-blind, trial comparing the efficacy and safety of first-line pembrolizumab 2 mg/kg every three weeks plus dabrafenib 150 mg BID (D) and trametinib 2 mg QD (T) [n=60] with placebo + D + T [n=60] in patients with *BRAF*$^{V600E/K}$ mutant unresectable or metastatic melanoma. The primary endpoint was progression-free survival (PFS), which was assessed based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by investigator. Secondary endpoints included overall response rate (ORR), duration of response (DOR), and overall survival (OS). Based on the analysis cutoff date of June 26, 2019, the median follow-up time was 29.6 months (range 2.7-42.9) and 26.3 months (range 3.2-41.3) for the pembrolizumab + D + T and placebo + D + T arms, respectively. The median PFS for pembrolizumab + D + T was 16.9 months (95% CI 11.3-27.9) compared to 10.7 months (95% CI 7.2-16.8) for placebo + D + T (HR 0.53; 95% CI 0.34-0.83). The Kaplan-Meier (KM) estimated PFS at 24 months was 41% vs. 16%, respectively. ORR for pembrolizumab + D + T was 63% (20% complete responses and 43% partial responses) compared with 72% for placebo + D + T (15% complete responses and 57% partial responses). The median DOR for pembrolizumab + D + T was 25.1 months (95% CI 14.1-not reached [NR]) compared with 12.1 months (95% CI 6.0-15.7) for placebo + D + T (HR 0.32; 95% CI 0.17-0.59). According to KM analysis, at 24 months, 55% of patients randomized to pembrolizumab + D + T had ongoing responses compared with 16% with placebo + D + T. The median OS for pembrolizumab + D + T was NR (95% CI 23.9-NR) compared to 26.3 months (95% CI 18.2-NR) for placebo + D + T (HR 0.64; 95% CI 0.38-1.06). The KM-estimated OS at 24 months was 63% vs. 52% in the pembrolizumab + D + T arms and placebo + D + T arms, respectively. Grade 3-5 treatment-related adverse events occurred in 58.3% and 25.0% of patients in the pembrolizumab + D + T arms and placebo + D + T arms, respectively. One patient in the pembrolizumab + D +T arm died due to treatment-related pneumonitis. Treatment-related adverse events leading to the discontinuation of ≥ 1 study drug occurred in 43.3% and 18.3% of patients in the pembrolizumab + D + T arms and placebo + D + T arms,

respectively. With a median follow-up of more than 2 years, the results support the antitumor activity of pembrolizumab, dabrafenib, and trametinib as a combination therapy in patients with advanced melanoma.[2]

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

1. KEYTRUDA (pembrolizumab) Prescribing Information. Merck & Co., Inc.

2. Ferrucci PF, Ascierto PA, Maio M, et al. Updated Survival In Patients With *BRAF*-mutant Melanoma Administered Pembrolizumab, Dabrafenib, And Trametinib. Presented at: Society of Melanoma Research; 20-23 November 2019; Salt Lake City, UT.

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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