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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 systemic treatment option for patients with unresectable or metastatic melanoma with *BRAF* V600-activating mutation in the appropriate sections of the NCCN Cutaneous Melanoma Guidelines v1.2021, including page ME-I (1 of 8).

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.
KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
Please refer to the KEYTRUDA prescribing information for other FDA-approved indications.[1]

Rationale: **Ferrucci et al.**[2] published results from part 3 of the KEYNOTE-022 trial (NCT02130466). This was the randomized, double-blind, phase 2 portion in which patients with previously untreated advanced melanoma were randomly assigned 1:1 to receive pembrolizumab 2 mg/kg intravenously every three weeks in combination with dabrafenib 150 mg orally two times daily and trametinib 2 mg orally once daily (triplet therapy, n=60) or placebo combined with dabrafenib 150 mg orally two times daily and trametinib 2 mg orally once daily (doublet therapy, n=60). Eligible patients were ≥18 years of age, had unresectable stage III or stage IV cutaneous melanoma, and had $BRAF^{V600E/K}$ mutation-positive disease. 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 the investigator. Secondary endpoints were objective response rate (ORR), duration of response (DOR), and overall survival (OS). At the cutoff date of June 26, 2019, the median follow-up time for this analysis was 36.6 months. The results of this updated analysis were not considered to carry statistical significance, as the trial had previously demonstrated at the median follow-up time of 9.6 months that triplet therapy improved PFS compared to doublet therapy without reaching statistical significance (16.0 months vs 10.3 months; HR 0.66; p=0.043).

In this updated analysis, the median PFS was 16.9 months (95% CI 11.3-27.9) in the triplet arm and 10.7 months (95% CI 7.2-16.8) in the doublet arm (HR 0.53; 95% CI 0.34-0.83). The 12-month Kaplan-Meier (KM) estimated PFS rates were 62% (95% CI 48.1%-73.5%) in the triplet arm and 47% (95% CI 33.4%-58.7%) in the doublet arm, and the 24-month PFS rates were 41% (95% CI 27.4%-54.2%) and 16% (95% CI 8.1%-27.1%), respectively. The ORR (RECIST v1.1 assessed by investigator) was 63.3% in the triplet arm and 71.7% in the doublet arm. The median KM-estimated DOR was 25.1 months in the triplet arm

and 12.1 months in the doublet arm (HR 0.32; 95% CI 0.17-0.59). The median OS was not reached in the triplet arm and was 26.3 months in the doublet arm (HR 0.64; 95% CI 0.38-1.06). The 12-month KM-estimated OS rates were 80% (95% CI 67.5%-88.1%) in the triplet arm and 73% (95% CI 60.2%-82.7%) in the doublet arm, and the 24-month OS rates were 63% (95% CI 49.4%-73.9%) and 52% (95% CI 38.4%-63.4%), respectively.

Treatment-related adverse events (TRAEs) occurred in 95% of patients in the triplet arm and 93% of patients in the doublet arm. Grade 3–5 TRAEs occurred in 58% of patients (including one death from pneumonitis) in the triplet arm and 25% of patients in the doublet arm. Adverse events led to treatment discontinuation in 47% of patients in the triplet arm and 20% of patients in the doublet arm.

With a median follow-up of more than 3 years, the results support the antitumor activity of pembrolizumab, dabrafenib, and trametinib as a first-line combination therapy in patients with unresectable or metastatic melanoma with a *BRAF*$^{V600E/K}$ mutation.

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

1. KEYTRUDA (pembrolizumab) Prescribing Information. Merck & Co., Inc.
2. Ferrucci PF, Di Giacomo AM, Del Vecchio M, et al. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma. *Journal for ImmunoTherapy of Cancer*;2020;8:e001806. doi:10.1136/jitc-2020-001806.

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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