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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 resected stage IV melanoma.

Specific Changes: We respectfully request the inclusion of pembrolizumab as a category 1 adjuvant treatment option for patients with resected stage IV melanoma with no evidence of disease in the appropriate sections of the NCCN Cutaneous Melanoma Guidelines v2.2021, including pages ME-16 and ME-16A.

FDA Clearance: 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: Grossman et al. presented data from a phase III trial to assess whether pembrolizumab administered over 1 year would improve relapse-free-survival (RFS) and overall survival (OS) in comparison to either ipilimumab or high-dose interferon in patients with high-risk resected melanoma. Eligible patients were age 18 years or older and had completely resected melanoma, including lymph node dissection for those with sentinel lymph node positive disease. Previous immunotherapy was not allowed, but prior adjuvant radiation was permitted. Of the 1,303 patients randomized to treatment, 11%, 49%, 34%, and 6% had stage IIIA(N2), IIIB, IIIC, and IV melanoma, respectively (American Joint Committee on Cancer 7th edition). Patients were randomized 1:1 to either the experimental arm or control arm as follows:

Experimental arm (n=648)

- Pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for 52 weeks

Control arm (n=655, investigator's choice, prespecified at enrollment)

- Interferon alfa-2b 20 million units per square meter (MU/m^2) IV on days 1-5 of weeks 1-4, followed by 10 MU/m^2/day subcutaneously on days 1, 3, and 5 of weeks 5-52

or

- Ipilimumab 10 mg/kg IV Q3W for 4 doses, then every 12 weeks for up to 3 years

The primary endpoints were RFS and OS in the total population and OS in patients with programmed-death ligand 1 positive (PD-L1+) melanoma at baseline.

The pre-specified analysis was performed per-protocol 3.5 years from the date the last patient was randomized and was time-driven, including 96% (512/536) of events for RFS and 53% (199/374) of

events for OS. Patients who received pembrolizumab had a statistically significant improvement in RFS compared to high-dose interferon or ipilimumab (HR 0.74; 99.62% CI 0.57-0.96; p<0.001). There was no statistically significant improvement in OS in the total population (HR 0.84; 96.3% CI 0.62-1.13; p=0.21) or in patients with PD-L1 positive melanoma (HR 0.88; 97.8% CI 0.60-1.29; p=0.45).

Treatment-related grade 3-5 adverse events (AEs) occurred in 19.5% of patients who received pembrolizumab compared to 49.2% with ipilimumab and 71.2% with high-dose interferon. AEs led to discontinuation in 16.9% of patients who received pembrolizumab compared to 64.8% and 24.7% for ipilimumab and high-dose interferon, respectively.

The results of this study support pembrolizumab as a treatment option for patients with completely resected stage IIIA(N2), IIIB, IIIC, or IV melanoma. Specifically, in the subgroup of patients with resected stage IV melanoma, the RFS HR was 0.60 (95% CI 0.32-1.14).

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

1. KEYTRUDA (pembrolizumab) Prescribing Information. Merck & Co., Inc.
2. Grossman KF, Othus M, Patel S, et al. Final analysis of overall survival and relapse-free survival in the SWOG S1404 phase III randomized trial comparing pembrolizumab to either high dose interferon or ipilimumab in patients with high risk resected melanoma. Presented at the American Society of Clinical Oncology (ASCO) 2021 Virtual Scientific Program; June 4-8, 2021.

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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