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NCCN Guidelines Panel: Melanoma Panel

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

Specific Changes: We respectfully request the inclusion of pembrolizumab in combination with lenvatinib as a second-line or subsequent therapy for patients with confirmed progression of unresectable or metastatic melanoma after treatment with an anti-PD-1/PD-L1 based therapy, including in combination with an anti-CTLA-4 therapy for ≥2 doses, in the appropriate sections of the NCCN Cutaneous Melanoma Guidelines v2.2021, including pages ME-7 and ME-I (1 of 8).

FDA Clearance: KEYTRUDA in combination with LENVIMA is currently not indicated for the treatment of patients with unresectable or metastatic melanoma.

- KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

Please refer to the KEYTRUDA and LENVIMA prescribing information for other FDA-approved indications.[1,2]

Rationale: As a follow-up to our submission request on October 1, 2020, this submission is based on the updated results of a phase II trial with pembrolizumab and lenvatinib in patients with unresectable or metastatic melanoma. Arance et al. [3] presented data from the phase II trial of patients with unresectable stage III or IV melanoma (N=103) with confirmed progressive disease (PD) on or within 12 weeks of the last dose of an anti-PD-1/L1 given alone or in combination (including with anti-CTLA-4) for ≥2 doses. Patients received treatment with pembrolizumab 200 mg intravenously every 3 weeks for up to 35 cycles in combination with lenvatinib 20 mg orally once daily. Treatment was continued until PD, unacceptable toxicity, or patient or physician decision. The primary endpoint was objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS) per RECIST v1.1 by BICR, overall survival (OS) and safety. Based on the data cutoff date of September 18, 2020 at the median follow-up of 15.3 months (range 12.1-19.0), 85 (82.5%) patients had discontinued pembrolizumab and lenvatinib (60.2% radiographic progression, 10.7% clinical progression, 7.8% adverse events, and 3.9% consent withdrawal). The ORR in the total population was 21.4% (95% confidence interval [CI], 13.9-30.5). The ORR in patients with PD on prior anti-CTLA-4 and anti-PD-1/L1 therapies (n=30) was 33.3% compared to 16.4% in patients without anti-CTLA-4 therapy (n=73). The median DOR was 8.3 months (range, 3.2 to 15.9+), with a 6-month and 9-month response rates of 77.3% and 38.6%, respectively. The median PFS was 4.2 months (95% CI, 3.8-7.1), with a 6-month PFS rate of 42.9% and a 12-month PFS rate of 18.5%. The median OS was 14.0 months (95% CI, 10.8-not reached), with a 6-month OS rate of 77.3% and a 12-month OS rate of 54.5%. Treatment-related adverse events (TRAEs) of any grade occurred in 96.1% (n=99) of patients. Grade 3-5 TRAEs occurred in 45.6% (n=47) of patients including one death due to platelet count decreased. The results of this study continue to support pembrolizumab plus lenvatinib as a potential treatment regimen for patients with unresectable or metastatic

melanoma that has progressed after treatment with an anti-PD-1/L1 based therapy, including in combination with an anti-CTLA-4 therapy for ≥2 doses.

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

1. KEYTRUDA (pembrolizumab) Prescribing Information. Merck & Co., Inc.
2. LENVIMA (lenvatinib) Prescribing Information. Eisai Inc.
3. Arance A, de la Cruz Merino L, Petrella T, et al. Lenvatinib plus pembrolizumab for patients with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: Updated findings of LEAP-004. Presented at: American Society of Clinical Oncology (ASCO) June 4-8 2021Virtual Meeting.

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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