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Date of Request: April 29, 2020
NCCN Guidelines Panel: Bone Cancer

NCCN Bone Cancer Panel: On behalf of Merck & Co., Inc., I respectfully request that the NCCN Bone Cancer Panel review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to updated dosing recommendations for pembrolizumab.

Specific Changes: We respectfully request the inclusion of the updated dosing recommendations for pembrolizumab, either 200 mg every 3 weeks or 400 mg every 6 weeks administered as a 30-minute intravenous (IV) infusion until disease progression, unacceptable toxicity, or up to 24 months for the treatment of adult patients with microsatellite instability-high (MSI-H) bone cancer, to BONE-B (page 1 of 5) in the NCCN Bone Cancer Guidelines.

FDA Clearance:

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- KEYTRUDA is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

MSI-H Cancer

- KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please refer to the KEYTRUDA (pembrolizumab) prescribing information for other FDA-approved indications.[1]

Rationale: KEYTRUDA (pembrolizumab) is now FDA-approved for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the

relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials. Based on the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data from an interim analysis of 41 patients with melanoma treated with pembrolizumab 400 mg every 6 weeks, there are no anticipated clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.[1] Additionally, this submission includes the pharmacokinetic modeling and simulation data published by Lala et al. [2] and the preliminary pharmacokinetic, efficacy and safety results from the KEYNOTE-555 trial (investigating a Q6W [every 6 weeks] dosing regimen for pembrolizumab in patients with advanced melanoma [NCT03665597]),[3] which support the recent label change.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Lala M, Li TR, De Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. *European Journal of Cancer*. 2020;131:68-75. doi: 10.1016/j.ejca.2020.02.016 [Epub ahead of print].
3. Lala M, Akala O, Chartash E, et al. Pembrolizumab 400 mg Q6W dosing: First clinical outcomes data from KEYNOTE-555 cohort B in patients with metastatic melanoma. Presented at the American Association for Cancer Research (AACR) Annual Meeting; April 27-28, 2020; Virtual 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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