Submitted by:
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NCCN Guidelines® Panel: Melanoma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully submit the enclosed OPDIVO® (nivolumab) prescribing information and clinical data which supports the most recent label change, that occurred on March 5, 2018 to reflect the new dosing for nivolumab to 240mg administered intravenously every 2 weeks or 480mg administered intravenously every 4 weeks over 30 minutes.[1] This information is being sent to the NCCN® Melanoma Panel for your consideration.

Specific Changes: Request for the inclusion as a footnote to ME-4, ME-5, ME-7, ME-12, ME-13 and ME-14, the following: FDA-recommended dosing of single agent nivolumab for adjuvant treatment of melanoma is 240mg IV every 2 weeks or 480mg IV every 4 weeks administered over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year.[1]

Request for the inclusion as a footnote to ME-H (1 OF 6), the following: FDA-recommended dosing for single-agent nivolumab is 240mg IV every 2 weeks or 480mg IV every 4 weeks administered over 30 minutes. FDA-recommended dosing for nivolumab/ipilimumab combination therapy is nivolumab 1 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 3 mg/kg on the same day, every 3 weeks for 4 doses; then single-agent nivolumab 240mg IV every 2 weeks or 480mg IV every 4 weeks administered over 30 minutes until disease progression or unacceptable toxicity.

On page MS-40 we have identified an inaccuracy and request to change the language to reflect the current FDA-recommended dosing for single agent nivolumab and nivolumab/ipilimumab combination therapy as stated above.

FDA Clearance of OPDIVO® (nivolumab) (indication in Melanoma):

- For the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- As a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma
- As a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- In combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Rationale: The Opdivo Prescribing Information was updated to reflect the new dosing of Opdivo to 240mg administered intravenously every 2 weeks or 480mg administered intravenously every 4 weeks over 30 minutes for all indications, except for metastatic colorectal cancer which is to be dosed at 240mg administered intravenously every 2 weeks over 30 minutes.[1] The dosing recommendations stated in the product label are different than the dose that was administered in the original protocol of the registrational clinical studies that support the current approved FDA indications.

As part of this submission, the published literature that support the pharmacokinetic analyses for the dosing of 240mg every 2 weeks, 480mg every 4 weeks, and a 30 minute infusion time are enclosed for your review.[2-4]

1. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. March 2018.
2. Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. *Ann Oncol*. 2017;28:2002-2008.
3. Zhao X, Ivaturi V, Gopalakrishnan M, et al. A model-based exposure-response (ER) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types. Poster presentation at the American Association for Cancer Research (AACR), April 1-5, 2017; Washington, DC.
4. Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. *Cancer Chemotherapy and Pharmacology*. 2018; DOI: 10.1007/s00280-018-3527-6.

Thank you for your consideration.
Sincerely,

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