



Submitted by:

Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology
Bristol-Myers Squibb Company
3401 Princeton Pike
Lawrence NJ, 08648
609-302-3927; awny.farajallah@bms.com

March 6, 2018

NCCN Guidelines® Panel: Hepatobiliary Cancers

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 240 mg administered intravenously every 2 weeks or 480mg administered intravenously every 4 weeks over 30 minutes.¹ This information is being sent to the NCCN® Hepatobiliary Cancers Panel for your consideration.

Specific Changes: Request for the inclusion as a footnote to HCC-5 and HCC 6, the following: nivolumab FDA approved dose is 240mg IV every 2 weeks or 480mg IV every 4 weeks administered over 30 minutes until disease progression or unacceptable toxicity.¹

FDA Clearance of OPDIVO® (nivolumab) (indication in Hepatocellular Carcinoma):

- OPDIVO® is indicated for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib

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 recommendation stated in the product label is different than the dose that was administered in the registrational clinical studies that supported the current approved 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,

A handwritten signature in black ink, appearing to read 'Awny Farajallah', with a stylized, flowing script.

Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology
Bristol-Myers Squibb Company