



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  
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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) clinical data to the NCCN® Melanoma Panel for your consideration. The first dataset is an ongoing phase 3, randomized, double-blind study of nivolumab versus ipilimumab as an adjuvant treatment in patients who have undergone complete resection of Stage IIIB/C or Stage IV melanoma. It has been published in New England Journal of Medicine on September 10, 2017<sup>1,2</sup>

Also enclosed for your consideration is OPDIVO® (nivolumab) and YERVOY® (ipilimumab) clinical data that has been presented at the 2017 European Society for Medical Oncology (ESMO) annual meeting and published simultaneously in New England Journal of Medicine on September 11, 2017. This is a 3-year update to CheckMate-067, a phase 3, randomized, double-blind trial that evaluated the combination of nivolumab plus ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy in patients with previously untreated advanced melanoma.<sup>3,4</sup>

The use of nivolumab for the treatment of adjuvant melanoma is considered investigational.

**FDA Clearance OPDIVO® (nivolumab) (indications in melanoma):** On January 23, 2016, the FDA approved first-line use of nivolumab in combination with ipilimumab 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.<sup>5</sup>

Additionally, nivolumab is indicated in melanoma:<sup>5</sup>

- As a single agent for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.
- As a single-agent for the treatment of 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.

**FDA Clearance YERVOY® (ipilimumab) (indications in melanoma):**

The FDA-approved ipilimumab on March 25, 2011 for the treatment of unresectable or metastatic melanoma.<sup>6</sup> Ipilimumab was also approved on October 28, 2015 for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.<sup>6</sup>

**Rationale:**

This data is being submitted in response to a standing request from NCCN for new clinical data.

The clinical evidence from the phase 3, randomized, double-blind study of nivolumab versus ipilimumab as an adjuvant treatment in patients who have undergone complete resection of Stage IIIB/C or Stage IV melanoma has been recently published as a manuscript in NEJM.<sup>1,2</sup>

The clinical evidence from the registrational phase 3 CA209-067 study was previously submitted to NCCN on April 4, 2017. A later database lock with a minimum follow-up of 36 months has recently been published as a manuscript in NEJM and is enclosed in this submission for your consideration.<sup>4</sup>

The following resources are included for your review. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med.* 2017; DOI: 10.1056/NEJMoa1709030.
2. Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma. *New England Journal of Medicine.* Online publication supplement
3. Grob JJ, Schadendorf D, Wagstaff J, et al. Regional Differences in Overall Survival (OS) in Patients With Advanced Melanoma (MEL) Who Received Nivolumab (NIVO) Combined With Ipilimumab (IPI) or NIVO Alone in a Phase 3 Trial (CheckMate 067). Oral Presentation at the 2017 European Society for Medical Oncology (ESMO) Annual Meeting September 8-12, 2017; Madrid, Spain.
4. Wolchok J, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival With Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2017; DOI: 10.1056/NEJMoa1709684
5. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. April 2017
6. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. March 2017

Thank you for your consideration.

Sincerely,



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