

Submitted by:

Awny Farajallah, MD, FACP
Vice President, Head US Medical Oncology,
Bristol-Myers Squibb Company
777 Scudders Mill Road
Plainsboro, NJ 08536
609-897-3945; awny.farajallah@bms.com
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NCCN Guidelines® Panel: Melanoma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully request the NCCN Melanoma Panel to consider inclusion of treatment with OPDIVO® (nivolumab) in combination with YERVOY® (ipilimumab) in the NCCN Guidelines for Melanoma. The FDA has approved (accelerated approval) this combination regimen for the initial treatment of metastatic or unresectable melanoma in patients with wild-type BRAF.¹

Specific Changes: We request that nivolumab and ipilimumab combination be included in the Guidelines for Melanoma for initial treatment of metastatic or unresectable melanoma, regardless of BRAF V600 mutation status.

FDA Clearance (indications in melanoma): The FDA approved ipilimumab for the treatment of unresectable or metastatic melanoma in Mar 2011.² In Dec 2014 the FDA approved nivolumab (accelerated approval) for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.¹ On 30 Sept 2015 the FDA approved nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.¹

Rationale for Proposed Change:

On-label trial, CA209-069:³ This Phase 2 randomized controlled trial in previously untreated patients with unresectable Stage III/IV melanoma, irrespective of BRAF V600 mutations, randomized patients to receive nivolumab in combination with ipilimumab or ipilimumab monotherapy (N=142, of these 109 were BRAF wild-type and 33 were BRAF V600 mutation-positive).

- The median PFS in the group receiving nivolumab in combination with ipilimumab was not reached in BRAF wild type patients and 8.5 months in BRAF V600 mutation-positive patients. Hazard ratio for death or disease progression, for combination therapy vs ipilimumab monotherapy, in BRAF wild-type and mutation-positive patients was 0.4 (95%CI, 0.23, 0.68) and 0.38 (95% CI: 0.15, 1.00), respectively. Objective response rates in the combination group were similar for BRAF wild-type and mutation-positive patients (61% vs 52%), with rate of complete response being the same in both (22%).³
- In the group that received nivolumab in combination with ipilimumab, treatment-related AEs of any grade were reported in 91% of the patients and Grade 3 or 4 AEs were reported in 54% of the patients.³

Supporting trial, CA209-067:⁴ The data from this Phase 3 double-blinded randomized controlled trial, with overall survival as one of the co-primary endpoints, has been filed with FDA for full approval of nivolumab monotherapy and in combination with ipilimumab for the initial treatment of unresectable or metastatic melanoma. The trial included patients irrespective of the BRAF V600 mutation status and 298 patients (31.5%) had BRAF V600 mutation.⁴

- The median PFS in the group receiving nivolumab in combination with ipilimumab was independent of BRAF V600 mutation status (11.7 mo [95% CI: 8.0, not reached] vs 11.2 mo [95% CI: 8.3, not reached]).⁴
- In the group that received nivolumab in combination with ipilimumab, treatment-related AEs of any grade were reported in 99.7% of the patients and Grade 3 or 4 AEs were reported in 68.7% of the patients.

The following resources are included for your review in support of this proposed inclusion/change:

- ¹ Product information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. September 2015.
- ² Product information, YERVOY (ipilimumab) injection, for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. August 2015.
- ³ Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. N Engl J Med. 2015; 372:2006-17.
- ⁴ Larkin J, Chiarion-Sileni V, Grob JJ, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Previously Untreated Melanoma. N Engl J Med. 2015; 373:23-34.

We acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications/ presentations. Thank you for your consideration of this request.

Sincerely,

A handwritten signature in black ink, appearing to read "Awny Farajallah". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

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