



June 18, 2019

Awany 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: Central Nervous System Cancers

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully submit the enclosed OPDIVO® (nivolumab) and YERVOY® (ipilimumab) clinical data that were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting to the NCCN® Central Nervous System Cancers Panel for your consideration.

CheckMate 204 is a phase 2 open-label study evaluated the safety and efficacy of nivolumab in combination with ipilimumab followed by nivolumab monotherapy for the treatment of patients with melanoma metastatic to the brain. This is the first disclosure of data on the use of nivolumab in combination with ipilimumab as treatment for patients with symptomatic melanoma brain metastases ¹

CheckMate 920 is a phase 3b/4 clinical trial of nivolumab in combination with ipilimumab in patients with previously untreated advanced renal cell carcinoma. Data presented at ASCO reports the interim safety and efficacy analysis for the cohort of patients with brain metastases from CheckMate 920.²

FDA Clearance OPDIVO® (nivolumab) (indications in melanoma and renal cell carcinoma)³:

- Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- Patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- Patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.

FDA Clearance YERVOY® (ipilimumab) (indications in melanoma and renal cell carcinoma)⁴:

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
- 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
- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.

The use of nivolumab or ipilimumab, monotherapy or in combination, for patients with melanoma or renal cell carcinoma metastatic to the brain is considered investigational.^{3,4}

The pivotal trial for previously untreated advanced renal cell carcinoma (CheckMate 214) excluded patients with any history of or concurrent brain metastases.

Rationale: These data are being submitted in response to a standing request from NCCN for new clinical data.

The following resources are included for your review.

1. Tawbi H, Forsyth P, Hodi S, et al. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). Oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2019; Chicago, IL, USA
2. Enamekhoo H, Olsen M, Carthon B, et al. Safety and Efficacy of Nivolumab Plus Ipilimumab in Patients With Advanced Renal Cell Carcinoma With Brain Metastases: Interim Analysis of CheckMate 920. Poster Presentation at the 2017 American Society for Clinical Oncology (ASCO) Annual Meeting June 2-6, 2017; Chicago, IL, USA
3. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. May 2019
4. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. May 2019

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Awny Farajallah', with a stylized flourish at the end.

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