Bristol Myers Squibb™

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NCCN Guidelines® Panel: Central Nervous System (CNS) Cancers Panel

Dear Panel Members,

On behalf of Bristol Myers Squibb Company, I respectfully submit the enclosed OPDIVO® (nivolumab) and YERVOY® (ipilimumab) clinical data that were recently presented at the 2020 American Association of Cancer Research (AACR) Annual Virtual Meeting II. This information is being submitted for the Panel's consideration.

A post hoc analysis was conducted to describe the efficacy and safety of nivolumab + ipilimumab in patients with and without baseline brain metastases in CheckMate 227 Part 1. Patients with untreated central nervous system metastases were excluded, and patients with adequately treated brain metastases were eligible if neurological findings had returned to baseline for at least 2 weeks prior to randomization.

CheckMate 227 is a Phase 3, randomized, multi-part, open-label study which evaluated nivolumab-based regimens versus platinum-doublet chemotherapy as a first-line treatment in patients with advanced non-small cell lung cancer across non-squamous and squamous tumor histologies. One of the cohorts, which is Part 1a, evaluated nivolumab plus low-dose ipilimumab or nivolumab monotherapy versus chemotherapy in patients whose tumors express PD-L1. The co-primary endpoint from Part 1a was overall survival with nivolumab + ipilimumab vs chemotherapy in patients with PD-L1–positive tumors. Another cohort, which is Part 1b, evaluated nivolumab plus low-dose ipilimumab or nivolumab plus chemotherapy versus chemotherapy in patients whose tumors do not express PD-L1. Analyses from Part 1b are descriptive in nature.

The primary disclosure of CheckMate 227, which included the co-primary endpoint from Part 1a, was published in the *New England Journal of Medicine* in September 2019. The article is enclosed for context of the primary analysis.[1,2,3]

FDA Clearance in Non-small Cell Cancer:
OPDIVO® in combination with YERVOY® is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (>1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.[4,5]

OPDIVO® in combination with YERVOY® and 2 cycles of platinum-doublet chemotherapy is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.[4,5]

OPDIVO® monotherapy is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor

aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO®.[4]

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

As part of this submission, the following resources are included for your review:

1. Borghaei H, Pluzanski A, Bernabe Caro R, et al. Nivolumab plus ipilimumab as first-line treatment for patients with advanced non-small cell lung cancer with brain metastases: results from CheckMate 227 Part 1. Poster presented at: American Association of Cancer Research (AACR) Annual Meeting II; June 22-24, 2020; Virtual Meeting.
2. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031. DOI: 10.1056/NEJMoa1910231.
3. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer [Supplementary Appendix]. *N Engl J Med*. 2019;381:2020-2031. DOI: 10.1056/NEJMoa1910231.
4. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. June 2020.
5. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol-Myers Squibb Company, Princeton, NJ. June 2020.

Thank you for your consideration.

Sincerely,

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