Bristol Myers Squibb™

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NCCN Guidelines® Panel: Non-Small Cell Lung Cancer Panel

Dear Panel Members,

On behalf of Bristol Myers Squibb, we respectfully request the Non-Small Cell Lung Cancer Panel to review the enclosed data recently presented at the American Society of Clinical Oncology (ASCO) 2021 Annual Meeting and published in the *Journal of Thoracic* Oncology from CheckMate 227 and CheckMate 9LA regarding the use of OPDIVO® (nivolumab) and YERVOY® (ipilimumab) with or without two cycles of chemotherapy in the first-line treatment of patients with stage IV or recurrent non-small cell lung cancer (NSCLC).[1-4]

Specific Changes: We respectfully request the panel's consideration of the enclosed data and the recommendations for nivolumab in combination with ipilimumab with or without 2 cycles of platinum-based chemotherapy in the NCCN Guidelines be revised to preferred category 1 recommendations for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations, regardless of histology or PD-L1 expression (pages NSCL-31, NSCL-32, NSCL-K [1, 2 and 3 of 5]).

FDA Clearance in Non-Small Cell Lung 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.[5,6]

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.[5,6]

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®.[5]

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

Please note there were previous submissions to NCCN regarding data from CheckMate 227 and CheckMate 9LA on the use of nivolumab and ipilimumab with or without chemotherapy in patients with advanced NSCLC on May 15, 2020, May 26, 2020, May 29, 2020, and January 18, 2021.

CheckMate 227 is a phase 3, randomized, multi-part, open-label study which evaluated nivolumab-based regimens vs platinum-doublet chemotherapy as first-line treatment in patients with advanced NSCLC across non-squamous and squamous tumor histologies. Part 1a evaluated nivolumab plus low-dose ipilimumab (n=396) or nivolumab monotherapy (n=396) vs chemotherapy (n=397) in patients whose tumors express PD-L1. The co-primary endpoint from Part 1a was overall survival with nivolumab plus ipilimumab vs chemotherapy in patients with PD-L1–positive tumors. Part 1b evaluated nivolumab plus

low-dose ipilimumab (n=187) or nivolumab plus chemotherapy (n=177) vs chemotherapy (n=186) in patients whose tumors do not express PD-L1. Analyses from Part 1b are descriptive in nature.[1]

At 4 years of minimum follow-up, nivolumab plus ipilimumab continued to demonstrate OS benefit vs chemotherapy in patients with PD-L1 ≥1% (HR [95% CI]: 0.76 [0.65-0.90]) and in those with PD-L1 <1% (HR [95% CI]: 0.64 [0.51-0.81]). Median OS (95% CI) for nivolumab plus ipilimumab vs chemotherapy was 17.1 (15.0-20.1) months vs 14.9 (12.7-16.7) months in patients with PD-L1 ≥1% and 17.2 (12.8-22.0) months vs 12.2 (9.2-14.3) months in patients with PD-L1 <1%. OS rates at 4 years for nivolumab plus ipilimumab vs chemotherapy were 29% vs 18% in patients with PD-L1 ≥1% and 24% vs 10% in patients with PD-L1 <1%. Safety was consistent with prior reports and no new safety signals were identified with longer follow-up.[1]

CheckMate 227 included pre-specified patient-reported outcomes (PRO) exploratory endpoints that were assessed using the Lung Cancer Symptom Scale (LCSS) average symptom burden index (ASBI) and 3-item global index (3-IGI), and the EQ-5D visual analog scale (VAS) and utility index (UI). In patients with PD-L1 expression ≥1%, nivolumab plus ipilimumab demonstrated delayed time to deterioration and numerical improvement in symptoms and health-related quality of life vs chemotherapy.[2,3]

CheckMate 9LA is a phase 3, randomized, open-label study which evaluated nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (n=361) vs chemotherapy (n=358) as a first-line treatment in patients with stage IV or recurrent NSCLC across non-squamous and squamous tumor histologies, regardless of PD-L1 expression. The primary endpoint was overall survival.[4]

At 2 years of follow-up, nivolumab plus ipilimumab and 2 cycles of chemotherapy continued to demonstrate OS benefit vs chemotherapy (HR [95% CI]: 0.72 [0.61-0.86]). Median OS (95% CI) was 15.8 (13.9-19.7) months for nivolumab plus ipilimumab and 2 cycles of chemotherapy and 11.0 (9.5-12.7) months for chemotherapy. OS rates at 2 years were 38% vs 26% for nivolumab plus ipilimumab and 2 cycles of chemotherapy vs chemotherapy. Grade 3-4 treatment-related AEs occurred in 48% of patients receiving nivolumab plus ipilimumab and 2 cycles of chemotherapy and 38% of patients receiving chemotherapy. Treatment-related deaths occurred in 2% of patients in each treatment group. Safety was consistent with prior reports and no new safety signals were identified with longer follow-up.[4]

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

1. Paz-Ares LG, Ciuleanu TE, Lee JS, et al. Nivolumab + ipilimumab vs chemotherapy as first-line treatment for advanced non-small cell lung cancer: Poster presented at: the American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021; Virtual Meeting.
2. Reck M, Ciuleanu T-E, Lee J-S, et al. First-line nivolumab plus ipilimumab vs chemotherapy in advanced non-small cell lung cancer with tumor PD-L1 > 1%: patient-reported outcomes from CheckMate 227 Part 1. *J Thorac Oncol*. 2021. doi:10.1016/j.jtho.2020.12.019.
3. Reck M, Ciuleanu T-E, Lee J-S, et al. First-line nivolumab plus ipilimumab vs chemotherapy in advanced non-small cell lung cancer with tumor PD-L1 > 1%: patient-reported outcomes from CheckMate 227 Part 1 [Supplementary Appendix]. *J Thorac Oncol*. 2021. doi:10.1016/j.jtho.2020.12.019.
4. Reck M, Cieuleanu TE, Cobo M, et al. First-line nivolumab + ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with advanced non-small cell lung cancer: 2-year update from CheckMate 9LA. Oral presentation at: the American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021; Virtual Meeting.
5. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. May 2021.
6. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. May 2021.

Thank you for your consideration of this request.

Sincerely,

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Samantha Gothelf, PharmD
Vice President, US Medical Oncology