Bristol Myers Squibb™

January 18, 2021

Anu Santhanagopal, PhD
Director, Oncology WW Scientific Content & Market Capabilities
Bristol Myers Squibb
3401 Princeton Pike
Lawrence, NJ 08648

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 regarding the use of OPDIVO® (nivolumab) and YERVOY® (ipilimumab) plus two cycles of chemotherapy in the first-line treatment of patients with stage IV or recurrent non-small cell lung cancer.[1-3]

Specific Changes: We request that nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy be recommended in the NCCN Guidelines as a preferred treatment option 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, with a preferred category 1 recommendation (changed from "category 2A recommendations"; pages NSCL-31, NSCL-32, and NSCL-K [1 and 2 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.[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: These data are being submitted in response to a standing request from the NCCN® for new data.

On behalf of Bristol Myers Squibb, we request the NCCN Panel to review the data recently published in *The Lancet Oncology* on January 18, 2021 and presented at the 2020 European Society for Medical Oncology (ESMO) Annual Meeting on the use of the use of nivolumab and ipilimumab plus chemotherapy in patients with advanced non-small cell lung cancer.

Please note there were previous submissions to NCCN regarding data from CheckMate 9LA on the use of the use of nivolumab and ipilimumab plus chemotherapy in patients with advanced non-small cell lung cancer which were submitted on May 26, 2020 and May 29, 2020.

CheckMate 9LA is a phase 3, randomized, open-label study which evaluated nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy 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 of overall survival (OS) for nivolumab + ipilimumab + chemotherapy vs chemotherapy in patients was met at the pre-specified interim analysis (minimum follow-up of 8.1 months), with a hazard ratio (HR) of 0.69 (96.71% CI: 0.55-0.87; P = 0.0006). Median OS (95% CI) was 14.1 months (13.2-16.2) for nivolumab + ipilimumab + chemotherapy and 10.7 months (9.5-12.4) for chemotherapy. With an additional 4.6 months of follow-up (minimum follow-up 12.7 months for OS), median OS (95% CI) was 15.6 months (13.9-20.0) for nivolumab + ipilimumab + chemotherapy and 10.9 months (9.5-12.6) for chemotherapy. Grade 3-4 treatment-related adverse events occurred in 47% of patients receiving nivolumab + ipilimumab + chemotherapy and in 38% of patients receiving chemotherapy.[1,2]

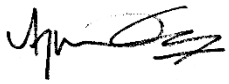
Checkmate 9LA included pre-specified PRO exploratory endpoints that assessed disease-related symptom burden (Lung Cancer Symptom Scale [LCSS] average symptom burden index [ASBI] and 3-item global index [3-IGI]) and overall health status (EQ-5D visual analog scale [VAS] and utility index [UI]). The combination of nivolumab + ipilimumab with 2 cycles of chemotherapy maintained or improved on-treatment symptom burden and overall health status compared with baseline, similar to chemotherapy alone (4 cycles). Additionally, a decreased risk and delayed time to definitive deterioration in health-related quality of life was observed with nivolumab + ipilimumab + chemotherapy vs chemotherapy alone.[3]

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

1. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021. DOI: 10.1016/ S1470- 2045(20)30641-0.
2. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial [Supplementary Appendix]. *Lancet Oncol*. 2021. DOI: 10.1016/S1470-2045(20)30641-0.
3. Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab + ipilimumab combined with 2 cycles of platinum-based chemotherapy versus 4 cycles of chemotherapy in advanced non-small cell lung cancer: patient-reported outcomes from CheckMate 9LA. Mini oral presentation at the European Society of Medical Oncology (ESMO) Annual Meeting; September 19- 21, 2020; Virtual Meeting.
4. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. December 2020.
5. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. November 2020.

Thank you for your consideration of this request.

Sincerely,



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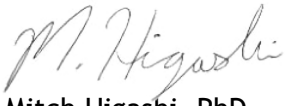
Samantha Gothelf, PharmD
Vice President, US Medical Oncology



Mitch Higashi, PhD
Vice President, US Health Economics & Outcomes Research