Bristol Myers Squibb™

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NCCN Guidelines® Panel: Malignant Pleural Mesothelioma Panel

Dear Panel Members,

On behalf of Bristol Myers Squibb, we respectfully request the Malignant Pleural Mesothelioma Panel to review the enclosed data regarding the use of OPDIVO® (nivolumab) and YERVOY® (ipilimumab) in adult patients with unresectable malignant pleural mesothelioma (MPM).[1,2,3]

Specific Changes: We request that nivolumab in combination with ipilimumab be recommended in the NCCN Guidelines as a preferred treatment option for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma, regardless of histology, with a preferred category 1 recommendation (changed from "category 2A recommendations"; page MPM-A [1 of 2]).

FDA Clearance in Malignant Pleural Mesothelioma:

OPDIVO® in combination with YERVOY®, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.[4,5]

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* on January 21, 2021 and presented at the 2020 European Society for Medical Oncology Immuno-Oncology Virtual Meeting on the use of nivolumab and ipilimumab in adult patients with unresectable MPM.[1,2,3]

CheckMate 743 is a phase 3, randomized, open-label trial evaluating nivolumab plus ipilimumab compared to chemotherapy (pemetrexed plus either cisplatin or carboplatin) as a first-line treatment in patients with unresectable malignant pleural mesothelioma. The primary endpoint was overall survival (OS) defined as the time from randomization to the date of death due to any cause. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) each confirmed by blinded independent central review (BICR), and PD-L1 expression as a predictive biomarker.[1,2]

CheckMate 743 met its primary endpoint of statistically improved overall survival with nivolumab plus ipilimumab (18.1 months [95% CI 16.8–21.4]) versus chemotherapy (14.1 months [95% CI 12.4–16.2]) at the pre-specified interim analysis, with a stratified HR of 0.74 (96.6% CI 0.60–0.91; $P = 0.0020$). Median overall survival with nivolumab plus ipilimumab was consistent between non-epithelioid and epithelioid subtypes. Grade 3–4 treatment-related adverse events were reported in 91/300 (30%) patients treated with nivolumab plus ipilimumab and 91/284 (32%) treated with chemotherapy. There were three (1%) and one (< 1%) treatment-related deaths, respectively.[1,2]

CheckMate 743 included two pre-specified patient-reported outcomes (PRO) exploratory endpoints. The first was disease-related symptom burden assessed using the mesothelioma lung cancer symptom scale (LCSS-Meso), average symptom burden index (ASBI) and 3-item global index (3-IGI). The other was

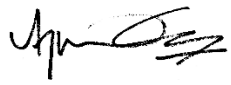
overall health status assessed using the EQ-5D-3L visual analog scale (VAS) and the utility index (UI). Nivolumab plus ipilimumab improved symptom burden and maintained overall health status compared with baseline. Additionally, nivolumab plus ipilimumab significantly delayed deterioration in health-related quality of life and illustrated a trend in symptom delay when compared with chemotherapy.[3]

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

1. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label phase 3 trial. *Lancet*. 2021. doi:10.1016/S0140-6736(20)32714-8.
2. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label phase 3 trial [Supplementary Appendix]. *Lancet*. 2021. doi:10.1016/S0140-6736(20)32714-8.
3. Scherpereel A, Antonia S, Bautista Y, et al. First-line nivolumab plus ipilimumab versus chemotherapy for the treatment of unresectable malignant pleural mesothelioma: patient-reported outcomes from CheckMate 743. Oral presentation at the European Society for Medical Oncology Immuno-Oncology (ESMO-IO); December 9-12, 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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