Submitted by:
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NCCN Guidelines® Panel: Non-Small Cell Lung Cancer (NSCLC)

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully request the NCCN NSCLC Panel to review the enclosed data and consider inclusion of OPDIVO® (nivolumab) in the NCCN Guidelines for treatment of NSCLC, subsequent to first line agents.

Specific Changes: I respectfully request that nivolumab be considered for inclusion in the NCCN Guidelines for treatment of NSCLC, subsequent to first line agents, irrespective of histology and biomarker status.

FDA Clearance: The FDA approved OPDIVO® (nivolumab) on March 4, 2015 for the treatment of patients with metastatic squamous cell NSCLC after platinum-based chemotherapy.[1] The other approved indication for nivolumab (accelerated approval) is unresectable or metastatic melanoma after disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.[1]

Rationale for the Proposed Change: Evidence from two randomized phase 3 studies of nivolumab demonstrated overall survival (OS) superior to that of the standard of care (docetaxel) across histologies. For non-squamous cell NSCLC an enhanced benefit was observed in subjects expressing PD-L1. Supportive data are also available from a phase 2 and a phase 1 study. A superior safety profile, including for Grade 3 and 4 treatment-related adverse events (AEs), was consistently demonstrated for nivolumab across all 4 studies.

Phase 3 Study in Non-squamous NSCLC, Second Line (CA209-057)[2]: This open-label, phase 3 study 1:1 randomized 582 subjects with stage IIIB or IV, non-squamous cell NSCLC who had received one prior platinum doublet-based chemotherapy regimen to receive either nivolumab or docetaxel. At the interim analysis (IA) nivolumab demonstrated superior OS (12.2 months [mo]) compared to docetaxel (9.4 mo) with a hazard ratio (HR) of 0.73 (96% CI, 0.59 to 0.89, *P*=0.0015). The median OS of nivolumab was enhanced in PD-L1 expressing subjects at specific cut off points; 17.2 mo at the 1% cut-off; 18.2 mo at the 5% cut-off; and 19.4% at the 10% cut-off. The overall response rate (ORR) was 19% for the nivolumab treated subjects and 12% for the docetaxel treated subjects. The median time to response was 2.1 mo for the nivolumab treated subjects and 2.6 mo for the docetaxel treated subjects. The duration of response for the nivolumab treated subjects was 17.2 mo and 5.6 mo for the docetaxel treated subjects. The rate (%) of all treatment-related AEs and grade 3 and 4 treatment-related AEs was 69% and 10%, respectively, for the nivolumab treated subjects, and 88% and 54%, respectively, for the docetaxel treated subjects.

Phase 3 Study in Squamous NSCLC, Second Line (CA209-017)[3]: This open-label, phase 3 study randomized 1:1 272 subjects with stage IIIB or IV, squamous cell NSCLC who had received one prior platinum doublet-based chemotherapy regimen to receive either nivolumab or docetaxel. At the IA nivolumab demonstrated superior OS (9.2 mo) compared to docetaxel (6.0 mo) with a HR of 0.59 (95% CI, 0.44 to 0.79, *P<0.001*). The OS of nivolumab compared to docetaxel was superior without regard for PD-L1 expression status. This secondary endpoint was exploratory and not fully powered to establish benefit by PD-L1 status. Landmark OS at 1-year (yr) was 42% for nivolumab treated subjects and 24% for docetaxel treated subjects. The ORR was 20% for the nivolumab treated subjects and 9% for the docetaxel treated subjects (*P*=0.*008*). The rate of all treatment-related AEs and grade 3 and 4 treatment-related AEs was 58% and 7%, respectively, for the nivolumab treated subjects, and 86% and 55%, respectively, for the docetaxel treated subjects. There were no grade 5 AEs in the

nivolumab treated subjects while three treatment-related deaths were reported in the docetaxel treated subjects.

Phase 2 Study in Squamous NSCLC, Third Line (CA209-063)[4]**:** In this single arm study of 117 subjects with Stage IIIB/ or Stage IV squamous cell NSCLC who had received platinum based chemotherapy and one additional systemic therapy the median OS was 8.2 months, the ORR was 14.5%, median time to response was 3.3 mo and the median duration of response was not reached. Responses were observed without regard for PD-L1 expression status. Treatment-related AEs of any grade were reported in 74% of subjects and grade 3 or 4 treatment-related AEs were reported in 17% of subjects. Treatment was discontinued in 12% of subjects due to treatment-related AEs. Two deaths were reported as treatment-related.

Phase 1 Study (CA209-003)[5]: This dose escalation (nivolumab doses: 1 mg/kg, 3 mg/kg, 10 mg/kg; Q2W for maximum of 96 weeks), cohort expansion study enrolled subjects with advanced cancers. In subjects with NSCLC (n=129, all doses) the median OS was 9.9 months and landmark OS rates at 1-yr, 2-yr, and 3-yr were 42%, 24% and 18%, respectively. At the clinically selected dose of 3 mg/kg in non-squamous cell subjects, the median OS was 18.2 mo (n = 19) and the landmark 1-yr, 2-yr and 3-yr OS rates were 62%, 48%, and 24%, respectively.

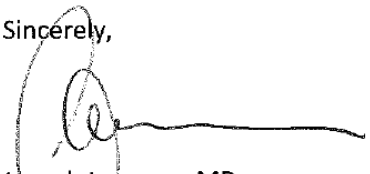
The following resources are included for your review in support of this proposed inclusion/change.

1. OPDIVO Prescribing Information
2. Paz-Ares L, Horn L, Borghaei H, et al. Phase III, Randomized Trial (CheckMate 057) of Nivolumab (NIVO) versus Docetaxel (DOC) in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC). Presented at the ASCO Annual Meeting, Chicago, Illinois, May 29- June 2, 2015.
3. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. Published online before print 31 May 2015
4. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncology 2015; 16: 257-265.
5. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients with Previously Treated Advanced Non–Small-Cell Lung Cancer. JCO Published online before print April 20, 2015.

We acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications/ presentations.

Thank you for your consideration of this request. Below is my contact information should you need to contact me for any additional information.

Sincerely,



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