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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Specific Changes:

On behalf of Merck & Co., Inc. we respectfully request the NCCN NSCLC Panel review the enclosed data and consider inclusion of KEYTRUDA® (pembrolizumab) as initial therapy for previously untreated, metastatic non-small cell lung cancer (NSCLC) patients whose tumors express PD-L1 on $\geq 50\%$ of tumor cells and lack epidermal growth factor receptor sensitizing mutations or anaplastic lymphoma kinase translocations.

FDA Clearance:

Melanoma

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

Non-Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Head and Neck Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Rationale:

In an article published in *The New England Journal of Medicine* on October 9, 2016, Reck et al. reported results from KEYNOTE-024, an open-label, phase 3 study, which randomized patients with previously untreated advanced NSCLC with PD-L1 expression on $\geq 50\%$ of tumor cells and no EGFR or ALK genomic tumor aberrations to receive pembrolizumab 200 mg every 3 weeks or investigator's choice of platinum-based chemotherapy (standard of care [SOC]). Patients randomized to the SOC arm had the option of receiving pembrolizumab upon disease progression. The primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate (ORR) and safety. Pembrolizumab significantly prolonged PFS compared with chemotherapy (HR 0.50; 95% CI, 0.37-0.68; $P < 0.001$). Median PFS was 10.3 months for pembrolizumab versus 6.0 months for chemotherapy. Overall survival was also significantly prolonged with pembrolizumab (HR 0.60, 95% CI, 0.41-0.89; $P = 0.005$), with median survival not reached in either group. Pembrolizumab was associated with a higher ORR (44.8% vs. 27.8%) and longer duration of response. Treatment-related adverse events of any grade (73.4% vs. 90.0%) and grade 3-5 severity (26.6% vs 53.3%) were less frequent with pembrolizumab. Based on these results, an independent data monitoring committee recommended that the trial be stopped early to allow those patients remaining on chemotherapy the opportunity to receive pembrolizumab.

To assist the committee with their review, I have included the following resources:

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Reck et al., Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *The New England Journal of medicine*. October 9, 2016. DOI: 10.1056/NEJMoa1606774

Thank you for your consideration of this request.

Sincerely,

A handwritten signature in black ink, appearing to read "Maria Rivas". The signature is fluid and cursive, with the first name "Maria" and last name "Rivas" clearly distinguishable.

Maria Rivas, MD, FACP, FACE
Senior Vice President
Global Medical Affairs
Merck & Co., Inc.