Name: Suzana Giffin, AVP
Company/Organization: Merck & Co., Inc.
Address: 2000 Galloping Hill Rd, Kenilworth, NJ 07033
Phone: 908-740-6708
Email: suzana.giffin@merck.com
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NCCN Guidelines Panel: Non-Small Cell Lung Cancer/Malignant Pleural Mesothelioma/Thymomas and Thymic Carcinomas

NCCN Non-Small Cell Lung Cancer Panel: On behalf of Merck & Co., Inc., I respectfully request that the NCCN Non-Small Cell Lung Cancer Panel review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to non-small cell lung cancer (NSCLC).

Specific Changes: We respectfully request that pembrolizumab monotherapy be included as a treatment option for patients with advanced NSCLC who are identified by high tumor mutational burden (TMB) in the appropriate sections of the NCCN NSCLC Guidelines v.6.2020, including pages NSCL-H, MS-13, and MS-77.

FDA Clearance:

Non-Small Cell Lung Cancer (NSCLC)

- KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
- KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
- KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) 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.

Tumor Mutational Burden-High (TMB-H) Cancer

- KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. 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. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

Please refer to the KEYTRUDA prescribing information for other FDA-approved indications.[1]

Rationale:

Herbst et al.[2] presented results of an exploratory analysis investigating the association between tissue TMB and clinical outcomes with pembrolizumab monotherapy versus chemotherapy in patients with PD-L1-positive (TPS ≥1%) advanced NSCLC in KEYNOTE-042, an open-label, phase 3, first-line study in treatment-naïve patients, and KEYNOTE-010, an open-label, phase 2/3, second-line or later study in previously treated patients. TMB was measured by whole exome sequencing (WES) of tumor tissue and matched normal DNA. In this exploratory analysis, higher TMB levels were associated with improved clinical outcomes in the pembrolizumab monotherapy arms. In KEYNOTE-042, the median overall survival (OS) for pembrolizumab versus chemotherapy was 21.9 versus 11.6 months (hazard ratio [HR], 0.62; 95% CI, 0.48-0.80) in the TMB-high (≥175 mut/exome) group, and 12.0 versus 12.3 months (HR, 1.09; 95% CI, 0.88-1.36) in the TMB-low (<175 mut/exome) group, respectively. In KEYNOTE-010, the median OS for pembrolizumab versus chemotherapy was 14.1 versus 7.6 months (HR, 0.56; 95% CI, 0.38-0.83) in the TMB-high group, and 9.3 versus 7.2 months (HR, 0.85; 95% CI, 0.56-1.30) in the TMB-low group, respectively. TMB was associated with OS as a continuous variable for pembrolizumab monotherapy in both KEYNOTE-042 ($p<0.001$) and KEYNOTE-010 ($p=0.006$). Overall, the results of this exploratory analysis support pembrolizumab monotherapy as a treatment option for patients with advanced NSCLC who are identified by high TMB.

The following resources are submitted to assist the committee with their review.

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Herbst RS, Lopes G, Kowalski DM, et al. Association between tissue TMB and clinical outcomes with pembrolizumab monotherapy in PD-L1-positive advanced NSCLC in the KEYNOTE-010 and 042 trials. Presented at: European Society for Medical Oncology. September 27-October 1, 2019; Barcelona, Spain. *Annals of Oncology*. 2019;30(5):916-917.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,

Suzana Giffin, AVP
Global Medical Affairs
Merck & Co., Inc.
2000 Galloping Hill Rd
Kenilworth, NJ 07033
908-740-6708
suzana.giffin@merck.com