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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of Merck & Co., Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer (NSCLC) Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V4.2018 for Non-Small Cell Lung Cancer.

Specific changes requested:

We respectfully request that KEYTRUDA (pembrolizumab) in combination with carboplatin and paclitaxel/nab-paclitaxel chemotherapy be recommended as first-line therapy for patients with metastatic squamous non-small cell lung cancer (NSCLC) as category 1 in the appropriate sections of the NCCN guidelines, including the section NSCL-28.

FDA Approval:

Non-Small Cell Lung Cancer

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression Tumor Proportion Score (TPS) $\geq 50\%$ as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) 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.

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Please refer to the KEYTRUDA Prescribing Information for other FDA-approved indications.¹

Rationale:

A double-blind, placebo-controlled phase 3 trial (KEYNOTE-407; NCT02775435) was conducted in patients with untreated, metastatic squamous NSCLC who received pembrolizumab 200 mg or placebo every 3 weeks (Q3W) plus carboplatin AUC 6 Q3W and paclitaxel 200 mg/m² Q3W or nab-paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 weeks), then followed by pembrolizumab 200 mg or placebo Q3W for a total of 35 cycles. Primary endpoints were progression-free survival (PFS) by independent central review (RECIST v1.1) and overall survival (OS). Secondary endpoints were objective response rate (ORR), duration of response (DOR) and safety. First interim analysis (IA1) evaluated ORR in 204 patients. Second interim analysis (IA2) assessed PFS and OS (N=559) with a medium follow-up of 7.8 months (range, 0.1-19.1). ORR at IA1 was 58.4% (95% CI, 48.2-68.1) for pembrolizumab/chemotherapy

vs. 35.0% (25.8-45.0) for chemotherapy (P=0.0004). Median PFS at IA2 in the ITT population was 6.4 months (95% CI, 6.2-8.3) for pembrolizumab/chemotherapy and 4.8 months (95% CI, 4.3-5.7) for chemotherapy with a PFS hazard ratio (HR) of 0.56 (95% CI, 0.45-0.70; P<0.0001). Median overall survival (OS) at IA2 in the ITT population for pembrolizumab/chemotherapy group was 15.9 months (95% CI, 13.2-NE) vs. 11.3 months (95% CI, 9.5-14.8) in the placebo-chemotherapy group (HR: 0.64; 95% CI, 0.49-0.85; P=0.0008). OS benefit was observed in these patients regardless of PD-L1 expression. Adverse events (AEs) frequency and severity were mostly similar between the two arms. Observed AEs were consistent with known safety profiles of pembrolizumab and chemotherapy, with no new safety signals identified. Treatment related AEs led to death in 10 (3.6%) patients in the pembrolizumab/chemotherapy group and in 6 (2.1%) patients in the chemotherapy group. Immune mediated AEs Grade \geq 3 occurred in 10.8% of the patients in the pembrolizumab/chemotherapy arm and in 3.2% of patients in chemotherapy arm. Immune-mediated AEs were more frequent in the pembrolizumab group, with frequency and severity consistent with those observed for pembrolizumab monotherapy.²

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Paz-Ares L, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab for patients with metastatic squamous non-small cell lung cancer. Presented at American Society of Clinical Oncology (ASCO); June 1-5, 2018: Chicago, IL USA.

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

Sincerely,



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