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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Specific Changes:
On behalf of Merck & Co., Inc. we request the NCCN NSCLC Panel review the enclosed data and amend the guidelines to include KEYTRUDA (pembrolizumab) in combination with pemetrexed and carboplatin as initial therapy for previously treated, metastatic non-squamous non-small cell lung cancer (NSCLC), regardless of PD-L1 status.

FDA Clearance (NSCLC indications):
Non-Small Cell Lung Cancer
KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS)≥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≥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.

Rationale:
The FDA granted approval for the use of KEYTRUDA in combination with pemetrexed and carboplatin on May 10th, 2017. This approval was based on results from the KEYNOTE-021 trial, cohort G1. Cohort G1 is a randomized, open-label, phase 2 cohort of a multi-cohort study. Patients with chemotherapy-naïve, metastatic non-squamous NSCLC, irrespective of tumor PD-L1 expression status, were randomly assigned to pembrolizumab plus pemetrexed and carboplatin or to pemetrexed and carboplatin (PC) alone. The primary endpoint was the proportion of patients who achieved an objective response. The key secondary endpoint was progression free-survival (PFS). Papadimitrakopoulou presented updated results at ASCO on June 3rd, 2017. At the time of this analysis, median follow-up was 14.5 months. With this additional 5 months of follow-up, the objective response rate of pembrolizumab plus PC was nearly doubled at 56.7% compared to 30.2% in the PC alone group. The difference of 26% had a p-value of 0.0016. The risk of progression or death was reduced by half (HR for PFS, 0.50; p=0.0038); with additional follow-up, the Kaplan-Meier curve for PFS in the pembrolizumab plus PC arm has plateaued and median PFS has not yet been reached. The median PFS for the PC arm was 8.9 months. The hazard ratio for overall survival (OS) was 0.69 (95% CI, 0.36-1.31; p=0.13) favoring the pembrolizumab plus PC arm. The 12-month Kaplan-Meier estimate of OS was 76% for pembrolizumab plus PC vs 69% for PC alone. The OS trend now emerging with more follow-up suggests that the large benefits in PFS and ORR first observed with the primary analysis may be translating into an OS benefit, despite a high crossover rate among patients in the PC arm. The incidence of grade 3 or worse treatment-related adverse events was similar between groups (23 [39%] of 59 patients in the pembrolizumab plus PC group and 18 [29%] of 62 in the PC alone group). This favorable benefit-risk profile and the recent FDA approval warrant strong consideration for inclusion in the NCCN guidelines. It is important to note that for patients without an *EGFR* or *ALK* tumor aberration, no other FDA-approved first-line regimen has a median PFS greater than one year.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.

2. Langer CJ, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The Lancet Oncology*. 2016;17(11):1497-1508.

3. Papadimitakopoulou VA, et al. First-Line Carboplatin and Pemetrexed With or Without Pembrolizumab for Advanced Nonsquamous NSCLC: Updated Results of KEYNOTE-021 Cohort G. Abstract # 9094; American Society of Clinical Oncology (ASCO) Annual Meeting. June 2-6, 2017. Chicago, IL, USA.

Thank you for your consideration of this request.

Sincerely,

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