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Maria Rivas, SVP
Merck & Co., Inc.
CRB-210
600 Corporate Drive
Lebanon, NJ 08833
908-236-1120
maria.rivas1@merck.com

NCCN Guidelines Panel: Bladder Cancer

Specific changes requested:

On behalf of Merck & Co., Inc., we respectfully request the NCCN Bladder Cancer Panel review the enclosed data and consider adding KEYTRUDA[®] (pembrolizumab) as a second-line systemic therapy for advanced or metastatic urothelial cancer (category1).

FDA Clearance (1):

Melanoma

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

Non-Small Cell Lung Cancer

KEYTRUDA 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 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.

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 February 17, 2017, Bellmunt et al. reported results from KEYNOTE-045, an open-label, randomized, phase III study, in patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Patients were randomized to receive pembrolizumab 200 mg every 3 weeks (n=270) or the investigator's choice of chemotherapy with either paclitaxel 175 mg/m² Q3W, docetaxel 75 mg/m² Q3W, or vinflunine 320 mg/m² Q3W (n=272). The co-primary end points were overall survival (OS) and progression-free survival (PFS), which were assessed among all patients and among patients who had a tumor PD-L1 combined positive score (CPS) of $\geq 10\%$.
 - Pembrolizumab significantly prolonged OS compared to chemotherapy (hazard ratio [HR] 0.73; 95% CI, 0.59 – 0.91; P=0.002) in the total study population, with a median OS of 10.3 months (95% CI, 8.0-11.8) in the pembrolizumab group compared with 7.4 months (95% CI, 6.1-8.3) in the chemotherapy group. Also pembrolizumab significantly prolonged OS compared to chemotherapy (HR 0.57; 95% CI, 0.37-0.88; P=0.005) in the CPS $\geq 10\%$ population, with a median OS of 8 months (95%

- CI, 5.0-12.3) in the pembrolizumab group compared with 5.2 months (95% CI, 4.0 – 7.4) in the chemotherapy group.
- PFS was not significantly different in the total study population with pembrolizumab compared to chemotherapy (HR 0.98 (95% CI, 0.81-1.19; P=0.42) or among patients who had a tumor PD-L1 CPS \geq 10% (HR 0.89 (95% CI, 0.61-1.28; P=0.24). Median PFS was 2.1 months (95% CI, 2.0 – 2.2) in the pembrolizumab group and 3.3 months (95% CI, 2.3 – 3.5) in the chemotherapy group.
 - Treatment-related AEs were 60.9% (n=162/266) in the pembrolizumab group and 90.2% (n=230/255) in the chemotherapy group. Of those, 15% and 49.4%, respectively, were grade 3-5.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc
2. Bellmunt, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma, NEJM, February 17, 2017. DOI: 10.1056/NEJMoa1613683 [Epub ahead of print]

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

Sincerely,



Maria Rivas, SVP
Merck & Co., Inc.
CRB-210
600 Corporate Drive
Lebanon, NJ 08833
908-236-1120 maria.rivas1@merck.com