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NCCN Guidelines Panel: Bladder/Penile Cancers

NCCN Bladder/Penile Cancers: On behalf of Merck & Co., Inc., I respectfully request the NCCN Bladder/Penile Cancers Panel to review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to the treatment of patients with metastatic urothelial cancer.

Specific Changes: We respectfully request the inclusion of pembrolizumab as a treatment option for maintenance therapy in patients with metastatic urothelial cancer, achieving at least stable disease with first-line platinum-based chemotherapy, to the section of BL-G (1–7) as well as the discussion section of MS-28 – MS-29 of the NCCN Bladder Cancer Guidelines.

FDA Clearance: KEYTRUDA is not indicated as a treatment option for maintenance therapy in patients with metastatic urothelial cancer, achieving at least stable disease with first-line platinum-based chemotherapy
KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
Please refer to the attached Prescribing Information of KEYTRUDA® for other approved indications.

Rationale: A randomized, double-blind, phase II study of maintenance pembrolizumab 200 mg IV Q3W compared to placebo after first-line chemotherapy in patients (N=107) with metastatic urothelial cancer, who had at least stable disease and had undergone ≤8 cycles of platinum-based chemotherapy prior to enrollment. Patients with disease progression on placebo (n=52) could cross over to pembrolizumab (n=55). With a median follow up of 12.9 month, progression free survival (PFS) was significantly longer with maintenance pembrolizumab compared to placebo (hazard ratio [HR], 0.65; log-rank P =0.04; maximum efficiency robust test P =0.039); the difference in 24-month restricted mean progression-free survival time with pembrolizumab vs placebo adjusted for the 2 stratification factors were 3.4 months (95% Confidence Interval [CI] 0.7 to 6.2; P=0.015); median PFS was (5.4 months [95% CI, 3.1 to 7.3 months] versus 3.0 months [95% CI, 2.7 to 5.5 months]. The HR for overall survival (OS) was 0.91 (95% CI, 0.52 to 1.59). The difference in 24-month restricted mean survival time with pembrolizumab vs placebo adjusted for the 2 stratification factors was 0.4 months (95% CI, -2.8 to 3.6) P=0.8); median

overall survival was 22 months (95% CI, 12.9 months to not reached) in the pembrolizumab arm and 18.7 months (95% CI, 11.4 months to not reached) in the placebo arm. The objective response rates (ORR) per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) were 23% (n=43/108) and 10% (n=42/108) in patients who received pembrolizumab and placebo, respectively, with 9% complete response rate in pembrolizumab arm and no complete response achieved in the placebo arm. Of the 27 patients in the placebo arm (n=52) who experienced disease progression and crossed over to receive pembrolizumab, the ORR was 22%, the median PFS from crossover was 2.7 months (95% CI, 2.5 to 9.3 months), and the median OS from crossover was 15.8 months (95% CI, 8 months to not reached). Grade 3-4 treatment-emergent adverse events were reported in 59% and 38% of patients receiving pembrolizumab and placebo, respectively; 20% of patients randomly assigned to initial pembrolizumab had immune-related adverse events, which required systemic steroid treatment. One patient in the pembrolizumab arm had fatal treatment-related adverse event, hepatitis.

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

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

2. Galsky M, Mortazavi A, Milowsky, MI et al. Randomized Double-Blind Phase II Study of Maintenance Pembrolizumab Versus Placebo After First-Line Chemotherapy in Patients with Metastatic Urothelial Cancer. *Journal of Clinical Oncology*. Published online April 09, 2020. DOI: 10.1200/JCO.19.03091

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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