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NCCN Guidelines Panel: Kidney Cancer Panel

On behalf of Merck & Co., Inc., I respectfully request the NCCN Kidney Cancer Panel to review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to renal cell carcinoma (RCC).

Specific Changes: We respectfully request the inclusion of pembrolizumab monotherapy for the adjuvant treatment of patients with clear cell RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions, in the appropriate sections of the NCCN Kidney Cancer Guidelines v4.2021, including pages KID-1 and KID-2.

FDA Clearance:

- KEYTRUDA, as a monotherapy, is currently not indicated for the adjuvant treatment of patients with clear cell RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.
- KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

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

Rationale: In KEYNOTE-564, a phase 3, double-blind, multicenter trial, the efficacy and safety of pembrolizumab 200 mg administered intravenously every 3 weeks was evaluated following nephrectomy in patients with clear cell RCC (N=994). Efficacy and safety results by Choueiri et al. were presented at a plenary session during ASCO 2021, with the analysis cutoff date of December 14, 2020, and a median follow-up time of 24.1 months (range: 14.9-41.5 months). The primary end point was disease-free survival (DFS) by investigator assessment, and the secondary end points included overall survival (OS) and safety. The study had 95% power to detect a hazard ratio (HR) of 0.67 for pembrolizumab vs. placebo at $\alpha = 2.5\%$ (one-sided) for the primary end point of DFS (tested first at $\alpha = 2.5\%$, and the α was passed to OS if the null hypothesis of DFS was rejected). DFS and OS were estimated by the Kaplan-Meier method. Patients were randomized to receive adjuvant pembrolizumab (n=496) or placebo (n=498), with similar baseline characteristics among the two groups. Patients were characterized based on prespecified disease risk categories, defined as intermediate-high risk [pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0, (n=427, pembrolizumab; n=433, placebo)], high risk [pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0, (n=40, pembrolizumab; n=36, placebo)], or M1 no evidence of disease [after primary tumor + soft tissue metastases completely resected ≤ 1 year from nephrectomy, (n=29, pembrolizumab; n=29, placebo)]. Pembrolizumab reduced the risk of disease recurrence or death by 32% vs. placebo [HR 0.68; 95% CI, 0.53-0.87, p=0.0010 (crossed prespecified p-value boundary for statistical significance of 0.0114)]. Pembrolizumab estimated DFS rate was 85.7% vs. 76.2% for placebo at 12 months, and 77.3% for pembrolizumab vs. 68.1% for placebo at 24 months. Median DFS was not reached for pembrolizumab or placebo. Median OS was not reached in either arm [HR for OS was 0.54; 95% CI, 0.30-0.96, p=0.0164 (did not cross prespecified p-value boundary for statistical significance of 0.0000093

for 51 events; final analysis for OS to occur after approximately 200 OS events)]. The estimated OS rate for pembrolizumab was 96.6% vs. 93.5% with placebo at 24 months. In the as-treated population (included all participants who received ≥ 1 dose of study treatment), all-cause adverse events (AEs) of any grade were reported in 96.3% (n=470) of patients who received pembrolizumab vs. 91.1% (n=452) of patients in the placebo group. Treatment-related AEs (TRAEs) were reported in 79.1% (n=386) of patients who received pembrolizumab vs. 53.4% (n=265) in the placebo group. Grade 3-5 TRAEs were reported in 18.9% (n=92) of patients in the pembrolizumab group vs. 1.2% (n=6) in the placebo group. The most common AEs ≥ 10% of any cause in the as-treated population for pembrolizumab were fatigue (20.3%), pruritis (18.6%), hypothyroidism (17.6%), diarrhea (15.8%), rash (15.0%) and hyperthyroidism (10.2%). No deaths due to TRAEs or immune-mediated events occurred. The efficacy and safety results from this study support the antitumor activity of pembrolizumab monotherapy for the adjuvant treatment of patients with clear cell RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

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

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

2. Choueiri T, Tomczak P, Park SH, et al. Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study. Presented at American Society for Clinical Oncology (ASCO), June 4-8, 2021. Virtual Meeting.

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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