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NCCN Guidelines Panel: Kidney Cancer Panel

NCCN 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 as a first-line treatment option for patients with stage IV clear cell RCC (ccRCC) with favorable or poor/intermediate IMDC risk, in the appropriate sections of the NCCN Kidney Cancer Guidelines v2.2021, including page KID-C 1 of 2.

FDA Clearance: KEYTRUDA monotherapy is currently not indicated for the first-line treatment of patients with advanced/metastatic ccRCC.

- 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 Cohort A of KEYNOTE-427, a single-arm, multicenter, open-label, global, nonrandomized phase 2 trial, the efficacy and safety of pembrolizumab 200 mg administered intravenously every 3 weeks was evaluated as a first-line monotherapy in adult patients with advanced/metastatic ccRCC (N=110). Efficacy and safety results for KEYNOTE-427 Cohort A were published by McDermott et al. with the analysis cutoff date of February 24, 2020, and a median time from enrollment of 35.9 months (range, 29.5-40.3 months). The primary end point was objective response rate (ORR), as assessed per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR). Secondary end points included duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) per RECIST v1.1 as assessed by BICR. Additional secondary endpoints included overall survival (OS) and safety. The ORR in the total population was 36.4% (95% Confidence Interval [CI], 27.4% to 46.1%). Complete response and partial response rates were 3.6% (n=4) and 32.7% (n=36), respectively. The DCR for the total population was 58.2% (95% CI, 48.4% to 67.5%). Median DOR was 18.9 months (range, 2.3-37.6+). Median PFS was 7.1 months (95% CI, 5.6 to 11.0 months), with PFS rates of 37.6% and 22.3% at 12 and 24 months, respectively. OS rates at 12 and 24 months for the total population were 88.2% and 70.8% respectively; median OS was not reached. In patients with favorable International Metastatic RCC Database Consortium (IMDC) risk category (n=42), ORR was 31.0% (95% CI, 17.6% to 47.1%). The ORR for intermediate/poor IMDC risk category patients (n=68) was 39.7% (95% CI, 28.0% to 52.3%). Patients with sarcomatoid differentiation (n=11) had an ORR of 63.6% (95% CI, 30.8% to 89.1%). Treatment-related adverse events (TRAEs) of any grade occurred in 82.7% of patients (n=91); grade 3-5 TRAEs occurred in 30% (n=33) of patients. The most common TRAEs (≥10%) were pruritis, fatigue, diarrhea, rash, arthralgia, hypothyroidism. Immune-mediated adverse events (AEs) occurred in 32.7% (n=36) patients; grade 3-5 immune-mediated AEs occurred in 15.5% (n=17) patients. Two patients died due to AEs (cerebral infarction and intracranial hemorrhage),

and one patient died due to treatment-related pneumonitis. The efficacy and safety results from this study support the antitumor activity of pembrolizumab monotherapy as an option for the first-line treatment of patients with Stage IV ccRCC.

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

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

2. McDermott DF, Lee J-L, Bjarnason GA, et al. Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Clear Cell Renal Cell Carcinoma. *J Clin Oncol*. 2021 Feb 2; JCO2002363. doi: 10.1200/JCO.20.02363.

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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