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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 WELIREG™ (belzutifan), in reference to von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC).

Specific Changes: We respectfully request the inclusion of belzutifan for the treatment of adult patients with VHL disease who require therapy for associated RCC, not requiring immediate surgery, in the appropriate sections of the NCCN Kidney Cancer Guidelines v1.2022, including pages HRCC-C 1 of 2 and HRCC-D.

FDA Clearance: WELIREG is indicated for the treatment of adult patients with VHL disease who require therapy for associated RCC, central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.[1]

Rationale: WELIREG is now FDA approved for the treatment of certain patients with VHL-associated disease who require therapy, not requiring immediate surgery. The efficacy and safety of belzutifan was investigated in Study-004 (NCT03401788), an open-label, phase 2 clinical trial in patients (N=61) with VHL-associated RCC diagnosed based on a VHL germline alteration and with at least one measurable solid tumor (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) localized to the kidney. Enrolled patients had other VHL-associated tumors including CNS hemangioblastomas and pNET, diagnosed based on the presence of at least one measurable solid tumor in brain/spine or pancreas, respectively as defined by RECIST v1.1 and identified by independent review committee (IRC). Patients received belzutifan at a dose of 120 mg by mouth once daily until disease progression or unacceptable toxicity. Patients median age was 41 years [range 19-66 years], and 77% of patients had prior RCC surgical procedures. The major efficacy endpoint for treatment of VHL-associated RCC was overall response rate (ORR) measured by radiology assessment using RECIST v1.1 as assessed by IRC. Additional efficacy endpoints included duration of response (DoR) and time to response (TTR).

The efficacy results for patients with VHL-associated RCC tumors included an ORR of 49% (95% confidence interval [CI], 36-62; n=30). All responses were partial responses. In this patient population, the median DoR was not reached (2.8+ to 22+ months). Of the 30 responding patients, 17 patients (56%) had a DoR of at least 12 months. Median TTR for patients with VHL-associated RCC tumors was 8 months (range: 2.7-19). Efficacy analyses were also conducted in patients with VHL-associated non-RCC tumors, including CNS hemangioblastomas (n=24) and pNET (n=12). Patients with CNS hemangioblastomas had an ORR of 63% (95% CI, 41-81; n=15), with a complete response (CR) of 4%, and a partial response (PR) of 58%. The median duration of response in this patient subgroup was not reached (3.7+, 22+), with a DoR of at least 12 months in 73% (11/15) of patients. The TTR for patients with CNS hemangioblastomas was 3.1 months (range: 2.5-11). Patients with pNET had an ORR of 83% (95% CI, 52-98; n=10), with a CR of 17%, and a PR of 67%. The median duration of response for patients with pNET was not reached (11+, 19+), with a DoR of at least 12 months in 50% (5/10) of patients. The TTR for patients with pNET was 8.1 months (range: 2.7-11).

The median duration of exposure to belzutifan was 68 weeks (range: 8.4-104.7 weeks). Belzutifan was permanently discontinued due to adverse reactions in 3.3% of patients. The most common adverse reactions in all grades (≥25%), including laboratory abnormalities, that occurred in patients treated with belzutifan were decreased hemoglobin (93%), anemia (90%), fatigue (64%), increased creatinine (64%), headache (39%), dizziness (38%), increased glucose (34%), and nausea (31%). Serious adverse reactions occurred for 15% of patients receiving belzutifan, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

The efficacy and safety results from this study and the FDA approval of WELIREG support our request for the inclusion of belzutifan as a treatment option for adult patients with VHL disease who require therapy for associated RCC, not requiring immediate surgery.

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

1. WELIREG (belzutifan) prescribing information. Merck & Co., Inc.
2. Srinivasan R, Donskov F, Iliopoulos O, et al. Phase 2 study of belzutifan (MK-6482), an oral hypoxia-inducible factor 2α inhibitor, for von Hippel-Lindau disease–associated clear cell renal cell carcinoma. J Clin Oncol. 2021;39(suppl 15):4555. DOI: 10.1200/JCO.2021.39.15_suppl.4555. Presented at: American Society of Clinical Oncology (ASCO) Virtual Meeting; June 4-8, 2021.

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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