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### **NCCN Guidelines Panel: Hepatobiliary Cancer**

On behalf of Merck & Co., Inc., I respectfully request the NCCN Hepatobiliary Cancer Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Guidelines V4.2018 for Hepatobiliary Cancer.

#### **Specific changes requested:**

We respectfully request that KEYTRUDA (pembrolizumab) be recommended for patients with hepatocellular carcinoma as a subsequent line therapy if disease progression, category 2A.

#### **FDA Approval:**

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. 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.

Please see enclosed prescribing information for other FDA-approved indications (PI).<sup>1</sup>

#### **Rationale:**

FDA granted accelerated approval for KEYTRUDA in patients with hepatocellular carcinoma who have been treated with sorafenib on November 9<sup>th</sup> based on data from KEYNOTE-224

KEYNOTE 224 (NCT02702414) is a single-arm, multicenter trial in patients with HCC who had disease progression on or after sorafenib or were intolerant to sorafenib; had measurable disease; and had Child-Pugh class A liver impairment. Patients with active autoimmune disease, greater than one etiology of hepatitis, a medical condition that required immunosuppression, or clinical evidence of ascites by physical exam were ineligible for the trial.

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity, investigator-assessed confirmed disease progression or completion of 24 months of KEYTRUDA. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR and duration of response according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by blinded independent central review committee (BICR).

A total of 104 patients were enrolled. The baseline characteristics were: median age 68 years (67% age 65 or older); 83% male; 81% White; 14% Asian; ECOG PS of 0 (61%) or 1 (39%). Child-Pugh class and score were A5 for 72%, A6 for 22%, B7 for 5%, and B8 for 1% of patients. Twenty-one percent of the patients were HBV seropositive and 25% HCV seropositive. There were 9 patients (9%) who were seropositive for both HBV and HCV. Sixty-four percent (64%) of patients had extrahepatic disease, 17% had vascular invasion, and 9% had both. Thirty-eight percent (38%) of patients had alfa-fetoprotein (AFP) levels  $\geq 400$   $\mu\text{g/L}$ . All patients received prior sorafenib; of these, 20% were unable to tolerate sorafenib. No patient received more than one prior systemic therapy (sorafenib).

In KEYNOTE-224, ORR was 17% (95% CI, 11-26), with a complete response rate of 1% and a partial response rate of 16%. Among the responding patients (n=18), 89% percent experienced a DOR for six months or longer and 56 percent experienced a DOR for 12 months or longer<sup>1</sup>

Among the 104 patients with HCC who received KEYTRUDA in KEYNOTE 224, the median duration of exposure to KEYTRUDA was 4.2 months (range: 1 day to 1.5 years). Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

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

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

Thank you for considering this request. Please contact me for any additional information.

Sincerely,



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