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NCCN Guidelines Panel: Hepatobiliary Cancers

On behalf of Merck & Co., Inc., I respectfully request the NCCN Hepatobiliary Cancers Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to the Hepatobiliary Cancers NCCN Guidelines V1.2018.

Specific changes requested:

We respectfully request that KEYTRUDA (pembrolizumab) be added to the NCCN guidelines for Hepatocellular Carcinoma as a treatment option for patients with advanced hepatocellular carcinoma who have been previously treated with an anti-angiogenic TKI.

FDA Approval:

KEYTRUDA (pembrolizumab) is not approved for the treatment of patients with advanced hepatocellular carcinoma, with the exception of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) hepatocellular carcinoma that has progressed following prior treatment and who have no satisfactory alternative treatment options. 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).[1]

Rationale:

KEYNOTE-224(NCT02702414) is a multicenter, non-randomized, open label, phase 2, trial in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Eligible patients had ECOG 0–1, adequate organ function, Child-Pugh class A, histologically or cytologically confirmed diagnosis of hepatocellular carcinoma, documented objective radiographic disease progression or intolerance to sorafenib. Participants received pembrolizumab 200mg IV every 3 weeks for up to about 2 years or until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision. The primary endpoint was objective response rate (ORR), defined as the percentage of patients with complete or partial response, radiologically confirmed using RECIST V1.1 by central review, over those who received at least one dose of pembrolizumab. Secondary endpoints included: disease control rate, duration of response, time to progression, progression-free survival, overall survival, safety and tolerability.

A total of 104 patients were treated with at least one dose of pembrolizumab and were included in the primary analysis. As of data cutoff on Feb 13, 2018, the median duration of follow-up was 12.3 months (IQR 7.6–15.1). An objective response was recorded in 18 (17%, 95% CI 11–26) of 104 participants. Among the 18 (17%) responders, one (1%) had complete response, and 17 (16%) had partial responses. 46 (44%) participants had stable disease as their best responses, 34 (33%) participants had progressive disease, and 6 patients (6%) had no response data after

treatment initiation. Responses were durable, with 12(77%) of responders having durations of response of 9 months or longer and median time to response of 2.1months (IQR 2.1-4.1) Further, ORR analyses by subgroup show consistency of benefit of pembrolizumab among important subgroups such as age, gender, etiology of HCC, and sorafenib intolerance versus progression. Overall survival and progression-free survival were also encouraging, with median OS of 12.9 months (95% CI 9.5-15.5) and median PFS of 4.9 months (95% CI 3.4-7.2). Disease control was reported in 64 (62%; 95% CI 52–71) of the 104 treated participants. The median duration of pembrolizumab treatment was 4.2 months (2.1–7.7). At 12 months, of the 104 patients, 29 were still alive and progression-free, giving a 12-month progression-free survival of 28% (95% CI 19‑37), and 56 patients were still alive, giving a 12-month overall survival of 54% (95% CI 44‑63).The most common reasons for treatment discontinuation were progressive disease in 59 (57%) participants and adverse events in 24(23%) participants.

At least one adverse event was reported in 101 (97%) participants and, of these events, 42 (40%) were deemed serious. Immune-mediated events of any attribution occurred in 15 (14%) participants and the most common events of any grade of severity were eight (8%) hypothyroidism and three (3%) adrenal insufficiency events. Four immune-mediated events of grade 3 severity were reported, including two (2%) participants with adrenal insufficiency, one (1%) with severe skin toxicity, and one (1%) with type 1 diabetes mellitus. There was one case of fatal ulcerative esophagitis, which the investigator thought was treatment related. Immune-mediated hepatitis was seen in three (3%) participants. No flares of hepatitis B or hepatitis C occurred during the study.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial [published online June 3, 2018]. *Lancet Oncol* 2018 http://dx.doi.org/10.1016/S1470-2045(18)30351-6

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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