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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 V2.2019.

**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 under category 1.

**FDA Approval:**

KEYTRUDA (pembrolizumab) 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:**

KEYNOTE-240(NCT02702401) is a multicenter, randomized, double-blind, placebo-controlled phase 3, trial in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Eligible patients had ECOG 0–1, adequate organ function, Child-Pugh class A, BCLC stage B/C, pathologically/ radiographically 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 overall survival (OS) and progression free survival (PFS) (RECIST v1.1, central review). Secondary endpoints included: objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), safety and tolerability.

A total of 278 patients were treated with at least one dose of pembrolizumab and were included in the primary analysis. The placebo arm had 135 patients. As of data cutoff on Jan 2, 2019, pembrolizumab reduced risk of death by 22% over placebo with a hazard ratio (HR) of 0.781 (95% CI, 0.611-0.998); one-sided p=0.0238 (significance threshold for OS: p≤0.0174 at the final analysis). PFS (primary analysis, data cutoff on Mar 26, 2018) HR was 0.775 (95% CI, 0.609-0.987); one-sided p=0.0186 (significance threshold for PFS: p≤0.0020). At the final analysis data cutoff (Jn 2, 2019), the PFS HR was 0.718 (95% CI, 0.570-0.904), ORR was 18.3% for pembrolizumab vs. 4.4% for placebo.

An objective response was recorded in 51 (18.3%, 95% CI 14–23.4) of 278 participants in the pembrolizumab arm. Among the 51 (18.3%) responders on the pembrolizumab arm, six (2.2%) had complete response, and 45 (16.2%) had partial responses. 122 (43.9%) participants had stable disease as their best responses, 90 (32.4%) participants had progressive disease, and 5 patients (1.79%) had no response data after treatment initiation. Disease control was reported in 173 (62.2%) of the 278 treated participants. Duration of response, median (range): Pembrolizumab: 13.8 mo (1.5+ mo – 23.6+ mo). The most common reasons for treatment discontinuation were progressive disease in 173 (62.2%) participants and adverse events in 48 (17.2%) participants.

At least one adverse event was reported in 269 (96.4%) participants and, of these events, 147 (52.7%) were deemed grade 3-4. Immune-mediated events of any attribution occurred in 51 (18.3%) participants. Twenty (7.2%) immune-mediated events of grade 3-4 severity were reported and ten (3.6%) discontinued treatment due to AE. Seven (2.5%) patients died in Pembrolizumab arm in the study compared with four (3%) in the placebo group.

Based on the magnitude of benefit as captured by the HR for OS and PFS, the ORR and response duration, favorable benefit-risk profile, clinically meaningful results and current unmet medical need for novel drugs with different mechanisms of action, the totality of data supports our request for the inclusion of pembrolizumab monotherapy in previously treated advanced HCC under category 1 recommendation.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Richard S Finn, Baek-Yeol Ryoo, Philippe Merle et al. Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma. Presented at 2019 ASCO Annual meeting; 31 May - 04 June 2019 at Chicago, Illinois USA.

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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