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Date of Request: 09/21/2020  
NCCN Guidelines Panel: Esophageal/Gastric Cancers

NCCN Esophageal/Gastric Cancers Panel: On behalf of Merck & Co., Inc., I respectfully request the NCCN Esophageal/Gastric Cancers Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Esophageal and Esophagogastric Junction Cancers Guidelines, v4.2020.

Specific Changes: We respectfully request the inclusion of pembrolizumab, in combination with chemotherapy, as a first-line treatment option for patients with locally advanced unresectable or metastatic esophageal and gastroesophageal junction (GEJ) carcinoma as a Category 1 recommendation to the NCCN Esophageal and Esophagogastric Junction Cancers Guidelines, v4.2020 (page ESOPH-F 3 of 15).

FDA Clearance:

Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Please refer to the KEYTRUDA (pembrolizumab) prescribing information for other FDA-approved indications.<sup>1</sup>

Rationale: This submission includes data from a phase 3, randomized, double-blind, placebo-controlled, international study, KEYNOTE-590, by Kato et al.,<sup>2</sup> which supports our request for the inclusion of pembrolizumab in combination with chemotherapy as a Category 1 recommendation for the first-line treatment option for patients with locally advanced unresectable or metastatic esophageal and GEJ carcinoma.

KEYNOTE-590 study (NCT03189719) evaluated the efficacy and safety of pembrolizumab plus chemotherapy (N=373) versus chemotherapy (N=376) in advanced unresectable or metastatic esophageal adenocarcinoma or esophageal squamous cell carcinoma (ESCC) or GEJ adenocarcinoma in the first-line setting. Pembrolizumab plus chemotherapy vs chemotherapy demonstrated an improvement in median overall survival (OS) in the overall patient population (12.4 vs 9.8 months; HR = 0.73, 95% CI, 0.62 - 0.86;  $P < 0.0001$ ). Median progression free survival (PFS) was superior for patients treated with pembrolizumab plus chemotherapy vs chemotherapy alone (6.3 vs 5.8 months; HR = 0.65; 95% CI, 0.55 - 0.76;  $P < 0.0001$ ). Confirmed overall response rate (ORR) was 45% in the pembrolizumab plus chemotherapy group as compared to 29.3% for chemotherapy alone,  $P < 0.0001$ . Adverse events (AE) were reported in 100% vs 99.5% of patients in pembrolizumab with chemotherapy vs chemotherapy groups respectively. Grade 3-5 drug-related AE rates were 71.9% vs 67.6% in pembrolizumab plus chemotherapy vs chemotherapy respectively.<sup>2</sup>

Overall, the totality of data in the study supports our request for the recommendation for pembrolizumab plus chemotherapy combination therapy as a first-line treatment option for patients with advanced unresectable or metastatic esophageal and GEJ carcinoma.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Kato K., Sun JM., Shah M. et al. Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: the phase 3 KEYNOTE-590 study. Presented at ESMO Annual Meeting; September 19-21, 2020; Virtual Meeting.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,

A handwritten signature in black ink, appearing to read 'Suzana Giffin', with a horizontal line extending from the end of the signature.

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