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Peter Piliero, AVP  
Merck & Co., Inc.  
2000 Galloping Hill Rd  
Kenilworth, NJ 07033  
908-740-6501  
[peter.piliero@merck.com](mailto:peter.piliero@merck.com)

#### **NCCN Guidelines: Gastric Cancer**

On behalf of Merck & Co., Inc., I respectfully request the **NCCN Gastric Cancer Panel** to review the enclosed data for the inclusion of KEYTRUDA (pembrolizumab) as a systemic treatment option for recurrent, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma.

#### Specific changes requested:

Recommend the addition of Keytruda (pembrolizumab) as a third line (3L) systemic therapy for the treatment of recurrent, locally advanced or metastatic gastric or gastroesophageal (GEJ) junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

#### FDA approval:

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the *treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)  $\geq 1$ ] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.*

*This indication was 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.*

#### Rationale:

Most patients with metastatic gastric and gastroesophageal junction cancer survive less than 1 year, and treatment advances for this population have been limited over the past decade. Patients with advanced gastric or gastroesophageal adenocarcinoma that progresses after second-line therapy have no optimal therapy in the third-line and later treatments.

The safety and efficacy of KEYTRUDA in patients with recurrent, locally advanced or metastatic Gastric and GEJ Adenocarcinoma was investigated in KEYNOTE-012(NCT01848834) and KEYNOTE-059 (NCT02335411).

KEYNOTE-012 primary objectives were safety and proportion of patients achieving overall responses. 39 patients (19 from East Asia and 20 from the rest of the world) with PD-L1 positive advanced gastric or gastroesophageal cancer were enrolled. Confirmed overall response was achieved by eight patients (22%, 95% CI 10–39). All responses were partial responses. Median time to response was 8 weeks by central review assessment. Median duration of response was 40 weeks. The overall toxicity profile in the study population was similar to that previously reported for pembrolizumab in patients with other advanced malignancies.

Microsatellite instability was analyzed in samples from 24 patients. 17% (4/24 patients) had microsatellite instability high (MSI-H) tumors (two [8%] patients from Asia and two [8%] patients from elsewhere) and 83% (20/24 patients) had tumors that were microsatellite stable (MSS).

KEYNOTE-059 is the registration, phase 2, multicenter, non-randomized, open-label multi-cohort trial. 259 patients with gastric or gastroesophageal junction adenocarcinoma were enrolled.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit.

For the 143 patients, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer.

Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The duration of response ranged from 5.3+ to 14.1+ months.

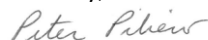
Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC.

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

1. KEYTRUDA (pembrolizumab) Prescribing Information. Merck & Co., Inc.
2. Muro, K.C., H.; Shankaran, V.; Geva, R.; Catenacci, D.; Gupta, S.; et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. The Lancet Oncology, 2016. 17(6): p. 717-726.

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

Sincerely,



Peter Piliero, AVP  
Merck & Co., Inc.  
2000 Galloping Hill Rd  
Kenilworth, NJ 07033  
908-740-6501  
[peter.piliero@merck.com](mailto:peter.piliero@merck.com)