Name: Suzana Giffin, AVP
Company/Organization: Merck & Co., Inc.
Address: 2000 Galloping Hill Rd. Kenilworth, NJ 07033
Phone: 908-740-6708
Email: suzana.giffin@merck.com
Date of Request: 5/18/2021
NCCN Guidelines Panel: Esophageal/Gastric Cancers

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 use in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient cancer (dMMR)[1].

Specific Changes: We respectfully request, as follow-up to the letter submitted on September 14, 2020, that pembrolizumab monotherapy, and pembrolizumab plus chemotherapy combination therapy be included as first-line treatment options for patients with MSI-H/dMMR gastric/gastroesophageal junction (GEJ) cancer who have PD-L1 CPS ≥ 1 in the NCCN Gastric Cancer Guidelines v2.2021 (page GAST-F 3 of 15) based on the post-hoc exploratory analysis from the KEYNOTE-062 study data published by Shitara et al. [2] and previously presented and now published by Chao et al. [3]

FDA Clearance:

KEYTRUDA, as a monotherapy and/or in combination with chemotherapy, is not FDA-approved for the first-line treatment of MSI-H/dMMR gastric cancer.[1]

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please refer to the KEYTRUDA prescribing information for the other FDA-approved indications.[1]

Rationale:

As follow-up to our submission request on September 14, 2020 with the KEYNOTE-062 results from the JAMA Oncology publication by Shitara et al. [2], this submission is based on the JAMA Oncology publication by Chao et al.[3] Both Chao et al.[3] and Shitara et al.[2] published data from an exploratory analysis in patients with MSI-H gastric tumors who have PD-L1 CPS ≥1. The median overall survival (OS) with pembrolizumab monotherapy in months was not reached (NR) (95% CI, 10.7 – NR) vs. 8.5 months (95% CI, 5.3 – 20.8) with the chemotherapy arm (HR = 0.29; 95% CI, 0.11 – 0.81)[2,3]. The median OS with pembrolizumab plus chemotherapy was NR (95% CI 3.6 – NR) vs. 8.5 months (95% CI, 5.3 – 20.8) with chemotherapy (HR = 0.37; 95% CI, 0.14 – 0.97)[2,3]. The median

progression-free survival (PFS) was 11.2 months (95% CI, 1.5-NR) for the pembrolizumab arm, NR (95% CI, 3.6 months-NR) for the pembrolizumab plus chemotherapy arm, and 6.6 months (95% CI 4.4-8.3) for the chemotherapy arm[2,3]. The median duration of response (DOR) was 21.2 months (95% CI, 1.4-33.6) for the pembrolizumab arm, NR (95% CI, 1.6-34.5) for the pembrolizumab plus chemotherapy arm and 7.0 months (95% CI, 2.0-30.4) in the chemotherapy arm[3].

Overall, the totality of data in the studies as reported in the references cited supports our request for the recommendation for pembrolizumab monotherapy and pembrolizumab plus chemotherapy combination therapy as first-line treatment options for patients with MSI-H/dMMR gastric/GEJ cancer who have PD-L1 CPS ≥ 1 [2,3].

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Shitara K, Van Custem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(10):1571-1580.
3. Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric/gastroesophageal junction cancer in patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol.* Published online April 1, 2021. doi:10.1001/jamaoncol.2021.0275.

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

Sincerely,

Suzana Giffin, AVP
Merck & Co., Inc.
2000 Galloping Hill Rd
Kenilworth, NJ 07033
908-740-6708
suzana.giffin@merck.com