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
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NCCN Guidelines Panel: Cervical/Uterine Cancers Panel

On behalf of Merck & Co., Inc., I respectfully request the NCCN Cervical/Uterine 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 (dMMR) endometrial cancer.[1]

Specific Changes: We respectfully request the change for pembrolizumab from "Useful in Certain Circumstances" to "Preferred Regimens" under the Biomarker-directed systemic therapy for second line treatment recommendations for patients with recurrent, metastatic, or high-risk MSI-H/dMMR endometrial carcinoma in the NCCN Uterine Neoplasms Guidelines (page ENDO-D 1 of 4) based on the data presentation at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting by Maio et al.[1]

FDA Clearance:

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 durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

Please refer to the KEYTRUDA (pembrolizumab) prescribing information for other FDA-approved indications.[2]

Rationale:

The efficacy and safety data of pembrolizumab in advanced MSI-H/dMMR solid tumors that have progressed on prior therapy in the KEYNOTE-158 study (all cohorts including cohort A to cohort K, N = 233) have been previously reported[3] and included in the NCCN Uterine Neoplasms Guidelines. In this updated analysis of Cohort K (N=351) in KEYNOTE-158, Maio et al.[1] presented the efficacy and safety results of pembrolizumab in advanced MSI-H/dMMR solid tumors, including 22.5% with endometrial, 14.5% with gastric, 7.4% with small intestine, 7.1% with ovarian, 6.3% with cholangiocarcinoma, 6.3% with pancreatic, and 6.0% with brain tumors. The primary endpoint of objective response rate (ORR, N=321 eligible patients) was 30.8% (95% CI 25.8-36.2), with complete response (CR) rate of 8.4% (n = 27/321) and partial response (PR) rate of 22.4% (n = 72/321). The median duration of response (DOR) was 47.5 months (range, 2.1+ to 51.1+ months).

Continued response at 3 years was noted in 70.1% of responders and at 2 years in 74.1% of responders. Median overall survival (OS) was 20.1 months (95% CI 14.1-27.1), while 3-year OS rate was 39.1%. Median progression free survival (PFS) was 3.5 months (CI 95% 2.3-4.2), while 3-year PFS rate was 24.0%. Treatment-related adverse events were noted in 64.7% of all treated patients, of which 12.0% experienced Grade 3-5 AEs. Immune-mediated AEs and infusion reactions were observed in 20.2% of all treated patients of which 4.8% were Grade 3-5.

Overall, the totality of the data presented by Maio et al.[1] supports our request for the recommendation of pembrolizumab as a Preferred Regimen under the Biomarker-directed systemic therapy for second line treatment recommendations for patients with recurrent, metastatic, or high-risk MSI-H/dMMR endometrial carcinoma.

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

1. Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in MSI-H/dMMR cancers: updated analysis from phase 2 KEYNOTE-158 study. *J Clin Oncol* 2021;39(suppl 15 abstr 2565).
2. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
3. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase 2 KEYNOTE-158 study. *J Clin Oncol* 2020;38(1):1-10.

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