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Date of Request: 06/01/2020  
NCCN Guidelines Panel: Colon/Rectal/Anal Cancers

NCCN Colon/Rectal/Anal Cancers Panel: On behalf of Merck & Co., Inc., I respectfully request the NCCN Colon/Rectal/Anal Cancers Panel to review the enclosed information for KEYTRUDA (pembrolizumab), in reference to NCCN Rectal Cancer Guidelines v3.2020.

### Specific Changes:

We respectfully request the inclusion of pembrolizumab as a first-line therapy for patients with MSI-H/dMMR metastatic rectal cancer as a Category 1 recommendation to the NCCN Rectal Cancer Guidelines v3.2020 (pages REC-13 and REC-F 1 of 13).

### 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 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 (pembrolizumab) prescribing information for other FDA-approved indications.<sup>1</sup>

Rationale: This submission includes data from the phase 3, randomized, open-label, multicenter KEYNOTE-177 study by Andre et al., which supports our request for the inclusion of pembrolizumab as a Category 1 recommendation for first-line therapy for patients with MSI-H/dMMR metastatic rectal cancer.<sup>2</sup>

KEYNOTE-177 study (NCT02563002) evaluated efficacy and safety of pembrolizumab (N=153) versus investigator-choice chemotherapy (N=154) in treatment naïve MSI-H or dMMR stage IV colorectal cancer (CRC) patients. The study demonstrated median progression free survival, PFS (primary end point), of 16.5 months (range 5.4-32.4 months) with pembrolizumab and 8.2 months (range 6.1-10.2 months) with chemotherapy (HR of 0.60, 95% CI, 0.45-0.80, P=0.0002); 24-month PFS rate was 48.3% for the pembrolizumab group and 19% for the chemotherapy group. Overall response rate, ORR, was 43.8% versus 33.1% (P=0.0275) for pembrolizumab and chemotherapy groups respectively. Median duration of response was not reached in pembrolizumab group as compared to 10.6 months in chemotherapy group. Median study follow up was 32.4 months (range, 24.0-48.3 months). Grade 3-5 adverse events were 22% in pembrolizumab and 66% in chemotherapy groups.<sup>2</sup>

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Andre T., Shiu K., Kim T. et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3, KEYNOTE-177 study. Presented at the ASCO Annual Meeting; May 29-31, 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 to the right.

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