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NCCN Guidelines Panel: Uterine Neoplasms

NCCN Uterine Neoplasms Panel: On behalf of Merck & Co., Inc., I respectfully request the NCCN Uterine Neoplasms Panel to review the enclosed information for KEYTRUDA® (pembrolizumab) in combination with Lenvima® (lenvatinib) in reference to the NCCN Guidelines v1.2021 for Uterine Neoplasms.

Specific Changes: We respectfully request the inclusion of pembrolizumab, in combination with lenvatinib, as a category 1 preferred treatment option for patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation, under systemic therapies on ENDO-D (page 1 of 4) in the NCCN Uterine Neoplasms Guidelines.

FDA Clearance:

Endometrial Carcinoma

- KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. 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.

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

Rationale: Makker et al., presented results from the KEYNOTE-775/Study 309 trial (NCT03517449) at the Society of Gynecologic Oncology (SGO) Virtual Annual Meeting on Women's Cancer 2021. KEYNOTE-775/Study 309 is a multicenter, open-label randomized phase 3 study that compared the efficacy and safety of pembrolizumab in combination with lenvatinib versus treatment of physician's choice (TPC), in patients with advanced endometrial cancer. The study enrolled 827 patients aged 18 years and older with advanced, metastatic or recurrent endometrial cancer, who were randomly assigned in a 1:1 ratio to receive either pembrolizumab 200 mg intravenously every 3 weeks (Q3W) in combination with lenvatinib 20 mg by mouth once daily, or TPC. TPC included doxorubicin 60 mg/m^2 IV Q3W (up to a maximum cumulative dose of 500 mg/m^2) or paclitaxel 80 mg/m^2 IV weekly (3 weeks on/1 week off). All patients were treated until documented disease progression or unacceptable toxicity, or, for pembrolizumab, up to 35 cycles. The primary endpoints were progression free survival (PFS) as assessed by blinded independent central review and overall survival (OS). Secondary endpoints included objective response rate (ORR) and safety.

The pembrolizumab plus lenvatinib arm (n=411) included 84.2% of patients with pMMR (mismatch repair proficient) tumors and the TPC arm (n=416) included 84.4% of patients with pMMR tumors. The median PFS in participants with pMMR tumors in the pembrolizumab plus lenvatinib arm was 6.6

months, compared to 3.8 months in the TPC arm (Hazard ratio [HR]: 0.60; 95% CI 0.50, 0.72; p<0.0001). The median PFS in all-comers (all trial participants, regardless of tumor MMR status) was 7.2 months in the pembrolizumab plus lenvatinib arm, compared to 3.8 months in the TPC arm (HR: 0.56; 95% CI 0.47, 0.66; p<0.0001). The median OS in participants with pMMR tumors in the pembrolizumab plus lenvatinib arm was 17.4 months, compared to 12.0 months in the TPC arm (HR: 0.68; 95% CI 0.56, 0.84; p=0.0001); with a median follow-up time of 11.4 months. The median OS in all-comers was 18.3 months in the pembrolizumab plus lenvatinib arm, compared to 11.4 months in the TPC arm (HR: 0.62; 95% CI 0.51, 0.75; p<0.0001). The ORR in participants with pMMR tumors in the pembrolizumab plus lenvatinib arm was 30.3% (95% CI 25.5, 35.5) [complete response of 5.2% and partial response of 25.1%], compared to 15.1% (95% CI 11.5, 19.3) [complete response of 2.6% and partial response of 12.5%] in the TPC arm. The ORR for all-comers was 31.9% (95% CI 27.4, 36.6) [complete response of 6.6% and partial response of 25.3%] in the pembrolizumab plus lenvatinib arm, compared to 14.7% (95% CI 11.4, 18.4) [complete response of 2.6% and partial response of 12.0%] in the TPC arm. In the pembrolizumab plus lenvatinib arm, 5.7% of patients died due to grade 5 events (gastrointestinal disorders: 1.2%, cardiac disorders: 0.5%, general disorders: 1.5%, infections: 0.7%, decreased appetite, neoplasms, nervous system, psychiatric, renal, reproductive, or respiratory disorders: 0.2% each). In the TPC arm, 4.9% of patients died due to grade 5 events (cardiac disorders: 1%, general disorders: 1.3%, infections: 1.5%, subdural hematoma: 0.3%, respiratory disorders: 0.8%). Treatment-emergent adverse events (TEAEs) (any grade) were observed in 99.8% of patients in the pembrolizumab plus lenvatinib arm and in 99.5% of patients in the TPC arm, with grade 3 or higher TEAEs occurring in 88.9% of patients in the pembrolizumab plus lenvatinib arm and in 72.7% of patients in the TPC arm. Pembrolizumab was discontinued for adverse reactions (any grade) in 18.7% of patients, regardless of action taken with lenvatinib. Lenvatinib was discontinued for adverse reactions (any grade) in 30.8% of patients, regardless of action taken with pembrolizumab. The results from KEYNOTE-775/Study 309 support the inclusion of pembrolizumab in combination with lenvatinib as a category 1 preferred treatment option for patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Makker V, Colombo N, Casado Herraez AC, et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775. Presented at the Society of Gynecologic Oncology Virtual Annual Meeting on Women's Cancer; March 19-25, 2021.

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

Sincerely,

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