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NCCN Guidelines Panel: Uterine Neoplasms

On behalf of Eisai Inc., I respectfully request the NCCN Uterine Neoplasms Panel to review the enclosed data for LENVIMA® (lenvatinib) capsules in combination with KEYTRUDA® (pembrolizumab) in reference to additional data to support this combination in patients with advanced endometrial carcinoma.

Specific Changes: We respectfully request the inclusion of lenvatinib, in combination with pembrolizumab, as a category 1 preferred regimen 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 Version 3.2021.

FDA Clearance: Lenvatinib in combination with pembrolizumab is FDA approved for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (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 trial.[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 carcinoma. 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 orally once daily, or TPC. TPC included doxorubicin 60 mg/m2 IV Q3W (up to a maximum cumulative dose of 500 mg/m2) or paclitaxel 80 mg/m2 IV weekly (3 weeks on/1 week off). All patients were treated until RECIST 1.1-documented disease progression as verified by blinded independent central review (BICR), or unacceptable toxicity, or, for pembrolizumab, up to 35 cycles or a maximum of 24 months. Treatment with lenvatinib could be continued beyond 24 months. Treatment was permitted beyond RECIST 1.1-defined disease progression if the treating investigator considered patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 8

weeks. The primary endpoints were progression free survival (PFS) as assessed by BICR 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 mismatch repair proficient (pMMR) 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.[2]

Lorusso et al. (2021), presented patient-reported health-related quality of life (HRQoL) results from the KEYNOTE-775/Study 309 trial (NCT03517449) at the 2021 American Society of Clinical Oncology (ASCO) Virtual Annual Meeting. Prespecified HRQoL patient-reported outcome endpoints included a secondary endpoint of the assessments from EORTC QLQ-C30 Global Health Status/quality of life (GHS/QoL). HRQoL exploratory endpoints included assessments from EORTC QLQ-C30 (other than GHS/QoL), EORTC QLQ-EN24, and EuroQoL EQ-5D-5L. No substantial differences were observed over time in HRQoL scores between the 2-drug combination regimen, lenvatinib + pembrolizumab, and the single-agent chemotherapy, TPC arm (doxorubicin or paclitaxel). Given the clinically meaningful and statistically significant improvement

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in PFS, OS, and ORR, and a safety profile that is as expected and consistent with previously reported studies, these HRQoL data further indicate that lenvatinib + pembrolizumab has an overall favorable benefit/risk profile compared to TPC for the treatment of patients with advanced EC previously treated.[3]

The following literature is submitted to assist the committee with their review.

1. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., December 2020.
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.
3. Lorusso D, Colombo N, Casado Herraez AC, et al. Health-related quality of life in advanced endometrial cancer patients treated with lenvatinib + pembrolizumab or treatment of physician's choice. Presented at the American Society of Clinical Oncology Annual Meeting; June 4-8, 2021.

Sincerely,

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