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NCCN Guidelines Panel: Thymomas and Thymic Carcinomas Panel

On behalf of Eisai, Inc., I respectfully request the *NCCN Thymomas and Thymic Carcinomas Panel* to review and consider the enclosed data for Lenvima® (*lenvatinib*) capsules, for the treatment of patients with unresectable advanced or metastatic thymic carcinoma following at least one previous platinum-based chemotherapy

Specific Changes: Inclusion of lenvatinib as a preferred category 2A systemic treatment for patients with unresectable advanced or metastatic thymic carcinoma following previous platinum-based chemotherapy

FDA Clearance: Currently, lenvatinib is not indicated for the treatment of thymic carcinoma.

Rationale:

A single-arm, multi-centered (in Japan) phase II REMORA trial evaluated the efficacy and safety of lenvatinib as a systemic treatment option for patients with thymic carcinoma. REMORA enrolled adults (≥20 years) with pathologically confirmed unresectable advanced (stage IIIa, IIIb, IVa, and IVb as defined by the Masaoka-Koga classification) or metastatic thymic carcinoma who had ≥ 1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; disease progression after at least one prior platinum-based chemotherapy; an ECOG performance status 0 or 1; asymptomatic brain metastasis; and those who were able to tolerate oral medication.

Patients received lenvatinib 24mg orally once daily in 4-week cycles until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST version 1.1 and by independent central review. Secondary endpoints included ORR per RECIST v1.1 by investigators, disease control rate by independent central review, progression-free survival (PFS) by investigators, overall survival (OS), and safety.

A total of 42 patients were enrolled from April 21, 2017 to February 22, 2018 and included in the analyses. At data-cut off (February 22, 2019) with a median follow-up duration of 15.5 months (Interquartile range: 13.1 – 17.5), 14 (33%) patients were still receiving lenvatinib. Baseline patient characteristics included median age of 55.5 years (range 49-65 years); 69% male; 69% ECOG PS 1; 71% squamous cell carcinoma; 12% adenocarcinoma; 33% had prior surgery; and 40% had prior radiation. The most commonly used first-line systemic treatments were 71% carboplatin and paclitaxel and 12% cisplatin/cyclosphosphamide/doxorubicin/vincristine. Twenty-five (60%) of 42 patients had received ≥ 2 lines of chemotherapy. Three (7%) of 42 patients had previously received immune checkpoint inhibitors.

In REMORA, lenvatinib resulted in an ORR of 38% (90% CI: 25.6 -52.0%), all partial responses. In those with an objective response (n=16/42), the median duration of response was 11.6 months (95% CI: 5.8-18 months).

Per independent central review, the disease control rate was 95% (95% CI: 83.8- 99.4%) with 57% stable disease. Per investigators, the ORR was consistent with independent central review at 38% (95% CI: 23.6-54.5) per RECIST version 1.1. The median PFS was 9.3 months (95% CI: 7.7-13.9 months) and the median OS was not reached (NR; 95% CI: 16.1-NR). At 12 months, the probability of PFS was 41% (95% CI: 25.8-54.7%) and the probability of OS was 83% (95% CI: 68.2–91.7).

Patients received a median 9.5 cycles of lenvatinib (range 2-24 cycles) with each cycle being 28-days. The median duration of treatment was 8.8 months (IQR: 5.6-15.6 months). The most frequent (>5%) grade 3 treatment-related adverse events (TRAEs) were hypertension (64%) and palmar-plantar erythrodysaesthesia syndrome (PPE; 7%). Eight (19%) of 42 patients developed serious adverse events related to lenvatinib, which were large intestine perforation, left ventricular dysfunction, pneumonitis, abdominal pain, electrocardiogram T wave abnormal, pneumonia, decreased appetite, and upper abdominal pain. The most frequent grade 1-3 TRAEs (>30%) were hypertension (88%), proteinuria (83%), PPE (69%), hypothyroidism (64%), decreased platelet count (53%), diarrhea (50%), appetite loss (42%), stomatitis (33%), malaise (33%), and dysphonia (31%). Adverse events led to at least one dose reduction in all patients. Seven (17%) patients discontinued lenvatinib due to adverse events, which included intestine perforation, ventricular dysfunction, pneumonitis, arthralgia, and pneumothorax. No patient died due to adverse events.

The following documents are submitted in support of this proposed change.

References

1. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol* 2020; 21: 843–50
2. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., 2020

Sincerely,

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