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**NCCN Guidelines Panel: Hepatobiliary Cancers**

On behalf of Eisai Inc., I respectfully request the *NCCN Hepatobiliary Panel* to review and consider the enclosed data for Lenvima® (*lenvatinib*) capsules for the treatment of unresectable hepatocellular carcinoma (uHCC).

Specific Changes: Recommend lenvatinib (category 1) as a treatment option for unresectable hepatocellular carcinoma (uHCC) (changed from "category 2A recommendation"), based on a post-hoc analysis of responders from the phase 3 REFLECT trial who received subsequent anticancer medication and the analysis of the association between survival and objective response (OR) in patients in the REFLECT trial.

FDA Clearance: On August 16, 2018 the Food and Drug Administration approved Lenvima (lenvatinib) capsules for the first-line treatment of patients with unresectable HCC. Please refer to the enclosed prescribing information for a complete list of FDA-approved indications for Lenvima and safety information. [1]

Rationale: The REFLECT study, a phase 3, global, randomized, open-label trial, with lenvatinib met its primary endpoint of overall survival (OS) by statistical confirmation of non-inferiority to sorafenib and is the first successful trial vs sorafenib in the first line setting in unresectable HCC.[2] A post hoc analysis of responders in the REFLECT trial showed approximately 1/3 of all patients in either arms received subsequent anticancer medication in poststudy survival follow-up. In a subset analysis of lenvatinib responders who received any subsequent anticancer medication, median OS was 26 months (95% CI: 18.5-34.6) compared with 22.3 months (95% CI: 14.6- non evaluable) in sorafenib responders. Safety analyses as reported in REFELCT were not re-analyzed.[3]

In an additional post hoc retrospective study, OR by mRECIST was shown to be an independent predictor of OS in patients with HCC regardless of treatment received. Responders were defined as patients who achieved complete or partial responses by mRECIST by investigator review. Median OS was 22.4 months for responders, irrespective of treatment, and 11.4 months for nonresponders (HR: 06.1; 95% CI: 0.49-0.76). Safety analyses as reported in REFELCT were not re-analyzed.[4]

The following literature is submitted in support of the proposed change. The data by Alsina et al. has been accepted for electronic publication ahead of print publication in *Liver Cancer* journal.

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References

1. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., September 2019.
2. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial. Lancet 2018; 391: 1163–73.
3. Alsina A, et al. Poster presented at: Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology; 2019; San Francisco, CA.
4. Kudo M, et al. Oral presentation at: Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology; 2019; San Francisco, CA.

Sincerely,

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