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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 proven treatment effect on Overall Survival (OS) by statistical confirmation of non-inferiority to sorafenib in the phase 3, global, randomized REFLECT study.¹

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.²

Rationale: The REFLECT study, a phase 3, global, randomized, open-label trial, with lenvatinib met its primary endpoint of 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 in 10 years.¹

Non-inferiority is a valid statistical approach agreed upon by regulatory authorities.³ The non-inferiority margin was set at 1.08 based on previous phase 3 trials of sorafenib. Noninferiority would be declared if the upper limit of the 2-sided 95% CI for HR was < 1.08. The median OS for patients treated with lenvatinib in the REFLECT study was 13.6 months compared with 12.3 months for sorafenib (HR, 0.92; 95% CI: 0.79-1.06) meeting the criteria for non-inferiority.¹

Lenvatinib was statistically significantly superior for clinically meaningful secondary outcomes of Progression Free Survival (PFS), Time to Progression (TTP), and Objective Response Rate (ORR). According to independent imaging review per mRECIST, of lenvatinib compared with sorafenib, median PFS was 7.3 months vs 3.6 months (HR 0.64; 95% CI: 0.55-0.75; P<0.001), median TTP was 7.4 months vs 3.7 months (HR 0.60; 95% CI: 0.51-0.71); and ORR was 41% vs 12% ORR (OR 5.01; 95% CI: 3.59-7.01; P<0.001), respectively. Independent imaging review by RECIST 1.1 were consistent with mRECIST.^{1,2}



In the REFLECT study, the safety profile of lenvatinib was found to be consistent with that observed in previous studies.¹ The most common any grade adverse events ($\geq 30\%$) for lenvatinib were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%) and abdominal pain (30%); for sorafenib were palmar-plantar erythrodysesthesia (52%), diarrhea (46%), fatigue (36%), and hypertension (31%).^{1,2}

The following literature is submitted in support of the proposed change. We would like to acknowledge the contributions NCCN panel members who are also co-authors or co-contributors of this publication.

References

1. 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
2. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., August 2018.
3. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) November 2016. Clinical/Medical.
<https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf>

Sincerely,

A handwritten signature in black ink, appearing to read "Adelle Berezinsky".

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