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**NCCN Guidelines Panel: Hepatobiliary Panel**

On behalf of Eisai, Inc., I respectfully request the *NCCN Hepatobiliary Panel* to review and consider the enclosed data for Lenvima® (*lenvatinib*) capsules in combination with pembrolizumab, for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

**Specific Changes**: Inclusion of lenvatinib in combination with pembrolizumab as a category 2A first-line treatment option for patients with unresectable HCC.

**FDA Clearance**: The investigational use of lenvatinib in combination with pembrolizumab as a first-line treatment option for patients with unresectable HCC is currently not FDA-approved. Please refer to the enclosed prescribing information for a complete list of FDA-approved indications for lenvatinib.

**Rationale**: A previous request was submitted on May 29, 2020 based on an ASCO 2020 poster presentation from Study 116 (NCT03006926). The Journal of Clinical Oncology published Study 116 results recently and this submission will include additional data from the manuscript for consideration of this request.

A multicenter, open-label and ongoing Phase 1b study, Study 116 (NCT03006926) evaluated the safety and efficacy of lenvatinib plus pembrolizumab as a treatment for unresectable HCC. Study 116 enrolled adults with histologically or cytology confirmed HCC according to AASLD criteria; BCLC Stage C or B HCC not suitable for Transarterial chemoembolization; at least one measurable target lesion according to mRECIST; Child-Pugh Class A (score 5-6); and an ECOG performance status 0 or 1. Study 116 had two phases: a dose-limiting toxicity (DLT) phase and an expansion phase including only patients with no prior systemic therapy for unresectable HCC.

Patients received lenvatinib 12 mg (if body weight ≥60 kg) or 8 mg (if body weight <60 kg) orally once daily and pembrolizumab 200 mg intravenously on day 1 of a 21-day cycle (for up to 2 years for pembrolizumab). The primary endpoints for first-line analysis included objective response rate (ORR) and duration of response (DOR) per mRECIST and RECIST version 1.1 based on independent imaging review (IIR). Secondary endpoints included progression-free survival (PFS), time to progression (TTP), and overall survival (OS).

The first-line analysis of lenvatinib plus pembrolizumab for unresectable HCC included 100 patients. Select baseline patient characteristics included 20% macroscopic vascular invasion; 19% HBV, 36% HCV, and 28% alcohol as HCC etiology; 52% radiographic evidence of cirrhosis based on IIR; and 93%, 18%, 30%, and 10% for disease sites at liver, lung, lymph nodes, and bones, respectively.

The median duration of treatment exposure was 7.9 months (range: 0.2-31.1 months) for lenvatinib plus pembrolizumab. Patients received a median of 69% (range: 23-100%) of their planned lenvatinib starting dose and a median of 11 administrations (range: 1-33 admin) for pembrolizumab. Serious adverse events

occurred in 65 patients (65%) and treatment-related AE (TRAE) were reported in 36 patients (36%). Thirteen grade 5 AEs occurred and only three were considered treatment related. TRAEs led to treatment interruption, dose reduction, and discontinuation of lenvatinib in 62%, 52%, and 14% of patients, respectively. TRAE led to pembrolizumab interruption and discontinuation in 43% and 10% of patients, respectively. Discontinuation of both lenvatinib and pembrolizumab from TRAE occurred in 6% of patients.

At data cutoff of October 31, 2019, 37 patients were still on treatment (lenvatinib ~~only~~ n=3; both drugs n=34) with a median follow-up of 10.6 months (95% CI: 9.2-11.5 months).

By mRECIST per IIR, the confirmed ORR was 46% (95% CI: 36.0- 56.3%) with 11% complete response (CR) and 35% partial response (PR). The median DOR was 8.6 months (95% CI: 6.9-NE months) with DOR $\geq$ 6 months probability of 0.83 (95% CI: 0.69-0.92). The median PFS was 9.3 months (95% CI: 5.6-9.7 months) with PFS rates of 59.9% and 26.4% at 6 and 12 months, respectively. The median TTP was 9.7 months (95% CI: 7.9-11.8 months).

By RECIST version 1.1 per IIR, the confirmed ORR was 36% (95% CI: 26.6-46.2%) with 1% CR and 35% PR. The median DOR was 12.6 months (95% CI: 6.9-NE months) with a DOR $\geq$ 6 months probability of 0.73 (95% CI: 0.52-0.86). The median PFS was 8.6 months (95% CI: 7.1-9.7 months) and the PFS rates of 64% and 27.4% at 6 and 12 months, respectively. The median TTP was 9.7 months (95% CI: 7.7-13.0 months).

The median OS was 22 months (95% CI: 20.4-NE months) with 34 deaths overall at the time of data cutoff. The OS rates were 81% and 67.5% at 6 and 12 months, respectively. Common subsequent anticancer medications during survival follow-up included sorafenib (7%), regorafenib (3%), cisplatin (2), ramucirumab (2), and antimetabolites (2).

We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of this publication.

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

References

1. Finn RS, Ikeda M, Zhu AX et al. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. *J Clin Oncol* Published online July 27, 2020 https://ascopubs.org/doi/abs/10.1200/JCO.20.00808
2. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., 2020

Sincerely,

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