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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 FDA has granted Breakthrough Therapy designation to the investigational combination of lenvatinib and pembrolizumab for the potential first-line treatment of patients with unresectable HCC not amenable to locoregional treatment.

Rationale: An open-label and Phase 1b study, Study 116 (NCT03006926), evaluated the safety and efficacy of lenvatinib plus pembrolizumab as a first-line treatment for unresectable HCC. Study 116 enrolled adults with unresectable HCC; had Child-Pugh Class A; BCLC Stage C or B HCC who were ineligible for liver-directed therapy; had an ECOG performance status 0 or 1; had at least one measurable target lesion according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). Study 116 had two parts: Part 1 (n=6), a dose-limiting evaluation, and Part 2 (n=98), dose expansion, for patients with no prior systemic therapy for unresectable HCC. Four patients from Part 1 were excluded from Part 2 because of prior sorafenib treatment. A total of 100 patients were included in the first-line analysis of lenvatinib plus pembrolizumab in unresectable HCC.

Patients were treated with lenvatinib 12 mg (if body weight ≥60 kg) or 8 mg (if body weight <60 kg)orally once daily plus pembrolizumab 200 mg intravenously on Day 1 of a 21-day cycle. 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, and overall survival.

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). Baseline patient characteristics included median age 66.5 years (range: 47-86 years); 81% male; 71% BCLC Stage C; 81% had body weight ≥ 60 kg; 62% ECOG PS 0; 67% had serum AFP < 400ng/mL; 71%/ 27%/ 2% Child Pugh Score 5/6/7, respectively; and 62% had macroscopic portal vein invasion, extrahepatic spread, or both.

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) with lenvatinib plus pembrolizumab. The median DOR was 8.6 months (95% CI: 6.9-NE months) with a median time to response (TTR) of 1.9 months (95% CI: 1.2 - 5.5 months). The median PFS was 9.3 months (95% CI: 5.6-9.7 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 with lenvatinib plus pembrolizumab. The median DOR was 12.6 months (95% CI: 6.9 – NE months) with a median TTR of 2.8 months (95% CI: 1.2-7.7 months). The median PFS was 8.6 months (95% CI: 7.1-9.7 months).

The median OS at data cutoff was 22 months (95% CI: 20.4-NE months).

For safety, the median duration of treatment exposure was 7.9 months (range: 0.2-31.1 months) for lenvatinib plus pembrolizumab. The most common treatment-related adverse events (TRAEs) ≥ 20% of patients with any grade were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), hypothyroidism (25%), palmar-planter erythrodysesthesia syndrome (23%), weight decrease (22%), dysphonia (21%), aspartate aminotransferase increased (20%), and proteinuria (20%). Grade ≥ 3 TRAEs occurred in 67% (n=67) of patients, with grade 3 at 63% (n=63), grade 4 at 1% (n=1; leukopenia/neutropenia), and grade 5 at 3% (n=3). The grade 5 TRAEs (n=3) were due to acute respiratory failure/acute respiratory distress syndrome (n = 1), abnormal hepatic function (n = 1), and intestinal perforation (n = 1); all of which are well-described potential adverse events for these drug classes. TRAEs led to discontinuation of lenvatinib in 14 patients (14%), of pembrolizumab in 10 patients (10%), and of both lenvatinib plus pembrolizumab in six patients (6%).

An ongoing phase 3 trial (LEAP-002; NCT03713593) is assessing lenvatinib in combination with pembrolizumab versus lenvatinib monotherapy, as a first-line option for patients with unresectable HCC.

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. Zhu AX, Finn RS, Ikeda M, et al. A phase 1b study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma (uHCC). Presented at American Society of Clinical Oncology Virtual 2020 Annual Meeting; Abstract #4519; May 29-31, 2020.
2. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., 2020

Sincerely,

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