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NCCN Guidelines Panel: Kidney Cancer

On behalf of Eisai Inc., I respectfully request the *NCCN Kidney Cancer Panel* to review the enclosed data for Lenvima® (*lenvatinib*) capsules in combination with everolimus for the treatment of patients with stage IV clear cell renal cell carcinoma (RCC).

Specific Changes: We respectfully request the inclusion of lenvatinib in combination with everolimus as a first-line treatment option for patients with Stage IV renal cell carcinoma with clear cell histology regardless of International Metastatic RCC Database Consortium (IMDC) risk group in the appropriate sections of the NCCN Kidney Cancer Guidelines v2.2021, including page KID-C 1 of 2.

FDA Clearance: Lenvatinib in combination with everolimus is approved for the treatment of patients with advanced RCC following one prior antiangiogenic therapy

Rationale: CLEAR/Study 307/KEYNOTE-581 is a phase 3, multicenter, randomized, open-label, study (N = 1069) comparing the efficacy and safety of lenvatinib in combination with pembrolizumab and lenvatinib in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced renal cell carcinoma (aRCC) with clear cell histology. Patients were randomized (1:1:1) to receive lenvatinib 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks, lenvatinib 18 mg in combination with everolimus 5 mg orally once daily, or sunitinib 50 mg orally once daily for 4 weeks on treatment followed by 2 weeks off. International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) risk group at baseline in the lenvatinib + everolimus group included 31.9% (n = 114) of patients in the favorable risk group, 54.6% (n = 195) in the intermediate risk group, 11.8% (n = 42) in the poor risk group, and 1.7% (n = 6) who were not evaluable. The primary endpoint was progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by independent review committee (IRC). Key secondary endpoints included confirmed objective response rate (ORR) per RECIST v1.1 by IRC and overall survival (OS). Data cutoff for the final PFS analysis and interim OS analysis was August 28, 2020. We report the results for lenvatinib plus everolimus versus sunitinib in CLEAR/Study 307/KEYNOTE-581.[1]

A total of 357 patients received lenvatinib + everolimus. Median follow-up for this analysis was 26.6 months. Median PFS with lenvatinib plus everolimus was 14.7 months (95% CI: 11.1-16.7) versus 9.2 months (95% CI: 6.0-11.0) with sunitinib (HR for PFS: 0.65; 95% CI: 0.53-0.80; p<0.001). The ORR was 53.5% (95% CI:48.3-58.7) in patients in the lenvatinib + everolimus group and 36.1% (95% CI: 31.2-41.1) in the sunitinib

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group (Relative Risk: 1.48; 95% CI: 1.26-1.74). Complete response was 9.8% (n = 35) with lenvatinib + everolimus versus 4.2% (n = 15) with sunitinib. Median duration of response of those with confirmed responses in the combination group was 16.6 months (95% CI: 14.6-20.6) and 14.6 months (95% CI: 9.4-16.7) in the sunitinib arm. Median OS was not evaluable (NE) in both the combination and sunitinib arms, OS with lenvatinib plus everolimus versus sunitinib was not statistically different (HR: 1.15; 95% CI: 0.88-1.50; p = 0.30).[1]

When stratified by IMDC risk groups, hazard ratios for PFS for lenvatinib + everolimus versus sunitinib was 0.55 (95% CI: 0.38-0.81) for favorable-risk, 0.67 (95% CI: 0.51-0.88) for intermediate-risk, and 0.73 (95% CI: 0.42-1.29) for poor-risk groups. Hazard ratios for OS for lenvatinib + everolimus versus sunitinib were 1.01 (95% CI: 0.46-2.19) for favorable-risk, 1.22 (95% CI: 0.86-1.72) for intermediate-risk, and 0.90 (95% CI: 0.52-1.54) for poor-risk groups.[1]

Median duration of treatment was 11.0 months (range: 0.1-40.0) in patients who received lenvatinib + everolimus. Median relative dose intensity of lenvatinib per patient was 70.4% (range: 22.9-100.0); median relative dose intensity of everolimus per patient was 89.3% (range: 27.6-100.0). Treatment-emergent adverse events (TEAEs) of any Grade were reported in 99.7% (n=354) of patients who received lenvatinib + everolimus. TEAEs led to discontinuation of lenvatinib in 22.0% of those receiving lenvatinib in combination with everolimus. Lenvatinib and/or everolimus dose reductions due to TEAEs were reported in 73.2% of patients. The most common TEAEs (≥25%) of any grade were diarrhea (66.5%), stomatitis (47.6%), hypertension (45.6%), fatigue (42.0%), decreased appetite (40.6%), nausea (39.7%), proteinuria (34.1%), weight decrease (32.7%), vomiting (31.8%), and hypothyroidism (26.8%). Grade ≥3 TEAEs were reported in 83.1% of patients; the most common Grade ≥3 TEAEs (≥6%) were hypertension (22.5%), diarrhea (11.5%), proteinuria (8.2%), fatigue (7.6%), weight decreased (7.3%), decreased appetite (6.2%), and stomatitis (6.2%). In the lenvatinib + everolimus group, of the 22 deaths that occurred, 3 deaths were considered to be treatment-related:(pneumonia, urosepsis, colon perforation; 1 patient each).[1]

References

1. Motzer et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. Published 2021. DOI: 10.1056/NEJMoa2035716
2. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc.

Sincerely,

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