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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 pembrolizumab 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 pembrolizumab 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 pembrolizumab is currently not approved for the treatment of patients with metastatic or advanced renal cell carcinoma.

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 + pembrolizumab group included 31.0% (n = 110) of patients with favorable risk, 59.2% (n = 210) with intermediate risk, 9.3% (n = 33) with poor risk, and 0.6% (n = 2) 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. Herein, we report the results for lenvatinib plus pembrolizumab versus sunitinib in CLEAR/Study 307/KEYNOTE-581.[1]

Median follow-up for this analysis was 26.6 months. Median PFS with lenvatinib plus pembrolizumab was 23.9 months (95% CI: 20.8-27.7) compared with 9.2 months (95% CI: 6.0-11.0) with sunitinib (Hazard Ratio [HR]: 0.39; 95% CI: 0.32-0.49; p<0.001). ORR was 71.0% (95% CI: 66.3-75.7) in the lenvatinib + pembrolizumab arm and 36.1% (95% CI: 31.2-41.1) in the sunitinib arm (Relative Risk vs sunitinib: 1.97; 95% CI: 1.69-

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2.29). Complete response was reported in 16.1% (n = 57) of the combination arm versus 4.2% (n = 15) with sunitinib. Median duration of response in those with confirmed responses was 25.8 months (95% CI: 22.1-27.9) in the lenvatinib + pembrolizumab arm and 14.6 months (95% CI: 9.4-16.7) in the sunitinib arm. Median OS was not evaluable (NE) in the combination (95% CI: 33.6-NE) and sunitinib arm (95% CI: NE, NE). The hazard ratio for lenvatinib plus pembrolizumab versus sunitinib for OS was 0.66 (95% CI: 0.49-0.88; p = 0.005).[1]

When stratified by IMDC risk groups, hazard ratios for PFS for lenvatinib + pembrolizumab versus sunitinib was 0.41 (95% CI: 0.28-0.62) for favorable-risk, 0.39 (95% CI: 0.29-0.52) for intermediate-risk, and 0.28 (95% CI: 0.13-0.60) for poor-risk groups. Hazard ratios for OS for lenvatinib + pembrolizumab versus sunitinib were 1.15 (95% CI: 0.55-2.4) for favorable-risk, 0.72 (95% CI: 0.50-1.05) for intermediate-risk, and 0.30 (95% CI: 0.14-0.64) for poor-risk groups.[1]

Median duration of treatment was 17.0 months (95% CI: 0.1-39.1) in the lenvatinib plus pembrolizumab group; median relative dose intensity of lenvatinib per patient in the combination group was 69.6% (range: 12.6-157.1%) and median number of pembrolizumab administrations was 22 (range, 1-39). Treatment-emergent adverse events (TEAEs) of any grade were reported in 99.7% (n=351) of patients who received lenvatinib plus pembrolizumab. Among patients who received lenvatinib in combination with pembrolizumab, TEAEs resulted in discontinuation of lenvatinib and pembrolizumab in 13.4%, and lenvatinib discontinuation in 25.6% of patients. Lenvatinib dose reductions were reported in 68.8% of patients. The most common TEAEs (≥25%) of any grade were diarrhea (61.4%), hypertension (55.4%), hypothyroidism (47.2%), decreased appetite (40.3%), fatigue (40.1%), nausea (35.8%), stomatitis (34.7%), weight decrease (29.8%), dysphonia (29.8%), proteinuria (29.5%), palmar-plantar erythrodysesthesia syndrome (28.7%), arthralgia (28.1%), rash (27.3%), vomiting (26.1%), and constipation (25.3%). Grade ≥3 TEAEs were reported in 82.4% of patients; the most common Grade ≥3 TEAEs (≥7%) were hypertension (27.6%), diarrhea (9.7%), weight decrease (8.0%), and proteinuria (7.7%). Of the 15 deaths, 4 deaths were considered to be treatment-related: (acute renal failure, uncontrolled hypertension, complications from myasthenic syndrome, and complications from autoimmune hepatitis; 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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