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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 metastatic clear cell renal cell carcinoma (RCC) following progression after prior treatment with a PD-1/PD-L1 immune checkpoint inhibitor (ICI).

Specific Changes: We respectfully request the inclusion of lenvatinib in combination with pembrolizumab as a subsequent therapy for metastatic renal cell carcinoma with clear cell histology in the appropriate sections of the NCCN Kidney Cancer Guidelines v1.2021, including page KID-C 1 of 2.

FDA Clearance: Lenvatinib + pembrolizumab is currently not indicated for the treatment of patients with metastatic or advanced renal cell carcinoma.

Rationale: KEYNOTE-146/Study 111 (NCT02501096) is a Phase 1b/2, multicenter, open-label, single-arm trial evaluating the efficacy and safety of lenvatinib + pembrolizumab in patients with selected solid tumors.[1] This phase 2, multicenter, single arm, open-label expansion trial is based on 104 patients with metastatic clear cell RCC who received lenvatinib 20 mg capsule daily + pembrolizumab 200 mg every 3 weeks intravenously until disease progression or toxicity. All patients had received prior anti-PD-1/PD-L1 ICI therapy, of whom 65% (n=68) received prior anti-PD-1/PD-L1 and anti-VEGF therapy, and 37% (n=37) received prior nivolumab + ipilimumab combination therapy. Median duration of prior ICI therapy was 7 months (range, 3 to 13 months). In total, 40% received 1 prior anticancer therapy and 60% received ≥2 prior anticancer therapies. Of the patients enrolled, 36% were in favorable, 42% in intermediate, and 22% in poor MSKCC risk groups. The primary endpoint was Objective Response Rate (ORR) at week 24 by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST). Secondary endpoints include ORR, Duration of Response (DOR), Progression-Free Survival (PFS), Overall Survival (OS), safety and tolerability. The objective responses per investigator-assessment were recently reported.[2] Herein, we report objective responses assessed by irRECIST per independent imaging review (IIR).[3]

At data cutoff (April 9, 2020), the ORR at week 24 was 49% (95% CI, 39.1–59.0) and the ORR was 52.9% (95% CI, 42.8–62.8). A confirmed partial response was recorded in 52 patients (50%) and a confirmed complete response was reported in 3 patients (2.9%). Median DOR was 10.6 months (95% CI, 9.7–16.6), the median PFS was 11.8 months (95% CI, 9.5–17.7), and the median OS was not reached (95% CI, 16.7–NR).[3]

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The median treatment duration was 8.3 months; the median lenvatinib dose intensity was 14.59 mg/day, and the median number of pembrolizumab administrations was 12 (range 1–35). Treatment-related adverse events (TRAEs) occurred in 99% of patients, of which 60% experienced Grade 3 or 4 TRAEs. The most common TRAEs of any grade (≥20%) were fatigue (55%), diarrhea (46%), proteinuria (38%), hypertension (38%), dysphonia (37%), stomatitis (33%), nausea (32%), decreased appetite (31%), arthralgia (30%), palmar-plantar erythrodysesthesia syndrome (26%), hypothyroidism (25%), and headache (23%). The most frequent Grade 3 TRAEs were hypertension (21%), proteinuria (10%), diarrhea (8%), fatigue (5%), nausea (2%), and arthralgia (1%). Discontinuation of lenvatinib and/or pemobrolizumab due to TRAEs occurred in 14% of patients. There were five Grade 4 TRAEs (aspartate aminotransferase increased, lipase increased, diverticulitis, large intestine perforation, myocardial infarction) and two Grade 5 TRAEs (upper gastrointestinal hemorrhage, sudden death).[3]

These results demonstrated antitumor activity for the combination of lenvatinib + pembrolizumab in patients with mccRCC who had experienced disease progression following prior PD-1/PD-L1 ICI therapy. The efficacy data demonstrated concordance between investigator assessment and IIR, regardless of prior PD-1/PD-L1 ICI + anti-VEGF or prior nivolumab + ipilimumab therapy.[3]

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

References

1. Taylor MH et al. Phase Ib/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. *J Clin Oncol*. 2020; 38(11): 1154–1163
2. Lee CH et al. Phase 2 trial of lenvatinib plus pembrolizumab for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mRCC). *J Clin Oncol*. 2020; 38(15): 5008-5008. DOI: 10.1200/JCO.2020.38.15_suppl.5008.
3. Lee CH et al. Phase 2 Trial of Lenvatinib + Pembrolizumab for Progressive Disease After PD-1/PD-L1 Immune Checkpoint Inhibitor in Metastatic Clear Cell Renal Cell Carcinoma: Results by Independent Imaging Review and Subgroup Analyses. Poster presented at: European Society for Medical Oncology Virtual Congress; 2020.
4. LENVIMA full prescribing information. Woodcliff Lake, NJ: Eisai Inc., July 2020.

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Sincerely,

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