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RE: FDA approval of LENVIMA® (lenvatinib) in combination with everolimus, for patients with advanced renal cell cancer (RCC) following one prior anti-angiogenic therapy

NCCN Guidelines Panel: Kidney Cancer

On behalf of Eisai Inc., I respectfully request the NCCN Kidney Panel to review the enclosed data for inclusion of Lenvima (*lenvatinib*) capsules in combination with everolimus for the treatment of advanced RCC following one prior anti-angiogenic therapy.

Specific Changes: Recommend the use of lenvatinib in combination with everolimus as a treatment option for subsequent therapy for relapse or for surgically unresectable Stage IV disease with predominant clear cell histology.

FDA Clearance: On May 13, 2016 the Food and Drug Administration (FDA) approved Lenvima (lenvatinib) capsules in combination with everolimus for the treatment of advanced RCC following one prior anti-angiogenic therapy.

Rationale: Results from a randomized, phase 2, open-label, multicenter, three-arm study (N=153) demonstrated the efficacy and safety of lennvatinib + everolimus in patients with advanced or metastatic clear cell RCC who have previously received anti-angiogenic therapy. Patients were randomized 1:1:1 to Lenvima 18 mg plus everolimus 5 mg, Lenvima 24 mg monotherapy, or everolimus 10 mg monotherapy. This trial met its primary outcome measure of investigator-assessed progression-free survival (PFS) in which patients taking lenvatinib + everolimus experienced a significantly prolonged median PFS of 14.6 months (95% CI: 5.9-20.1) compared with a median PFS of 5.5 months (95% CI: 3.5-7.1) in patients taking everolimus alone (HR, 0.37; 95% CI 0.22-0.62). The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs compared with the everolimus monotherapy arm (HR, 0.43; 95% CI: 0.24-0.75). A significant improvement in confirmed objective response rate (ORR) was observed in patients who received Lenvima + everolimus (37% [95% CI: 24-52], 2% CR + 35% PR) compared with everolimus alone (6% all PR [95% CI: 1-17]. An analysis conducted when 63% of deaths occurred in the lenvatinib + everolimus arm and 74% of deaths occurred in the everolimus only arm demonstrated an improvement in median overall survival (OS) in the combination arm compared with everolimus monotherapy (25.5 months vs 15.4 months; HR, 0.67: 0.42-1.08). The most common adverse reactions (≥ 30%) for Lenvima + everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria. These safety data also include patients on the dose

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escalation portion of the study who received Lenvima 18 mg + everolimus 5 mg (n=11). (Lenvima full prescribing information)

The results provided in the Lenvima full prescribing information conform to FDA labeling requirements to show only confirmed ORR in which a response was required ≥ 4 weeks after an initial response was observed. This differs from RECIST 1.1 in which confirmed responses are not required in randomized trials where response is not the primary endpoint. Further, Study 205 was a phase 2 trial and no multiplicity adjustments were planned; therefore, label requirements for P value inclusion were not met and are not provided in the full prescribing information.

The results of the above clinical trial have been published in *The Lancet Oncology* journal in 2015. 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 this publication.

1. LENVIMA (lenvatinib) full prescribing information. Woodcliff Lake, NJ: Eisai Inc., 05/2016.
2. Motzer RJ, Hutson TE, Glen H, et al. Randomized phase 2 three-arm trial of lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma. *Lancet Oncology*. 2015; 16(15):1473-82.
3. Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol. 2016 Jan;17(1):e4-5. doi: 10.1016/S1470-2045(15)00543-4. Epub 2015 Dec 23.

Sincerely,

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