



Unicel-Anne Flores, PharmD

Eisai Inc.

100 Tice Blvd

Woodcliff Lake, NJ 07677

Phone: 201-746-2635

Unicel-Anne_Flores@eisai.com

October 27, 2017

NCCN Guidelines Panel: Thyroid Carcinoma

On behalf of Eisai Inc., I respectfully request the NCCN Thyroid Panel to review for inclusion the enclosed new published data (Brose 2017) of overall survival (OS) observed in a prespecified analysis from a randomized, phase 3 study (SELECT trial, Schlumberger et al. 2015). The SELECT trial compared Lenvima (*lenvatinib*) capsules to placebo for the treatment of patients with advanced radioactive iodine-refractory differentiated thyroid cancer (RR-DTC). This prespecified analysis evaluated patients age ≤ 65 years vs patients age > 65 years.

Suggested Specific Changes: Inclusion of the following in support of lenvatinib as a treatment option for clinically progressive or symptomatic disease (MS-28):

Results of a prespecified subanalysis of the SELECT trial demonstrated significant improvement in OS in patients age > 65 years treated with lenvatinib compared with placebo (not estimable [NE] vs 18.4 months, respectively; HR, 0.53; 95% CI, 0.31 to 0.91; $P = 0.020$). Within age group analysis of patients treated with lenvatinib, the OS was not significantly different between either age groups (HR, 0.78; 95% CI, 0.49 to 1.26; $P = 0.30$). In patients that received placebo, patients > 65 years had shorter OS compared with patients ≤ 65 years (median OS 18.4 months vs NE, respectively; HR, 0.48; 95% CI, 0.27 to 0.85; $P = .010$) (Brose 2017).

FDA Clearance: On February 13, 2015, the Food and Drug Administration (FDA) approved Lenvima (*lenvatinib*) capsules for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

Rationale: To our knowledge, these data represent the first time that a kinase inhibitor used for the treatment of advanced RR-DTC has demonstrated improvement in OS in a prespecified analysis (Brose 2017). The efficacy and safety of lenvatinib was established in the SELECT trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled trial which included patients ($n=392$) with locally recurrent or metastatic RAI-R DTC and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. This trial met its primary outcome measure of progression-free survival (PFS) in which patients treated with lenvatinib had a statistically significant prolonged mPFS of 18.3 months compared with a mPFS of 3.6 months in patients receiving placebo (HR, 0.21; 99% CI, 0.14 to 0.31; $P < 0.001$). Adverse events incidence and severity were higher and more severe with lenvatinib and most were managed with dose interruptions, modifications, discontinuations and appropriate medical therapy. The most common adverse reactions ($\geq 30\%$) for lenvatinib are hypertension, fatigue, diarrhea, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome,



abdominal pain, and dysphonia. (Lenvima Full Prescribing Information 2017, Schlumberger 2015)

Prespecified subanalyses of the SELECT trial evaluated the effect of age on the efficacy, safety, and tolerability of lenvatinib treatment in patients age ≤ 65 years vs patients age > 65 years. (Brose et al. 2017)

- The primary endpoint of this subanalysis was PFS in which benefit was maintained with lenvatinib vs placebo, mPFS was 20.2 vs 3.2 months (HR, 0.19; 95% CI, 0.13 to 0.27; $P < 0.001$) in patients age ≤ 65 years and 16.7 vs 3.7 months (HR, 0.53; 95% CI, 0.17 to 0.43; $P < 0.001$) in patients > 65 years, respectively. Secondary endpoints included objective response rate (ORR), OS, and safety.
- ORR was improved in lenvatinib-treated patients age ≤ 65 years (Odds Ratio [OR], 45.7; 95% CI, 14.8 to 141.0; $P < 0.001$) vs lenvatinib-treated patients age > 65 years (OR, 16.8; 95% CI, 4.7 to 60.0; $P < 0.001$) compared with placebo regardless of age. (Brose 2017)

Significant improvement in OS was observed in patients age > 65 years treated with lenvatinib compared with placebo (HR, 0.53; 95% CI, 0.31 to 0.91; $P = 0.020$). In addition, OS was not significantly different between age groups in patients treated with lenvatinib (HR, 0.78; 95% CI, 0.49 to 1.26; $P = 0.30$), while a statistically significant improvement in OS was observed in patients age ≤ 65 years vs patients age > 65 years in patients that received placebo (HR, 0.48, 95% CI, 0.27 to 0.85; $P = 0.010$). When age was analyzed as a continuous variable, a significant correlation between age and shorter OS was observed in patients that received placebo ($P = 0.18$) but not in patients treated with lenvatinib ($P = 0.82$). These data support the finding that age is considered an important prognostic factor for thyroid cancer mortality. Exploratory analyses examining patient baseline characteristics and post-study interventions did not identify any confounding factors that could potentially explain the improvement in OS in older patients who received lenvatinib.

Dose modifications and study drug discontinuation occurred more frequently in patients age > 65 years vs patients age ≤ 65 years and these patients were more likely to experience grade ≥ 3 treatment-related AEs (88.7% vs 67.1%), including hypertension and proteinuria. Serious and fatal AEs were similar in both age groups treated with lenvatinib.

I have attached the following references for your review.

1. LENVIMA (lenvatinib) [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2017.
2. Brose MS, Worden FP, Newbold KL, Guo M, Hurria A.. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial. *J Clin Oncol*. 2017.
3. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-630.

Sincerely,

Unice-Anne Flores, PharmD
Sr. Specialist, Medical Education
Medical Affairs, Eisai Inc.