No.16-63

September 15, 2016
Eisai Co., Ltd.

EISAI RECEIVES LICENSE FOR NEW INDICATION FOR ANTICANCER AGENT KISPLYX® ▼ (LENVATINIB MESYLATE) FOR TREATMENT OF ADVANCED RENAL CELL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced that its European regional headquarters Eisai Europe Ltd. (Location: U.K.) has received license from the European Commission for anticancer agent Kisplyx® ▼ (generic name: lenvatinib mesylate, "lenvatinib") in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF) targeted therapy. Following the United States, Europe marks the second region where lenvatinib has been licensed for the advanced renal cell carcinoma indication.

This license was based on a Phase II clinical study (Study 205)[1] that evaluated the safety and efficacy of lenvatinib in combination with everolimus in patients with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy. From the results of the study, the lenvatinib plus everolimus group (n=51) demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group (n=50) (median PFS for the lenvatinib plus everolimus group: 14.6 months vs median PFS for the everolimus alone group: 5.5 months; Hazard Ratio (HR) 0.40 [95% CI: 0.24-0.68], p=0.0005). Furthermore, updated median overall survival in the study population was 25.5 months in the lenvatinib plus everolimus group compared with 15.4 months in the everolimus alone group (HR 0.59 [95% CI: 0.36-0.97]).[2] The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher (Common Terminology Criteria for Adverse Events) were diarrhea, hypertension and fatigue.

The number of patients with renal cancer is estimated to be approximately 338,000 worldwide, including approximately 115,000 in Europe, 58,000 in the United States and 17,000 in Japan.[3] Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,[4] and originates from malignant cells in the lining of the tubules of the kidney. The incidence of renal cell carcinoma in people over 55 years of age is rising, and it is more likely to affect men than women. For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

In Europe, lenvatinib has been designated as an orphan drug for thyroid cancer and is marketed as Lenvima® for this indication. In Europe, renal cell carcinoma does not meet the criteria for orphan drug designation. Accordingly, under European regulations, any licensed medicine that previously received orphan drug designation for an indication and subsequently receives license for a non-orphan indication must be marketed under a different trade name. As such, lenvatinib will be marketed as Kisplyx® ▼ in the European Union for the indication covering renal cell carcinoma.

Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. Eisai remains committed to providing further clinical evidence for lenvatinib aimed at maximizing value of the drug as it seeks to contribute further to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families, and healthcare providers.

*Please refer to the following notes for the licensed indications in the United States, Japan and Europe

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[Notes to editors]

1. About lenvatinib mesylate (generic name, "lenvatinib")

Discovered and developed in-house, lenvatinib is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFRα; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained license for lenvatinib as a treatment for refractory thyroid cancer in over 45 countries including in the United States, Japan, in Europe, Korea, Canada, and Mexico, and has submitted applications for regulatory review in countries throughout the world including South Africa and Malaysia. Specifically, Eisai has obtained license for the agent indicated in the United States for treatment for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, in Japan for the treatment of unresectable thyroid cancer, and in Europe for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine, respectively.

Furthermore, lenvatinib was also licensed in the United States in May 2016 for an additional indication in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy.

Meanwhile, Eisai is conducting clinical studies of lenvatinib in several other tumor types such as hepatocellular carcinoma (Phase III), endometrial carcinoma (Phase II), biliary tract cancer (Phase II), and in combination with an immune checkpoint inhibitor for various types of cancer (Phase Ib/II).

Lenvatinib is marketed globally for use in the treatment of thyroid cancer and also in the United States for use in the treatment of renal cell carcinoma under the brand name Lenvima. Lenvatinib has been designated as an orphan drug for thyroid cancer by the regulatory authorities in Japan, the United States and Europe. Under European regulations, any licensed medicine that previously received orphan drug designation for an indication and now received license for a non-orphan indication must be marketed under a different trade name. As such, lenvatinib will be marketed as Kisplyx® ▼ in the European Union for the indication covering renal cell carcinoma.

2. About the Phase II Clinical Study (Study 205)[1]

Study 205 was a multicenter, randomized, open-label study of the combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg), and everolimus alone (10 mg) in patients with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy, and was conducted in Europe and the United States. 153 patients were randomized in a 1:1:1 ratio to one of three treatment arms to compare the efficacy and safety of these three regimens.

From the results of the study, the combination of lenvatinib plus everolimus group demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group (median PFS for the lenvatinib plus everolimus group: 14.6 months vs median PFS for the everolimus alone group: 5.5 months; Hazard Ratio (HR) 0.40 [95% CI: 0.24-0.68], p=0.0005). Additionally, median PFS for the lenvatinib alone group was 7.4 months, demonstrating an extension in PFS compared to the everolimus alone group (HR: 0.61 [95% CI: 0.38-0.98]).

The study also assessed objective response rate (ORR) and overall survival (OS) as secondary endpoints. Regarding ORR, both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in ORR compared to the everolimus alone group (lenvatinib plus everolimus: 43%, lenvatinib alone: 27%, everolimus alone: 6%). Furthermore, regarding OS, updated median overall survival in the study population was 25.5 months in the lenvatinib plus everolimus group compared with 15.4 months in the everolimus group (HR 0.59; 95% CI 0.36 - 0.97). [2]

The most common any-grade treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher (Common Terminology Criteria for Adverse Events) were diarrhea, hypertension and fatigue.

1 Motzer, R, et al. "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial." *The Lancet Oncology*, 2015; 16, 1473-1482.

2 Kisplyx Summary of Product Characteristics (SmPC), September 2016

3 Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, http://globocan.iarc.fr/
Motzer, R, et al. "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial." *The Lancet Oncology*, 2015; 16, 1473-1482.

4 Eble J.N, ed. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. 3rd ed. *World Health Organization Classification of Tumours*, vol.7 (IARC, 2004).