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Eisai Co., Ltd.

## **GERMAN FEDERAL JOINT COMMITTEE (G-BA) CONFIRMS ADDITIONAL BENEFIT OF ANTICANCER AGENT KISPLYX® (LENVATINIB MESYLATE) IN TREATMENT OF ADVANCED RENAL CELL CARCINOMA**

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the German Federal Joint Committee (G-BA) has confirmed the additional benefit of in-house developed anticancer agent Kisplyx® (lenvatinib mesylate) in combination with everolimus for the treatment of advanced renal cell carcinoma (RCC) compared to everolimus alone in its assessment for insurance reimbursement. Based on this additional benefit assessment, price negotiations with the Head Association of German Sick Funds (GKV-SV) will be conducted, and a reimbursement price has to be agreed.

The G-BA's assessment was based on a Phase II clinical study (Study 205)<sup>1</sup> that evaluated the safety and efficacy of Kisplyx in combination with everolimus in patients with unresectable advanced or metastatic RCC following one prior vascular endothelial growth factor (VEGF) targeted therapy. From the results of the study, the Kisplyx plus everolimus group demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group. Furthermore, the Kisplyx plus everolimus group demonstrated an extension in median overall survival (OS) compared to the everolimus alone group.<sup>2</sup>

The most common treatment-emergent adverse events (TEAEs) reported in the Kisplyx 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 115,000 in Europe in 2012.<sup>3</sup> Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,<sup>4</sup> 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 RCC that is difficult to treat with surgery, the standard treatment is molecular targeted drug therapy. However, with low 5-year survival rates, RCC remains a disease with a significant unmet medical need.

In Europe, lenvatinib mesylate has been designated as an orphan drug for thyroid cancer and is marketed as Lenvima® for this indication.

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 expanding access to Kisplyx and 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.

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## **[Notes to editors]**

### **1. Glossary of Terms**

#### **1) German Federal Joint Committee (G-BA)**

The German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany. It issues directives for the benefit catalog of statutory health insurance funds (GKV) and thus specifies which drugs and medical services are reimbursed by the GKV.

#### **2) About additional benefit assessment conducted by the G-BA**

In Germany, the enactment of the Act on the Reform of the Market for Medical Products (Arzneimittelmarkt-Neuordnungsgesetz, AMNOG) came into effect on January 2011. Under this amendment, all eligible new drugs launched on the German market must undergo an additional benefit assessment conducted by the G-BA, with later price negotiations to be based on this assessment, and a reimbursement price to be agreed upon within one year from the drug's launch.

Furthermore, when a new drug is launched, the pharmaceutical company must submit to the G-BA a benefit dossier demonstrating the drug's additional benefit over a comparator. The G-BA then usually commissions the country's Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: IQWiG) to evaluate the dossier to decide whether any additional benefit exists over the comparator. The pharmaceutical company is next given an opportunity to comment on the IQWiG's evaluation, after which the G-BA carries out its final decision regarding any additional benefit of the drug.

If an additional benefit is recognized by the G-BA, the drug proceeds to the price negotiation stage with the lead association of the German sick funds (GKV-Spitzenverbandes: GKV-SV), and a reimbursement price has to be agreed upon based on the level of additional benefit as decided by the G-BA. On the other hand, if a drug is deemed to offer no recognized additional benefit or if the additional benefit cannot be proven, the drug is designated a reference price group as well as a reimbursement price based on the price of the comparator used during the benefit assessment.

### **2. About lenvatinib mesylate (brand names: Lenvima, Kisplyx, "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 PDGFR $\alpha$ ; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained approval for lenvatinib as a treatment for refractory thyroid cancer in over 50 countries including in the United States, Japan, in Europe, Korea, Mexico, and Brazil. Specifically, Eisai has obtained approval for the agent indicated in the United States for the treatment of 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.

Lenvatinib was also approved 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 (RCC) following one prior anti-angiogenic therapy. Furthermore, lenvatinib was approved in combination with everolimus for the treatment of adult patients with advanced RCC following one prior VEGF-targeted therapy in Europe in August 2016.

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.

Furthermore, Eisai is currently preparing global submissions for lenvatinib in the treatment of unresectable hepatocellular carcinoma (HCC). In addition, Eisai is currently conducting several clinical trials, including a Phase III clinical study of lenvatinib in combinations with both pembrolizumab and everolimus in RCC (first-line therapy), a Phase II clinical study in biliary tract cancer, and in combination with pembrolizumab for various types of cancer (Phase Ib/II).

### **3. About the Phase II Clinical Study (Study 205) <sup>1</sup>**

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%). Additionally, regarding OS, an updated analysis carried out in December 2014 suggested that lenvatinib plus everolimus extends OS compared to everolimus alone (HR 0.51 [95% CI=0.30-0.88]).

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]). <sup>2</sup>

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.

<sup>1</sup> Robert Motzer, 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

<sup>2</sup> Kisplyx Summary of Product Characteristics (SmPC), September 2016.

<sup>3</sup> Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, <http://globocan.iarc.fr/>

<sup>4</sup> 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)