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Eisai Co., Ltd.

EISAI SIGNS AGREEMENT WITH MERCK & CO., INC., KENILWORTH, NJ, USA TO EXPAND ENROLLMENT OF COMBINATION STUDY FOR LENVIMA® (LENVATINIB) AND PEMBROLIZUMAB DUE TO ENCOURAGING INITIAL DATA IN ENDOMETRIAL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that it has signed an agreement with Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside of the United States and Canada) to increase the target number of endometrial carcinoma patients to be enrolled in a Phase Ib/II clinical study of its in-house discovered and developed multi-kinase inhibitor lenvatinib mesylate (product names: Lenvima® / Kisplyx®, "lenvatinib") in combination with anti-PD-1 therapy pembrolizumab (brand name: KEYTRUDA®), developed by Merck & Co., Inc., Kenilworth, NJ, USA, due to encouraging initial data.

The decision to expand the target number of enrolled patients is based on favourable interim analysis results of the endometrial cohort in a Phase Ib/II study (Study 111) of lenvatinib in combination with pembrolizumab for multiple solid cancers, which is being jointly conducted by Eisai and Merck & Co., Inc., Kenilworth, NJ, USA. The interim analysis (n = 23)[1] results indicated an objective response rate* to the combination therapy at 24 weeks of 52.2% (95% CI = 30.6 – 73.2) based on independent radiologic review and 47.8% (95% CI = 26.8 - 69.4) based on investigator review. Additionally, tumor regression was observed regardless of the state of microsatellite instability. In this study, the most frequently observed adverse events (Top 5) were hypertension, fatigue, arthralgia, diarrhea, and nausea. Based on the results of the interim analysis of Study 111, the target number of enrolled endometrial carcinoma patients will be increased to approximately 100. Patient enrollment is already underway.

Endometrial carcinoma is the sixth most common cancer in women worldwide, with 320,000 new cases diagnosed in 2012.[2] In the United States, it is estimated that there will be 60,000 new cases and 10,000 deaths by endometrial carcinoma in 2017.[3] There currently is no drug approved in 2nd line and this is where the unmet need lies.

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 creating new treatments for cancers with high unmet medical needs such as endometrial carcinoma, 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.

*Objective Response Rate: The ratio of patients whose cancer regressed at least a 30% decrease (Partial Response) or disappeared (Complete Response) after treatment.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

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[Notes to editors]

1. About lenvatinib mesylate (generic name, "lenvatinib", product name: Lenvima / Kisplyx)

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 approval for lenvatinib as a treatment for refractory thyroid cancer in over 50 countries, including the United States, Japan, and in Europe, under the brand name Lenvima. Additionally, Eisai has obtained approval for the agent in combination with everolimus as a treatment for renal cell carcinoma (second-line) in over 35 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx for renal cell carcinoma.

Furthermore, in a Phase III clinical study (Study 304) comparing safety and efficacy of the agent versus the comparator sorafenib for the treatment of hepatocellular carcinoma, the agent achieved its primary endpoint of overall survival, meeting the statistical criteria for non-inferiority to sorabenib. Following the submission of applications in Japan (June 2017), the United States and Europe (July 2017), Eisai also plans to submit an application for lenvatinib for the treatment of hepatocellular carcinoma in China within the latter half of fiscal 2017.

2. About Phase Ib/II clinical study (Study 111) of lenvatinib in combination with pembrolizumab

Study 111 is a multicenter, open-label Phase Ib/II clinical study to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab. The primary endpoint of the Phase Ib part was to determine the maximum tolerated dose. Thirteen patients with unresectable solid tumors (non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, head and neck cancer, and melanoma) who had progressed after treatment with approved therapies or for which there are no standard effective therapies available were administered 24 mg (3 patients) or 20 mg (10 patients) of lenvatinib orally daily, as well as 200 mg of pembrolizumab intravenously every three weeks. The Phase II part was conducted on patients with select solid tumors who had previously undergone less than 2 chemotherapy regimens, with a recommended dosage of 20 mg of lenvatinib daily and 200 mg of pembrolizumab every three weeks as determined based on the results of the Phase Ib part. The primary endpoint of the Phase 2 part was objective response rate, with disease control rate, clinical benefit rate, progression-free survival, and duration of response measured as secondary endpoints. Currently, the Phase II part is ongoing in the United States.

In addition, Phase Ib clinical studies of lenvatinib in combination with pembrolizumab for the treatment of select solid tumors (Study 115) and hepatocellular carcinoma (Study 116) are ongoing in Japan.

3. About research on mechanisms of action in combination of lenvatinib and anti-PD-1 antibody [4]

In a non-clinical study where mouse models were inoculated with mouse liver cancer, melanoma or colon cancer cell lines and treated with a combination of lenvatinib with an anti-mouse PD-1 antibody, synergistic anti-tumor activity was demonstrated, based on an immunostimulatory response due to the reduction in tumor associated macrophages and the enhancement of the ratio of memory T cells by lenvatnib.

4. About Microsatellite Instability

When DNA replicates, there are often errors in the base sequence of DNA (mismatches). If there is a defect in the ability to repair these mismatches, the damaged DNA results in cells becoming cancerous. Microsatellites are short repeated sequences of DNA in which mismatches are very likely to occur, causing mistakes in the number of iterations. This inability to repair mismatches in the microsatellites is known as microsatellite instability (MSI). Anti-PD-1 antibodies are generally more effective in patients with a high frequency of MSI and less effective in other patients.[5]

[1] Makker V, et al. A phase Ib/II trial of lenvatinib (LEN) plus pembrolizumab (Pembro) in patients (Pts) with endometrial carcinoma. *ASCO Meeting Abstract*, 2017; #5598

[2] World Cancer Research Found International: http://www.wcrf.org/

[3] National Cancer Institute、Cancer Stat Facts: https://seer.cancer.gov/statfacts/html/corp.html

[4] Kato Y, et al. Upregulation of memory T cell population and enhancement of Th1 response by lenvatinib potentiate anti-tumor activity of PD-1 signaling blockade : Lenvatineb and PD-1 mAb combination. *AACR Meeting Abstract*, 2017; #4614

[5] Dung T. Le. et al, PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, *The New England Journal of Medicine* 372:2509-2520, 2015.