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Eisai Co., Ltd.

EISAI TO PRESENT RESULTS OF PHASE Ib/II STUDY OF ANTICANCER AGENT LENVIMA® (LENVATINIB) IN COMBINATION WITH ANTI-PD-1 ANTIBODY PEMBROLIZUMAB FOR THE TREATMENT OF ENDOMETRIAL CARCINOMA AT 53RD ASCO ANNUAL MEETING

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced the first results for metastatic endometrial carcinoma obtained from a Phase Ib/II study (Study 111) of its in-house developed multi-kinase inhibitor lenvatinib mesylate (product names: Lenvima® / Kisplyx®, "lenvatinib") in combination with the MSD (known as Merck & Co., Inc, Kenilworth, NJ, USA in the United States and Canada) anti-PD-1 antibody pembrolizumab (brand name: KEYTRUDA®*), during a presentation at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO), taking place in Chicago, the United States. The two companies are collaborating to develop this combination therapy. Study 111 is being conducted to evaluate the activity of the lenvatinib/pembrolizumab combination in select solid tumors.

The presentation covers an analysis of a combined total of 23 endometrial carcinoma patients over both the Phase Ib and Phase II parts of the study, who had previously undergone at least one chemotherapy regimen. After being treated with a combination of lenvatinib and pembrolizumab, the results of the analysis showed the primary endpoint of objective response rate was 52.2% (95% Confidence Interval [CI] = 30.6 – 73.2) based on an independent radiologic review (IRR) and 47.8% (95% CI: 26.8 – 69.4) by investigator review.
The secondary endpoints of clinical benefit rate** were 65.2% (95% CI: 42.7 – 83.6) by IRR and 73.9% (95% CI: 51.6 – 89.8) by investigator review. Disease control rate*** were 91.3% (95% CI: 72.0 – 98.9) by IRR and 95.7% (95% CI: 78.1 – 99.9) by investigator review. Median progression-free survival was 9.7 months (95% CI: 4.2 – NE) based on investigator assessment and was not reached by IRR. Median duration of response was not reached at the time of analysis.
Anti-PD-1 antibodies are generally more effective in patients with a high frequency of microsatellite instability (MSI), a biomarker that results in dysfunctional DNA mismatch repair, and less effective in other patients.[1] However, in this study, the combination therapy resulted in tumor response regardless of the state of their MSI.
The most frequently observed adverse events for the combination regimen (Top 5) were hypertension, fatigue, arthralgia, diarrhea, and nausea.

Endometrial cancer 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 approximately 60,000 women will be newly diagnosed with endometrial cancer, and approximately 10,000 women will die from the disease in 2017.[3] Therefore, this remains a disease with significant unmet medical needs and necessitates the development of new treatments.

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 generating scientific evidence aimed at maximizing the value of lenvatinib 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.

* KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Kenilworth, NJ, USA.
** Clinical benefit rate: Percentage of patients who had complete response, partial response, or maintained disease stability for 23 weeks or longer.
*** Disease control rate: Percentage of patients who had complete response, partial response, or maintained disease stability for 5 weeks or longer.

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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 50 countries, including the United States, Japan, and in Europe. Additionally, Eisai has obtained approval for lenvatinib in combination with everolimus in the United States, Europe, and other countries, as a treatment for renal cell carcinoma (second-line). In Europe, lenvatinib was launched under the brand name Kisplyx® for this indication.

A Phase III study of lenvatinib in separate combinations with everolimus and pembrolizumab in renal cell carcinoma (first-line) was initiated and is underway. A Phase Ib/II study to investigate the agent in combination with pembrolizumab in select solid tumors (non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, head and neck cancer, and melanoma) is underway. Additionally, a Phase Ib study of the agent in hepatocellular carcinoma is also underway.

2. About Study 111

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, a Phase Ib clinical trial (Study 115) of lenvatinib in combination with pembrolizumab for the treatment of select solid tumors is ongoing in Japan.

3. About research data on mechanisms of action in combination of lenvatinib and anti-PD-1 antibody (Presented at AACR 108th Annual Meeting)[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.

[1] Dung T. Le. et al, PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, *The New England Journal of Medicine* 72:2509-2520, 2015.

[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.