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Eisai Co., Ltd.

EISAI PRESENTS DATA OF MECHANISMS OF ACTION RELATING TO TUMOR IMMUNE RESPONSE REGARDING COMBINATION OF ANTICANCER AGENT LENVATINIB WITH ANTI-PD-1 ANTIBODY AT AACR 108TH ANNUAL MEETING

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has presented the latest research data regarding a mechanism of action that led to increased anti-tumor activity in mouse models which had been dosed with a combination of the in-house developed anticancer agent lenvatinib mesylate (lenvatinib) and an anti-mouse PD-1 antibody, at the American Association for Cancer Research (AACR) 108th Annual Meeting.

The results presented at the AACR meeting¹ showed that when syngeneic model mice inoculated with mouse liver cancer, melanoma or colon cancer cell lines were dosed with a combination of lenvatinib (10 mg/kg, once daily) and an anti-mouse PD-1 antibody (500 µg/mouse, twice a week), lenvatinib alone or an anti-mouse PD-1 antibody alone, a substantial inhibitory effect on tumor growth was observed in mice that had been dosed with the combination therapy compared to the single treatments.

Additionally, an increased number of mice in the combination therapy group showed Complete Response (CR) of tumor compared to the single treatment group. Specifically, in the combination therapy group, 7 out of 30 mice showed CR (colon cancer models: 2/10, melanoma models: 2/10, liver cancer models: 3/10), whereas in each single treatment group, 1 out of 30 mice showed CR (colon cancer models: 1/10, melanoma models: 0/10, liver cancer models: 0/10).

Furthermore, in the liver cancer mouse model, even when identical cancer cell lines were re-inoculated into mice with complete tumor remission, no *in vivo* growth was observed.

RNA analysis of the cancer tissue and other tests confirmed a reduction in immunosuppressive tumor associated macrophages, a reduction in immunosuppressive signal receptors, and an increase in the ratio of memory T cells in model mice dosed with lenvatinib.

This non-clinical research suggested synergistic anti-tumor activity when combining lenvatinib with an anti-mouse PD-1 antibody in the mouse models, based on an immunostimulatory response due to the reduction in tumor associated macrophages and the enhancement of the ratio of memory T cells by lenvatinib.

Eisai has positioned oncology as a key therapeutic area of focus and remains committed to providing further evidence for 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.

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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 PDGFR α ; 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, and is undergoing regulatory review in other countries including South Africa and Indonesia. Specifically, Eisai has obtained approval for the agent 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 vascular endothelial growth factor (VEGF) targeted therapy in Europe in August 2016. Lenvatinib has been launched in Europe under the brand name Kisplyx® for this indication.

Additionally, in January 2017, a Phase III clinical trial of lenvatinib as a first-line treatment for patients with unresectable hepatocellular carcinoma has achieved its primary endpoint.

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

2. About memory T cells

After being activated by an antigen presented on cancer cells or infected cells, CTL (cytotoxic T lymphocyte) cells turn into effector T cells, which can attack and eliminate the antigen. Afterwards, the majority of the effector T cells will die, but a portion of them remain in the body as memory T cells, which retain the “experience” of fighting off cancer cells or infection. If the same cancer cells or infection appear again, they will once again become effector T cells, and attack the invader with high efficiency.

¹ 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: Lenvatinib and PD-1 mAb combination. *AACR Meeting Abstract*, 2017; #4614