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Eisai Co., Ltd.

EUROPEAN MEDICINES AGENCY ACCEPTS THE MARKETING AUTHORISATION APPLICATIONS FOR TWO ADDITIONAL INDICATIONS OF ANTI CANCER AGENT LENVATINIB IN COMBINATION WITH PEMBROLIZUMAB AS A TREATMENT FOR ADVANCED RENAL CELL CARCINOMA AND ADVANCED ENDOMETRIAL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the European Medicines Agency (EMA) has confirmed it has accepted for review applications for the use of its in-house discovered multiple receptor tyrosine kinase inhibitor, lenvatinib mesylate (product name: LENVIMA® / Kisplyx®, "lenvatinib"), in combination with anti-PD-1 therapy pembrolizumab (brand name: KEYTRUDA®), developed by Merck & Co., Inc., Kenilworth, N.J., U.S.A., (known as MSD outside the United States and Canada) as a treatment f or patients with advanced renal cell carcinoma (RCC) and advanced endometrial carcinoma (EC), respectively.

The application requesting an indication of lenvatinib in combination with pembrolizumab for RCC is based on the results of the pivotal Phase 3 CLEAR study (Study 307/KEYNOTE-581) for the first-line treatment of patients with advanced RCC, which were presented at 2021 Genitourinary Cancers Symposium (ASCO GU), and simultaneously published in *the New England Journal of Medicine* in February 2021. In this trial, lenvatinib plus pembrolizumab demonstrated statistically significant and clinically meaningful improvements in the primary endpoint of progression-free survival (PFS) as well as key secondary endpoints of overall survival (OS) and objective response rate (ORR) versus sunitinib.

In addition, the application requesting an indication of lenvatinib in combination with pembrolizumab for EC is based on the results of the pivotal Phase 3 Study 309/KEYNOTE-775 for the treatment of patients with advanced endometrial carcinoma, following one prior platinum-based regimen in any setting, which were presented at the Society of Gynecologic Oncology (SGO) 2021 Annual Meeting on Women's Cancer in March 2021. In this trial, lenvatinib plus pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in the primary endpoints of PFS and OS as well as the secondary endpoint of ORR versus chemotherapy (treatment of physician's choice of doxorubicin or paclitaxel).

The safety profile of the lenvatinib plus pembrolizumab combination in these studies was generally consistent with previously reported studies.

Worldwide, it is estimated that there were more than 430,000 new cases of kidney cancer diagnosed and nearly 180,000 deaths from the disease in 2020.[1] In Europe, there were more than 138,000 new cases and more than 54,000 deaths in 2020.[1] RCC is by far the most common type of kidney cancer; about nine out of 10 kidney cancers are RCC.[2] Approximately 30% of patients with RCC will have metastatic disease at diagnosis, and as many as 40% will develop metastases after primary surgical treatment for localized RCC.[3,4]

In 2020, it is estimated there were more than 417,000 new cases of uterine body cancer diagnosed worldwide and nearly 97,000 deaths from the disease.[5] In Europe, there were more than 130,000 new cases and more than 29,000 deaths in 2020.[5] EC is the most common type of uterine body cancer. It is considered that more than 90% of uterine body cancers occur in the endometrium.[6]
Survival rates vary highly depending on the stage of diagnosis, and the five-year survival rates for metastatic RCC and metastatic EC are 12% and 17%, respectively. Both diseases have poor prognoses.

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A., through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of lenvatinib, both as monotherapy and in combination with the anti-PD-1 therapy pembrolizumab from Merck & Co., Inc., Kenilworth, N.J., U.S.A.

Eisai positions oncology as a key therapeutic area and is aiming to discover innovative new medicines with the potential to cure cancer. Eisai is committed to expanding the potential clinical benefits of lenvatinib for cancer treatment, as it seeks to contribute to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families and healthcare professionals.

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[Notes to editors]

1. About lenvatinib mesylate (product name: LENVIMA / Kisplyx)

Lenvatinib, discovered and developed by Eisai, is an orally available kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.
In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.
Currently, lenvatinib has been approved for monotherapy as a treatment for thyroid cancer in over 70 countries including Japan, in Europe, China and in Asia, and the United States for radioiodine-refractory differentiated thyroid cancer. In addition, lenvatinib has been approved for monotherapy as a treatment for unresectable hepatocellular carcinoma in over 65 countries including Japan, the United States, in Europe, China and in Asia. It is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including the United States, in Europe and Asia. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. In addition, it is approved in combination with pembrolizumab as a treatment for endometrial cancer that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation in over 10 countries including the United States, Canada and Australia. Continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials. Lenvima has also been approved for monotherapy as a treatment for unresectable thymic carcinoma in Japan.

2. About the CLEAR Study (Study 307/KEYNOTE-581)

The CLEAR Study (Study 307/KEYNOTE-581) is a Phase 3, multi-center, randomized, open-label trial (ClinicalTrials.gov, NCT02811861) evaluating lenvatinib in combination with pembrolizumab or in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced RCC. The primary endpoint is PFS by independent review per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key secondary endpoints include OS, ORR and safety. A total of 1,069 patients were randomized to one of three treatment arms to receive lenvatinib (20 mg orally once daily) in combination with pembrolizumab (200 mg intravenously every three weeks); or lenvatinib (18 mg orally once daily) in combination with everolimus (5 mg orally once daily); or sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment).

In the trial's primary endpoint of PFS, as assessed by independent review per RECIST v1.1, lenvatinib plus pembrolizumab reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI: 0.32-0.49]; p<0.001), with a median PFS of 23.9 months (95% CI: 20.8-27.7) versus 9.2 months (95% CI: 6.0-11.0) for patients who received sunitinib. In the trial's key secondary endpoints, lenvatinib plus pembrolizumab reduced the risk of death by 34% (HR=0.66 [95% CI: 0.49-0.88]; p=0.005) versus patients who received sunitinib. Median OS was not reached in either treatment arm after a median follow-up of 27 months. Treatment with lenvatinib plus pembrolizumab resulted in an ORR of 71.0% (95% CI: 66.3-75.7), with a complete response (CR) rate of 16.1% and a partial response (PR) rate of 54.9%, versus an ORR of 36.1% (95% CI: 31.2-41.1), with a CR rate of 4.2% and a PR rate of 31.9%, for patients who received sunitinib (relative risk=1.97 [95% CI: 1.69-2.29]). Median duration of response (DOR) for patients who received lenvatinib plus pembrolizumab was 25.8 months (95% CI: 22.1-27.9) versus 14.6 months (95% CI: 9.4-16.7) for patients who received sunitinib.

In the lenvatinib plus pembrolizumab arm, treatment-related adverse events (TRAEs) led to discontinuation of lenvatinib in 18.5% of patients, of pembrolizumab in 25.0% of patients, and of both in 9.7% of patients. In the sunitinib arm, TRAEs led to discontinuation of sunitinib in 10.0% of patients. Grade 5 TRAEs occurred in 1.1% of patients in the lenvatinib plus pembrolizumab arm versus 0.3% of patients in the sunitinib arm. Grade ≥3 TRAEs occurred in 71.6% of patients in the lenvatinib plus pembrolizumab arm versus 58.8% of patients in the sunitinib arm. The most common TRAEs of any grade occurring in at least 20% of patients in the lenvatinib plus pembrolizumab arm were diarrhea (54.5%), hypertension (52.3%), hypothyroidism (42.6%), decreased appetite (34.9%), fatigue (32.1%) and stomatitis (32.1%). In the sunitinib arm, the most common TRAEs of any grade occurring in at least 20% of patients were diarrhea (44.4%), hypertension (39.1%), stomatitis (37.4%), hand-foot syndrome (35.9%), fatigue (32.1%) and nausea (27.6%).

3. About Study 309/KEYNOTE-775

Study 309/KEYNOTE-775 is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, NCT03517449) evaluating lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer following one prior platinum-based regimen in any setting. The dual primary endpoints are PFS, as assessed by blinded independent central review (BICR) per RECIST v1.1, and OS. Select secondary endpoints include ORR by BICR per RECIST v1.1 and safety/tolerability. Of the 827 patients enrolled, 697 patients had tumors that were mismatch repair proficient (pMMR), and 130 patients had tumors that were mismatch repair deficient (dMMR). Patients were randomized 1:1 to receive lenvatinib (20 mg orally once daily) in combination with pembrolizumab (200 mg intravenously [IV] every three weeks) for up to 35 cycles (approximately two years); or chemotherapy treatment of physician's choice (TPC) of either doxorubicin 60 mg/m^2 IV every three weeks for up to a maximum cumulative dose of 500 mg/m^2 or paclitaxel 80 mg/m^2 IV on a 28-day cycle [three weeks of receiving weekly paclitaxel and one week of not receiving paclitaxel]).

The study met the dual primary endpoints of PFS, as assessed by BICR per RECIST v1.1, OS, as well as the secondary efficacy endpoint of ORR, as assessed by BICR per RECIST v1.1, in the all-comer population (pMMR and dMMR) and

in the pMMR subgroup. Median follow-up was 11.4 months for both the all-comer population and pMMR subgroup. A statistically significant and clinically meaningful improvement in PFS was seen in the all-comer population, in which lenvatinib plus pembrolizumab (n=411) reduced the risk of disease progression or death by 44% (HR=0.56 [95% CI: 0.47-0.66]; p<0.0001), with a median PFS of 7.2 months (95% CI: 5.7-7.6; number of events=281) versus 3.8 months (95% CI: 3.6-4.2; number of events=286) for patients who received TPC (n=416). Additionally, a statistically significant and clinically meaningful improvement in OS was seen in the all-comer population, in which lenvatinib plus pembrolizumab reduced the risk of death by 38% (HR=0.62 [95% CI: 0.51-0.75]; p<0.0001), with a median OS of 18.3 months (95% CI: 15.2-20.5; number of events=188) versus 11.4 months (95% CI: 10.5-12.9; number of events=245) for patients who received TPC. The safety profile of lenvatinib plus pembrolizumab was generally consistent with the established safety profiles of the individual monotherapies.

In the all-comer population, the secondary efficacy endpoint of ORR was 31.9% (95% CI: 27.4-36.6), with a CR rate of 6.6% and a PR rate of 25.3%, for patients who received lenvatinib plus pembrolizumab versus 14.7% (95% CI: 11.4-18.4), with a CR rate of 2.6% and a PR rate of 12.0% for patients who received TPC (ORR difference versus TPC: 17.2 percentage points; p<0.0001). For patients who responded, the median duration of response (DOR) was 14.4 months (range: 1.6-23.7) for patients who received lenvatinib plus pembrolizumab versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

Results were similar across the all-comer population and the pMMR subgroup. In the pMMR subgroup, lenvatinib plus pembrolizumab reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI: 0.50-0.72]; p<0.0001), with a median PFS of 6.6 months (95% CI: 5.6-7.4; number of events=247) versus 3.8 months (95% CI: 3.6-5.0; number of events=238) for patients who received TPC. Lenvatinib plus pembrolizumab reduced the risk of death by 32% (HR=0.68 [95% CI: 0.56-0.84]; p =0.0001), with a median OS of 17.4 months (95% CI: 14.2-19.9; number of events=165) versus 12.0 months (95% CI: 10.8-13.3; number of events=203) for patients who received TPC. The secondary endpoint of ORR was 30.3% (95% CI: 25.5-35.5), with a CR rate of 5.2% and a PR rate of 25.1%, for patients who received lenvatinib plus pembrolizumab versus 15.1% (95% CI: 11.5-19.3), with a CR rate of 2.6% and a PR rate of 12.5%, for patients who received TPC (ORR difference versus TPC: 15.2 percentage points: p<0.0001). For patients who responded, the median DOR was 9.2 months (range: 1.6-23.7) for patients who received lenvatinib plus pembrolizumab versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

In the all-comer population, in the lenvatinib plus pembrolizumab arm (n=406), any grade treatment-emergent adverse events (TEAEs) led to discontinuation of lenvatinib in 30.8% of patients, of pembrolizumab in 18.7% of patients, and of both in 14.0% of patients. In the TPC arm (n=388), any grade TEAEs led to discontinuation of chemotherapy in 8.0% of patients. Grade 5 TEAEs of any cause occurred in 5.7% of patients in the lenvatinib plus pembrolizumab arm and in 4.9% of patients in the TPC arm. Grade ≥3 TEAEs occurred in 88.9% of patients in the lenvatinib plus pembrolizumab arm and in 72.7% of patients in the TPC arm. In the lenvatinib plus pembrolizumab arm, the most common TEAEs of any grade occurring in at least 25% of patients were hypertension (64.0%), hypothyroidism (57.4%), diarrhea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decrease (34.0%), fatigue (33.0%), arthralgia (30.5%), proteinuria (28.8%), anemia (26.1%), constipation (25.9%), and urinary tract infection (25.6%). In the TPC arm, the most common TEAEs of any grade occurring in at least 25% of patients were anemia (48.7%), nausea (46.1%), neutropenia (33.8%), alopecia (30.9%), and fatigue (27.6%). Median treatment duration was 231 days (range: 1-817) with lenvatinib plus pembrolizumab and 104.5 days (range: 1-785) with TPC.

4. About the Merck & Co., Inc., Kenilworth, N.J., U.S.A. and Eisai Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A., known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of lenvatinib. Under the agreement, the companies will jointly develop, manufacture and

commercialize lenvatinib, both as a monotherapy and in combination with pembrolizumab, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A.

In addition to ongoing clinical studies evaluating the lenvatinib plus pembrolizumab combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in 14 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer, pancreatic cancer and triple-negative breast cancer) across more than 20 clinical trials.

5. Eisai's Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds, such as eribulin mesylate (product name: Halaven®) and Lenvatinib) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (*Ricchi*) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these *Ricchi*, with the aim of contributing to the cure of cancers.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A.

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