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Eisai Co., Ltd.

EISAI RECEIVES APPROVAL FOR NEW INDICATION FOR ANTICANCER AGENT HALAVEN® FOR TREATMENT OF ADVANCED LIPOSARCOMA IN EUROPE

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its European regional headquarters Eisai Europe Ltd. (Location: U.K.) has received from the European Commission approval for anticancer agent Halaven® (eribulin mesylate) for the treatment of adult patients with unresectable liposarcomas who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease. Halaven is the first and only single agent to demonstrate a statistically significant overall survival (OS) benefit in a Phase III trial in patients with advanced, recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma). Following approval for use in the treatment of metastatic breast cancer, this marks the second indication for which Halaven has received approval based on an extension of OS.

The approval was based on the results of a Phase III study (Study 309)[1] comparing the efficacy and safety of Halaven versus dacarbazine in 452 patients (aged 18 or over) with locally advanced, recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) who had disease progression following standard therapies which must have included an anthracycline and at least one other additional regimen. Halaven demonstrated a statistically significant extension in the study's primary endpoint of OS over the comparator treatment dacarbazine (Halaven median OS: 13.5 months vs dacarbazine median OS: 11.5 months; Hazard Ratio (HR) 0.77 [95% CI=0.62-0.95], p=0.0169). For patients with liposarcoma, Halaven demonstrated a significant improvement in OS over dacarbazine (Halaven, median OS: 15.6 months vs dacarbazine, median OS: 8.4 months; HR 0.51 [95% CI=0.35-0.75]).
In this study, the most common treatment-emergent adverse events (incidence greater than or equal to 25%) in patients treated with Halaven were fatigue, neutropenia, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia, which was consistent with the known side-effect profile of Halaven.

Halaven is a halichondrin class microtubule dynamics inhibitor with a distinct binding profile. Recent non-clinical studies showed that Halaven is associated with increased vascular perfusion and permeability in tumor cores.[2] Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.[3] Halaven is currently approved for use in the treatment of breast cancer in approximately 60 countries including Japan and countries in Europe, the Americas and Asia. Halaven was approved in the United States for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen in January 2016, and was approved in Japan for the treatment of soft tissue sarcoma in February 2016.

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissue (fat, muscle, nerves, fibrous tissues and blood vessels). Approximately 29,000 patients in Europe are diagnosed with soft tissue sarcoma each year or about 1% of all cancers diagnosed in Europe. Liposarcoma is one of the most common forms of soft tissue sarcoma. As outcomes are poor for patients with advanced disease, it remains a disease with significant unmet medical need.

Eisai remains committed to providing additional clinical evidence for Halaven aimed at 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. About Halaven

Halaven is the first in the halichondrin class of microtubule dynamics inhibitors with a novel mechanism of action. Structurally Halaven is a simplified and synthetically produced version of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Halaven is believed to work by inhibiting the growth phase of microtubule dynamics which prevents cell division. In addition, recent non-clinical studies showed that Halaven is associated with increased vascular perfusion and permeability in tumor cores.[2] Halaven promotes the epithelial state and decreases the capacity of breast cancer cells to migrate.[3]

Halaven was first approved in November 2010 in the United States as a treatment for patients with metastatic breast cancer who have received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. Halaven is currently approved for use in the treatment of breast cancer in approximately 60 countries worldwide, including Japan and countries in Europe, the Americas and Asia. In Japan, Halaven has been approved to treat inoperable or recurrent breast cancer and was launched in the country in July 2011. In addition, Halaven has been approved in countries in Europe and Asia indicated as a treatment for patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

Regarding soft tissue sarcoma, Halaven was approved in the United States for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen in January 2016, approved in Japan for the treatment of soft tissue sarcoma in February 2016, and approved in Europe for the treatment of adult patients with unresectable liposarcomas who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease in May 2016. Applications seeking approval for use in the treatment of soft tissue sarcoma are currently under review in Switzerland, Russia, Australia, Brazil, and Malaysia. Furthermore, Halaven has been designated as an orphan drug for soft-tissue sarcoma in the United States and Japan.

2. About Study 309[1]

Conducted primarily in Europe and the United States, Study 309 was a multicenter, open-label, randomized Phase III study comparing the efficacy and safety of Halaven versus dacarbazine in 452 patients (aged 18 or over) with locally advanced, recurrent or metastatic soft tissue sarcoma (liposarcoma or leiomyosarcoma) who had disease progression following standard therapies which must have included an anthracycline and at least one other additional regimen. Patients received either Halaven (1.4 mg/m^2 administered intravenously on Day 1 and Day 8) or dacarbazine (850–1200 mg/m^2 administered intravenously on Day 1) every 21 days until disease progression.

From the results for the study, Halaven demonstrated a statistically significant extension in the study's primary endpoint of overall survival (OS) over the comparator treatment dacarbazine (Halaven median OS: 13.5 months vs dacarbazine median OS: 11.5 months; Hazard Ratio (HR) 0.77 [95% CI=0.62-0.95], p=0.0169). Furthermore, in the study's secondary endpoints, there was no statistically significant difference found between Halaven and dacarbazine in either progression-free survival (PFS) (median PFS: 2.6 months in both arms) or progression-free rate at 12 weeks (PFR_{12wks}) (Halaven PFR_{12wks}: 33% vs dacarbazine PFR_{12wks}: 29%).

For patients with liposarcoma (143 patients), Halaven demonstrated a statistically significant improvement in OS over dacarbazine (Halaven, median OS: 15.6 months vs dacarbazine, median OS: 8.4 months; HR 0.51 [95% CI=0.35-0.75]).
In this study, the most common treatment-emergent adverse events (incidence greater than or equal to 25%) in patients treated with Halaven were fatigue, neutropenia, nausea, alopecia, constipation, peripheral neuropathy, abdominal pain, and pyrexia, which was consistent with the known side-effect profile of Halaven.

3. About Soft Tissue Sarcoma

Soft tissue sarcoma is a collective term for a diverse group of malignant tumors that occur throughout the soft tissue (including fat, muscle, nerves, fibrous tissues and blood vessels). Approximately 12,000 patients in the United States and 29,000 patients in Europe are diagnosed with soft tissue sarcoma each year. According to a patient survey conducted by Japan's Ministry of Health, Labour and Welfare, there are approximately 4,000 patients with soft tissue sarcoma in Japan. As the structures where the tumors originate are diverse, there are various types of soft tissue sarcoma, and the most common types include leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. While treatment of soft tissue sarcoma is focused on curative surgery, if the stage of the disease is advanced, treatment then becomes a combination of chemotherapy and radiation therapy. As outcomes are poor for patients with advanced disease, it remains a disease with significant unmet medical need.

[1] Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *The Lancet.* 2016; 387, 1629-1637.
[2] Funahashi Y et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. *Cancer Sci.,* 2014; 105, 1334-1342
[3] Yoshida T et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. *Br J Cancer,* 2014; 110, 1497-1505