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Eisai Co., Ltd.

INTERIM ANALYSIS OF PHASE Ib/II STUDY OF ERIBULIN AND PEMBROLIZUMAB COMBINATION REGIMEN IN METASTATIC TRIPLE NEGATIVE BREAST CANCER PRESENTED AT SAN ANTONIO BREAST CANCER SYMPOSIUM

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the results of an interim analysis of a Phase Ib/II clinical study (Study 218) of its in-house discovered and developed anticancer agent eribulin mesylate (halichondrin class microtubule dynamics inhibitor, product name: Halaven®, "eribulin") in combination with the anti-PD-1 antibody pembrolizumab developed by Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the U.S. and Canada), in patients with metastatic triple-negative breast cancer have been presented at the 39th Annual San Antonio Breast Cancer Symposium held from December 6 to 10, 2016. Development of this combination regimen is being conducted jointly under the cooperation of both companies.

Study 218 is a Phase Ib/II clinical study which examined the activity and safety of eribulin in combination with pembrolizumab in 95 patients with metastatic triple-negative breast cancer previously treated with 0 – 2 lines of chemotherapy in the metastatic setting. The primary objective of the Phase Ib part was safety and tolerability, and the primary objective of the Phase II part was objective response rate (ORR).

This presentation reported on the results of an interim analysis of 39 evaluable patients out of the 89 patients enrolled in the study as of July 2016. Eribulin (1.4 mg/m^2 intravenously on Day 1 and Day 8) and pembrolizumab (200 mg intravenously on Day 1) were administered to patients over 21 day cycles. From the results of the study, ORR was 33.3% (1 patient experienced a complete response and 12 patients experienced a partial response). In addition, the ORR was similar between PD-L1 positive and negative cohorts.

In this study, the most common treatment-emergent adverse events (incidence greater than or equal to 35%) in patients treated with the combination regimen were fatigue, nausea, peripheral neuropathy, neutropenia and alopecia, with Grade 3 or higher Treatment-Emergent Adverse Events (TEAEs) observed in 66.7% of patients. The most common Grade 3 or higher TEAEs (incidence greater than or equal to 7%) observed were neutropenia (30.8%) and fatigue (7.7%).

Eribulin is a halichondrin class microtubule dynamics inhibitor with a novel mechanism of action. Recent non-clinical studies showed that eribulin is associated with increased vascular perfusion and permeability in tumor cores.[1] Eribulin promotes the epithelial state and decreases the capacity of breast cancer cells to migrate and invade.[2] It was first approved for use in the treatment of metastatic breast cancer in the United States in November 2010, and is currently approved for use in the treatment of patients with breast cancer in over 60 countries including Japan and countries in Europe, the Americas and Asia.

Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. As exemplified by this combination regimen, Eisai remains committed to providing further clinical evidence for eribulin 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.

*Please refer to the following notes for the approved indications in the United States, Japan and Europe

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. About eribulin mesylate (product name: Halaven, "eribulin")

Eribulin is a halichondrin class microtubule dynamics inhibitor with a novel mechanism of action. Structurally, eribulin is a simplified and synthetically produced version of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin is believed to work by inhibiting the growth phase of microtubule dynamics which prevents cell division. In addition, recent non-clinical studies showed that eribulin is associated with increased vascular perfusion and permeability in tumor cores.[1] Eribulin promotes the epithelial state and decreases the capacity of breast cancer cells to migrate and invade.[2]

Eribulin was first approved for use in the treatment of metastatic breast cancer in the United States in November 2010. Eribulin is currently approved for use in the treatment of breast cancer in over 60 countries worldwide, including Japan and countries in Europe, the Americas and Asia.
Furthermore, eribulin was first approved as a treatment for liposarcoma in the United States in January 2016, and is also approved for liposarcoma in countries in Europe and soft tissue sarcoma in Japan.

Specifically, eribulin is approved for the following indications.
In the United States for the treatment of patients with:

- Metastatic breast cancer who have previously 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.
- Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

In Japan for the treatment of patients with:

- Inoperable or recurrent breast cancer
- Soft tissue sarcoma

In Europe for the treatment of adult 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.
- Unresectable liposarcomas who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.

2. About the Phase Ib/II Study (Study 218)

Study 218 is a multicenter, single-arm, open-label Phase 1b/II clinical study which examined the activity and safety of eribulin in combination with pembrolizumab in 95 patients (12 patients for the Phase Ib part, 83 patients for the Phase II part) with metastatic triple-negative breast cancer previously treated with 0-2 lines of chemotherapy in the metastatic setting. Eribulin (1.4 mg/m^2 intravenously on Day 1 and Day 8) and pembrolizumab (200 mg intravenously on Day 1) were administered to patients over 21 day cycles. The primary objective of the Phase Ib part was safety and tolerability, and the primary objective of the Phase II part was ORR. Progression-free survival was assessed as a secondary objective.

In this interim analysis of 39 patients, 22 patients were previously treated with 1 to 2 lines of chemotherapy in the metastatic setting. The ORR was similar between PD-L1 positive (17 patients, ORR 29.4%) and negative (18 patients, ORR 33.3%) cohorts and it was 50% for PD-L1 unknown cohorts. Pembrolizumab alone demonstrated the tendency to increase the antitumor activity with PD-L1 positive in triple-negative breast cancer patients (KEYNOTE-012 study)[3]
In this study, eribulin in combination with pembrolizumab is expected to show similar antitumor activity regardless of PD-L1 status.

3. About triple-negative breast cancer

Triple-negative breast cancer is a type of breast cancer where the cancer cells tested negative for expression of estrogen receptors, progesterone receptors and HER-2 receptors. Since the tumor cells lack the necessary receptors, common treatments like hormone therapy and drugs that target HER-2 are ineffective. This remains a disease with significant unmet medical need. Therefore, the development of new medicines is necessary to advance the treatment of triple-negative breast cancer.

4. About non-clinical research related to the mechanism of action for eribulin in combination with pembrolizumab

Eribulin contributes to maintaining or increasing the activity of cytotoxic T lymphocytes (CTLs), which play a leading role in attacking cancer cells, via reduction of immune suppressive Treg cells and M2 tumor macrophages[4]. The anti-PD-1 antibody pembrolizumab maintains or activates CTLs via its immune-checkpoint blockade. Eribulin in combination with pembrolizumab is expected to work synergistically in cancer immunotherapy.

[1] 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

[2] 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

[3] Nanda R et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. *J Clin Oncol,* 2016; 34, 2460-2467

[4] Albu D. I et al. Eribulin mesylate alters immune homeostasis in mice bearing syngeneic tumors. *AACR*, 2012; Abstract #271603_1