

EISAI SIGNS AGREEMENT WITH MERCK & CO., INC., KENILWORTH, NJ, USA TO EXPAND ENROLLMENT OF STUDY FOR HALAVEN® (ERIBULIN) AND PEMBROLIZUMAB COMBINATION DUE TO ENCOURAGING INITIAL DATA IN TRIPLE-NEGATIVE BREAST CANCER

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) has announced that it has signed an agreement with Merck & Co., Inc., Kenilworth, NJ, USA. (known as MSD outside of the United States and Canada) to increase the target number of enrolled patients in a Phase Ib/II clinical study of its in-house discovered and developed microtubule dynamics inhibitor eribulin mesylate (product name: Halaven®, “eribulin”) in combination with anti-PD-1 therapy pembrolizumab (brand name: KEYTRUDA®) developed by Merck & Co., Inc., Kenilworth, NJ, USA, for the treatment of triple-negative breast cancer, due to encouraging initial data.

The decision to expand the target number of enrolled patients is based on favourable interim analysis results of a Phase Ib/II study (Study 218) of eribulin in combination with pembrolizumab for metastatic triple-negative breast cancer, which is being jointly conducted by Eisai and Merck & Co., Inc, Kenilworth, NJ, USA. The interim analysis results (n = 39)¹ indicated an objective response rate* to the combination therapy of 33.3% (1 patient experienced a complete response and 12 patients experienced a partial response). Additionally, the combination therapy demonstrated similar antitumor activity regardless of whether PD-L1 was expressed or not. In this study, the most frequently observed adverse events (Top 5) were fatigue, nausea, peripheral neuropathy, neutropenia, and alopecia. Based on the results of the interim analysis of Study 218, the target number of enrolled patients will be increased to approximately 150.

Triple-negative breast cancer is a type of breast cancer where the cancer cells tested negative for expression of estrogen receptors and progesterone receptors, which are both targets for hormone therapy, and negative for expression of HER-2 receptors, which are targets for HER-2 inhibitors (a type of molecular target drug). Therefore, triple-negative breast cancer is extremely difficult to treat, and the development of new medicines is necessary.

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 creating new treatments for cancers with high unmet medical needs such as triple negative breast cancer, 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.

*Objective Response Rate: The ratio of patients whose cancer regressed at least a 30% decrease (Partial Response) or disappeared (Complete Response) after treatment.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

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 the first in the halichondrin class of microtubule dynamics inhibitors 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.² Eribulin promotes the epithelial state and decreases the capacity of breast cancer cells to migrate and invade.³

Eribulin 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. 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. In Japan, eribulin has been approved to treat inoperable or recurrent breast cancer and was launched in the country in July 2011. In addition, eribulin 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, eribulin 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.

2. About Phase Ib/II clinical study (Study 218) of eribulin in combination with pembrolizumab

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/m² 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 the PD-L1 unknown cohort. Pembrolizumab alone demonstrated the tendency to increase the antitumor activity with PD-L1 positive in triple-negative breast cancer patients (KEYNOTE-012 study)⁴

In this study, eribulin in combination with pembrolizumab is expected to show similar antitumor activity regardless of PD-L1 status.

3. About research data on mechanisms of action in combination of eribulin and anti-PD-1 antibody

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 macrophages⁵. The anti-PD-1 therapy pembrolizumab maintains or activates CTLs via its immune-checkpoint blockade. Eribulin in combination with pembrolizumab is expected to work synergistically in cancer immunotherapy.

¹ Tolaney S, et al. Phase 1b/2 study to evaluate eribulin mesylate in combination with pembrolizumab in patients with metastatic triple-negative breast cancer. *SABCS Abstract*, 2016; P5-15-02

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

⁴ 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.

⁵ Albu D I et al. Eribulin mesylate alters immune homeostasis in mice bearing syngeneic tumors. *AACR*, 2012; Abstract #271603_1