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Eisai Co., Ltd.

UPDATED 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 a presentation on the updated analysis of a global Phase Ib/II clinical study (ENHANCE 1 / 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 therapy pembrolizumab (product name: KEYTRUDA®) developed by Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the United States and Canada), in patients with metastatic triple-negative breast cancer was given at a spotlight session of the 40th Annual San Antonio Breast Cancer Symposium (SABCS) held from December 5 to 9, 2017. Both companies are cooperatively developing the combination.

ENHANCE 1 is a multicenter, single-arm, open-label Phase Ib/II clinical study which examined the activity and safety of eribulin in combination with pembrolizumab in 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 an updated analysis of 106 evaluable patients out of the 107 patients enrolled in the study as of May 31, 2017. 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 combination achieved an ORR of 26.4% (3 patients experienced a complete response and 25 patients experienced a partial response, 95% CI = 18.3-35.9). In addition, the ORRs were similar regardless of PD-L1 status or prior chemotherapy, and of the 3 patients who experienced a complete response, 1 patient was PD-L1 negative.
Regarding secondary objectives, favorable results were suggested with median progression free survival (PFS) of 4.2 months (95% CI = 4.1-5.6) and median overall survival (OS) of 17.7 months (95% CI = 13.7-not estimable). Furthermore, median duration of response (DOR) was 8.3 months for the 28 patients who achieved a complete or partial response.
In this study, the five most common treatment-emergent adverse events in patients were fatigue, peripheral neuropathy, nausea, alopecia, and constipation.

Other presentations at the symposium include an update from a Phase II clinical study of administration of eribulin in 14 day cycles as well as the latest non-clinical data on H3B-6545 (selective estrogen receptor α covalent antagonist), discovered by Eisai's U.S. research subsidiary H3 Biomedicine Inc.

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, cancer patients, their families, and healthcare providers.

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

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[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.[1] Eribulin promotes the epithelial state and decreases the capacity of breast cancer cells to migrate and invade.[2]

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.

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 the Phase Ib/II Study (ENHANCE 1 / 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 patients 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. PFS, OS and DOR were assessed as secondary objectives.

In this updated analysis of 106 patients, 65 patients had no prior treatment with chemotherapy and 41 patients were previously treated with 1 to 2 lines of chemotherapy in the metastatic setting. The combination achieved an ORR of 26.4% (3 patients experienced a complete response and 25 patients experienced a partial response, 95% CI = 18.3-35.9). In addition, ORR was similar between patients with or without prior chemotherapy (without prior chemotherapy: 29.2%, previous treatment with 1 to 2 lines of chemotherapy: 22.0%).

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 suggested similar ORR regardless of PD-L1 status (PD-L1 positive: 49 patients, ORR 30.6%, PD-L1 negative: 49 patients, ORR 22.4%).

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[4,5]

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 regulatory T cells (Tregs) and M2 tumor macrophages. 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

[5] Goto W et al. Clinical verification of antitumor autoimmune response in eribulin chemotherapy for breast cancer. *AACR*, 2016; Abstract 5127