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[Notes to editors]

1. About Halaven (eribulin mesylate)

Halaven is a halichondrin class microtubule dynamics inhibitor 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 as a treatment in the United States in November 2010 for patients with metastatic breast cancer. Halaven 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, Halaven was first approved as a treatment for soft tissue sarcoma in the United States in January 2016, and is approved in countries including Japan and in Europe. Applications seeking approval for use in the treatment of soft tissue sarcoma are currently under review throughout the world including Switzerland, Australia, Brazil, and countries in Asia. Furthermore, Halaven has been designated as an orphan drug for soft tissue sarcoma in the United States and Japan.

Specifically, Halaven 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 Soft Tissue Sarcoma

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) in the body. 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. 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. While treatment of soft tissue sarcoma is focused on curative surgery, if the degree of malignancy is high, 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.

3. 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 endpoint of progression-free rate at 12 weeks (PFR_{12wks}), while there was a numerical difference in PFR_{12wks} between the Halaven and dacarbazine arms (33% vs 29%), this was not statistically significant. Median progression-free survival was 2.6 months in both arms.

The most common adverse reactions (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.

In Study 309 patients with liposarcoma were categorized into three subtypes, dedifferentiated liposarcoma, myxoid/round liposarcoma and pleomorphic liposarcoma, and additional analyses were carried out on each subtype. The respective results of these additional analyses are as follows:

Dedifferentiated liposarcoma: eribulin median OS: 18.0 months vs dacarbazine median OS: 8.1 months (Hazard Ratio [HR]: 0.43 [95% CI=0.23-0.79])

Myxoid/round liposarcoma: eribulin median OS: 13.5 months vs dacarbazine median OS: 9.6 months (HR: 0.79 [95% CI=0.42-1.49])

Pleomorphic liposarcoma: eribulin median OS: 22.2 months vs dacarbazine median OS: 6.7 months (HR: 0.18 [95% CI=0.04-0.85])

[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