June 20, 2025

To Shareholders,

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(Code: 4889 TSE Growth)
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Announcement of completion of patient registration in a Phase II clinical trial with paclitaxel and PAI-1 inhibitor (RS5614) combination therapy for cutaneous angiosarcoma

We are pleased to announce that the number of registered patients has reached 16 for a Phase II investigator-initiated clinical trial to evaluate the safety and efficacy of the combination of paclitaxel[2)] and RS5614 for cutaneous angiosarcoma[1)] , which is being conducted with seven medical institutions including Tohoku University. After the administration period (28 weeks), we plan to compile the results of the evaluation and data analysis of this study in a clinical trial summary report.

Cutaneous angiosarcoma is a rare cancer with an extremely poor prognosis, with a 5-year survival rate of less than 10 %, and is caused by the cancerization of vascular endothelial cells[3)] . The number of patients in Japan is higher than the incidence in Europe and the United States (2.5 cases *per* million), and the incidence has been increasing in recent years. The first-line treatment for angiosarcoma is the apoptosis-inducer paclitaxel, but the overall survival rate is short at 649 days, and even with the combination of chemotherapy with paclitaxel and radiation therapy, it is difficult to achieve long-term shrinkage or disappearance of the cancer in most cases. The response rate of eribulin[4)] and pazopanib[5)] , which are used as second-line treatments, is about 15-20%, and serious adverse events occur in the majority of patients. There is no effective treatment for the second-line treatment, which is important in the treatment of angiosarcoma, and the development of new drugs is urgently needed.

PAI-1 is expressed in vascular endothelial cells, and is abundantly expressed in angiosarcoma, and it has been reported that the effect of paclitaxel is insufficient in patients with abundant PAI-1 expression. In addition, paclitaxel induces apoptosis[6)] in angiosarcoma, but it is also known that cancer cells that abundantly express PAI-1 are less likely to undergo apoptosis. These findings strongly suggest that the combined use of paclitaxel and the PAI-1 inhibitor RS5614 may enhance the therapeutic effect of paclitaxel on unresectable angiosarcoma.

This clinical trial is a phase II investigator-initiated clinical trial to examine the efficacy and safety of combined administration of paclitaxel and RS5614 in patients with cutaneous angiosarcoma for which

first-line treatment is ineffective (unresectable and paclitaxel ineffective). The medical institutions involved are Tohoku University Hospital, Saitama Medical Center, Sapporo Medical University Hospital, Cancer Research Institute Ariake Hospital, Nagoya City University Hospital, Kyushu University Hospital, and Kumamoto University Hospital (coordinating physician: Associate Professor Taku Fujimura, Department of Dermatology, Tohoku University Hospital). The trial began in October 2023, and 16 cases were enrolled by June 20, 2025. After the administration period (28 weeks), the results of the evaluation and data analysis of this trial will be compiled into a clinical trial report.

If this study proves effective, it will be possible to propose a new treatment for patients with cutaneous angiosarcoma, for whom there are no effective treatments. The Phase II clinical protocol has been published in the Experimental Dermatology.

Fujimura T, Yoshino K, Nakamura M, et al. Efficacy and safety of TM5614 in combination with paclitaxel in the treatment of paclitaxel-resistant cutaneous angiosarcoma: Phase II study protocol. Experimental Dermatology 33: e14976, 2024.

RS5614 has already obtained proof of concept in patients with malignant melanoma, was designated as an orphan disease drug by the Ministry of Health, Labor and Welfare in August 2024, and is currently undergoing a phase 3 clinical trial (placebo-controlled blinded).

At this time, there is no particular impact on our performance due to this matter.

End

[1)] Cutaneous angiosarcoma

Angiosarcoma is a type of skin cancer, and scalp angiosarcoma in particular is rare, occurring in approximately 2.5 cases per million people, but it is highly malignant, progresses rapidly, and has a 5-year disease-free survival rate of less than 20 %, and no standard treatment has been established. Multiple treatments will be immediately implemented at each facility.

[2)] Paclitaxel

A chemotherapy agent (anticancer drug) found to have anticancer effects in the bark of the Pacific yew tree, and is currently chemically synthesized. It is believed that it binds to microtubules involved in cell division, stopping the division of cancer cells and causing them to die (cell death).

[3)] Vascular endothelial cells

Cells that line the lumen of blood vessels. Vascular endothelial cells are not only components of blood

vessels, but also function as a site for the exchange of oxygen, nutrients, and other substances between blood and tissues, and also produce various physiologically active substances to maintain the functions of tissues and organs.

4) Eribulin

An anti-cancer drug developed from marine natural products. It acts on microtubules, one of the cell components necessary for cell division, inhibiting the growth of cancer cells or killing them. Side effects include infections due to bone marrow suppression, fatigue, and numbness in the hands and feet.

5) Pazopanib

A type of "molecular targeted therapy drug" that prevents cancer cells from growing by suppressing blood flow to the cells. It is mainly used to treat renal cell carcinoma and soft tissue sarcoma. The incidence of side effects is high at 93.5%, and the main side effects are diarrhea, high blood pressure, fatigue, nausea/vomiting, liver dysfunction, and taste abnormalities.

6) Apoptosis

A phenomenon of cell death in which cells themselves commit suicide by activating a program in order to remove unnecessary cells.