February 18, 2025

To Shareholders,

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Representative: Keisuke Furuta, President & CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Announcement of initiation (patient administration begins) of the Phase III trial of malignant melanoma treatment drug RS5614

We are pleased to announce that the first subject has been administered our PAI-1 inhibitor RS5614 at Tohoku University Hospital in the Phase III trial of for malignant melanoma[*1] and the trial has begun. This Phase III trial is a randomized, placebo-controlled, double-blind[*3] investigator-initiated clinical trial to verify the efficacy and safety of combining nivolumab[*2] with RS5614 in 124 patients with unresectable melanoma and is conducted as a multi-center collaborative study at 18 facilities in Japan, including Tohoku University Hospital.

[Overview of this study]

Subjects	Anti-PD-1 antibody-refractory advanced melanoma
Clinical trial design	Multicenter, double-blind, placebo-controlled comparative study
Number of cases	124 cases
Primary endpoint	Overall survival (OS)
Clinical trial sites (Planned)	Tohoku University Hospital, Sapporo Medical University Hospital, Hirosaki University Hospital, Jichi Medical University Saitama Medical Center, National Cancer Center Hospital East, National Cancer Center Hospital, Cancer Institute Hospital, Niigata Cancer Center Hospital, Shizuoka Cancer Center, Nagoya City University Hospital, University of Tsukuba Hospital, Gifu University Hospital, Shimane University Hospital, Ehime University Hospital, Kyushu University Hospital, National Hospital Organization Kyushu Cancer Center, Kumamoto University Hospital, and National Hospital Organization Kagoshima Medical Center (18 sites)
Period	February 2025 to July 2029 (Planned enrollment period: 1.5 years, planned observation period: 3 years)

In Japan, the incidence rate of melanoma is 1.5-2 *per* 100,000, with a total patient population of

approximately 5,000. In the United States, however, the incidence rate is 21.0 per 100,000, with a total of 1.4 million people suffering from this rare disease.

With the introduction of the anti-PD-1 antibody nivolumab, an immune checkpoint inhibitor[*4], treatment of malignant melanoma has improved significantly. In addition, the anti-CTLA-4 antibody ipilimumab[*5] has been developed, and combination therapy is being implemented to increase the response rate (approximately 20 %) of anti-PD-1 antibodies alone. However, due to their severe side effects such as autoimmune diseases, the incidence of treatment discontinuation is four times higher than with monotherapy, and there is also the issue of high medical costs, so the development of a drug that has little side effects and increases the response rate is eagerly awaited.

After the Proof-of-Concept[*6] was obtained in humans in a Phase II investigator-initiated clinical trial aimed to test the efficacy and safety (see below), our PAI-1 inhibitor RS5614 was designated as an orphan disease drug[*7] by the Ministry of Health, Labor and Welfare in Japan on August 28, 2024.

Results of Phase II investigator-initiated clinical trial

Efficacy

- ☐ The primary efficacy endpoint, "response rate[*8] at the time of 8 weeks of concomitant use of RS5614," was 24.1 %.
- ☐ Disease control rate (complete response CR+ partial response PR+ stable SD) was 62.0 %.

Safety

- ☐ Of the 34 cases analyzed for safety, 9 cases (11 cases) had serious adverse events during the 8 weeks of treatment, and 2 cases (5.9 %) of liver dysfunction were possibly causally related to the investigational drug.

RS5614 is a small molecule drug that is extremely safe and can be taken orally at home, making it a convenient medicine. This Phase III trial is a verification study to obtain pharmaceutical approval for RS5614 for malignant melanoma.

There is currently no particular impact on business performance for the fiscal year ending March 2025 due to this matter.

End

[*1] Malignant melanoma

Malignant melanoma is a type of skin cancer that occurs when skin cells called melanocytes, which

produce melanin pigment related to skin color, become malignant. It has a high metastasis rate and is considered to be extremely malignant among skin cancers. The incidence rate of malignant melanoma patients in Japan is low at 0.6 per 100,000, but in the United States, the incidence rate is 12.7 people, and in Australia, the incidence rate is 33.6 people, which is several tens of times higher than in Japan. Malignant melanoma is a highly malignant cancer (the 5-year survival rate is about 50 % if the cancer is over 4 mm in size, about 40 % if there is regional lymph node metastasis, and several percent if there is distant metastasis). In addition, it has been reported that the progression of malignant melanoma in Japan is about three times higher than in the United States. This is thought to be because melanoma in Japan is genetically different from those in Europe and the United States, making it difficult for treatments to be effective.

*2 Placebo-controlled double-blind

This is a clinical trial method in which subjects are randomly divided into a group that receives the investigational drug (RS5614 in this case) and a group that receives a control drug (an ineffective placebo in this case), and both groups are administered the same drug under the same condition that neither the doctor nor the patient knows which drug will be administered. This is a clinical trial method to reduce the opportunity for doctors to administer the investigational drug to patients who are expected to benefit, and to avoid the possibility that preconceived notions that the drug should be effective will be reflected in the evaluation, or that patients may become aware of the effect and the effect on the response to the treatment or evaluation.

*3 Nivolumab

This is an antibody drug (human anti-human PD-1 monoclonal antibody) that targets the immune checkpoint molecule programmed cell death 1 (PD-1), and is a drug that aims to have an anti-cancer effect by deactivating the suppression of the immune system. The response rate of nivolumab against melanoma in Japan is 22.2 %, and the development of new combination therapies is desired.

*4 Immune checkpoint inhibitors

Drugs that inhibit the action of immune checkpoint molecules. All drugs currently used are antibody drugs that directly bind to and inhibit immune checkpoint molecules.

*5 Ipilimumab

An antibody drug (human anti-human CTLA-4 monoclonal antibody) that targets the immune checkpoint molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4), an immune checkpoint inhibitor with a different target than nivolumab. For cases where nivolumab is ineffective, the combination of nivolumab and ipilimumab is covered by insurance, and the response rate is thought to be 21 %

overseas and 13.5 % in Japan. However, more than half of patients experience severe side effects with nivolumab-ipilimumab combination therapy, and the incidence of severe immune-related side effects that lead to discontinuation of treatment is four times higher than with monotherapy, which poses problems such as the need for hospitalization for several months and interruption of cancer treatment. In addition, there is the issue of high medical costs, and a combination drug that can be administered orally with a different antibody modality, has few side effects, increases response rate, and is inexpensive is eagerly awaited.

*6 Proof-of-Concept (POC)

This refers to confirming the effectiveness of a new drug candidate substance in clinical trials, and if the expected results are obtained, it is said that POC has been obtained.

*7 Orphan disease drug

This is a drug that is mainly used for diseases that are considered intractable, such as those with a small number of patients and no established treatment. There are designation criteria such as targeting fewer than 50,000 patients, targeting serious diseases such as intractable diseases, high medical need, lack of suitable alternative drugs or treatments, expected to be significantly more effective or safe than existing drugs, and high possibility of development. If a drug is designated as an orphan disease drug, it will be subject to priority review by the PMDA (shortening the review period), a marketability premium in drug price calculation, and an extended reexamination period after approval, resulting in a longer monopoly period for this treatment drug business. In addition, preferential treatment such as subsidies through the National Institutes of Biomedical Innovation, Health and Nutrition will be available.

*8 Response rate

This is a general evaluation standard used to determine the effectiveness of treatment for solid cancers. Before starting treatment, the size of the tumor is measured using imaging diagnosis such as CT, and large tumors are selected as target lesions, and others are called non-target lesions. The change in size of these lesions during treatment is expressed as "complete response (CR)", "partial response (PR)", "stable disease (SD)", or "progression (PD)".

Complete response (CR): Disappearance of all target lesions or, in the case of lymph nodes, shrinkage to less than 10 mm in short axis

Partial response (PR): Shrinkage of 30 % or more from before the start of treatment

Progressive disease (PD): Tumor growth of 20 % or more from its smallest size during treatment or growth of 5 mm or more in diameter

Stable disease (SD): Between partial response (PR) and progressive disease (PD)

The response rate is defined as the ratio of complete response (CR) + partial response (PR).