January 6, 2024

To Shareholders,

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Announcement of approval by the Institutional Review Board of Tohoku University for Phase III trial of drug for the treatment of malignant melanoma

We would like to announce that the Phase III investigator-initiated clinical trial of the plasminogen activator inhibitor 1 (PAI-1) inhibitor RS5614 in malignant melanoma[*1] has been approved by the Institutional Review Board (IRB) at Tohoku University Hospital. We will submit the clinical trial notification to the Pharmaceuticals and Medical Devices Agency (PMDA) and conduct the Phase III clinical trial.

This is a randomized, double-blind[*2], placebo-controlled, investigator-initiated Phase III trial to evaluate the efficacy and safety of the combination of nivolumab[*3] and RS5614 in 124 patients with unresectable malignant melanoma. This is a multicenter trial conducted at 18 medical centers in Japan, including Tohoku University Hospital.

【Overview of the Trial】

Target	Progressive malignant melanoma refractory to anti-PD-1 antibody
Clinical trial design	Multicenter, double-blind, placebo-controlled, comparative study
Number of cases	124 cases
Primary endpoint	Overall survival; OS
Clinical trial site (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 of Japanese Foundation for Cancer Research, Niigata Cancer Center Hospital, Shizuoka Cancer Center, Shizuoka Cancer Center, Nagoya City University Hospital, University of Tsukuba Hospital, Gifu University Hospital, Shimane University Hospital, Ehime University Hospital, Kyushu University Hospital, Kyushu Cancer Center, Kumamoto

	University Hospital, Kagoshima Medical Center.
Implementation Period	February 2025 - July 2029 (Planned registration period: 1.5 years, observation period: 3 years)

In the near future, the patient enrolment will begin at each medical center after consideration by the Institutional Review Board.

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

【Treatment Issues in Malignant Melanoma】

The introduction of the immune checkpoint inhibitor[*4] anti-PD-1 antibody nivolumab has greatly improved the treatment of advanced malignant melanoma (melanoma). The anti-CTLA-4 antibody ipilimumab[*5] has also been developed, and combination therapies are being used to increase the response rate (around 20%) of anti-PD-1 antibodies alone. However, due to the serious side effects of autoimmune diseases, with four times the rate of treatment discontinuation compared to monotherapy, and the high cost of treatment, there is a strong desire to develop drugs that have no side effects and increase the response rate.

PAI-1 inhibitor RS5614 is a small-molecule drug with an extremely high safety profile and a very convenient oral formulation that can be taken at home. We also obtained proof-of-concept[*6] in humans in an investigator-initiate Phase II clinical trial to confirm efficacy and safety (see below), and received orphan drug designation[*7] from the Japanese Ministry of Health, Labor and Welfare on 28 August 2024.

【Results of Phase II investigator-initiate clinical trial】

Efficacy

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

Safety

- Of the 34 patients included in the safety analysis, 11 serious adverse events occurred in 9 patients up to 8 weeks of treatment, with 2 cases of liver dysfunction (5.9%) possibly related to the study drug.

[*1] Malignant melanoma

Malignant melanoma is a type of skin cancer, a tumor formed by malignant transformation of

melanocytes, skin cells that produce melanin pigment, which is related to skin color. Among skin cancers, malignant melanoma has a high rate of metastasis and is considered to be extremely malignant. The incidence of malignant melanoma in Japan is as low as 0.6 per 100,000 people, but in the United States it is 12.7, and in Australia it is 33.6, which is several tens of times higher than the incidence in Japan. Malignant melanoma is a highly malignant cancer (5-year survival rate is about 50% if the size of the cancer exceeds 4 mm, 40% if there are regional lymph node metastases, and several percent if there are distant metastases). Furthermore, the degree of progression of malignant melanoma in Japan is reported to be about three times higher than in the United States. This may be due to the fact that malignant melanoma in Japan is genetically different from that in the Western countries, making it more difficult to respond to therapeutic agents.

*2 Double-blind

A clinical trial method in which patients 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 drugs at the same time under the condition that neither the doctor nor the patient knows which drug will be administered. This is a test method to reduce the opportunity for doctors to administer the investigational drug to patients who are expected to respond to the drug, and to avoid the possibility that preconceived notions that the drug should be effective will be reflected in the evaluation, or that even if the patient knows, it will affect the response to the treatment or the evaluation.

*3 Nivolumab

It is an antibody therapeutic (human monoclonal anti-human PD-1 antibody) that targets an immune checkpoint molecule called programmed cell death-1 (PD-1), and is intended to have an anticancer effect by de-suppressing the immune system. It is a typical immune checkpoint inhibitor. The response rate of nivolumab for malignant melanoma in Japan is 22.2%, and the development of new concomitant therapies is eagerly anticipated.

*4 Immune checkpoint inhibitors

Immune checkpoint inhibitors are pharmaceuticals that inhibit immune checkpoint molecules. All drugs currently used as therapeutic agents are antibodies that bind directly to immune checkpoint molecules and inhibit them.

*5 Ipilimumab

It is an antibody therapeutic (human monoclonal anti-human CTLA-4 antibody) targeting an immune checkpoint molecule called cytotoxic T-lymphocyte antigen-4 (CTLA-4), and is an immune checkpoint inhibitor to the different target from nivolumab. It is approved for use in combination with nivolumab in patients with nivolumab failure, and the response rate of the

combination is 21% overseas and 13.5% in Japan. However, the combination therapy of nivolumab and ipilimumab causes serious side effects in more than half of patients, and the incidence of severe immune-related side effects that result in discontinuation of treatment is four times higher than that of monotherapy, requiring several months of hospitalization or cessation of cancer treatment. Furthermore, due to the high cost of medical care, there is a long-awaited need for combination drugs that can be orally administered differently from antibody therapeutics, have fewer side effects, increase response rates, and are less expensive.

*6 Proof-of-Concept (POC)

When the efficacy of a new drug candidate is confirmed in non-clinical and/or clinical studies, the POC is said to have been obtained.

*7 Orphan disease drugs

Orphan disease drug is mainly used for diseases with few patients and no established treatment, such as intractable diseases. There are designation criteria such as the number of target patients being less than 50,000, targeting serious diseases such as intractable diseases, high medical need, no 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, a marketability premium in drug price calculation, and an extended reexamination period after approval, which will extend the monopoly period of this treatment drug business. In addition, it may be possible to obtain preferential treatment such as subsidies through the National Institutes of Biomedical Innovation, Health and Nutrition.

*8 Response rate

This is a general evaluation criterion used to determine the effectiveness of treatment for solid tumors. Prior to the start of treatment, tumor size is measured by CT and other diagnostic imaging, and large tumors are selected as target lesions, while others are called non-target lesions. Changes in the size of these lesions during treatment are expressed as "complete response (CR)," "partial response (PR)," "stable disease (SD)," and "progressive disease (PD).

Complete response (CR)	All target lesions disappear, or pathological lymph nodes must have reduction in short axis to < 10 mm.
Partial response (PR)	Reduction of more than 30% from before the start of treatment
Progressive disease (PD)	Tumor has increased by more than 20% or by more than 5 mm in diameter during treatment from the time when the tumor was smallest.
Stable disease (SD)	Between partial response (PR) and progressive disease (PD)

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