September 2, 2024

To Shareholders,

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

Announcement of the orphan drug designation of our malignant melanoma treatment drug, RS5614

We would like to inform you that our malignant melanoma treatment drug, RS5614, has been designated as an orphan disease drug[*1] by the Ministry of Health, Labor and Welfare on July 28, 2024.

The basics of cancer treatment are (1) surgical therapy, (2) radiation therapy, (3) chemotherapy (anticancer drugs), and (4) immunotherapy (immune checkpoint inhibitors[*2]). The human body has the immune system that protects the body from foreign viruses, bacteria, and microorganisms, but the body has immune checkpoint molecules[*3] that suppress excessive immunity. On the other hand, cancer abuses these immune checkpoint molecules to prevent the immune system from working against cancer itself. Immune checkpoint inhibitors inhibit these immune checkpoint molecules, releasing the brakes and allowing the immune system to attack cancer. We have discovered that plasminogen activator inhibitor 1 (PAI-1) inhibits the immunity against cancer by affecting immune checkpoint molecules. In fact, in non-clinical trials using animal models, we found that oral administration of the PAI-1 inhibitor RS5614 developed by our company resulted in regression of cancers such as malignant melanoma, colon cancer, and lung cancer, and that this effect was significantly augmented when combined with the immune checkpoint inhibitor nivolumab (opdivo)[*4].

Based upon these resuts, we thus conducted a phase II investigator-initiated clinical trial in collaboration with Tohoku University Hospital, University of Tsukuba Hospital, Tokyo Metropolitan Komagome Hospital, Nagoya City University Hospital, Kinki University Hospital, and Kumamoto University Hospital, in order to assess the efficacy and safety of combining RS5614 with the immune checkpoint inhibitor nivolumab in malignant melanoma that is difficult to completely remove surgically. As a result, the combination of RS5614 and nivolumab in the second-line treatment of malignant melanoma showed efficacy and safety equivalent to or superior to the existing combination therapy of ipilimumab[*5] and nivolumab (final results reported on February 22, 2024). In this study, 39 patients were administered RS5614 for two months, and the symptoms of more than half of the patients did not worsen for six months, and the effects of nivolumab continued even after the end of administration. While approximately 60% of patients experienced serious side effects when using conventional medications (a combination of nivolumab and ipilimumab[*6]), the rate was 7.7% with our combination with RS5614, making it highly safe.

The clinical protocol for a Phase III trial had already been finalized following face-to-face advice from the PMDA in December 2023, and a Phase III trial for the regulatory approval is scheduled to begin in fiscal year 2024.

As a result of receiving the orphan disease drug designation, a market premium will be added to the drug price calculation for the melanoma treatment drug RS5614, and the re-examination period after approval will be extended, lengthening the exclusivity period of this treatment business. In addition, there are preferential

treatment measures such as subsidies through the National Institutes of Biomedical Innovation, Health and Nutrition.

There will be no changes to the earnings forecast for the fiscal year ending March 2025 due to this matter.

*1 Orpahn disease drugs

Orpahn 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 orpahn 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.

*2 Immune checkpoint inhibitors

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

*3 Immune checkpoint molecules

A group of molecules that inhibit immune responses against oneself and suppress excessive immune responses in order to maintain immune homeostasis. Immune checkpoint molecules exist to suppress the excessive activation of lymphocytes and prevent them from attacking the self, but cancer cells abuse immune checkpoint molecules to avoid attacks from the immune system. Currently, various immune checkpoint molecules such as PD-1 and CTLA-4 have been identified.

*4 Nivolumab

An antibody drug (human anti-human PD-1 monoclonal antibody) that targets the immune checkpoint molecule, programmed cell death 1 (PD-1), a representative immune checkpoint inhibitor that aims to achieve anti-cancer effects by deactivating the inhibition of the immune system.

*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 has been approved for insurance coverage, and the response rate is thought to be 21% overseas and 13.5% in Japan. However, more than half of patients with nivolumab and ipilimumab combination therapy experience very severe side effects, and the incidence of severe immune-related side effects that lead to treatment discontinuation is four times higher than with monotherapy, which can result in hospitalization lasting several months or the interruption of cancer treatment. In addition, there is the issue of high medical costs, so there is a need for an inexpensive combination drug that has a different modality from antibodies, can be administered orally, has fewer side effects, and increases the response rate.

*6 Nivolumab/ipilimumab combination

In a Phase III multicenter clinical trial targeting untreated advanced or recurrent non-small cell lung cancer, deaths for which

a causal relationship to treatment could not be denied occurred in approximately 7.4% (11 of 148 patients), exceeding the expected range, in patients who received the immune checkpoint inhibitor combination therapy of nivolumab/ipilimumab. The trial was discontinued on March 30, 2023.