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(Translation)

February 22, 2024

To Shareholders,

Company Name Renascience Inc.
Representative: Koji Naito, President & CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Final Results of Phase II Investigator-Initiated Clinical Trial of PAI-1 inhibitor RS5614 for Malignant Melanoma Refractory to Nivolumab

The Company conducted a phase II investigator-initiated clinical trial (the "Clinical Trial") to investigate the efficacy and safety of the combination of the plasminogen activator inhibitor 1 (PAI-1) inhibitor RS5614[*1] and an immune checkpoint inhibitor[*2] nivolumab[*3] for malignant melanoma[*4] that is difficult to surgically remove by radical surgery in collaboration with Tohoku University Hospital, University of Tsukuba Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Nagoya City University Hospital, Kinki University Hospital, and Kumamoto University Hospital. The results of the Clinical Trial are now compiled.

In conclusion, this single-arm, open-label study [*5] confirmed the efficacy and safety of RS5614 in combination with nivolumab in patients with malignant melanoma that is difficult to surgically resect and refractory to nivolumab (Proof-of-Concept[*6] was obtained).

The following is the outline of the results.

[Result]

Efficacy

- The primary efficacy endpoint of the response rate[*7] 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.

[Discussion]

- The combination of nivolumab and ipilimumab[*8] has been approved for the treatment of malignant melanoma refractory to nivolumab, with response rates of 21% overseas and 13.5% in Japan, and the combination of nivolumab and RS5614 has shown efficacy comparable to or better than this existing therapy in the Clinical Trial.
- The combination of nivolumab and ipilimumab has been associated with severe immune-related side effects that result in discontinuation of treatment in more than half of patients, four times more frequent than with nivolumab alone, requiring several months of hospitalization and cessation of cancer treatment. In fact, a recent clinical study of the combination of nivolumab and ipilimumab in non-small cell lung cancer was terminated due to a high incidence of deaths[*9] , raising concerns about the safety of the combination of these two antibody therapeutics. This Clinical Trial showed that the combination of nivolumab and RS5614 is safe.
- RS5614 is not only useful for the treatment of unresectable malignant melanoma as a safe nivolumab concomitant medication, but can also contribute to reducing medical costs because, unlike antibody therapeutics, it is a small molecule drug that can be administered orally.

The following is the detailed explanation of this Clinical Trial.

[Background of this Clinical Trial]

The basic treatment for cancer is (1) surgical therapy, (2) radiation therapy, (3) chemotherapy (anticancer drugs), and (4) immunotherapy (immune checkpoint inhibitors). The human body has a system called immunity that protects the body from foreign viruses, bacteria, and microbes. The body is equipped with immune checkpoint molecules[*10] that suppress excessive immunity. Cancer abuses these immune checkpoint molecules to prevent the immune system from working against itself. Immune checkpoint inhibitors block these immune checkpoint molecules, thereby releasing the brakes and allowing the immune system to attack cancer.

The Company has discovered that PAI-1 inhibits cancer immunity via immune checkpoint molecules. In preclinical studies using animal models, the Company found that oral administration of RS5614, a PAI-1 inhibitor, regressed malignant melanoma, colorectal cancer, and lung cancer, and

that this effect was significantly enhanced when RS5614 was combined with nivolumab, an immune checkpoint inhibitor.

[Details of the Clinical Trial]

Under the support of the Japan Agency for Medical Research and Development (AMED) "Translational Research Program (Seeds C)," a multicenter, investigator-initiated clinical trial (single-arm, open-label study) was started in April 2021 at Tohoku University Hospital, University of Tsukuba Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Nagoya City University Hospital, Kinki University Hospital and Kumamoto University Hospital. Patients with malignant melanoma that was difficult to surgically resect and in which nivolumab was ineffective received RS5614 120 mg once daily (the dose was increased to 180 mg if there were no safety issues at the fourth week after the start of treatment) for eight weeks under the use of nivolumab (240 mg every two weeks or 480 mg every four weeks) to investigate the efficacy and safety of RS5614.

The results showed that the response rate (CR+PR) at 8 weeks, the primary endpoint, was 24.1%, and it was equivalent to or higher than that of nivolumab-ipilimumab combination (response rate: 21% overseas, 13.5% in Japan), which is already an approved therapy. The disease control rate (CR+PR+SD) of nivolumab/RS5614 combination reached 62.0%. Furthermore, the nivolumab/RS5614 combination was shown to be safer than the nivolumab/ipilimumab combination, with 11 serious adverse events in 9 nivolumab-negative patients by 8 weeks of treatment and only 2 (5.9%) liver dysfunction events possibly related to the study drug.

Primary Endpoint

<Response rate>

Number of subjects	29 cases
Number of responders (%)	7 cases (24.1%)
95% confidence interval	[10.3%, 43.5%].

<Details>

Classification.	Number of cases (%)
Complete response (CR)	1 (3.4%)
Partial response (PR)	6 (20.7%)
Stable (SD)	11 (37.9%)
Progression (PD)	11 (37.9%)

[Future Plan]

A phase III study for malignant melanoma is currently being prepared; the clinical protocol for the

study was finalized in December 2023 after the PMDA face-to-face advice, and the study is expected to begin during fiscal 2024.

Following the acquisition of POC in this Clinical Trial, the Company has also initiated phase II investigator-initiated clinical trials for other solid tumors such as non-small cell lung cancer[*11] and cutaneous angiosarcoma[*12] based on RS5614's immune checkpoint inhibitory effects (non-small cell lung cancer, initiated September 2023; cutaneous angiosarcoma, initiated October 2023).

There will be no impact of this matter on the financial results for the fiscal year ending March 31, 2024.

End

*1 RS5614

Based on the structure of the human PAI-1 molecule, the Company obtained 96 PAI-1 inhibitory candidate compounds from a library of approximately 2 million virtual compounds using computer engineering. The Company synthesized more than 1,300 new inhibitory compounds over the past 10 years, using PAI-1 inhibition as an indicator, and have obtained RS5275, a compound that can be orally administered with excellent safety. From RS5275, the Company further conducted further synthetic and evaluation of new compounds to obtain four clinical candidates, RS5441, RS5484, RS5509, and RS5614. Among them, RS5614 was finally selected, which has the highest efficacy and safety profile, as the clinical development candidate compound. In fact, RS5614 has passed all the non-clinical safety studies required for clinical trials and commercialization as a pharmaceutical product. RS5614 has been administered to more than 200 subjects (chronic myeloid leukemia, novel coronavirus lung injury, etc.) to date, and in chronic myeloid leukemia, RS5614 has been administered for one-year long-term treatment, and no serious side effects due to RS5614 have been reported. The drug has excellent safety.

*2 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.

*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 Malignant melanoma (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.

*5 Single-arm, open-label study

A clinical trial in which both the physicians in charge of the clinical trial and the subjects are informed of the drug, dose, etc. to be administered is called an open-label study. Generally, clinical trials are conducted in a blinded fashion in which the physicians nor the subjects are informed of the drug, dose, etc. However, it is ethically problematic to use an ineffective placebo in combination with nivolumab in the patients refractory to nivolumab. Therefore, this study is a single-arm, open-label study in which RS5614 is used in combination with nivolumab.

*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 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.

*8 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.

*9 A clinical study of the combination of nivolumab and ipilimumab

In a phase III multicenter clinical trial in untreated advanced or recurrent non-small cell lung cancer (JCOG2007 trial, a specific clinical study), deaths in patients treated with the combination of nivolumab and ipilimumab, in which a causal relationship to the treatment could not be ruled out, were observed in approximately 7.4% (11 of 148 patients), exceeding the expected range. The study was terminated on March 30, 2023.

*10 Immune checkpoint molecules

They are a group of molecules that inhibit the immune response to self and suppress excessive immune responses in order to maintain immune homeostasis. Immune checkpoint molecules exist to prevent lymphocytes from attacking self by suppressing their excessive activation, but cancer

cells exploit immune checkpoint molecules to evade attacks from the immune system. Various immune checkpoint molecules have now been identified, including PD-1 and CTLA-4.

*11 Non-small cell lung cancer

The number of people newly diagnosed with lung cancer is increasing each year, and in 2018 it was estimated that about 123,000 people (about 82,000 men and 41,000 women) were newly diagnosed with lung cancer, making it the most common cancer among all cancers in terms of deaths. About 80% of lung cancers are non-small cell lung cancers. First-line treatment for advanced non-small cell lung cancer patients who do not have mutations in the driver genes (genes that play a direct role in cancer development and progression) includes platinum-based chemotherapy and immune checkpoint inhibitory antibodies, but the number of cases that are cured is small. Second-line chemotherapy such as docetaxel is used as second-line treatment, but the stable condition is as short as 3 months, and third-line treatment is required. The combination of nivolumab and ipilimumab, both of which are immune checkpoint blocking antibodies, is an option for third-line treatment, but it is problematic because of the increased incidence of immune-related side effects and the high medical costs associated with using two antibodies. As with malignant melanoma, based on the immune checkpoint inhibition by RS5614, a phase II study has been conducted since September 26, 2023, in collaboration with Hiroshima University and other medical institutions. This is a phase II investigator-initiated clinical trial designed to evaluate the efficacy and safety of RS5614 in combination with nivolumab in patients with unresectable advanced or recurrent non-small cell lung cancer (third-line treatment) who have received at least two prior chemotherapies.

*12 Cutaneous angiosarcoma

Cutaneous angiosarcoma is a cancerous transformation of the inner cells of blood vessels (vascular endothelial cells). Angiosarcomas are extremely rare but highly malignant tumors that form in soft tissues. PAI-1 is strongly expressed on vascular endothelial cells, and its tumor, angiosarcoma, also expresses high levels of PAI-1. It has been reported that patients with high expression of PAI-1 are less likely to respond to taxane anticancer agents used in first-line therapy. Taxane anticancer agents induce apoptosis, a type of cell death, in angiosarcoma, but it is known that cancer cells that express high levels of PAI-1 are less likely to undergo apoptosis. Therefore, it is strongly suggested that the combination of a taxane anticancer agent and a PAI-1 inhibitor, RS5614, may enhance the therapeutic effect of taxane anticancer agents on angiosarcoma. A phase II investigator-initiated clinical trial to evaluate the efficacy and safety of RS5614 in combination with paclitaxel in patients with cutaneous angiosarcoma who have failed paclitaxel, a taxane anticancer drug, has been conducted since October 26, 2023.