(Translation)

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To Shareholders,

Company Name: Renascience Inc.
Representative: Koji Naito, President & CEO
(Code: 4889 TSE Growth)
Inquiries: Department of Administration

# Results of Phase II Investigator-Initiated Clinical Trial to Evaluate the Safety and Efficacy of RS5614 in Combination with Nivolumab for the Treatment of Malignant Melanoma

The Company has been conducting a Phase II investigator-initiated clinical trial from April 2021 to investigate the efficacy and safety of RS5614 in combination with nivolumab[*1] in patients with malignant melanoma[*2] who are not eligible for complete surgical resection, 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 Company is pleased to inform the progress of the clinical trial.

## Summary

- A multicenter, open-label, Phase II investigator-initiated clinical trial (open study) has been conducted to confirm the efficacy and safety of RS5614, a plasminogen activator inhibitor 1 (PAI-1) inhibitor, in combination with nivolumab in patients with malignant melanoma who are not eligible for complete surgical resection and are refractory to nivolumab.
- The primary efficacy endpoint is the response rate[*3] at 8 weeks of concomitant use of RS5614 in at least 28 patients refractory to nivolumab. Seven (7) of the 29 patients who completed 8 weeks of concomitant treatment with nivolumab and RS5614 had a response, with the response rate of 24.1%. Although RS5614 administration was completed in the study and there is still an 8-week observation period, the response rate is not expected to fall below 20.6%, even taking into account the FAS[*4]. These results are comparable to or better than the response rate for the approved combination of nivolumab and ipilimumab[*5] (21% overseas, 13.5% in Japan). The number of serious adverse events in the patients refractory to nivolumab during up to 8 weeks of treatment was 7 cases in 7 subjects, of which 2 were liver dysfunction, possibly related to the study drug.
- In Japan, nivolumab is used as a single agent for the primary treatment of malignant melanoma (with a response rate of 20% for the primary treatment in a post-marketing survey). However, there is currently no good treatment for cases of nivolumab failure or relapse. The combination of nivolumab and ipilimumab (covered by insurance) causes severe immune-related side effects that result in discontinuation of treatment in more than half of patients, four times more frequently than with nivolumab alone, requiring months of hospitalization and cessation of cancer treatment. In fact, a recent clinical study of nivolumab/ipilimumab combination in non-small cell lung cancer was terminated due to a high incidence of deaths, raising concerns about the safety of the combination of the two antibodies.

- ☐ For the patients refractory to nivolumab, the RS5614/nivolumab combination is as effective as or more effective than the nivolumab/ipilimumab combination in this study, but the RS5614/nivolumab combination has a higher safety profile than the nivolumab/ipilimumab combination. Thus, RS5614 may be useful as a safe concomitant medication for nivolumab to treat unresectable malignant melanoma. Furthermore, unlike antibody drugs, RS5614 is a small molecule drug that can be orally administered, which can contribute to reducing medical costs.
- ☐ Now that the Company has confirmed the immune checkpoint inhibitor activity of RS5614 in malignant melanoma, the Company will work on the next phase study necessary to file an application for regulatory approval for malignant melanoma, and also plans to conduct phase II investigator-initiated clinical trials for other solid tumors such as non-small cell lung cancer and cutaneous angiosarcoma beginning this fiscal year.

The treatment for cancer involves (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 also equipped with immune checkpoint molecules[*6] that suppress excessive immunity. Cancers abuse these immune checkpoint molecules to prevent the immune system from working against themselves. Immune checkpoint inhibitors[*7] inhibit these immune checkpoint molecules, thereby releasing the brakes and allowing the immune system to attack cancers.

The Company has discovered that plasminogen activator inhibitor 1 (PAI-1) inhibits cancer immunity via immune checkpoint molecules. In the preclinical studies using animal models, the Company also discovered that oral administration of RS5614, a PAI-1 inhibitor, regressed malignant melanoma, colorectal cancer, lung cancer, and other cancers, and that this effect significantly increased when RS5614 was combined with nivolumab, an immune checkpoint inhibitor antibody.

This clinical trial has been conducted as a multicenter, investigator-initiated clinical trial (open study) 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 from April 2021 under the support of the "Translational Research Program (Seeds C)" of the Japan Agency for Medical Research and Development (AMED). The study has evaluated the efficacy and safety of RS5614 in the patients with malignant melanoma who are not eligible for complete surgical resection and are refractory to nivolumab. The patients received RS5614 120 mg once daily (the dose increases to 180 mg if there are no safety issues in the fourth week after the start of the administration) for 8 weeks under nivolumab use (240 mg every 2 weeks or 480 mg every 4 weeks continuously) in this study. The results showed that the combination of RS5614 and nivolumab was as effective as or more effective than the combination of nivolumab and ipilimumab in terms of response rate (CR + PR) at 8 weeks (response rate: 24.1%), as the primary endpoint. The combination of RS5614 and nivolumab was safer than the combination of nivolumab and ipilimumab, with 7 serious adverse events in 7 patients and only 2 cases of liver dysfunction possibly related to the study drug. Although RS5614 administration was completed in this study and the subsequent 8-week observation period remains, the response rate is not expected to fall below 20.6%, even taking FAS into account. These results are comparable or better than the response rate for the approved treatment combination of nivolumab and ipilimumab (21% overseas, 13.5% in Japan). The disease control rate (CR + PR + SD) by RS5614 and nivolumab was 62.0%.

For reference, the following are the results for the primary endpoint of this study.

<Response rate>

| Number of subjects | 29 cases |
|---|---|
| Number of responders (%) | 7 cases (24.1%) |

| | |
|---|---|
| 95% confidence interval | [8.6 %, 39.7 %]. |

<Details>

| Classification. | Number of cases (%) |
|---|---|
| Complete response (CR) | 0 (0 %) |
| Partial response (PR) | 7 (24.1 %) |
| Stable disease (SD) | 11 (37.9 %) |
| Progressive disease (PD) | 11 (37.9 %) |

As for the safety, there were two serious adverse events with a possible causal relationship to the investigational drug: liver dysfunction .

Upon completion of the 8-week observation period, the clinical study report will be prepared, and the results will be presented in an academic paper or at an academic conference. In addition, the Company will proceed with discussions with the regulatory authorities, including the next-phase study required for regulatory approval. Having confirmed the immune checkpoint inhibitor activity of RS5614 in malignant melanoma, the Company plans to conduct further Phase II investigator-initiated clinical trials for other solid tumors such as non-small cell lung cancer and cutaneous hemangiosarcoma beginning this fiscal year.

There is no impact on the financial results for the fiscal year ending March 31, 2024. However, if any matters arise that should be disclosed in the future, the Company will disclose them in a timely manner.

End

*1 Nivolumab

It is an antibody drug (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 combination therapy is eagerly anticipated.

*2 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 extremely malignant. The incidence of malignant melanoma in Japan is as low as 0.6 per 100,000 people, but it is 12.7 in the UNITED STATES, and it is 33.6 in Australia, which is several dozen times higher than the incidence in Japan. Malignant melanoma is a highly malignant cancer (5-year survival rate is about 50% when the size of the cancer exceeds 4 mm; 40% when there are metastases in regional lymph nodes; and several % when there are distant metastases). Furthermore, the progression of malignant melanoma in Japan is reported to be about three times higher than that in the UNITED STATES. This may be due to the fact that malignant melanoma in Japan is genetically different from that in the UNITED STATES. and Europe, making it more difficult to respond to the therapeutic agents.

*3 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.

*4 FAS

The largest analysis set, which excludes the minimum number of excludable subjects from the total number of subjects, is called the Full Analysis Set (FAS). The excluded subjects are those who did not have unresectable malignant melanoma or who never took RS5614, and the FAS also includes subjects who stopped taking RS5614 during the study.

*5 Ipilimumab

It is an antibody drug (human monoclonal anti-human CTLA-4 antibody) that targets an immune checkpoint molecule called cytotoxic T-lymphocyte antigen-4 (CTLA-4), and is intended to have an anticancer effect by releasing suppression of the immune system (immune checkpoint inhibitor). The combination of nivolumab and ipilimumab is approved for use in patients with nivolumab failure and covered by insurance, and the response rate of the combination is 21% overseas and 13.5% in Japan. However, the combination therapy with nivolumab and ipilimumab causes serious side effects in more than half of the patients, and the incidence of severe immune-related side effects that result in discontinuation of treatment is four times higher than that of the monotherapy with nivolumab, requiring months of hospitalization or interruption of cancer treatment. Furthermore, due to the high cost of medical care, orally available concomitant medications are eagerly anticipated that are different from antibody in therapeutic modality, have fewer side effects, increase response rates, and are less expensive.

*6 Immune checkpoint molecules

They are a group of molecules that inhibit the immune response to self and suppress excessive immune responses 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.

*7 Immune checkpoint inhibitors

They inhibit immune checkpoint molecules, and all inhibitors currently used as therapeutic agents are antibody drugs that bind directly to immune checkpoint molecules.

[Reference: Q&A regarding this timely disclosure]

**What kind of cancer is 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 extremely malignant. In Japan, the number of patients with malignant melanoma is as low as 0.6 per 100,000 people, but the number is 12.7 in the UNITED STATES. and 33.6 in Australia, dozens of times higher than that of Japanese. Malignant melanoma is an extremely malignant cancer (5-year survival rate is about 50% when the size of the cancer exceeds 4 mm; 40% when there is metastasis in the regional lymph nodes; and a few percent when there is distant metastasis). 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 UNITED STATES and Europe, making it more difficult to respond to therapeutic agents.

**How is malignant melanoma treated?**

It is first necessary to remove the tumor surgically. However, in many cases, the cancer is already advanced when detected, and drug therapy (pharmaceuticals) is required. Radiation therapy is not very effective for malignant melanoma. With the advent of antibody drugs (immune checkpoint inhibitors) that target immune checkpoint molecules such as nivolumab, drug therapy has made epoch-making progress. However, the response rate of nivolumab for malignant melanoma in Japan is 22.2%. Combination therapy with nivolumab and ipilimumab has been approved for patients who do not respond to nivolumab alone, but the response rate is 21% overseas and 13.5% in Japan. Furthermore, more than half of patients treated with nivolumab/ipilimumab combination therapy experience serious side effects, and the incidence of severe immune-related side effects that result in discontinuation of treatment is four times higher than with the nivolumab therapy, requiring several months of hospitalization or interruption of cancer treatment. In addition, the cost of medical care is high for the antibody combination, and other concomitant medications are eagerly anticipated that are different from antibodies in therapeutic modality, can be orally administered, has fewer side effects, and increases the response rate .

**What are the results of this clinical trial?**

In 29 patients with malignant melanoma who were not eligible for complete surgical resection and who were refractory to the immune checkpoint inhibitor nivolumab, the combination treatment with RS5614, a PAI-1 inhibitor, for 8 weeks resulted in a response in 7 patients (the response rate of 24.1%) as the primary endpoint. Although RS5614 administration was already completed in the study with a subsequent 8-week observation period remaining, the response rate is not expected to fall below 20.6%, even taking FAS into account. This efficacy is comparable to or higher than the already approved response rate for the combination of nivolumab and ipilimumab (21% overseas, 13.5% in Japan).

**How will RS5614 change the treatment of malignant melanoma?**

Currently, the combination of nivolumab and ipilimumab has been approved for patients with nivolumab failure and covered by insurance, but the serious side effects of the nivolumab/ipilimumab combination have become a problem. In fact, the Japan Clinical Oncology Group (JCOG) conducted a phase III study (JCOG2007) at 59 centers nationwide from April 2021 to compare the efficacy of nivolumab/ipilimumab combination therapy and found that about 7.4% (11 out of 148 patients) of the patients in the

nivolumab/ipilimumab combination group had treatment-related death, which was higher than expected. The study was terminated on March 30, 2023.

The combination of RS5614 and nivolumab is as effective as or more effective than the combination of nivolumab and ipilimumab in patients with nivolumab failure, but the combination of RS5614 and nivolumab is safer than the combination of nivolumab and ipilimumab. The combination of nivolumab and RS5614 is expected to be a highly effective and safe drug therapy for patients with unresectable malignant melanoma who are not eligible for complete surgical resection and refractory to the monotherapy with immune checkpoint inhibitors.

**What are the advantages of RS5614 compared to previous immune checkpoint inhibitors?**

All current immune checkpoint inhibitors are antibody drugs that require hospitalization and administration by injection. Existing antibody drugs are also known to have various side effects. RS5614 is an oral drug that is safe and can be taken at home. In addition, RS5614 is chemically synthesized, so its price is considered lower than that of antibodies.

**Is RS5614 useful in the treatment of other solid tumors?**

The preclinical studies in animal models have shown that oral administration of RS5614, the PAI-1 inhibitor, regresses malignant melanoma as well as colorectal and lung cancers, and that this effect significantly increases when combined with immune checkpoint inhibitory antibodies. Therefore, the Company plans to start Phase II investigator-initiated clinical trials for non-small cell lung cancer and for cutaneous hemangiosarcoma beginning this fiscal year. The Company will disclose any matters that need to be disclosed in the future in a timely manner.

**What is the medical significance of this clinical trial?**

It has long been reported that many cancers with high PAI-1 expression have high malignancy and poor prognosis, which has been called the "PAI-1 paradox". Through collaboration with many universities in Japan and overseas, the Company has discovered that cancer cells produce PAI-1 and enhance the expression of immune checkpoint molecules such as PD-L1, thereby evading attacks by the immune system. In the preclinical studies using animal models, we have demonstrated that oral administration of RS5614, the PAI-1 inhibitor, can regress malignant melanoma, colorectal cancer, lung cancer, and other types of cancer. The current clinical trial confirmed the response in 7 patients with malignant melanoma who were not eligible for complete surgical resection and were refractory to nivolumab, when administered in combination of RS5614 with nivolumab for 8 weeks in 29 patients with malignant melanoma. The efficacy of RS5614 for chronic myeloid leukemia (CML), a hematological cancer, has already been demonstrated in the early and late Phase II studies, and a Phase III trial is currently ongoing. The Company has demonstrated in humans that the "PAI-1 paradox" is indeed important in cancer therapy, that PAI-1 is a target of therapy in some types of cancer, and that the PAI-1 inhibitor is effective as drug therapy.