Notice: This is a translation of a notice in Japanese and is made solely for the convenience of foreign shareholders. In the case of any discrepancy between the translation and the Japanese original, the latter shall prevail.

(Translation)

September 26, 2023

To Shareholders

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

Announcement of Initiation of Phase II Study for Non-Small Cell Lung Cancer.

The Company is pleased to announce that a phase II investigator-initiated clinical trial of the PAI-1 inhibitor RS5614 for non-small cell lung cancer[*1] has started.

The phase II investigator-initiated clinical trial to investigate the efficacy and safety of RS5614 in combination with nivolumab[*2], an immune checkpoint inhibitor[*3] in 39 patients with unresectable advanced or recurrent non-small cell lung cancer (the third-line treatment) who have been treated with multiple anticancer agents is being conducted at six hospitals: Hiroshima University Hospital, Okayama University Hospital, Shimane University Hospital, Tottori University Hospital, National Hospital Organization Shikoku Cancer Center, and Hiroshima City Hiroshima Citizens Hospital.

The first-line therapy for advanced non-small cell lung cancer without mutations in the driver gene[*4] includes chemotherapy with platinum-containing drugs[*5] and immune checkpoint inhibitors such as nivolumab, but few patients are cured, and chemotherapy such as docetaxel[*6] is used as the second-line therapy. However, the progression-free survival is very short (3 months) in the second-line therapy and the third-line therapy is required. Re-administration of nivolumab is an option for the third-line treatment, but its efficacy is limited in patients previously treated with nivolumab. A concomitant treatment with ipilimumab[*7] to potentiate the effects of nivolumab has also developed as the third-line therapy, but it is associated with serious immune-related side effects, and in fact, a recent clinical trial of nivolumab plus ipilimumab combined with chemotherapy in non-small cell lung cancer was terminated because of a high incidence of death[*8] . Therefore, a combination drug that has fewer side effects and increases the response rate of nivolumab is eagerly awaited.

The Company has discovered that the oral PAI-1 inhibitor, RS5614, has immune checkpoint inhibitory activity and that its efficacy is further enhanced when combined with nivolumab, and has confirmed the efficacy and safety of RS5614 in combination with nivolumab in the phase II investigator-initiated clinical trial for the patients with malignant melanoma that is surgically unresectable and refractory to nivolumab. The Proof-of-Concept (POC)[*9] was thus obtained (announced on August 16, 2023).

In October 2022, the Company entered into a collaboration agreement with Hiroshima University for non-clinical and clinical studies of the PAI-1 inhibitor RS5614 for non-small cell lung cancer. From the joint research, it was discovered that PAI-1 is involved in the proliferation and angiogenesis of lung cancer, and in the development of lung cancer cells resistant to anti-PD-1 antibodies (with the same mechanism of action as nivolumab). The efficacy of the combination of the anti-PD-1 antibody and RS5614 was also confirmed in a preclinical study using a mouse model of non-small cell lung cancer. In April 2023, the Company entered into a comprehensive collaboration agreement with Hiroshima University to conduct clinical development (including investigator-initiated clinical trials) of pharmaceuticals and software as a medical device (SaMD) utilizing the features and strengths of Hiroshima University, to improve the efficiency and promotion of research and development, and to develop human resources. The clinical trial protocol notice was submitted on August 14, 2023, and the first subject was enrolled on September 26. The phase II investigator-initiated clinical trial to evaluate the efficacy and safety of RS5614 in combination with nivolumab as the third-line treatment in patients with unresectable advanced or recurrent non-small cell lung cancer who have received multiple prior anticancer therapies has been initiated. This clinical trial will be conducted primarily at HiREx. If the efficacy and safety are confirmed in this clinical trial, it can be a new treatment for non-small cell lung cancer.

There is no impact of this matter on our business performance at this time.

End

*1 Non-small cell lung cancer

Lung cancer is the leading cause of cancer death with a poor prognosis. The number of lung cancer in Japan is 84,325 in male and 42,221 in female in 2019, the number of deaths is 53,247 in male (1st) and 22,338 in female (2nd) in 2020, and 80-85% of lung cancer cases are non-small cell lung cancer.

*2 Immune checkpoint inhibitors

Immune checkpoint molecules have been discovered as 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 abuse immune checkpoint molecules to evade attacks from the immune system. Various immune checkpoint molecules have now been identified, including programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Immune checkpoint inhibitors are drugs that block the action of immune checkpoint molecules, and all drugs currently used as therapeutic agents are antibodies that bind directly to immune checkpoint molecules and block 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.

*4 Driver genes

Research on cancer has revealed that cancer cells have abnormalities or increased amounts of certain genes and proteins compared to normal cells. These abnormal genes are called "oncogenes" and are thought to be responsible for cancer development and cancer growth. In particular, the genes that play a direct role in cancer development and progression are called "driver genes".

*5 Platinum-containing drug

It is a type of anticancer drugs (cytotoxic agent) used in the treatment of lung cancer. By binding to DNA (gene) in cancer cells, the drug stops the cancer cells from dividing and eventually kill them. Cisplatin and carboplatin are included in this category.

*6 Docetaxel

It is a semi-synthetic compound made from plant components. It inhibits the growth of cancer cells by stabilizing and overexpressing microtubules, one of the cellular components necessary for cells to divide.

*7 Ipilimumab

It is an antibody drug (a human monoclonal anti-human CTLA-4 antibody) that targets an immune checkpoint molecule called cytotoxic T-lymphocyte antigen-4 (CTLA-4) and is an immune checkpoint inhibitor targeting a molecule different from nivolumab.

*8 “a recent clinical trial of nivolumab plus ipilimumab combined with chemotherapy in non-small cell lung cancer”

Although the combination is not the third-line treatment, in a phase III multicenter clinical trial in untreated advanced or recurrent non-small cell lung cancer (JCOG 2007 trial, a specified clinical research), death was observed in approximately 7.4% (11 of 148 patients) exceeding the expected range in the patients treated with the combination of immune checkpoint inhibitors, nivolumab and ipilimumab, in the presence of chemotherapy. The causal relationship to the treatment cannot be ruled out, and the study was terminated on March 30, 2023.

*9 Proof-of-Concept (POC)

It refers to confirming the expected efficacy of a new drug candidate in non-clinical and clinical trials. If the results are as expected, the POC is said to have been obtained.

[Reference: QA regarding this timely disclosure]

How is non-small cell lung cancer treated?

Surgery is the mainstay of treatment for relatively early-stage non-small cell lung cancer. When the cancer is advanced and cannot be removed by surgery, drug therapy is the mainstay of treatment. Drugs used for the treatment of non-small cell lung cancer can be broadly classified into "cytotoxic anticancer drugs", "molecular targeted drugs", and "immune checkpoint inhibitors", and sometimes a combination of several types of drugs is used.

A combination chemotherapy with platinum-based drugs (a combination of two cytotoxic drugs including a platinum-based drug) and immune checkpoint inhibitors such as nivolumab is used as the first-line treatment of advanced non-small cell lung cancer, but since few cases are cured, the second-line treatment with docetaxel or other chemotherapy is used. However, the progression-free survival after the second-line therapy is as short as 3 months, necessitating the third-line therapy. Re-administration of nivolumab is an option for the third-line therapy, but its efficacy in patients previously treated with nivolumab is limited, and the new therapy is being developed to augment the antitumor immune response by nivolumab in combination with ipilimumab. However, the combination of nivolumab and ipilimumab poses significant challenges, including increased immune-related side effects and higher medical costs, a combination drug is eagerly awaited which increases the response rate of nivolumab with fewer side effects and better medical economics.

How will RS5614 change non-small cell lung cancer treatment?

Serious side effects of nivolumab-ipilimumab combination have become a problem. In fact, the Japan Clinical Oncology Group (JCOG) conducted a phase III study (JCOG2007 study) comparing the efficacy of nivolumab plus ipilimumab in combination with chemotherapy at 59 centers nationwide since April 2021. However, the study was terminated on March 30, 2023, due to the unexpectedly high rate of treatment-related deaths (approximately 7.4% (11 out of 148 patients) in the nivolumab-ipilimumab combination group.

In the phase II investigator-initiated clinical trial in patients with malignant melanoma refractory to nivolumab, the Company demonstrated that the combination of nivolumab and RS5614 was more effective than the combination of nivolumab and ipilimumab (response rate for the combination of nivolumab and RS5614 vs. 24.1%, response rate for the combination of nivolumab and ipilimumab: 13.5%) (Proof-of-Concept obtained). Furthermore the combination of nivolumab and RS5614 proved to be safer than the combination of nivolumab and ipilimumab. If the safety and efficacy of the combination of nivolumab and RS5614 in non-small cell lung cancer are confirmed in this clinical trial, it can be a useful and convenient drug therapy.

RS5614 effective for cancers other than non-small cell lung cancer?

It has been reported in many cancers that cancers with high expression of PAI-1 have high malignancy and poor prognosis, and the phenomenon is called the "PAI-1 paradox". Through collaborations with many universities in Japan and overseas, the Company has discovered that cancer cells produce PAI-1 and it in turn enhances the expression of immune checkpoint molecules such as

PD-L1, thereby evading attacks by the immune system. In nonclinical studies using animal models, oral administration of the PAI-1 inhibitor RS5614 can regress malignant melanoma, colorectal cancer, lung cancer, and other types of cancer.

In the phase II study of malignant melanoma, the combination of nivolumab and RS5614 proved to be more effective and safer than the existing combination of nivolumab and ipilimumab in patients with malignant melanoma that was surgically unresectable and refractory to nivolumab (nivolumab plus RS5614 combination: 24.1% vs. nivolumab plus ipilimumab: 13.5%). In addition, the phase II studies (early and late stage) have already confirmed the efficacy of RS5614 for chronic myeloid leukemia, one of the hematological cancers, and the phase III study is currently underway. Thus, the Company has confirmed in humans that the "PAI-1 paradox" is indeed important in cancer therapy, that PAI-1 is an important target for therapy in some types of cancer, and that the PAI-1 inhibitor is effective as drug therapy. The Company is being studying the efficacy of RS5614 in malignant melanoma, non-small cell lung cancer, and cutaneous angiosarcoma.