July 3, 2025

To Shareholders,

Company Name: Renascience Inc.
Representative: Toshio Miyata, Chairman and CEO
(Code: 4889 TSE Growth)
For inquiries, please contact Administration Dept.

Announcement of completion of patient registration in a Phase II study of nivolumab and PAI-1 inhibitor (RS5614) combination therapy for non-small cell lung cancer

We are pleased to announce that we have completed patient enrollment for a Phase II investigator-initiated clinical trial to evaluate the safety and efficacy of nivolumab[2] and PAI-1 inhibitor (RS5614) combination therapy for small cell lung cancer[1]," which is being conducted with six medical institutions including Hiroshima University (36 registered patients). After the administration period (up to 24 weeks), we plan to compile the results of the evaluation and data analysis of this study in a clinical trial report.

In Japan, the estimated number of patients diagnosed with advanced non-small cell lung cancer without driver gene[3] mutations *per* year is 23,000. Currently, platinum combination chemotherapy[4] and immune checkpoint inhibitors such as nivolumab[5] are used for first-line treatment, but there are few cases that lead to a cure, and chemotherapy such as docetaxel[6] is performed as second-line treatment. However, the progression-free survival time[7] is short at three months, making third-line treatment necessary. Nivolumab re-administration is also an option for third-line treatment, but its effectiveness is limited in patients with a history of nivolumab treatment. In order to enhance the tumor immune response of nivolumab, ipilimumab[8] is used in combination with the treatment, but there are issues such as an increase in severe immune-related side effects and high medical costs. In fact, a recent clinical trial[9] of chemotherapy combined with nivolumab and ipilimumab in non-small cell lung cancer was discontinued due to the high number of deaths. Therefore, a combination drug with fewer side effects and an increase in the response rate of nivolumab is eagerly awaited.

We discovered that the oral medication RS5614 has an immune checkpoint inhibitory effect, and that its effect is further enhanced when combined with nivolumab. In a Phase II investigator-initiated clinical trial targeting patients with malignant melanoma who are difficult to surgically resect and for whom nivolumab is ineffective, we confirmed the efficacy and safety of the combination of nivolumab and RS5614, obtained proof-of-concept (POC) [10], and received an orphan disease drug designation

from the Ministry of Health, Labor and Welfare in August 2024, and are currently conducting a Phase III clinical trial (placebo-controlled blinded).

We have been conducting a Phase II trial to examine the efficacy and safety of the combination of nivolumab and RS5614 in patients with unresectable, advanced or recurrent non-small cell lung cancer (third-line treatment patients) who have had multiple anti-cancer drug treatments since September 2023 at Hiroshima University, Shimane University, Okayama University, Tottori University, Shikoku Cancer Center, and Hiroshima City Hospital (Clinical trial coordinator: Professor Noboru Hattori, Department of Respiratory Medicine, Hiroshima University Hospital), and completed patient enrollment (36 registered patients) on July 3, 2025. After the administration period (up to 48 weeks), we plan to compile the results of the evaluation and data analysis of this study in a clinical trial report.

If the efficacy of this study can be verified, a new treatment for non-small cell lung cancer can be proposed.

At this time, this matter has no particular impact on our business performance.

End

[1)] Non-small cell lung cancer

Lung cancer is a disease with a poor prognosis and is the leading cause of cancer deaths. In Japan, the number of lung cancer cases (2019) was 84,325 men and 42,221 women, and the number of deaths (2020) was 53,247 men (1st in men) and 22,338 women (2nd in women), with 80-85 % of lung cancers being non-small cell lung cancer.

[2)] Nivolumab

An antibody drug (human anti-human PD-1 monoclonal antibody) that targets the immune checkpoint molecule PD-1. It is a representative immune checkpoint inhibitor that aims to have an anti-cancer effect by releasing the inhibition of the immune system.

[3)] Driver gene

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

[4] Platinum preparations

A type of anticancer drug (cytotoxic anticancer drug) used to treat lung cancer. By binding to DNA, the main gene in cancer cells, they stop the division of cancer cells and kill them. These include cisplatin and carboplatin.

[5] Immune checkpoint inhibitors

Immune checkpoint molecules were discovered as 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 exploit 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. Immune checkpoint inhibitors are drugs that inhibit the action of immune checkpoint molecules, and all drugs currently used as treatments are antibody drugs that directly bind to and inhibit immune checkpoint molecules.

[6] Docetaxel

A semi-synthetic compound made from plant components. It inhibits the proliferation of cancer cells by stabilizing and overexpressing microtubules, one of the cell components necessary for cell division.

[7] Progression-free survival

One of the indicators for evaluating the effectiveness of cancer treatment, it refers to the period from the start of treatment until the progression or recurrence of cancer is confirmed, or until the patient dies. The longer this period, the more effective the treatment.

[8] Ipilimumab

An antibody drug (human anti-human CTLA-4 monoclonal antibody) that targets the immune checkpoint molecule cytotoxic T-lymphocyte antigen-4 (CTLA-4), it is an immune checkpoint inhibitor with a different target than nivolumab.

[9] Clinical study of nivolumab and ipilimumab combination therapy

In a phase III multicenter clinical trial (JCOG2007 study, specific clinical study) targeting untreated advanced and recurrent non-small cell lung cancer, deaths in which a causal relationship with the treatment could not be denied were observed in approximately 7.4% (11 out of 148 patients), exceeding the expected range, in patients who received chemotherapy and the immune checkpoint inhibitor nivolumab/ipilimumab combination therapy, and the study was discontinued on March 30, 2023.

[10] Proof-of-Concept (POC)

This refers to confirming the effectiveness of a new drug candidate substance in clinical trials, and if the expected results are obtained, it is said that POC has been obtained.