November 26, 2025

To Shareholders,

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

Announcement of the Initiation of a Phase II Investigator-Initiated Clinical Trial of a PAI-1 Inhibitor (RS5614) Combination Therapy in Chemoradiotherapy and Immune Checkpoint Inhibitor Consolidation Therapy (First-Line Treatment) for Locally Advanced Non-Small Cell Lung Cancer

We are pleased to announce that on November 26, 2025, we entered into an agreement with Hiroshima University regarding a clinical trial of a PAI-1 inhibitor (RS5614) combination therapy with chemo-radiotherapy[1)] and immune checkpoint inhibitor[2)] consolidation therapy[3)], the initial standard treatment for locally advanced non-small cell lung cancer[4)], with 12 medical institutions, including Hiroshima University Hospital.

We are currently conducting a Phase II investigator-initiated clinical trial (coordinating investigator: Professor Noboru Hattori, Department of Respiratory Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences) in collaboration with six medical institutions, including Hiroshima University Hospital, evaluating the combination of the immune checkpoint inhibitor nivolumab[5)] and RS5614 for non-small cell lung cancer (third-line or later treatment). The completion of patient enrollment for 35 patients was announced on July 3, 2025. This clinical trial is being conducted as an open-label study[6)], and all patients have been administered RS5614, so results are gradually emerging. The principal investigator and other investigators have confirmed efficacy (response rate) in some patients and have requested an extension of the clinical trial period in order to continue administration of RS5614. Additionally, as some patients wish to continue receiving RS5614, the trial period has been extended by three months, with RS5614 administration continuing during that time. The final clinical study report is scheduled for August 2026. While the enhanced efficacy of immune checkpoint inhibitors in combination with RS5614 is suggested to be due to factors such as the suppression of epithelial-mesenchymal transition[7)], activation of T lymphocytes, reduction of tumor- Associated macrophages (TAM) [8)], increased intra-tumoral T lymphocyte counts, reduced expression of immune checkpoint molecules on cancer cells, removal of cancer cell resistance to immune

checkpoint molecule inhibitors, improvement of the tumor immune microenvironment[9], and activation of tumor immunity (Company news, November 11, 2025).

An ongoing Phase II investigator-initiated clinical trial, targeting third-line and later treatments, has demonstrated promising results for the enhanced efficacy of immune checkpoint inhibitors in non-small cell lung cancer, so we are considering a next-phase investigator-initiated clinical trial. Because RS5614's enhanced efficacy over immune checkpoint inhibitors has shown greater efficacy with earlier treatment, we are planning to begin a Phase II investigator-initiated clinical trial (coordinating investigator: Takeshi Masuda, Associate Professor, Department of Respiratory Medicine, Hiroshima University Hospital) in April 2026 to evaluate the efficacy and safety of a PAI-1 inhibitor (RS5614) combination therapy in locally advanced non-small cell lung cancer as consolidation therapy with chemo-radiotherapy and the immune checkpoint inhibitor durvalumab [10] (the standard initial treatment).

We have already completed face-to-face consultations with the Pharmaceuticals and Medical Devices Agency (PMDA) on November 14, 2025, and the clinical protocol has been finalized. The investigator-initiated clinical trial will commence following approval by the Institutional Review Board (IRB) and submission of a clinical trial notification to the PMDA. This investigator-initiated clinical trial will be conducted at Hiroshima University's Renascience Open Innovation Lab (HiREx) based on a comprehensive collaboration agreement concluded with Hiroshima University in April 2023.

[Background of the Phase Next Trial]

Challenges facing initial standard treatment for non-small cell lung cancer include 1) resistance to radiation therapy, 2) resistance to chemotherapy, 3) resistance to immune checkpoint inhibitors, and 4) lung injury associated with radiation and immune checkpoint inhibitors (side effects).

Accordingly, previously reported rates of transition from chemo-radiotherapy to durvalumab consolidation therapy in initial treatment for non-small cell lung cancer are approximately 80 %. (Of the 20 % who fail to transition, 10 % are due to disease progression and 10 % to treatment discontinuation due to pneumonitis or other reasons.) Thus, a significant challenge exists: a certain number of patients are unable to transition to immune checkpoint inhibitors (durvalumab) due to cancer progression during chemo-radiotherapy or lung injury caused by radiation therapy. Therefore, there is a need for the development of a treatment that enhances the efficacy of the

current initial standard of care, chemo-radiotherapy and durvalumab consolidation therapy, while also suppressing the lung damage associated with radiation therapy and durvalumab.

[Purpose and Rationale of the Phase Next Trial]

1. PAI-1-Mediated Resistance Relief to Radiation Therapy and the Enhancement Effect of RS5614

In a collaborative study with Associate Professor Takeshi Masuda of the Department of Respiratory Medicine at Hiroshima University Hospital, we demonstrated in a mouse lung cancer model that residual cancer cells after radiation overexpress PAI-1, that PAI-1 conferred radiation resistance to cancer cells by suppressing apoptosis[11)], and that the combination of the PAI-1 inhibitor RS5614 and radiation therapy demonstrated significantly stronger anti-tumor effects than radiation therapy alone (presented by Associate Professor Takeshi Masuda and his team at the 66th Annual Meeting of the Japan Lung Cancer Society on November 7, 2025).

2. PAI-1 Resistance Relief and Enhancement by RS5614

In a collaborative study with Associate Professor Takeshi Masuda of the Department of Respiratory Medicine at Hiroshima University Hospital, we have confirmed in a mouse lung cancer model that PAI-1 is involved in resistance to chemotherapy drugs used in chemo-radiotherapy, that a PAI-1 inhibitor reverses resistance, and that the antitumor effect of RS5614 in combination with chemotherapy alone is enhanced compared to chemotherapy alone (unpublished data).

3. Resistance Relief and Enhancement by Immune Checkpoint Inhibitors

This is currently being investigated in an ongoing Phase II investigator-initiated clinical trial (targeting third-line and later treatments) (the scientific evidence was presented in our November 11, 2025, Company News release).

4. Improvement of Lung Injury Caused by Radiation Therapy and Durvalumab

Radiation pneumonitis occurs as a side effect of radiation therapy (with an incidence rate of approximately 30 % in concurrent chemo-radiotherapy, and a fatal radiation pneumonitis rate of approximately 2 %). Symptoms include shortness of breath, cough, and fever, although some cases are asymptomatic. Pneumonitis occurs during or within six months of treatment completion. Mild cases may resolve spontaneously, but severe cases can lead to decreased lung function and fibrosis.

The incidence of pneumonitis during durvalumab treatment has been reported to be approximately 33 %. Patients who develop pneumonitis require hospitalization with oxygen administration and steroid therapy, and durvalumab treatment is often interrupted or discontinued. Furthermore, many cases experience long-term dyspnea and reduced activities of daily living due to residual fibrosis even after improvement of pneumonitis, contributing to a serious decline in quality of life both in Japan and overseas.

PAI-1 is known to play a central role in pulmonary fibrosis, and we have investigated the efficacy of PAI-1 inhibitors against lung injury through investigator-initiated clinical trials in COVID-19 lung injury and systemic sclerosis interstitial pneumonia. In this study, we will utilize RS5614 not only for its anti-tumor effect on non-small cell lung cancer, but also to suppress lung injury associated with radiation and immune checkpoint inhibitors (side effects), thereby ensuring treatment safety.

[Phase 2 Trial Overview]

Subjects	Locally advanced non-small cell lung cancer
Trial Design	Open-label, uncontrolled, multicenter trial
Number of Patients	27
Primary Endpoint	1-year progression-free survival rate[12)]
Trial Sites (Planned)	Hiroshima University Hospital, Okayama University Hospital, Shimane University Hospital, Hiroshima City Hiroshima Citizens Hospital, Tottori University Hospital, Kagawa University Hospital, Kochi Medical School Hospital, National Hospital Organization Iwakuni Clinical Center, Ehime University Hospital, Nara Medical University Hospital, Tohoku University Hospital, and Hiroshima Prefectural Hospital (12 sites)
Trial Period	April 2026 - March 2030 Planned Enrollment Period: April 2026 - September 2028 (29 months) Planned Observation Period: April 2026 - September 2029 (41 months)

The objective of this phase 2 clinical trial is to evaluate whether the PAI-1 inhibitor RS5614, combined with chemo-radiotherapy and durvalumab consolidation therapy, can 1) improve cure rates by enhancing the antitumor effects of chemoradiotherapy and durvalumab, and 2) improve treatment safety by suppressing lung injury caused by radiation therapy and durvalumab (side

effects), in patients with locally advanced non-small cell lung cancer who are ineligible for curative surgery. This study aims to clarify whether the RS5614 combination therapy can be a novel treatment that surpasses the current initial standard of care.

At this time, there is no particular impact of this transaction on our financial results for the fiscal year ending March 2026.

[1)] Chemo-radiotherapy
This is the initial standard treatment, combining drugs that attack cancer cells (chemotherapy) with radiation therapy (radiotherapy) that targets the cancerous area. It is one of the standard treatments for cases where surgery is difficult.

[2)] Immune Checkpoint Inhibitors
Immune checkpoint molecules have been discovered as a group of molecules that inhibit immune responses against the self and suppress excessive immune responses in order to maintain immune homeostasis. Immune checkpoint molecules exist to suppress excessive lymphocyte activation and prevent self-attack, but cancer cells exploit immune checkpoint molecules to evade attack from the immune system. Various immune checkpoint molecules have been identified, including PD-L1, PD-1, and CTLA-4. Immune checkpoint inhibitors are drugs that block the action of immune checkpoint molecules. All currently used therapeutic drugs are antibody drugs that directly bind to and inhibit immune checkpoint molecules.

[3)] Consolidation Therapy
This is additional treatment administered after initial treatment (e.g., chemo-radiotherapy) has suppressed cancer to some extent, with the aim of maintaining and strengthening the therapeutic effect. It aims to prevent recurrence and progression.

[4)] Locally Advanced Non-Small Cell Lung Cancer
This refers to cancer that originates in the lungs and has spread so locally that surgery is difficult.

[5)] Nivolumab
Nivolumab is 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 achieve anti-cancer effects by deactivating immune system suppression.

[6)] Open-Label study

This is a trial design in which both trial participants and medical professionals are aware of the treatment they are receiving.

[7] Epithelial-Mesenchymal Transition
This is a phenomenon in which epithelial cells, which form tissue through cell-to-cell adhesion, transform into highly mobile mesenchymal cells. This is one of the triggers that promotes tissue fibrosis, cancer invasion, and metastasis.

[8] Tumor-Associated macrophages (TAM)
Macrophages accumulate in tumor tissue and are known to form the tumor microenvironment and play a role in tumor growth, angiogenesis, immunosuppression, and other processes.

[9] Tumor Immune Microenvironment
This refers to a tissue state that differs from normal tissue due to interactions between cancer cells and surrounding cells. Anti-cancer drugs make cancer cells less susceptible to immune attack, which is thought to be one factor in acquiring resistance.

[10] Durvalumab
Durvalumab is an immune checkpoint inhibitor that binds to a substance called PD-L1 to enhance the attacking power of immune cells. It is primarily used to treat non-small cell lung cancer (especially as maintenance therapy after definitive chemo-radiotherapy). Side effects can affect various immune-related organs, such as interstitial lung disease and liver dysfunction. Both durvalumab and nivolumab are classified as immune checkpoint inhibitors, but durvalumab is an anti-PD-L1 (cancer) antibody, while nivolumab is an anti-PD-1 (lymphocyte) antibody.

[11] Suppressing apoptosis
Apoptosis is a physiological mechanism by which cells die, and "apoptosis inhibition" refers to a state in which this mechanism is impaired or does not function properly.

[12] Progression-Free Survival Rate
This is an indicator of the percentage of patients who have not experienced cancer progression or death since the start of treatment.