March 5, 2026

To Shareholders,

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Representative: Toshio Miyata, Chairman and CEO
(Code: 4889 TSE Growth)
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Preliminary results of a Phase II study with nivolumab and PAI-1 inhibitor (RS5614) combination therapy for non-small cell lung cancer

We are pleased to announce the preliminary results of a Phase II study conducted with six medical institutions, including Hiroshima University, to evaluate the safety and efficacy of nivolumab[1)] and PAI-1 inhibitor (RS5614) combination therapy for non-small cell lung cancer[2)].

In Japan, an estimated 23,000 patients are diagnosed with advanced non-small cell lung cancer without driver gene[3)] mutations each year. Currently, first-line treatment consists of platinum-based chemotherapy[4)] and immune checkpoint inhibitors[5)] such as nivolumab, but few cases are cured. Second-line treatment involves chemotherapy such as docetaxel[6)]. However, progression-free survival[7)] is short at three months, necessitating third-line treatment. While rechallenge with nivolumab is an option for third-line treatment, its efficacy is limited in patients previously treated with nivolumab. Nivolumab is currently being used in combination with ipilimumab[8)] to enhance tumor immune responses, but this approach faces challenges such as increased immune-related serious side effects and high medical costs. In fact, a recent clinical trial of nivolumab in combination with chemotherapy[9)] for non-small cell lung cancer was discontinued due to a high number of deaths. Therefore, a combination drug with fewer side effects that increases the response rate of nivolumab is eagerly awaited.

A Phase II trial evaluating the efficacy and safety of nivolumab in combination with RS5614 in patients with unresectable, advanced, or recurrent non-small cell lung cancer who have received multiple prior anticancer drug therapies (third-line or later treatment patients) was initiated in September 2023 at Hiroshima University, Shimane University, Okayama University, Tottori University, Shikoku Cancer Center, and Hiroshima City Hospital (coordinating investigator: Professor Noboru Hattori, Department of Respiratory Medicine, Hiroshima University Hospital). Enrollment of 36 patients was completed on July 3, 2025. This clinical trial was conducted as an open-label study, so all patients received RS5614. The coordinating investigator (principal investigator) requested an extension of the trial period to allow continued administration of

RS5614 to patients for whom efficacy was confirmed. Accordingly, the trial period was extended by three months.

[Phase II Clinical Trial Results (Preliminary)]

An interim analysis of 36 patients was conducted.

Efficacy

In the overall evaluation of all patients (third-line or later), the primary endpoint of objective response rate (ORR)[10] was 8.3%, and the secondary endpoint of 6-month progression-free survival rate (PFS) was 22.5%. In the 11 patients who received this study treatment as third-line treatment, ORR was 18.2% and PFS was 27.5%, demonstrating high efficacy of the RS5614 combination therapy. This result demonstrated an approximately 10% increase in antitumor efficacy compared to nivolumab monotherapy, as previously reported (Clin Cancer Res. 2022 28: OF1-OF7. doi: 10.1158/1078-0432.CCR-22-0602). In early third-line treatment, the PAI-1 inhibitor (RS5614) combination therapy demonstrated high efficacy in both ORR and 6-month PFS. Even after the fourth line of treatment, the 6-month PFS was high with the RS5614 combination therapy.

Treatment	Number of Patients	ORR(%)	6-month PFS
RS5614＋Nivolumab	Third-line treatment n ＝11	**18.2%**	**27.5%**
	Overall n＝36	8.3%	22.5%
Nivolumab monotherapy*	n＝59	8.5%	15.0%

* (Clin Cancer Res. 2022 28: OF1–OF7. doi:10.1158/1078-0432.CCR-22-0602)

Safety

Regarding safety, the incidence of serious adverse events (Grade 3 or higher) related to the investigational treatment was 13.8%, compared to the previously reported 20.3% for nivolumab monotherapy. No new adverse events were observed associated with the combination. There were no serious or unknown side effects.

This Phase II study confirmed that the antitumor effect of nivolumab was enhanced when combined with RS5614. As higher efficacy has been confirmed for patients receiving early treatment (third-line treatment), the next phase of the study will be an investigator-initiated clinical trial (coordinating investigator: Takeshi Masuda, Associate Professor, Department of

Respiratory Medicine, Hiroshima University Hospital) to evaluate the efficacy and safety of the PAI-1 inhibitor (RS5614) combination therapy in patients with early-stage, locally advanced non-small cell lung cancer[11] following initial standard treatment, chemoradiotherapy[12] and consolidation therapy[13] with the immune checkpoint inhibitor durvalumab[14]. Face-to-face consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) has already been completed on November 14, 2025, and the clinical protocol has been finalized. Following approval by the Institutional Review Board (IRB) and submission of a clinical trial notification to the PMDA, the investigator-initiated clinical trial is scheduled to begin in April 2026 or later. Based on a comprehensive collaboration agreement concluded with Hiroshima University in April 2023, the investigator-initiated clinical trial will be conducted at Hiroshima University's Renascience Open Innovation Lab (HiREx).

Suggested reasons for the enhanced antitumor effect of combined use of RS5614, a plasminogen activator inhibitor (PAI)-1, include inhibition of epithelial-mesenchymal transition (EMT)[15], reduction in tumor-infiltrating macrophages (TAM), increase in intratumoral T lymphocyte count, reduction in immune checkpoint molecule expression on cancer cells, thereby reversing resistance to immune checkpoint molecule inhibitors, improvement of the tumor immune microenvironment[16], and activation of tumor immunity (see our news release dated November 11, 2025).

Overview of next clinical trial (disclosed November 26, 2025)

Subjects	Locally advanced non-small cell lung cancer
Trial Design	Open-label, uncontrolled, multicenter trial
Number of Patients	27
Primary Endpoint	1-year PFS
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 purpose of the next clinical trial is to evaluate whether the PAI-1 inhibitor RS5614, combined

with chemoradiotherapy including definitive irradiation and consolidation therapy with durvalumab, will 1) improve the objective response rate (ORR) by enhancing the antitumor effects of chemoradiotherapy and durvalumab, and 2) improve treatment safety by suppressing lung damage (side effects) caused by radiation therapy and durvalumab, in patients with locally advanced non-small cell lung cancer who are not candidates for curative surgery. The purpose is to clarify whether the RS5614 combination treatment can be a new treatment that surpasses the current initial standard of care.

Going forward, we will compile the results of this clinical trial in a clinical study report and proceed with preparations for the next phase of trials and practical application.

There is currently no impact on our financial results for the fiscal year ending March 31, 2026, but we will make timely disclosures if any matters requiring disclosure arise in the future.

[1)] 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 the suppression of the immune system.

[2)] Non-Small Cell Lung Cancer
Lung cancer is the leading cause of cancer deaths and has a poor prognosis. In Japan, the incidence of lung cancer (2019) was 84,325 men and 42,221 women. The death toll (2020) was 53,247 men (leading among men) and 22,338 women (leading among women), with non-small cell lung cancer accounting for 80-85% of lung cancer cases.

[3)] Driver Gene
Cancer research has revealed that cancer cells have abnormalities (increased amounts) of certain genes and proteins compared to normal cells. These abnormal genes, called "oncogenes," are thought to be the cause of carcinogenesis and cancer growth. In particular, genes that play a direct role in the development and progression of cancer are called "driver genes."

[4)] Platinum-Based Chemotherapy
A type of anticancer drug (cytotoxic anticancer drug) used to treat lung cancer. By binding to the

DNA (genetic code) within cancer cells, they stop the division of cancer cells and kill them. Examples include cisplatin and carboplatin.

[5] Immune Checkpoint Inhibitors

Immune checkpoint molecules were 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-1 and CTLA-4. Immune checkpoint inhibitors are drugs that block the action of immune checkpoint molecules. All drugs currently used as treatments are antibody drugs that directly bind to and inhibit immune checkpoint molecules.

[6] Docetaxel

This compound is semi-synthesized from plant ingredients. It inhibits cancer cell proliferation by stabilizing and overexpressing microtubules, a cellular component necessary for cell division.

[7] Progression-Free Survival (PFS)

This is one of the indicators used to evaluate the effectiveness of cancer treatment. It refers to the period from the start of treatment until cancer progression or recurrence is confirmed, or until the patient dies. The longer this period, the more effective the treatment.

[8] Ipilimumab

This antibody drug (human anti-human CTLA-4 monoclonal antibody) 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 trial of nivolumab in combination with chemotherapy

In a Phase III multicenter clinical trial (JCOG2007 Study, Specific Clinical Research) targeting untreated advanced or recurrent non-small cell lung cancer, approximately 7.4% (11 of 148 patients) of patients receiving chemotherapy and the immune checkpoint inhibitors nivolumab and ipilimumab combined therapy experienced deaths for which a causal relationship to treatment could not be ruled out. This exceeded the expected range, resulting in the study being discontinued on March 30, 2023.

[10] Response Rate(ORR)

The percentage of patients whose tumors shrank or disappeared after chemotherapy or radiation therapy.

[11] Locally Advanced Non-Small Cell Lung Cancer
This refers to locally advanced non-small cell lung cancer (NSCLC) that develops in the lungs and has spread so locally that surgery is difficult.

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

[13] Consolidation Therapy
This is additional treatment administered after initial treatment (e.g., chemoradiotherapy) has achieved some degree of cancer suppression, with the aim of maintaining and strengthening the effects of treatment. It aims to prevent recurrence and progression.

[14] 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 chemoradiotherapy). Side effects can affect various immune-related organs, such as interstitial lung disease and liver dysfunction. Both durvalumab and nivolumab are cancer treatments classified as immune checkpoint inhibitors, but durvalumab is an anti-PD-L1 (cancer) antibody, while nivolumab is an anti-PD-1 (lymphocyte) antibody.

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

[16] Tumor immune microenvironment
This refers to the state of tissue that differs from normal tissue due to interactions between cancer cells and surrounding cells. Anticancer drugs make cancer cells less susceptible to immune attack, which is thought to be one factor in the acquisition of resistance.