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To Shareholders,

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Representative: Toshio Miyata, Chairman and CEO
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Announcement of initiation of an investigator-initiated clinical trial with a PAI-1 inhibitor RS5614 in combination with gemcitabine and nab-paclitaxel for treatment of patients with unresectable or recurrent metastatic pancreatic cancer

We are pleased to announce that we have completed the agreement with Tohoku University to initiate a Phase II clinical trial with a PAI-1 inhibitor RS5614[1)] in combination with gemcitabine and nab-paclitaxel treatment[2)] in patients with unresectable or recurrent pancreatic cancer with distant metastasis, in multiple medical institutions, including Tohoku University Hospital.

[Challenges in pancreatic cancer treatment]

Pancreatic cancer is the third leading cause of death among malignant tumors, yet early detection is extremely difficult. Only 15-20% of pancreatic cancers are resectable at the time of diagnosis, and 46.3% are diagnosed as having distant metastasis[3)]. This malignant disease has a very poor prognosis. While curative resection is essential for long-term survival, even when curative resection is achieved, recurrence after resection is extremely common, resulting in a poor prognosis of 18.8-31.3%. Chemotherapy is the standard treatment for pancreatic cancer with distant metastasis or recurrence after resection, but there are few effective treatments. The response rates[4)] and median overall survival (OS)[5)] of gemcitabine hydrochloride[6)] and fluorouracil[7)] are inadequate, at 5.4% and 5.65 months, respectively, and 0% and 4.41 months, respectively. In recent years, treatments such as FOLFIRINOX therapy[8)] (response rate: 31.6%, OS: 11.1 months) and gemcitabine and nab-paclitaxel therapy (GnP therapy, response rate: 29%, OS: 8.5 months) have emerged, but the overall five-year survival rate is around 10% (1-3% at the stage 4: when cancer has spread to distant organs and lymph nodes), and there is a need for new treatments or drugs that enhance existing standard treatments.

In recent years, the emergence of immune checkpoint inhibitors (ICI)[9)] has brought about revolutionary advances in cancer treatment, but the efficacy of ICI varies greatly depending on the types of cancer. ICI are highly effective in hot tumors[10)] characterized by high expression of the immune checkpoint molecule[11)] PD-L1 and high intra-tumoral T-cell infiltration[12)]. By contrast, pancreatic cancers are cold tumors[13)] characterized by low PD-L1 expression and low intra-tumoral T-cell infiltration, making ICI extremely ineffective. Pancreatic cancer possesses an

immunosuppressive intra tumor microenvironment[14] characterized by an abundance of cancer-associated fibroblasts (CAF)[15], which is one of the reasons why it is a cold tumor. This contributes to treatment resistance not only to ICI but also to existing cytotoxic anti-cancer drugs and molecularly targeted drugs[16].

[Pancreatic Cancer and PAI-1 Inhibitors]

High expression of plasminogen activator inhibitor 1 (PAI-1) has previously been reported as a poor prognostic factor in many types of cancer, and this has also been confirmed in pancreatic cancer.

A series of non-clinical studies have confirmed that the PAI-1 inhibitor RS5614, when used in combination with immune checkpoint inhibitors such as nivolumab, enhances the efficacy of nivolumab. RS5614 has several benefits for treatment of cancers, including the inhibition of epithelial-mesenchymal transition (EMT)[17], activation of T lymphocytes, reduction of tumor-infiltrating macrophages (TAM) [18], increase in the number of T lymphocytes within the tumor, reduction of immune checkpoint molecule expression on cancer cells, overcoming cancer cell resistance to immune checkpoint molecule inhibitors, improving the tumor immune microenvironment, and activating tumor immunity (disclosed on November 11, 2025). Furthermore, the pharmacological actions of PAI-1 inhibitors, such as their anti-thrombotic and anti-fibrotic effects, as well as the reduction of cancer-associated fibroblasts (CAF), are thought to be useful benefits when considering the tumor environment of pancreatic cancer.

Pharmacological benefits of RS5614 for the treatment of cancers (published papers using our PAI-1 inhibitors)

- Anti-thrombotic effects (Arterioscler Thromb Vasc Biol. 2008: 28: 672-677; J Cereb Blood Flow Metab. 2010: 30: 904-912)
- Anti-fibrotic effects (Proc Natl Acad Sci USA. 2014: 111: 7090-7095; Am J Respir Cell Mol Biol. 2020: 62: 319-330)
- Anti-inflammatory effects (Arterioscler Thromb Vasc Biol. 2013: 33: 935-42)
- Inhibition of tumor-associated macrophage (TAM) infiltration and of cancer-associated fibroblasts (CAF) (Front Immunol 2024:15:1365894)
- Immune checkpoint inhibition (Front Immunol 2024:15:1365894)
- Inhibition of cancer-associated fibroblasts (J Cell Mol Med. 2019: 23: 2984-2994, Front Immunol 2024:15:1365894)
- Inhibition of epithelial-mesenchymal transition (EMT) of cancer cells (Mol Cancer Ther 2025: 10.1158/1535-7163)
- Improvement of cancer resistance to chemotherapy and immunotherapy (Cancers 2023: 10.3390/cancers15041092;Mol Cancer Ther 2025: 10.1158/1535-7163)

Sebastiano *et al.* reported that PAI-1 expression levels correlate with the degree of fibrosis and immunosuppression in human pancreatic cancer specimens, and that pancreatic cancers with

high PAI-1 expression have a poor prognosis (Science Advances 2020; 6; eabb9200). Furthermore, in a preclinical pancreatic cancer mouse model, they confirmed that PAI-1 promotes the proliferation of tumor-infiltrating macrophages (TAM) and cancer-associated fibroblasts (CAF) and inhibits cytotoxic T cells. They also demonstrated in mice that a PAI-1 inhibitor (a different PAI-1 inhibitor from ours, PAI-039, with an IC50 of 9-12 μM; for reference, RS5614 has an IC50 of 3.63 μM) suppresses TAM and CAF, activates cytotoxic T cells, and significantly improves resistance to gemcitabine and ICI. In collaboration with Tokai University, we have obtained similar preclinical findings in mice using RS5614 (our unpublished data).

[Phase 2 trial]

Based on these preclinical findings, we have conducted investigator-initiated clinical trials with a PAI-1 inhibitor RS5614 in patients with unresectable melanoma, non-small cell lung cancer, cutaneous angiosarcoma, and other cancers (disclosed on December 1, 2025). We have already confirmed Complete Response (CR) and Partial Responses(PR) in melanoma patients, confirming the effectiveness of combining RS5614 with the PAI-1 inhibitor in some cancer types. RS5614 has received orphan drug designation for melanoma from the Ministry of Health, Labour and Welfare (disclosed September 2, 2024), and we have begun a Phase III clinical trial in melanoma, which will serve as a validation study for pharmaceutical approval (disclosed on February 18, 2025).

In order to initiate a new clinical trial with high unmet medical need[19], we have signed an agreement with Tohoku University to initiate a Phase II trial of a PAI-1 inhibitor RS5614 combination therapy with gemcitabine and nab-paclitaxel (coordinating investigator: Professor Michiaki Unno, Department of Digestive Surgery, Tohoku University Graduate School of Medicine), in some medical institutions, including Tohoku University Hospital.

We have already completed face-to-face consultations with the Pharmaceuticals and Medical Devices Agency (PMDA) on March 19, 2025, and the clinical protocol has been finalized. Following approval from the Institutional Review Board (IRB) and submission of a clinical trial notification to the PMDA, we plan to begin an investigator-initiated clinical trial.

[Phase 2 Trial Overview]

Subjects	Unresectable or recurrent pancreatic cancer with distant metastasis
Trial Design	Open-label, uncontrolled, multicenter trial
Number of Patients	50
Primary Endpoint	Main: Response rate Secondary outcomes: overall survival, progression-free survival[20], disease control rate[21]
Trial Sites (Planned)	Tohoku University and other medical institutions
Trial Period	May 2026 - December 2029

	Planned Enrollment Period: (24 months) Planned Observation Period: (12 months)

The purpose of this Phase II study is to determine whether combining the PAI-1 inhibitor RS5614 with gemcitabine and nab-paclitaxel therapy for unresectable or recurrent pancreatic cancer with distant metastasis could be a new treatment that surpasses the current standard of care.

There will be no changes to the earnings forecast for the fiscal year ending March 2026 due to this matter.

[1] PAI-1 inhibitor RS5614

PAI-1 is an important protein in pathological conditions such as thrombosis, fibrosis, and inflammation.RS5614 is an oral PAI-1 inhibitor developed in our company and Tohoku University. In addition to its thrombolytic properties, anti-fibrotic, and anti-inflammatory effects, it also enhances the immune system, which helps eliminate cancer and senescent cells. (disclosed on December 1, 2025.)

[2] Combination therapy with gemcitabine and nab-paclitaxel

This combination chemotherapy is considered the standard of care for pancreatic cancer, and its effectiveness against advanced pancreatic cancer has been clinically established.

[3] Diagnosed as having distant metastasis

This refers to the spread of cancer to organs other than the pancreas where it originated.

[4] Response rate

This is a general evaluation standard used to determine the effectiveness of treatment for solid cancers. Before starting treatment, the size of the tumor is measured using imaging diagnosis such as CT, and large tumors are selected as target lesions, and others are called non-target lesions. The change in size of these lesions during treatment is expressed as "complete response (CR)", "partial response (PR)", "stable disease (SD)", or " progressive disease (PD)".

[5] Overall survival (OS)

This refers to the period from the start of treatment to the patient's death, and is one of the main indicators used to evaluate the effectiveness of cancer treatment.

[6] Gemcitabine hydrochloride

An anticancer drug (nucleic acid synthesis inhibitor) used for solid cancers including pancreatic

cancer. It is widely used as a standard treatment both in Japan and overseas.

[7] Fluorouracil
An anticancer drug that suppresses cancer growth by interfering with the production of DNA materials necessary for cancer cell proliferation. It is used in the treatment of many solid cancers, including colon cancer, stomach cancer, and pancreatic cancer.

[8] FOLFIRINOX therapy
This chemotherapy combines four anticancer drugs (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and is primarily used to treat pancreatic cancer. Combining multiple drugs is expected to have a stronger effect in suppressing cancer growth.

[9] Immune checkpoint inhibitors (ICI)
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.

[10] Hot tumor
This type of cancer has a high T cell infiltration rate within the tumor, and tends to respond well to immunotherapy such as immune checkpoint inhibitors.

[11] Immune checkpoint molecule
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 abuse 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.

[12] Intra-tumoral T-cell infiltration
This is an index showing the extent to which T cells (immune cells) have infiltrated into cancer

tissue. The greater the infiltration, the more likely immunotherapy is to be effective.

[13] Cold tumor
Immunotherapy tends to be less effective for cancers with low T cell infiltration within the tumor.

[14] Intratumor microenvironment
This refers to a tissue state 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 of the factors that contribute to the acquisition of resistance.

[15] Cancer-associated fibroblasts (CAF)
Fibroblasts, present in the tumor stroma (tissue that supports cancer cells), deposit abundant extracellular matrix (such as collagen) around cancer cells, acting as a physical barrier. This prevents anticancer drugs and immune cells from reaching the cancer tissue, reducing the effectiveness of treatment. Cancer-associated fibroblasts also modulate the tumor immune microenvironment and suppress the function of immune cells such as T cells, thereby weakening the effects of cancer immunity.

[16] Molecularly targeted drugs
These drugs act directly on specific molecules and pathways involved in the proliferation and survival of cancer cells. Compared to conventional anticancer drugs, they are expected to attack cancer cells while minimizing the impact on normal cells.

[17]Epithelial-mesenchymal transition（EMT）
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.

[18]Tumor-Associated macrophages（TAM）
Tumor-infiltrating macrophages are a type of immune cell that accumulates in cancer tissue, and high levels of these cells are associated with poor patient prognosis. Specifically, they produce cell growth factors and promote cancer cell proliferation, release angiogenic factors and increase the blood supply to tumors, and promote the invasion and metastasis of cancer cells into surrounding tissues.

[19]Unmet medical need

This refers to medical needs for diseases and symptoms that are not adequately addressed by current treatments, and is an area where the development of new treatments and drugs is particularly required.

[20)]Progression-free survival

This is one of the indicators used to evaluate the effectiveness of cancer treatment, and 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.

[21)]Disease control rate

This is an index that shows the percentage of patients whose cancer has shrunk (complete response or partial response) or stopped progressing as a result of treatment. It is used to comprehensively evaluate the effectiveness of treatment.