May 12, 2026

To Shareholders,

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

Announcement of Initiation of a Phase II Trial for Unresectable Pancreatic Cancer with Distant Metastasis or Recurrent Pancreatic Cancer

We are pleased to announce that our Phase II, investigator-initiated clinical trial of our PAI-1 inhibitor RS5614[1)] for unresectable pancreatic cancer with distant metastasis or recurrent pancreatic cancer has been initiated, with the first patient enrolled on May 12, 2026.

Challenges in pancreatic cancer treatment

Pancreatic cancer is the third leading cause of cancer-related death, 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[2)]. 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[3)] and median overall survival (OS)[4)] of gemcitabine hydrochloride[5)] and fluorouracil[6)] 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[7)] (response rate: 31.6%, OS: 11.1 months) and gemcitabine and nab-paclitaxel therapy (GnP therapy[8)], response rate: 29%, OS: 8.5 months) have emerged, but the overall five-year survival rate is around 10% (1-3% at 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 type of cancer. ICIs 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-tumoral 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

It has long been reported across many cancer types that high PAI-1 expression is a poor prognostic factor, and this has also been confirmed in pancreatic cancer. In preclinical studies conducted in collaboration with Tohoku University, Tokai University, and others, it was found that PAI-1 inhibitors suppress tumor-associated macrophages (TAM)[17] and CAF, activate cytotoxic T cells[18], and markedly overcome resistance to gemcitabine hydrochloride and immunotherapy.

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)[19] 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)

Study Overview

This Phase II investigator-initiated clinical trial will evaluate the efficacy and safety of combining the PAI-1 inhibitor RS5614 with the standard gemcitabine plus nab-paclitaxel regimen in 50 patients with unresectable pancreatic cancer with distant metastasis or recurrent pancreatic cancer. The trial will be conducted at three medical institutions: Tohoku University Hospital, Kanagawa Cancer Center, and National Cancer Center Hospital (principal investigator: Professor Michiaki Unno, Department of Surgery, Division of Gastroenterological Surgery, Tohoku

University Graduate School of Medicine).
The purpose of this study is to determine whether adding RS5614 to the current standard treatment of gemcitabine plus nab-paclitaxel could become a new therapy superior to the existing standard of care.

Subjects	Unresectable pancreatic cancer with distant metastasis or recurrent pancreatic cancer
Trial design	Open-label, uncontrolled, multicenter study
Number of patients	50 patients
Endpoint:	Primary: Response rate Secondary: overall survival, progression-free survival[20], disease control rate[21]
Trial Sites	Tohoku University, Kanagawa Prefectural Cancer Center, National Cancer Center Hospital
Trial period	May2026 to December 2029 Planned enrollment period: 24 months Planned observation period: 12 months

[Impact on Financial Performance]
As costs related to this matter have already been incorporated into the full-year earnings forecast for the fiscal year ending March 2027, there will be no further impact on financial performance as a result of 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) Diagnosed as having distant metastasis
This refers to the spread of cancer to organs other than the pancreas, where it originated.

3) 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 classified as "complete response (CR)", "partial response (PR)", "stable disease (SD)", or " progressive disease (PD)".

4) 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.

5) 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.

6) 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.

7) 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.

8) Combination therapy with gemcitabine and nab-paclitaxel (GnP therapy)

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

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 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 exploit immune checkpoint molecules to avoid attacks from the immune system. Currently, various immune checkpoint molecules such as PD-L1 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] Intra-tumoral microenvironment

This refers to a tissue state that differs from normal tissue due to interactions between cancer cells and surrounding cells. This immunosuppressive environment renders cancer cells less susceptible to immune attack, which is thought to be one of the factors contributing to the acquisition of treatment 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, which acts 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] 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.

[18] Cytotoxic T cells

These immune cells identify and directly attack abnormal cells, such as virus-infected or cancer cells, destroying them to prevent the spread of disease and protect the body.

[19] 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.

[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.