Press Release

J-Pharma

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J-Pharma Co., Ltd.

J-Pharma announces Publication of the Abstract on the Japan Phase 2 study of *nanvuranlat* (development code: JPH203) for advanced refractory biliary tract cancer patients at the American Society of Clinical Oncology (ASCO) Annual Meeting. *Nanvuranlat* is an L-type amino acid transporter 1 (LAT1) inhibitor

Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of *nanvuranlat* in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to *nanvuranlat*（Abstract Code Number:　4011）

J-Pharma Co., Ltd. (Headquarters: Yokohama City, Kanagawa Prefecture; President & CEO: Masuhiro Yoshitake) announced that the results of a subgroup analysis of a Japan Phase 2 study (hereinafter referred to as the Study) for advanced and refractory biliary tract cancer was nominated for an oral presentation at the Clinical Science Symposium (June 4, 2023, 4: 30 p.m. to 6:00 p.m. Central Time) at the 2023 ASCO Annual Meeting. The full abstract was published by ASCO on May 25 (5:00 pm U.S. Eastern Time).

At the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI 2023) held on Friday, January 20, 2023, *nanvuranlat* demonstrated efficacy in patients with advanced and refractory biliary tract cancer who had been previously treated. In an oral presentation, the primary endpoint (progression-free survival: PFS) showed a statistically significant improvement and a favorable safety profile. In this presentation, when we analyzed the subgroup LAT1 high expression group, we will report that the *nanvuranlat* administration group showed a statistically significant improvement and a favorable safety profile.

Details of the Abstract

- **Title**
  Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of *nanvuranlat* in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to *nanvuranlat*. (Abstract Number：4011)

- **Presenter：**

  Dr. Masafumi Ikeda, Director, Department of Hepatobiliary and Pancreatic Medicine, National Cancer Center Hospital East

- **Contents**
  - LAT1 (generic code: SLC7A5) is expressed at the cell membrane when cells become cancerous and attempt to proliferate rapidly[1].
  - LAT1 has been scientifically elucidated in recent years, and the complex molecular structure of LAT1 has recently been reported, attracting attention as a drug target for cancer treatment[2].
  - Cancer patients with high LAT1 expression have been reported to have a worse prognosis than those with low LAT1 expression[3].
  - *Nanvuranlat* is a novel small-molecule compound that selectively inhibits LAT1[2]

- **Study Outline**

  A randomized, double-blind, placebo-controlled phase 2 study of *nanvuranlat* in patients with previously treated advanced or refractory biliary tract cancer. Fourteen facilities in Japan participated, consent was obtained from 211 patients, and 104 patients entered the clinical trial. (*nanvuranlat* 69 patients, placebo 35 patients) Patients were stratified based on the polymorphism of the drug-metabolizing enzyme (NAT2) The study enrolled cases of four different subtypes of biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and papilla carcinoma), and 83% of patients were treated with standard chemotherapy. Advanced biliary tract cancer intolerant to therapy and at least two other investigational agents. The primary endpoint was Progression-Free Survival (PFS) as assessed by a blinded independent central review (BICR) based on the new guidelines for determining therapeutic response in solid tumors (RECIST 1.1). Key secondary endpoints included overall survival (OS) and disease control rate (DCR: CR+PR+SD).

- **Study Results**
  - PFS in the *Nanvuranlat* group showed a statistically significant improvement compared to the placebo group (hazard ratio 0.56, 95% confidence interval 0.34-0.90, p = 0.016). Adverse drug reactions (side effects) were 41.4% for *nanvuranlat* and 57.1% for placebo, and grade 3 or higher adverse events were 30.0% for *nanvuranlat* and 22.9% for placebo, but there were no events leading to treatment discontinuation/dose reduction or death.
  - In a pre-defined subgroup analysis, the PFS of *nanvuranlat* in patients with high LAT1 expression (*nanvuranlat* group: 47 patients, placebo group: 18 patients) showed statistically significantly improvement compared to the placebo group (hazard ratio 0.44, 95% confidence interval 0.23-0.85, p = 0.01).
  - Disease control was achieved in 17 (24.6%) patients with *nanvuranlat* and 4 (11.4%) with placebo.
  - OS did not show a statistically significant prolongation, but OS in the LAT1 high expression group

showed a longer prolongation.

- Forest plot subgroup analysis of PFS suggests efficacy in extrahepatic bile duct cancer and gall bladder cancer.

- **Conclusion**
  - In subgroup analyzes of this study, *nanvuranlat* demonstrated further improvements in PFS and OS in LAT1 high expression compared to placebo. Side effects were comparable to placebo. This suggests that *nanvuranlat* will be one treatment option for these biliary tract cancers after second-line therapy.

Based on the results of this study, J-Pharma will proceed with preparations for filing an application for approval in Japan and the U.S., in order that it can be promptly provided to patients with advanced refractory biliary tract cancer. We expect that the results of this study will provide a new treatment option for patients with biliary tract cancer who currently have extremely limited treatment options.

1 Häfliger P, et al. Int J Mol Sci 2019

2 Kanai Y. Pharmacol Ther 2022

3 Otani R, et al. Cancers (Basel) 2023

Inquiries Regarding this matter:

J-Pharma Co. Ltd.

Administration Department

Public Relations

Tel: 045-506-1155

Fax: 045-506-1156

info@j-pharma.com

Reference Materials

1. ※About LAT 1

More than 50 types of amino acid transporters have been discovered thus far, but in 1988 J-Pharma's founder, Dr. Hitoshi Endo, discovered the SLC transporter LAT1 (generic code: SLC7A5) is upregulated at the cell membrane when cells become cancerous or rapidly proliferate, and actively incorporates amino acids to cause explosive cell proliferation. LAT1 (SLC7A5) has been scientifically elucidated in recent years, and the complex molecular structure of LAT1 has recently been reported, attracting attention has a drug target. In addition, LAT1 has been confirmed to be expressed not only in cancer cells, but also in rapidly proliferating cells such as immune cells. In recent years there have been many reports that LAT1 plays an important role in autoimmune disease such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis. We are promoting the application of LAT1 inhibitors to autoimmune diseases as the next target.

2. ※About *Nanvuranlat*

Nanvuranlat is a novel low-molecular-weight compound that J-Pharma independently discovered targeting LAT1. Since 2015 J-Pharma has conducted phase 1 clinical trials targeting multiple solid tumors and discovered the potential for biliary tract cancer. It is the world's first compound that targets LAT1 and is undergoing clinical development and will become a first-in-class new drug when approved by competent authorities. In April 2022, *nanvuranlat* was designated as an orphan drug (orphan drug) by the U.S. Food and Drug Administration (FDA). Companies can receive preferential treatment such as exemption and grant of exclusive sales rights for seven years in the United States under the 1983 Orphan Drug Act.

3. ※Biliary Tract Cancer

Biliary tract cancer is a general term for cancer that develops in the biliary tract, Biliary tract cancer is classified into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and duodenal papilla cancer, depending on where it occurs. Extrahepatic cholangiocarcinoma is further classified into perihilar region cholangiocarcinoma and distal cholangiocarcinoma. Biliary tract cancer may be found during examinations and other examinations if the disease is in its early stages, but in many cases biliary tract cancer progresses without symptoms. In many cases, the diagnosis of cancer is made after the disease condition has occurred. According to the cancer statistics of the Japan National Cancer Center, the number of gallbladder and bile duct cancer patients is 22,159 (2019), which ranks 16th among all cancer types. On the other hand, the number of deaths is 18,172 (2021), and the 5-year relative survival rate (2009-2011 regional cancer registry survival rate data) is as low as 24.5%, indicating an extremely poor prognosis. Of the 18,750 registered cases of gallbladder/bile duct cancer, 88% were 65 years old or older at the time of diagnosis, and 60% were 75 years old or older. In addition, the percentage of gallbladder cancer in the TNM classification comprehensive stage IV is extremely high at 45.1%, and the percentage of stage IV without treatment such as surgery or drug treatment accounts for nearly half, 42.4%. The curative

treatment for biliary tract cancer is excision of the lesion by surgical resection. Chemotherapy is performed for biliary tract cancer that is difficult to resect and is not indicated for surgery. In Japan, combination therapy with *gemcitabine* and *cisplatin* (GC), combination therapy with *gemcitabine* and *tegafur/gimeracil/oteracil potassium* (S-1) (GS), and combination therapy with GC and S-1 (GCS) are standard treatments. Once resistant to these standard therapies (GC, GS or GCS), there are currently no established second-line therapies. In recent years, *pemigatinib*, a tyrosine kinase activity inhibitor, was approved in Japan in March 2021 for the treatment of FGFR2 fusion gene-positive unresectable biliary tract cancer that has progressed after chemotherapy. The immune checkpoint inhibitor *durvalumab* was approved in December 2022 for "unresectable biliary tract cancer" in combination with chemotherapy.

Inquiries Regarding this matter:
J-Pharma Co. Ltd.
Administration Department
Public Relations
Tel: 045-506-1155
Fax: 045-506-1156
info@j-pharma.com