Press Release

J-Pharma

June 5, 2023

J-Pharma Co., Ltd.

LAT1 inhibitor *Nanvuranlat* (development code: JPH203): Significant improvement in biliary tract cancer with high LAT1 expression, extrahepatic cholangiocarcinoma, and gallbladder cancer

Study Outline

- For advanced and refractory biliary tract cancer, the *nanvuranlat* group (69 cases) showed a statistically significant improvement in PFS compared to the placebo group (35 cases). The primary endpoint was achieved. (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, PFS of *nanvuranlat* in patients with biliary tract cancer with high LAT1 expression (47 in the *nanvuranlat* group, 18 in the Placebo group) showed a substantially significant improvement compared to the placebo group. (hazard ratio 0.44, 95% confidence interval 0.23-0.85, p = 0.01).
- There was no significant OS prolongation in the overall *nanvuranlat*-treated group, but OS in the LAT1-high biliary tract cancer group showed a greater prolongation.
- Disease control was achieved in 17 (24.6%) patients with *nanvuranlat* and 4 (11.4%) with placebo. Of the patients whose disease was controlled with *nanvuranlat*, eleven (11/17) were in the biliary tract cancer group with high LAT1 expression. This suggests that *nanvuranlat* is more clinically useful in biliary tract cancer patients with high LAT1 expression, who are known to have a poor disease prognosis.
- The Forest plot analysis of PFS subgroups suggested a benefit in extrahepatic cholangiocarcinoma and gallbladder cancer among the four biliary tract cancer subtypes, and since both cancer types have similar embryology and gene metastasis patterns, both groups were combined for an exploratory analysis (31 patients in the *nanvuranlat* group and 14 in the placebo group). The results showed a more significant improvement in PFS compared to the placebo group (hazard ratio 0.22, 95% confidence interval 0.10-0.49, p <0.001).
- In these subgroup analyses of this study, *nanvuranlat* demonstrated further improvements in PFS and OS in high LAT1 biliary tract cancer, extrahepatic cholangiocarcinoma and gallbladder cancer compared to placebo. Side effects were comparable to placebo. This suggests that *nanvuranlat* will be one of the treatment options for these biliary tract cancers after second-line therapy.

J-Pharma Co., Ltd. (Headquarters: Yokohama City, Kanagawa Prefecture; President & CEO: Masuhiro Yoshitake) announced that it has developed a novel low molecular weight compound called *nanvuranlat* that targets the L-type amino acid transporter 1 (LAT1) (Development Code; JPH203) in patients with advanced and refractory biliary tract cancer. These results were presented 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.

At the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI 2023) held on Friday, January 20, 2023, The oral presentation showed that *nanvuranlat* demonstrated statistically significant improvement in the primary endpoint (progression-free-survival: PFS) and a favorable safety profile in previously treated patients with advanced and refractory biliary tract cancer.

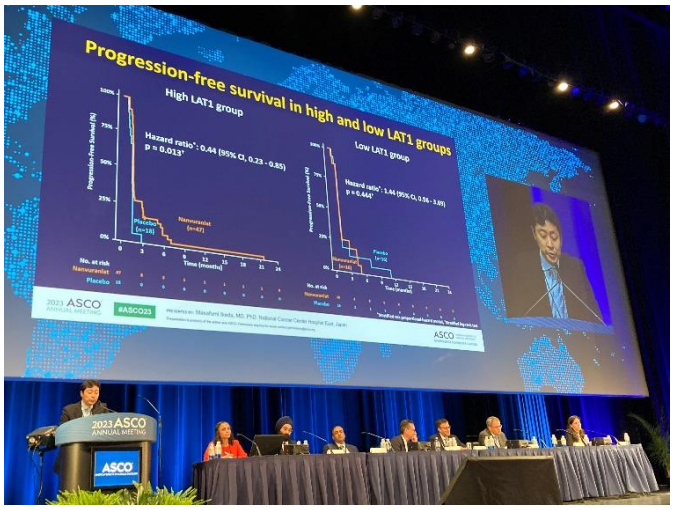
Presentation Contents

- **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：**

  Masafumi Ikeda, M.D., Ph.D, Department of Hepatobiliary and Pancreatic Medicine, National Cancer Center Hospital East



The Clinical Science Symposium (2023 ASCO Annual Meeting)

National Cancer Center Hospital East, Department of Hepato-Biliary-Pancreatic Medicine, Dr. Masafumi Ikeda, said, "The LAT 1 inhibitor *nanvuranlat* exerts its anti-tumor effect through a mechanism different from that of conventional anticancer drugs. This drug showed favorable therapeutic effects in a randomized Phase 2 study comparing *nanvuranlat* and placebo in patients with advanced biliary tract cancer who were refractory/intolerant to standard therapy among which LAT 1 was highly expressed. The results of the analysis supported the mechanism of action, showing that progression-free survival, disease control, and overall survival were better in patients with high LAT1 expression than in those with low LAT1 expression. This is an unprecedented achievement in that we were able to demonstrate the mechanism of action of *nanvuranlat* in a clinical setting, and I believe that this will provide momentum for future development of *nanvuranlat*."

Masuhiro Yoshitake, President and CEO of J-Pharma, said, "Based on the results of this study, we are preparing to apply for approval in Japan as well as in the United States in order that we can promptly provide this drug to patients with advanced intractable biliary tract cancer. We hope that the results of this study will provide a new treatment option for biliary tract cancer patients, who have very few treatment options, and we would like to thank all the patients and medical professionals who participated in this study."

Häfliger P, et al. Int J Mol Sci 2019[1]; Kanai Y. Pharmacol Ther 2022[2]; Otani R, et al. Cancers (Basel) 2023[3]

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

- LAT1 (generic code: SLC7A5), which J-Pharma's founder, Dr. Hitoshi Endo, discovered in 1998, is an amino acid transporter that increases expression on the cell membrane when cells become cancerous and try to proliferate rapidly. Intensive uptake of amino acids causes explosive cell proliferation[1].
- LAT1 has been the subject of recent scientific elucidation, and the complex molecular structure of LAT1 has recently been reported, attracting attention as a drug target in cancer therapy.[2]
- Cancer patients with high LAT1 expression have been reported to have a worse disease prognosis than those with low LAT1 expression.[3]

Häfliger P, et al. Int J Mol Sci 2019[1]; Kanai Y. Pharmacol Ther 2022[2]; Otani R, et al. Cancers (Basel) 2023[3]

2. ※About *Nanvuranlat*

Nanvuranlat is a novel low-molecular-weight compound that J-Pharma independently discovered that selectively inhibits 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 granted an orphan drug designation by the U.S. Food and Drug Administration (FDA). Organizations can receive preferential treatment such as fee payment exemptions and a 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, and is classified into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of vater carcinoma, 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 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.

Study Details

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 the patients were stratified based on the polymorphism of the drug-metabolizing enzyme (NAT2) has been registered. The study enrolled cases of four different subtypes of biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of vater 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).

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