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Press Release

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J-Pharma presented Japanese Phase II Trial of Nanvuranlat at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium 2023

Nanvuranlat met primary endpoint in Japanese Phase II Trial for patients with refractory, advanced biliary tract cancers

J-Pharma Co., Ltd. (Head office: Tsurumi, Yokohama Kanagawa, President & CEO: Max Yoshitake) announces LAT1 inhibitor monotherapy with Nanvuranlat, discovered and developed by J-Pharma, demonstrated efficacy in the largest controlled clinical trial in Japan for advanced biliary tract cancer (the "Study"). The result of the study was presented orally at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI 2023) on Friday, January 20, 2023 (U.S. Pacific Standard Time).

Gastrointestinal Cancers Symposium : (ASCO GI 2023)
Rapid Abstract Session
Oral presentations by Junji Furuse, M.D., Ph.D.
President, Kanagawa Cancer Center
Place: San Francisco
Local time: January 20, 2023, 7:10 AM-7:15 AM

In an interview with ASCO PR, Dr. Furuse said “Nanvuranlat, LAT1 Inhibitor, demonstrated a statistically significant progression-free survival with a good safety profile for patients with pretreated advanced refractory biliary tract cancer. Treatments in later lines of chemotherapy for biliary tract cancer are very limited. Nanvuranlat would contribute to improve the survival in biliary tract cancer patients who are refractory to standard treatments”.

1. Summary of the Study

Nanvuranlat for pre-treated patients with advanced, refractory biliary tract cancer: a randomized, double-blind, placebo-controlled, phase II study.

211 BTC patients were consented at 14 centers in Japan. Using *NAT2* testing for classification, a total of 106 patients were enrolled (Nanvuranlat: 70, Placebo: 36). When cells become cancerous, LAT1 is highly expressed on the cell surface and known to take up essential amino acids necessary for proliferation. High expression of LAT1 is associated with more malignant cancers and a worse prognosis for the patients. Patients with four different subtypes of biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer) were enrolled in the study, and 83% of patients had advanced biliary tract cancer with refractory to standard chemotherapy and other investigational medicines. Primary endpoint is Progression-Free Survival (PFS) as assessed by blinded independent central review (BICR) based on the RECIST 1.1.

*Clinical trial information: UMIN000034080

2. About results of the Study (Summary)

The study met its primary endpoint showed a statistically significant improvement in PFS for Nanvuranlat compared to the placebo group (Hazard ratio= 0.557, 95% CI=0.3435-0.9029, p = 0.0164). LAT1 inhibitor monotherapy with Nanvuranlat demonstrated efficacy in patients with four different subtypes of pre-treated, advanced, refractory biliary tract cancer. Nanvuranlat, a specific inhibitor of LAT1 has been shown to have efficacy as a single agent in patients with advanced refractory biliary tract cancer with multiple pre-treatments. Its efficacy was consistently confirmed across patients' gender, age, prior treatment, metastatic organs, and biliary tract cancer subtypes. The disease control rate (DCR) in the Nanvuranlat group was approximately 25% (average = 24.6%) across all BTC subtypes, while it was 11.4% in the placebo group. Treatment-related adverse events were respectively 41.4% and 51.7% in the Nanvuranlat and placebo groups. Grade 3 or higher adverse events were 30.0% for Nanvuranlat and 22.9% for placebo, but none resulted in discontinuation/dose reduction or death.

※About LAT1

More than 50 types of amino acid transporters have been discovered to date. L-type amino acid transporter 1 (gene code: *SLC7A5.* LAT1) is expressed on the cell surface and discovered by our founder Endou in 1998. LAT1 is upregulated on the cell membrane when cells become cancerous or proliferate rapidly, causing explosive cell proliferation by taking in amino acids rapidly. This leads to explosive cell proliferation. LAT1 attracts attention as a drug target thanks to the recent scientific elucidation and reports of the complex molecular structure of LAT1. Moreover, LAT1

has been shown to be expressed not only in cancer cells but also in highly proliferating cells such as immune cells. Especially, LAT1 has been reported to play an important role in many autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, multiple sclerosis, etc. in recent years. J-Pharma is now moving forward with the application of LAT1 inhibitors to autoimmune diseases.

※About Nanvuranlat

Nanvuranlat is a novel small molecule discovered and developed by J-Pharma.

J-Pharma has been conducting Phase I clinical trials for multiple solid tumors since 2015, found potential for biliary tract cancer and has spent three and a half years since 2018 conducting the Study. Nanvuranlat is the first LAT1-targeted compound undergoing clinical studies and will become the first-in-class medicine when approved by competent authorities. The U.S. Food and Drug Administration (FDA) granted orphan drug designation to Nanvuranlat in April 2022. With this designation, J-Pharma will receive benefits, including tax credits for qualified clinical trials, Waiver of new drug application (NDA) application fee, and eligibility for market exclusivity for 7 years post approval in the United States.

※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 cancer. Extrahepatic cholangiocarcinoma is further classified into perihilar rand distal cholangiocarcinoma. Biliary tract cancer is not found in the early stages of the disease and, in most cases, the disease passes asymptomatically. As the disease progresses, symptoms such as jaundice, pain in the right side of the abdomen, and weight loss may occur, and the diagnosis is often made after the disease has progressed. According to the National Cancer Center Japan's cancer statistics, the number of patients with gallbladder and bile duct cancer is 22,159 (2019), ranking 16th among all cancer types. Nevertheless, the prognosis is extremely poor, with 18,172 deaths (in 2021) and 5-year relative survival as low as 24.5% (survival rate data from the Regional Cancer Registries from 2009 to 2011). According to the Hospital-based Cancer Registry (2020), of the 18,750 registered cases of biliary tract cancer of the gallbladder and bile duct cancer, 88% were aged 65 years or older and 60% were aged 75 years or older at the time of diagnosis, showing that the disease is diagnosed at an older age. In addition, the percentage of TNM classification overall stage IV in gallbladder cancer is very high at 45.1%, and the percentage of stage IV patients who are not treated with surgery or drug therapy accounts for nearly half at 42.4%.

The curative treatment for biliary tract cancer is surgical resection of the tumor. Chemotherapy is used for difficult-to-resecting biliary tract cancers that are not eligible for surgical resection. 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) is the standard treatments. Once resistant to these standard therapies (GC, GS, or GCS), there is no established second-line therapy at present. Recently, pemigatinib, for the treatment of patients with unresectable biliary tract cancer (BTC) with a fibroblast growth factor receptor 2 (FGFR2) fusion, worsening after cancer chemotherapy was approved in Japan in March 2021. Durvalumab, an immune checkpoint inhibitor, was approved in December 2022 for " unresectable biliary tract cancer" in combination with chemotherapy.