ONO PHARMACEUTICAL CO.,LTD.

December 9, 2019

Two Clinical Results for Tirabrutinib (ONO-4059), a BTK Inhibitor, in Patients with "Primary Central Nervous System Lymphoma", and "Waldenstrom Macroglobulinemia and Lymphoplasmacytic Lymphoma" Presented at ASH 2019

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that the following two clinical results for tirabrutinib hydrochloride (ONO-4059) ("Tirabrutinib"), a Bruton's tyrosine kinase ("BTK") inhibitor, in patients with "relapsed or refractory primary central nervous system lymphoma (PCNSL)", and "Waldenstrom macroglobulinemia ("WM") and lymphoplasmacytic lymphoma ("LPL")" were presented on Saturday, December 7 and Sunday, December 8, respectively, at the American Society of Hematology (ASH) annual meeting 2019 in Florida, USA:

- A multi-center, open-label, single-arm Phase I/II study (ONO-4059-02) in patients with relapsed or refractory PCNSL
- A multi-center, open-label, single-arm Phase II study (ONO-4059-05) in patients with untreated recurrent or refractory WM and LPL

<PCNSL: Abstract #1586 >

Title: Phase 1/2 Study of Tirabrutinib (ONO/GS-4059), a Next-Generation Bruton's Tyrosine Kinase (BTK) Inhibitor, Monotherapy in Patients with Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL)

Date: Saturday, December 7, 2019, 5:30 PM - 7:30 PM, Poster session

This study is a multi-center, open-label, single-arm Phase I/II study (ONO-4059-02) evaluating the efficacy and safety of a monotherapy with Tirabrutinib in patients with relapsed or refractory PCNSL. In this study, 44 patients were recruited and received Tirabrutinib 320 mg (20 patients), 480 mg (7 patients) and 480 mg fasted (17 patients), once daily in either groups. Patients were treated until disease progression or unacceptable toxicity.

In this study, the overall response rate (ORR) assessed by an independent review committee (IRC), a primary endpoint, was 63.6% (28/44 patients) (95% confidence interval (CI): 47.8 - 77.6). The ORR of each treatment group was 60.0% (12/20 patients) (95% CI: 36.1 - 80.9), 100.0% (7/7 patients) (95% CI: 59.0 - 100.0) and 52.9% (9/17 patients) (95% CI: 27.8 - 77.0), respectively. The median progression-free survival (PFS), a secondary endpoint, was 2.9 months (95% CI: 1.8 - 11.1), and the median PFS of each treatment group was 2.1 months (95% CI: 1.8 - NE), 11.1 months (95% CI: 1.4 - NE) and 5.8 months (95% CI: 1.0 - 5.8), respectively. Median overall survival (OS) was not reached (95% CI: NE - NE). The most commonly observed grade ≥3 adverse events (AEs) were neutropenia (9.1%), lymphopenia, leukopenia and erythema multiforme (6.8% each).

<WM and LPL: Abstract #345>

Title: Phase 2 Study of Tirabrutinib (ONO/GS-4059), a Second-Generation Bruton's Tyrosine Kinase Inhibitor, Monotherapy in Patients with Treatment-Naïve or Relapsed/Refractory Waldenström Macroglobulinemia

Date: Sunday, December 8, 2019: 8:00 AM – 8:15 AM, Oral session

This study is a multi-center, open-label, single-arm Phase II study (ONO-4059-05) evaluating the efficacy and safety of a monotherapy with Tirabrutinib in patients with WM and LPL. In this study, 27 patients were recruited (untreated 18 patients and relapsed/refractory 9 patients). Patients received Tirabrutinib 480 mg (fasted) once daily and were treated until disease progression or unacceptable toxicity.

In this study, the overall response rate (partial response or greater) assessed by an independent review committee (IRC), a primary endpoint, was 88.9% (16/18 patients) (95% CI: 65.3 - 98.6) in the untreated group, and 88.9% (8/9 patients) (95% CI: 51.8 - 99.7) in the relapsed/refractory group. The secondary endpoints of progression-free survival (PFS) and overall survival (OS) were 100% at 6 months both in the untreated group and relapsed/refractory group. The most commonly observed grade ≥3 adverse events (AEs) were neutropenia and lymphopenia (11.1% each), and leukopenia (7.4%).

About Primary Central Nervous System Lymphoma (PCNSL)

PCNSL is a malignant lymphoma in which the lesion is localized in the cerebrospinal cord (including the eyes) at the first onset. It is estimated that there are approximately 980 new cases with PCNSL per year in Japan[*1, 2]. The signs and symptoms presented by patients with PCNSL vary depending on the site of the lesion, and include localized neuropathy, neuropsychiatric symptoms, symptoms associated with increased intracranial pressure, seizure, eye symptoms, headache, difficulty in movement, cranial neuropathy and radiculopathy.

Currently, untreated PCNSL patients receive high-dose methotrexate-based treatment followed by whole-brain radiation therapy, by which a certain patient population shows long-term remissions, but many patients will relapse. There are also refractory patients who do not respond to the initial treatment. Standard treatment has not been established for patients with relapsed or refractory PCNSL, and treatment options are limited for them. Therefore, a new treatment option is expected for patients with relapsed or refractory PCNSL[*3].

On August 28, 2019, ONO submitted an application of Tirabrutinib for the manufacturing and marketing approval in Japan for the treatment of recurrent or refractory PCNSL.

[*1]: Neurol Med Chir (Tokyo). 2017;57(Supplement 1):9-102.

[*2]: Jpn J Neurosurg VOL.24 NO.10 2015.10

[*3]: Practical Guidelines for Neuro-Oncology 2019

About Waldenstrom macroglobulinemia (WM) and lymphoplasmacytic lymphoma (LPL)

WM and LPL are one of the malignant lymphomas and are classified as "indolent lymphoma" which means one with relatively slow progression[*4]. It is estimated that there are approximately 240 new cases[*5,6] with LPL per year in Japan.

WM and LPL generally grow and spread slowly in the clinical course, with a median survival of more than 5 years, but these are intractable diseases that cannot be cured with existing therapies[*7]. In Japan, standard treatment has not been established in patients with untreated and relapsed or refractory WM and LPL, so a new treatment option is expected for these patient populations.

On November 27, 2019, ONO submitted an application of Tirabrutinib for the manufacturing and marketing approval in Japan for the treatment of WM and LPL.

[*4] : Center for Cancer Control and Information Services, National Cancer Center, National Research and Development Agency

[*5] : Cancer Incidence of Japan 2016

[*6] : Pathology International 2000;50:696–702.

[*7] : Practical Guidelines for Hematological Malignancies 2018

About Tirabrutinib

Tirabrutinib, discovered and developed by ONO, is a highly selective, oral BTK inhibitor and has been developed for the treatment in patients with B-cell tumors and autoimmune diseases in Japan. B cell receptor (BCR) signaling plays a core role in the survival, activation, proliferation, maturation and differentiation of B cell lymphocyte. The BCR signaling pathway is known to be permanently activated, particularly B cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL). Tirabrutinib is expected to have a therapeutic effect because it inhibits BTK, a mediator located downstream of BCR.

In December 2014, ONO out-licensed Tirabrutinib to Gilead Sciences, Inc. (Gilead) to allow Gilead the right to develop and commercialize the product in all countries of the world, except Japan, South Korea, Taiwan, China and ASEAN countries where ONO retains the development and commercialization rights of the product.

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