ONO PHARMACEUTICAL CO.,LTD.

April 14, 2021

ONO Submits Supplemental Application for Approval for Opdivo® (Nivolumab) to Expand the Use for Cancer of Unknown Primary in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") today announced that ONO has submitted a supplemental application for Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody in Japan, to expand the use for the treatment of cancer of unknown primary, for a partial change in approved items of the manufacturing and marketing approval.

This application is based on the result from an investigator-initiated clinical study (NivoCUP study), conducted under the initiative of Kindai University Hospital, evaluating Opdivo in patients with cancer of unknown primary (CUP). In this study, the observed response rate (ORR) in patients previously treated with chemotherapy (central assessment), the primary endpoint, was 22.2% (95% confidence interval: 11.2-37.1). Since the lower limit of the confidence interval exceeded a preset threshold ORR of 5%, the study met the primary endpoint. The ORR in the entire patient population regardless of treatment history (central assessment) was 21.4% (95% confidence interval: 11.6-34.4), indicating the antitumor effect of Opdivo across treatment history [1)].

CUP is defined as a malignant tumor of which primary lesion is unknown despite thorough search and is histologically proven to be a metastatic lesion [2)]. CUP is a pathological condition that has already advanced or metastasized at the time of diagnosis, and more than half of patients have metastasis to multiple organs [3)]. CUP is a serious and life-threatening disease having extremely poor prognosis with a median survival of 6-9 months [4)], and 5-year survival rate of 2-6% [5), 6)].

The number of CUP patients in Japan is estimated to be about 3,000 to 13,680 patients [7), 8)]. CUP is roughly divided into a favorable prognosis group for which specific treatment is indicated according to the estimated primary lesion and a poor prognosis group for which no treatment method has been established (80% of CUP) [2)]. The main treatment for this poor prognosis group is drug therapy, but there has been no drug approved in Japan nor overseas for the treatment of CUP. As standard treatment has not yet been established, drug development is eagerly desired.

Opdivo was designated as an orphan drug by the Ministry of Health, Labor and Welfare (MHLW) for the indication of CUP on March 11, 2021, and accepted for priority review.

1) Tanizaki J et al. J Clin Oncol. 2020;38:Issue 15 suppl 106-1062.
2) Practical Guideline for Carcinoma of Unknown Primary, 2nd Edition, Japanese Society of Medical Oncology 2018.
3) Seve P et al. Cancer. 2006;107:2698-705.
4) Pavlidis N et al. Eur J Cancer. 2003;39:1990-2005.
5) Greager JA et al. J Surg Oncol. 1983;23:73-6.
6) Altman E et al. Cancer. 1986;57:120-4.
7) Patient Survey 2017, Ministry of Health, Labour and Welfare 2019
8) Cancer Incidence of Japan. 2017, Cancer and Disease Control Division, Ministry of Health, Labour and Welfare 2020

About NivoCUP study

NivoCUP study is an open-label, Phase II clinical trial conducted under the investigator-initiated clinical study led by Kindai University Hospital, with the aim of evaluating the efficacy and safety of Opdivo in patients with CUP (poor prognosis group) who have been previously treated or untreated with chemotherapy. The primary endpoint of this study is observed response rate (ORR) in patients who have been previously treated with chemotherapy (central assessment). Secondary endpoints include ORR (in the whole patient population regardless of treatment history), overall survival and progression-free survival.

About Opdivo

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response by blocking the interaction between PD-1 and its ligands. By harnessing the body's own immune system to fight cancer, Opdivo has become an important treatment option across multiple cancers since the approval for the treatment of melanoma in Japan in July 2014. Opdivo is currently approved in more than 65 countries, including Japan, South Korea, Taiwan, China, the US and European Union.

In Japan, ONO launched Opdivo for the treatment of unresectable melanoma in September 2014. Thereafter, Opdivo received an approval for additional indications of unresectable, advanced or recurrent non-small cell lung cancer in December 2015, unresectable or metastatic renal cell carcinoma in August 2016, relapsed or refractory classical Hodgkin lymphoma in December 2016, recurrent or metastatic head and neck cancer in March 2017, unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy in September 2017, unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy in August 2018, and microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following chemotherapy and unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy in February 2020.

In addition, ONO is conducting clinical development program including esophago-gastric junction cancer, hepatocellular carcinoma, urothelial cancer, ovarian cancer, bladder cancer, prostate cancer, pancreatic cancer, biliary tract cancer, etc.

About the ONO and Bristol Myers Squibb Collaboration

In 2011, through a collaboration agreement with Bristol Myers Squibb (BMS), ONO granted BMS its territorial rights to develop and commercialize Opdivo globally except in Japan, South Korea and Taiwan, where ONO had retained all rights to Opdivo except the US at the time. In July 2014, ONO and BMS further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agent and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

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