December 24, 2021

ONO Receives Supplemental Approval of Opdivo® (Nivolumab)
for Expanded Use for Treatment of Cancer of Unknown Primary in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Shinjuku, Tokyo; President, Jean-Christophe Barland) today announced that ONO has received a supplemental approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody in Japan, for expanded use for the treatment of cancer of unknown primary, for a partial change in approved items of the manufacturing and marketing approval.

This approval 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. Furthermore, 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 treatment for this poor prognosis group is mainly drug therapy, but there has been no drug approved in Japan nor overseas for the treatment of CUP.

With this approval, Opdivo is expected to become a new treatment option for patients with CUP.

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.

1) Tanizaki J et al. Ann Oncol. 2021;S0923-7534(21)04824-9.
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 investigator-initiated open-label Phase II clinical study conducted and 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.

Overview of Opdivo® Intravenous Infusion

Product name	Opdivo® Intravenous Infusion 20mg, 100mg, 120mg and 240mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable or metastatic renal cell carcinoma ○ Recurrent or refractory classical Hodgkin lymphoma ○ Recurrent or metastatic head and neck cancer ○ Unresectable advanced or recurrent gastric cancer ○ Unresectable advanced or recurrent malignant pleural mesothelioma ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary
Dosage and administration	**<Melanoma>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In the adjuvant treatment of melanoma, the administration period does not exceed 12 months. In combination therapy with ipilimumab for unresectable melanoma, usually, for adults, administer 80 mg of nivolumab every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <**Unresectable, advanced or recurrent non-small cell lung cancer, and unresectable advanced or recurrent gastric cancer>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with other anti-tumor drugs, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Unresectable or metastatic renal cell carcinoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination with cabozantinib, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.

	In combination therapy with ipilimumab for unresectable or metastatic renal cell carcinoma previously untreated with chemotherapy, usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <**Recurrent or refractory classical Hodgkin lymphoma**> Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. Usually for pediatrics, administer 3 mg/kg (body weight) of nivolumab every 2 weeks as intravenous infusion. For pediatrics weighing 40 kg (body weight) or more, nivolumab can be administered at 240 mg every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Recurrent or metastatic head and neck cancer, and cancer of unknown primary>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent malignant pleural mesothelioma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy, and adjuvant treatment of esophageal cancer>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In the adjuvant treatment of esophageal cancer, the administration period does not exceed 12 months.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb K.K.

Note: Underlined parts show the revised ones according to this approval.

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, 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, and cancer of unknown primary in December 2021.

In addition, ONO has submitted supplemental application for the adjuvant treatment of urothelial cancer, and is conducting clinical development program including hepatocellular carcinoma, 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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