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Ono Pharmaceutical Co., Ltd.
Bristol-Myers Squibb K.K.

ONO Receives Supplemental Approval of Opdivo® in Japan for Expanded Use for Treatment of Malignant Mesothelioma (Excluding Malignant Pleural Mesothelioma)

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President and CEO, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Tokyo, Japan; President: Steve Sugino) today announced that ONO has received 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 malignant mesothelioma (excluding malignant pleural mesothelioma), for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on the result from the investigator-initiated clinical trial (VIOLA trial), conducted under the leadership of the Hyogo Medical University Hospital, in 20 patients with malignant mesothelioma (excluding malignant pleural mesothelioma). The trial met the primary endpoint, objective response rate (ORR) in patients with measurable lesions as assessed by central review, which was 35.7% (5/14 patients, 95% confidence interval: 12.8 - 64.9%) *1. In addition, ORR as assessed by central review for malignant mesothelioma (excluding malignant pleural mesothelioma) in patients with or without a history of drug treatment was 42.9% (3/7 patients) in previously non-treated patients and 28.6% (2/7 patients) in previously treated patients, demonstrating the responses regardless of a history of drug treatment. The safety profile of Opdivo in this trial was consistent with those previously reported in the clinical trials with Opdivo.

*1: In case that efficacy data obtained after the prohibited treatment was performed in this trial are excluded from the analysis, the ORR as assessed by central review in the overall patient population was 20.0% (4/20 patients, 95% confidence interval: 5.7 - 43.7%).

With this approval, we expect Opdivo to become one of new treatment options for malignant mesothelioma (excluding malignant pleural mesothelioma).

Opdivo was designated as an orphan drug for the indication of malignant mesothelioma (excluding malignant pleural mesothelioma) in February 2023 by the Ministry of Health, Labor and Welfare (MHLW).

As for malignant pleural mesothelioma, Opdivo was designated as an orphan drug in December 2017. Opdivo monotherapy and Opdivo in combination with Yervoy® (generic name: ipilimumab) were approved in Japan for the treatment of unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy in August 2018 and for the treatment of unresectable advanced or recurrent malignant pleural mesothelioma in May 2021, respectively.

About VIOLA Trial

VIOLA trial is an investigator-initiated, multi-center, unblinded, non-comparative Phase 2 trial evaluating the efficacy and safety of Opdivo in naïve or previously chemotherapy-treated patients with malignant mesothelioma (excluding malignant pleural mesothelioma). Patients received Opdivo at 240 mg every two weeks. The primary endpoint of the trial is objective response rate (central review). Secondary endpoints include objective response rate (physician judgment at medical institutions), disease control rate (DCR), overall survival (OS) and progression-free survival (PFS).

About Malignant Mesothelioma

Malignant mesothelioma is a malignant tumor derived from undifferentiated mesenchymal cells of the mesothelium covering the surface of the body cavity and the underlying connective tissue in the thoracic cavity, pericardial cavity, abdominal cavity and tunica vaginalis testis cavity, and is classified into malignant pleural mesothelioma, malignant pericardial mesothelioma, malignant peritoneal mesothelioma, and malignant mesothelioma of the tunica vaginalis testis depending on the occurrence site.

It is estimated that there are 2,283 patients with malignant mesothelioma per year[1)] in Japan. It is reported that 1,605 deaths per year result from the disease in Japan[2)] in 2020. The proportion of patients with malignant mesothelioma by site is reported to be 85.5% for malignant pleural mesothelioma, 13.2% for malignant peritoneal mesothelioma, 0.8% for malignant pericardial mesothelioma, and 0.5% for malignant mesothelioma of the tunica vaginalis testis[3)].

Malignant mesothelioma is a disease with poor prognosis with median and average overall survival being reported to be 7.7 months[4)] and 8.6 months[5)], respectively, and the 3-year and 5-year survival rates to be 18.6% and 9.9%[6)], respectively.

1) Globocan 2020: Japan, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
2) Annual changes in the number of deaths due to mesothelioma by prefecture (1995-2020), Vital Statistics Annual Report (Fixed Number), Ministry of Health, Labour and Welfare
3) Gemba K, et al. Cancer Science, 2012;103(3):483-90.
4) Gemba K, et al. Acta Oncologica. 2013;52:803-8.
5) Solomons K. S Afr Med J. 1984;66:407-12.
6) Cancer Survival Rates at Japanese Association of Clinical Cancer Centers (November 2021) http://www.zengankyo.ncc.go.jp/etc/index.html.

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 ○ Neoadjuvant treatment of 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 ○ Malignant mesothelioma (excluding 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 ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary ○ Adjuvant treatment of urothelial carcinoma
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. **<Neoadjuvant treatment of non-small cell lung cancer>** In combination therapy with other anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab every 3 weeks as intravenous infusion. The administration frequency does not exceed 3 doses. **<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, malignant mesothelioma (excluding malignant pleural mesothelioma, 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>** Usually, for adults, administer 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, 360 mg every 3 weeks or 480 mg every 4 weeks as intravenous infusion. **<Adjuvant treatment of esophageal cancer, and adjuvant treatment of urothelial carcinoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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, cancer of unknown primary in December 2021, and adjuvant treatment of urothelial carcinoma in March 2022.

In addition, ONO has submitted a supplemental application for the treatment of malignant epithelial tumors, and is conducting clinical development program including hepatocellular carcinoma, ovarian cancer, prostate 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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