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Opdivo Approved for Supplemental Applications for Expanded Indications of Malignant Pleural Mesothelioma and Adjuvant Treatment of Melanoma, Change in Dosage and Administration (D&A) of Single Dosing Regimen, and Expanded indication of Renal Cell Carcinoma in Opdivo and Yervoy Combination Therapy

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it has received approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody, for the following supplemental applications:

- Unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy (expanded indication)
- Adjuvant treatment of melanoma (expanded indication)
- Change in D&A from the one calculated from body weight to flat dose (Change)

In addition, ONO and Bristol-Myers Squibb K.K. (Shinjuku, Tokyo; President, Jean-Christophe Barland: "BMSKK") announced that the companies have received approval for expanded indication of unresectable or metastatic renal cell carcinoma in the combination therapy of Opdivo and Yervoy® (generic name: ipilimumab) Injection 50 mg ("Yervoy"), a human anti-human CTLA-4 monoclonal antibody, as well as additional D&A of Opdivo in the same indication in Japan as a partial change in approved items of the manufacturing and marketing approval.

< Malignant pleural mesothelioma >

Malignant pleural mesothelioma (MPM) is a malignant tumor derived from undifferentiated mesenchymal cells of the mesothelium covering the thoracic surface and its underlying connective tissue. It is estimated that there are about 2,000 patients[*1] affected patients with MPM in Japan. It is known that the cause of its occurrence is highly related to asbestos inhaled into the body in occupational or living environment and that MPM develops after a period of about 30 to 50 years following asbestos exposure. The initial drug treatment for MPM is combination therapy of pemetrexed and cisplatin. There is no standard therapy for patients who are resistant or intolerant to its combination therapy; new treatment options are desired. This approval allows Opdivo to be used first in the world for unresectable advanced or recurrent MPM which has progressed after chemotherapy.

<Melanoma>

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) which are deeply related with the skin color, and said to be the most metastatic and deadliest form of the disease. It is reported that the number of melanoma patients is about 4,000 patients[*2] with about 700 deaths[*3] per year in Japan. While Opdivo has been approved for unresectable malignant melanoma, this approval allows to expand use of Opdivo for adjuvant treatment of melanoma.

<Renal cell carcinoma>

Renal cell carcinoma (RCC) is a type of kidney cancer. Kidney cancer is a malignant tumor arising from the renal parenchyma and is the most common cancer among renal malignant tumor. Globally, about 270,000 cases of kidney cancer are diagnosed yearly and 116,000 people[*4] die from the disease. RCC constitutes 90%[*4] of all kidney cancer patients. This approval allows the combination therapy of Opdivo and Yervoy to be used for the treatment of previously untreated with chemotherapy, unresectable or metastatic RCC.

< Dosage and administration of Opdivo>

As for the dosage and administration (D&A) of Opdivo, in addition to the approval of unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy, the D&A of Opdivo is changed to “240 mg every 2 weeks as an intravenous infusion over 30 minutes” from “3 mg/kg (body weight) every 2 weeks as an intravenous infusion over 1 hour” in the following 6 approved indications:

- Unresectable melanoma
- Unresectable, advanced or recurrent non-small cell lung cancer
- Unresectable or metastatic renal cell carcinoma
- Relapsed or refractory classical Hodgkin lymphoma
- Recurrent or metastatic head and neck cancer
- Unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy

Regarding adjuvant treatment of melanoma, the D&A of Opdivo is applied for 240 mg every 2 weeks as an intravenous infusion over 30 minutes.

In combination therapy with Yervoy for unresectable melanoma, the D&A for Opdivo is changed to “80 mg every 3 weeks as an intravenous infusion for 4 doses, and then 240 mg every 2 weeks as an intravenous infusion over 30 minutes” from “1 mg/kg (body weight) every 3 weeks as an intravenous infusion for 4 doses and then 3 mg/kg every 2 weeks as an intravenous infusion over 1 hour”. It is anticipated that this approval for flat dosing will lead to the enhancement of convenience in preparing a product compared to preparing based on body weight, as well as to the resolution of the problem in leftover or unused product.

In addition, in combination therapy with Yervoy for previously untreated with chemotherapy, unresectable or metastatic RCC, Opdivo is administered intravenously at 240 mg with Yervoy at 1 mg/kg (body weight) every 3 weeks for 4 doses, and then Opdivo is intravenously administered at 240 mg every 2 weeks.

*1: Patient Survey 2014, Statistics and Information Department of the Minister's Secretariat at the Ministry of Health, Labour and Welfare (MHLW)
*2: CANCER STATISTICS IN JAPAN 2013, Patient Survey (Basic Disease Classification), Ministry of Health, Labour and Welfare 2011
*3: Vital Statistics, Ministry of Health, Labour and Welfare 2012
*4: The epidemiology of renal cell carcinoma. Euro Urol. 2011;60;615-621.

ONO and BMSKK consider it to be important to accumulate further data, in order to make sure that Opdivo and Yervoy can be used more properly. In accordance with the conditional approval, ONO and BMSKK are committed to taking actions necessary for the proper use of the products by collecting clinical data on the safety and efficacy of the products.

Overview of OPDIVO® Intravenous Infusion

Product name	OPDIVO® Intravenous Infusion
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	• Melanoma • Unresectable, advanced or recurrent non-small cell lung cancer • Unresectable or metastatic renal cell carcinoma • Relapsed or refractory classical Hodgkin lymphoma • Recurrent or metastatic head and neck cancer • Unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy • Unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy
Dosage and administration	1. Melanoma Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. 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 as intravenous infusion every 2 weeks. 2. Unresectable or metastatic renal cell carcinoma Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. 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 as intravenous infusion every 2 weeks. 3. Unresectable, advanced or recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, ~~and~~ unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy, unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb KK
Conditions for approval	Risk Management Plan should be designed and appropriately implemented.

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

Overview of Yervoy® Injection 50 mg

Product name	Yervoy® Injection 50 mg
Generic name (JAN)	Ipilimumab (Genetical recombination)
Indication	Unresectable melanoma Unresectable or metastatic renal cell carcinoma
Dosage and administration	1. Unresectable melanoma Usually, for adults, administer 3 mg/kg (body weight) of ipilimumab every 3 weeks for 4 doses. In combination therapy with other anti-cancer drugs, nivolumab should be co-administered. 2. Unresectable or metastatic renal cell carcinoma In combination therapy with nivolumab, usually, for adults, administer 1 mg/kg of ipilimumab as intravenous infusion every 3 weeks for 4 doses.
Manufacturer/distributor	Bristol-Myers Squibb KK
Co-promotion	Ono Pharmaceutical Co., Ltd.
Conditions for approval*	Risk Management Plan should be designed and appropriately implemented.

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.

In Japan, ONO launched Opdivo for the treatment of unresectable melanoma in September 2014. Thereafter, ONO received an approval for additional indication of unresectable, advanced or recurrent non-small cell lung cancer in December 2015, unresectable or metastatic renal cell cancer 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, and combination therapy with Yervoy for unresectable melanoma in May 2018. In addition, ONO is conducting clinical development program including esophageal cancer, esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, biliary tract cancer, etc.

In abroad, Bristol-Myers Squibb (BMS) has a robust clinical development program for Opdivo monotherapy and in combination with other Immuno-Oncology and non-Immuno-Oncology therapies across more than 350 clinical trials. BMS is studying Opdivo in approximately 50 types of cancer, across solid tumors and hematologic malignancies, and is utilizing its translational medicine capabilities to tailor approaches with the goal of providing maximal benefit for individual patients.

Opdivo is currently approved in more than 60 countries, including Japan, South Korea, Taiwan, the US and European Union.

About Yervoy

Yervoy, which is a recombinant, human monoclonal antibody, binds to the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. Yervoy binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response. On March 25, 2011, the U.S. Food and Drug Administration (FDA) approved Yervoy 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. In Japan, BMSKK received a manufacturing and marketing approval of Yervoy for the treatment of unresectable melanoma in July 2015. Yervoy is now approved in more than 60 countries. There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types.

About the ONO and Bristol-Myers Squibb Collaboration

In 2011, through a collaboration agreement made between ONO and 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 their 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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