May 25, 2018

ONO and BMSKK Receive Approval for Opdivo® and Yervoy®
Combination Therapy for Treatment of Unresectable Melanoma as a Partial Change in Approved Items of Manufacturing and Marketing Approval 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: "BMSKK") announced today that they have received an approval for a partial change in approved items of the manufacturing and marketing approval of Opdivo® (generic name: nivolumab) Intravenous Infusion 20 mg and 100 mg ("Opdivo"), a human anti-human PD-1 monoclonal antibody, and Yervoy® (generic name: ipilimumab) Injection 50 mg ("Yervoy"), a human monoclonal antibody against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) in combination therapy for the treatment of unresectable melanoma in Japan.

This is the first Immuno-Oncology (I-O) combination therapy of the two I-O products approved in Japan.

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) which are related deeply 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 [*1] with about 700 deaths [*2] per year in Japan.

Both Opdivo and Yervoy have been approved for the treatment of unresectable melanoma as mono-therapy for the treatment of unresectable melanoma in Japan. This approval allows the drugs to be used as combination therapy, where Opdivo is administered intravenously at 1 mg/kg (body weight) plus Yervoy 3 mg/kg (body weight) every 3 weeks for four doses, followed by Opdivo 3 mg/kg (body weight) every two weeks.

In ONO-4538-17 study conducted in Japan, a multi-center, open-label, non-comparative Phase II study in patients with previously untreated unresectable or recurrent melanoma, the combination therapy of Opdivo and Yervoy showed an objective response rate (ORR; primary endpoint) of 33.3% (95% confidence interval: 17.3 - 52.8), assessed by Independent Central Review.

In CheckMate-067 conducted abroad, a double-blind, randomized Phase III study in patients with previously untreated advanced melanoma, the Opdivo plus Yervoy combination therapy significantly improved overall survival (OS), the primary endpoint, versus Yervoy alone and reduced the risk of death 45% (hazard ratio 0.55; 98% confidence interval: 0.42 - 0.72; P<0.0001 [stratified log-rank test]).

In these studies, there has been no remarkable difference observed in the safety profile of the combination therapy of Opdivo plus Yervoy compared to the one of Opdivo or Yervoy mono-therapy.

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 data on the safety and efficacy of the products.

*1: CANCER STATISTICS IN JAPAN 2013, Patient Survey (Basic Disease Classification), Ministry of Health, Labour and Welfare 2011

*2: Vital Statistics, Ministry of Health, Labour and Welfare 2012

Overview of OPDIVO® Intravenous Infusion 20 mg and 100 mg

Product name	OPDIVO® Intravenous Infusion 20 mg and 100 mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	• 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
Dosage and administration	1. Unresectable melanoma Unresectable melanoma patients previously untreated with chemotherapy: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab every 2 weeks. <u>In combination therapy with ipilimumab, usually, for adults, infuse intravenously at 1 mg/kg (body weight) every 3 weeks for four doses, followed by nivolumab 3 mg/kg (body weight) every two weeks</u> Unresectable melanoma patients previously treated with chemotherapy: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab every 2 weeks or 2 mg/kg (body weight) of nivolumab every 3 weeks. 2. 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, and unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab 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
Dosage and administration	Previously untreated with chemotherapy: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of ipilimumab every 3 weeks for 4 doses. In combination therapy with other anti-cancer drugs, nivolumab should be administered. Previously treated with chemotherapy: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of ipilimumab every 3 weeks for four 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 and unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy in September 2017. In addition, ONO has submitted supplemental application for treatment of malignant pleural mesothelioma, adjuvant melanoma, etc. and 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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