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ONO and BMSKK Submit Supplemental Application for Opdivo and Yervoy Combination Therapy for Unresctable or Metastatic Renal Cell Carcinoma in Japan for a Partial Change in Approved Items of Manufacturing and Marketing Approval

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 the companies have submitted a supplemental application for combination therapy of Opdivo® Intravenous Infusion 20 mg and 100 mg (nivolumab, "Opdivo"), a human anti-human PD-1 (programmed cell death-1) monoclonal antibody, and Yervoy® Injection 50 mg (ipilimumab, "Yervoy"), a human monoclonal antibody against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) for the treatment of unresectable or metastatic renal cell carcinoma in Japan, for a partial change in approved items of the manufacturing and marketing approval..

This regulatory application is based on the result of a global randomized, open-label Phase III study (ONO-4538-16/CA209214; CheckMate-214 study) including Japan, evaluating the combination therapy of Opdivo plus Yervoy versus sunitinib in patients with previously untreated advanced or metastatic renal cell carcinoma. In this study, the combination therapy of Opdivo plus Yervoy showed a significant improvement of overall survival in intermediate- and poor-risk patients, the co-primary endpoint, versus sunitinib.

About Renal Cell Carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults, accounting for more than 100,000 deaths worldwide each year. Clear-cell RCC is the most prevalent type of RCC and constitutes 80% to 90% of all patients. RCC is approximately twice as common in men as in women, with the highest rates of the disease in North America and Europe. Globally, the five-year survival rate for those diagnosed with advanced or metastatic kidney cancer is 12.1%.

About CheckMate -214

CheckMate -214 is a phase III, randomized, open-label study evaluating the combination of Opdivo plus Yervoy versus sunitinib in patients with previously untreated advanced or metastatic renal cell carcinoma. Patients in the combination group received Opdivo 3 mg/kg plus Yervoy 1 mg/kg every 3 weeks for 4 doses followed by Opdivo 3 mg/kg every 2 weeks. Patients in the comparator group received sunitinib 50 mg once daily for 4 weeks, followed by 2 weeks off before continuation of treatment. Patients were treated until progression or unacceptable toxic effects. The primary endpoints of the trial are overall survival, progression-free survival and objective response rate in an intermediate to poor-risk patient population (approximately 75% of patients). Safety is a secondary endpoint. The study met the co-primary endpoints of improved overall survival and objective response rate compared to sunitinib in intermediate- and poor-risk patients. While the combination

demonstrated an improvement in progression-free survival relative to sunitinib, another co-primary endpoint, it did not reach statistical significance.

Adverse drug reactions (ADRs) leading to discontinuation were reported in 22% of patients (547) in the combination group, compared with 12% of patients in the sunitinib group (535). The most common grade 3/4 ADRs in the combination group were fatigue (4%), diarrhea (4%), rash (2%), nausea (2%), and, in less than 1% each, pruritus, hypothyroidism, vomiting and hypertension. In the sunitinib group, the most common grade 3/4 ADRs were hypertension (16%), fatigue (9%), Palmar-plantar erythrodysaesthesia syndrome (9%), stomatitis (3%), mucosal inflammation (3%), vomiting (2%), nausea (1%), decreased appetite (1%), hypothyroidism (<1%) and dysgeusia (<1%). There were seven treatment-related deaths in the combination group and four in the sunitinib group.

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

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.

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, including the 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. Yervoy is now approved in more than 50 countries. There is a broad, ongoing development program in place for

Yervoy spanning multiple tumor types. In Japan, BMSKK received a manufacturing and marketing approval of Yervoy for the treatment of unresectable melanoma in July 2015.

About the Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Collaboration

In 2011, through a collaboration agreement made with Bristol-Myers Squibb (BMS), Ono Pharmaceutical Co., Ltd. (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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