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ONO and BMSKK Submit Supplemental Applications for Opdivo and Yervoy in Combination Treatment to Expand the Use for First-line Treatment of Unresectable Advanced or Recurrent Malignant Pleural Mesothelioma 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 the companies have submitted supplemental applications in Japan for Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human programmed cell death-1 (PD-1) monoclonal antibody and Yervoy® (generic name: ipilimumab) Injection ("Yervoy"), a human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), in combination treatment to expand the use for first-line treatment of unresectable advanced or recurrent malignant pleural mesothelioma, for a partial change in approved items of the manufacturing and marketing approval.

This application is based on the results of interim analysis from a global multi-center, randomized, open-label Phase III clinical study (CheckMate -743 study), evaluating Opdivo plus Yervoy combination treatment, compared to standard of care platinum-based chemotherapy (combination therapy with pemetrexed and either of cisplatin or carboplatin) for the first-line treatment of patients with unresectable malignant pleural mesothelioma. In this analysis, Opdivo plus Yervoy combination treatment demonstrated a significant extension of overall survival (OS), the primary endpoint, versus chemotherapy. The safety profile of Opdivo plus Yervoy combination treatment observed in this study was consistent with those previously reported in the studies for the combination treatment.

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 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. This application is expected to allow Opdivo plus Yervoy combination treatment to become one of new treatment options for this patient population.

* : Patient Survey 2017, Statistics and Information Department of the Minister's Secretariat at the Ministry of Health, Labour and Welfare (MHLW)

About CheckMate -743

CheckMate -743 is a global multi-center, randomized, open-label Phase 3 trial evaluating Opdivo plus Yervoy combination treatment compared to chemotherapy (combination treatment of pemetrexed and either of cisplatin or carboplatin) in patients with previously untreated malignant pleural mesothelioma (n=605). In the trial, 303 patients were randomized to receive Opdivo at 3 mg/kg every two weeks and Yervoy at 1 mg/kg every six weeks for up to 24 months or until disease progression or unacceptable toxicity, and 302 patients were randomized to receive cisplatin 75 mg/m^2 or carboplatin AUC 5 plus pemetrexed 500 mg/m^2 in 21-day cycles for six cycles or until disease progression or unacceptable toxicity. The primary endpoint of the trial was OS in all randomized

patients. Key secondary endpoints were objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS).

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 and adjuvant treatment of melanoma in August 2018, and 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.

In addition, ONO is conducting clinical development program including esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, bladder cancer, pancreatic cancer, biliary tract cancer, etc.

About Yervoy

Yervoy is a recombinant, human monoclonal antibody, and 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 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. In Japan, BMSKK received an approval of Yervoy for the treatment of unresectable melanoma in July 2015.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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