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ONO and BMSKK Submit Supplemental Application for Approval of Additional Indication of Opdivo and Yervoy Combination Therapy in Japan for the Treatment of MSI-H Colorectal Cancer

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® (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 Japan for an additional indication of microsatellite instability high (MSI-H) unresectable advanced or recurrent colorectal cancer (CRC) that has progressed following chemotherapy, for a partial change in approved items of the manufacturing and marketing approval.

This application is mainly based on the result from the Opdivo and Yervoy combination therapy cohort of a multicenter, open-label Phase II clinical study (CheckMate-142) conducted by Bristol-Myers Squibb (NYSE: BMY, "BMS") in patients with MSI-H or mismatch repair deficient (dMMR), recurrent or metastatic CRC that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs.

Colorectal cancer (CRC) is the third most common type of cancer with an estimated 1,800,000 new diagnoses and about 861,000 deaths per year worldwide. In Japan alone, CRC is the most common type of cancer, with approximately 146,000 new cases and about 57,000 deaths per year*1.

CRC with MSI-H tumors occurs in approximately 5% of unresectable CRC patients. As there is a tendency of poor prognosis in this patient population with poor efficacy of current chemotherapy including the standard therapy with fluoropyrimidine anticancer drugs*2, an innovative drug is expected to be developed as a treatment option in this patient population.

*1: Globocan 2018. Available at: http://globocan.iarc.fr/

*2: Guidelines 2019 for the Treatment of Colorectal Cancer, Japanese Society for Cancer of Colon and Rectum (JSCCR)

About CheckMate-142 study

This study is a multicenter, multi-cohort, open-label Phase II clinical study of Opdivo or Opdivo combinations in patients with MSI-H or dMMR and non-MSI-H recurrent or metastatic CRC that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs. In Opdivo and Yervoy combination cohort, patients received Opdivo 3 mg/kg plus Yervoy 1 mg/kg as a combination therapy every 3 weeks for 4 doses followed by Opdivo 3 mg/kg every 2 weeks. Patients were treated until disease progression or onset of unacceptable toxicity is observed. The primary endpoint of this combination cohort is an investigator-assessed overall response rate using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.

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 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, unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy and adjuvant treatment of melanoma, etc. in August 2018.

In addition, ONO has submitted supplemental applications for the treatment of microsatellite instable High (MSI-H) colorectal cancer and esophageal cancer, and is conducting clinical development program including esophageal cancer, esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, bladder cancer, colorectal 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 60 countries. There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types.

In Japan, BMSKK received an approval of Yervoy for the treatment of unresectable melanoma in July 2015. Yervoy was also approved in combination therapy with Opdivo for the treatment of unresectable melanoma in May 2018, followed by unresectable or metastatic renal cell carcinoma in August 2018.

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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