May 27, 2021

Opdivo and Yervoy Combination Therapy Approved in Japan for First-line Treatment of Unresectable Advanced or Recurrent Malignant Pleural Mesothelioma

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") today announced that the companies have received approvals in Japan for Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human PD-1 monoclonal antibody, and Yervoy® (generic name: ipilimumab) Injection ("Yervoy"), a human monoclonal antibody against CTLA-4, in combination therapy for the 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 approval is based on the results of the preplanned 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 cisplatin or carboplatin) in patients with previously untreated 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 standard of care treatment for MPM is combination therapy of pemetrexed and cisplatin. This approval is expected to allow Opdivo plus Yervoy combination treatment to become a new treatment option 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. In the trial, patients were randomized to receive either Opdivo at 3 mg/kg every two weeks and Yervoy at 1 mg/kg every six weeks for up to 24 months, or cisplatin 75 mg/m^2 or carboplatin AUC 5 plus pemetrexed 500 mg/m^2 in 21-day cycles for six cycles 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).

Overview of OPDIVO® Intravenous Infusion

Product name	OPDIVO® Intravenous Infusion 20mg, 100mg, 120mg and 240mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable or metastatic renal cell carcinoma ○ Recurrent 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 ~~that has progressed after chemotherapy~~ ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy
Dosage and administration	**<Melanoma>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <**Unresectable, advanced or recurrent non-small cell lung cancer>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with other anti-tumor drugs, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Unresectable or metastatic renal cell carcinoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent malignant pleural mesothelioma ~~that has progressed after chemotherapy~~>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following chemotherapy>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer

	240 mg of nivolumab as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Recurrent or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy, ~~unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after chemotherapy,~~ and unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb K.K.
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

Product name	Yervoy® Injection 50mg
Generic name (JAN)	Ipilimumab (Genetical recombination)
Indication	○ Unresectable melanoma ○ Unresectable or metastatic renal cell carcinoma ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable advanced or recurrent malignant pleural mesothelioma
Dosage and administration	**<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. **<Unresectable or metastatic renal cell carcinoma, and microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy>** In combination therapy with nivolumab, usually, for adults, administer 1 mg/kg of ipilimumab as intravenous infusion every 3 weeks for 4 doses. <**Unresectable advanced or recurrent non-small cell lung cancer>** In combination therapy with other anti-tumor drugs, usually, for adults, administer 1 mg/kg of ipilimumab as intravenous infusion every 6 weeks. **<Unresectable advanced or recurrent malignant pleural mesothelioma >** In combination therapy with nivolumab, usually, for adults, administer 1 mg/kg of ipilimumab as intravenous infusion every 6 weeks.
Manufacturer/distributor	Bristol-Myers Squibb K.K.
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. 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 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 hepatocellular carcinoma, urothelial cancer, ovarian cancer, bladder cancer, prostate 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. 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.

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 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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