September 25, 2020

Opdivo and Yervoy Combination Therapy Approved in Japan to Expand Use for the Treatment of Microsatellite Instability High (MSI-High) Colorectal Cancer, and Opdivo for Additional Dosage and Administration in Monotherapy Dosing Regimen

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 received approval 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 to expand the combination use for the treatment of microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following chemotherapy, for a partial change in approved items of the manufacturing and marketing approval.

In addition, ONO announced that it has also received approval of Opdivo for additional dosage and administration to intravenously infuse at "480 mg (over 30 minutes) every 4 weeks" in the monotherapy dosing regimen, for a partial change in approved items of the manufacturing and marketing approval.

<MSI-high colorectal cancer>

This approval 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-High or deficient mismatch repair (dMMR), advanced or recurrent colorectal cancer (CRC) that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs. In this study, Opdivo and Yervoy combination therapy demonstrated the efficacy in the primary endpoint, an investigator-assessed overall response rate. The safety profile of Opdivo plus Yervoy in this study was consistent with previously reported findings in clinical studies, with no new safety signals.

While Opdivo has been approved for MSI-High unresectable advanced or recurrent CRC that has progressed following chemotherapy in the monotherapy, this approval allows Opdivo to be used for the same indication in combination therapy with Yervoy.

About CheckMate-142 study

This study is a multicenter, multi-cohort, open-label Phase II clinical study of Opdivo alone or Opdivo combination with other drugs in patients with MSI-High or dMMR and non-MSI-High advanced or recurrent CRC. In Opdivo and Yervoy combination cohort, patients with CRC that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs 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 ORR using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other key endpoints are ORR per blinded independent central review (BICR), duration of response (DOR), progression-free survival (PFS), overall survival (OS).

About colorectal cancer

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon or the rectum. It is estimated that approximately 146,000 new cases are diagnosed with CRC per year in Japan (about 1,800,000 cases worldwide) and approximately 57,000 deaths (about 861,000 worldwide) per year resulting from this disease[1)]. Approximately 5% of unresectable CRC patients have MSI-High tumors. There is a tendency of poor prognosis in this patient population compared with those having non MSI-High tumors. As it is reported that the efficacy of current chemotherapy including the Standard of Care with fluoropyrimidine anticancer drugs is poor[2)], an innovative treatment option is needed in this patient population.

*[1]: Globocan 2018. Available at: http://gco.iarc.fr/today/fact-sheets-populations
*[2]: Guidelines 2019 for the Treatment of Colorectal Cancer, Japanese Society for Cancer of Colon and Rectum (JSCCR)

<Dosage and administration of Opdivo>

In addition to the currently available dosage and administration (D&A) of Opdivo monotherapy of “240 mg i.v. infusion (over 30 minutes) every two weeks” in the approved all 9 types of cancers, the approval allows to include the D&A of “480 mg i.v. infusion (over 30 minutes) every 4 weeks” in the Opdivo monotherapy.

This approval of additional D&A increases the treatment option for dosing intervals of Opdivo, allowing to make flexible treatment planning according to the patients' medical condition and clinical course. Furthermore, it is expected that this will help improve the convenience of patients and medical staff by reducing the number of patient visits and the burden on medical staff.

Overview of OPDIVO® Intravenous Infusion

Product name	OPDIVO® Intravenous Infusion 20mg, 100mg 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 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. **<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. <**Unresectable, advanced or recurrent non-small cell lung cancer, 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
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.
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 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. 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 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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