March 28, 2022

ONO Receives Supplemental Approval of Opdivo® (Nivolumab) for Adjuvant Treatment of Urothelial Carcinoma in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Tokyo, Japan; President, Jean-Christophe Barland) today announced that ONO has received a supplemental approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody, in Japan for the adjuvant treatment of urothelial carcinoma, for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on the results from the global multi-center, randomized, double-blind Phase 3 CheckMate -274 study (ONO-4538-33), evaluating Opdivo monotherapy compared to placebo as an adjuvant treatment in patients with muscle-invasive urothelial carcinoma at a high risk of recurrence after radical surgery. In this study, Opdivo showed a statistically significant improvement in disease-free survival (DFS), compared to placebo, both in all randomized patients and in patients whose tumor cells express PD-L1 ≥1%, the primary endpoints of the study.

In all randomized patients, Opdivo nearly doubled the median DFS compared to placebo, with a median DFS of 20.8 months in the Opdivo group and 10.8 months in the placebo group. Opdivo reduced the risk of disease recurrence or death by 30% compared to placebo (Hazard Ratio [HR] 0.70, 98.22% Confidence Interval [CI]: 0.55 - 0.90, p=0.0008). In patients whose tumor cells express PD-L1 ≥1%, Opdivo reduced the risk of disease recurrence or death by 45%, with the median DFS not reached for the Opdivo group vs. 8.4 months for the placebo group (HR 0.55, 98.72% CI: 0.35 - 0.85, p=0.0005). The safety profile of Opdivo in this study was consistent with previously reported studies with Opdivo in solid tumors.

About CheckMate -274 Study (ONO-4538-33)

CheckMate -274 study is a global multi-center, randomized, double-blind Phase 3 study evaluating Opdivo monotherapy compared to placebo in patients who have undergone radical resection of muscle-invasive urothelial carcinoma originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at a high risk of recurrence. In this study, patients were randomized 1:1 to receive Opdivo 240 mg or placebo every two weeks. Patients continued treatment for up to one year, until disease recurrence, unacceptable toxicity or withdrawal of consent. The primary endpoints of the study are disease-free survival (DFS) in all randomized patients and in patients whose tumor cells express PD-L1 ≥1%. Key secondary endpoints are overall survival, non-urothelial tract recurrence free survival and disease-specific survival.

About Urothelial Carcinoma

Urothelial carcinoma is a tumor that begins in the renal pelvis, ureter, bladder and urethra, most of which is bladder cancer. Histopathologically, urothelial carcinoma (transitional epithelial cancer) accounts for more than 90% of bladder cancer[1]. It is estimated that about 36,900 new cases[2] of

bladder cancer are diagnosed per year in Japan (about 573,200 cases worldwide[3]) and about 10,900 deaths[2] (about 212,500 deaths worldwide[3]) per year result from this disease. Standard treatment for bladder cancer is neoadjuvant chemotherapy followed by radical resection, but it is reported that more than 50% of patients will relapse after radical resection[4]. Since the prognosis of patients who have relapsed as metastatic cancer is poor, it is considered that there is a high medical need for postoperative adjuvant therapy for prevention of recurrence.

1): Lynch CF, Cohen MB. Urinary System. Cancer. 1995;75:316-29.
2): Globocan 2020: Bladder Cancer, Japan, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
3): Globocan 2020: Bladder Cancer, World, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
4): Clinical Practice Guidelines for Bladder Cancer 2019 edition. The Japanese Urological Association

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 ○ Unresectable advanced or recurrent malignant pleural mesothelioma ○ 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 ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary ○ Adjuvant treatment of urothelial carcinoma
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, and unresectable advanced or recurrent gastric 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 with cabozantinib, 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. <**Recurrent or refractory classical Hodgkin lymphoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. Usually for pediatrics, administer 3 mg/kg (body weight) of nivolumab every 2 weeks as intravenous infusion. For pediatrics weighing 40 kg (body weight) or more, nivolumab can be administered at 240 mg every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Recurrent or metastatic head and neck cancer, and cancer of unknown primary>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent malignant pleural mesothelioma>** 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 after 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 esophageal cancer that has progressed after chemotherapy, and adjuvant treatment of esophageal cancer>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In the adjuvant treatment of esophageal cancer, the administration period does not exceed 12 months.

	<Adjuvant treatment of urothelial carcinoma> Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. The administration period does not exceed 12 months.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb K.K.

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, cancer of unknown primary in December 2021, and adjuvant treatment of urothelial carcinoma in March 2022.

In addition, ONO is conducting clinical development program including hepatocellular carcinoma, ovarian cancer, bladder cancer, prostate cancer, pancreatic cancer, biliary tract cancer, etc.

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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