September 27, 2021

ONO Receives Approval of Opdivo® (nivolumab) for Dosage and Administration for Treatment of Pediatric Patients with Recurrent or Refractory Classical Hodgkin Lymphoma 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") today announced that ONO has received an approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-PD-1 monoclonal antibody in Japan for the dosage and administration for the treatment of pediatric patients with recurrent or refractory classical Hodgkin lymphoma, for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on the result of the investigator-initiated clinical study (NCCH1606, Study abbreviation: PENGUIN), conducted at the National Cancer Center Hospital, in patients with refractory malignant solid tumors and Hodgkin lymphoma (malignant lymphoma) that are resistant to the standard treatment (after two or more chemotherapy regimens) among cancer patients of the childhood and AYA (adolescent and young adult) generation.

With this approval, in addition to the dosage and administration for adult patients, Opdivo can be allowed to be administered for pediatric patients with the following dosage and administration:

Dosage and administration for pediatrics:
Usually for pediatrics, administer 3 mg/kg (body weight) of nivolumab (genetical recombination) every 2 weeks as intravenous infusion. For pediatrics weighing 40 kg or more, nivolumab (genetical recombination) can be intravenously infused at 240 mg every 2 weeks or 480 mg every 4 weeks.

Hodgkin lymphoma (HL) is a localized or diffuse malignant cell cancer derived from the lymphatic system. It is estimated that there are approximately 1,720 patients with HL including about 70 pediatric HL patients annually in Japan. The treatment for pediatric HL patients is initially conducted with chemotherapy. When patients relapse or are treatment-resistant, the treatment will be shifted further to chemotherapy or brentuximab vedotin, etc. However, as pediatric patients with recurrent or refractory HL have a poor prognosis, new treatment options are expected. With this approval, Opdivo is expected to become a new treatment option for this pediatric population.

PENGUIN study

PENGUIN study is an investigator-initiated Phase I clinical study, evaluating the safety, pharmacokinetics and exploratory efficacy of Opdivo, conducted at the National Cancer Center Hospital, in patients with refractory malignant solid tumors and Hodgkin lymphoma that are resistant to the standard treatment (after two or more chemotherapy regimens) among cancer patients of the childhood and AYA generation. In addition, pediatric patients were enrolled as subjects in this study, because the high efficacy of Opdivo has been confirmed in adult patients with classical Hodgkin

lymphoma in clinical studies and the similar efficacy can be expected in pediatric patients. The primary outcome endpoint is a frequency of adverse events equivalent to dose-limiting toxicity. The key secondary outcome endpoints are overall survival, progression-free survival, overall response rate, etc.

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 that has progressed after chemotherapy ○ 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
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 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 of 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. **<~~Recurrent or refractory classical Hodgkin lymphoma,~~ Recurrent or metastatic head and neck cancer, unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy, and unresectable advanced or recurrent esophageal cancer 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.
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.

In addition, ONO has submitted supplemental applications for the adjuvant treatment of urothelial cancer and cancer of unknown primary, and 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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