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Bristol Myers Squibb™

Press Release

February 9, 2024

Ono Pharmaceutical Co., Ltd.
Bristol-Myers Squibb K.K.

ONO Receives Supplemental Approval of Opdivo® in Japan for Expanded Use for Treatment of Unresectable Advanced or Recurrent Malignant Epithelial Tumors

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President and CEO: Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Tokyo, Japan; President: Steve Sugino) 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 expanded use for the treatment of unresectable advanced or recurrent malignant epithelial tumors, for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on the result from the investigator-initiated clinical trial (NMSC-PD1 Study: KCTR-D014), conducted under the initiative of the Keio University Hospital, in 31 patients with malignant epithelial tumors. The trial met the primary endpoint of objective response rate (ORR) as assessed by central review, which was 19.4% (6/31 patients, 95% confidence interval: 7.5 – 37.5%). The safety profile of Opdivo in this trial was consistent with those previously reported in the clinical trials with Opdivo.

The standard treatment for unresectable advanced or recurrent malignant epithelial tumors has not yet been established in Japan. With this approval, we expect Opdivo to become a new treatment option for patients with unresectable advanced or recurrent malignant epithelial tumors.

Opdivo was designated as an orphan drug for the indication of unresectable advanced or recurrent malignant epithelial tumors in May 2023 by the Ministry of Health, Labor and Welfare (MHLW).

About NMSC-PD1 Study (KCTR-D014)

This study is an investigator-initiated, multi-center, unblinded, non-comparative Phase 2 clinical trial evaluating the efficacy and safety of Opdivo in patients with unresectable advanced or recurrent malignant epithelial tumors. Patients received Opdivo at 480 mg every four weeks. The primary endpoint of the study is objective response rate (Central Judgment). Secondary endpoints include objective response rate (Physician Judgment), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), safety, etc.

About Malignant Epithelial Tumors

Malignant epithelial tumors are a general term for skin cancers that are systematically classified as epithelial tumors, and include squamous cell carcinoma, basal cell carcinoma, extramammary Paget's disease, skin appendage cancers (sweat gland carcinoma, sebaceous carcinoma, hair follicle carcinoma), etc.[1), 2)]

The number of patients with malignant epithelial tumors in Japan is estimated to be 25,000 to 38,315 patients (Patient survey in 2020) [3), 4)]. More than 90% of patients are expected to be cured by local treatment mainly with surgical therapy[5), 6)]. On the other hand, the number of patients with unresectable advanced or recurrent malignant epithelial tumors is reported to be 933 cases per year[7)] with its poor prognosis in Japan.

Reference:
1) General Rules for Clinical and Pathological Studies on Malignant Neoplasms of the Skin (2nd edition), Japanese Skin Cancer Society. August 2010
2) Outlines of Various Rare Cancer (Skin Cancer), Rare Cancer Center, National Cancer Center. April 28, 2014 (updated on December 13, 2022) https://www.ncc.go.jp/jp/rcc/about/skin_tumor/index.html (available only in Japanese)
3) Patient Survey 2020, Ministry of Health, Labour and Welfare. 2023
4) P-Market patient number analysis (August 2021 - July 2022). JMDC Inc.
5) Japanese Guidelines for Skin Cancer (3rd edition). 2022 Japanese Dermatological Association/Japanese Skin Cancer Society
6) Japanese Guidelines for Skin Cancer (2nd edition). 2015 Japanese Dermatological Association
7) Fujisawa Y, et al. J Dermatol Sci. 2018 Dec;92(3):230-6.

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 ○ Neoadjuvant treatment of 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 ○ Malignant mesothelioma (excluding 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 ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary ○ Adjuvant treatment of urothelial carcinoma ○ Unresectable advanced or recurrent malignant epithelial tumors
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. **<Neoadjuvant treatment of non-small cell lung cancer>** In combination therapy with other anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab every 3 weeks as intravenous infusion. The administration frequency does not exceed 3 doses. **<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, malignant mesothelioma (excluding malignant pleural mesothelioma), cancer of unknown primary, and unresectable advanced or recurrent malignant epithelial tumors>** 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> Usually, for adults, administer 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, 360 mg every 3 weeks or 480 mg every 4 weeks as intravenous infusion. **<Adjuvant treatment of esophageal cancer, and 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, 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, adjuvant treatment of urothelial carcinoma in March 2022 and malignant mesothelioma (excluding malignant pleural mesothelioma) in November 2023.

In addition, ONO is conducting clinical development program including hepatocellular carcinoma, ovarian 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.

Contact:
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono-pharma.com