ONO PHARMACEUTICAL CO.,LTD.

May 14, 2019

Opdivo® (Nivolumab) Intravenous Infusion
Received Additional Approvals related to Three Indications in Taiwan

ONO PHARMACEUTICAL CO., LTD. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced that ONO PHARMA TAIWAN CO., LTD. ("OPTW") received the approval of Opdivo® Intravenous Infusion 20 mg, 100 mg ("Opdivo"), a human anti-human PD-1 monoclonal antibody, for the following indications as partial change of approved items on May 10 from the Taiwan Food and Drug Administration (TFDA) in Taiwan:

- Adjuvant Treatment of Melanoma:
  Adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- Classical Hodgkin lymphoma:
  Treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT
- Metastatic Colorectal Cancer:
  As a single agent or in combination with ipilimumab, treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

< Melanoma>

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) which are deeply related with the skin color, and said to be the most metastatic and deadliest form of the disease. It is estimated that there are approximately 250 new diagnoses[*1] with melanoma per year in Taiwan. While Opdivo has been approved for unresectable or metastatic melanoma, this approval allows to expand use of Opdivo for adjuvant treatment of melanoma to decrease the risk for disease recurrence after surgical removal.

< Hodgkin lymphoma >

Hodgkin lymphoma is a localized or diffuse malignant cell cancer derived from the lymphatic system, with an estimated about 190 patients[*1] newly diagnosed with Hodgkin lymphoma annually in Taiwan. While Opdivo has been approved for the treatment of classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin, this approval allows to expand use of Opdivo for the treatment of cHL that has relapsed or progressed, regardless of the order of pre-treatment after auto-HSCT and brentuximab vedotin, as well as after 3 or more lines of systemic therapy that includes auto-HSCT.

< Colorectal cancer>

Colorectal cancer (CRC) is the third most common type of cancer with an estimated about 1.8 million new diagnoses and about 861,000 deaths per year worldwide. It is estimated that there are about 19,270 new case diagnoses[*1] per year in Taiwan. Approximately 5% of metastatic CRC patients have dMMR or MSI-H tumors. There is a tendency of poor prognosis in this patient population compared with those having non dMMR or MSI-H tumors.[*3] As it is reported that the efficacy of current chemotherapy including the standard therapy with fluoropyrimidine anticancer drugs is poor*[3], there is a need for a new treatment option in this patient population.

OPTW is committed to taking measures necessary for proper use of Opdivo by collecting clinical data on the safety and efficacy of Opdivo. In Taiwan, OPTW and Bristol-Myers Squibb (Taiwan) Ltd. continue to co-promote the sales of Opdivo, based on the strategic collaboration agreement made between ONO and Bristol-Myers Squibb in July 2014.

*1: Cancer Registry Annual Report, 2016 Taiwan

*2: Globocan 2018. Available at: http://globocan.iarc.fr/

*3: Venderbosch S, Nagteagaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014;20:5322-5330.

Outline of Opdivo® Intravenous Infusion 20 mg, 100 mg

Product name	Opdivo® Intravenous Infusion 20 mg, 100 mg
Generic name (INN)	Nivolumab
Indication	1. Unresectable or metastatic melanoma Unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab 2. Adjuvant treatment of melanoma Adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease that has undergone complete resection 3. Non-small cell lung cancer Advanced non-squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression after treatment with EGFR or ALK inhibitor 4. Advanced renal cell carcinoma 4.1 Advanced renal cell carcinoma after prior anti-angiogenic therapy 4.2 Intermediate and poor risk previously untreated advanced renal cell carcinoma in combination therapy with ipilimumab 5. Squamous cell carcinoma of the head and neck Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy 6. Classical Hodgkin lymphoma Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT 7. Urothelial carcinoma Locally advanced unresectable or metastatic urothelial carcinoma after failure of prior platinum-containing therapy 8. Unresectable advanced or recurrent gastric cancer Advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior chemotherapy regimens 9. Hepatocellular carcinoma Hepatocellular carcinoma (HCC) previously treated with sorafenib 10. Metastatic Colorectal Cancer: As a single agent or in combination with ipilimumab, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
Dosage and administration	1. Unresectable or metastatic melanoma As a single agent, infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes every 2 weeks. In combination with ipilimumab, infuse intravenously at 1 mg/kg (body weight) of Opdivo over 60 minutes, followed by intravenous infusion of ipilimumab at 3 mg/kg on the same day, every 3 weeks for the first 4 doses. Thereafter, infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes every 2 weeks.

	2. Renal cell carcinoma and colorectal cancer As monotherapy, infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes every 2 weeks. In combination with ipilimumab, infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes, followed by intravenous infusion of ipilimumab at 1 mg/kg on the same day, every 3 weeks for the first 4 doses. Thereafter, infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes every 2 weeks. 3. Adjuvant treatment of melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, classical Hodgkin lymphoma, urothelial carcinoma, gastric cancer and hepatocellular carcinoma: Infuse intravenously at 3 mg/kg (body weight) of Opdivo over 60 minutes every 2 weeks. In case of adjuvant treatment of melanoma, the administration period does not exceed 1 year.
Approval date	May 10, 2019
Manufacturer	Ono Pharmaceutical Co., Ltd.
Importer/distributor	Ono Pharma Taiwan Co., Ltd.
Distribution collaboration	Bristol-Myers Squibb (Taiwan) Ltd.

* Underlined part shows the revised one according to this approval

About Ono Pharma Taiwan Co., Ltd.

Ono Pharma Taiwan Co., Ltd. (OPTW), in Taipei, Taiwan, was established as an ONO's wholly-owned subsidiary in December 2014. OPTW has marketed specialty products such as anti-cancer agent, including Opdivo. OPTW is committed to developing and marketing its products created internally for further penetration into the Taiwanese market.

About Opdivo

Opdivo is a 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.

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 cancer 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, and unresectable advanced or recurrent malignant pleural mesothelioma which has progressed after chemotherapy and adjuvant treatment of melanoma, etc. in August 2018.

In addition, ONO has submitted a supplemental application for the treatment of MSI-H CRC, and is conducting clinical development program including esophageal cancer, esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, bladder cancer, ovarian cancer, biliary tract cancer, etc.

Opdivo is currently approved in more than 65 countries, including Japan, South Korea, Taiwan, China, the US and European Union.

About ONO and BMS Collaboration

In 2011, through a collaboration agreement made between ONO and 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 their 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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