ONO PHARMACEUTICAL CO.,LTD.

June 5, 2020

Opdivo® (Nivolumab) Intravenous Infusion
Approved for Additional Indication of Unresectable Advanced or Recurrent Squamous Cell Carcinoma of Esophageal Cancer in Taiwan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced that Ono Pharma Taiwan Co., Ltd. ("OPTW"), a Taiwanese subsidiary of ONO, received the approval of Opdivo® (nivolumab) Intravenous Infusion 20 mg, 100 mg Inj. ("Opdivo"), a human anti-human PD-1 monoclonal antibody, on June 3, from the Taiwan Food and Drug Administration (TFDA) in Taiwan for additional indication of unresectable advanced or recurrent squamous cell carcinoma of esophageal cancer progressing after fluoropyrimidine- and platinum-based chemotherapy, for partial change of approved items.

Esophageal cancer is a malignant tumor that occurs in the inner layer (mucosa) of the esophagus and grows outside (toward the deeper layer). There are two main types of esophageal cancer; squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the predominant histological type accounting for about 90% of all esophageal cancer in Taiwan. It is estimated that about 2,600 new cases are diagnosed with esophageal cancer per year in Taiwan and approximately 1,700 deaths per year resulting from this disease[1)]. As there have been no available drugs in Taiwan, showing the definitive efficacy in extension of overall survival (OS) in the second line treatment of esophageal cancer which failed in the treatment with fluoropyrimidine- and platinum-based drug, an innovative treatment option is needed in this patient population.

This approval is based on the result of a global multi-center, randomized, open-label Phase III clinical study (ATTRACTION-3 study: ONO-4538-24/CA209-473) conducted by ONO and Bristol-Myers Squibb (NYSE: BMY; "BMS") in patients with esophageal cancer who have been refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based drug.

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. have co-promoted the sales of Opdivo, based on the strategic collaboration agreement made between ONO and BMS in July 2014.

1): Cancer Registry Annual Report, 2016 Taiwan

About ATTRACTION-3 study (ONO-4538-24/CA209-473)

ATTRACTION-3 study is a global multi-center, randomized, open-label Phase III clinical study to evaluate the efficacy on OS, the primary endpoint, and safety of Opdivo versus chemotherapy (docetaxel or paclitaxel) in 419 patients with esophageal cancer (unselected for tumor PD-L1 expression level) who have been refractory to or intolerant of one prior combination therapy with fluoropyrimidine and platinum-based drug. In this study, patients received Opdivo 240 mg every two weeks intravenously (n=210), or chemotherapy (n=209), either of docetaxel 75 mg/m^2 every 3 weeks intravenously or paclitaxel 100 mg/m^2 weekly for 6 weeks followed by 2-week no treatment period, until disease progression, or onset of unacceptable toxic effect is observed. The primary endpoint of this study is OS. The secondary endpoints include progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR).

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 11. Squamous cell carcinoma of esophageal cancer Unresectable advanced or recurrent squamous cell carcinoma of esophageal cancer who are refractory or intolerant to prior fluoropyrimidine- and platinum-based chemotherapy
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. 4. <u>Squamous cell carcinoma of esophageal cancer</u> <u>Infuse intravenously at 240 mg of Opdivo over 30 minutes every 2 weeks.</u>
Approval date	June 3, 2020
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 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 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, 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 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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