ONO PHARMACEUTICAL CO.,LTD.

April 13, 2020

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

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced that Ono Pharma Korea Co., Ltd. ("OPKR"), a Korean 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 April 10 from the Ministry of Food and Drug Safety (MFDS) in South Korea, for additional indication of unresectable advanced or recurrent squamous cell carcinoma of esophageal cancer which is refractory or intolerant to prior fluoropyrimidine- and platinum-based chemotherapy.

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 South Korea. It is estimated that about 2,590 new cases are diagnosed with esophageal cancer per year in South Korea (about 572,000 cases worldwide) and approximately 1,700 deaths (about 508,000 worldwide) per year resulting from this disease[1)]. As there have been no available drugs in South Korea, showing the definitive efficacy in extension of 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.

OPKR is committed to taking measures necessary for proper use of Opdivo by collecting clinical data on the safety and efficacy of Opdivo. In South Korea, OPKR and BMS Pharmaceutical Korea Limited continue to co-promote the sales of Opdivo, based on the strategic collaboration agreement made between ONO and BMS in July 2014.

1): Globocan 2018. Available at: http://gco.iarc.fr/today/fact-sheets-populations

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

ATTRACTION-3 study is a global multi-center, randomized, open-label Phase III clinical study (ONO-4538-24/CA209-473) 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 investigator's choice (n=209) of docetaxel 75 mg/m^2 every 3 weeks intravenously or paclitaxel 100 mg/m^2 weekly for 6 weeks followed by 1-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® 20 mg, 100 mg Inj.
Generic name (INN)	Nivolumab
Indication	1. Unresectable or metastatic melanoma, as monotherapy or combination with ipilimumab 2. Adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection 3. Locally advanced or metastatic non-small cell lung cancer after prior platinum-based chemotherapy failure 4. Advanced renal cell carcinoma 4.1 Patients who have received prior anti-angiogenic therapy, as a single agent 4.2 Patients who have intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab 5. Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and pre/post-transplantation brentuximab vedotin 6. Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy 7. Locally advanced or metastatic urothelial carcinoma 7.1 Patients who have disease progression during or following platinum-containing chemotherapy 7.2 Patients who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy 8. Advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after two or more prior chemotherapy regimens 9. 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. Melanoma: For unresectable or metastatic melanoma, as monotherapy, infuse intravenously at either of the following dose of nivolumab over 30 minutes: • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks For adjuvant treatment of melanoma, as monotherapy, infuse intravenously at either of the following dose of nivolumab over 30 minutes (The treatment period is up to 1year): • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks For unresectable or metastatic melanoma, as combination with ipilimumab, infuse intravenously at 1 mg/kg of nivolumab over 30 minutes, followed by intravenous infusion of ipilimumab at 3 mg/kg over 90 minutes on the same day, every 3 weeks for 4 doses.

	Thereafter, infuse intravenously at either of the following dose of nivolumab over 30 minutes: • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks 2. Renal cell carcinoma: As monotherapy, infuse intravenously at either of the following dose of nivolumab over 30 minutes: • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks As combination with ipilimumab, infuse intravenously at 3 mg/kg of nivolumab over 30 minutes, followed by intravenous infusion of ipilimumab at 1 mg/kg over 30 minutes on the same day, every 3 weeks for 4 doses. Thereafter, infuse intravenously at either of the following dose of nivolumab over 30 minutes: • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks 3. Non-small cell lung cancer, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, gastric or gastroesophageal junction adenocarcinoma: Infuse intravenously at either of the following dose of nivolumab over 30 minutes: • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks 4. <u>Squamous cell carcinoma of esophageal cancer</u> <u>Infuse intravenously at either of the following dose of nivolumab over 30 minutes:</u> • <u>240 mg every 2 weeks or</u> • <u>480 mg every 4 weeks</u>
Approval date	April 10, 2020
Manufacturer	Ono Pharmaceutical Co., Ltd.
Importer/distributor	Ono Pharma Korea Co., Ltd.
Distribution collaboration	BMS Pharmaceutical Korea Limited

* Underlined parts show the revised ones due to this approval.

About Ono Pharma Korea Co., Ltd.

Ono Pharma Korea Co., Ltd. (OPKR), in Seoul, Korea, was established as an ONO's wholly-owned subsidiary in December 2013. OPKR has started to market specialty products such as anti-cancer agents, including Opdivo. OPKR has been committed to developing and marketing its products created internally for further penetration into the South Korean 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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