ONO PHARMACEUTICAL CO.,LTD.

December 17, 2020

Opdivo® (Nivolumab) Intravenous Infusion Approved for First–Line Treatment of Unresectable Advanced or Recurrent Non-Small Cell Lung 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 approval of Opdivo® (generic name: nivolumab) intravenous Infusion 20 mg, 100 mg Inj. ("Opdivo"), a human anti-programmed death-1 (PD-1) monoclonal antibody, on December 16 from the Ministry of Food and Drug Safety (MFDS) in South Korea, for the first-line treatment of unresectable, advanced or recurrent non-small cell lung cancer, in the following combination therapies:

1) Combination therapy with Opdivo and Yervoy* (tumors express PD-L1 ≧1%)
2) Combination therapy with Opdivo, Yervoy plus platinum-based chemotherapy

* : YERVOY® (generic name: ipilimumab) Injection is a human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4（CTLA-4）

This approval is based on the results from the following clinical studies conducted by ONO and Bristol Myers Squibb (NYSE: BMY; "BMS"):

1): CheckMate -227 Study (Part 1a): a global, multi-center, multi-part, randomized, open-label Phase III study evaluating Opdivo, or Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy compared to platinum-doublet chemotherapy in patients with previously untreated unresectable advanced or recurrent non-small cell lung cancer (NSCLC)

2): CheckMate -9LA Study: a global multi-center, randomized, open-label Phase III study evaluating Opdivo plus Yervoy in combination with platinum-doublet chemotherapy (two cycles) compared to platinum-doublet chemotherapy alone in patients with previously untreated unresectable advanced or recurrent NSCLC

About CheckMate -227 study

This study is a global, multi-center, multi-part, randomized, open-label Phase III clinical study, evaluating Opdivo, or Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy compared to platinum-doublet chemotherapy in patients with previously untreated unresectable advanced or recurrent NSCLC. This study consists of the following three Parts:

1) Part 1a: Evaluating the efficacy and safety of Opdivo or Opdivo plus Yervoy in patients whose tumors express PD-L1 ≧1%
2) Part 1b: Evaluating the efficacy and safety of Opdivo plus Yervoy or Opdivo plus platinum-doublet chemotherapy in patients whose tumors express PD-L1 <1%
3) Part 2: Evaluating the efficacy and safety of Opdivo plus platinum-doublet chemotherapy, regardless of PD-L1 expression level

In the Opdivo and Yervoy combination therapy arm of Part 1, patients received Opdivo 3 mg/kg

every 2 weeks plus Yervoy 1 mg/kg every 6 weeks for up to 24 months, until disease progression or onset of unacceptable toxicity is observed. In Part 1a, one of the primary endpoints was overall survival (OS) in patients whose tumors expressed PD-L1 ≧1%.

About CheckMate -9LA study

CheckMate -9LA study is a global, multi-center, randomized, open-label Phase III clinical study evaluating Opdivo (360 mg Q3W) plus Yervoy (1 mg/kg Q6W) in combination with platinum-doublet chemotherapy (two cycles Q3W) compared to platinum-doublet chemotherapy alone in patients with previously untreated unresectable advanced or recurrent NSCLC, regardless of PD-L1 expression and histology. Patients in the combination treatment arm were treated for up to 24 months with Opdivo and Yervoy or until disease progression or unacceptable toxicity. Patients in the control arm were treated with up to four cycles of chemotherapy and optional pemetrexed maintenance (if eligible) until disease progression or toxicity. The primary endpoint of the trial was OS in the intent to treat population. Secondary endpoints were progression-free survival (PFS), overall response rate (ORR), and efficacy measures according to biomarkers.

About Lung Cancer

Lung cancer is considered to be a form of malignant tumor that arises from cells in the trachea, bronchi and alveoli. Lung cancer is divided into two types, small cell lung cancer and non-small cell lung cancer (NSCLC), depending on the broad histological subtypes. NSCLC is one of the most common types of lung cancer, accounting for about 80-85% of lung cancer [1)]. NSCLC is further classified into adenocarcinoma (about 40% of lung cancer), squamous cell carcinoma (about 25%) and large cell carcinoma (about 10%) [2)]. About 29,000 new cases are diagnosed with lung cancer per year in South Korea [3)] (about 2,090,000 cases worldwide [4)]). It is estimated that approximately 20,000 deaths resulting from the disease per year in South Korea [3)] (about 1,760,000 cases worldwide [4)]), showing the first leading cause of cancer-related deaths in both cases[3)]. Survival rates vary depending on the stage and type of the cancer when diagnosed. For patients diagnosed with metastatic lung cancer, the five-year survival rate is about 5%.

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) American Cancer Society; What Is Non-Small Cell Lung Cancer? : https://www.cancer.org/content/cancer/en/cancer/lung-cancer/about/what-is.html
2) Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version, National Cancer Institute: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_12_toc
3) Globocan 2018; Patient Fact Sheets, Korea, Republic of. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
4) Globocan 2018; Patient Fact Sheets, World. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

Outline of Opdivo® Intravenous Infusion 20 mg, 100 mg

Product name	Opdivo® 20 mg, 100 mg Inj.
Generic name (INN)	Nivolumab
Indication	1. Melanoma • Unresectable or metastatic melanoma, as a single agent or combination with ipilimumab • Adjuvant treatment of melanoma with lymph node involvement or metastatic disease after complete resection 2. Non-small cell lung cancer: • First-line treatment of metastatic or recurrent non-small cell lung cancer expressing PD-L1 (≥1%) with no EGFR or ALK genomic tumor aberrations, in combination with ipilimumab • First-line treatment of metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy • Locally advanced non-small cell lung cancer after prior platinum-based chemotherapy failure, as a single agent 3. Advanced renal cell carcinoma • Advanced renal cell carcinoma previously treated with anti-angiogenic therapy, as a single agent • Previously untreated advanced renal cell carcinoma in intermediate or poor risk, in combination with ipilimumab 4. Classical Hodgkin lymphoma Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and pre/post-transplantation brentuximab vedotin 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. Urothelial carcinoma • Locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-based chemotherapy • Locally advanced or metastatic urothelial carcinoma with disease progression within 12 months of neo-adjuvant or adjuvant treatment with platinum-based chemotherapy 7. Gastric or gastroesophageal junction adenocarcinoma Advanced or recurrent gastric or gastroesophageal junction adenocarcinoma after two or more prior chemotherapy regimens 8. Esophageal squamous cell carcinoma Unresectable advanced or recurrent esophageal squamous cell carcinoma that is refractory or intolerant to prior fluoropyrimidine- and platinum-based chemotherapy

Dosage and administration	**<Monotherapy>** **1. Melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, gastric or gastroesophageal junction adenocarcinoma, esophageal squamous cell carcinoma** Infuse intravenously at either of the following doses of Opdivo. For adjuvant treatment of melanoma, the treatment period is up to 1 year. • 3 mg/kg every 2 weeks or • 240 mg every 2 weeks or • 480 mg every 4 weeks **2. Esophageal squamous cell carcinoma** Infuse intravenously at either of the following doses of Opdivo. • 240 mg every 2 weeks or • 480 mg every 4 weeks **<Combination therapy>** **1. Melanoma** As combination with ipilimumab, infuse intravenously at 1 mg/kg of Opdivo, 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 doses of Opdivo: • 3 mg/kg every 2 weeks, • 240 mg every 2 weeks or • 480 mg every 4 weeks **2. <u>Non-small cell lung cancer:</u>** <u>As combination with ipilimumab, infuse intravenously at 3 mg/kg of Opdivo every 2 weeks and 1 mg/kg of ipilimumab every 6 weeks. The treatment period is up to 2 years.</u> <u>As combination with ipilimumab and platinum-based chemotherapy, infuse intravenously at 360 mg of Opdivo every 3 weeks, 1 mg/kg of ipilimumab every 6 weeks and 2 cycles of platinum-based chemotherapy every 3 weeks. The treatment period is up to 2 years.</u> **3. Renal cell carcinoma:** As combination with ipilimumab, infuse intravenously at 3 mg/kg of Opdivo, followed by intravenous infusion at 1 mg/kg of ipilimumab on the same day every 3 weeks for 4 doses. Thereafter, infuse intravenously at either of the following doses of Opdivo: • 3 mg/kg every 2 weeks, • 240 mg every 2 weeks or • 480 mg every 4 weeks *: Unless otherwise described, Opdivo and ipilimumab should be infused intravenously over 30 minutes.
Approval date	December 16, 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 agent, 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, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, bladder cancer, pancreatic cancer, biliary tract cancer, prostate 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.

Contact
ONO PHARMACEUTICAL CO., LTD.
Corporate Communications
public_relations@ono.co.jp