ONO PHARMACEUTICAL CO.,LTD.

June 14, 2021

Opdivo® Intravenous Infusion Approved for Two Expanded Indications as First-Line Treatment of "Gastric Cancer, Gastroesophageal Junction Cancer and Esophageal Adenocarcinoma" and "Malignant Pleural Mesothelioma" 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 approvals of Opdivo® (nivolumab) Intravenous Infusion 20 mg, 100 mg Inj. ("Opdivo"), a human anti-human PD-1 monoclonal antibody, on June 10, 2021 from the Ministry of Food and Drug Safety (MFDS) in South Korea for the following two indications in combination therapies:

1) In combination with fluoropyrimidine- and platinum-containing chemotherapy, the first-line treatment of "advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma"
2) In combination with Yervoy® (ipilimumab)*, the first-line treatment of adults with "unresectable malignant pleural mesothelioma"

*: Yervoy is a human anti-human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody.

<Indication of gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma>

This approval is based on the results from the global, multi-center, randomized, open-label Phase 3 clinical study (CheckMate -649 study) conducted by ONO and Bristol Myers Squibb (NYSE: BMY; "BMS"), evaluating Opdivo plus chemotherapy combination treatment compared to chemotherapy alone in patients with previously untreated, advanced or metastatic gastric cancer (GC), gastroesophageal junction cancer (GEJC) or esophageal adenocarcinoma (EAC). In this study, Opdivo plus chemotherapy combination treatment demonstrated a statistically significant improvement of overall survival (OS) and progression-free survival (PFS) in PD-L1 positive patients with a combined positive score (CPS) ≥ 5, the primary endpoints of the study, versus chemotherapy in the treatment of previously untreated, advanced or metastatic GC, GEJC or EAC. Opdivo plus chemotherapy also demonstrated a statistically significant OS benefit in all randomized patient population. The safety profile of Opdivo plus chemotherapy in this study was consistent with the known safety profile of the individual treatments.

About CheckMate -649 study

Checkmate -649 study is a multi-center, randomized, open-label Phase 3 clinical study evaluating Opdivo plus chemotherapy combination treatment compared to chemotherapy alone in patients with previously untreated, non-human epidermal growth factor receptor 2 (HER2) positive, advanced or metastatic GC, GEJC or EAC. Patients in the Opdivo plus chemotherapy arm received Opdivo 240 mg plus 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) every two weeks or Opdivo 360 mg plus

capecitabine and oxaliplatin (CapeOX) every three weeks. Patients in the chemotherapy arm received FOLFOX or CapeOX every two or three weeks, respectively. All patients continued treatment for two years or until disease progression, unacceptable toxicity or withdrawal of consent. The primary endpoints of the study are OS in PD-L1 positive patients with a CPS ≥ 5 and PFS as assessed by Blinded Independent Central Review (BICR) in PD-L1 CPS ≥ 5 patients compared to chemotherapy alone. Key secondary endpoints are OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and overall response rate (ORR) as assessed by BICR in patients with PD-L1 CPS ≥ 1 and ≥ 5, and in all randomized patients.

<About gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma>

Gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma are classified as upper gastrointestinal cancers.

- Gastric cancer (GC): In South Korea, it is estimated that approximately 28,000 new cases of gastric cancer diagnosed per year, with approximately 7,500 deaths per year resulting from this disease[1]. There are several cancers that can be classified as GC, including certain types of cancers that form in the gastroesophageal junction, the area of the digestive tract where the esophagus and stomach connect. As there has been little progression in the standard of care of first-line chemotherapy for the HER2 negative unresectable, advanced, recurrent GC in the past decade in South Korea, a new treatment option is needed in this patient population.
- Esophageal cancer: In South Korea, it is estimated that approximately 2,600 new cases of esophageal cancer diagnosed per year, with approximately 1,500 deaths per year resulting from this disease[1]. 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 histological types of esophageal cancer; squamous cell carcinoma (SCC) and adenocarcinoma, accounting for 91.5% and 2.5% of all esophageal cancer, respectively, in South Korea[2].

1: Globocan 2020. Available at: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
2: National Cancer Information Center in Korea: https://www.cancer.go.kr/

<Indication of malignant pleural mesothelioma>

This approval is based on the results of the pre-planned interim analysis from a global multi-center, randomized, open-label Phase 3 clinical study (CheckMate -743 study), evaluating Opdivo plus Yervoy combination treatment, compared to standard of care platinum-based chemotherapy in patients with previously untreated unresectable malignant pleural mesothelioma. In this analysis, Opdivo plus Yervoy combination treatment demonstrated a significant extension of overall survival (OS), the primary endpoint, versus chemotherapy. The safety profile of Opdivo plus Yervoy combination treatment observed in this study was consistent with those previously reported in the studies for the combination treatment.

About CheckMate -743 study

CheckMate -743 is a global multi-center, randomized, open-label Phase 3 clinical study evaluating Opdivo plus Yervoy combination treatment compared to chemotherapy (combination treatment of pemetrexed and either cisplatin or carboplatin) in patients (n=605) with previously untreated unresectable malignant pleural mesothelioma. In this study, 303 patients were randomized to receive

Opdivo 3 mg/kg every two weeks and Yervoy 1 mg/kg every six weeks for up to 24 months or until disease progression or unacceptable toxicity, and 302 patients were randomized to receive cisplatin 75 mg/m^2 or carboplatin AUC 5 plus pemetrexed 500 mg/m^2 in 21-day cycles for six cycles or until disease progression or unacceptable toxicity. The primary endpoint of the study was OS in all randomized patients. Key secondary endpoints were objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS).

About malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is a malignant tumor derived from undifferentiated mesenchymal cells of the mesothelium covering the thoracic surface and its underlying connective tissue. It is known that the cause of its occurrence is highly related to asbestos inhaled into the body in occupational or living environment and that MPM develops after a period of about 30 to 50 years following asbestos exposure. The standard of care treatment for MPM is combination therapy of pemetrexed and cisplatin. This approval is expected to allow Opdivo plus Yervoy combination treatment to become a new treatment option for this patient population.

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, 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 hepatocellular carcinoma, urothelial cancer, ovarian cancer, bladder cancer, prostate cancer, pancreatic cancer, biliary tract cancer, etc.

About 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 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.

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.

Contact
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono.co.jp