ONO PHARMACEUTICAL CO.,LTD.

February 15, 2022

Opdivo® Intravenous Infusion Approved in South Korea for Two Adjuvant Treatments and Three Combination Treatments

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced that Ono Pharma Korea Co., Ltd. ("OPKR"), a South Korean subsidiary of ONO, received the following approvals of Opdivo® (nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody, on February 14 from the Ministry of Food and Drug Safety (MFDS) in South Korea for two adjuvant treatments and for three combination treatments:

[Approval for the Following Two Adjuvant Treatments]

1. Adjuvant treatment in patients with esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT) and complete resection
2. Adjuvant treatment in patients with muscle-invasive bladder carcinoma (MIBC) at a high risk of recurrence after undergoing radical resection

[Approval for the Following Three Combination Treatments]

1. In combination with bevacizumab and chemotherapy, in the first-line treatment of adult patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations
2. In combination with cabozantinib, in the first-line treatment of advanced renal cell carcinoma
3. In combination with ipilimumab, in 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

[Approval for the Following Two Adjuvant Treatments]

<Adjuvant treatment in patients with esophageal or gastroesophageal junction cancer>

This approval is based on the results from a global multi-center, randomized, double-blind Phase 3 clinical study, CheckMate -577 study (ONO-4538-43), evaluating Opdivo monotherapy as an adjuvant treatment in patients with resected esophageal or gastroesophageal junction cancer compared to placebo. In this study, Opdivo monotherapy showed a statistically significant improvement in disease-free survival (DFS), the primary endpoint of the study, compared to placebo. The safety profile of Opdivo in this study was consistent with previously reported studies of Opdivo monotherapy.

About CheckMate -577 Study (ONO-4538-43)

CheckMate -577 study is a global multi-center, randomized, double-blind Phase 3 clinical study, evaluating Opdivo monotherapy as an adjuvant treatment in patients with resected esophageal cancer or gastroesophageal junction cancer who have received neoadjuvant chemoradiotherapy (CRT) and have not achieved a pathological complete response. Following neoadjuvant CRT and complete tumor surgical resection (also known as trimodality therapy), patients were randomized to receive Opdivo monotherapy or placebo. In patients receiving Opdivo, it was administered at 240 mg every two weeks for 16 weeks, followed by Opdivo 480 mg every four weeks until disease recurrence,

unacceptable toxicity or withdrawal of consent, with a maximum of one year total treatment duration. The primary endpoint of the study is disease-free survival (DFS) and the secondary endpoint is overall survival (OS).

About Esophageal Cancer and Gastroesophageal Junction Cancer

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) accounting for 91.5% of all esophageal cancer, and adenocarcinoma for 2.5% in South Korea[1)]. In South Korea, about 2,600 new cases of esophageal cancer are diagnosed per year and approximately 1,500 deaths per year result from this disease[2)]. Gastroesophageal junction cancer is a malignant tumor that occurs in the area of the body that connects the lower part of the esophagus to the stomach[3)].

1) National Cancer Information Center in Korea: https://www.cancer.go.kr/
2) Globocan 2020; Patient Fact Sheets, Korea, Republic of. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
3) American Cancer Society. What is Cancer of the Esophagus? https://www.cancer.org/cancer/esophagus-cancer/about/what-is-cancer-of-the-esophagus.html. Updated March 20, 2020. Accessed April 26, 2021.

<Adjuvant treatment in patients with bladder cancer>

This approval is based on the results from a global multi-center, randomized, double-blind Phase 3 clinical study, CheckMate -274 study (ONO-4538-33), evaluating Opdivo monotherapy compared to placebo as an adjuvant treatment in patients with muscle-invasive urothelial cancer at a high risk of recurrence after radical resection. In this study, Opdivo showed a statistically significant improvement in disease-free survival (DFS), compared to placebo, both in all randomized patients and in the patients whose tumor cells express PD-L1 ≥ 1%, meeting both primary endpoints. The safety profile of Opdivo in this study was consistent with previously reported studies with Opdivo monotherapy.

About CheckMate -274 Study (ONO-4538-33)

CheckMate -274 study is a global multi-center, randomized, double-blind Phase 3 clinical study, evaluating Opdivo monotherapy compared to placebo in patients with muscle-invasive urothelial cancer at a high risk of recurrence after radical resection. In this study, patients were randomized 1:1 to receive Opdivo 240 mg or placebo every two weeks. Patients continued treatment for up to one year, until disease recurrence, unacceptable toxicity or withdrawal of consent. The primary endpoints of the study are disease-free survival (DFS) in all randomized patients and in patients whose tumors express PD-L1 ≥ 1%. Key secondary endpoints include overall survival (OS), non-urothelial tract recurrence free survival and disease-specific survival.

About Bladder Cancer

Urothelial cancer is a tumor that begins in the renal pelvis, ureter, bladder and urethra, most of which is bladder cancer. Histopathologically, urothelial cancer (transitional epithelial cancer) accounts for more than 90% of bladder cancer[1)]. It is estimated that about 4,900 new cases of bladder cancer are diagnosed per year and about 1,800 deaths per year result from this disease[2)] in South Korea.

1) Lynch CF, Cohen MB. Urinary System. Cancer. 1995;75:316-29.
2) Globocan 2020; Patient Fact Sheets, Korea, Republic of. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf

[Approval for the Following Three Combination Treatments]

<In combination with bevacizumab and chemotherapy, in the first-line treatment of non-squamous non-small cell lung cancer>

This approval is based on the results from Phase 3 clinical study, TASUKI-52 study (ONO4538-52), evaluating Opdivo in combination with bevacizumab and chemotherapy (Opdivo combination group), versus placebo in combination with bevacizumab and chemotherapy (control combination group) in patients with chemotherapy-naïve stage IIIB/IV or recurrent non-squamous non-small cell lung cancer (NSCLC) unsuitable for radical radiation. In the interim analysis of this study, Opdivo combination group demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (PFS) as assessed by the Independent Radiologic Review Committee (IRRC), compared to control combination group.

About TASUKI-52 Study (ONO-4538-52)

TASUKI-52 study is a multi-center, randomized, double-blind, placebo-controlled Phase 3 clinical study (ONO-4538-52), evaluating Opdivo in combination with bevacizumab and chemotherapy (Opdivo combination group), versus placebo in combination with bevacizumab and chemotherapy (control combination group), in chemotherapy-naïve patients with stage IIIB/IV or recurrent non-squamous non-small cell lung cancer (NSCLC) unsuitable for radical radiation. Patients in the Opdivo combination group received Opdivo 360 mg, carboplatin at area under the blood concentration time curve (AUC) 6, paclitaxel 200 mg/m^2 and bevacizumab 15 mg/kg, every 3 weeks (as one cycle). Patients in the control combination group received placebo, carboplatin AUC 6, paclitaxel 200 mg/m^2 and bevacizumab at 15 mg/kg, every 3 weeks (as one cycle). Patients in both groups received carboplatin and paclitaxel up to 4 cycles and if deemed safe, the drugs may be continued for up to a maximum of 6 cycles. Thereafter, Opdivo and bevacizumab were given in the Opdivo combination group, and placebo and bevacizumab given in the control combination group until disease progression or unacceptable toxicity are observed. The primary endpoint of this study is progression-free survival (PFS) as assessed by the Independent Radiologic Review Committee (IRRC). Key secondary endpoints are overall survival (OS), PFS as assessed by the study site's investigator, and objective response rate (ORR).

About Lung Cancer

Lung cancer is 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)]. In South Korea, it is estimated that 29,000 new cases of lung cancer are diagnosed per year, with approximately 20,000 deaths resulting from the disease per year, making it the leading cause of cancer-related death[3)]. Survival rates vary depending on the stage and type of the cancer when diagnosed. For patients diagnosed with metastatic lung cancer.

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 2020; Patient Fact Sheets, Korea, Republic of. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf

<In combination with cabozantinib, in the first-line treatment of renal cell carcinoma>

This approval is based on the results from the global, multi-center, randomized, open-label Phase 3 CheckMate -9ER study, evaluating Opdivo and CABOMETYX® (generic name: cabozantinib) combination therapy versus sunitinib alone in patients with previously untreated advanced or metastatic RCC. In this study, Opdivo and CABOMETYX combination therapy demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS) as assessed by the blinded independent central review (BICR), compared to sunitinib alone at the final analysis, as well as the secondary endpoints of overall survival (OS) and objective response rate (ORR) as assessed by the BICR. The safety profiles of Opdivo and CABOMETYX combination therapy in the study were consistent with the previously reported safety profile of each product.

About CheckMate -9ER Study

CheckMate -9ER study is a global, multi-center, randomized, open-label Phase 3 study, evaluating Opdivo and CABOMETYX combination therapy in patients with previously untreated advanced or metastatic RCC, versus sunitinib alone. Patients were randomized 1:1 to the Opdivo and CABOMETYX combination therapy group receiving Opdivo 240 mg by intravenous infusion every 2 weeks and CABOMETYX 40 mg orally once daily, or the control group receiving sunitinib 50 mg orally once daily for 4 weeks, followed by a 2-week non-treatment period until disease progression or unacceptable toxicity. The primary endpoint of the study is progression-free survival (PFS) as assessed by the blinded independent central review (BICR). The secondary endpoints are overall survival (OS) and objective response rate (ORR) as assessed by the BICR.

About Kidney Cancer

Kidney cancer is a malignant tumor arising from the renal parenchyma. Among kidney cancer, renal cell carcinoma (RCC) is the most common cancer, constituting almost 90% of all kidney cancers[1)]. It is estimated that about 4,900 new cases of RCC are diagnosed per year in South Korea[2)].

1) The epidemiology of renal cell carcinoma. Euro Urol. 2011;60;615-621.
2) National cancer information center in 2018: https://www.cancer.go.kr/

<In combination with ipilimumab, in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer>

This approval is based on the results from the Opdivo and Yervoy® (generic name: ipilimumab) combination therapy cohort of a multicenter, open-label Phase 2 clinical study (CheckMate -142 study) in patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR), advanced or recurrent colorectal cancer (CRC) that has progressed on or after prior treatment with a fluoropyrimidine, oxaliplatin- or irinotecan-based chemotherapy. In this study, Opdivo and Yervoy combination therapy demonstrated efficacy in the primary endpoint, overall response rate (ORR) as assessed by an investigator. The safety profile of Opdivo plus Yervoy in this study was consistent with previously reported findings in clinical studies, with no new safety signals.

About CheckMate-142 Study

CheckMate -142 study is a multicenter, multi-cohort, open-label Phase 2 clinical study of Opdivo alone or Opdivo combination with other drugs in patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) and non-MSI-H advanced or recurrent colorectal cancer (CRC). In Opdivo and Yervoy combination cohort, patients with CRC that has progressed on or after prior treatment with a fluoropyrimidine, oxaliplatin- or irinotecan-based chemotherapy received Opdivo 3 mg/kg plus Yervoy 1 mg/kg as a combination therapy every 3 weeks for 4 doses followed by Opdivo 3 mg/kg every 2 weeks. Patients were treated until disease progression or onset of unacceptable toxicity is observed. The primary endpoint of this combination cohort is overall response rate (ORR) as assessed by an investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and duration of response (DOR), etc.

About Colorectal Cancer

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon or the rectum. It is estimated that approximately 29,000 new cases of CRC are diagnosed per year in South Korea[1)]. Approximately 5% of unresectable CRC patients have MSI-H or dMMR tumors. There is a tendency of poor prognosis in this patient population compared with those having non-MSI-H tumors. As it is reported that the efficacy of current chemotherapy including the standard of care with fluoropyrimidine anticancer drugs is poor[2)], an innovative treatment option is needed in this patient population.

1) Globocan 2020; Patient Fact Sheets, Korea, Republic of. World Health Organization: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
2) 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.

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, 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, and cancer of unknown primary in December 2021.

In addition, ONO has submitted supplemental application for the adjuvant treatment of urothelial cancer, and is conducting clinical development program including hepatocellular carcinoma, 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. (Seoul, Korea; “OPKR”) is an ONO’s wholly-owned subsidiary established in December 2013. OPKR has established its own sales organization in South Korea and marketed Opdivo, an anti-PD-1 antibody/anti-neoplastic drug since 2015. OPKR has been committed to developing and marketing its products created internally at ONO to bring more innovative new products to meet unmet medical needs to patients in South Korea as soon as possible.

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