February 21, 2020

ONO Receives Approval of Opdivo® (Nivolumab) for Additional Indications of Unresectable Advanced or Recurrent Esophageal Cancer, and MSI-High Unresectable Advanced or Recurrent Colorectal Cancer in Japan for a Partial Change in Approved Items of Manufacturing and Marketing Approval

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Head office: Shinjuku, Tokyo; Representative Director and President: Jean-Christophe Barland) announced today that ONO received approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human programmed cell death-1 (PD-1) monoclonal antibody in Japan for the following two additional indications, for a partial change in approved items of the manufacturing and marketing approval:

- Unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy
- Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following chemotherapy

<Additional Indication of esophageal cancer>

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. In the result of this study, Opdivo showed a statistically significant improvement in overall survival (OS), the primary endpoint, compared with chemotherapy (docetaxel or paclitaxel). The safety profile of Opdivo in this study was consistent with previously reported findings in clinical studies with Opdivo, with no new safety signals.

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).

About esophageal 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 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 Japan. It is estimated that about 20,000 new cases are diagnosed with esophageal cancer per year in Japan (about 572,000 cases worldwide) and approximately 12,000 deaths (about 508,000 worldwide) per year resulting from this disease[1]. As there have been no available drugs, in Japan, showing the definitive efficacy in extension of OS in the second line treatment of esophageal cancer which failed in the treatment with cisplatin and 5-FU[2], an innovative treatment option is needed in this patient population.

1): Globocan 2018. Available at: http://gco.iarc.fr/today/fact-sheets-populations
2): Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, The Japan Esophageal Society

<Additional Indication of MSI-High colorectal cancer>

This approval is based on the result from Opdivo monotherapy cohort of a multi-center, open-label Phase II study (CheckMate-142 study) conducted by BMS, evaluating Opdivo in patients with microsatellite instability high (MSI-High) or mismatch repair deficient (dMMR) recurrent or metastatic colorectal cancer (CRC) that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs. In this study, Opdivo demonstrated the efficacy on investigator-assessed ORR, the primary endpoint. The safety profile of Opdivo in this study was consistent with previously reported findings in clinical studies with Opdivo, with no new safety signals.

About CheckMate-142 study

This study is a global multi-center, open-label, Phase II study evaluating Opdivo in patients with MSI-H or dMMR recurrent or metastatic CRC that has progressed on or after, or been intolerant of prior treatment with chemotherapy including fluoropyrimidine anticancer drugs. The efficacy endpoints include investigator-assessed and blinded independent central review committee-assessed objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, duration of response (DOR), progression-free survival (PFS) and overall survival (OS). Opdivo was continuously administered every 2 weeks until disease progression, or onset of unacceptable toxicity is observed.

About colorectal cancer

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon or the rectum. It is estimated that approximately 146,000 new cases are diagnosed with CRC per year in Japan (about 1,800,000 cases worldwide) and approximately 57,000 deaths (about 861,000 worldwide) per year resulting from this disease[1]. Approximately 5% of unresectable CRC patients have MSI-High tumors. There is a tendency of poor prognosis in this patient population compared with those having non MSI-High tumors. As it is reported that the efficacy of current chemotherapy including the standard therapy with fluoropyrimidine anticancer drugs is poor[2], an innovative treatment option is needed in this patient population.

1): Globocan 2018. Available at: http://gco.iarc.fr/today/fact-sheets-populations
2): Guidelines 2019 for the treatment of colorectal cancer, Japanese Society for Cancer of the Colon and Rectum (JSCCR)

Overview of OPDIVO® Intravenous Infusion

Product name	OPDIVO® Intravenous Infusion
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable or metastatic renal cell carcinoma ○ Relapsed or refractory classical Hodgkin lymphoma ○ Recurrent or metastatic head and neck cancer ○ Unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy ○ Unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after chemotherapy ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following chemotherapy ○ Unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy
Dosage and administration	<Melanoma> Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. In the adjuvant treatment of melanoma, the administration period does not exceed 12 months. In combination therapy with ipilimumab for unresectable melanoma, usually, for adults, administer 80 mg of nivolumab every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. <Unresectable or metastatic renal cell carcinoma> Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. In combination therapy with ipilimumab for unresectable or metastatic renal cell carcinoma previously untreated with chemotherapy, usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab as intravenous infusion every 2 weeks. <Unresectable, advanced or recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy, unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after chemotherapy, 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> Usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 2 weeks.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb KK
Conditions for approval	Risk Management Plan should be designed and appropriately implemented.

Note: Underlined parts show the revised ones according to this approval.

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, bladder cancer, ovarian cancer, pancreatic cancer, biliary tract cancer, etc.

About the 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 the companies' 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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