November 25, 2021

ONO Receives Approval of Opdivo® (nivolumab) for Expanded Use for Two Indications in Japan

First-line Treatment of Unresectable Advanced or Recurrent Gastric Cancer in Combination with Chemotherapy

Adjuvant Treatment of Esophageal Cancer

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Shinjuku, Tokyo; President, Jean-Christophe Barland) today announced that ONO has received the approvals of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-PD-1 monoclonal antibody in Japan, for expanded use for the first-line treatment of unresectable advanced or recurrent gastric cancer in combination with chemotherapy, and adjuvant treatment of esophageal cancer, for a partial change in approved items of the manufacturing and marketing approval.

<Approval for the first-line treatment of unresectable advanced or recurrent gastric cancer>

This approval is based on the results from the following 2 clinical studies:

1) CheckMate -649 study (ONO-4538-44): A global multi-center, randomized, open-label Phase 3 clinical study, evaluating Opdivo plus chemotherapy or Opdivo plus Yervoy (ipilimumab) combination compared to chemotherapy alone in patients with previously untreated, non-human epidermal growth factor receptor 2 (non-HER2)-positive, unresectable advanced or recurrent gastric cancer (GC), gastroesophageal junction cancer (GEJC) or esophageal adenocarcinoma (ESA), conducted on a world-wide basis including Japan, South Korea and Taiwan

   In this study, Opdivo plus chemotherapy showed a statistically significant and clinically meaningful improvement in overall survival (OS) both in all randomized patient population and OS in PD-L1 positive patients with a combined positive score (CPS) ≥5, one of the primary endpoints, versus chemotherapy. Furthermore, Opdivo plus chemotherapy demonstrated a statistically significant extension in progression-free survival (PFS) in PD-L1 positive patients with CPS ≥5, the other primary endpoint, versus chemotherapy. The safety profile of Opdivo plus chemotherapy in the study was consistent with the known safety profiles of the individual treatments.

2) ATTRACTION-4 study (ONO-4538-37): A multi-center, randomized Phase 2/3 clinical study, evaluating Opdivo plus chemotherapy compared to placebo plus chemotherapy in patients with previously untreated, HER-2 negative, unresectable advanced or recurrent GC or GEJC, conducted in Japan, South Korea and Taiwan

   In this study, Opdivo plus chemotherapy showed a statistically significant extension in PFS, one of the primary endpoints, versus placebo plus chemotherapy. On the other hand, Opdivo plus chemotherapy did not demonstrate a statistically significance in OS, the other of the primary

endpoints. The safety profile of Opdivo plus chemotherapy in the study was consistent with the known safety profiles of the individual treatments.

About CheckMate -649 study (ONO-4538-44)

Checkmate -649 is a multi-center, randomized, open-label Phase 3 clinical study, evaluating Opdivo plus chemotherapy or Opdivo plus Yervoy combination compared to chemotherapy alone in patients with previously untreated, non-HER2-positive, unresectable advanced or recurrent gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma. Patients in the Opdivo plus chemotherapy arm received Opdivo 240 mg plus fluorouracil, calcium folinate 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 up to two years or until disease progression, unacceptable toxicity or withdrawal of consent. The primary endpoints of the study are overall survival (OS) in PD-L1 positive patients with a combined positive score (CPS) ≥ 5 treated with Opdivo plus chemotherapy and progression-free survival (PFS) in CPS ≥ 5 patients treated with Opdivo plus chemotherapy. Key secondary endpoint is OS in CPS ≥ 1 and all-randomized patients treated with Opdivo plus chemotherapy.

About ATTRACTION-4 study (ONO-4538-37)

ATTRACTION-4 study is a multi-center, randomized Phase 2/3 clinical study, evaluating Opdivo plus chemotherapy (oxaliplatin + S-1 or capecitabine) compared to placebo plus chemotherapy in patients with previously untreated, HER2 negative unresectable advanced or recurrent gastric cancer or gastroesophageal junction cancer. Patients received Opdivo 360 mg or placebo every 3 weeks until disease progression or unacceptable toxicity is observed. The primary endpoints of the study are progression-free survival (PFS) and overall survival (OS).

About Gastric cancer

It is estimated that about 138,000 new cases[1)] are diagnosed with gastric cancer per year in Japan (about 1,089,000 cases worldwide[2)]) and approximately 46,000 deaths[1)] (about 768,000 worldwide[2)]) per year resulting from this disease[1)], which is the 2nd most common type of cancer after lung cancer in Japan. As there has been little progression in the standard of care of first-line chemotherapy for the HER2 negative unresectable, advanced or recurrent gastric cancer in the past decade in Japan, an innovative treatment option is needed in this patient population.

1) Globocan 2020: Stomach Cancer, Japan, World Health Organization
   Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
2) Globocan 2020: Stomach Cancer, World, World Health Organization
   Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

<Approval for the adjuvant treatment of esophageal 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 cancer (ESC) or gastroesophageal junction cancer (GEJC) compared to placebo.

In this study, Opdivo 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 (GEJC) who have received chemoradiation therapy (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 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

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. SCC is the predominant type accounting for about 90% of all esophageal cancer in Japan. It is estimated that about 26,000 new cases[1)] are diagnosed with esophageal cancer per year in Japan (about 604,000 cases worldwide[2)]) and approximately 12,000 deaths[1)] (about 544,000 worldwide[2)]) per year resulting from this disease. In Japan, radical resection following neoadjuvant therapy is performed as a treatment for resectable locally advanced esophageal cancer that does not have distant metastasis, but recurrence has been observed in 28-47% after radical resection. Furthermore, since the prognosis of recurrent cases after radical resection of esophageal cancer is extremely poor[3)], it is considered that there is a high medical need for postoperative adjuvant therapy aimed at suppressing recurrence.

1) Globocan 2020: Esophageal Cancer, Japan, World Health Organization
   Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
2) Globocan 2020: Esophageal Cancer, World, World Health Organization
   Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
3) Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, The Japan Esophageal Society

Overview of Opdivo® Intravenous Infusion

Product name	Opdivo® Intravenous Infusion 20mg, 100mg, 120mg and 240mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable or metastatic renal cell carcinoma ○ Recurrent or refractory classical Hodgkin lymphoma ○ Recurrent or metastatic head and neck cancer ○ Unresectable advanced or recurrent gastric cancer ~~that has progressed after chemotherapy~~ ○ Unresectable advanced or recurrent malignant pleural mesothelioma ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy ○ Adjuvant treatment of esophageal cancer
Dosage and administration	**<Melanoma>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <**Unresectable, advanced or recurrent non-small cell lung cancer, and unresectable advanced or recurrent gastric cancer ~~that has progressed after chemotherapy~~>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with other anti-tumor drugs, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Unresectable or metastatic renal cell carcinoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination with cabozantinib, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <**Recurrent or refractory classical Hodgkin lymphoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. Usually for pediatrics, administer 3 mg/kg (body weight) of nivolumab every 2 weeks as intravenous infusion. For pediatrics weighing 40 kg

	(body weight) or more, nivolumab can be administered at 240 mg of every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<u><Recurrent or metastatic head and neck cancer></u>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent malignant pleural mesothelioma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy>** Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab, usually, for adults, administer 240 mg of nivolumab as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<u><Unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy,</u> and adjuvant treatment of esophageal cancer>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. <u>In the adjuvant treatment of esophageal cancer, the administration period does not exceed 12 months.</u> ~~**<Recurrent or metastatic head and neck cancer, unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy, and unresectable advanced or recurrent esophageal cancer that has progressed after chemotherapy>**~~ ~~Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.~~
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb K.K.

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

<u>About Opdivo</u>

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 has submitted supplemental applications for the adjuvant treatment of urothelial cancer and cancer of unknown primary, and is conducting clinical development program including hepatocellular carcinoma, ovarian cancer, bladder cancer, prostate 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.

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