

September 22, 2017

**ONO Receives Approval for OPDIVO<sup>®</sup> (Nivolumab) Intravenous Infusion  
for Treatment of Unresectable Advanced or Recurrent Gastric Cancer  
which Has Progressed after Chemotherapy as a Partial Change in Approved Items of  
Manufacturing and Marketing Approval in Japan**

ONO PHARMACEUTICAL CO., LTD. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb Company (NYSE: BMY) announced today that ONO received an approval for a partial change in approved items of the manufacturing and marketing approval of OPDIVO<sup>®</sup> Intravenous Infusion 20 mg and 100 mg ("Opdivo"), the human anti-human PD-1 (programmed cell death-1) monoclonal antibody, for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy in Japan.

It is predicted that there are about 133,000 new patients with gastric cancer with about 47,000 death cases in Japan in 2017\*. The progress of chemotherapy has been realizing higher efficacy in tumor shrinkage (objective response rate) as a treatment of unresectable advanced or recurrent gastric cancer. However, it is still difficult to achieve complete cures by the treatment with chemotherapies. There is a high need for a novel therapeutic drug in this patient population, because the target treatment with chemotherapies is even now to delay the onset timing of clinical symptoms and extend survival period associated with cancer progression\*\*.

Opdivo is the first and only immune checkpoint inhibitor to demonstrate overall survival (OS) for the treatment of patients with unresectable advanced or recurrent gastric cancer who have been previously treated with chemotherapy, and the first approved specifically for the indication of gastric cancer anywhere in the world. In a global Phase III clinical study with Opdivo (ONO-4538-12 / ATTRACTION-2 study) in patients, including the Japanese patients, with unresectable advanced or recurrent gastric cancer (including esophago-gastric junction cancer) refractory to or intolerant of standard therapy, Opdivo demonstrated a statistically significant extension in overall survival (OS), the primary endpoint, with median OS of 5.26 months (95% confidence interval [CI]: 4.60 - 6.37) versus 4.14 months (95% CI: 3.42 - 4.86) with placebo (hazard ratio [HR] 0.63; 95% CI: 0.51 - 0.78;  $p < 0.0001$  [stratified log-rank test]). The survival rate at 12 months was 26.2% for Opdivo, compared to 10.9% for placebo. The Grade 3 or more treatment-related adverse events (AEs) occurred in 11.5% of patients treated with Opdivo and 5.6% of patients treated with placebo. The treatment was discontinued in 2.7% of Opdivo-treated patients and 2.5% of placebo-treated patients due to treatment-related AEs of any grade.

ONO considers it to be important to accumulate further clinical data, in order to make sure that Opdivo can be used more properly and effectively. In accordance with the conditional approval, ONO is committed to taking actions necessary for the proper use of Opdivo by collecting clinical data on the safety and efficacy of Opdivo.

\* : Projected Cancer Statistics, 2016, Center for Cancer Control and Information Services, National Cancer Center

\*\* : Japanese gastric treatment guideline (ver. 4), Japanese Gastric Cancer Association

## **Overview of OPDIVO® Intravenous Infusion 20 mg and 100 mg**

Product name	OPDIVO® Intravenous Infusion 20 mg and 100 mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	<ul style="list-style-type: none"><li>• Unresectable melanoma</li><li>• Unresectable, advanced or recurrent non-small cell lung cancer</li><li>• Unresectable or metastatic renal cell carcinoma</li><li>• Relapsed or refractory classical Hodgkin lymphoma</li><li>• Recurrent or metastatic head and neck cancer</li><li>• <u>Unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy</u></li></ul>
Dosage and administration	<p>1. Unresectable melanoma Chemotherapy-naive patients: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab every 2 weeks. Chemotherapy-treated patients: Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab every 2 weeks or 2 mg/kg (body weight) of nivolumab every 3 weeks.</p> <p>2. 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, <u>and unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy</u> Usually, for adults, infuse intravenously at 3 mg/kg (body weight) of nivolumab every 2 weeks.</p>
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.

\*: Conditional approval to unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy

### **About Opdivo**

Opdivo is an 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.

In Japan, ONO launched Opdivo for the treatment of unresectable melanoma in September 2014. Thereafter, ONO received an approval for additional indication 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 and recurrent or metastatic head and neck cancer in March 2017. In addition, ONO is conducting clinical development program including esophageal cancer, gastro-esophageal junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, malignant pleural

mesothelioma, ovarian cancer, biliary tract cancer, etc. Opdivo is currently approved in more than 60 countries, including Japan, South Korea, Taiwan, the US and European Union.

Bristol-Myers Squibb (BMS) has a robust clinical development program for Opdivo monotherapy and in combination with other Immuno-Oncology and non-Immuno-Oncology therapies across more than 350 clinical trials. BMS is studying Opdivo in more than 50 types of cancer, across solid tumors and hematologic malignancies, and is utilizing its translational medicine capabilities to tailor approaches with the goal of providing maximal benefit for individual patients.

In Japan, ONO and BMS (and BMS Japan subsidiary BMSKK) have formed a strategic partnership that includes co-development, co-commercialization, and co-promotion of multiple immunotherapies for patients with cancer.

### **About the ONO and BMS Collaboration**

In 2011, through a collaboration agreement with 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.

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