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## **Revision of Package Insert of Opdivo relating to Additional Combination Therapy with Bevacizumab and Chemotherapy in Unresectable, Advanced or Recurrent Non-small Cell Lung Cancer**

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; “ONO”) today announced that it has revised the package insert of Opdivo® (generic name: nivolumab) Intravenous Infusion (“Opdivo”), a human anti-human PD-1 monoclonal antibody, because a new combination therapy of Opdivo with bevacizumab\* and chemotherapy has become available for the already approved indication of unresectable, advanced or recurrent non-small cell lung cancer.

The revision of the package insert is based on the result from Phase III TASUKI-52 study (ONO-4538-52), evaluating Opdivo in combination treatment with bevacizumab and chemotherapy (Opdivo combination group: n=275), versus placebo in combination treatment with bevacizumab and chemotherapy (control combination group: n=275) in chemotherapy-naïve patients with 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.

With this revision, additional combination treatment of Opdivo with bevacizumab and chemotherapy becomes available to patients with unresectable, advanced or recurrent NSCLC.

\*: Bevacizumab (Brand name: Avastin®) is an antineoplastic/anti-VEGF (vascular endothelial growth factor) humanized monoclonal antibody.

### **About TASUKI-52 study (ONO-4538-52)**

TASUKI-52 study is a multi-center, randomized, double-blind, placebo-controlled Phase III clinical study (ONO-4538-52), evaluating Opdivo in combination treatment 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 NSCLC unsuitable for radical radiation. Patients in the Opdivo combination group received Opdivo at 360 mg, carboplatin at area under the blood concentration time curve (AUC) 6, paclitaxel at 200 mg/m<sup>2</sup> and bevacizumab at 15 mg/kg, every 3 weeks (as one cycle). Patients in the control combination group received placebo, carboplatin at AUC 6, paclitaxel at 200 mg/m<sup>2</sup> 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 PFS as assessed by the IRRC. The secondary endpoints are overall survival (OS), progression-free survival (PFS) as assessed by the study site's investigator and objective response rate (ORR), etc.

## **About Lung Cancer**

Lung cancer is considered to be 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 85% of lung cancer<sup>1)</sup>. NSCLC is further classified into adenocarcinoma (about 40% of lung cancer), squamous cell carcinoma (about 25%) and large cell carcinoma (about 10%)<sup>2)</sup>. Lung cancer is the most common type of cancer with an estimated 138,000 new diagnoses per year in Japan<sup>3)</sup> (about 2,200,000 cases worldwide<sup>4)</sup>). It is estimated that approximately 82,000 deaths per year resulting from the disease in Japan<sup>3)</sup> (approximately 1,790,000 worldwide<sup>4)</sup>), showing the first leading cause of cancer-related deaths in both cases<sup>3, 4)</sup>. Survival rates vary depending on the stage and type of the cancer when diagnosed. For patients diagnosed with metastatic lung cancer, the five-year survival rate is about 5%.

- 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](https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_12_toc)
- 3) Globocan 2020: Japan, World Health Organization. Available at:  
<https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf>
- 4) Globocan 2020: World, World Health Organization. Available at:  
<https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>

## **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 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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