ONO PHARMACEUTICAL CO.,LTD.

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# Ono and Takeda Receive an Approval for Opdivo® (nivolumab) and CABOMETYX® (cabozantinib) Combination Therapy in Japan for Treatment of Unresectable or Metastatic Renal Cell Carcinoma

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; Representative Director, President, Gyo Sagara; "ONO") and Takeda Pharmaceutical Co., Ltd. (Osaka, Japan; President and CEO, Christophe Weber; "Takeda") today announced that the companies have received an approval for combination therapy of ONO's Opdivo® (nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody, and Takeda's CABOMETYX® (cabozantinib s-malate) tablets ("CABOMETYX"), a tyrosine kinase inhibitor, which Takeda has licensed from Exelixis, Inc. ("Exelixis") for development and commercialization in Japan, in combination therapy for the treatment of unresectable or metastatic renal cell carcinoma (RCC), for a partial change in approved items of the manufacturing and marketing approval.

This approval is based on results from the global, multi-center, randomized, open-label Phase 3 CheckMate -9ER study, evaluating Opdivo and CABOMETYX combination therapy versus sunitinib alone in patients with previously untreated advanced or metastatic RCC. In this study, Opdivo and CABOMETYX combination therapy demonstrated a 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 observed 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 was PFS as assessed by the BICR. The secondary endpoints were OS and ORR as assessed by the BICR.

Since August 2018, ONO and Takeda have participated in Japan in this global study which has been ongoing under the collaboration among Bristol Myers Squibb (New York, US), Exelixis and their other partner, Ipsen Pharma SAS (France).

## Kidney Cancer

Kidney cancer is a malignant tumor arising from the renal parenchyma. Among kidney cancer, RCC is the most common cancer, constituting almost 90% of all kidney cancer[1]. It is estimated that

about 25,000 new cases of kidney cancer are diagnosed per year in Japan[2] (about 431,000 cases worldwide[3]) and approximately 8,550 deaths per year in Japan[2] (about 179,000 worldwide[3]) result from this disease.


1: The epidemiology of renal cell carcinoma. Euro Urol. 2011;60;615-621.
2: Globocan 2020, Japan, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
3： 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 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.

**About CABOMETYX**

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In Japan, CABOMETYX was

approved for the treatment of curatively unresectable or metastatic RCC in March 2020 by the Ministry of Health, Labour and Wealth, and has been launched under the product name of CABOMETYX® tablets 20mg and 60mg since May 2020. In addition, a supplemental approval was granted in November 2020 for the treatment of unresectable HCC that has progressed following chemotherapy.

**About the Takeda and Exelixis Collaboration**

In January 2017, Takeda entered into a collaboration agreement with Exelixis for the exclusive rights of commercialization and for the further clinical development of cabozantinib for all future indications in Japan.

Exelixis retains exclusive rights to develop and commercialize cabozantinib in the United States and has licensed exclusive rights to commercialize cabozantinib outside of the US and Japan to Ipsen Pharma SAS.

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