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Press Release

Ono Pharmaceutical Co., Ltd.
Bristol-Myers Squibb K.K.

Ono and Bristol-Myers Squibb KK Receive Supplemental Approval of Opdivo® and Yervoy® in Combination Treatment in Japan to Expand the Use for Unresectable Hepatocellular Carcinoma

Osaka and Tokyo, Japan, June 24, 2025 - Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President and COO: Toichi Takino; "Ono") and Bristol-Myers Squibb K.K. (Headquarters: Tokyo, Japan; President: Hidehito Katsuma) today announced that the companies have received a supplemental approval of Ono's anti-PD-1 antibody, Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo") and BMSKK's anti-CTLA-4 antibody, Yervoy® (generic name: ipilimumab) Injection ("Yervoy") in combination therapy in Japan, to expand the use for the treatment of unresectable hepatocellular carcinoma (HCC).

This approval is based on the results from the CheckMate -9DW study, a global multi-center Phase 3 clinical study (CA209-9DW: ONO-4538-92), evaluating Opdivo plus Yervoy compared to investigator's choice of lenvatinib or sorafenib monotherapy for patients with unresectable HCC who have not received prior systemic anti-cancer therapy. In this study, in which 85% of patients in the comparator arm were treated with lenvatinib and 15% were treated with sorafenib, Opdivo plus Yervoy met its primary endpoint of overall survival (OS), demonstrating a statistically significant and clinically meaningful improvement in OS compared to lenvatinib or sorafenib monotherapy. The median OS with Opdivo plus Yervoy (n=335) was 23.7 months (95% CI: 18.8-29.4) vs. 20.6 months (95% CI: 17.5-22.5) with lenvatinib or sorafenib (n=333; HR=0.79; 95% CI: 0.65-0.96 P=0.0180), reducing the risk of death by 21%.[1)] The safety profile of Opdivo plus Yervoy was consistent with previously reported data, with no new safety signals identified.

About CheckMate -9DW Study (CA209-9DW: ONO-4538-92)

CheckMate -9DW study is a global multicenter randomized open-label Phase 3 study evaluating the combination of Opdivo plus Yervoy compared to investigator's choice of lenvatinib or sorafenib monotherapy in patients with advanced hepatocellular carcinoma who have not received prior systemic anti-cancer therapy.
668 patients were randomized to receive Opdivo plus Yervoy (Opdivo 1 mg/kg plus Yervoy 3 mg/kg Q3W for up to four doses, followed by Opdivo monotherapy 480 mg Q4W) infusion, or single agent lenvatinib or sorafenib as oral capsules in the control arm (335 patients in the Opdivo and Yervoy combination therapy arm, 333 patients in the control arm). The primary endpoint of the study is OS and key secondary endpoints include objective response rate (ORR), duration of response (DOR) and time to symptom deterioration (TTSD).

About Hepatocellular Carcinoma

Liver cancer is the third most frequent cause of cancer death worldwide. It is estimated that there were approximately 866,000 new cases of liver cancer worldwide in 2022, with an estimated approximately 758,000 deaths[2)]. In Japan, it is estimated that there were approximately 41,000 new cases of liver cancer in 2022, with an estimated approximately 26,000 deaths[2)]. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for 90% of all liver

cancers[3]. In the past, many cases of HCC developed caused by viral liver disease, such as infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV), but in recent years, the number of cases caused by non-viral liver diseases has been increasing[4]. With the rise in non-viral liver cancer, HCC is often diagnosed in an advanced stage, where effective treatment options are limited and are usually associated with poor outcomes.
Up to 70% of patients experience recurrence within five years, particularly those still considered to be at high risk after surgery or ablation[5].

References:

1): Opdivo Prescribing Information. Opdivo U.S. Product Information. Last updated: April 2 025. Princeton, NJ: Bristol Myers Squibb Company.
2): Globocan 2022: Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf
3): Kim E, Viatour P. Hepatocellular carcinoma: old friends and new tricks. Exp Mol Med. 2020; 52: 1898–07.
4): The Japan Society of Hepatology, Liver Cancer White Paper 2022
5): Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391: 1301–14.

Overview of Opdivo® Intravenous Infusion

Product name	Opdivo® Intravenous Infusion 20mg, 100mg, 120mg and 240mg
Generic name	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Neoadjuvant treatment of 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 ○ Unresectable advanced or recurrent malignant pleural mesothelioma ○ Malignant mesothelioma (excluding 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 ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary ○ Adjuvant treatment of urothelial carcinoma ○ Unresectable urothelial carcinoma ○ Unresectable advanced or recurrent malignant epithelial tumors ○ Unresectable hepatocellular carcinoma
Dosage and administration	**<Melanoma>** Usually, for adults, administer at 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) for unresectable melanoma, usually, for adults, administer 80 mg of

	nivolumab (genetical recombination) every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab (genetical recombination) 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>** Usually, for adults, administer at 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) every 2 weeks or 360 mg every 3 weeks as intravenous infusion. **<Neoadjuvant treatment of non-small cell lung cancer>** In combination therapy with other anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab (genetical recombination) every 3 weeks as intravenous infusion. The administration frequency does not exceed 3 doses. **<Unresectable or metastatic renal cell carcinoma>** Usually, for adults, administer 240 mg of nivolumab (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination with cabozantinib, usually, for adults, administer 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. Usually for pediatrics, administer 3 mg/kg (body weight) of nivolumab (genetical recombination) every 2 weeks as intravenous infusion. For pediatrics weighing 40 kg (body weight) or more, nivolumab (genetical recombination) can be administered at 240 mg every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Recurrent or metastatic head and neck cancer, malignant mesothelioma (excluding malignant pleural mesothelioma), cancer of unknown primary, and unresectable advanced or recurrent malignant epithelial tumors>** Usually, for adults, administer 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab (genetical recombination), usually, for adults, administer 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination therapy with ipilimumab (genetical recombination), usually, for adults, administer 240 mg of nivolumab (genetical recombination) as intravenous infusion every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<Unresectable advanced or recurrent esophageal cancer>** Usually, for adults, administer 240 mg of nivolumab (genetical recombination) 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 (genetical recombination) every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks as intravenous infusion. **<Adjuvant treatment of esophageal cancer, and adjuvant treatment of urothelial carcinoma>** Usually, for adults, administer 240 mg of nivolumab (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. The administration period does not exceed 12 months. **<Unresectable urothelial carcinoma>** In combination with gemcitabine hydrochloride and platinum-containing anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab (genetical recombination) as intravenous infusion every 3 weeks for 6 doses. After that, administer 240 mg of nivolumab (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion. **<u><Unresectable hepatocellular carcinoma></u>** <u>In combination therapy with ipilimumab (genetical recombination), usually, for adults, administer 80 mg of nivolumab (genetical recombination) every 3 weeks for 4 doses. After that, administer 240 mg of nivolumab (genetical recombination) every 2 weeks or 480 mg every 4 weeks as intravenous infusion.</u>
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Co-promotion	Bristol-Myers Squibb K.K.

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

Overview of Yervoy® Injection

Product name	Yervoy® Injection 20mg and 50mg
Generic name	Ipilimumab (Genetical recombination)
Indication	○ Unresectable melanoma ○ Unresectable or metastatic renal cell carcinoma ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable advanced or recurrent malignant pleural mesothelioma ○ Unresectable advanced or recurrent esophageal cancer ○ Unresectable hepatocellular carcinoma
Dosage and administration	**<Unresectable melanoma>** Usually, for adults, administer 3 mg/kg (body weight) of ipilimumab (genetical recombination) every 3 weeks for 4 doses. In combination therapy with other anti-cancer drugs, nivolumab (genetical recombination) should be co-administered. **<Unresectable or metastatic renal cell carcinoma, and microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy>** In combination therapy with nivolumab (genetical recombination), usually, for adults, administer 1 mg/kg (body weight) of ipilimumab (genetical recombination) as intravenous infusion every 3 weeks for 4 doses. **<Unresectable advanced or recurrent non-small cell lung cancer>** In combination therapy with other anti-tumor drugs, usually, for adults, administer 1 mg/kg (body weight) of ipilimumab (genetical recombination) as intravenous infusion every 6 weeks. **<Unresectable advanced or recurrent malignant pleural mesothelioma, and unresectable advanced or recurrent esophageal cancer>** In combination therapy with nivolumab (genetical recombination), usually, for adults, administer 1 mg/kg (body weight) of ipilimumab (genetical recombination) as intravenous infusion every 6 weeks. **<Unresectable hepatocellular carcinoma>** In combination therapy with nivolumab (genetical recombination), usually, for adults, administer 3 mg/kg (body weight) of ipilimumab (genetical recombination) as intravenous infusion every 3 weeks for 4 doses.
Manufacturer/distributor	Bristol-Myers Squibb K.K.
Co-promotion	Ono Pharmaceutical Co., Ltd.

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, 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, 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, cancer of unknown primary in December 2021, adjuvant treatment of urothelial carcinoma in March 2022, malignant mesothelioma (excluding malignant pleural mesothelioma) in November 2023, unresectable advanced or recurrent malignant epithelial tumors in February 2024, and unresectable urothelial carcinoma in December 2024.

About Yervoy

Yervoy is a recombinant, human monoclonal antibody, and binds to the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. Yervoy binds to CTLA-4, and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including anti-tumor immune response. On March 25, 2011, the U.S. Food and Drug Administration (FDA) approved Yervoy 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. Yervoy is now approved in more than 50 countries. There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types. In Japan, Yervoy was approved for the indication of unresectable malignant melanoma in July 2015.

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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