ONO PHARMA

Bristol Myers Squibb®

**Press Release**

December 27, 2024

# Ono Receives Supplemental Approval of Opdivo® in Combination with Cisplatin and Gemcitabine for Treatment of Unresectable Urothelial Carcinoma in Japan

Osaka and Tokyo, Japan, December 27, 2024 - Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President: Toichi Takino; "Ono") and Bristol-Myers Squibb K.K. (Headquarters: Tokyo, Japan; President: Steve Sugino) today announced that Ono has received a supplemental approval of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), an anti-PD-1 antibody, in combination with cisplatin and gemcitabine for the treatment of unresectable urothelial carcinoma in Japan. This approval is related to the additional indication for a partial change in approved items of the manufacturing and marketing approval in Japan.

This approval is based on the results from the global, multi-center Phase 3 CheckMate -901 clinical trial (CA209-901/ONO-4538-56), evaluating Opdivo in combination with cisplatin and gemcitabine followed by Opdivo monotherapy compared to standard-of-care chemotherapy alone, in patients with untreated, unresectable or metastatic urothelial carcinoma. In this study, Opdivo in combination with cisplatin and gemcitabine followed by Opdivo monotherapy demonstrated statistically significant improvements in the primary efficacy endpoints of overall survival (OS) and progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR) compared to cisplatin and gemcitabine alone. The safety profile of Opdivo in combination with cisplatin and gemcitabine followed by Opdivo monotherapy was consistent with the known safety profiles of the combination with chemotherapy and Opdivo monotherapy. No new safety concerns were identified.

With respect to the indication of urothelial carcinoma, Opdivo was approved in Japan for the adjuvant treatment of eligible patients with urothelial carcinoma as a monotherapy in March 2022.

## About CheckMate -901 Trial (CA209-901/ONO-4538-56)

CheckMate -901 trial is a global, multi-center, randomized, open-label Phase 3 clinical trial, evaluating Opdivo in combination with Yervoy or Opdivo in combination with cisplatin and gemcitabine followed by Opdivo monotherapy compared to standard-of-care chemotherapy alone, in patients with untreated, unresectable or metastatic urothelial carcinoma.

In the study of Opdivo in combination with cisplatin and gemcitabine followed by Opdivo monotherapy, a part of the CheckMate -901 trial, patients eligible for cisplatin-based chemotherapy were randomized 1:1 to receive either Opdivo 360 mg in combination with cisplatin and gemcitabine every 3 weeks for six cycles followed by Opdivo 480 mg monotherapy every 4 weeks or cisplatin-gemcitabine alone every 3 weeks for six cycles. Patients received Opdivo until disease progression or death up to a maximum of 2 years. The primary endpoints of this study are overall survival (OS) and progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR). The OS and PFS outcomes are based on the final efficacy analyses for these endpoints.

**About Urothelial Carcinoma**

Urothelial carcinoma is a tumor that begins in the renal pelvis, ureter, bladder and urethra, most of which is bladder cancer. Histopathologically, urothelial carcinoma (transitional epithelial cancer) accounts for more than 90% of bladder cancer[1]. In Japan, it is estimated that about 34,000 new cases[2] are diagnosed with bladder cancer per year (about 614,000 cases worldwide[3]) and that about 10,000 deaths[2] from this disease occur per year (about 220,000 deaths worldwide[3]).


1): Lynch CF, Cohen MB. Urinary System. Cancer. 1995;75:316-29.

2): Globocan 2022: Bladder Cancer, Japan, World Health Organization. Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/392-japan-fact-sheet.pdf

3): Globocan 2022: Bladder Cancer, World, World Health Organization. Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf


**Overview of Opdivo® Intravenous Infusion**

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| Product name | Opdivo® Intravenous Infusion 20mg, 100mg, 120mg and 240mg |
| Generic name | Nivolumab (Genetical recombination) |
| Indication | ○ Melanoma<br>○ Unresectable, advanced or recurrent non-small cell lung cancer<br>○ Neoadjuvant treatment of non-small cell lung cancer<br>○ Unresectable or metastatic renal cell carcinoma<br>○ Recurrent or refractory classical Hodgkin lymphoma<br>○ Recurrent or metastatic head and neck cancer<br>○ Unresectable advanced or recurrent gastric cancer<br>○ Unresectable advanced or recurrent malignant pleural mesothelioma<br>○ Malignant mesothelioma (excluding malignant pleural mesothelioma)<br>○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy<br>○ Unresectable advanced or recurrent esophageal cancer<br>○ Adjuvant treatment of esophageal cancer<br>○ Cancer of unknown primary<br>○ Adjuvant treatment of urothelial carcinoma<br>○ Unresectable urothelial carcinoma<br>○ Unresectable advanced or recurrent malignant epithelial tumors |
| Dosage and administration | **<Melanoma>**<br>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.<br>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.<br>**<Unresectable, advanced or recurrent non-small cell lung cancer, and unresectable advanced or recurrent gastric cancer>**<br>Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>In combination therapy with other anti-tumor drugs, usually, for adults, |

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| | administer 240 mg of nivolumab every 2 weeks or 360 mg every 3 weeks as intravenous infusion.<br>**<Neoadjuvant treatment of non-small cell lung cancer>**<br>In combination therapy with other anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab every 3 weeks as intravenous infusion. The administration frequency does not exceed 3 doses.<br>**<Unresectable or metastatic renal cell carcinoma>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>In combination with cabozantinib, usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>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.<br><**Recurrent or refractory classical Hodgkin lymphoma>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>**<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>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>**<Unresectable advanced or recurrent malignant pleural mesothelioma>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>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.<br>**<Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy>**<br>Usually, for adults, administer at 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>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. |

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| | **<Unresectable advanced or recurrent esophageal cancer>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion.<br>In combination therapy with other anti-tumor drugs, usually, for adults, administer 240 mg of nivolumab every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks as intravenous infusion.<br>**<Adjuvant treatment of esophageal cancer, and adjuvant treatment of urothelial carcinoma>**<br>Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. The administration period does not exceed 12 months.<br>**<Unresectable urothelial carcinoma>**<br>In combination with gemcitabine hydrochloride and platinum-containing anti-tumor drugs, usually, for adults, administer 360 mg of nivolumab as intravenous infusion every 3 weeks for 6 doses. After that, 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

**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, and unresectable advanced or recurrent malignant epithelial tumors in February 2024.

In addition, Ono has submitted a supplemental application for the treatment of hepatocellular carcinoma.

**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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