May 26, 2022

Two Combination Treatments of Opdivo + Yervoy and Opdivo + Chemotherapy Approved in Japan for First-line Treatment of Unresectable Advanced or Recurrent Esophageal Cancer

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Shinjuku, Tokyo; President, Jean-Christophe Barland; "BMSKK") today announced that the companies have received an approval in Japan for the combination treatment of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), an anti-PD-1 antibody, and Yervoy® (generic name: ipilimumab) Injection ("Yervoy"), an anti-CTLA-4 antibody, for the first-line treatment of unresectable, advanced or recurrent esophageal cancer. This approval is related to the additional indication for a partial change in approved items of the manufacturing and marketing approval in Japan.

Furthermore, ONO also received an approval of Opdivo in combination with chemotherapy* for the above same indication.

These approvals are based on results from the global multi-center, randomized, open-label Phase 3 CheckMate -648 study (ONO-4538-50/CA209648), evaluating Opdivo plus Yervoy and Opdivo plus chemotherapy*, compared to chemotherapy* alone in patients with previously untreated unresectable advanced or recurrent metastatic esophageal squamous cell carcinoma (ESCC). In this study, both Opdivo-based treatment combinations (Opdivo plus Yervoy and Opdivo plus chemotherapy) demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS), compared to chemotherapy at the pre-specified interim analysis in patients with tumor cell PD-L1 expression ≥1%, as well as in the all-randomized population. The safety profiles of Opdivo plus Yervoy and Opdivo plus chemotherapy were consistent with the known safety profiles of the individual components.

*: Fluorouracil and cisplatin combination therapy (FP therapy)

About CheckMate -648 Study (ONO-4538-50/CA209648)

CheckMate -648 is a global multi-center, randomized, open-label Phase 3 study, evaluating Opdivo plus Yervoy and Opdivo plus chemotherapy (fluorouracil and cisplatin combination therapy) versus chemotherapy (fluorouracil and cisplatin combination therapy) alone in patients with previously untreated unresectable advanced or recurrent metastatic esophageal squamous cell carcinoma (ESCC). The primary endpoints of the study are overall survival (OS) and progression-free survival (PFS) as assessed by the blinded independent central review (BICR) in patients whose tumors express PD-L1 ≥1% for both Opdivo-based combination therapies versus chemotherapy. The secondary endpoints of the study include OS and PFS as assessed by the BICR in the all-randomized population.

In the Opdivo plus Yervoy arm, patients received treatment with Opdivo at 3 mg/kg every 2 weeks and Yervoy at 1 mg/kg every 6 weeks up to 24 months or until disease progression or unacceptable toxicity. In the Opdivo plus chemotherapy arm, patients received treatment with Opdivo at 240 mg every 2 weeks, fluorouracil 800 mg/m²/day on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m² on Day 1 of four-week cycle. Patients received Opdivo for up to 24 months or until disease progression or unacceptable toxicity, and chemotherapy until disease progression or unacceptable toxicity.

About esophageal cancer

Esophageal cancer is a malignant tumor that occurs in the inner layer (mucosa) of the esophagus and grows outside (toward the deeper layer). There are two main histological types of esophageal cancer; squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the predominant type accounting for about 90% of all esophageal cancer in Japan. It is estimated that there are about 26,000 new cases per year[1)] diagnosed with esophageal cancer in Japan (about 604,000 cases worldwide[2)]) and approximately 12,000 deaths per year[1)] (about 544,000 worldwide[2)]) resulting from this disease.

1): Globocan 2020: Japan, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
2): Globocan 2020: World, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

Overview of Opdivo® Intravenous Infusion

Product name	Opdivo® Intravenous Infusion 20mg, 100mg, 120mg and 240mg
Generic name (JAN)	Nivolumab (Genetical recombination)
Indication	○ Melanoma ○ Unresectable, advanced or recurrent 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 ○ Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed after chemotherapy ○ Unresectable advanced or recurrent esophageal cancer ~~that has progressed after chemotherapy~~ ○ Adjuvant treatment of esophageal cancer ○ Cancer of unknown primary ○ Adjuvant treatment of urothelial carcinoma
Dosage and administration	**<Melanoma>** 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. 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. **<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 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 every 2 weeks or 360 mg every 3 weeks as intravenous infusion.

	<Unresectable or metastatic renal cell carcinoma> Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. In combination with cabozantinib, usually, for adults, administer 240 mg of nivolumab 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 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. **<Recurrent or refractory classical Hodgkin lymphoma>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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. **<Recurrent or metastatic head and neck cancer, and cancer of unknown primary>** Usually, for adults, administer 240 mg of nivolumab 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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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. **<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 every 2 weeks or 480 mg every 4 weeks as intravenous infusion. 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. **<Unresectable advanced or recurrent esophageal cancer ~~that has progressed after chemotherapy, and adjuvant treatment of esophageal cancer~~>** Usually, for adults, administer 240 mg of nivolumab every 2 weeks or 480 mg every 4 weeks as intravenous infusion. ~~In the adjuvant treatment of esophageal cancer, the administration period does not exceed 12 months.~~ 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.

	<Adjuvant treatment of esophageal cancer, and adjuvant treatment of urothelial carcinoma> 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.
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 (JAN)	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
Dosage and administration	**<Unresectable melanoma>** Usually, for adults, administer 3 mg/kg (body weight) of ipilimumab every 3 weeks for 4 doses. In combination therapy with other anti-cancer drugs, nivolumab 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, usually, for adults, administer 1 mg/kg of ipilimumab 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 of ipilimumab 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, usually, for adults, administer 1 mg/kg of ipilimumab as intravenous infusion every 6 weeks.
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, 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, 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, and adjuvant treatment of urothelial carcinoma in March 2022.

In addition, ONO is conducting clinical development program including hepatocellular carcinoma, ovarian cancer, bladder cancer, prostate cancer, pancreatic cancer, etc.

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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