November 27, 2020

Combination Therapy concerning Opdivo and Yervoy Approved in Japan for First–Line Treatment of Unresectable Advanced or Recurrent Non-Small Cell Lung 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 approval in Japan for the following combination therapies of Opdivo® (generic name: nivolumab) intravenous Infusion ("Opdivo"), a human anti-programmed death-1 (PD-1) monoclonal antibody, and Yervoy® (generic name: ipilimumab) Injection ("Yervoy"), a human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) for the first-line treatment of unresectable, advanced or recurrent non-small cell lung cancer, for a partial change in approved items of the manufacturing and marketing approval in Japan.

1) Combination therapy with Opdivo and Yervoy (ONO/BMSKK)
2) Combination therapy with Opdivo, Yervoy plus chemotherapy (ONO/BMSKK)
3) Combination therapy with Opdivo and chemotherapy (ONO)

Note: The companies' names in the brackets show those which received the approval. (ONO: Opdivo and BMSKK: Yervoy)

These approvals are based on the results from the following clinical studies conducted by ONO and Bristol Myers Squibb (NYSE: BMY; "BMS"):

1) and 3): CheckMate -227 Study: a global, multi-center, multi-part, randomized, open-label Phase III study evaluating Opdivo, or Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy compared to platinum doublet chemotherapy in patients with previously untreated unresectable advanced or recurrent non-small cell lung cancer (NSCLC)

2): CheckMate -9LA Study: a global multi-center, randomized, open-label Phase III study evaluating Opdivo plus Yervoy in combination with platinum-doublet chemotherapy (two cycles) compared to platinum-doublet chemotherapy alone in patients with previously untreated unresectable advanced or recurrent NSCLC

About CheckMate -227 study

This study is a global, multi-center, multi-part, randomized, open-label Phase III clinical study, evaluating Opdivo, or Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy compared to platinum-doublet chemotherapy in patients with previously untreated unresectable advanced or recurrent NSCLC. This study consists of the following 3 Parts:

1) Part 1a: Evaluating the efficacy and safety of Opdivo, or Opdivo plus Yervoy in patients whose tumors express PD-L1 ≧1%
2) Part 1b: Evaluating the efficacy and safety of Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy in patients whose tumors express PD-L1 <1%
3) Part 2: Evaluating the efficacy and safety of Opdivo plus platinum-doublet chemotherapy, regardless of PD-L1 expression level

In Opdivo and Yervoy combination therapy of Part 1, patients received Opdivo 3 mg/kg every 2 weeks plus Yervoy 1 mg/kg every 6 weeks for up to 24 months, until disease progression or onset of unacceptable toxicity is observed. In the combination treatment with Opdivo plus platinum-doublet chemotherapy of Part 1 and Part 2, patients received Opdivo 360 mg every 3 weeks and platinum-doublet chemotherapy based on histological subtypes every 3 weeks up to 4 cycles; patients were treated with Opdivo for up to 24 months or until disease progression or onset of unacceptable toxicity is observed. Patients with non-squamous cancer were continuously treated with pemetrexed maintenance therapy until disease progression or onset of unacceptable toxicity is observed, unless disease progression is observed after completion of 4 cycles of chemotherapy. In Part 1, overall survival (OS) is set up as one of the primary endpoints in patients whose tumors expressed PD-L1 ≧ 1% in Part 1a. In Part 2, the primary endpoint is OS in patients with non-squamous cancer.

About CheckMate -9LA study

CheckMate -9LA study is a global, multi-center, randomized, open-label Phase III clinical study evaluating Opdivo (360 mg Q3W) plus Yervoy (1 mg/kg Q6W) in combination with platinum-doublet chemotherapy (two cycles Q3W) compared to platinum-doublet chemotherapy alone in patients with previously untreated unresectable advanced or recurrent NSCLC, regardless of PD-L1 expression and histology. Patients in the combination treatment arm were treated for up to 24 months with Opdivo or until disease progression or unacceptable toxicity. Patients in the control arm were treated with up to four cycles of chemotherapy and optional pemetrexed maintenance (if eligible) until disease progression or toxicity. The primary endpoint of the trial is OS in the intent to treat population. Secondary endpoints are progression-free survival (PFS), overall response rate (ORR), and efficacy measures according to biomarkers.

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 80-85% of lung cancer[1)]. NSCLC is further classified into adenocarcinoma (about 40% of lung cancer), squamous cell carcinoma (about 25%) and large cell carcinoma (about 10%) [2)]. Lung cancer is one of the most common types of cancer with an estimated 2,090,000 new diagnoses per year worldwide (about 118,000 cases in Japan). It is estimated that approximately 1,760,000 deaths resulting from the disease per year worldwide (approximately 81,000 in Japan), showing the first leading cause of cancer-related deaths in both cases[3)]. 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 less than 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
3) Globocan 2018; Lung Cancer: Estimated cancer incidence, mortality and prevalence worldwide. World Health Organization. Available from: https://gco.iarc.fr/today/fact-sheets-populations

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 which has progressed after chemotherapy ○ Unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after chemotherapy ○ 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
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>** 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 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 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. **<Microsatellite instability high (MSI-High) unresectable advanced or recurrent colorectal cancer that has progressed following 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.

	<Recurrent or refractory classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy, unresectable advanced or recurrent malignant pleural mesothelioma that has progressed after chemotherapy, and unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy> Usually, for adults, 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.
Conditions for approval	Risk Management Plan should be designed and appropriately implemented.

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

Overview of Yervoy® Injection

Product name	Yervoy® Injection 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
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.
Manufacturer/distributor	Bristol-Myers Squibb K.K.
Co-promotion	Ono Pharmaceutical Co., Ltd.
Conditions for approval*	Risk Management Plan should be designed and appropriately implemented.

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 and adjuvant treatment of melanoma 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 esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, bladder cancer, pancreatic cancer, biliary tract 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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