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ONO and BMSKK Submit Supplemental Application for Approval of Opdivo and Yervoy Combination Therapy to Expand the Use for First-Line Treatment of Unresectable, Advanced or Recurrent Non-Small Cell Lung Cancer in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") and Bristol-Myers Squibb K.K. (Shinjuku, Tokyo; President, Jean-Christophe Barland) announced today that the companies have submitted a supplemental application for combination therapy of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human programmed cell 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), in Japan to expand the use for first-line treatment of unresectable, advanced or recurrent non-small cell lung cancer (NSCLC), for a partial change in approved items of the manufacturing and marketing approval.

This application is mainly based on the result from Part 1 of CheckMate -227, a global multipart, open-label, randomized Phase III clinical study, conducted by ONO and Bristol-Myers Squibb (NYSE: BMY, "BMS"), in patients with chemotherapy-naive Stage IV or recurrent NSCLC. In this result, Opdivo and Yervoy combination therapy achieved a significant improvement in the independent co-primary endpoint of overall survival (OS) in patients whose tumors expressed PD-L1 ≧1%, compared to chemotherapy.

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 NSCLC, depending on the broad histological subtypes. NSCLC is one of the most common types of lung cancer, accounting for about 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 the most common type 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: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf

About CheckMate-227 study

This study is a global multipart, open-label, randomized Phase III clinical study, evaluating Opdivo, or Opdivo plus Yervoy, or Opdivo plus platinum-doublet chemotherapy compared to platinum doublet chemotherapy in patients with chemotherapy-naive Stage IV 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 versus chemotherapy 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 versus chemotherapy in patients whose tumors express PD-L1 <1%
3) Part 2: Evaluating the efficacy and safety of Opdivo plus platinum-doublet chemotherapy versus chemotherapy, regardless of PD-L1

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 as a combination therapy up to 24 weeks, until disease progression or onset of unacceptable toxicity is observed. The primary endpoints of Part 1 are overall survival (OS) in patients whose tumors expressed PD-L1 ≧1% in Part 1a, and progression-free survival (PFS) in patients with tumor mutational burden (TMB) ≧10 mut/Mb (mutations/megabase) in Part 1a and 1b.

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 cancer 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, etc. in August 2018.

In addition, ONO has submitted supplemental applications for the treatment of microsatellite instable High (MSI-H) colorectal cancer and esophageal cancer, and is conducting clinical development program including esophageal cancer, esophago-gastric junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, ovarian cancer, bladder cancer, colorectal 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 60 countries. There is a broad, ongoing development program in place for Yervoy spanning multiple tumor types.

In Japan, BMSKK received an approval of Yervoy for the treatment of unresectable melanoma in July 2015. Yervoy was also approved in combination therapy with Opdivo for the treatment of unresectable melanoma in May 2018, followed by unresectable or metastatic renal cell carcinoma in August 2018.

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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