ONO PHARMACEUTICAL CO.,LTD.

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ONO Submits Supplemental Application for Approval of Opdivo® (Nivolumab) in Combination with Chemotherapy to Expand its Use as Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") today announced that it has submitted a supplemental application of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody in Japan, to expand its use as neoadjuvant treatment of resectable non-small cell lung cancer in combination with chemotherapy, for a partial change in approved items of the manufacturing and marketing approval.

This application is based on the results from a global multi-center, randomized, open-label Phase 3 clinical study, CheckMate -816 study (ONO-4538-55), evaluating Opdivo in combination with chemotherapy compared to chemotherapy alone as a neoadjuvant treatment in patients with resectable non-small cell lung cancer (NSCLC). In this study, three cycles of Opdivo in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in event-free survival (EFS) as assessed by Blinded Independent Central Review (BICR) and pathologic complete response (pCR) as assessed by Blinded Independent Pathology Review (BIPR) versus chemotherapy alone when given before surgery. The safety profile of Opdivo with chemotherapy in this study was consistent with previously reported studies with Opdivo and chemotherapy in patients with NSCLC.

About CheckMate -816 (ONO-4538-55) study

CheckMate -816 is a global multi-center, randomized, open-label Phase 3 clinical trial, evaluating Opdivo with chemotherapy compared to chemotherapy alone as neoadjuvant treatment in patients with resectable stage IB - IIIA non-small cell lung cancer (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control staging criteria), regardless of PD-L1 expression. Patients were randomized to receive either Opdivo 360 mg plus histology-based platinum doublet chemotherapy every three weeks for three cycles, or platinum doublet chemotherapy every three weeks for three cycles, followed by surgery. The primary endpoints of the study are event-free survival (EFS) as assessed by Blinded Independent Central Review (BICR) and pathologic complete response (pCR) as assessed by Blinded Independent Pathology Review (BIPR). Secondary endpoints include overall survival (OS), major pathologic response (MPR), and time to death or distant metastases.

About Lung Cancer

Lung cancer is 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 the most common type of lung cancer, accounting for about 80 - 85% of lung cancer[1)]. NSCLC is further classified into mainly 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 138,000 new diagnoses per year in Japan[3] (about 2,200,000 cases worldwide[4]). It is estimated that approximately 82,000 deaths per year result from the disease in Japan[3] (approximately 1,790,000 worldwide[4]), representing the leading cause of cancer-related deaths in both cases[3, 4]. Curative surgery is performed in patients with stages I - IIIA and some patients with stage IIIB NSCLC. However, even if surgery is performed, 30 - 55% of NSCLC patients relapse and die of the disease[5]. The 5-year survival rates in NSCLC patients undergoing surgery are 74.8 - 91.6% in stage IA, 71.5% in stage IB, 60.2% in stage IIA, 58.1% in stage IIB, 50.6% in stage IIIA, and 40.5% in stage IIIB[6].

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 2020: Japan, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
4) Globocan 2020: World, World Health Organization. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
5) Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res. 2014;3:242-9.
6) Okami J, Shintani Y, Okumura M, et al. Demographics, Safety and Quality, and Prognostic Information in Both the Seventh and Eighth Editions of the TNM Classification in 18,973 Surgical Cases of the Japanese Joint Committee of Lung Cancer Registry Database in 2010. J Thorac Oncol. 2019;14:212-22.

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, biliary tract cancer, etc.

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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