ONO PHARMACEUTICAL CO.,LTD.

February 18, 2021

ONO Submits Supplemental Application for Approval for Opdivo® (Nivolumab) to Expand the Use for Adjuvant Therapy of Resected Esophageal Cancer in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") today announced that ONO has submitted a supplemental application for Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-human PD-1 monoclonal antibody in Japan, to expand the use for the adjuvant therapy of resected esophageal cancer, for a partial change in approved items of the manufacturing and marketing approval.

This application has been filed based on the results from a global multi-center, randomized, double-blind Phase 3 clinical study, CheckMate -577 (ONO-4538-43) study, evaluating Opdivo monotherapy as an adjuvant therapy in patients with resected esophageal cancer or gastroesophageal junction (GEJ) cancer compared to placebo. In this study, Opdivo showed a statistically significant improvement in disease-free survival (DFS), the primary endpoint of the study, compared to placebo. The median DFS was 22.4 months [95% Confidence Interval (CI): 16.6 - 34.0)] in patients receiving Opdivo and 11.0 months (95% CI: 8.3 - 14.3) in those receiving placebo (Hazard Ratio 0.69; 96.4% CI: 0.56 - 0.86; p=0.0003). The safety profile of Opdivo in this study was consistent with previously reported studies of Opdivo monotherapy.

About CheckMate -577 (ONO-4538-43) study

CheckMate -577 (ONO-4538-43) study is a global multi-center, randomized, double-blind Phase 3 clinical study evaluating Opdivo monotherapy as an adjuvant therapy in patients with resected esophageal cancer or GEJ cancer who have received chemoradiation therapy (CRT) and have not achieved a pathological complete response. The primary endpoint of the study is DFS and the secondary endpoint is overall survival (OS). Following neoadjuvant CRT and complete tumor surgical resection (also known as trimodality therapy), patients were randomized to receive Opdivo or placebo. In patients receiving Opdivo, it was administered at 240 mg by intravenous infusion every two weeks for 16 weeks followed by Opdivo 480 mg every four weeks until disease recurrence, unacceptable toxicity or withdrawal of consent, with a maximum of one year total treatment duration.

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 about 26,000 new cases [1)] are diagnosed with esophageal cancer per year in Japan (about 604,000 cases worldwide [2)]) and approximately 12,000 deaths [1)] (about 544,000 worldwide [2)]) per year resulting from this disease. In Japan, radical resection following neoadjuvant therapy is performed as a treatment for resectable locally advanced esophageal cancer that does not have distant metastasis, but recurrence has been observed in 28-47% after radical resection. Furthermore, since the prognosis of recurrent cases after radical resection of esophageal cancer is extremely poor [3)], it is considered that there is a high medical need for postoperative adjuvant therapy aimed at suppressing recurrence.

1): Globocan 2020. Available at: https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf
2): Globocan 2020. Available at: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf
3): Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017, The Japan Esophageal Society

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, 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, hepatocellular carcinoma, urothelial cancer, 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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