September 14, 2021

Applications Submitted for Combination Therapy of Opdivo + Yervoy and Opdivo + Chemotherapy for First-line Treatment of Unresectable Advanced or Recurrent Esophageal 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; "BMSKK") today announced that the companies have submitted supplemental application in Japan for the combination therapy of Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo"), a human anti-PD-1 monoclonal antibody, and Yervoy® (generic name: ipilimumab) Injection ("Yervoy"), a human anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody, for the first-line treatment of unresectable, advanced or recurrent esophageal cancer, for a partial change in approved items of the manufacturing and marketing approval in Japan.

Furthermore, ONO also submitted a supplemental application for the combination therapy of Opdivo and chemotherapy for the above same indication.

The applications 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 (ONO-4538-50/CA209648) study

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 ESCC. The primary endpoints of the study are 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 major secondary endpoints of the study are 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. In Japan, the combination therapy of fluorouracil and cisplatin (FP therapy) is widely used as one of the first-line treatment options for unresectable advanced or recurrent esophageal cancer[3)], but additional treatment options are needed because of the insufficient effectiveness of the currently available therapies in the extension of OS.

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 has submitted supplemental applications for the adjuvant treatment of urothelial cancer and cancer of unknown primary, and is conducting clinical development program including hepatocellular carcinoma, ovarian cancer, bladder cancer, prostate 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.

Contact
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono.co.jp