Press Release

Ono Pharmaceutical Co., Ltd.
Bristol-Myers Squibb K.K.

Ono and Bristol-Myers Squibb KK Submit Supplemental Application of Opdivo and Yervoy in Combination Treatment in Japan to Expand the Use for Unresectable Hepatocellular Carcinoma

Osaka and Tokyo, Japan, August 9, 2024 - Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President: Toichi Takino; "Ono") and Bristol-Myers Squibb K.K. (Headquarters: Tokyo, Japan; President: Steve Sugino; "BMSKK") today announced the submission of supplemental application of Ono's anti-PD-1 antibody, Opdivo® (generic name: nivolumab) Intravenous Infusion ("Opdivo") and BMSKK's anti-CTLA-4 antibody, Yervoy® (generic name: ipilimumab) Injection ("Yervoy") in combination therapy in Japan, to expand the use for the treatment of unresectable hepatocellular carcinoma (HCC). This application is related to the additional indication for a partial change in approved items of the manufacturing and marketing approval in Japan.

This application is based on the results from interim analysis of the CheckMate -9DW study, a global multi-center Phase 3 clinical study (CA209-9DW: ONO-4538-92), evaluating Opdivo plus Yervoy compared to investigator's choice of lenvatinib or sorafenib monotherapy for patients with unresectable HCC who have not received prior systemic therapy. In this study, Opdivo plus Yervoy met its primary endpoint of overall survival (OS), demonstrating a statistically significant and clinically meaningful improvement in OS compared to lenvatinib or sorafenib monotherapy. The safety profile of Opdivo plus Yervoy was consistent with previously reported data, with no new safety signals identified.

About CheckMate -9DW Study (CA209-9DW: ONO-4538-92)

CheckMate -9DW study is a global multicenter randomized open-label Phase 3 study evaluating the combination of Opdivo plus Yervoy compared to investigator's choice of lenvatinib or sorafenib monotherapy in patients with advanced hepatocellular carcinoma who have not received prior systemic therapy.

668 patients were randomized to receive Opdivo plus Yervoy (Opdivo 1 mg/kg plus Yervoy 3 mg/kg Q3W for up to four doses, followed by Opdivo monotherapy 480 mg Q4W) infusion, or single agent lenvatinib or sorafenib as oral capsules in the control arm. The primary endpoint of the study is overall survival (OS) and key secondary endpoints include objective response rate (ORR) and time to symptom deterioration (TTSD).

About Hepatocellular Carcinoma

Liver cancer is the third most frequent cause of cancer death worldwide. It is estimated that there were approximately 866,000 new cases of liver cancer worldwide in 2022, with an estimated approximately 758,000 deaths[1)]. In Japan, it is estimated that there were approximately 41,000 new cases of liver cancer in 2022, with an estimated approximately 26,000 deaths[1)]. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for 90% of all liver cancers[2)]. HCC is often diagnosed in an advanced stage, where effective treatment options are limited and are usually associated with poor outcomes.

Up to 70% of patients experience recurrence within five years, particularly those still considered to be at high risk after surgery or ablation[3]. While most cases of HCC are caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, metabolic syndrome and nonalcoholic steatohepatitis (NASH) are rising in prevalence and expected to contribute to increased rates of HCC.

1): Globocan 2022: Available at: https://gco.iarc.fr/today/en/fact-sheets-populations#countries
2): Kim E, Viatour P. Hepatocellular carcinoma: old friends and new tricks. Exp Mol Med. 2020; 52: 1898–07.
3): Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391: 1301–14.

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, 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, adjuvant treatment of urothelial carcinoma in March 2022, malignant mesothelioma (excluding malignant pleural mesothelioma) in November 2023 and unresectable advanced or recurrent malignant epithelial tumors in February 2024.

In addition, Ono has been conducting clinical development program including hepatocellular carcinoma, 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 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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