ONO PHARMACEUTICAL CO.,LTD.

March 4, 2020

ONO Submits Supplemental Application of BRAFTOVI® Capsule, a BRAF Inhibitor and MEKTOVI® Tablet, a MEK Inhibitor for Additional Indication of Unresectable, Advanced or Recurrent BRAF-Mutant Colorectal Cancer in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it has submitted a supplemental application for BRAFTOVI® (generic name: encorafenib) Capsule ("BRAFTOVI"), a BRAF inhibitor, and MEKTOVI® (generic name: binimetinib) Tablet ("MEKTOVI"), a MEK inhibitor, in Japan for an additional indication of unresectable advanced or recurrent BRAF-mutant colorectal cancer, in combination therapy with cetuximab, an anti-human EGFR monoclonal antibody. This application is for a partial change in approved items of the manufacturing and marketing approval.

This application is based on results of a global randomized, open label Phase 3 study (BEACON CRC study) in patients with unresectable, advanced or recurrent $BRAF^{V600E}$-mutant colorectal cancer whose disease has progressed after one or two prior treatments. In the results from the study, the triplet combination therapy with BRAFTOVI, MEKTOVI and cetuximab (triplet arm) demonstrated a statistically significant extension in median overall survival (OS), one of the co-primary endpoints of the study, versus control (irinotecan-based therapy and cetuximab) (control arm) with 9.0 months for the triplet arm and 5.4 months for the control arm (Hazard Ratio 0.52; 95% Confidence Interval: 0.39 - 0.70; $p<0.0001$). The triplet arm also demonstrated a statistically significant improvement in objective response rates (ORR) based on assessment by a Blinded Independent Central Review (BICR), the other co-primary endpoint, compared to the control arm, with 26.1% for the triplet arm and 1.9% for the control arm ($p<0.0001$). No unexpected toxicities were observed in the triplet arm.

About colorectal cancer

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon or the rectum. It is estimated that approximately 146,000 new cases are diagnosed with CRC per year in Japan (about 1,800,000 cases worldwide) with approximately 57,000 deaths (about 861,000 worldwide) per year resulting from this disease[1]. In Japan, 4.5 - 6.7% (5 - 12% in the US and EU) of CRC patients have $BRAF^{V600E}$-mutant tumors. There is a tendency of poor prognosis in this patient population compared with those having no $BRAF^{V600E}$-mutant tumors[2]. As no approved drugs are available for the treatment of BRAF-mutant CRC, there is a high unmet need in this area and innovative treatment options are needed.

1): Globocan 2018: Population Fact Sheets Available at: http://gco.iarc.fr/today/fact-sheets-populations
2): Guidelines on genetic-related testing for colorectal cancer treatment, Vol. 4, December 2019, Japanese Society of Medical Oncology

About BEACON CRC study

BEACON CRC study is a global randomized, open-label Phase 3 study, evaluating the efficacy and safety of BRAFTOVI, MEKTOVI and cetuximab in patients with $BRAF^{V600E}$-mutant unresectable, advanced or recurrent colorectal cancer whose disease has progressed after one or two prior treatments.

In the randomized portion of the study, 665 patients were randomized 1:1:1 to receive the triplet combination therapy (BRAFTOVI, MEKTOVI and cetuximab), the doublet combination therapy (BRAFTOVI and cetuximab) or the control arm (irinotecan-based chemotherapy and cetuximab). The patients in the triplet arm received BRAFTOVI 300 mg daily, MEKTOVI 45 mg twice daily and cetuximab 400 mg/m^2 only at initial dose, followed by 250 mg/m^2 once a week. The administration was given to the patients until disease progression or unaccepted toxicity. The co-primary endpoints of the study were overall survival (OS) and objective response rates (ORR) based on assessment by a Blinded Independent Central Review (BICR) of the triplet combination, compared to the control arm. Secondary endpoints include progression-free survival (PFS), duration of response (DOR), safety, etc.

About BRAFTOVI and MEKTOVI

BRAFTOVI is a small molecule BRAF kinase inhibitor and MEKTOVI is a small molecule MEK inhibitor. BRAF and MEK are important protein kinases in the MAPK signalling pathway (RAS-RAF-MEK-ERK), which regulates several key cellular activities including proliferation, differentiation, survival and angiogenesis. Inappropriate activation of proteins in this pathway has been shown to occur in many types of cancers including melanoma and colorectal cancer. Both BRAFTOVI and MEKTOVI target key enzymes in this pathway.

In Japan, ONO received a manufacturing and marketing approval of BRAFTOVI and MEKTOVI for the treatment of unresectable melanoma with a BRAF mutation in combination therapy with the products in January and launched the products in February 2019. Currently, the products are under clinical development, including Phase 3 study in combination therapy for the treatment of unresectable melanoma with a BRAF mutation (COLUMBUS study) and Phase 2 study in combination with both products, as well as both products and cetuximab for the treatment of previously untreated $BRAF^{V600E}$ mutant colorectal cancer (ANCHOR study).

Abroad, Array BioPharma Inc. (currently, a subsidiary of Pfizer) and its collaboration partner received an approval of the products for the treatment of “unresectable or metastatic $BRAF^{V600}$-mutant melanoma” and launched them in the US and EU in 2018, respectively. Furthermore, the companies filed applications for BRAFTOVI for the treatment of “metastatic $BRAF^{V600E}$ -mutant colorectal cancer after prior therapy” in the US and EU in 2019.

About the Ono Pharmaceutical Co., Ltd. and Pfizer Inc. Collaboration

In May 2017, ONO entered into the license agreement with Array BioPharma Inc. (became a subsidiary of Pfizer Inc. as from July 30, 2019) regarding BRAFTOVI (encorafenib), a BRAF inhibitor and MEKTOVI (binimetinib), a MEK inhibitor and received rights to develop and commercialize both products in Japan and South Korea.

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