ONO PHARMACEUTICAL CO.,LTD.

August 20, 2021

BRAFTOVI® Capsule, a BRAF Inhibitor, Approved in South Korea for Treatment of Advanced or Recurrent BRAF^{V600E}-Mutant Colorectal Cancer

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; Representative Director, President, Gyo Sagara; "ONO") announced that Ono Pharma Korea Co., Ltd. ("OPKR"), a South Korean subsidiary of ONO, received a marketing approval of BRAFTOVI® (generic name: encorafenib) Capsule 75mg ("BRAFTOVI"), a BRAF inhibitor, on August 19, 2021 from the Ministry of Food and Drug Safety (MFDS) in South Korea for the treatment of adult patients with advanced or recurrent BRAF^{V600E}-mutant colorectal cancer after prior therapy, in combination therapy with cetuximab, an anti-human EGFR monoclonal antibody.

This approval is based on the result from 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 this study, BRAFTOVI and cetuximab combination treatment group demonstrated a statistically significant extension in overall survival (OS), versus the control group (irinotecan and cetuximab-based combination treatment) [HR 0.60; 95% Confidence Interval (CI): 0.45 - 0.79; p=0.0003]. The median OS was 8.4 months for BRAFTOVI and cetuximab combination treatment group, and 5.4 months for the control group. In addition, BRAFTOVI and cetuximab combination treatment group demonstrated a statistically significant improvement in objective response rate (ORR) as assessed by the blinded independent central review (BICR), with 20% for BRAFTOVI and cetuximab combination treatment group, versus 2% for the control group (p<0.0001). Furthermore, median progression-free survival (PFS) was 4.2 months with BRAFTOVI and cetuximab combination treatment group versus 1.5 months with the control group (HR 0.40; 95% CI: 0.31 - 0.52; p<0.0001]. No unexpected toxicities were observed in BRAFTOVI and cetuximab combination treatment group of the study.

About BEACON CRC study

BEACON CRC study is a global randomized, open-label Phase 3 study, evaluating the efficacy and safety of BRAFTOVI, MEKTOVI (generic name: binimetinib), a MEK inhibitor, and cetuximab (triplet combination treatment), and BRAFTOVI and cetuximab (doublet combination treatment) in patients with unresectable, advanced or recurrent BRAF^{V600E}-mutant colorectal cancer whose disease has progressed after one or two prior treatments.

In the randomized part of the study, patients were randomized to 1:1:1 to receive the triplet combination treatment, the doublet combination treatment or the control (irinotecan and cetuximab-based combination treatment). Patients received BRAFTOVI 300 mg, orally once daily, MEKTOVI 45 mg orally twice daily and cetuximab 400 mg/m^2 intravenously only at initial dose, followed by 250 mg/m^2 intravenously once a week. The administration was given to the patients until disease progression or unaccepted toxicity. The key endpoint of efficacy was OS. Additional endpoints included PFS, ORR and DOR as assessed by the BICR.

About Colorectal Cancer

Colorectal cancer (CRC) is a malignant tumor that occurs primarily in the colon or the rectum. It is estimated that approximately 28,600 new cases with CRC are diagnosed per year in South Korea with approximately 9,700 deaths per year resulting from this disease[1)].

In South Korea, 4.7% 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 2020: Available at: https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf
2): Lee Y, Lee S, Sung JS, et al. Clinical Application of Targeted Deep Sequencing in Metastatic Colorectal Cancer Patients: Actionable Genomic Alteration in K-MASTER Project. Cancer Res Treat. 2021;53(1):123-130. doi:10.4143/crt.2020.559

About BRAFTOVI

BRAFTOVI is a small molecule BRAF kinase inhibitor. BRAF is an 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.

In Japan, ONO received a manufacturing and marketing approval of BRAFTOVI and MEKTOVI, a MEK inhibitor, for the treatment of unresectable melanoma with a BRAF mutation in combination therapy with the products in January 2019 and launched them under the product name of BRAFTOVI® Capsule and MEKTOVI® Tablet, respectively, in February 2019.

Thereafter, ONO received a supplemental approval of the products in Japan in November 2020 for the treatment of unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed after chemotherapy, in the triplet combination therapy with BRAFTOVI, MEKTOVI and cetuximab, as well as in the doublet combination therapy with BRAFTOVI and cetuximab. Currently, Phase 2 ANCHOR CRC study is ongoing for the treatment of previously untreated $BRAF^{V600E}$ mutant colorectal cancer in the triplet combination treatment with BRAFTOVI, MEKTOVI and cetuximab.

Abroad, BRAFTOVI was approved in combination treatment with MEKTOVI for the treatment of unresectable or metastatic BRAF-mutant melanoma and launched in 2018 in the US and EU. Furthermore, BRAFTOVI was approved in combination treatment with cetuximab for the treatment of metastatic $BRAF^{V600E}$ -mutant colorectal cancer after prior therapy in 2020 in the US and EU.

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 of 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.

About Ono Pharma Korea Co., Ltd.

Ono Pharma Korea Co., Ltd. (OPKR), in Seoul, Korea, was established as an ONO's wholly-owned subsidiary in December 2013. OPKR has started to market specialty products such as anti-cancer agent, including Opdivo. OPKR has been committed to developing and marketing its products created internally for further penetration into the South Korean market.

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