ONO PHARMACEUTICAL CO.,LTD.

November 27, 2020

ONO Receives Approval 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 ONO has obtained an approval of 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 that has progressed after chemotherapy, in triplet combination therapy with BRAFTOVI, MEKTOVI and cetuximab, an anti-human EGFR monoclonal antibody, and in doublet combination therapy with BRAFTOVI and cetuximab. This approval is related to the additional indication for a partial change in approved items of the manufacturing and marketing approval.

This approval 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 metastatic colorectal cancer whose disease has progressed after one or two prior treatments.

In the results from the study, the median overall survival (OS) was 9.0 months for the combination therapy with BRAFTOVI, MEKTOVI and cetuximab (triplet arm) and 5.4 months for the therapy with irinotecan-based therapy and cetuximab (control arm). The triplet arm demonstrated a statistically significant extension in OS compared between the triplet arm and the control arm, one of the primary endpoints of the study, versus the control arm [Hazard Ratio (HR) 0.52; 95% Confidence Interval (CI): 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 primary endpoint, compared to the control arm, with 26.1% for the triplet arm and 1.9% for the control arm ($p<0.0001$).

In addition, the median OS was 8.4 months for the therapy with BRAFTOVI and cetuximab (doublet arm). The doublet arm demonstrated a statistically significant extension in OS, one of the secondary endpoints of the study, versus the control arm (HR 0.60; 95% CI: 0.45 - 0.79; $p=0.0002$). The doublet arm demonstrated a statistically significant improvement in ORR based on assessment by the BICR, with 20.4%, versus the control arm ($p<0.0001$).

Regarding the safety profile of BRAFTOVI and MEKTOVI of the study, no unexpected toxicities were observed both in the triplet arm and the doublet arm.

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 unresectable, advanced or recurrent $BRAF^{V600E}$-mutant metastatic colorectal cancer whose disease has progressed after one or two prior treatments.

In the randomized part of the study, 665 patients were randomized to 1:1:1 to receive the triplet combination therapy (BRAFTOVI, MEKTOVI and cetuximab), the doublet combination therapy (BRAFTOVI and cetuximab) or the control (irinotecan-based chemotherapy and cetuximab). The patients received BRAFTOVI 300 mg once 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 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 included OS and ORR based on the BICR of the doublet combination, compared to the control arm.

Overview of BRAFTOVI® Capsule 50 mg and 75 mg

Product Name	BRAFTOVI® Capsule 50 mg and 75 mg
Generic name (JAN)	Encorafenib
Indication	○ Unresectable melanoma with a BRAF mutation ○ Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed following chemotherapy
Dosage and administration	<Unresectable melanoma with a BRAF mutation> In combination with binimetinib, usually, for adults, administer 450 mg of encorafenib orally once a day. According to patients' condition, the dose should be reduced. <Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed following chemotherapy> In combination with cetuximab (genetical recombination) or with binimetinib and cetuximab (genetical recombination), usually, for adults, administer 300 mg of encorafenib orally once a day. According to patients' condition, the dose should be reduced.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	November 27, 2020
Conditions for approval	Risk Management Plan should be designed appropriately implemented.

Note: Underlined parts show the revised ones due to this approval.

Overview of MEKTOVI® Tablet 15 mg

Product Name	MEKTOVI® Tablet 15 mg
Generic name (JAN)	Binimetinib
Indication	○ Unresectable melanoma with a BRAF mutation ○ Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed following chemotherapy
Dosage and administration	<Unresectable melanoma with a BRAF mutation> In combination with encorafenib, usually, for adults, administer 45 mg of encorafenib orally twice a day. According to patients' condition, the dose should be reduced. <Unresectable advanced or recurrent BRAF-mutant colorectal cancer that has progressed following chemotherapy> In combination with encorafenib and cetuximab (genetical recombination), usually, for adults, administer 45 mg of binimetinib orally twice a day. According to patients' condition, the dose should be reduced.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	November 27, 2020
Conditions for approval	Risk Management Plan should be designed appropriately implemented.

Note: Underlined parts show the revised ones due to this approval.

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 per year in Japan (about 861,000 worldwide) 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 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 and cetuximab for the treatment of previously untreated $BRAF^{V600E}$ mutant colorectal cancer (ANCHOR study).

Abroad, Array BioPharma Inc. (a wholly owned subsidiary of Pfizer Inc.) and its collaboration partner, Pierre Fabre 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 received an approval for BRAFTOVI in combination with cetuximab for the treatment of “metastatic $BRAF^{V600E}$ -mutant colorectal cancer after prior therapy” in the US and EU in 2020.

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.

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