ONO PHARMACEUTICAL CO.,LTD.

January 8, 2019

ONO Receives a Manufacturing and Marketing Approval for BRAFTOVI® Capsule, a BRAF Inhibitor and MEKTOVI® Tablet, a MEK Inhibitor for Indication of Unresectable BRAF-Mutant Melanoma in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it has received the manufacturing and marketing approval of BRAFTOVI® (encorafenib) Capsule ("BRAFTOVI"), a BRAF inhibitor and MEKTOVI® (binimetinib) Tablet ("MEKTOVI"), a MEK inhibitor, in Japan for the indication of unresectable melanoma with a BRAF mutation.

This approval is based on the result of a global randomized, open label Phase 3 study (COLUMBUS study) conducted in and outside Japan in patients with BRAF-mutant advanced, unresectable or metastatic melanoma. The result showed that the combination treatment with encorafenib 450 mg once daily and binimetinib 45 mg twice daily (COMBO450) demonstrated statistically significant extension of a median progression-free survival (mPFS) as assessed by a Blinded Independent Central Review (BICR) with a mPFS of 14.9 months, compared to vemurafenib, with 7.3 months (hazard ratio 0.54; 95% confidence interval: 0.41 - 0.71, P<0.0001).

Melanoma is a form of skin cancer that develops from the pigment-producing cells (melanocytes) which are deeply related with the skin colour, and said to be the most metastatic and deadliest form of the disease. It is reported that the number of melanoma patients is about 4,000[*1] with about 700 deaths[*2] due to melanoma per year in Japan.

BRAFTOVI and MEKTOVI suppress the proliferation of tumors by targeting and selectively inhibiting the key enzymes of BRAF and MEK1/MEK2, respectively, which are different kinases of a family of serine/threonine kinases in the MAPK signaling pathway (RAS-RAF-MEK-ERK) associated with melanoma and various cancers. The combination therapy is expected to provide more potent anti-tumor effects by inhibiting BRAF kinase activity and MEK1/MEK2 activity simultaneously.

In May 2017, ONO executed a license agreement regarding BRAFTOVI and MEKTOVI with U.S.-based Array BioPharma Inc. ("Array"), for exclusive rights to develop and commercialize both products in Japan and South Korea. Array retains exclusive rights to BRAFTOVI and MEKTOVI in the U.S. and Canada. The products are currently in Phase 3 study for the treatment of patients with metastatic colorectal cancer.

ONO considers it to be important to accumulate further data to ensure that BRAFTOVI and MEKTOVI can be used more properly. In accordance with the conditional approval, ONO is committed to taking actions necessary for the proper use of the products by collecting clinical data on the safety and efficacy of the products.

*1: CANCER STATISTICS IN JAPAN 2013, Patient Survey (Basic Disease Classification), Ministry of Health, Labour and Welfare 2011

*2: Vital Statistics, Ministry of Health, Labour and Welfare 2012

Overview of BRAFTOVI® Capsule 50 mg

Product Name	BRAFTOVI® Capsule 50 mg
Generic name (JAN)	Encorafenib
Indication	Unresectable melanoma with a BRAF mutation
Dosage and administration	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.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	January 8, 2019
Conditions for approval	1. Risk Management Plan should be designed appropriately implemented. 2. Because of the very limited number of patients treated with the product in Japanese clinical trials, a post-marketing use-results survey covering all cases should be performed until data on a certain minimum number of patients have been accumulated. Through these activities, actions necessary to ensure the proper use of the product should be taken by identifying the characteristics of patients to be treated with the product and collecting safety and efficacy data as soon as possible.

Overview of MEKTOVI® Tablet 15 mg

Product Name	MEKTOVI® Tablet 15 mg
Generic name (JAN)	Binimetinib
Indication	Unresectable melanoma with a BRAF mutation
Dosage and administration	In combination with encorafenib, usually, for adults, administer 45 mg of binimetinib every 12 hours as a guide orally twice a day.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	January 8, 2019
Conditions for approval	1. Risk Management Plan should be designed appropriately implemented. 2. Because of the very limited number of patients treated with the product in Japanese clinical trials, a post-marketing use-results survey covering all cases should be performed until data on a certain minimum number of patients have been accumulated. Through these activities, actions necessary to ensure the proper use of the product should be taken by identifying the characteristics of patients to be treated with the product and collecting safety and efficacy data as soon as possible.

About BRAFTOVI and MEKTOVI

BRAFTOVI is an oral small molecule BRAF kinase inhibitor and MEKTOVI is an oral small molecule MEK inhibitor which target key enzymes in the MAPK signalling pathway (RAS-RAF-MEK-ERK). Inappropriate activation of proteins in this pathway has been shown to occur in many cancers including melanoma, colorectal cancer, non-small cell lung cancer and others. In the U.S., BRAFTOVI + MEKTOVI are approved for the treatment of unresectable or metastatic melanoma with a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation. BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma. In Europe, the combination is approved for adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation.

The Swiss Medicines Agency (Swissmedic) and the Australian Therapeutic Goods Administration (TGA) are currently reviewing the Marketing Authorization Applications for BRAFTOVI and MEKTOVI submitted by Pierre Fabre.

BRAFTOVI and MEKTOVI are being investigated in a global Phase 3 BEACON CRC trial evaluating the efficacy and safety of BRAFTOVI in combination with cetuximab with or without MEKTOVI compared to cetuximab and irinotecan-based therapy in patients with $BRAF^{V600E}$ mutant metastatic colorectal cancer.

About Array BioPharma

Array BioPharma Inc. is a fully-integrated, biopharmaceutical company focused on the discovery, development and commercialization of transformative and well-tolerated targeted small molecule drugs to treat patients afflicted with cancer and other high-burden diseases. Array markets in the United States BRAFTOVI® (encorafenib) capsules in combination with MEKTOVI® (binimetinib) tablets for the treatment of patients with unresectable or metastatic melanoma with a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation. Array's lead clinical programs, encorafenib and binimetinib, are being investigated in over 30 clinical trials across a number of solid tumor indications, including a Phase 3 trial in BRAF-mutant colorectal cancer. Array's pipeline includes several additional programs being advanced by Array or current license-holders, including the following programs currently in registration trials: selumetinib (partnered with AstraZeneca), ipatasertib (partnered with Genentech), tucatinib (partnered with Seattle Genetics) and ARRY-797. For more information on Array, please visit www.arraybiopharma.com.

ONO PHARMACEUTICAL CO., LTD.
Corporate Communications
public_relations@ono.co.jp