ONO PHARMA

Press Release

Ono Receives Approvals of BRAFTOVI® and MEKTOVI® for Expanded Use for Two New Indications in Japan

- Unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy -
- Unresectable anaplastic thyroid cancer with a BRAF mutation -

Osaka, Japan, May 17, 2024 - Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President: Toichi Takino; "Ono") today announced that it has received supplemental approvals for BRAFTOVI® (generic name: encorafenib) Capsule ("BRAFTOVI"), a BRAF inhibitor, and MEKTOVI® (generic name: binimetinib) Tablet ("MEKTOVI"), a MEK inhibitor, when used in combination, in Japan for the two new indications of "unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy", and "unresectable anaplastic thyroid cancer with a BRAF mutation".

These approvals are based on the results of a Phase 2 study (ONO-7702/7703-03), conducted in Japan in 22 patients with unresectable $BRAF^{V600}$-mutant thyroid cancer, including 5 patients with anaplastic thyroid cancer. The study met its primary endpoint of objective response rate (ORR) as assessed by the Independent Central Review in the overall patient population, which was 54.5% (12/22 cases, 95% confidence interval: 32.2 - 75.6%) in the combination therapy of BRAFTOVI and MEKTOVI. The safety profile of the combination therapy of BRAFTOVI and MEKTOVI in the study was consistent with those previously reported in the clinical trials of BRAFTOVI and MEKTOVI.

About Phase 2 study (ONO-7702/7703-03)

The study is a multi-centre, open-label, uncontrolled Phase 2 study (ONO-7702/7703-03), conducted in Japan, evaluating the efficacy and safety of the combination therapy of BRAFTOVI and MEKTOVI in patients with unresectable $BRAF^{V600}$-mutant thyroid cancer. Patients received the combination therapy with BRAFTOVI 450 mg once daily, and MEKTOVI 45 mg twice daily, until it was determined that treatment could not be given due to disease progression or safety reasons. The primary endpoint of the study was objective response rate (ORR) as assessed by the Independent Central Review. Secondary endpoints include ORR as assessed by physician of each medical institutes, disease control rate (DCR), overall survival (OS) and progression-free survival (PFS).

About Thyroid Cancer

Thyroid cancer (TC) is a malignant tumor that develops in the thyroid tissue located around the trachea or in front of the neck. Histologically, it is roughly divided into differentiated carcinoma (approximately 97% of TC), undifferentiated carcinoma (1 - 2%), and medullary carcinoma (1 - 2%). In Japan, it is estimated that approximately 18,700 new cases are diagnosed with TC per year with approximately 1,900 deaths per year resulting from the disease in 2023*. BRAF mutation is reported in 37 - 68% of TC patients.

*: Cancer Statics in Japan, 2024, The Editorial Board of Cancer Statistics, Foundation for Promotion of Cancer Research (FPCR), March 2024

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 colorectal cancer with a BRAF mutation that has progressed following chemotherapy ○Unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy ○Unresectable anaplastic thyroid cancer with a BRAF mutation
Dosage and administration	**<Unresectable melanoma with a BRAF mutation, Unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy, Unresectable anaplastic thyroid cancer 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 colorectal cancer with a BRAF mutation 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.

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 colorectal cancer with a BRAF mutation that has progressed following chemotherapy ○Unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy ○Unresectable anaplastic thyroid cancer with a BRAF mutation
Dosage and administration	**<Unresectable melanoma with a BRAF mutation, Unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy, Unresectable anaplastic thyroid cancer 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 colorectal cancer with a BRAF mutation 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.

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

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, colorectal cancer and thyroid 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 of the products in January 2019 and launched them in February 2019. Thereafter, Ono received additional approval in November 2020 for the treatment of unresectable advanced or recurrent colorectal cancer with a BRAF mutation that has progressed following chemotherapy, in triplet combination treatment of BRAFTOVI, MEKTOVI and cetuximab, an anti-human EGFR monoclonal antibody, as well as in doublet combination treatment of BRAFTOVI and cetuximab.

Abroad, Array BioPharma Inc. (a wholly owned subsidiary of Pfizer Inc.) and its collaboration partner, Pierre Fabre, received an approval of BRAFTOVI and MEKTOVI for the treatment of unresectable or metastatic melanoma with $BRAF^{V600E \text{ or } V600K}$ mutation and launched them in 2018 in the US and EU, respectively. Thereafter, the companies received supplemental approval for the treatment of metastatic colorectal cancer with a $BRAF^{V600E}$ mutation following prior therapy in the US and EU in 2020. Additionally, Pfizer received supplemental approval in the US for the treatment of metastatic non-small cell lung cancer with a $BRAF^{V600E}$ mutation in 2023.

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.

Contact:
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono-pharma.com