ONO PHARMA

Press Release

Ono Receives Supplemental Approval of Combination Therapy with BRAFTOVI® Capsule, a BRAF Inhibitor, for the Indication of Colorectal Cancer

- Combination therapy with Braftovi, cetuximab, and chemotherapy was approved in Japan based on the results of clinical trial for the first-line treatment of unresectable, advanced or recurrent colorectal cancer with BRAF mutation
- Braftovi combination therapy demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint in a global multicenter Phase 3 clinical trial

Osaka, Japan, November 20, 2025 – Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President and COO: Toichi Takino; "Ono") today announced that Ono received a supplemental approval for BRAFTOVI® (generic name: encorafenib) Capsule ("Braftovi"), a BRAF inhibitor, in combination with cetuximab, an anti-human EGFR monoclonal antibody, and chemotherapy for the indication of unresectable, advanced or recurrent colorectal cancer (CRC) with BRAF mutation.

This approval is based on the results of a global multicenter, Phase 3 BREAKWATER study (ONO-7702-03/C4221015). In the randomized Phase 3 part of the trial, the patients who received Braftovi in combination with cetuximab and FOLFOX (5-FU/levoleucovorin/oxaliplatin) (Braftovi combination therapy arm) demonstrated a statistically significant and clinically meaningful improvement in the objective response rate (ORR) assessed by a blinded independent central review (BICR), one of the primary endpoints, compared with the chemotherapy arm* (60.9% vs 40.0%, $p = 0.0008$). In addition, the Braftovi combination therapy arm demonstrated a statistically significant and clinically meaningful prolongation in the progression-free survival (PFS) assessed by BICR, the other primary endpoint, compared with the chemotherapy arm (median PFS: 12.8 months vs 7.1 months, hazard ratio = 0.53; 95% confidence interval: 0.407 to 0.677; $p < 0.0001$). The safety profile of Braftovi combination therapy arm in the trial was consistent with the known safety profile of each drug, and no new safety signals identified.

Regarding the indication of CRC, Braftovi was approved in November 2020 for the treatment of unresectable advanced or recurrent CRC with BRAF mutation that has progressed following chemotherapy, in triplet combination therapy with Braftovi, MEKTOVI® (generic name: binimetinib) Tablet, a MEK inhibitor and cetuximab, as well as in doublet combination therapy with Braftovi and cetuximab.

On June 19, 2024, Braftovi was designated as an orphan drug by the Ministry of Health, Labour and Welfare for the indication of unresectable, advanced or recurrent CRC with BRAF mutation.

*: chemotherapy with or without bevacizumab, an anti-human VEGF monoclonal antibody

About BREAKWATER study (ONO-7702-03/C4221015)

The BREAKWATER study is a global multicenter, randomized, open-label Phase 3 trial evaluating the efficacy and safety of the combination of Braftovi with cetuximab and chemotherapy (FOLFOX [5-FU/levoleucovorin/oxaliplatin] or FOLFIRI [5-FU/levoleucovorin/irinotecan]) compared with chemotherapy in patients with unresectable advanced or recurrent CRC with BRAF ^{V600E} mutation.

In the randomized Phase 3 part of the trial, the efficacy and safety of Braftovi in combination with cetuximab and FOLFOX was evaluated in the first-line treatment of unresectable advanced or recurrent CRC with BRAF ^{V600E} mutation compared with chemotherapy. Patients received 300 mg of Braftovi once daily, cetuximab once every 2 weeks, and FOLFOX once every 2 weeks until disease progression or safety concerns. The primary endpoints of the randomized Phase 3 part of the trial are objective response rate (ORR) and progression-free survival (PFS) as assessed by a blinded independent central review (BICR). Secondary endpoints include overall survival (OS), and ORR and PFS both as assessed by the medical institutions, etc.
Additionally, a cohort set up separately from the Phase 3 part is underway to evaluate the efficacy and safety of the combination therapy with Braftovi, cetuximab, and FOLFIRI, compared with chemotherapy.

About colorectal cancer (CRC)

CRC is a malignant tumor that occurs primarily in the colon or the rectum. In Japan, CRC is the most common cancer with approximately 145,000 new cases diagnosed annually[1)] (approximately 1,926,000 cases worldwide[2)]), and approximately 60,000 deaths reported annually[1)] (approximately 904,000 deaths worldwide[2)]), making it the second most common cancer after lung cancer.
In Japan, BRAF ^{V600E} mutation-positive patients are found in 4.5 to 6.7% of CRC patients (5 to 12% in the US and EU), and the prognosis is poorer than in those without the BRAF ^{V600E} mutation[3)]. As no drugs have been approved for the first-line treatment of BRAF-mutant CRC, there is a high unmet need for this cancer and Braftovi will be a new treatment option.

1): Globocan 2022: Colorectal Cancer, Japan, World Health Organization Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/392-japan-fact-sheet.pdf
2): Globocan 2022: Colorectal Cancer, World, World Health Organization Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf
3): Guidelines on genetic-related testing for colorectal cancer treatment, Japanese Society of Medical Oncology, Vol. 5, March 2023

Overview of BRAFTOVI® Capsule 50 mg, 70 mg

Brand name	BRAFTOVI® Capsule 50 mg, 75 mg
Generic name (JAN)	Encorafenib
Indications	○ Unresectable melanoma with a BRAF mutation ○ Unresectable advanced or recurrent colorectal cancer with a BRAF mutation ~~that has progressed after chemotherapy~~ ○ Unresectable thyroid cancer with a BRAF mutation that has progressed after 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 after 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. The dose should be reduced according to patients' condition.

	<Unresectable advanced or recurrent colorectal cancer with a BRAF mutation ~~that has progressed after chemotherapy~~> In combination with ~~cetuximab (genetical recombination) or with binimetinib and~~ cetuximab (genetical recombination) and other antineoplastic agents, or with cetuximab (genetical recombination), usually, for adults, administer 300 mg of encorafenib orally once a day. The dose should be reduced According to patients' condition.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.

* Revised parts due to this approval are shown with strikethrough and underline.

About Braftovi

Braftovi is a small molecule BRAF kinase inhibitor. BRAF is an important protein kinase 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, thyroid cancer, and CRC. Braftovi targets key enzymes in this pathway.

In Japan, Ono received a manufacturing and marketing approval of Braftovi in combination with Mektovi for the indication of unresectable melanoma with a BRAF mutation 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 CRC with a BRAF mutation that has progressed following chemotherapy, in triplet combination treatment of Braftovi, Mektovi and cetuximab, as well as in doublet combination treatment of Braftovi and cetuximab. Ono also received additional approval for Braftovi in May 2024 in combination with Mektovi for the indications of unresectable thyroid cancer with a BRAF mutation that has progressed following chemotherapy, and unresectable anaplastic thyroid cancer with a BRAF mutation.

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 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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