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U.S. FDA Grants Full Approval to Pfizer's BRAFTOVI Combination Regimen in First-Line Metastatic Colorectal Cancer

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- *The BRAFTOVI combination regimen is the only approved targeted regimen for first-line* BRAF-V600E *mutant metastatic colorectal cancer*
- *Pivotal results from the Phase 3 portion with mFOLFOX6 of the BREAKWATER trial demonstrated a clinically meaningful and statistically significant 51% risk reduction in death and a 47% risk reduction in disease progression or death compared to chemotherapy treatment with or without bevacizumab*
- *Expanded indication enables flexibility to use BRAFTOVI in combination with cetuximab and different fluorouracil-based chemotherapy regimens*

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced that the U.S. Food and Drug Administration (FDA) has granted full approval to BRAFTOVI® (encorafenib) in combination with cetuximab (marketed as ERBITUX®) and fluorouracil-based chemotherapy for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation based on results from the global Phase 3 BREAKWATER trial (NCT04607421).

BRAFTOVI in combination with cetuximab and mFOLFOX6 was granted accelerated approval by the FDA in December 2024 based on objective response rate (ORR) results, one of the BREAKWATER trial's dual primary endpoints. The conversion from accelerated approval to full approval is based on significant benefit in outcomes for both progression-free survival (PFS), the trial's other primary endpoint, and overall survival (OS), a key secondary endpoint, from the Phase 3 portion of the study that evaluated BRAFTOVI in combination with cetuximab and mFOLFOX6, as well as the ORR results from the Cohort 3 portion of the study, which evaluated BRAFTOVI in combination with cetuximab and FOLFIRI.

"This landmark approval, achieved through the robust clinical benefit demonstrated in the BREAKWATER trial, validates that this targeted therapy can impact outcomes for people living with an aggressive, hard-to-treat cancer," said Aamir Malik, Executive Vice President, Chief U.S. Commercial Officer, Pfizer. "As the only targeted combination regimen shown to deliver a significant improvement in certain outcomes for patients with *BRAF V600E*?mutant metastatic colorectal cancer, BRAFTOVI is uniquely positioned to redefine first?line treatment and establish a new standard of care. This approval reinforces our leadership in bringing differentiated, potentially practice?changing cancer therapies to patients and healthcare providers who urgently need improved options."

"This approval gives oncologists confidence to use encorafenib plus cetuximab in combination with fluorouracil-based chemotherapy as a first-line standard of care for patients with *BRAF V600E*-mutant metastatic colorectal cancer," said Scott Kopetz, M.D., Ph.D., FACP, Professor and Deputy Chair of Gastrointestinal Medical

Oncology at The University of Texas MD Anderson Cancer Center and co-principal investigator of the BREAKWATER trial. “The BREAKWATER study demonstrated that these targeted combination regimens provided statistically significant benefit, providing the robust evidence we need to make treatment decisions that can meaningfully impact patient outcomes.”

In the BREAKWATER study, the safety profile of both combination regimens continued to be consistent with the known safety profile of each respective agent in the regimen. No new safety signals were identified. The most common side effects (?25%) in the mFOLFOX6 regimen were peripheral neuropathy, nausea, fatigue, diarrhea, decreased appetite, rash, vomiting, hemorrhage, abdominal pain, arthralgia, pyrexia, and constipation. The most common side effects (?25%) in the FOLFIRI regimen were nausea, diarrhea, fatigue, vomiting, alopecia, constipation, abdominal pain, decreased appetite, and rash.

Among patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6, 14% experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI. There was no substantial difference in chemotherapy discontinuation due to side effects in the BRAFTOVI in combination with cetuximab and mFOLFOX6 arm compared with the chemotherapy, with or without bevacizumab arm. Among patients receiving BRAFTOVI in combination with cetuximab and FOLFIRI, 9% experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI.

The BRAFTOVI combination regimen with mFOLFOX6 is also under regulatory review in Europe, where Pierre Fabre Laboratories has exclusive commercialization rights, and was recently approved for use in several other countries.

About BREAKWATER
BREAKWATER is a Phase 3, randomized, active-controlled, open-label, multicenter trial of BRAFTOVI with cetuximab, alone or in combination with mFOLFOX6 or FOLFIRI (both fluorouracil-based chemotherapies) in participants with previously untreated *BRAF V600E*-mutant mCRC.

Phase 3 Analysis: BRAFTOVI in combination with cetuximab and mFOLFOX6:
Patients were randomized to receive BRAFTOVI 300 mg orally once daily in combination with cetuximab (discontinued after randomization of 158 patients), BRAFTOVI 300 mg orally once daily in combination with cetuximab and mFOLFOX6 (n=236) or mFOLFOX6, FOLFOXIRI, or CAPOX, with or without bevacizumab (control arm) (n=243). The dual primary endpoints for these study groups are ORR and PFS as assessed by BICR. OS is a key secondary endpoint.

At the time of the PFS primary analysis, BRAFTOVI in combination with cetuximab and mFOLFOX6 significantly reduced the risk of disease progression or death by 47% compared to chemotherapy with or without bevacizumab (hazard ratio [HR] 0.53; 95% confidence interval [CI], 0.41, 0.68; p<0.0001) as assessed by blinded independent central review (BICR). Median PFS was 12.8 months (95% CI, 11.2, 15.9) with the BRAFTOVI combination regimen compared to 7.1 months (95% CI, 6.8, 8.5) with chemotherapy with or without bevacizumab. In a second interim analysis of median OS, BRAFTOVI plus cetuximab and mFOLFOX6 significantly reduced the risk of death by 51% compared to chemotherapy, with or without bevacizumab (HR 0.49; 95% CI, 0.38, 0.63; p<0.0001). Median OS doubled from 15.1 months with chemotherapy, with or without bevacizumab (95% CI, 13.7, 17.7) to 30.3 months (95% CI, 21.7, Not Estimated) with the BRAFTOVI combination regimen. These data were presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in the *New England Journal of Medicine*.

Cohort 3 Analysis: BRAFTOVI in combination with cetuximab and FOLFIRI:
In Cohort 3, patients were randomized to receive BRAFTOVI 300 mg orally once daily in combination with cetuximab and FOLFIRI (n=73) or FOLFIRI, with or without bevacizumab (control arm) (n=74). The primary

endpoint of Cohort 3 is ORR as assessed by BICR. PFS is a key secondary endpoint; OS is a secondary endpoint summarized descriptively.

BRAFTOVI plus cetuximab and FOLFIRI demonstrated a clinically meaningful and statistically significant improvement in confirmed ORR assessed by BICR compared to patients receiving FOLFIRI with or without bevacizumab (64% vs 39%, odds ratio =2.76, p=0.0011). These data were presented at the 2026 American Society of Clinical Oncology Gastrointestinal (ASCO GI®) Cancers Symposium. Detailed PFS results from Cohort 3 will be submitted for presentation at an upcoming medical meeting.

About Colorectal Cancer (CRC)
CRC is the third most common type of cancer in the world, with approximately 1.8 million new diagnoses in 2022.[1] It is the second leading cause of cancer-related deaths.[2] Overall, the lifetime risk of developing CRC is about 1 in 24 for men and 1 in 26 for women.[2] In the U.S. alone, an estimated 158,850 people will be diagnosed with cancer of the colon or rectum in 2026, and approximately 55,000 are estimated to die from the disease each year.[3] For 20% of those diagnosed with CRC, the disease has metastasized, or spread, making it harder to treat, and up to 50% of patients with localized disease eventually develop metastases.[4]

BRAF mutations are estimated to occur in 8-12% of people with mCRC and are associated with a poor prognosis for these patients.[5] The *BRAF V600E* mutation is the most common *BRAF* mutation, and the risk of mortality in CRC patients with the *BRAF V600E* mutation is more than double that of patients with no known mutation present.[5-7] Despite the high unmet need in *BRAF V600E*-mutant mCRC, prior to the BRAFTOVI accelerated FDA approval in this indication on December 20, 2024, there were no approved biomarker-driven therapies specifically indicated for people with previously untreated *BRAF V600E*-mutant mCRC.[8,9]

About BRAFTOVI® (encorafenib)
BRAFTOVI is an oral small molecule kinase inhibitor that targets *BRAF V600E*. Inappropriate activation of proteins in the MAPK signaling pathway (RAS-RAF-MEK-ERK) has been shown to occur in certain cancers, including CRC.

Pfizer has exclusive rights to BRAFTOVI in the U.S., Canada, Latin America, Middle East, and Africa. Ono Pharmaceutical Co., Ltd. has exclusive rights to commercialize the product in Japan and South Korea, Medison has exclusive rights to commercialize the product in Israel and Pierre Fabre Laboratories has exclusive rights to commercialize the product in all other countries, including Europe and Asia (excluding Japan and South Korea).

INDICATION AND USAGE

BRAFTOVI® (encorafenib) is indicated, in combination with cetuximab and fluorouracil-based chemotherapy, for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation, as detected by an FDA-authorized test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type *BRAF* CRC.

IMPORTANT SAFETY INFORMATION

Refer to the prescribing information for cetuximab and individual product components of mFOLFOX6 and FOLFIRI for recommended dosing and additional safety information.

WARNINGS AND PRECAUTIONS

New Primary Malignancies: New primary malignancies, cutaneous and noncutaneous, can occur. In the BREAKWATER trial, the following cutaneous malignancies occurred in patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6: melanocytic nevus in 5.6%, skin papilloma in 3%, basal cell carcinoma in 1.3%, squamous cell carcinoma of skin in 0.9%, keratoacanthoma in 0.4% and malignant melanoma in situ in 0.4%. In patients who received BRAFTOVI in combination with cetuximab and FOLFIRI, skin papilloma occurred in 2.8% and keratoacanthoma in 1.4% of patients. Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Dose modification is not recommended for new primary cutaneous malignancies. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of noncutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive noncutaneous malignancies. Monitor patients for new malignancies prior to initiation of treatment, while on treatment, and after discontinuation of treatment.

Tumor Promotion in *BRAF* Wild-Type Tumors: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation using an FDA-authorized test prior to initiating BRAFTOVI.

Cardiomyopathy: Cardiomyopathy manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety has not been established in patients with a baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur. In the BREAKWATER trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6 was 2.6% for alkaline phosphatase, 1.3% each for ALT and AST. In patients receiving BRAFTOVI in combination with cetuximab and FOLFIRI, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 1.5% each for ALT and AST. Monitor liver laboratory tests before initiation of BRAFTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur. In the BREAKWATER trial, hemorrhage occurred in 34% of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6; Grade 3 or 4 hemorrhage occurred in 3% of patients. In patients receiving BRAFTOVI in combination with cetuximab and FOLFIRI, hemorrhage occurred in 21% of patients. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Uveitis: Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI. In BREAKWATER, the incidence of uveitis among patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6 was 0.4%. Assess for visual symptoms at each visit. Perform an ophthalmological evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

QT Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the BREAKWATER trial, an increase of QTcF >500 ms was measured in 4% (9/226) of patients receiving

BRAFTOVI in combination with cetuximab and mFOLFOX6. In patients receiving BRAFTOVI in combination with cetuximab and FOLFIRI, an increase of QTcF >500 ms was measured in 1.5% (1/65) of patients. Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc >500 ms.

Embryo-Fetal Toxicity: BRAFTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with BRAFTOVI and for 2 weeks after the final dose.

Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with cetuximab and mFOLFOX6 or FOLFIRI. Refer to the prescribing information for cetuximab and individual product components of mFOLFOX6 and FOLFIRI for additional risk information.

Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility.

ADVERSE REACTIONS
***BRAF* V600E mutation-positive mCRC, in combination with cetuximab and mFOLFOX6**

- **Serious adverse reactions** occurred in 46% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. Serious adverse reactions in >3% of patients included intestinal obstruction (4.7%), pyrexia (3.9%), sepsis (3.4%), and abdominal pain (3.4%)
- **Fatal intestinal obstruction** occurred in 0.9%, and **fatal large intestinal perforation andgastrointestinal perforation** occurred in 0.4% (each) in patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6
- **Most common adverse reactions** (?25%, all grades) in the BRAFTOVI with cetuximab and mFOLFOX6 arm compared to the control arm (mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab), and a subset of the control arm (mFOLFOX6 ± bevacizumab), respectively were: peripheral neuropathy (64% vs 53% and 57%), nausea (54% vs 50% and 44%), fatigue (53% vs 41% and 45%), diarrhea (42% vs 50% and 44%), decreased appetite (38% vs 27% and 30%), rash (36% vs 6% and 5%), vomiting (36% vs 22% and 17%), hemorrhage (34% vs 21% and 15%), abdominal pain (32% vs 31% and 30%), arthralgia (32% vs 6% and 7%), pyrexia (29% vs 16% and 17%), and constipation (27% vs 23% and 25%)
- **Most common laboratory abnormalities**(?10%, grade 3 or 4) in the BRAFTOVI with cetuximab and mFOLFOX6 arm compared to the control arm (mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab), and a subset of the control arm (mFOLFOX6 ± bevacizumab), respectively were: increased lipase (53% vs 28% and 23%), decreased neutrophil count (37% vs 35% and 33%), decreased hemoglobin (19% vs 6% and 7%), decreased white blood cell count (12% vs 8% and 6%), and increased glucose (11% vs 2% and 1%)

***BRAF* V600E mutation-positive mCRC, in combination with cetuximab and FOLFIRI**

- **Serious adverse reactions** occurred in 39% of patients who received BRAFTOVI in combination with cetuximab and FOLFIRI. Serious adverse reactions in >3% of patients included febrile neutropenia (5.6%) and infusion related reaction (4.2%)

- **Fatal gastrointestinal perforation** occurred in 1.4% of patients who received BRAFTOVI in combination with cetuximab and FOLFIRI
- **Most common adverse reactions** (>25%, all grades) in the BRAFTOVI with cetuximab and FOLFIRI arm compared to the control arm (FOLFIRI ± bevacizumab) were nausea (61% vs 57%), diarrhea (55% vs 49%), fatigue (47% vs 50%), vomiting (47% vs 31%), alopecia (35% vs 22%), constipation (31% vs 29%), abdominal pain (30% vs 22%), decreased appetite (30% vs 32%), and rash (27% vs 1.5%)
- **Most common laboratory abnormalities** (?10%, grade 3 or 4) in the BRAFTOVI with cetuximab and FOLFIRI arm compared to the control arm (FOLFIRI ± bevacizumab) were: decreased neutrophil count (30% vs 32%), increased lipase (22% vs 12%), decreased white blood cell count (20% vs 6%), and decreased hemoglobin (10% vs 3%)

DRUG INTERACTIONS

Strong or moderate CYP3A4 inhibitors: Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose.

Strong CYP3A4 inducers: Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

Sensitive CYP3A4 substrates: Avoid the coadministration of BRAFTOVI with CYP3A4 substrates (including hormonal contraceptives) for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. If the coadministration cannot be avoided, see the CYP3A4 substrate product labeling for recommendations.

Dose reductions of drugs that are **substrates of OATP1B1, OATP1B3, or BCRP** may be required when used concomitantly with BRAFTOVI.

Avoid coadministration of BRAFTOVI with **drugs known to prolong QT/QTc interval.**

View the full Prescribing Information. There may be a delay as the document is updated with the latest information. It will be available as soon as possible. Please check back for the updated full information shortly.

About Pfizer Oncology
At Pfizer Oncology, we are at the forefront of a new era in cancer care. Our industry-leading portfolio and extensive pipeline includes three core mechanisms of action to attack cancer from multiple angles, including small molecules, antibody-drug conjugates (ADCs), and multispecific antibodies, including other immune-oncology biologics. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, gastrointestinal cancer, genitourinary cancer, hematology-oncology, and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to help people with cancer live better and longer lives.

About Pfizer: Breakthroughs That Change Patients' Lives
At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For 175 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and

follow us on X at @Pfizer and @Pfizer News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Disclosure Notice
The information contained in this release is as of February 24, 2026. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about BRAFTOVI® (encorafenib) and an approval in the U.S. for BRAFTOVI in combination with cetuximab and fluorouracil-based chemotherapy for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a BRAF V600E mutation, including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of BRAFTOVI plus cetuximab and fluorouracil-based chemotherapy; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any drug applications may be filed in any additional jurisdictions for BRAFTOVI plus cetuximab and fluorouracil-based chemotherapy for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation or in any jurisdictions for any other potential indications for BRAFTOVI; whether and when any such other applications may be approved by other regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether BRAFTOVI plus cetuximab and fluorouracil-based chemotherapy will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of BRAFTOVI or BRAFTOVI plus cetuximab and fluorouracil-based chemotherapy; risks and uncertainties related to issued or future executive orders or other new, or changes in, laws or regulations; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2024 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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