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Pfizer’s BRAFTOVI® Combination Regimen Demonstrates Improved Response in Patients with BRAF V600E-Mutant Metastatic Colorectal Cancer

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- *Clinically meaningful and statistically significant results from the Phase 3 BREAKWATER trial show objective response rate of 61% with Pfizer’s BRAFTOVI combination regimen compared to 40% with investigator’s choice of chemotherapy, representing a doubling of the odds of achieving an objective response*
- *BRAFTOVI combination regimen is the first and only targeted therapy approved by the U.S. FDA for treatment-naïve patients with metastatic colorectal cancer with a* BRAF V600E *mutation*

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced positive results from the Phase 3 BREAKWATER trial evaluating BRAFTOVI® (encorafenib) in combination with cetuximab (marketed as ERBITUX®) and mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) in patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation. At the time of this analysis, the BRAFTOVI combination regimen demonstrated a clinically meaningful and statistically significant improvement in confirmed objective response rate (ORR) assessed by blinded independent central review (BICR) compared to patients receiving chemotherapy with or without bevacizumab (60.9% vs 40.0%, odds ratio =2.443, p=0.0008). These results will be presented today in an oral presentation (Abstract 16) at the 2025 American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) and were simultaneously published in *Nature Medicine* .

“Despite the high unmet need in this patient population, prior to the recent encorafenib combination regimen approval, there were no approved biomarker-driven therapies indicated for people with previously untreated *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. “These data from the BREAKWATER study show the potential for this targeted treatment regimen to become the new standard of care for people with *BRAF V600E* -mutant metastatic colorectal cancer, for whom long-term disease control is critical.”

The estimated median duration of response as assessed by BICR was 13.9 months (95% Confidence Interval [CI]: 8.5-not estimable [NE]) with BRAFTOVI plus cetuximab and mFOLFOX6 and 11.1 months (95% CI: 6.7-12.7) with chemotherapy with or without bevacizumab. Of patients on BRAFTOVI plus cetuximab and mFOLFOX6, 22.4% (n=15) had a response lasting 12 months or longer, compared to 11.4% (n=5) with chemotherapy with or without bevacizumab. The median time to response as assessed by BICR was 7.1 weeks (range 5.7-53.7) with BRAFTOVI plus cetuximab and mFOLFOX6 and 7.3 weeks (range 5.4-48.0) with chemotherapy with or without bevacizumab.

Overall survival (OS) data were immature at the time of this analysis but demonstrated a promising trend in favor of BRAFTOVI plus cetuximab and mFOLFOX6 compared to patients receiving chemotherapy with or without bevacizumab. Median OS with BRAFTOVI plus cetuximab with chemotherapy was not estimable (95% CI: 19.8-NE) and 14.6 months (95% CI: 13.4-NE) with chemotherapy with or without bevacizumab (Hazard Ratio [HR]: 0.47, 95% CI: 0.318-0.691). The BREAKWATER trial is ongoing for OS and progression-free survival (PFS), with PFS results expected in 2025.

“These results of this first analysis were the basis for the first approval of a targeted therapy regimen for use in the first-line setting for patients with metastatic colorectal cancer with a *BRAF V600E* mutation,” said Roger Dansey, M.D., Chief Oncology Officer, Pfizer. “We are highly encouraged by these response results, which are indicative of the clinically meaningful benefit of BRAFTOVI in reducing tumor size or having no detectable cancer, along with the promising interim analysis of overall survival. We look forward to additional read-outs from the BREAKWATER trial this year.”

The safety profile of BRAFTOVI in combination with cetuximab and mFOLFOX6 in the BREAKWATER trial was consistent with the known safety profile of each respective agent. No new safety signals were identified. Serious treatment-emergent adverse events occurred in 37.7% of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6 compared to 34.6% of patients receiving chemotherapy with or without bevacizumab.

BRAFTOVI in combination with cetuximab and mFOLFOX6 was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of patients with *BRAF V600E* -mutant mCRC in December 2024. The approval was among the first in the industry to be conducted under the FDA’s Project FrontRunner, which seeks to support the development and approval of new cancer drugs for advanced or metastatic disease. The BREAKWATER data are also being discussed with other regulatory authorities around the world to support potential future additional license applications for the BRAFTOVI combination regimen in this indication.

Pfizer is continuing its commitment to help non-scientists understand the latest findings with the development of abstract plain language summaries (APLS) for company-sponsored research being presented, which are written in non-technical language. Those interested in learning more can visit www.Pfizer.com/apls to access the summaries.

About BREAKWATER

BREAKWATER is a Phase 3, randomized, active-controlled, open-label, multicenter trial of BRAFTOVI with cetuximab, alone or in combination with mFOLFOX6 in participants with previously untreated *BRAF* V600E-mutant mCRC. 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 each with or without bevacizumab (control-arm) (n=243). The dual primary endpoints are ORR, which was met at the time of analysis, and PFS as assessed by BICR. OS is a key secondary endpoint.

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 154,270 people will be diagnosed with cancer of the colon or rectum in 2025, and approximately 53,000 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 represent 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.[5,6] Despite the high unmet need in *BRAF V600E* -mutant mCRC, prior to December 20, 2024, there were no approved biomarker-driven therapies specifically indicated for people with previously untreated *BRAF V600E* -mutant mCRC.[7,8]

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 mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test. This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

BRAFTOVI is also indicated, in combination with cetuximab, for the treatment of adult patients with mCRC with a *BRAF V600E* mutation, as detected by an FDA-approved test, after prior therapy.

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 for recommended dosing and additional safety information.

WARNINGS AND PRECAUTIONS

New Primary Malignancies: New primary malignancies, cutaneous and non-cutaneous, can occur. In BEACON CRC (previously treated *BRAF V600E* mutation-positive mCRC), cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 1.4% of patients with CRC, and a new primary melanoma occurred in 1.4% of patients who received BRAFTOVI in combination with cetuximab. In BREAKWATER (previously untreated *BRAF V600E* mutation-positive mCRC) skin papilloma was reported in 2.6%, 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% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. 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 non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous 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-approved 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 multi-gated 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 BREAKWATER (previously untreated *BRAF V600E* mutation-positive mCRC), the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6 was 2.2% for alkaline phosphatase, 1.3% for ALT, and 0.9% for 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: In BEACON CRC (previously treated *BRAF V600E* mutation-positive mCRC), hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with cetuximab; Grade 3 or higher hemorrhage occurred in 1.9% of patients, including fatal gastrointestinal hemorrhage in 0.5% of patients. The most frequent hemorrhagic events were epistaxis (6.9%), hematochezia (2.3%), and rectal hemorrhage (2.3%). In BREAKWATER (previously untreated *BRAF V600E* mutation-positive mCRC), hemorrhage occurred in 30% of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6; Grade 3 or 4 hemorrhage occurred in 3% 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. 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 BREAKWATER (previously untreated *BRAF V600E* mutation-positive mCRC), an increase of QTcF >500 ms was measured in 3.6% (8/222) of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6. 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, or in combination with cetuximab and mFOLFOX6. Refer to the prescribing information for cetuximab and individual product components of mFOLFOX6 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

BREAKWATER Trial (previously untreated *BRAF V600E* mutation-positive mCRC)

- **Serious adverse reactions** occurred in 38% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. Serious adverse reactions in >3% of patients included intestinal obstruction (3.5%) and pyrexia (3.5%).
- **Fatal gastrointestinal perforation**occurred in 0.9% of 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) were peripheral neuropathy (62% vs 53%), nausea (51% vs 48%), fatigue (49% vs 38%), rash (31% vs 4%), diarrhea (34% vs 47%), decreased appetite (33% vs 25%), vomiting (33% vs 21%), hemorrhage (30% vs 18%), abdominal pain (26% vs 27%), and pyrexia (26% vs 14%).
- **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) were: increased lipase (51% vs 25%), decreased neutrophil count (36% vs 34%), decreased hemoglobin (13% vs 5%), decreased white blood cell count (12% vs 7%), and increased glucose (11% vs 2%).

BEACON CRC Trial (previously treated *BRAF V600E* mutation-positive mCRC)

- **Most common adverse reactions**(?25%, all grades) in the BRAFTOVI with cetuximab arm compared to irinotecan with cetuximab or FOLFIRI with cetuximab (control) were: fatigue (51% vs 50%), nausea (34% vs 41%), diarrhea (33% vs 48%), dermatitis acneiform (32% vs 43%), abdominal pain (30% vs 32%), decreased appetite (27% vs 27%), arthralgia (27% vs 3%), and rash (26% vs 26%).
- **Other clinically important adverse reactions**occurring in <10% of patients who received BRAFTOVI in combination with cetuximab was pancreatitis.
- **Most common laboratory abnormalities** (all grades) (?20%) in the BRAFTOVI with cetuximab arm compared to irinotecan with cetuximab or FOLFIRI with cetuximab (control) were: anemia (34% vs 48%) and lymphopenia (24% vs 35%).

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.

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 bispecific 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, 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 January 25, 2025. 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 the BRAFTOVI® (encorafenib) plus cetuximab and mFOLFOX6 combination and an indication in the U.S. for the treatment of metastatic colorectal cancer (mCRC) with a BRAF V600E *mutation, as detected by an FDA-approved test, including their potential benefits and discussions with other regulatory authorities to support potential future additional license applications for the BRAFTOVI combination regimen in this indication, 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 mFOLFOX6; 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; whether the BREAKWATER trial will meet the primary endpoint of PFS or the secondary endpoint of OS; 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 mFOLFOX6 for the treatment of patients with metastatic CRC with a BRAFV600E mutation or in any jurisdictions for any other potential indications for BRAFTOVI; whether and when any such other applications may be approved by regulatory authorities, which will depend on a 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 mFOLFOX6 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 mFOLFOX6; 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, 2023, 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 .

Erbitux® is a registered trademark of Eli Lilly and Company and Merck KGaA, Darmstadt, Germany.

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