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U.S. FDA Approves BRAFTOVI® (Encorafenib) in Combination with Cetuximab for the Treatment of BRAFV600E-Mutant Metastatic Colorectal Cancer (CRC) After Prior Therapy

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BRAFTOVI plus cetuximab is the first-and-only FDA-approved targeted regimen specifically for adults with previously treated metastatic CRC with a $BRAF^{V600E}$ mutation

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced that the U.S. Food and Drug Administration (FDA) has approved BRAFTOVI® (encorafenib) in combination with cetuximab (marketed as ERBITUX®) for the treatment of adult patients with metastatic colorectal cancer (CRC) with a $BRAF^{V600E}$ mutation, as detected by an FDA-approved test, after prior therapy.[1] The approval is based on results from the BEACON CRC trial, the only Phase 3 trial to specifically study patients with previously treated metastatic CRC with a $BRAF^{V600E}$ mutation.

“We are pleased by the FDA’s approval of BRAFTOVI in combination with cetuximab, as we are committed to developing targeted medicines that can help people living with certain mutation-driven cancers,” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “We are grateful to the patients and study investigators who participated in the Phase 3 BEACON CRC trial and are proud to now be able to offer a targeted treatment option for people with $BRAF^{V600E}$-mutant metastatic CRC who have received prior therapy. Looking ahead, we’re committed to continuing to investigate this treatment regimen across earlier lines of therapy.”

Based on results from the BEACON CRC trial, BRAFTOVI plus cetuximab showed a median overall survival (OS) of 8.4 months (95% CI: 7.5, 11.0) compared with 5.4 months (95% CI: 4.8, 6.6) for Control (irinotecan with cetuximab or FOLFIRI with cetuximab) ([HR 0.60, (95% CI: 0.45, 0.79), p=0.0003]). Additionally, BRAFTOVI plus cetuximab showed an improved objective response rate (ORR) of 20% (95% CI: 13%, 29%) compared with 2% (95% CI: 0%, 7%) for Control (p<0.0001) and median progression-free survival (mPFS) was 4.2 months with BRAFTOVI plus cetuximab (95% CI: 3.7, 5.4) versus 1.5 months with Control (95% CI: 1.4, 1.7) ([HR 0.40, (95% CI: 0.31, 0.52), p<0.0001]).

“*BRAF* mutations are estimated to occur in up to 15% of people with metastatic colorectal cancer and represent a poor prognosis for these patients,” said Scott Kopetz, M.D., Ph.D., FACP, Associate Professor of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center. “As the first-and-only targeted regimen for people with $BRAF^{V600E}$-mutant metastatic CRC who have received prior therapy, BRAFTOVI in combination with cetuximab is a much-needed new treatment option for these patients.”

The most common adverse reactions (AR) (? 25%) seen in patients treated with BRAFTOVI in combination with cetuximab were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia and rash. The full prescribing information for BRAFTOVI can be found here.

The FDA granted this application Priority Review and Breakthrough Therapy designation. The FDA grants Priority Review to medicines that may offer significant advances in treatment or may provide a treatment where no adequate therapy exists.

Pfizer is committed to ensuring that patients who are prescribed BRAFTOVI have access to this important treatment option. Pfizer is here to help patients in the U.S. understand their benefits and connect them with financial assistance resources for their prescribed Pfizer Oncology medicines.

For more information about treatment of BRAFTOVI in combination with cetuximab, visit www.braftovihcp.com.

About Colorectal Cancer

Worldwide, colorectal cancer is the third most common type of cancer in men, and the second most common in women, with approximately 1.8 million new diagnoses in 2018.[2,3] In the U.S. alone, an estimated 147,950 people will be diagnosed with cancer of the colon or rectum in 2020, and approximately 53,000 are estimated to die of their disease each year.[4] *BRAF* mutations are estimated to occur in up to 15% of people with metastatic CRC and represent a poor prognosis for these patients.[5,6,7,8,9,10] 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 two times higher than for those with wild-type *BRAF*.[7,8] *BRAF*^{V600E}-mutant metastatic CRC is an area of high unmet need as there are currently no approved therapies specifically indicated for people with *BRAF*^{V600E}-mutant metastatic CRC.[11,12,13]

About BEACON CRC

BRAFTOVI in combination with cetuximab was evaluated in the randomized, active-controlled, open-label, multicenter, Phase 3 BEACON CRC trial. Eligible patients were required to have *BRAF*^{V600E} mutant metastatic CRC, as detected by an FDA-approved test, with disease progression after one or two prior regimens.

Patients were randomized 1:1:1 to one of the following treatment arms:

- BRAFTOVI 300 mg orally once daily in combination with cetuximab (BRAFTOVI/cetuximab arm)
- BRAFTOVI 300 mg orally once daily in combination with cetuximab and binimetinib
- Irinotecan with cetuximab or FOLFIRI with cetuximab (control arm)

The major efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomized patients. ORR and DoR were assessed in the subset of the first 220 patients included in the randomized portion of the BRAFTOVI/cetuximab and control arm of the study. A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm.

The trial was conducted at over 200 investigational sites in North America, South America, Europe and the Asia Pacific region. The BEACON CRC trial was conducted with support from Ono Pharmaceutical Co. Ltd., Pierre Fabre and Merck KGaA, Darmstadt, Germany (support is for sites outside of North America).

About BRAFTOVI® (encorafenib) in Metastatic Colorectal Cancer

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 colorectal cancer.

In the U.S., BRAFTOVI is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) 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.

Pfizer has exclusive rights to BRAFTOVI in the U.S. and Canada. 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 has exclusive rights to commercialize the product in all other countries, including Europe, Latin America and Asia (excluding Japan and South Korea).

IMPORTANT SAFETY INFORMATION

Refer to the cetuximab prescribing information for recommended dosing and safety information.

WARNINGS AND PRECAUTIONS

New Primary Malignancies, cutaneous and non-cutaneous, can occur with BRAFTOVI. In the BEACON CRC trial, 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. 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 mutationpositive non-cutaneous malignancies.

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.

Hemorrhage: In BEACON CRC, 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%). 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. 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 a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Advise females to contact their healthcare provider of a known or suspected pregnancy.

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.

Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with cetuximab. Refer to the prescribing information for cetuximab for additional risk information.

ADVERSE REACTIONS

The 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.

The most common laboratory abnormalities (?20%, all grades) 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

Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors (including grapefruit juice) or CYP3A4 inducers and use caution with sensitive CYP3A4 substrates. Modify BRAFTOVI dose if coadministration with a strong or moderate CYP3A4 inhibitor cannot be avoided. Avoid coadministration of BRAFTOVI with drugs known to prolong QT/QTc interval or hormonal contraceptives.

Please see full Prescribing Information for BRAFTOVI for additional information.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of patients. Today, Pfizer Oncology has an industry-leading portfolio of 22 approved innovative cancer medicines and biosimilars across more than 30 indications, including breast, prostate, kidney and lung cancers, as well as leukemia and melanoma.

Pfizer Inc.: 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 more than 150 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 Twitter 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 April 8, 2020. 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) and cetuximab combination and a new indication in the U.S. for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF^{V600E} mutation, as detected by an FDA-approved test, after prior therapy, including its 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;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 applications for BRAFTOVI plus cetuximab *for the new indication may be filed in any other jurisdictions; whether and when regulatory authorities in any other jurisdictions where applications may be pending or filed may approve any such applications, 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 will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability and/or commercial potential of BRAFTOVI®or BRAFTOVI® plus cetuximab; 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, 2019 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 ImClone LLC.

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[1] BRAFTOVI® (encorafenib) Prescribing Information. Boulder. CO: Array BioPharma Inc. (a wholly owned subsidiary of Pfizer Inc.): 2020

[2] Global Cancer Facts & Figures 4th Edition. American Cancer Society. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-4th-edition.pdf. Accessed April 2020

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