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U.S. FDA Accepts and Grants Priority Review to sNDA for BRAFTOVI® (encorafenib) in Combination with ERBITUX® (cetuximab) (BRAFTOVI Doublet) for the Treatment of BRAFV600E-Mutant Metastatic Colorectal Cancer After Prior Therapy

Wednesday, December 18, 2019 - 10:30am

NEW YORK--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) today announced that the U.S. Food and Drug Administration (FDA) has accepted and granted priority review to the Company's supplemental New Drug Application (sNDA) for BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) (BRAFTOVI Doublet) based on results from the Phase 3 BEACON CRC trial, which evaluated the efficacy and safety of BRAFTOVI in combination with ERBITUX with or without MEKTOVI® (binimetinib) in patients with advanced *BRAF*V600E-mutant metastatic colorectal cancer (mCRC), following one or two lines of therapy.

As published in *The New England Journal of Medicine* (*NEJM*), results from the BEACON CRC trial showed improvements in overall survival (OS) and objective response rates (ORR) for both the BRAFTOVI Doublet and BRAFTOVI Triplet (BRAFTOVI, MEKTOVI and ERBITUX) combination, compared to ERBITUX plus irinotecan-containing regimens (Control).1 In descriptive analyses comparing the Doublet and Triplet arms, the results showed comparable efficacy between the Doublet and Triplet in the overall population. The BRAFTOVI Triplet and Doublet showed no unexpected toxicities.

"The FDA's acceptance of our application for the BRAFTOVI Doublet is highly encouraging news for patients with mCRC harboring a *BRAF*V600E mutation," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "Currently, there are no FDA-approved treatments specifically for patients with *BRAF*-mutant mCRC who have received prior treatment. If approved, the BRAFTOVI Doublet would become the first targeted regimen for this patient population, who typically have a poor prognosis. We also look forward to continuing to explore this targeted Doublet regimen with or without MEKTOVI in earlier lines of *BRAF*-mutant mCRC, including in the ongoing, Phase 2 ANCHOR study in previously untreated patients."

The FDA grants Priority Review to medicines that may offer significant advances in treatment or may provide a treatment where no adequate therapy exists. The Prescription Drug User Fee Act (PDUFA) goal date for a decision by the FDA is in April 2020.

On November 2, 2019, the European Medicines Agency (EMA) also started the review procedure for Pierre Fabre's Type II variation applications based on the BEACON CRC trial.

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 140,250 patients were diagnosed with cancer of the colon or rectum in 2018, and approximately 50,000 are estimated to die of their disease each year.4 *BRAF* mutations are estimated to occur in up to 15% of patients with mCRC and represent a poor prognosis for these patients.5,6,7,8,9,10 The V600 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 mCRC is an area of high unmet need as there are currently no approved therapies specifically indicated for patients with *BRAF*-mutant mCRC.11,12, 13

About BEACON CRC

BEACON CRC is a randomized, open-label, global trial evaluating the efficacy and safety of BRAFTOVI, MEKTOVI and ERBITUX in patients with *BRAF*V600E-mutant mCRC whose disease has progressed after one or two prior regimens.

The randomized portion of the BEACON CRC trial is designed to assess the efficacy and safety of BRAFTOVI in combination with ERBITUX with or without MEKTOVI compared to ERBITUX and irinotecan-based therapy. 665 patients were randomized 1:1:1 to receive the Triplet combination, the Doublet combination (BRAFTOVI and ERBITUX) or the control arm (irinotecan-based therapy and ERBITUX). The study was amended to include an interim analysis of endpoints including ORR. The primary overall survival endpoint is a comparison of the Triplet combination to the control arm. Secondary endpoints address efficacy of the Doublet combination compared to the control arm, and the Triplet combination compared to the doublet therapy. Other secondary endpoints include progression-free survival, duration of response, safety and tolerability. The trial is being conducted at over 200 investigational sites in North America, South America, Europe and the Asia Pacific region. The BEACON CRC trial is being 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 + MEKTOVI

BRAFTOVI is an oral small molecule BRAF kinase inhibitor and MEKTOVI is an oral small molecule MEK inhibitor which target key enzymes in the MAPK signaling pathway (RAS-RAF-MEK-ERK). Inappropriate activation of proteins in this pathway has been shown to occur in many cancers including melanoma and colorectal cancer. In the U.S., BRAFTOVI + MEKTOVI are approved for the treatment of unresectable or metastatic melanoma with a *BRAF*V600E or *BRAF*V600K mutation, as detected by an FDA-approved test. BRAFTOVI is not indicated for treatment of patients with wild-type *BRAF* melanoma. In Europe, the combination is approved for adult patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation, as detected by a validated test. In Japan, the combination is approved for unresectable melanoma with a *BRAF* mutation.

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

Indications and Usage

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or

V600K mutation as detected by an FDA-approved test.

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

BRAFTOVI + MEKTOVI Important Safety Information

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

WARNINGS AND PRECAUTIONS

New Primary Malignancies, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 months. 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.

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 prior to initiating BRAFTOVI.

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% of patients. Assess LVEF by echocardiogram or 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.

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism.

Hemorrhage: In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ? Grade 3 hemorrhage occurred in 3.2% of patients. Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%).

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma across multiple clinical trials, 0.1% of patients experienced retinal vein occlusion (RVO). The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO including uncontrolled

glaucoma or a history of hyperviscosity or hypercoagulability syndromes. Perform ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination 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.

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% of patients with BRAF mutation-positive melanoma across multiple clinical trials. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD.

Hepatotoxicity: In the COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation. Monitor liver laboratory tests before initiation of MEKTOVI, monthly during treatment, and as clinically indicated.

Rhabdomyolysis: In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% of patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib across multiple clinical trials. Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated.

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) 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 or MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. Grades 3 or 4 dermatologic reactions occurred in 21% of BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

ADVERSE REACTIONS

The most common adverse reactions (?20%, all Grades, in the COLUMBUS trial): were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%), serous retinopathy (20%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS Trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity and colitis.

In the COLUMBUS Trial, the most common laboratory abnormalities (all grades) (? 20%) included increased creatinine (93%), increased creatine phosphokinase (58%), increased gamma glutamyl transferase (GGT) (45%), anemia (36%), increased ALT (29%), hyperglycemia (28%), increased AST (27%), and increased alkaline

phosphatase (21%).

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.14,15

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 Oncology is striving to change the trajectory of cancer.

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 Dec. 18, 2019. 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 ERBITUX® (cetuximab) combination (*BRAFTOVI Doublet)*and a potential new indication for the treatment of advanced BRAFV600E-mutant metastatic colorectal cancer, following one or two lines of 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 the BRAFTOVI Doublet; 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; risks associated with interim 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 drug applications for the Doublet combination for the*

potential new indication may be filed with regulatory authorities in any other jurisdictions; whether and when the FDA and the European Medicines Agency will approve the pending applications for the potential new indication and whether and when regulatory authorities in any other jurisdictions may approve any such other applications that may be pending or filed, 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 the Doublet combination for the potential new indication 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®, MEKTOVI® or the Doublet Combination; 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, 2018 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.

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14 BRAFTOVI® (encorafenib) Prescribing Information. Array BioPharma Inc., June 2018

15 MEKTOVI® (binimetinib) Prescribing Information. Array BioPharma Inc., June 2018

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