Pfizer Logo

Pfizer Presents Interim Analysis Results from Phase 3 BEACON CRC Trial of BRAFTOVI® (Encorafenib), MEKTOVI® (Binimetinib) and Cetuximab for the Treatment of BRAFV600E-Mutant Metastatic Colorectal Cancer

Sunday, September 29, 2019 - 10:30pm

- Results to be presented during a late-breaking oral session at the 2019 ESMO Congress and simultaneously published in The New England Journal of Medicine – - As previously announced, BRAFTOVI combinations showed statistically significant improvements in OS and ORR versus control –

Pfizer Inc. (NYSE: PFE) today announced detailed results from the interim analysis of the Phase 3 BEACON CRC trial evaluating the combination of BRAFTOVI® (encorafenib), MEKTOVI® (binimetinib), and cetuximab (BRAFTOVI Triplet), in patients with advanced *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC), following one or two lines of therapy. The results show significant improvements in overall survival (OS) and objective response rates (ORR) for the BRAFTOVI Triplet and BRAFTOVI Doublet combination (BRAFTOVI and cetuximab), compared to cetuximab plus irinotecan-containing regimens (Control), and provide analysis of the efficacy and safety of the BRAFTOVI Triplet compared to the BRAFTOVI Doublet. These data will be presented today during a late-breaking oral session at the 2019 European Society for Medical Oncology (ESMO) Congress in Barcelona, Spain, and simultaneously published online in *The New England Journal of Medicine (NEJM)*. Pfizer intends to submit the results of the BEACON CRC trial for marketing approval in the U.S. in the fourth quarter of 2019. The use of BRAFTOVI, MEKTOVI and cetuximab for the treatment of patients with *BRAF*^{V600E}-mutant mCRC is investigational and not approved by the FDA.

As previously announced, the BRAFTOVI Triplet showed a median OS of 9.0 months for patients treated with the Triplet, compared to 5.4 months for Control ([HR 0.52, (95% CI 0.39-0.70), p<0.0001]). The BRAFTOVI Triplet also demonstrated a significantly improved ORR of 26% (95% CI: 18%, 35%) compared to 2% (95% CI: 0%, 7%) for Control (p<0.0001).

“We are pleased to share these data from the BEACON CRC trial with the oncology community,” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “With no approved therapies currently indicated specifically for *BRAF*-mutant mCRC, we believe that the evidence so far shows encouraging potential for the BRAFTOVI Triplet to make a meaningful impact on the lives of those living with this disease.”

The study also showed improvements in secondary efficacy endpoints. As previously announced, the BRAFTOVI Doublet showed a statistically significant improvement in OS (median 8.4 months vs. 5.4 months, [HR 0.60, 95% CI (0.45-0.79), p=0.0003]) compared to Control. Additional analysis showed depth of responses in favor of the BRAFTOVI Triplet.

“The BEACON CRC trial results show meaningful improvements compared to an available standard of care for patients with *BRAF*^{V600E}-mutant mCRC," said Scott Kopetz, M.D., Ph.D., FACP, Associate Professor of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center. “These data presented at ESMO and published in The NEJM further support the potential of the BRAFTOVI Triplet to be the first chemotherapy-free, targeted regimen for this patient population, who have a poor prognosis and limited treatment options."

Further, the data provide additional details on the primary and secondary endpoints, including observations of response rates by number of lines of prior therapy, as well as a descriptive analysis of OS comparing the BRAFTOVI Triplet to the BRAFTOVI Doublet.

The BEACON CRC study was not powered to compare the two experimental arms directly and such a comparison is further limited by the interim nature of the analysis. In the data being presented at ESMO, results of the descriptive analysis of survival comparing the BRAFTOVI Triplet to the BRAFTOVI Doublet favored the Triplet combination.

As previously reported, the BRAFTOVI Triplet and Doublet were generally well-tolerated with no unexpected toxicities. Grade 3 or higher adverse events (AEs) were seen in 58%, 50% and 61% of patients in the BRAFTOVI Triplet, Doublet and Control arms, respectively. Discontinuation of therapy due to adverse events was seen in 7%, 8% and 11% of patients in the Triplet, Doublet and Control arms, respectively. The most common Grade 3 or higher AEs seen in patients treated with the BRAFTOVI Triplet were diarrhea (10% vs. 2% in the Doublet arm and 10% in the Control arm), abdominal pain (6% vs. 2% in the Doublet arm and 5% in the Control arm) and nausea (5% vs. <1% in the Double arm and 1% in the Control arm).

Details for the late-breaking oral presentation are below. The abstract can be accessed through the ESMO website: https://www.esmo.org/Conferences/ESMO-Congress-2019.

Title/Abstract Number	**Date/Time (CEST)**	**Location**
(LBA32) Encorafenib plus cetuximab with or without binimetinib for BRAF V600E–mutant metastatic colorectal cancer: expanded results from a randomized, 3-arm, phase 3 study vs. the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) Tabernero J	Monday, September 30 8:30-8:45 AM	Barcelona Auditorium

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.[1,2] 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.[3] *BRAF* mutations are estimated to occur in up to 15% of patients with mCRC and represent a poor prognosis for these patients.[4,5,6,7,8,9] 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.[10,[11],11]

About BEACON CRC

BEACON CRC is a randomized, open-label, global trial evaluating the efficacy and safety of BRAFTOVI, MEKTOVI and cetuximab in patients with *BRAF*^{V600E}-mutant mCRC whose disease has progressed after one or two prior regimens. BEACON CRC is the first and only Phase 3 trial designed to test a BRAF/MEK combo targeted therapy in *BRAF*^{V600E}-mutant mCRC.

Thirty patients were treated in a safety lead-in conducted prior to initiation of the randomized part of the trial and received the Triplet combination (BRAFTOVI 300 mg daily, MEKTOVI 45 mg twice daily and cetuximab per label). Of the 30 patients, 29 had a *BRAF*^{V600} mutation. As previously announced, the Triplet combination showed an acceptable safety profile that supported initiation of the randomized portion of the trial.

The randomized portion of the BEACON CRC trial is designed to assess the efficacy of BRAFTOVI in combination with cetuximab with or without MEKTOVI compared to cetuximab and irinotecan-based therapy. 665 patients were randomized 1:1:1 to receive the Triplet combination, the Doublet combination (BRAFTOVI and cetuximab) or the control arm (irinotecan-based therapy and cetuximab). 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. Health related quality of life data will also be assessed. 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, colorectal cancer, non-small cell lung cancer and others. 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. BRAFTOVI + MEKTOVI have received regulatory approval in Australia and the Swiss Medicines Agency (Swissmedic) is currently reviewing the Marketing Authorization Applications for BRAFTOVI and MEKTOVI submitted by Pierre Fabre.

Pfizer has exclusive rights to BRAFTOVI and MEKTOVI in the U.S. and Canada. Pfizer has granted Ono Pharmaceutical Co. Ltd. exclusive rights to commercialize both products in Japan and South Korea, Medison

exclusive rights to commercialize both products in Israel and Pierre Fabre 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 *BRAF* ^{V600K} mutation, as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for the 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, including keratoacanthoma, occurred in 2.6% and basal cell carcinoma occurred in 1.6% 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 non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies.

Tumor Promotion in *BRAF* Wild-Type Tumors: 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, cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. Cardiomyopathy resolved in 87% of patients. Assess left ventricular ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. 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. 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. 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. Assess for visual symptoms at each visit. Perform ophthalmological evaluation at regular intervals and for any 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) and 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. Monitor liver laboratory tests before and during treatment and as clinically indicated.

Rhabdomyolysis: In the COLUMBUS trial, elevation of laboratory values of serum creatine phosphokinase (CPK) occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% of patients with *BRAF* mutation-positive melanoma 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. 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. Non-hormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + MEKTOVI.

Adverse Reactions

The most common adverse reactions (?20%, all Grades, in the COLUMBUS trial): were fatigue, nausea, diarrhea, vomiting, abdominal pain, arthralgia, myopathy, hyperkeratosis, rash, headache, constipation, visual impairment, serous retinopathy.

In the COLUMBUS trial, the most common laboratory abnormalities (?20%, all Grades): included increased creatinine, increased CPK, increased gamma glutamyl transferase, anemia, increased ALT, hyperglycemia, increased AST, and increased alkaline phosphatase.

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 co-administration 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.[12,13]

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 September 30, 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), MEKTOVI® (binimetinib), and cetuximab (BRAFTOVI Triplet) combination as well as the BRAFTOVI Doublet combination (BRAFTOVI and cetuximab) *and a potential new indication for the treatment of advanced BRAF^{V600E}-mutant metastatic colorectal cancer, following one or two lines of therapy, including its potential benefits and the expected timing of a potential regulatory submission in the U.S., 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® and MEKTOVI®; 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 Triplet Combination for the potential new indication may be filed with regulatory authorities in any jurisdictions; whether and when regulatory authorities in any jurisdictions 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 the Triplet 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 Triplet 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.

---

[1] Global Cancer Facts & Figures 3rd 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-3rd-edition.pdf. Accessed January 2018

[2] Bray, F., Ferlay, J., Soerjomataram, I., et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 68*(6), 394-424. doi:10.3322/caac.21492

[3] Cancer Facts & Figures 2018. American Cancer Society. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-factsand-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed January 2018.

[4] Saridaki, Z., Tzardi, M., Sfakianaki, M., et al. (2013). BRAFV600E Mutation Analysis in Patients with Metastatic Colorectal Cancer (mCRC) in Daily Clinical Practice: Correlations with Clinical Characteristics, and Its Impact on Patients' Outcome. *PLoS ONE, 8*(12). doi:10.1371/journal.pone.0084604

[5] Loupakis, F., Ruzzo, A., Cremolini, C., et al. (2009). KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. *British journal of cancer*, *101*(4), 715–721. doi:10.1038/sj.bjc.6605177

[6] Corcoran, R. B., Ebi, H., Turke, A. B., Coffee, et al. (2012). EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer discovery*, *2*(3), 227–235. doi:10.1158/2159-8290.CD-11-0341

[7] Sorbye, H., Dragomir, A., Sundström, M., et al. (2015). High BRAF Mutation Frequency and Marked Survival Differences in Subgroups According to KRAS/BRAF Mutation Status and Tumor Tissue Availability in a Prospective Population-Based Metastatic Colorectal Cancer Cohort. *PloS one*, *10*(6), e0131046. doi:10.1371/journal.pone.0131046

[8] Safaee Ardekani, G., Jafarnejad, S. M., Tan, L., et al. (2012). The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. *PloS one*, *7*(10), e47054. doi:10.1371/journal.pone.0047054

[9] Vecchione, L., Gambino, V., Raaijmakers, J., et al. (2016). A Vulnerability of a Subset of Colon Cancers with Potential Clinical Utility. *Cell,165*(2), 317-330. doi:10.1016/j.cell.2016.02.059

[10] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. V.2.2019.

[11] Van Cutsem, E., Cervantes, A., Adam, R., et al. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol. 27*(8):1386-422. doi: 10.1093/annonc/mdw235

[11] Ursem, C., Atreya, C. E., & Van Loon, K. (2018). Emerging treatment options for *BRAF*-mutant colorectal cancer. *Gastrointestinal cancer : targets and therapy*, *8*, 13–23. doi:10.2147/GICTT.S125940

[12] BRAFTOVI® (encorafenib) Prescribing Information. Array BioPharma Inc., June 2018

[13] MEKTOVI® (binimetinib) Prescribing Information. Array BioPharma Inc., June 2018

Pfizer Media Contact: Lisa O’Neill (EU) (44) 7929 339 560 Lisa.O'Neill@pfizer.com Jessica Smith (212) 733-6213 Jessica.M.Smith@pfizer.com Pfizer Investor Contact: Ryan Crowe (212) 733-8160 Ryan.Crowe@pfizer.com