Array BioPharma Receives FDA Breakthrough Therapy Designation for BRAFTOVI™ in combination with MEKTOVI® and cetuximab for BRAFV600E-mutant Metastatic Colorectal Cancer

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- Designation based on Phase 3 BEACON CRC safety lead-in data -

BOULDER, Colo., Aug. 7, 2018 /PRNewswire/ -- Array BioPharma Inc. (NASDAQ: ARRY) today announced it has received Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA) for encorafenib (BRAFTOVI™), in combination with binimetinib (MEKTOVI®) and cetuximab for the treatment of patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC) as detected by an FDA-approved test, after failure of one to two prior lines of therapy for metastatic disease. *BRAF*^{V600E}-mutant mCRC patients have a mortality risk more than double that of mCRC patients without the mutation, and currently there are no therapies specifically approved for this high unmet need population. [1-6]

Breakthrough Therapy Designation is an FDA process designed to expedite the development and review of drugs that are intended to treat a serious condition where preliminary clinical evidence indicates that they may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

"We are delighted that the FDA has recognized the potential of this combination for patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer," said Victor Sandor, M.D., Chief Medical Officer. "As there are no regimens approved specifically for *BRAF*^{V600E}-mutant mCRC, this designation provides us with the opportunity to work closely with the FDA to potentially accelerate our effort to bring an important treatment option to these patients in critical need."

As presented at the ESMO 20thWorld Congress on Gastrointestinal Cancer in June 2018, the results from the safety lead-in of the ongoing randomized Phase 3 BEACON CRC trial showed that, at the time of analysis, the overall survival (OS) data were fully mature through 12.6 months and that the median OS had not yet been reached.

- One-year overall survival rate for this cohort was 62%.
- Median progression-free survival (mPFS) for patients treated with the triplet was 8 months [95% CI 5.6-9.3] and is similar between patients receiving one prior line of therapy and patients receiving two prior lines of therapy.
- Confirmed overall response rate (ORR) was 48% and among the 17 patients who received only one prior line of therapy the ORR was 62%.
- The triplet combination was generally well-tolerated with no unexpected toxicities. The most common grade 3 or 4 adverse events seen in at least 10% of patients were fatigue (13%), anemia (10%), increased blood creatine kinase (10%) and increased aspartate aminotransferase (10%).

The triplet combination of BRAFTOVI, MEKTOVI and cetuximab for the treatment of patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer is investigational and not approved by the FDA.

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 1.4 million new diagnoses in 2012. Globally in 2012, approximately 694,000 deaths were attributed to colorectal cancer. [7] In the U.S. alone, an estimated 140,250 patients will be diagnosed with cancer of the colon or rectum in 2018, and approximately 50,000 are estimated to die of their disease. [8] In the U.S., *BRAF* mutations are estimated to occur in 10% to 15% of patients with colorectal cancer and represent a poor prognosis for these patients. [5,6,9,10] 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*. [11] Several irinotecan plus cetuximab-containing regimens, similar to the BEACON CRC control arm, have established clinical activity benchmarks in *BRAF*^{V600E}-mutant mCRC patients, whose disease has progressed after one or two prior lines of therapy, between 4% to 8% ORR, 1.8 and 2.5 months mPFS and 4 and 6 months mOS. [1-6,12]

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 the safety lead-in 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*^{V600E} mutation. MSI-H, resulting from defective DNA mismatch repair, was detected in only 1 patient. As previously announced, the triplet combination demonstrated good tolerability, supporting 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. Approximately 615 patients are expected to be randomized 1:1:1 to receive triplet combination, doublet combination (BRAFTOVI and cetuximab) or the control arm (irinotecan-based therapy and cetuximab). The primary endpoint of the trial is overall survival of the triplet combination compared 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 PFS, ORR, 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. Patient enrollment is expected to be completed around the end of 2018.

About BRAFTOVI + MEKTOVI
BRAFTOVI (encorafenib) is an oral small molecule BRAF kinase inhibitor and MEKTOVI (binimetinib) 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, thyroid 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.

Array has exclusive rights to BRAFTOVI and MEKTOVI in the U.S. and Canada. Array has granted Ono Pharmaceutical 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, Asia and Latin America.

BRAFTOVI and MEKTOVI are not approved outside of the United States. The European Medicines Agency (EMA), the Swiss Medicines Agency (Swissmedic) and the Australian Therapeutic Goods Administration (TGA) are currently reviewing the Marketing Authorization Applications, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan is currently reviewing the Manufacturing and Marketing Approval Applications for BRAFTOVI and MEKTOVI.

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.

Warnings and Precautions

New Primary Malignancies: 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. Discontinue BRAFTOVI for *RAS* mutation-positive non-cutaneous malignancies.

Tumor Promotion in *BRAF* Wild-Type Tumors: Confirm evidence of *BRAF*^{V600E} or *BRAF*^{V600K}mutation prior to initiating BRAFTOVI.

Cardiomyopathy: 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. 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.

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.

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. In patients with *BRAF* mutation-positive melanoma across multiple clinical trials, 0.1% of patients experienced retinal vein occlusion (RVO). 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 ophthalmic evaluation at regular intervals and for any visual disturbances.

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). 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 periodically and as clinically indicated.

QTc Prolongation: 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. Nonhormonal 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.

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information. You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Array at 1-844-Rx-Array (1-844-792-7729).

About Array BioPharma

Array BioPharma Inc. is a fully-integrated, biopharmaceutical company focused on the discovery, development and commercialization of transformative and well-tolerated targeted small molecule drugs to treat patients afflicted with cancer and other high-burden diseases. Array markets in the United States BRAFTOVI™ (encorafenib) capsules in combination with MEKTOVI® (binimetinib) tablets for the treatment of patients with unresectable or metastatic melanoma with a *BRAF*^{V600E} or *BRAF*^{V600K} mutation. Array's lead clinical programs, encorafenib and binimetinib, are being investigated in over 30 clinical trials across a number of solid tumor indications, including a Phase 3 trial in *BRAF*-mutant colorectal cancer. Array's pipeline includes several additional programs being advanced by Array or current license-holders, including selumetinib (partnered with AstraZeneca), larotrectinib (partnered with Loxo Oncology), ipatasertib (partnered with Genentech), tucatinib (partnered with Seattle Genetics) and ARRY-797 (being developed by Yarra Therapeutics, a wholly-owned subsidiary of Array), all of which are currently in registration trials. Ganovo® (danoprevir, partnered with Roche) was recently approved in China for the treatment of viral hepatitis C. For more information on Array, please visit www.arraybiopharma.com or follow @arraybiopharma on Twitter and LinkedIn.

References

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Array BioPharma Forward-Looking Statement

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements about the future development plans of encorafenib and binimetinib; expectations regarding approval of encorafenib and binimetinib for *BRAF*-mutant melanoma and timing of such approvals; expectations that events will occur that will result in greater value for Array; and the potential for the results of current and future clinical trials to support regulatory approval or the marketing success of encorafenib and binimetinib. Specifically, there is no assurance that results from the BEACON CRC and COLUMBUS trials will satisfy the requirements of regulatory authorities necessary for approval. These statements involve significant risks and uncertainties, including those discussed in our most recent annual report filed on Form 10-K, in our quarterly reports filed on Form 10-Q, and in other reports filed by Array with the Securities and Exchange Commission. Because these statements reflect our current expectations concerning future events, our actual results could differ materially from those anticipated in these forward-looking statements as a result of many factors. These factors include, but are not limited to, the determination by the FDA, EMA or other regulatory agencies that results from clinical trials are not sufficient to support registration or marketing approval of encorafenib and binimetinib; our ability to effectively and timely conduct clinical trials in light of increasing costs and difficulties in locating appropriate trial sites and in enrolling patients who meet the criteria for certain clinical trials; risks associated with our dependence on third-party service providers to successfully conduct clinical trials and to manufacture drug substance and product within and outside the U.S.; our ability to grow and successfully develop commercialization capabilities; our ability to achieve and maintain profitability and maintain sufficient cash resources; and our ability to attract and retain experienced scientists and management. We are providing this information as of August 7, 2018. We undertake no duty to update any forward-looking statements to reflect the occurrence of events or circumstances after the date of such statements or of anticipated or unanticipated events that alter any assumptions underlying such statements.

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