European Commission Approves BRAFTOVI® (encorafenib) in Combination with MEKTOVI® (binimetinib) for Advanced BRAF-mutant Melanoma

September 20, 2018

- European Commission approval applies to all 28 European Union member states, Liechtenstein, Iceland and Norway -

- Approval is based on Phase 3 COLUMBUS trial which demonstrated nearly 15 months median progression-free survival and over 30 months median overall survival -

- Builds on recent U.S. FDA approval of BRAFTOVI + MEKTOVI -

BOULDER, Colo., Sept. 20, 2018 /PRNewswire/ -- Array BioPharma Inc. (NASDAQ: ARRY) today announced that the European Commission (EC) has approved BRAFTOVI® in combination with MEKTOVI® for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation, as detected by a validated test. This approval is applicable to all 28 European Union (EU) member states, as well as Liechtenstein, Iceland and Norway.

"With an even greater number of patients with advanced *BRAF*-mutant melanoma in Europe than in the U.S., we are delighted BRAFTOVI + MEKTOVI will be available to these patients who are in critical need of additional options that delay disease progression and improve overall survival," said Ron Squarer, Chief Executive Officer. "Our European partner, Pierre Fabre, has a strong legacy in oncology, and with over a thousand employees dedicated to this therapeutic area, we are very pleased they have made BRAFTOVI + MEKTOVI a top priority for their team."

The EC approval is based on results from the Phase 3 COLUMBUS trial, of which the primary endpoint was median progression-free survival (mPFS). BRAFTOVI + MEKTOVI achieved an mPFS of nearly 15 months [14.9 months versus vemurafenib monotherapy at 7.3 months; hazard ratio (HR) 0.54 (95% CI, 0.41–0.71), p<0.0001].

BRAFTOVI + MEKTOVI is the first targeted treatment to achieve over 30 months median overall survival (OS). As published in *The Lancet Oncology* in September 2018, BRAFTOVI + MEKTOVI reduced the risk of death compared to vemurafenib [HR (0.61), (95% CI 0.47,0.79), p <0.0001]. Median OS was 33.6 months for patients treated with the combination, compared to 16.9 months for patients treated with vemurafenib.

Detailed recommendations for the use of these products in the EU are described in the summary of product characteristics (SmPC), which are published in the European public assessment report (EPAR) and made available in all official EU languages at http://www.ema.europa.eu.

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, Latin America and Asia (excluding Japan and South Korea).

In June 2018, the U.S. Food and Drug Administration (FDA) approved BRAFTOVI + MEKTOVI 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.

Only 5% of patients who received BRAFTOVI + MEKTOVI discontinued treatment due to adverse reactions. The most common adverse reactions (≥25%) in patients receiving BRAFTOVI + MEKTOVI were fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia.

About *BRAF*-mutant Metastatic Melanoma

Melanoma develops when unrepaired DNA damage to skin cells triggers mutations that may lead them to multiply and form malignant tumors. Metastatic melanoma is the most serious and life-threatening type of skin cancer and is associated with low survival rates. [1,2] There are a variety of gene mutations that can lead to metastatic melanoma. The most common genetic mutation in metastatic melanoma is *BRAF*. There are about 200,000 new cases of melanoma diagnosed worldwide each year, approximately half of which have *BRAF* mutations, a key target in the treatment of metastatic melanoma. [1-5]

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.

The Swiss Medicines Agency (Swissmedic) and the Australian Therapeutic Goods Administration (TGA) are currently reviewing the Marketing Authorization Applications for BRAFTOVI and MEKTOVI submitted by Pierre Fabre, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) is currently reviewing the Manufacturing and Marketing Approval applications submitted by Ono Pharmaceutical Co, Ltd.

About COLUMBUS

The COLUMBUS trial (NCT01909453) is a two-part, international, randomized, open label Phase 3 trial evaluating the efficacy and safety of BRAFTOVI (encorafenib) in combination with MEKTOVI (binimetinib) compared to vemurafenib and encorafenib monotherapy in 921 patients with locally advanced, unresectable or metastatic melanoma with *BRAF*^{V600} mutation. The primary endpoint of the trial was mPFS; all secondary efficacy analyses, including the prospectively planned analysis overall survival, are descriptive in nature. Over 200 sites across North America, Europe, South America, Africa, Asia and Australia participated in the trial.

BRAFTOVI + MEKTOVI Indications and Usage

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600E} mutation.
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 [6,7]. 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.

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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, among others, statements about the future development plans of encorafenib and binimetinib; expectations that events will occur that will create 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. Because these statements reflect our current expectations concerning future events and involve significant risks and uncertainties, 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 potential that the FDA, EMA or other regulatory agencies determine 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. Additional information concerning these and other risk factors can be found 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. We are providing this information as of September 20, 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.

CONTACTS:
Investor Relations
Array BioPharma
Andrea N. Flynn, Ph.D.
Senior Director, Investor Relations & Corporate Communications
(303) 381-6600
ir@arraybiopharma.com

Media
Y&R PR
Erika Hackmann, Media Relations
212-303-2305
erika.hackmann@yr.com

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