YOU ARE INVITED

ARRAY BIOPHARMA
invites you to an educational program

BRAFTOVI® (encorafenib) capsules **+** **MEKTOVI®** (binimetinib) tablets **:**

An oral therapy for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation

BRAFTOVI® (encorafenib) capsules + MEKTOVI® (binimetinib) tablets

Featured Speaker

Sunandana Chandra, MD
Assistant Professor of Medicine
Northwestern Memorial Hospital

Thursday, June 13, 2019
6:15 PM

Ruth's Chris Steak House
314 South Fourth Avenue
Ann Arbor, MI 48104

The purpose of the meeting will be to educate health care professionals on the role of BRAFTOVI (encorafenib) capsules + MEKTOVI (binimetinib) tablets in the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation as detected by an FDA-approved test. BRAFTOVI is not indicated for treatment of patients with wild-type *BRAF* melanoma.

To RSVP* or for information regarding BRAFTOVI + MEKTOVI, contact your local Array BioPharma Oncology Therapeutic Specialist (OTS), Laura Masztak, at (720) 471-9484 or

Sunandana Chandra, MD, MS, received her medical degree from Michigan State University in East Lansing, Michigan. She completed an Internal Medicine residency at Case Western University Hospitals in Cleveland, Ohio, and then went on to complete a Hematology Oncology fellowship at New York University in New York, New York.

Dr. Chandra has been the Principal Investigator for numerous therapeutic clinical trials in early phase development as well as phase II and III trials, and is the Co-Leader for the Northwestern Skin Disease Team. She has presented at regional and national conferences on her research interests including melanoma. She has coauthored numerous peer-reviewed articles in melanoma and other advanced cutaneous malignancies.

*Array abides by the PhRMA Code of Conduct as well as state and federal transparency reporting laws (eg, the Sunshine Act).

State laws and federal entities may restrict your ability to receive meals or other in-kind benefits. You are responsible for complying with any restrictions or limitations related to such requirements.

When you RSVP, please indicate whether you will accept or opt out of Array's in-kind benefits (eg, meals, parking) at the program. For any attendee who receives in-kind benefits, Array reports the attendee's name and value of the in-kind benefits provided as required by federal and state disclosure laws.

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.

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.

ARRAY BIOPHARMA