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Clinical Trial Data for a Treatment Regimen for Adults With *BRAF* V600E/K-Mutant Unresectable or Metastatic Melanoma

Announcer:
Welcome to ReachMD. This medical industry feature is for US healthcare professionals only and is intended to be played in the context of its original location online. This presentation has been created and paid for by Pfizer. This promotional activity is not certified for continuing medical education. Here's your host, Dr Jennifer Caudle.

Dr Caudle:
Welcome to a new podcast series about *BRAF*-mutant unresectable or metastatic melanoma. In our first episode, "Trial data for a treatment regimen for adults with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma," we're going to discuss a Category 1 treatment recommendation included in the NCCN Clinical Practice Guidelines in Oncology. My name is Dr Jennifer Caudle, and I'm your host. Joining me today is Dr Pauline Funchain. Dr Funchain, welcome to the program.

Dr Funchain:
My pleasure.

Dr Caudle:
Well, it's great to have you here today to talk about your experience treating adults with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma.

Dr Funchain:
Thanks for having me. To introduce myself, I'm a medical oncologist who specializes in treating melanoma, and I now direct the melanoma and genomics programs here in Cleveland, Ohio.

Dr Caudle:
I'd like to talk with you about the combination of BRAFTOVI, also known as encorafenib, and MEKTOVI, also known as binimetinib, for treating adults with *BRAF*-positive V600E or V600K unresectable or metastatic melanoma. First, let's review the indication and select safety information for BRAFTOVI and MEKTOVI.

Announcer:
INDICATIONS AND USAGE
BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are indicated to be used in combination for the treatment of adult 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.

Select Safety Information for BRAFTOVI and MEKTOVI
New Primary Malignancies, cutaneous and non-cutaneous, can occur. Monitor for malignancies and perform dermatologic evaluations prior to, while on therapy, and following discontinuation of treatment.

BRAFTOVI in combination with MEKTOVI may cause New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Venous Thromboembolism, Hemorrhage, Ocular Toxicities, Interstitial Lung Disease, Hepatotoxicity, Rhabdomyolysis, QTc Prolongation, and Embryo-Fetal Toxicity. In addition, there are Risks Associated with BRAFTOVI as a Single Agent.

Please listen to additional Important Safety Information later in this podcast or view Important Safety Information at braftovimektovihcp.com.

Please see the full Prescribing Information and Medication Guide for BRAFTOVI and full Prescribing Information and Patient Information for MEKTOVI. You can also access the full Prescribing Information for these products at braftovimektovihcp.com.

Dr Caudle:
Before we jump into the clinical trial results, let's talk a bit about the design of the COLUMBUS trial that assessed BRAFTOVI in combination with MEKTOVI for adults with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma. This was a global, randomized, open-label, multicenter, active-controlled, parallel-group study involving 577 adult patients with a *BRAF* V600E and/or K mutation. Patients were randomized to one of three arms: BRAFTOVI and MEKTOVI (n=192) or vemurafenib (n=191) or BRAFTOVI alone (n=194). Please note that BRAFTOVI monotherapy is not approved for use by the FDA. Prior use of BRAF or MEK inhibitors was prohibitive, and all patients had an ECOG performance status of 0 or 1. Patients could have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable or metastatic disease.

Patients were stratified by prior immunotherapy, ECOG performance status, and by stage using the AJCC, also known as the American Joint Committee on Cancer. Treatment was continued until disease progression or unacceptable toxicity.

The major efficacy outcome measure was progression-free survival (PFS) by blinded independent central review of BRAFTOVI and MEKTOVI versus vemurafenib. Other efficacy outcome measures included overall survival, as well as objective response rate and duration of response, which were assessed by a blinded independent central review.

Dr Funchain:
What we saw in the primary analysis was that patients treated with BRAFTOVI and MEKTOVI had more than double the median progression-free survival of patients treated with vemurafenib. In the primary analysis, patients in the BRAFTOVI and MEKTOVI cohort had a median progression-free survival of 14.9 months (the 95% confidence interval was 11.0 to 18.5), compared to 7.3 months (the 95% confidence interval was 5.6 to 8.2) in the vemurafenib arm. In addition, the hazard ratio was 0.54 (the 95% confidence interval was 0.41 to 0.71), which means there was a 46% lower risk of progression or death with BRAFTOVI and MEKTOVI compared to vemurafenib. The *P* value was <0.0001. In the primary analysis with a median follow-up of 16.6 months, the number of events observed in each arm was 98 out of 192, or 51%, with BRAFTOVI and MEKTOVI and a 106 out of 191, or 55%, with vemurafenib. In an updated nonprespecified analysis of progression-free survival by a blinded independent central review with the median follow-up time of 40.8 months for progression-free survival (the data cutoff of November 2019), median progression-free survival was the same as previously reported with a hazard ratio of 0.51; the 95% confidence interval was 0.39 to 0.66. The number of events observed in each arm was 119 out of 192, or 62%, with BRAFTOVI and MEKTOVI and 119 out of 191, or 62%, with vemurafenib. It's important to note that the updated PFS results are descriptive. No formal statistical testing was performed, and therefore no conclusions can be drawn.

Dr Caudle:
These data are encouraging for adults living with *BRAF*-mutant unresectable or metastatic melanoma and physicians looking for a treatment option for these patients.

Announcer:
Now, let's review some additional Safety Information for BRAFTOVI and MEKTOVI.

Tumor Promotion in BRAF Wild-Type Tumors: Increased cell proliferation can occur with BRAF inhibitors.

Cardiomyopathy: Assess left ventricular ejection fraction, or LVEF, before initiating treatment, after one month of treatment, then every 2 to 3 months thereafter. The safety of MEKTOVI has not been established in patients with LVEF below 50%.

Dr Caudle:
One of the other efficacy outcome measures in the trial was overall survival. Can you tell us a bit about the median OS, for both the primary and updated analyses?

Dr Funchain:
Well, before I do that, I do want to point out that the hierarchical testing procedure prevented a formal assessment of the statistical significance of overall survival; therefore, the overall survival results should be considered descriptive in nature only. This information shouldn't be used to make comparisons between treatment arms.

Dr Caudle:
That's good to note.

Dr Funchain:
With that in mind, back to your question about overall survival. In the primary analysis, a median overall survival of 33.6 months for BRAFTOVI and MEKTOVI versus 16.9 months for vemurafenib. The 95% confidence intervals do not cross, with 24.4 to 39.2 for the

BRAFTOVI and MEKTOVI arm, and 14.0 to 24.5 for the vemurafenib arm, with a hazard ratio of 0.61, for which the 95% confidence interval was 0.47 to 0.79. The median follow-up here was 36.8 months (the 95% confidence interval was 35.9 to 37.5), and the number of patients with events observed in each arm was 105 in 192, or 55%, with BRAFTOVI and MEKTOVI and 127 in 191, or 67% with vemurafenib. Remember, the median represents a single point on the Kaplan-Meier curve. It's important to consider the entire curve when evaluating overall survival.

Dr Caudle:
Can you tell us any more about the updated OS analysis?

Dr Funchain:
In the updated analysis, the median overall survival was, again, 33.6 months for BRAFTOVI and MEKTOVI (the 95% confidence interval was 24.4 to 39.2) versus again, 16.9 months for vemurafenib (the 95% confidence interval was 14.0 to 24.5). A hazard ratio of 0.61 (with a 95% confidence interval of 0.48 to 0.78) was observed. Data collection for the trial is still ongoing. The landmark overall survival data as is. The median follow-up was 60.6 months (with a 95% confidence interval of 59.8 to 61.3) with data cutoff in November of 2019. The number of events observed in each arm was 125 out of 192, or 65%, with BRAFTOVI and MEKTOVI and 145 out of 191, or 76%, with vemurafenib.

The updated overall survival analysis showed 39% of patients in the BRAFTOVI and MEKTOVI arm (the 95% confidence interval was 32 to 46) were alive at 4 years versus 26% for vemurafenib (the 95% confidence interval was 19 to 32). In the BRAFTOVI and MEKTOVI arm versus the vemurafenib arm, 1-year overall survival was 76% (the 95% confidence interval was 69 to 81) versus 63% (the 95% confidence interval was 56 to 70); 2-year overall survival was 58% (the 95% confidence interval was 50 to 64) versus 43% (the 95% confidence interval was 36 to 50); 3-year overall survival was 47% (the 95% confidence interval was 39 to 53) versus 31% (the 95% confidence interval was 25 to 38), respectively. The trial is ongoing and the landmark overall survival data are as is.

I do want to make the point that the hierarchical testing procedure prevented formal assessment of the statistical significance of overall survival, so these overall survival results should be considered descriptive in nature only. This information should not be used to make comparisons between treatment arms.

Dr Caudle:
Thank you for sharing that updated overall survival analysis where we see that 39% of patients were still alive at 4 years.

Announcer:
Here's some additional Safety Information for BRAFTOVI and MEKTOVI.

Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur.

Hemorrhage: Major hemorrhagic events can occur.

Please listen to additional Important Safety Information later in this podcast or view Important Safety Information at braftovimektovihcp.com.

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Dr Caudle:
What were the other additional efficacy outcome measures in the study?

Dr Funchain:
The study also assessed the additional efficacy outcome measures of the combination, and we see that patients treated with BRAFTOVI and MEKTOVI had higher response rates and more durable responses compared to those treated with vemurafenib.

The overall response rate for BRAFTOVI and MEKTOVI was 63% (the 95% confidence interval was 56 to 70) versus 40% for vemurafenib (the 95% confidence interval was 33 to 48%). These responses were determined by a blinded independent central review. BRAFTOVI and MEKTOVI had a complete response rate of 8% and a partial response rate of 55% versus a complete response rate of 6% and a partial response rate of 35% for vemurafenib. Please note that the overall response rate was assessed at the time of the primary progression-free survival analysis. This was a prespecified endpoint assessed by a blinded independent central review and used RECIST version 1.1, but these values do not evaluate statistical significance.

Dr Caudle:
And what was the duration of response?

Dr Funchain:
In the central review, the median duration of response for BRAFTOVI and MEKTOVI was 16.6 months (where the 95% confidence interval was 12.2 to 20.4) versus 12.3 months for vemurafenib (where the 95% confidence interval was 6.9 to 16.9). Duration of response was assessed at the time of the primary PFS analysis. As with overall response rate, this prespecified endpoint was assessed by a blinded independent central review using RECIST version 1.1, but does not evaluate statistical significance.

Dr Caudle:
Based on these data, it looks like BRAFTOVI and MEKTOVI may help patients achieve high and durable responses.

Announcer:
Here's some additional Safety Information for BRAFTOVI and MEKTOVI.

Serous retinopathy, retinal vein occlusion, or RVO, and uveitis have occurred. Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances.

Dr Caudle:
Let's talk about the adverse reactions seen in the trial.

Dr Funchain:
Yes, these are some of the most important details when it comes to choosing therapies. The most common adverse reactions of any grade that occurred in 25% or more patients in the BRAFTOVI and MEKTOVI arm were the following: comparing BRAFTOVI and MEKTOVI to vemurafenib, fatigue occurred in 43% of patients versus 46% in the vemurafenib arm; 41% of patients experienced nausea versus 34%; 36% had diarrhea versus 34%; and 30% had vomiting versus 16%. Abdominal pain was seen in 28% of patients compared to 16% of patients, and arthralgia was seen in 26% versus 46%, respectively.

Please review the complete table of adverse drug reactions for the COLUMBUS trial and recommended dosage reductions and modifications for adverse reactions in the full Prescribing Information for BRAFTOVI and the full Prescribing Information for MEKTOVI.

In terms of laboratory abnormalities, the most common of any grade that occurred in 25% or more patients in the BRAFTOVI and MEKTOVI arm were increased creatinine in 93% of patients in the combination arm versus 92% of patients in the vemurafenib arm; 58% of patients had increased creatine phosphokinase, or CPK, versus 3.8%; 45% had increased gamma glutamyl transferase, or GGT, versus 34%; 36% had anemia versus 34%; 29% had increased ALT versus 27%; 28% had hyperglycemia versus 20%; and 21% had increased alkaline phosphatase versus 35%.

Again, please see additional information on treatment-emergent lab abnormalities in the full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI.

5% of patients in the BRAFTOVI and MEKTOVI arm permanently discontinued treatment due to adverse reactions. The most common adverse reactions resulting in permanent discontinuation were hemorrhage in 2% of patients and headache in 1% of patients. Again, please review the recommended dosing reductions and modifications for adverse reactions in the full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI.

Dr Caudle:
Let's discuss adverse reactions leading to dose interruptions.

Dr Funchain:
Sure. Adverse reactions leading to dose interruptions of BRAFTOVI happened in 30% of patients. The most common were nausea and vomiting, both at 7%, and pyrexia at 4%. Adverse reactions leading to dose interruptions of MEKTOVI happened in 33% of patients. The most common were left ventricular dysfunction at 6% and serous retinopathy at 5%.

Dr Caudle:
I would like to discuss pyrexia in more detail. Pyrexia is an adverse reaction that can cause treatment interruptions and permanent discontinuation. Approximately 1 in 5 patients receiving BRAFTOVI and MEKTOVI experience pyrexia.

Dr Funchain:
What we saw in the trial was that the rates of pyrexia in patients who received BRAFTOVI and MEKTOVI versus vemurafenib were 18 versus 30% for all grades, and 4 versus 0% for Grades 3 and 4. By grade, we saw that 12% had Grade 1 pyrexia, 2% Grade 2, and 4% Grade 3. This meant that 82% of patients did not experience pyrexia.

In the trial, 4% of patients in the BRAFTOVI and MEKTOVI arm had dose interruptions of BRAFTOVI due to pyrexia, and less than 1% of patients who received BRAFTOVI and MEKTOVI discontinued treatment due to pyrexia.

Announcer:
Here's some additional Safety Information for BRAFTOVI and MEKTOVI.

Interstitial Lung Disease, or ILD: Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD.

Hepatotoxicity: Monitor liver function tests before and during treatment and as clinically indicated.

Dr Funchain:
So, let me go over some additional helpful prescribing information. First, BRAFTOVI and MEKTOVI is an orally administered treatment combination that can be taken with or without food, so there's no need to fast. Second, avoid coadministration of strong or moderate CYP3A4 inhibitors, including grapefruit juice and inducers, with BRAFTOVI. Third, both treatments are kept at room temperature, so there's no refrigeration requirement. Fourth, both BRAFTOVI and MEKTOVI are intended to be taken every day without any breaks in treatment. Fifth, and this is crucial, before starting treatment, confirm the presence of a *BRAF* V600E– or K–mutation by an FDA-approved test. As for dosing, another key topic, the recommended dose is 450 mg of BRAFTOVI once a day in combination with 45 mg of MEKTOVI, followed by a second dose of MEKTOVI 45 mg 12 hours later. Treatment with BRAFTOVI and MEKTOVI should be continued until disease progression or unacceptable toxicity. For both BRAFTOVI and MEKTOVI, there is no need for a new prescription if dose adjustments are needed. Patients can be instructed by their care team to reduce dose and, if needed, take fewer pills.

Dose adjustments for both BRAFTOVI and MEKTOVI are recommended for adverse reactions. Please review the recommended dosing reductions and modifications for adverse reactions in the dosing administration section in the full Prescribing Information for BRAFTOVI and MEKTOVI.

Announcer:
Here's some additional Safety Information for BRAFTOVI and MEKTOVI.

Rhabdomyolysis: Monitor creatine phosphokinase and creatinine periodically and as clinically indicated.

QTc Prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold BRAFTOVI for QTc of 500 ms or greater.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective non-hormonal method of contraception.

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 patients treated with 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.

Dr Caudle:
I think it's clear from the Phase 3 trial results that BRAFTOVI and MEKTOVI is a compelling treatment combination for adult patients with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma.

Dr Funchain:
What's important to understand, the takeaways, about BRAFTOVI and MEKTOVI is the more-than-double median progression-free survival versus control, the combination's safety profile, and dosing attributes. Together, these three things are what make BRAFTOVI and MEKTOVI a compelling option to consider for adults with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma. In the NCCN Guidelines, encorafenib and binimetinib are a Category 1 recommendation as a first-line systemic therapy option for patients with metastatic or unresectable cutaneous melanoma with a *BRAF* V600–activating mutation.

Dr Caudle:
That's great insight for us to consider. Let's review some additional Important Safety Information.

Announcer:
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 using an FDA-approved test 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 left ventricular ejection fraction (LVEF), by echocardiogram or multi-gated acquisition (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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

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. Retinal vein occlusion (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 receiving MEKTOVI with BRAFTOVI (n=690), 1 patient experienced RVO (0.1%). 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

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 who received BRAFTOVI in combination with MEKTOVI. 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 and 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 patients treated with 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) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). 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%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

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.

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.

Dr Caudle:

Join us for our next episode on *BRAF* V600E– or K–mutant unresectable or metastatic melanoma. Please see the full Prescribing Information and Medication Guide for BRAFTOVI and full Prescribing Information and Patient Information for MEKTOVI. You can also access the full Prescribing Information for these products at braftovimektovihcp.com.

I'd like to thank my guest, Dr Pauline Funchain, for helping us better understand this combination treatment option. Dr Funchain, it was great speaking with you today.

Dr Funchain:

Thank you for having me.

Dr Caudle:

I'm Dr Jennifer Caudle, thank you for listening.

Announcer:

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