Transcript Details
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Hypothetical Patient Case Study for a Treatment Regimen for Adults With *BRAF* V600E/K–Mutant Unresectable or Metastatic Melanoma

Announcer:
Welcome to ReachMD. This medical industry feature is titled "Hypothetical patient case study for a treatment regimen for adults with *BRAF* V600E/K–mutant unresectable or metastatic melanoma." This podcast is for US healthcare professionals only. A note to our listeners that this presentation has been created and paid for by Pfizer. The information is intended for healthcare professionals in the United States. This promotional activity is not certified for continuing medical education.

Dr Caudle:
Welcome to ReachMD. I am your host, Dr Jennifer Caudle. On this episode, we're going to discuss a treatment option for adult patients with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma. Joining me today is Dr Daniel Johnson. Dr Johnson, welcome to the program.

Dr Johnson:
Thank you so much for having me.

Dr Caudle:
Well, it's great to have you here today. To start, can you give us a brief overview of your experience with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma?

Dr Johnson:
Sure. As a skin cancer specialist, I often see adult patients with unresectable or metastatic melanoma. I work at a large institution where I see about five patients a month with unresectable or metastatic melanoma that have a *BRAF* V600E or K mutation.

Dr Caudle:
With that in mind, today we are going to discuss a hypothetical patient with a *BRAF* V600E– or K–mutant unresectable or metastatic melanoma an oncologist might see in their practice who could be appropriate for treatment with BRAFTOVI and MEKTOVI. Before we start, let's review the indications and warnings for these treatment options.

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 on the ReachMD landing page for this podcast. You can also access the full Prescribing Information for these products at braftovimektovihcp.com.

Dr Caudle:
Dr Johnson, can you give us an example of an adult patient with *BRAF* V600E– or K–mutant unresectable or metastatic melanoma you might see in your practice?

Dr Johnson:
Sure. Before we begin, I'd like to note that this is a case study discussion of a hypothetical patient, whose description is built on the baseline characteristics of patients that were enrolled to the COLUMBUS trial. So, the COLUMBUS trial studied the use of BRAFTOVI and MEKTOVI in adults with unresectable or metastatic melanoma with a *BRAF* V600E or K mutation. For this example, let's discuss Larry, a 56-year-old teacher who is the sole caregiver to his parents.

Larry first presented to the dermatologist with an ulcerated nevus on his back shoulder, and a shave biopsy was done, revealing melanoma. A CT scan revealed multiple pulmonary metastases, and he was then referred to an oncologist for further evaluation. We determined Larry's ECOG performance status to be 0, and he had an LDH of 170 units per liter, which was within normal limits.

An FDA-approved test revealed that he had metastatic melanoma with a *BRAF* V600E mutation.

Dr Caudle:
And can you share with us some of the characteristics of the patients seen in the COLUMBUS trial?

Dr Johnson:
So, to give you some background, the COLUMBUS trial, which studied the efficacy and safety of BRAFTOVI and MEKTOVI in adults with unresectable or metastatic melanoma with a *BRAF* V600E or K mutation, included patients aged 20 to 89, and the median age for patients was 56 years in the BRAFTOVI and MEKTOVI arm.

72% of the patients had an ECOG performance status of 0. 24% of patients had 1 organ with metastases, and 72% of patients had an LDH level below the upper limit of normal. More than 90% of patients received BRAFTOVI and MEKTOVI as their first-line treatment.

Dr Caudle:
Thanks for sharing that with us, Dr Johnson. Before we dive more into this case, let's review some additional Safety Information for BRAFTOVI and MEKTOVI.

Announcer:
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 1 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:
After Larry was diagnosed with metastatic melanoma with a *BRAF* V600E mutation, what therapy was ultimately chosen for him?

Dr Johnson:
So, when choosing front-line or second-line treatments for adults with unresectable or metastatic melanoma with a *BRAF* V600E or K mutation, there's many approved treatment options, which is wonderful for patients with metastatic melanoma.

I would consider dosing and administration of these different treatments, along with patient factors, such as comorbidities, disease burden, and symptomatology from the cancer, to help with my treatment choices. Because of this, BRAFTOVI and MEKTOVI could be an appropriate treatment option for Larry. The recommended dose for this treatment combination is 450 mg of BRAFTOVI once a day in combination with 45 mg of MEKTOVI twice daily.

Dr Caudle:
Was Larry's response to treatment similar to what was seen in the COLUMBUS trial?

Dr Johnson:
Larry's results were similar to those reported in the COLUMBUS trial. And before we get 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 *BRAF* V600E and/or K mutation. Patients were randomized to one of three arms: BRAFTOVI and MEKTOVI, that arm had 192 patients, or vemurafenib with 191 patients, or BRAFTOVI alone, 194 patients. Please note that BRAFTOVI monotherapy is not approved for use by the FDA.

Prior use of BRAF or MEK inhibitors was prohibited, 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 AJCC staging, 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 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 central review.

In the COLUMBUS trial, the median progression-free survival was 14.9 months for patients receiving BRAFTOVI and MEKTOVI, where the 95% confidence interval was 11 to 18.5 months, versus 7.3 months seen with vemurafenib, and 95% confidence interval was 5.6 to 8.2 months. The hazard ratio was 0.54, and the 95% confidence interval was 0.41 to 0.71, with a *P* value of less than 0.0001. And in the primary analysis of progression-free survival with median follow-up of 16.6 months, the number of events observed in each arm was 98 events out of 192 patients, or 51%, with the combination of BRAFTOVI and MEKTOVI, and 106 events out of 191 patients, or 55%, with vemurafenib.

In an updated non-prespecified analysis of progression-free survival by blinded independent central review with a median follow-up time of 40.8 months for progression-free survival, data cutoff of November 2019, median PFS was the same as previously reported. The hazard ratio was 0.51 with 95% confidence interval of 0.39 to 0.66. And the number of events observed in each arm was 119 out of 192 patients, or 62%, with BRAFTOVI and MEKTOVI, and 119 out of 191 patients, or 62%, with vemurafenib.

It's important to note that the updated progression-free survival results are descriptive. No formal statistical testing was performed, and therefore no conclusions can be drawn.

63% of patients who received BRAFTOVI and MEKTOVI in the COLUMBUS trial responded to therapy. The 95% confidence interval was 56 to 70, versus 40% for vemurafenib, 95% confidence interval was 33 to 48.

Of those patients who received BRAFTOVI and MEKTOVI and responded, 55% had a partial response and 8% had a complete response. It’s important to note that overall response rates were assessed at the time of the primary progression-free survival analysis. This prespecified endpoint was assessed by a blinded independent central review using RECIST version 1.1, but does not evaluate statistical significance. Patients in the COLUMBUS trial also had durable responses, where the median duration of response was 16.6 months for BRAFTOVI and MEKTOVI, the 95% confidence interval was 12.2 to 20.4 months, versus 12.3 months for vemurafenib, 95% confidence interval was 6.9 to 16.9. Duration of response was assessed at the time of the primary progression-free survival analysis. This prespecified endpoint was assessed by a blinded independent central review using RECIST version 1.1, but does not evaluate statistical significance.

In the primary analysis, the median overall survival was 33.6 months for BRAFTOVI and MEKTOVI, 95% confidence interval was 24.4 to 39.2, versus 16.9 months for vemurafenib, 95% confidence interval was 14 to 24.5 months, with a hazard ratio of 0.61. The 95% confidence interval was 0.47 to 0.79.

It's important to note that in the trial, formal assessment of the statistical significance of overall survival was not performed in the primary and updated analyses. The overall survival results are descriptive, and therefore, no conclusion can be drawn.

The median represents a single point in time. It’s important to consider the entire Kaplan-Meier curve when evaluating overall survival. The median follow-up for the primary analysis was 36.8 months, 95% confidence interval 35.9 to 37.5 months. And the number of patients with events observed in each arm was 105 out of 192 patients, 55% with BRAFTOVI and MEKTOVI, and 127 out of 191, or 67%, with vemurafenib.

The most common adverse reactions of any grade in the BRAFTOVI and MEKTOVI arm that occurred in 25% or more patients was fatigue, with 43% of patients in the combination arm versus 46% of patients in the vemurafenib arm. Also, 41% of patients experienced nausea versus 34%; 36% had diarrhea versus 34%; and 30% had vomiting versus 16%. 28% of patients experienced abdominal pain compared to 16%, and arthralgia was seen in 26% of patients 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 MEKTOVI.

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:
Please see the full Prescribing Information and Medication Guide for BRAFTOVI, and full Prescribing Information and Patient Information for MEKTOVI on the ReachMD landing page for this podcast. You can also access the full Prescribing Information for these

products at braftovimektovihcp.com.

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

Dr Johnson:
It was a pleasure.

Dr Caudle:
I'm Dr Jennifer Caudle, and thanks for listening.

Announcer:
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