Transcript Details
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Reconsidering Your Approach for Patients With Low Tumor Burden in BRAF Mutation-Positive Metastatic Melanoma

Announcer:
Welcome to ReachMD. This medical industry feature titled, *Reconsidering Your Approach for Patients With Low Tumor Burden: Why Targeted Treatment With TAFINLAR® (dabrafenib) capsules plus MEKINIST® (trametinib) tablets May Be Appropriate for Patients With BRAF Mutation-Positive Metastatic Melanoma* is sponsored by Novartis.

Our medical expert is Dr George Ansstas, Associate Professor of Medicine in the Division of Medical Oncology at The Washington University School of Medicine in Saint Louis, Missouri.

Your host for this program is Dr Matt Birnholz.

Dr Birnholz:
Among patients who have *BRAF* mutation-positive metastatic melanoma, there's a subpopulation with low tumor burden. So on today's program, we'll explore the clinical data for TAFINLAR plus MEKINIST and discuss how the results of these trials demonstrate the potential benefit of this combination therapy in patients with low tumor burden.

This is ReachMD. I'm Dr Matt Birnholz. Joining me today is Dr George Ansstas. Dr Ansstas is Associate Professor of Medicine in the Division of Medical Oncology at The Washington University School of Medicine in Saint Louis, Missouri.

Dr Birnholz:
Dr Ansstas, welcome to the program.

Dr Ansstas:
Thank you so much for having me.

Dr Birnholz:
Great to have you with us.

Dr Birnholz:
Well, before we get started, let's review some information about TAFINLAR plus MEKINIST, including indication, limitation of use, and safety.

Announcer:
TAFINLAR, in combination with MEKINIST, is indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by a US Food and Drug Administration (FDA)-approved test.

Limitation of Use: TAFINLAR is not indicated for the treatment of patients with wild-type *BRAF* melanoma.

Confirm the presence of *BRAF* V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and MEKINIST. Information on FDA-approved tests for the detection of *BRAF* V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

TAFINLAR and MEKINIST can cause serious adverse reactions. These include new primary malignancies, tumor promotion in *BRAF* wild-type tumors, hemorrhage, colitis and gastrointestinal perforation, venous thromboembolic events, cardiomyopathy, ocular toxicities, interstitial lung disease or pneumonitis, serious febrile reactions, serious skin toxicities, hyperglycemia, glucose-6-phosphate

dehydrogenase deficiency, and embryo-fetal toxicity.

Additional important safety information can be found immediately following this discussion. Please see the full prescribing information for TAFINLAR and full prescribing information for MEKINIST.

Dr Birnholz:
So to start us off, Dr Ansstas, in the two clinical trials evaluating treatment with TAFINLAR in combination with MEKINIST, the patients with *BRAF* mutation-positive metastatic melanoma had a wide range of characteristics, including low tumor burden, but before we get deep into the data, can you just define the low tumor burden population for us?

Dr Ansstas:
Sure. In the pooled analysis of COMBI-d and COMBI-v, which were the two clinical trials with TAFINLAR plus MEKINIST in metastatic melanoma the patient population was subsequently identified that, for the purposes of this discussion, has been termed low tumor burden. This patient population consisted of patients who had fewer than three organ sites of metastases at baseline and normal lactate dehydrogenase, or LDH, which was defined as less than or equal to the upper limit of normal. It is important to note that elevated LDH levels have been shown to be a predictor of poor outcomes in patients with advanced melanoma. The subset of patients evaluated in the clinical trials is representative of a key population that could potentially benefit from treatment with TAFINLAR plus MEKINIST.

Dr Birnholz:
And turning to the clinical trials now, can you review some of the key findings of these studies?

Dr Ansstas:
Yes, but first let's look at the primary analyses for both trials. TAFINLAR plus MEKINIST was studied as first-line in patients with *BRAF* V600E and K mutations in two phase III clinical trials.

Dr Ansstas:
COMBI-d was a double-blind randomized trial versus TAFINLAR alone. Primary endpoint was investigator-assessed progression-free survival, or PFS. The secondary endpoints were overall survival, duration of response, overall response rate, and safety. The data cutoff date was December 10, 2018 for the five-year analysis.

Dr Ansstas:
Median PFS as the primary analysis for the TAFINLAR plus MEKINIST arm was 9.3 months versus 8.8 months for TAFINLAR plus placebo arm.

Dr Ansstas:
On the other hand, COMBI-v trial was an open-label randomized trial versus vemurafenib. Primary endpoint was overall survival, or OS. The secondary endpoints were progression-free survival, duration of response, overall response rate, and safety. The data cutoff was October 8, 2018, for the five-year analysis.

Dr Ansstas:
Median OS at the interim analysis for TAFINLAR plus MEKINIST arm was not reached versus 17.2 months for the vemurafenib arm.

Dr Birnholz:
And as I understand it, Dr Ansstas, an updated five-year pooled analysis of both studies was performed, so can you tell us more about that?

Dr Ansstas:
The five-year pooled analysis of COMBI-d and COMBI-v included 563 treatment-naïve patients with *BRAF* V600E and K mutant metastatic melanoma who were randomized to receive TAFINLAR 150 milligrams twice daily plus MEKINIST 2 milligrams once daily. The median follow-up was 22 months. The range, in fact, was between 0 to 76 months. Results at five years were not pre-specified and are observational in nature. As such, there was no pre-specified statistical procedure controlling for type 1 error.

Dr Birnholz:
So delving in deeper, Dr Ansstas, could you go into a little bit more detail on the specific patient subpopulation of this study that was characterized as having low tumor burden?

Dr Ansstas:
Certainly. In this pooled analysis of COMBI-d and COMBI-v at five years, 38% of patients had low tumor burden. The numbers were 216 patients out of 563 patients. In the baseline assessment of the intent-to-treat population at five years, there was 51% of patients who had less than three sites of metastases and 65% who had LDH less than or equal to the upper limit of normal.

Dr Birnholz:
And the data in the five-year pooled analysis also showed long-term results of patients with low tumor burden. So, can you talk a bit about those results?

Dr Ansstas:
Certainly. The survival outcomes in these patients showed that more than half of patients – in fact, 55% with low tumor burden – were alive at five years. In addition, as mentioned earlier, elevated LDH levels have been shown to be a predictor of poor outcomes in patients with advanced melanoma. It is unknown whether data suggesting better outcomes in the subgroup of patients with normal LDH at baseline compared with all patients treated with TAFINLAR plus MEKINIST are results of underlying disease status and prognosis or if this is a treatment effect. Further prospective controlled studies are of need, and it's necessary to determine whether baseline LDH is a predictor of PFS and OS in patients treated with TAFINLAR and MEKINIST.

Dr Birnholz:
For those just joining us, this is ReachMD. I'm Dr Birnholz and joining me to talk about trial results with TAFINLAR plus MEKINIST in patients with *BRAF* mutation-positive metastatic melanoma who had low tumor burden is Dr George Ansstas.

Dr Birnholz:
So, Dr Ansstas, based on the overall survival data you just discussed, what should our audience know about response rates in this analysis?

Dr Ansstas:
Response rates, nearly one in five patients had a complete response in the intent-to-treat pooled population at five years.

In the pooled five-year analysis of COMBI-d and COMBI-v, complete response was 19%, and partial response was 49%. The five-year overall survival was 71% for patients with a complete response. In the primary analysis of COMBI-d, complete response in the TAFINLAR plus MEKINIST arm was 10%; the partial response was 56%. In the TAFINLAR monotherapy arm, complete response was 8%, and partial response was 42%. In the interim analysis of COMBI-v, complete response in the TAFINLAR plus MEKINIST arm was 13%, partial response was 51%, while in the vemurafenib arm complete response was 8%, and partial response was 43%.

It should be noted that out of all patients who had complete response in the five-year analysis, 90% had LDH less than or equal to the upper limit of normal, and 84% had fewer than three organ sites of metastases at baseline. This supports the potential therapeutic benefit of TAFINLAR plus MEKINIST in patients with low tumor burden. One more note about the five-year pooled analysis, adverse events regardless of the cause were reported in 548 patients out of 559 patients, or 98% of patients.

No unexpected adverse events were reported with extended follow-up. The most common adverse events occurring in at least 20% of patients taking TAFINLAR plus MEKINIST in this pooled analysis were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, vomiting, arthralgia, hypertension, and cough.

Dr Birnholz:
Thanks for sharing those insights, Dr Ansstas. Now before we close, are there any key takeaways you'd like to leave with our audience?

Dr Ansstas:
Yeah, definitely, Matt, there are many important things to learn from these trials. TAFINLAR plus MEKINIST was studied in patients with low tumor burden, which was defined as normal LDH less than or equal to the upper limit of normal and fewer than three organ sites of metastases at baseline.

Dr Ansstas:
In the pooled analysis of COMBI-d and COMBI-v at five years, 38% of these patients had low tumor burden. More than half of these patients with low tumor burden were alive at five years, in fact, was 55% of these patients who stayed alive at five years. Of patients who achieved a complete response in the intent-to-treat population, 90% had normal LDH, 84% of these patients had less than three organ sites of metastases, and the overall survival at five years was 71%. There were no new safety signals in the five-year pooled analysis. With these results in mind, we can say that, TAFINLAR plus MEKINIST may be an appropriate treatment option in patients with *BRAF* mutation-positive unresectable or metastatic melanoma with low tumor burden.

Dr Birnholz:
Well, you've certainly given us a lot to consider regarding the treatment of *BRAF* mutation-positive metastatic melanoma. I very much want to thank you, Dr Ansstas, for joining me today.

Dr Ansstas:

Thank you so much for having me.

Dr Birnholz:
I'm Dr Matt Birnholz. Please stay with us for additional important safety information.

Important Safety Information

New Primary Malignancies.

Cutaneous Malignancies

Across clinical trials of TAFINLAR® (dabrafenib) capsules administered with MEKINIST® (trametinib) tablets ("the combination"), the incidence of cutaneous squamous cell carcinomas (cuSCCs), including keratoacanthomas, occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and <1% of patients, respectively.

Perform dermatologic evaluations prior to initiation of the combination, every 2 months while on therapy, and for up to 6 months following discontinuation.

Noncutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of monomeric G protein (RAS) through mutation or other mechanisms. Across clinical trials of TAFINLAR monotherapy and the combination, noncutaneous malignancies occurred in 1% of patients.

Monitor patients receiving the combination for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation–positive noncutaneous malignancies. No dose modification is required for MEKINIST in patients who develop noncutaneous malignancies.

Tumor Promotion in *BRAF* Wild-type Tumors. In vitro experiments have demonstrated paradoxical activation of mitogen-activated protein kinase (MAPK) signaling and increased cell proliferation in *BRAF* wild-type cells that are exposed to *BRAF* inhibitors. Confirm evidence of *BRAF* V600E or V600K mutation status prior to initiation of therapy.

Hemorrhage. Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur with the combination. Fatal cases have been reported.

Across clinical trials of the combination, hemorrhagic events occurred in 17% of patients. Gastrointestinal hemorrhage occurred in 3% of patients who received the combination. Intracranial hemorrhage occurred in 0.6% of patients who received the combination. Fatal hemorrhage occurred in 0.5% of patients who received the combination. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

Permanently discontinue TAFINLAR for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for grade 3 hemorrhagic events; if improved, resume at the next lower dose level. Permanently discontinue MEKINIST for all grade 4 hemorrhagic events and for any grade 3 hemorrhagic events that do not improve. Withhold MEKINIST for grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. Across clinical trials of the combination, colitis occurred in <1% of patients and gastrointestinal perforation occurred in <1% of patients. Monitor patients closely for colitis and gastrointestinal perforations.

Venous Thromboembolic Events. Across clinical trials of the combination, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST for life-threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks; if improved, MEKINIST may be resumed at a lower dose level.

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. Across clinical trials of the combination, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of TAFINLAR in 3% and <1% of patients, respectively, and in 3% and <1% of patients receiving MEKINIST, respectively. Cardiomyopathy resolved in 45 of 50 patients who received the combination.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of the combination, 1 month after initiation, and

then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic left ventricular dysfunction of >20% from baseline that is below institutional LLN. Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared to baseline. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the LLN, withhold MEKINIST for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEKINIST. For symptomatic cardiomyopathy or an absolute decrease in LVEF of >20% from baseline that is below LLN, permanently discontinue MEKINIST.

Ocular Toxicities.

Retinal Vein Occlusion (RVO): There were no cases of RVO across clinical trials of the combination. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmologic evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO.

Retinal Pigment Epithelial Detachment (RPED): RPED can occur. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In clinical trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown.

Perform ophthalmologic evaluation periodically, and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmologic evaluation within 3 weeks, resume MEKINIST at the same or a reduced dose. If no improvement after 3 weeks, resume at a reduced dose or permanently discontinue MEKINIST.

Uveitis: Uveitis occurred in 2% of patients treated with the combination across trials. Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.

Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose modification. If severe uveitis (ie, iridocyclitis) or if mild or moderate uveitis does not respond to ocular therapy, withhold TAFINLAR and treat as clinically indicated. Resume TAFINLAR at the same or lower dose if uveitis improves to grade 0 or 1. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of >6 weeks.

Interstitial Lung Disease (ILD)/Pneumonitis. Across clinical trials of the combination, interstitial lung disease or pneumonitis occurred in 1% of patients.

Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis.

Serious Febrile Reactions. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur. The incidence and severity of pyrexia are increased when TAFINLAR is administered with MEKINIST.

Across clinical trials of the combination, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in <1% of patients.

Withhold TAFINLAR for temperature of ≥101.3°F or fever complicated by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Withhold MEKINIST for a temperature of >104°F or fever complicated by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Monitor serum creatinine and other evidence of renal function during and following severe pyrexia. Upon resolution, resume at same or lower dose. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR and/or MEKINIST if the patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (eg, prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications such as hypotension, severe rigors or chills, dehydration, or renal failure, and there is no evidence of active infection.

Serious Skin Toxicities. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with the combination. Across clinical trials of the combination, other serious skin toxicity occurred in <1% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue the combination for SCARs. For other skin toxicities, withhold TAFINLAR and/or MEKINIST for intolerable or severe skin toxicity. Resume TAFINLAR and/or MEKINIST at a lower dose in

patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue TAFINLAR and/or MEKINIST if skin toxicity has not improved within 3 weeks.

Hyperglycemia. Across clinical trials of the combination, 15% of patients with a history of diabetes required more intensive hypoglycemic therapy. Grade 3 and grade 4 hyperglycemia occurred in 2% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate in patients with preexisting diabetes or hyperglycemia. Initiate or optimize antihyperglycemic medications as clinically indicated.

Glucose-6-Phosphate Dehydrogenase Deficiency. TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.

Embryo-fetal Toxicity. TAFINLAR and MEKINIST can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective nonhormonal contraception during treatment, and for 4 months after treatment.

Most Common Adverse Reactions. In the COMBI-d and COMBI-v studies, the most common adverse reactions (≥20%) for the combination were pyrexia (54%), nausea (35%), rash (32%), chills (31%), diarrhea (31%), headache (30%), vomiting (27%), hypertension (26%), arthralgia (25%), peripheral edema (21%), and cough (20%). In the COMBI-d and COMBI-v studies, the most common grade 3 or 4 adverse reactions (≥2%) for the combination were hypertension (11%), pyrexia (5%), and hemorrhage (2%).

Other Clinically Important Adverse Reactions. In the COMBI-d and COMBI-v studies, other clinically important adverse reactions observed in <10% of patients receiving the combination were pancreatitis, panniculitis, bradycardia, and rhabdomyolysis.

Laboratory Abnormalities. In the COMBI-d and COMBI-v studies, treatment-emergent laboratory abnormalities occurring in ≥10% of patients receiving the combination were hyperglycemia (60%), increased aspartate aminotransferase (AST) (59%), increased blood alkaline phosphatase (49%), increased alanine aminotransferase (ALT) (48%), hypoalbuminemia (48%), neutropenia (46%),anemia (43%), hypophosphatemia (38%), lymphopenia (32%), hyponatremia (25%), and thrombocytopenia (21%).

Please see full Prescribing Information for TAFINLAR and full Prescribing Information for MEKINIST.

Announcer:
If you missed any part of this discussion, visit reach-m-d-dot-com-slash-b-raf-low-tumor-burden. This is ReachMD. Be part of the knowledge.

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