Transcript Details
This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/braf-mutations--role-targeted-therapy-patients-stage-III-or-IV-melanoma/11495/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Testing for BRAF Mutations and the Role of Targeted Therapy in Patients With Stage III or IV Melanoma

Announcer:
Welcome to ReachMD. This medical industry feature on "Testing for *BRAF* Mutations and the Role of Targeted Therapy in Patients with *BRAF*+ Stage III or IV Melanoma" is sponsored by Novartis.

Our medical expert is Dr Brent Hanks, Assistant Professor of Pharmacology and Cancer Biology at Duke University Medical Center in Durham, North Carolina.

Your host for this program is Dr Jennifer Caudle.

Dr Caudle:
Approximately half of all patients with melanoma harbor *BRAF* mutations and the prognostic implications can't be overlooked. On today's program we'll explore the evidence supporting mutation testing in *BRAF* positive stage III or IV melanoma and how this information can inform the use of targeted treatment options such as TAFINLAR plus MEKINIST. Joining me in this episode of ReachMD is Dr Brent Hanks.

Dr Caudle:
Dr Hanks, welcome to the program.

Dr Hanks:
Thanks very much for having me.

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

Announcer:
TAFINLAR, or dabrafenib in combination with MEKINIST, or trametinib, is indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test.

TAFINLAR, in combination with MEKINIST, is indicated for the adjuvant treatment of patients with melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. Limitation of Use: TAFINLAR is not indicated for the treatment of patients with wildtype *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.

© 2021 ReachMD

Dr Caudle:
So, to start us off, Dr Hanks, can you give us a brief overview of why testing for *BRAF* mutation status is important for patients with *BRAF* positive stage III or stage IV melanoma?

Dr Hanks:
Absolutely. So, *BRAF* mutations are quite common in patients with melanoma.

Dr Hanks:
Approximately one-half or 50% of all cutaneous melanomas harbor a *BRAF* mutation. In addition, the *BRAF* mutation may also be prognostic in that *BRAF* mutated melanomas may be associated with a higher risk of disease relapse as well as a shorter overall survival. So, we typically test all of our stage III or IV melanoma patients for the *BRAF* mutation.

Dr Caudle:
Excellent. And what clinical evidence supports this prognosis of worse outcomes for patients with *BRAF* mutation positive melanoma?

Dr Hanks:
Well, as we saw in a study published by Georgina Long and colleagues in Journal of Clinical Oncology in 2011, they showed that melanomas that harbor *BRAF* mutations were associated with worse median overall survival at the time of their initial diagnosis of distant metastatic disease.

Dr Hanks:
This particular study was comprised of 197 patients, 11 of whom had unresectable stage IIIC melanoma, while 186 had stage IV melanoma, and of these, 102 were wild type for the *BRAF* gene, or unmutated and 95 had *BRAF* mutations. So, what was interesting in the study is that those *BRAF* wild type melanomas had a much longer median overall survival, at the time of their initial diagnosis of metastatic disease, at 46 months versus only 11 months for patients with *BRAF* mutated melanoma. This was found to be statistically significant. Interestingly, *BRAF* mutations have also been associated with, increased, or higher risk of disease relapse in patients with stage IIIC or stage IIIB melanoma.

Dr Caudle:
Can you provide us with some clinical support for the higher risk of relapse in these patients?

Dr Hanks:
Absolutely. So, in a prospective study comprised of 134 patients, in this case with stage IIIB and stage IIIC melanoma, who also underwent a lymph node resection procedure, without neoadjuvant therapy, these patients were comprised of 67, melanomas that were found to be wild type for the *BRAF* gene, 57 actually harbored *BRAF* mutations while 10, failed mutation testing. And what was really interesting is the results – the three-year post-surgical relapse rate was 77% for *BRAF* mutated melanoma while it was only 54% for *BRAF* wild type melanomas. And this was also found to be statistically significant.

Dr Caudle:
For those of you who are just joining us, this is ReachMD, and I'm your host, Dr Jennifer Caudle. And joining me to talk about *BRAF* mutation status in patients with stage III or IV melanoma is Dr Hanks.

Dr Caudle:
Given the potential impact of *BRAF* mutations on survival and relapse rates in patients with melanoma, what should we know about this mutation at the molecular level and its role in melanoma development?

Dr Hanks:
So, *BRAF* mutations actually occur quite early in the development of melanomas and they're considered driver mutations in that once the mutation develops, it causes constitutive activity of the *BRAF* protein that leads to activation of downstream kinases MEK1 and MEK2 which in turn activates ERK. This in turn promotes gene transcription and drives cellular proliferation and ultimately tumor growth.

Dr Caudle:
So, with this melanoma signaling pathway in mind, let's turn to therapeutic considerations towards disrupting that pathway. And if we look at TAFINLAR in combination with MEKINIST as a targeted therapy option for patients with *BRAF* positive stage III or IV melanoma, what is this combination targeting, specifically within the MAP kinase pathway?

Dr Hanks:
Interesting question, Dr Caudle. So, the combination of TAFINLAR and MEKINIST actually targets two distinct points along the MAP kinase pathway, including the *BRAF* kinase as well as the MEK1 and MEK2 kinases. Compared with either drug alone, TAFINLAR in combination with MEKINIST results in a greater growth inhibition of *BRAF* mutated melanoma of cell lines in vitro as well as prolonged

© 2021 ReachMD

inhibition of tumor growth of *BRAF* mutated melanomas in vivo.

Dr Caudle:
Thank you. Now, Dr Hanks, would you tell us a bit more about TAFINLAR in combination with MEKINIST?

Dr Hanks:
Sure. Absolutely. So, TAFINLAR and MEKINIST are approved in combination for treatment of patients with unresectable or metastatic melanoma that harbor *BRAF* V600E or V600K mutations as detected by an FDA-approved test as well as in the adjuvant treatment setting for patients with melanoma that harbor *BRAF* V600E or V600K mutations with lymph node involvement following previous resection. The combination has been studied in more than 1,000 patients that harbor *BRAF* mutations in four pivotal trials across two melanoma indications. The combination is the only oral targeted therapy approved for the management of *BRAF* mutative positive melanoma in the adjuvant setting as well as the only targeted combination therapy with five-year Phase 3 data in patients with *BRAF* mutated stage III or IV melanoma. Importantly, the combination shows a well-established safety profile and has been approved since 2013.

Dr Caudle:
Before we close, Dr Hanks, are there any takeaways you'd like to leave with our audience today?

Dr Hanks:
Of course. So, to summarize I'd say that testing the *BRAF* mutations is very important in patients with stage III or stage IV metastatic melanoma because this can help guide the management of this patient population. There is some data that also indicates that *BRAF* mutated melanomas are associated with a higher risk of relapse as well as a worse overall survival. The combination treatment with TAFINLAR and MEKINIST actually has two, distinct points along the MAP kinase pathway, including the *BRAF* kinase as well as the MEK1 and MEK2 kinases. So, considering the positive study outcomes and the safety profile of this combination, they suggest that the combination of TAFINLAR and MEKINIST should be considered for the management of patients with *BRAF* mutated stage III or IV metastatic melanoma.

Dr Caudle:
Thank you. Considering that approximately 50% of patients with melanoma harbor *BRAF* mutations based on your earlier comments, I think this reminder about the role of genetic testing to guide treatment decisions is a good closing thought for today's discussion. I'd like to thank my guest, Dr Hanks, for joining me today. Dr Hanks, it was great speaking with you, and thanks to all of you in the audience.

Dr Hanks:
Thanks very much for having me.

Dr Caudle:
Please stay tuned for the full Important Safety Information.

Announcer:

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.

© 2021 ReachMD

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.

© 2021 ReachMD

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%). In the COMBI-AD study, the most common adverse reactions (≥20%) for the combination were pyrexia (63%), fatigue (59%), nausea (40%), headache (39%), rash (37%), chills (37%), diarrhea (33%), vomiting (28%), arthralgia (28%), and myalgia (20%). The most common grade 3 or 4 adverse reactions (≥2%) for the combination were pyrexia (5%) and fatigue (5%).

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. In the COMBI-

© 2021 ReachMD

AD study, other clinically important adverse reactions observed in <20% of patients receiving the combination were blurred vision (6%), decreased ejection fraction (5%), rhabdomyolysis (<1%), and sarcoidosis (<1%).

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%). In the COMBI-AD study, treatment-emergent laboratory abnormalities occurring in ≥20% of patients receiving the combination were hyperglycemia (63%), increased AST (57%), increased ALT (48%), neutropenia (47%), hypophosphatemia (42%), increased blood alkaline phosphatase (38%), lymphopenia (26%), anemia (25%), and hypoalbuminemia (25%).

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 *BRAF* dash testing dash melanoma. This is ReachMD. Be part of the knowledge.

6/21 128398

© 2021 ReachMD