Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/guidance-for-initiating-a-targeted-combination-treatment-for-braf-mutationpositive-stage-iii-or-advanced-melanoma/11831/

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Guidance for Initiating a Targeted Combination Treatment for BRAF Mutation-Positive Stage III or Advanced Melanoma

Announcer:
Welcome to ReachMD. This medical industry feature on *Guidance for Initiating Treatment With TAFINLAR® (dabrafenib) capsules + MEKINIST® (trametinib) tablets for Patients With BRAF Mutation-Positive Stage III or Advanced Melanoma* is sponsored by Novartis.

Our medical experts for today's program are Suzanne McGettigan, MSN, and Grace Cherry, RN, MSN, NP.

Suzanne McGettigan:
Today we would like to discuss screening and monitoring recommendations that are important for your patients with BRAF V600E or V600K mutation–positive stage III or advanced melanoma before and during adjuvant or advanced melanoma treatment with TAFINLAR® (dabrafenib) capsules + MEKINIST® (trametinib) tablets.

Grace Cherry:
Before we get started, let's cover some important information about TAFINLAR + MEKINIST, including indications and limitation of use.

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 wild-type BRAF melanoma.

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.

Please watch this video in its entirety to learn about the full Important Safety Information.

Patient Assessments and Monitoring Prior to and During Treatment With TAFINLAR + MEKINIST.

Grace Cherry:
When treating patients with stage III or metastatic and/or unresectable melanoma, specific tests and assessments are required both prior to initiating treatment with TAFINLAR + MEKINIST and while treatment is ongoing in order to monitor patient health and identify potential adverse reactions. Please note that this is a summary of information for select adverse reactions with a focus on combination therapy use. The full Prescribing Information for each medication should be consulted for full details.

Suzanne McGettigan:
First, let's review the key assessments that are required prior to or during initiation of treatment with TAFINLAR + MEKINIST:

- Confirm evidence of BRAF V600E or V600K mutation status
- Assess left ventricular ejection fraction, or LVEF, by echocardiogram or multigated acquisition, or MUGA, scan
- Verify pregnancy status in women of reproductive potential prior to initiating

- Monitor serum glucose levels in patients with preexisting diabetes or hyperglycemia
- Monitor INR levels in patients receiving warfarin during initiation and discontinuation of TAFINLAR
- Perform a dermatologic evaluation

Grace Cherry:
Once your patients start treatment with TAFINLAR + MEKINIST, it is important to monitor them for certain adverse reactions, including:

- New primary malignancies, both cutaneous and noncutaneous
- Hemorrhage
- Colitis and gastrointestinal perforation
- Thromboembolic events
- Cardiomyopathy
- Ocular toxicities
- Interstitial lung disease or pneumonitis
- Serious febrile reactions
- Serious skin toxicities
- Hyperglycemia (in patients with preexisting diabetes or hyperglycemia)
- Signs of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency
- Drug interactions
- Other select adverse reactions, such as hypertension or diarrhea

Announcer:
TAFINLAR + MEKINIST Dosing.

Grace Cherry:
Prior to starting treatment, discuss the recommended dosing of TAFINLAR and MEKINIST and when each should be administered

- TAFINLAR is taken as 2 75-mg capsules twice a day, 12 hours apart
- MEKINIST is taken as a 2-mg tablet once a day, with either the morning or evening dose of TAFINLAR. MEKINIST must be taken at the same time every day

It is also important to let patients know that

- TAFINLAR and MEKINIST should be taken at least 1 hour before or 2 hours after a meal
- A missed dose of TAFINLAR should not be taken within 6 hours of the next regular dose
- And a missed dose of MEKINIST should not be taken within 12 hours of the next regular dose

Patients undergoing adjuvant therapy following complete resection of stage III melanoma should continue treatment for 12 months or until disease recurrence or unacceptable toxicity occurs.

Patients with unresectable or metastatic melanoma should continue treatment until disease progression or unacceptable toxicity occurs.

Announcer:
TAFINLAR + MEKINIST Storage and Handling.

Suzanne McGettigan:
Make sure patients know that TAFINLAR and MEKINIST have different storage and handling requirements that must be followed closely

- TAFINLAR should be stored at room temperature, which is 68°F to 77°F or 20°C to 25°C
  - o Excursions between 59°F to 86°F or 15°C to 30°C are permitted
- Instruct patients never to open, crush, or break TAFINLAR capsules
- MEKINIST requires refrigeration at temperatures from 36°F to 46°F or 2°C to 8°C
- MEKINIST must be stored in the original bottle and protected from moisture and light. The desiccant contained in the bottle should not be removed and pills should never be transferred to a pill box
- As with all medicine, TAFINLAR and MEKINIST should be kept out of the reach of children

Announcer:
TAFINLAR + MEKINIST Dose Reduction Guidelines.

Grace Cherry:
When patients experience adverse reactions that require dose modification of TAFINLAR and/or MEKINIST, follow the recommended dose reduction guidelines.

For TAFINLAR, the first dose reduction is to 100 mg, twice daily. The second is to 75 mg, twice daily and the third is to 50 mg, twice daily. Permanently discontinue TAFINLAR if patients are unable to tolerate 50 mg, twice daily.

For MEKINIST, the first dose reduction is to 1.5 mg, once daily and the second is to 1 mg, once daily. Permanently discontinue MEKINIST if patients are unable to tolerate 1 mg, once daily.

Suzanne McGettigan:
Thank you for taking the time today to learn about screening and monitoring, as well as dose modification, for patients with BRAF V600E or V600K mutation–positive stage III or advanced melanoma who are being treated with TAFINLAR + MEKINIST.

Grace Cherry:
Remember to view the Important Safety Information at the end of this video.

Important Safety Information

- Across clinical trials of TAFINLAR administered with MEKINIST (“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. 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.

- TAFINLAR can cause paradoxical tumor growth in patients with BRAF wild-type tumors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of therapy.

- 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.

- 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.

- Across clinical trials of the combination, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients. Advise patients to seek medical care immediately if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling.

- 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.

- Ocular toxicities, including retinal vein occlusion (RVO), retinal pigment epithelial detachment, and uveitis can occur. There were no cases of RVO across clinical trials of the combination; uveitis occurred in 2% of patients treated with the combination across trials. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

- Interstitial lung disease/pneumonitis occurred in 1% of patients across trials of the combination.

- Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur. 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.

- 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.

- 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.

- Monitor patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as TAFINLAR confers a potential risk of hemolytic anemia in these patients.

- TAFINLAR and MEKINIST can cause fetal harm when administered to a pregnant woman.

- 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%). 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%).

- 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-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%).

- 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 via the links adjacent to this video.

Announcer:

If you missed any part of this discussion, visit reachMD.com/braf-treatment-safety. This is ReachMD. Be part of the knowledge.

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