



## Cardiovascular Adverse Events After Treatment With BRAF and MEK Inhibitors



Melanoma accounts for nearly 55500 cancer deaths annually worldwide. Most mutations in melanoma occur at the level of BRAF with an upregulation of the MAPK pathway. BRAF mutations prompted the development of BRAF inhibitors which cause resistance through a signalling cascade mediated by MEK. This, in turn, led to the development of MEK inhibitor therapies. Today, the combination of BRAF and MEK inhibitor therapy is considered an optimal treatment strategy for metastatic BRAF-mutated melanoma and has shown improved survival rates compared with monotherapy.

Three BRAF inhibitors (dabrafenib, vemurafenib, and encorafenib) and three MEK inhibitors (trametinib, cobimetinib, and binimetinib) are approved both in Europe and the US. Common combination therapies include dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and binimetinib. However, several studies have reported the incidence of cardiovascular adverse events (CVAEs) associated with BRAF and MEK inhibitors, especially a reduction in left ventricular ejection fraction (LVEF), arterial hypertension, and prolongation of QTc interval.

In this review, the researchers wanted to clarify the type, incidence, and risk of CVAEs in patients with melanoma and who are treated with a combination of BRAF and MEK inhibitor therapy compared with patients who received BRAF inhibitor monotherapy. The endpoints of the study included pulmonary embolism, a decrease in LVEF, arterial hypertension, myocardial infarction, atrial fibrillation, and QTc interval prolongation. Patients were divided into two groups - the BRAF+MEK inhibitor group and the BRAF inhibitor monotherapy group.

Key findings from the study were as follows:

- BRAF+MEK inhibitor therapy was associated with a higher risk ratio of pulmonary embolism, decrease in LVEF, and arterial hypertension compared with BRAF inhibitor monotherapy.
- BRAF+MEK inhibitor therapy was not associated with higher rates of myocardial infarction, atrial fibrillation, or QTc interval prolongation compared with BRAF inhibitor monotherapy.
- The risk ratio of high-grade decrease in LVEF and high-grade arterial hypertension were higher in the BRAF+MEK inhibitor group compared to the BRAF inhibitor monotherapy group.
- A higher risk of a decrease in LVEF was associated with patients with a mean age younger than 55 years.
- BRAF+MEK inhibitor therapy was associated with a higher risk of pulmonary embolism.

These findings clearly indicate the need for greater awareness of CVAEs in patients with melanoma who are treated with BRAF and MEK inhibitors. Guidelines clearly state that therapy with BRAF and MEK inhibitors should be stopped in patients with stage 2 hypertension (systolic BP more than 160 mmHg or diastolic BP more than 100 mm Hg). In patients with an asymptomatic decrease in LVEF of 10% or more from baseline, BRAF inhibitors can be continued, but MEK inhibitors must be stopped. Therapy with MEK inhibitors should only be resumed in the event of recovery of LVEF to normal values. In the event of heart failure or a decrease in LVEF of 20% or more from baseline, therapy with BRAF inhibitors should be stopped and should be resumed at the same dosage if the patient recovers. MEK therapy should be discontinued permanently in such patients. Treatment with BRAF inhibitors should not be initiated in patients with QTc of more than 500 milliseconds, and BRAF treatment should be stopped at a QTc of more than 500 milliseconds or at an increase in QTc of more than 60 milliseconds from baseline. Overall, BRAF and MEK inhibitor treatment should be considered separately for every individual.

Treatment with BRAF and MEK inhibitors is associated with an increased risk of CVAEs and should be used with caution and carefully discussed and analysed by cardio-oncology teams for the optimal treatment of patients with melanoma.

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