FDA approval of revolutionary two-drug combo to treat advanced melanoma

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Moffitt Cancer Center researchers have laid the groundwork for a revolutionary new combination therapy for the treatment of advanced melanoma – melanoma that cannot be removed surgically or has spread to other areas of the body. The newly FDA-approved therapy, Mekinist (trametinib) in combination with Tafinlar (dabrafenib), is one of the biggest advancements in melanoma treatment in the past 30 years.

"Melanoma is the most aggressive type of skin cancer and the leading cause of death from skin disease," said Jeffrey S. Weber, M.D., Ph.D., director of Moffitt's Melanoma Research Center of Excellence. "This new combination therapy is a huge step in the right direction for the treatment of melanoma, and our researchers played a large role in bringing this treatment option to patients."

Mekinist and Tafinlar are used to block signaling in different sites of the same molecular pathway – the MAP kinase pathway. Keiran S. Smalley, Ph.D., scientific director of the Melanoma Research Center of Excellence, and his team began investigating this pathway in 2010 and discovered the best way to block its ability to promote cancer cell growth was with combined inhibitor therapy.

The new combination therapy is indicated for melanoma patients whose tumors express gene mutations called BRAF V600E and V600K. Approximately half of all metastatic melanoma patients' tumors have a BRAF mutation, an abnormal change that can enable melanoma tumor cells to grow and spread.

BRAF-inhibitor resistance has long been a problem in the melanoma field, but Moffitt researchers found that using two inhibitors to block different growth pathways during treatment prevented resistance in patients with this mutation.

"A clinical trial in which Moffitt was the major contributor showed a 76 percent success rate for patients treated with the Mekinist and Tafinlar combination. We also found this therapy reduced the incidence and severity of some of the toxic effects patients experienced when the drugs were used alone," said Weber.

The FDA approved the combination of Mekinist and Tafinlar through its accelerated approval program, which allows the agency to approve drugs to treat a serious disease based on clinical data showing the therapy has a proven effect and clinical benefit to patients. The FDA also reviewed this combination of drugs under the agency's priority review because they demonstrated the potential to be a significant improvement in safety or effectiveness in the treatment of melanoma.

More information: The *New England Journal of Medicine*, Nov. 2012, Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations - www.nejm.org/doi/pdf/10.1056/

British Journal of Cancer, June 2010, Recovery of phospho-ERK activity allows melanoma cells to escape from BRAF inhibitor therapy - www.nature.com/bjc/journal/v10 … n12/pdf/6605714a.pdf

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