Intermittent treatment with vemurafenib may prevent lethal drug resistance in melanoma

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Vemurafenib-resistant tumors in patients with melanoma showed reduced growth after cessation of treatment, and in animal models, drug resistance was prevented by intermittent treatment, according to data presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

"It was exciting to witness the discovery of BRAF mutations in melanoma and the translation of this discovery into an effective therapy with vemurafenib," said Darrin Stuart, Ph.D., senior research investigator at the Novartis Institutes for Biomedical Research in Emeryville, Calif. "It was, however, disappointing to see patients stop responding to such a promising therapy after six to eight months of treatment."

BRAF mutations are found in more than half of all cases of melanoma, and previous studies have shown vemurafenib increases survival for these patients, according to Stuart. However, most patients relapse with lethal, drug-resistant disease.

In a previous study to investigate the mechanisms causing melanomas to become resistant to vemurafenib, Stuart and his colleagues grew patient-derived tumors expressing BRAF mutations in mice and demonstrated that not only do these tumors develop vemurafenib resistance, but they become dependent on the drug to grow. Tumors stopped growing and

regressed after cessation of the drug in these animals.

To evaluate whether the drug dependency observed in animals is seen in humans as well, Stuart and his team collaborated with colleagues who evaluated 42 patients with vemurafenib-resistant tumors at the Royal Marsden Hospital in London, United Kingdom. Computed tomography scans of the tumors taken after cessation of treatment were available for 19 patients. Of these patients, 14 showed a decrease in the rate of their tumor growth.

"This is the first evidence that the drug-addicted state that we observed in our mouse models may also occur in humans," said Stuart.

He and his colleagues also implanted mice with human patient-derived tumors and treated them with vemurafenib either continuously or intermittently—four weeks on and two weeks off. They found that none of the tumors in animals assigned to intermittent dosing developed drug resistance.

"Continuous dosing maintained the selective pressure required for the few surviving tumor cells to develop resistance, and alternating the selective pressure through intermittent dosing appeared to prevent the evolution and expansion of resistant cells," said Stuart. "This study provides insight into how vemurafenib-resistant tumors evolve. Alternative dose regimens could prolong the durability of response to vemurafenib in BRAF-mutant melanoma."

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