New approaches may prevent certain side effects in BRAF mutation-positive melanoma

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Findings from preclinical studies in a skin cancer model showed that next-generation BRAF inhibitors used alone, or first-generation BRAF inhibitors used in combination with an epidermal growth factor receptor inhibitor, may have the potential to prevent drug-induced skin lesions in BRAF mutation-positive patients treated for melanoma.

The studies, presented at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, held Nov. 12-16, 2011, further elucidated the potential mechanism of action underlying this skin lesion side effect, which could further the development of next-generation drugs with improved safety and efficacy profiles for the treatment of BRAF mutation-positive melanoma, according to the researchers.

"Our data suggest that adding an epidermal growth factor receptor (EGFR) inhibitor may prevent skin lesions that sometimes appear during treatment with a first-generation BRAF inhibitor," said Gideon Bollag, Ph.D., senior vice president of research at Plexxikon in Berkley, Calif. "Perhaps more importantly, our data also suggest that our next-generation BRAF inhibitors (which we call 'paradox breakers') represent a novel, single-agent treatment that may avoid this side effect and may also extend treatment durability."

In a laboratory study, Bollag and colleagues used skin cells activated by oncogenes such as HRAS or by signaling through the EGFR receptor with a first-generation BRAF inhibitor. They observed that treatment led

to upregulation of ligands for the family of HER receptors, consequent skin cell transformation and enhanced growth. In contrast, Plexxikon's novel "paradox breakers" did not induce this upregulation and, therefore, may prevent the skin lesion side effect observed for all first-generation BRAF inhibitors to date.

Bollag said he and his research team were initially surprised by the upregulation of growth factor expression but were able to identify its cause with a model system. They then used this model system to differentiate the new "paradox breaker" compounds.

The "paradox breakers," which are in preclinical development, are being studied in BRAF-mutant cancer, and Plexxikon is aiming to file an investigational new drug application in 2012.

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