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GENETICS

A new tool for the *KIT*

The incidence of skin cancers is rising and, of these, melanoma is the cause of the highest levels of morbidity and mortality. For patients diagnosed with metastatic melanoma the prognosis is grim, with only the recently approved antibody ipilimumab and the small molecule vemurafenib shown to improve overall survival over previous standards of care. Although ipilimumab and vemurafenib have offered hope to patients, there are melanoma subtypes for which they are not effective; research for alternative therapies is ongoing.

An open-label phase II study has recently sought to identify the subtype of patients with melanoma who might respond best to the multi-kinase inhibitor imatinib mesylate. "A subset of melanomas is characterized by activating alterations in the gene coding for the kinase KIT. We sought to assess whether KIT inhibition in this subset of melanomas could impact tumor progression," stated Richard Carvajal, first author of the study.

Out of 295 cases of melanoma enrolled into the study, 51 patients were identified to have *KIT* mutations or amplifications. These cases were from a cohort of patients with melanoma subtypes previously shown to be enriched for these types of genetic alterations (from acral, musocal and chronically sun-damaged sites). The identified patients were offered treatment with imatinib and 28 patients went on to receive the therapy. Two patients had durable complete responses, two had durable partial responses and five had stable disease that lasted for at least 12 weeks, with two of these lasting for more than 6 months. As Carvajal pointed out, "our study serves as an important proof of concept that inhibition of the protein KIT in patients with advanced melanoma that are biologically driven by activating mutations in *KIT* can lead to significant clinical benefit." Importantly, not all mutations in *KIT* had the same responses. All six of the durable responses were observed in patients with L576P or K642E amino acid substitutions, which are the most common KIT alterations in melanoma.

This study seems to offer clinical evidence to support the more-recent drive to understand the molecular biology behind driver mutations prior to using them for patient selection in clinical trials. In previous trials, in which the patients were not selected based on activating mutations in *KIT*, no evidence of imatinib efficacy was observed.

This work will need to be built on to provide patients with the optimal therapy for their subtype of melanoma. Carvajal states, "we now need to further refine how we select patients for imatinib therapy and investigate other agents or combinations of agents." But, our therapy 'tool kit' is expanding!

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Original article Carvajal, R. D. *et al*. KIT as a therapeutic target in metastatic melanoma. *JAMA* **305**, 2327–2334 (2011)