Nature Reviews Clinical Oncology **9**, 5 (2012); published online 6 December 2011; doi:10.1038/nrclinonc.2011.195

SKIN CANCER

NOVEL RESISTANCE MECHANISM REVEALED

Patients with metastatic melanoma have a dismal prognosis but major advances have been made as a result of the FDA approval of vemurafenib—the first kinase inhibitor to prolong survival in patients with melanoma who have the V600E BRAF mutant protein. Unfortunately, despite showing dramatic initial responses, many patients develop resistance to vemurafenib after only a few months. Therefore, David Solit and collaborators wanted to investigate the molecular basis for resistance to vemurafenib and have published a study in *Nature* that reveals a novel mechanism of acquired resistance to the drug. As Solit explains, "we found that resistance in a subset of patients was the result of the expression of a short, truncated form of the mutant BRAF protein. These truncated forms are generated by alternative splicing".

Solit's team generated cell lines that were resistant to vemurafenib by exposing them to high doses of the drug and showed that resistant cells expressed a variant form of the BRAF protein, p61BRAF(V600E). This mutant form lacked the RAS-binding domain and demonstrated enhanced dimerization in cells with low RAS activity. When p61BRAF(V600E) was overexpressed, ERK signaling downstream of RAS was no longer inhibited by vemurafenib. However, introducing a mutation to abolish the dimerization capability of p61BRAF(V600E) restored sensitivity to vemurafenib. They also identified splice variants of BRAF(V600E) that lacked the RAS-binding domain in tumors from six of 19 patients with acquired resistance to vemurafenib.

"This work is novel in many respects. It represents the first mechanism of BRAF inhibitor resistance in which the basis for drug resistance is the result of a second change in the BRAF protein. It also suggests for the first time that alternative splicing of kinases can alter kinase inhibitor sensitivity," says Solit.

The results imply that if vemurafenib is used in combination with MEK inhibitors resistance might be delayed or prevented. Solit's team plans to use information about drug-resistance mechanisms to generate more-effective BRAF inhibitors and explore new combinations of inhibitors that might have more-durable effects in patients.

Lisa Hutchinson

Original article Poulikakos, P. I. *et al*. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature* doi:10.1038/nature10662