Published in final edited form as:
Clin Cancer Res. 2014 December 15; 20(24): 6631. doi:10.1158/1078-0432.CCR-14-0058.

"Melanoma BRAF fusions" - Letter

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Dear Editor,

We read with interest the article by Hutchinson et al. (1) describing melanomas harboring BRAF fusions and their sensitivity to MEK inhibition. We also have reported recurrent BRAF fusions in melanocytic neoplasms, including melanomas, and would like to comment on some of the conclusions reached by Hutchinson et al, which we think are of clinical relevance.

In our recently published study (2), we analyzed a clinical CGH database of 848 melanocytic tumors and found 10 cases with copy number transition within the BRAF locus. Massively parallel sequencing identified in-frame fusions of different 5' partners to the intact kinase domain of BRAF similarly as in Hutchinson et al. Noticeably, all of the BRAF fusion tumors that we described presented spitzoid morphology, i.e. were primary tumors comprised of large epithelioid or spindled melanocytes.

In an independent study analyzing 140 melanocytic tumors with a spitzoid morphology, we identified similar BRAF fusions in 5% cases. Remarkably, a total of 51% of the spitzoid lesions had fusions, mostly involving the receptor tyrosine kinases ALK, ROS1, RET, and NTRK1 (3). We noted that patients with kinase fusions were significantly younger than those without. Our findings suggest that melanocytic tumors presenting a spitzoid morphology might be enriched for fusion events, including those of BRAF, and thus likely overlap with the molecular subset of melanomas proposed by Hutchinson et al. Detailed histologic characterization of the BRAF fusions tumors described in this report would be of interest.

We also add a more nuanced perspective to the statement that the signaling of BRAF fusions would be "sensitive to MEK, but not BRAF, inhibition". While we also found that the melanoma cell line C0902 harboring an AGK-BRAF fusion was comparatively resistant to vemurafenib, it was highly sensitive to sorafenib (2). The relevance of this observation was strongly supported by the dramatic and prolonged clinical response to sorafenib of the 17-year-old patient with widespread spitzoid melanoma (4). Similar response to a regimen containing sorafenib was recently described in a patient presented with an undifferentiated spindle cell neoplasm harboring a KIAA1549-BRAF fusion (5).

Conflict of interest:
The authors declare no conflict of interest.

Thus, sensitivity of BRAF fusions may strongly depend on the type of RAF inhibitor.

In conclusion, we think that clinicians should be particularly alerted of potential fusions in melanomas presenting in younger patients with a spitzoid morphology of the primary, and that sorafenib should be considered as an additional therapeutic option, for patients presenting melanomas with a BRAF fusion.

Acknowledgements

This work was supported by National Institutes of Health Grant P01 CA025874.

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