Published in final edited form as:
Clin Cancer Res. 2012 December 15; 18(24): 6792–6793. doi:10.1158/1078-0432.CCR-12-2974.

"Distinguishing Clinicopathologic Features of Patients with V600E and V600K *BRAF*-Mutant Metastatic Melanoma" – Letter

Rosalyn Jewell[1], **Philip Chambers**[2], **Mark Harland**[1], **Jon Laye**[1], **Caroline Conway**[1], **Angana Mitra**[1], **Faye Elliott**[1], **Martin G. Cook**[3], **Andy Boon**[4], and **Julia Newton-Bishop**[1]

[1]Section of Epidemiology and Biostatistics, Cancer Research UK Centre, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK

[2]Genomics Facility, Cancer Research UK Centre, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK

[3]Royal Surrey County Hospital NHS Foundation Trust and Division of Medicine University of Surrey, Guildford, UK

[4]Leeds Teaching Hospitals NHS Trust, Leeds, UK

Dear Editor,

The presence of a *BRAF* mutation in a melanoma tumor predicts response to BRAF inhibitors, however the biological characteristics of tumors with different *BRAF* mutations have not been investigated until recently. Menzies and colleagues reported that the rarer V600K *BRAF* mutations were found more commonly in metastatic tumors of patients who were older at diagnosis, had evidence of chronic sun damage at the primary site and had shorter distant metastasis-free survival time compared to V600E *BRAF*-mutated tumors (1). Here, we report similar findings, but in a large cohort of 279 primary melanoma specimens. Formalin-fixed tumors were genotyped using pyrosequencing. *BRAF* mutations were identified in 50.5% of tumors, 12.8% being V600K mutations and 83.7% V600E mutations. Patients with a V600K mutated tumor were significantly older at diagnosis than those with a V600E mutation (V600K median 60.7 years, V600E 50.5 years, p=0.005) and a greater proportion of patients with V600K mutations were male (V600K 77.8%, V600E 46.6%, p=0.02). Patients with V600K mutated tumors were at a significantly increased risk of relapse (hazard ratio (HR) 2.64 (95% CI 1.20-5.80), p=0.02) compared with tumors without a mutation (baseline, HR 1.0), V600E mutated tumors (HR 0.80 (95% CI 0.45-1.42), p=0.45) or *NRAS* mutated tumors (HR 0.89 (95% CI 0.49-1.62), p=0.69) in analyses adjusted for the effect of having a sentinel node biopsy. The association between V600K mutation status and relapse persisted in multivariate analysis adjusting for known prognostic factors (sex, age at diagnosis, site of tumor, Breslow thickness, ulceration status and mitotic rate) (HR 2.58 (95% CI 1.03-6.48), p=0.04). There was also evidence that V600K mutations shorten overall survival (HR for death 2.03 (95% CI 0.95-4.33), p=0.07) and melanoma-specific survival (HR 1.97 (95% CI 0.89-4.34), p=0.09). Our findings with those of Menzies *et al.* suggest that V600K-mutated tumors are biologically distinct from V600E-mutated tumors in both metastatic and primary specimens. The higher incidence of V600K mutations in primary tumors from older and male patients, perhaps also related to chronic sun exposure (1) may suggest different aetiological routes to melanoma. These tumors also appeared to behave differently, being associated with poorer prognosis, than the commoner V600E

Corresponding author: Dr. Rosalyn Jewell, Clinical Research Fellow, Section of Epidemiology and Biostatistics, Cancer Research UK Centre, Leeds Institute of Molecular Medicine, St James's Hospital, Beckett Street, Leeds. LS9 7TF, Tel +44 113 2066532, Fax +44 113 2340183, r.a.jewell@leeds.ac.uk.

Europe PMC Funders Author Manuscripts

mutation (2, 3). Both V600K and E mutations cause elevated kinase activity and ERK activation (4); but these data suggest a need for further investigation *per se* and with reference to treatment with BRAF inhibitors.

Acknowledgments

This work was supported by Cancer Research UK (project grants C8216/A6129 and C8216/A8168), and program grants C588/A4994 and C588/A10589), and by the NIH (R01 CA83115). RJ is in receipt of a Bramall Fellowship and a Medical Research Council Clinical Research Training Fellowship (G0802123). AM was funded by a grant from the Leeds Teaching Hospitals Trust Charitable Fund.

References

1. Menzies AM, Haydu LE, Visintin L, Carlino MS, Howle JR, Thompson JF, et al. Distinguishing Clinicopathologic Features of Patients with V600E and V600K BRAF-Mutant Metastatic Melanoma. Clin Cancer Res. 2012
2. Edlundh-Rose E, Egyhazi S, Omholt K, Mansson-Brahme E, Platz A, Hansson J, et al. NRAS and BRAF mutations in melanoma tumors in relation to clinical characteristics: a study based on mutation screening by pyrosequencing. Melanoma Res. 2006; 16:471–8. [PubMed: 17119447]
3. Ellerhorst JA, Greene VR, Ekmekcioglu S, Warneke CL, Johnson MM, Cooke CP, et al. Clinical correlates of NRAS and BRAF mutations in primary human melanoma. Clinical cancer research: an official journal of the American Association for Cancer Research. 2011; 17:229–35. [PubMed: 20975100]
4. Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004; 116:855–67. [PubMed: 15035987]

Europe PMC Funders Author Manuscripts