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 as compared with 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 [HR, 2.64; 95% confidence interval (CI), 1.20–5.80; \( P = 0.07 \)] 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 and colleagues 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 etiological routes to melanoma. These tumors also seemed to behave differently, being associated with poorer prognosis, than the more common V600E mutation (2, 3). Both V600K and E mutations cause elevated kinase activity and extracellular signal–regulated kinase (ERK) activation (4), but these data suggest a need for further investigation per se and with reference to treatment with BRAF inhibitors.

Disclosure of Potential Conflicts of Interest

J. Newton-Bishop is a consultant/advisory board member of Roche. No potential conflicts of interest were disclosed by the other authors.

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