Tumor Genetic Analyses of Patients with Metastatic Melanoma Treated with the BRAF Inhibitor Dabrafenib (GSK2118436)

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Abstract

**Purpose:** Dabrafenib is a selective inhibitor of V600-mutant BRAF kinase, which recently showed improved progression-free survival (PFS) as compared with dacarbazine, in metastatic melanoma patients. This study examined potential genetic markers associated with response and PFS in the phase I study of dabrafenib.

**Experimental Design:** Baseline (pretreatment or archival) melanoma samples were evaluated in 41 patients using a custom genotyping melanoma-specific assay, sequencing of PTEN, and copy number analysis using multiplex ligation amplification and array-based comparative genomic hybridization. Nine patients had on-treatment and/or progression samples available.

**Results:** All baseline patient samples had BRAFV600E/K confirmed. Baseline PTEN loss/mutation was not associated with best overall response to dabrafenib, but it showed a trend for shorter median PFS (18.3 weeks (95% CI, 14.1–33)) vs. 32.1 weeks (95% CI, 24.1–33), P = 0.059. Higher copy number of CCND1 (P = 0.009) and lower copy number of CDKN2A (P = 0.012) at baseline were significantly associated with decreased PFS. Although no melanomas had high-level amplification of BRAF, the two patients with progressive disease as their best response had BRAF copy gain in their tumors.

**Conclusions:** Copy number changes in CDKN2A, CCND1, and mutation/copy number changes in PTEN correlated with the duration of PFS in patients treated with dabrafenib. The results suggest that these markers should be considered in the design and interpretation of future trials with selective BRAF inhibitors in advanced melanoma patients. *Clin Cancer Res; 19(17); 4868–78. ©2013 AACR.*

Introduction

Melanoma is the most lethal form of skin cancer. In the United States, it is estimated that there will be 76,250 new cases and 9,180 deaths related to melanoma in 2012, and the incidence in increasing (1). Melanomas are characterized by a high rate of single-base mutations, as compared to other solid cancer types, associated with an UV light induced signature, as well as a characteristic profile of genomic amplifications and deletions (2, 3). Mutations in BRAF are found in ~45% of melanomas (4, 5), the majority of which are at codon 600 and result in constitutive kinase activity of BRAF and subsequent downstream signaling through the MAP kinase pathway (6). Seventy to ninety percent of BRAF mutations are due to the substitution of glutamic acid for valine (V600E mutation; c.1799T>A), and 10% to 30% are due to the substitution with lysine (V600K; refs. 4, 5, 7). Common genomic changes in melanoma include deletion of PTEN, and CDKN2A and amplifications of KIT, MITF, TERT, CCND1, among others (3). PTEN deletions are most commonly observed in conjunction with BRAF mutations, in approximately 30%, whereas CDKN2A mutations are seen across all mutational (BRAF/NRAS/WT)
**Translational Relevance**

Multiple studies have evaluated acquired mutations in melanomas from patients who progress on BRAF inhibitor therapies. This study focuses on pretreatment predictors of outcome when treated with the BRAF inhibitor dabrafenib. Common genetic mutation and genomic aberrations in melanoma were examined, with those in *CDKN2A*, *CCND1*, and *PTEN* found to correlate with the duration of progression-free survival. Interestingly, these genetic changes have been previously implicated as associated with outcome in natural history studies of melanoma, and preclinically, in response to treatment with BRAF inhibition, so we cannot discriminate if they are predictive or prognostic markers. Our data suggest that genetic analysis of *PTEN*, *CDKN2A*, and *CCND1* may be used to identify patients who should be considered for frontline combinatorial approaches, particularly using agents targeting pathways activated by aberrations in these genes. This study also emphasizes the continued importance of trials with associated biopsies on a large number of patients, so that we may gain insights into predictors of clinical outcome.

subtypes of melanomas (8, 9). The frequency of these genomic changes allows their study in conjunction with outcome upon treatment of melanoma.

Until recently, most systemic therapy options available for patients with advanced stage melanoma were ineffective, and the 5-year survival rate was less than 15%. In addition to immunotherapeutic agents, therapies directed at the MAPK signaling pathway have been developed, in particular targeted inhibition of the mutant V600E BRAF protein. Dabrafenib is a reversible ATP-competitive inhibitor that selectively inhibits mutant BRAF<sub>V600E</sub>, with an IC<sub>50</sub> (concentration required for 50% inhibition) 5-fold lower than for wild-type BRAF or CRAF (10). Treatment of BRAF-mutant metastatic melanoma with the RAF inhibitors dabrafenib or vemurafenib results in response rates of approximately 50% and significantly improved progression-free survival (PFS) and overall survival (OS) as compared with dacarbazine chemotherapy (11–14). The emergence of acquired resistance in the majority of patients, for which multiple mechanisms have been described, involving both reactivation of the MAPK signaling pathway and by-pass mechanisms, remains the greatest barrier to better clinical outcomes (15–22).

Preclinical studies have also identified several mechanisms of *de novo* or intrinsic resistance to BRAF inhibitors, including PTEN loss (alone or in conjunction with Rb1 loss), MET, and SRC activation (associated with amplification of *MET*, *CTNNB1*, and *CCND1*), activation of P70S6K and S6, and hepatocyte growth factor mediated MET expression (21–26). To improve our understanding of the clinical significance of these DNA-based aberrations implicated in intrinsic resistance, and other candidate genes previously identified as aberrant in melanoma, we report here the molecular analysis of a large collection of human melanoma tumor samples from patients treated on the phase I clinical trial of the BRAF inhibitor dabrafenib (11).

**Patients and Methods**

**Patients and clinical outcome**

Melanoma tumor samples were collected from patients enrolled on the first-time-in-human BRF112680 phase I trial of dabrafenib (GSK2118436; clinical trial number NC100880321) between May 27, 2009 and March 20, 2012, at 8 study centers in Australia and the United States (11). Samples were collected either at baseline ("pretreatment" and/or archival samples), "on-treatment," and when possible, at time of progression. Informed consent was obtained from all patients before the start of treatment and collection of tumor samples; the study complied with all local guidelines. Patients commenced on variable doses of dabrafenib (35–300 mg; Table 1); all were escalated to a total daily dose of ≥300 mg/day. The clinical outcome measures used in this study included the objective response and PFS using computed tomography and RECIST 1.0 as previously reported (11).

**Tumor QC, DNA extraction**

All samples were formalin-fixed and paraffin embedded and processed for hematoxylin and eosin (H&E) staining and pathologist review of tumor content at the ACC Histology Core Facility by QCY. Samples with over 70% tumor content were processed for DNA extraction directly; whereas those with less than 70% tumor underwent H&E-guided macrodissection before DNA extraction. DNA was extracted using standard methods.

**iPlex genotyping and PTEN sequencing**

Genotyping conducted using a custom iPlex (Sequenom, Inc.) single nucleotide extension panel Genotyping was done at the Perelman School of Medicine Molecular Profiling Facility. Analysis of data was done using the iSeq software; we assessed the ratio of wildtype:mutant (T:A) nucleotide in *BRAF<sub>V600E</sub>* using the peak height chromatograms. Sanger sequencing of *PTEN* exons 1 to 9 was conducted using standard methods and published primers (27). Detailed methods are included in Supplementary Methods.

**Copy number analysis**

Multiplex ligation dependent probe amplification (MLPA) was used to detect copy number aberrations of genes located on chromosome 10q23 [MLPA kit P225-B2 PTEN; MRC-Holland]. MLPA was conducted according to the manufacturer’s instructions and analyzed with their software—MRC-Coffalyser Stand Alone Alpha Version 1.0.0.43 software. The fragments were analyzed on ABI 3130xl capillary sequencer using GeneMapper software (Applied Biosystems, Inc.). Variation in peak height was evaluated by comparing each test sample to 3 normal controls present in the same experiment. Normalization
was done intrasample by dividing the peak area of each probe’s amplification product by the total area of only the reference probes in this probe mix. Single regression for control and tumor data slope correction was conducted. Normal ratio limits were set at −0.70 and 1.2. This program identifies a peak as deleted when showing a ratio < 0.7 and amplified when showing a ratio > 1.2. The copy number of PTEN was measured in 17 samples using both MLPA and aCGH for cross-validation; all samples had the same copy number profiles.

Array-based comparative genomic hybridization was done using the Agilent SurePrint G3 Human CGH 1 × 1 M microarrays following manufacturer’s instructions. Arrays were scanned using Agilent’s High-Resolution C Scanner. Extracted data were analyzed using BioDiscovery’s Nexus 6 copy-number software (Nexus Genomics Inc.). Copy number variation (CNV) was assessed using the CBS-like Rank Segmentation algorithm provided with Nexus 6; genes mapping was done to hg19, Feb 2009 build. Copy number gain was defined as log2 scale value ≥ 0.3 and loss as log2 scale value ≤ −0.3, with at least 3 contiguous single-nucleotide polymorphisms needed. Segments were particularly examined for the presence of high copy gains (log2 scale value ≥ 1.14) and homozygous loss (log2 scale value ≤ −1.1). In addition, only segments derived from >16 probes were included in subsequent analysis.

Chromosomal instability analysis
Characterizing cytogenetic instability was used as an alternative to analyzing specific, recurring copy number changes across the tumor set. To this end, copy number alterations were first identified in the segmented data for each tumor and mapped to a specific chromosomal arm. Considering gains and losses separately, the total accumulation of copy number altered regions was calculated for each arm (i.e., total bases altered) and the fraction of the arm altered (total bases gained or lost/total size of arm).

Statistical analysis
PFS was compared in patients whose tumors had wild-type or nondeleted/mutant PTEN status versus those with deleted or mutant PTEN using the log-rank test and Kaplan–Meier analysis. Correlation between copy number values among 36 genes was assessed using Spearman’s correlation analysis. Association between copy number values and PFS was evaluated using proportional hazards regression. In this analysis, \( P < 0.05 \) was considered statistically significant. Cytogenetic instability was analyzed between patients with pre- or early dose tissue. Comparisons were made using the median PFS of 24 weeks, with 12 patients having a PFS over 24 weeks and 11 patients with a PFS less than 24 weeks, using a \( t \) test.

Results

Description of patient population
A total of 91 samples were available from 77 patients. Eleven patients had multiple samples available. Twenty-seven samples were determined to have no tumor or in an amount too small to allow for adequate DNA extraction. We obtained \( \text{BRAF} \) mutational data on 57 melanoma tumor samples from 45 patients. Of these samples, 2 were on-treatment and 11 were progression samples, with the remaining 44 baseline (pretreatment or archival) samples. Patient characteristics for the 41 patients with baseline samples available are in Table 1.

Mutational characteristics
In the 41 patients with baseline samples available, 6 had \( \text{BRAF}^{\text{V600E}} \), 35 \( \text{BRAF}^{\text{V600K}} \) mutations (Table 2). Two melanoma samples carrying the \( \text{BRAF}^{\text{V600E}} \) mutation exhibited a T(wild-type):A(mutant) ratio favoring the mutant allele, one suggestive of amplification of that allele (patient 32, 1:4). Of the 7 \( \text{BRAF}^{\text{V600K}} \) mutations observed, 2 samples showed T:A ratio favoring the mutant allele, suggestive of amplification of the mutant allele (patients 11, 19). The highest ratio favoring the mutant allele was seen in the archival sample from a patient also with a pretreatment sample, which had a ratio favoring the wild-type allele. Two patients with V600E mutations had additional concurrent mutations, one with \( \text{CTNNB1} \) (β-catenin) p.S45del and another with \( \text{MAP2K2} \) (MEK2) p.Q60P. The biopsy with the mutation in \( \text{MAP2K2} \) was taken at time of progression on trametinib (MEK inhibitor), before treatment with dabrafenib. Melanoma tumor samples, all taken from the same lesion, at multiple time points—archival, before treatment, and on-treatment with trametinib—were available for this patient and did not show the \( \text{MAP2K2} \) p.Q60P mutation.
Table 2. Mutational status using targeted assays and copy number analysis of PTEN

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sample type</th>
<th>BRAF</th>
<th>WT/mutant (T:A) ratios</th>
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(Continued on the following page)
suggesting it arose after treatment with trametinib (Infante; Nathanson; unpublished data). This patient had progressive disease as their best response to treatment with dabrafenib.

Data were available from 2 on-treatment and 11 progression samples from 10 patients (Table 2). Both of the on-treatment samples were from patients who also had progression samples. The 10 patients had melanomas carrying the following mutations: \( \text{BRAF}^{V600E} (6), \text{BRAF}^{V600K} (2), \text{BRAF}^{K601E} (1), \) and \( \text{NRAS}^{Q61K} (1). \) The progression sample with the \( \text{NRAS} \) mutation did not have a concurrent \( \text{BRAF} \) mutation, so it is possible that the patient had more than one primary melanoma, did not have \( \text{BRAF} \) mutant melanoma as no pretreatment sample was available for validation, or that the \( \text{BRAF}^{V600E} \) mutation was present but undetectable based on the sensitivity of the assay. Six patients had matched pretreatment/archival and progression samples. In general, the ratio of mutant to wild-type allele was the same in both samples.

### Association of baseline PTEN status with PFS

As we were particularly interested in the relationship of PTEN status to PFS upon treatment with dabrafenib, we evaluated it genetically with copy number analysis, using MLPA and/or aCGH, and sequencing of all exons. For this analysis, we focused on pretreatment and archival samples; data from the pretreatment sample was used preferentially for all analyses. Three patients had both archival and pretreatment samples. One patient had an archival sample with amplified PTEN; the pretreatment sample showed diploid PTEN. In one patient, a mutation in PTEN was observed in the pretreatment, but not archival sample. This mutation was the only one observed in PTEN, p.P95L, and has been previously reported in association with cancer (27–29). For four samples, we obtained only mutational, but not copy number data; these samples were removed from further analysis. Thus, 34 patients had melanoma samples with PTEN data available for analysis (Table 2); patient characteristics are reported in Supplementary Table S1.

PTEN status was available for 11 progression and 2 on-treatment samples. Five progression samples had matched archival or pretreatment samples; in all but one case the copy number status was the same in both samples. Of note, homozygous deletion of PTEN was more frequently observed in progression tumor samples (4 of 10) than in archival or pretreatment samples (2 of 34), \( P = \) 0.017.

The relationship between best overall response (BOR) and PFS were evaluated. No association was seen between BOR and PTEN status with patients with melanomas having wild-type or nondeleted/nonmutant PTEN status having a response rate (CR+PR) of 43% [10/23; 95% confidence interval (CI), 21–65.9%] versus those with deleted or mutant PTEN of 36% (4/11; 95% CI, 3.4–69.3%), \( P = 0.059 \) (Fig. 1A). However, the patients with wild-type or nondeleted/nonmutant PTEN status had a longer PFS (32.1 weeks; 95% CI, 24.1–39.4), \( P = 0.059 \) (Fig. 1B). As the PTEN status for 4 samples with exonic amplification could not be precisely determined to be either wild type or deleted, as potentially they could indicate rearrangements leading to PTEN loss, as in prostate cancer (30), they were removed for a secondary analysis. The PFS in the 18 patients with wild-type PTEN status was 32.1 weeks (95% CI, 24.1–33) and those with deleted/mutant PTEN (18.3 weeks; 95% CI, 9.1–24.3; \( P = 0.059 \)), \( P = 0.059 \) (Fig. 1B). As the PTEN status for 4 samples with exonic amplification could not be precisely determined to be either wild type or deleted, as potentially they could indicate rearrangements leading to PTEN loss, as in prostate cancer (30), they were removed for a secondary analysis. The PFS in the 18 patients with wild-type PTEN status was 32.1 weeks (95% CI, 24.1–39.4), longer than those with deleted/mutant PTEN, but this difference did not reach statistical significance (\( P = 0.066 \)).

PTEN immunohistochemistry (IHC) was conducted on a subset (\( n = 17 \)) of the samples with complete genetic data (Supplementary Table S2). The correlation between IHC data and genetic status was 75% (95% CI, 50.5–89.8);

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sample type</th>
<th>BRAF</th>
<th>WT/mutant (T:A) ratios</th>
<th>PTEN mutation status and copy no.</th>
<th>Additional mutations</th>
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aWT/No CN, sequence wild-type, copy number could not be obtained.

bHomo-Del, homozygous deletion.

cHemi-Del, hemizygous deletion.

dDup Ex 1, duplication of exon 1.

eAmp/Del, duplication of exon 1, deletion of other exons.

1AF, assay failed.
presence/absence of staining data was not predictive of PFS in this small subset of patients (data not shown).

**aCGH data**

aCGH data were generated on 34 samples from 26 patients. Twenty-four archival and pretreatment samples were analyzed from 23 patients (1 patient had both archival and pretreatment samples). Eight patients had progression samples analyzed (2 for which we also had on-treatment samples). Three patients had both archival or pretreatment samples and progression samples. Overall, the copy number analysis (Fig. 2A) was similar to that previously published for *BRAF* mutant cutaneous melanoma, with frequent copy number gains of 6p, 7q, and 22q, and frequent losses of 6q, 9p, and 10q (31–34). We also examined the overall genomic profile of pretreatment melanomas in relationship to PFS (Fig. 2B), BOR (Supplementary Fig. S1), and *BRAF*V600E versus *BRAF*V600K mutation status (Supplementary Fig. S2). The percentage of individual chromosome arms and total fraction of the genome that was altered...
in patients with PFS > 24 weeks (n = 12) was compared to those with PFS ≤ 24 weeks (n = 11). Although the overall fraction of the genome gained or lost did not significantly differ between groups (P = 0.19 and 0.11, respectively), there were some notable qualitative differences. Most notably, when considering large alterations defined as those encompassing >25% of the size of a chromosomal arm (indicative of broad instability), gains of 6p seemed more frequent in the patients showing >24 versus ≤24 week PFS (58% vs. 27%, respectively). Similarly, large losses of 11q seemed more frequent in those patients with PFS >24 weeks versus ≤24 weeks (33% vs. 9% of patients, respectively). Conversely, losses of 9p (25% vs. 55%), and 4q (0% vs. 27%) were qualitatively more frequent in those with shorter PFS. Although none of these differences achieved statistical significance (P > 0.05 in all cases), the overall rarity of such large genomic changes could suggest relationships with response in a subset of patients.

Specific genes from aCGH data

We selected 36 genes (Supplementary Table S3) implicated in melanoma pathogenesis for CNV characterization. A correlation analysis between copy number gains and losses of various genes, both positive and negative (i.e., gain–gain, gain–loss) was done, and is shown in Supplementary Table S4. Correlation of CNV results to PFS showed that copy gain of CCND1 (P = 0.009) and loss of CDKN2A (P = 0.012) were independently predictive of shorter PFS. For visualization purposes of the association between copy number and outcome, the samples were divided by median copy number and Kaplan–Meier curves for PFS were generated (Fig. 3A and B). For CCND1, patients whose tumors had greater than the median copy number (n = 11) had a median PFS of 27 weeks (95% CI, 15–32 weeks), which was shorter (HR = 2.22) than those with a lower copy number (n = 12, median PFS 33 weeks, 95% CI, 24–45 weeks). Patients with less than median copy number of CDKN2A (n = 11) had a median PFS of 25 weeks (95% CI, 17–32 weeks), whereas patients with a higher copy number had a median PFS of 31 weeks (95% CI, 15–56 weeks, HR = 0.59). Of note, neither copy number of CDKN2A nor CCND1 was associated with BOR. High-level amplification of the BRAF locus (>5 copies) was not observed in these 25 patients, and BRAF copy number did not significantly correlate with BOR or PFS (Fig. 3C).

Discussion

To the authors’ knowledge, this study represents the largest genetic and genomics-based examination of human melanoma tissue from patients treated with BRAF inhibitors, specifically patients treated with dabrafenib on the phase I/II trial (11), to identify correlates associated with response. We focused on the genes encoding the proteins of the MAPK (Ras/Raf/MEK/ERK) and PI3K/Akt pathways, as they are the principal signaling pathways shown to be crucial in melanoma initiation and progression (6, 35). Cell-cycle regulatory proteins, such as p16, CDK4, and cyclin D1, also have been shown to play important roles in melanoma, and those genetic and genomic aberrations involving these also were specifically interrogated (36–38). We also took a more comprehensive unbiased approach, using aCGH, to identify additional genomic aberrations which might be associated with response. All baseline (pretreatment and archival) samples had confirmed V600 mutations in BRAF, a study eligibility requirement. High-level copy (over 5) amplification of BRAF was not observed in any of the samples. A few samples showed relative increases in the ratio of the BRAF V600 mutant to wild-type allele, either in the pretreatment samples, or at the time of progression; most samples showed equivalent or increased wild-type allele. Of note, 2 of the 3 samples from patients with progressive disease as best
response had copy number gain of \textit{BRAF}, however 1 was from a progression sample without a matching pretreatment specimen. Although our numbers are too small to draw any definitive conclusion from, they are consistent with prior findings suggesting that increased copy number of \textit{BRAF} is associated with progressive disease in some...
patients who are treated with BRAF or MEK inhibitors (15, 39). Importantly, preclinical studies suggest that this mechanism of resistance may potentially be overcome with increased doses of selective BRAF inhibitors (15).

We conducted detailed analysis of PTEN genetic status in association with response to BRAF inhibition, as several preclinical studies have suggested that PTEN loss contributes to intrinsic BRAF resistance (23, 24). Our data suggest that PTEN loss is associated with a shorter PFS in patients treated with BRAF inhibitors, although it is not predictive of best overall clinical response. This finding is not unexpected, as degree of response is not necessarily correlated with duration with targeted agents. Interestingly, PFS correlated with OS in the phase 3 study of vemurafenib, the only study able to use OS as a primary endpoint (40). It has been suggested that PTEN loss, as measured through IHC, is a negative prognostic factor for melanoma, independent of BRAF inhibition (41, 42). PTEN loss also is found more frequently in brain than lung or liver metastases, which are associated with worse prognosis (35). However, genetic analysis of PTEN status has not been previously assessed as a predictive or prognostic marker in melanoma, and has not been correlated with immunohistochemistry analyses. Although our data suggest that analyses using genetic methods may ultimately be better predictors of outcome than immunohistochemistry measurements, analyses of larger cohorts of patients with parallel genetics and proteomic analysis are needed to make definitive conclusions.

Copy number analysis of 36 genes previously observed to be altered in melanoma was conducted on samples from 23 dabrafenib-treated patients. Among those genes, lower copy number of CDKN2A and higher copy number of CCND1 were significantly associated with shorter PFS. The regions containing these genes also were implicated in our overall (unbiased) analysis of aCGH data, as CCND1 is located on 11q and CDKN2A on 9p. Both deletion/loss of CDKN2A (p16) and amplification/overexpression of CCND1 (cyclin D1) previously have been implicated as poor prognostic markers in melanoma (43–47). Thus, these genetic changes may function as either prognostic or predictive markers in response to BRAF inhibition. Amplification of CCND1 also has been associated with intrinsic resistance to BRAF inhibition in preclinical studies (25, 48). Other genes which have been implicated in intrinsic resistance to BRAF inhibition, including Rb1 loss, MET and SRC amplification, did not emerge as associated with PFS in our analysis (24, 25).

Although this study contains a large set of melanoma tissue samples from patients treated with dabrafenib, samples were not available from all patients enrolled in the clinical trial, potentially limiting the generalizability of our results. However, the characteristics of the patients included in the correlative studies, as reviewed in Table 1, did not differ from those on the trial as a whole (data not shown). We were not able to determine whether the genetic alterations identified as correlates of clinical outcome were predictive, prognostic or both, and prior clinical and preclinical data support both interpretations of the data. Some tissue samples collected at progression lacked a paired baseline specimen, limiting our interpretation of the genetic and genomic findings in the progression samples. Several studies have showed intertumoral heterogeneity using massively parallel sequencing (49, 50). Based on our own studies using massively parallel sequencing in a similar sample set (data not shown), low-level point mutations (<5–10% allele frequency), such as in NRAS, could have been missed. However, copy number changes (other than high-level amplification) are more difficult to interpret without matched germline samples using massively parallel sequencing, particularly for capture-based methods. Thus, it is less likely that massively parallel sequencing would have provided greatly improved sensitivity in this context. Finally, as we mainly focused on known genetic alterations and genomic aberrations associated with melanoma, it is possible that we did not identify novel predictors of clinical outcome in this dataset. Of note, however, our unbiased analysis of copy number also pointed towards CDKN2A (9p) and CCND1 (11q).

In summary, we identified PTEN loss, CDKN2A deletion, and CCND1 amplification as associated with decreased PFS upon treatment with dabrafenib. An exploratory analysis (data not shown) showed that carriage of two genomic alterations, or all three together, was associated with a trend toward worsening PFS. Although the interpretation of this analysis was limited by the small number of patients in each group, this approach should be considered for larger sample sets in the future. Ultimately, if validated in future patients, genetic analysis of PTEN, CDKN2A, and CCND1 may be used to identify patients who should be considered for frontline combinatorial approaches, particularly using agents that are activated by aberrations in these genes. Thus, these data suggest where potential combination therapies in conjunction with dabrafenib might be most effectively targeted. These studies also emphasize the continued importance of trials with associated biopsies on a large number of patients, so that we may gain insights into predictors of clinical outcome.

Disclosure of Potential Conflicts of Interest

K.L. Nathanson and S. O’Day have commercial research grants from GSK. A.M. Martin, J. Groschock, and B. Ma have ownership interest (including patents) in GlaxoSmithKline. G.S. Falchook has commercial research grant from GlaxoSmithKline. G.S. Falchook has also received travel reimbursement from GlaxoSmithKline for ESMO 2010. M. Millward is a consultant/advisory board member of GlaxoSmithKline. M.P. Brown is a consultant/advisory board member of GSK. A. Pavlick has commercial research grant from BMS, Genentech, Millennium, and Merck. A. Pavlick also has honoraria from Speakers Bureau of Genentech and BMS. M.A. Davies has commercial research grants from GlaxoSmithKline, Genentech, Merck, Myriad, Oncobodyneon, and AstraZeneca. M.A. Davies is a consultant/advisory board member of GlaxoSmithKline, Genentech, and Novartis. R. Gagnon is employed (other than primary affiliation; e.g., consulting) as a statistician for GlaxoSmithKline. C.M. Curtis has ownership interest (including patents) in GlaxoSmithKline. R.F. Kefford is a consultant/advisory board member of GSK, Roche, and Novartis. C.V. Long is a consultant/advisory board member of GSK, Roche, Amgen, Novartis, and BMS. No potential conflicts of interest were disclosed by the other authors.

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Authors' Contributions

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Tumor Genetic Analyses of Patients with Metastatic Melanoma Treated with the BRAF Inhibitor Dabrafenib (GSK2118436)

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