

KIT as a Therapeutic Target in Metastatic Melanoma

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MELANOMA CAUSES THE greatest morbidity and mortality of all skin cancers.¹ An estimated 68 130 invasive melanomas were diagnosed and 8700 deaths due to metastatic disease were recorded in the United States in 2010.² Dacarbazine,³ interleukin 2,⁴ and ipilimumab are approved for the treatment of metastatic melanoma by the US Food and Drug Administration. Only ipilimumab has been shown to improve overall survival.³⁻⁵

Melanoma is composed of several biologically distinct subtypes, each with unique genetic and clinical features,⁶ and each likely to respond differently to any

See also Patient Page.

Context Some melanomas arising from acral, mucosal, and chronically sun-damaged sites harbor activating mutations and amplification of the type III transmembrane receptor tyrosine kinase KIT. We explored the effects of KIT inhibition using imatinib mesylate in this molecular subset of disease.

Objective To assess clinical effects of imatinib mesylate in patients with melanoma harboring *KIT* alterations.

Design, Setting, and Patients A single-group, open-label, phase 2 trial at 1 community and 5 academic oncology centers in the United States of 295 patients with melanoma screened for the presence of *KIT* mutations and amplification between April 23, 2007, and April 16, 2010. A total of 51 cases with such alterations were identified and 28 of these patients were treated who had advanced unresectable melanoma arising from acral, mucosal, and chronically sun-damaged sites.

Intervention Imatinib mesylate, 400 mg orally twice daily.

Main Outcome Measures Radiographic response, with secondary end points including time to progression, overall survival, and correlation of molecular alterations and clinical response.

Results Two complete responses lasting 94 (ongoing) and 95 weeks, 2 durable partial responses lasting 53 and 89 (ongoing) weeks, and 2 transient partial responses lasting 12 and 18 weeks among the 25 evaluable patients were observed. The overall durable response rate was 16% (95% confidence interval [CI], 2%-30%), with a median time to progression of 12 weeks (interquartile range [IQR], 6-18 weeks; 95% CI, 11-18 weeks), and a median overall survival of 46.3 weeks (IQR, 28 weeks-not achieved; 95% CI, 28 weeks-not achieved). Response rate was better in cases with mutations affecting recurrent hotspots or with a mutant to wild-type allelic ratio of more than 1 (40% vs 0%, $P = .05$), indicating positive selection for the mutated allele.

Conclusions Among patients with advanced melanoma harboring *KIT* alterations, treatment with imatinib mesylate results in significant clinical responses in a subset of patients. Responses may be limited to tumors harboring *KIT* alterations of proven functional relevance.

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one therapeutic strategy. The most common melanoma subtype in the United States arises from non-chronically sun-

damaged (non-CSD) skin and often harbors activating mutations in *BRAF*.⁷ Melanoma arising from mucosal, acral,

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and CSD sites infrequently have *BRAF* mutations, but commonly have amplifications or activating mutations of *KIT*.^{8,9} *KIT* is a type III transmembrane receptor tyrosine kinase.¹⁰ Binding of its ligand, stem cell factor, results in receptor dimerization, autophosphorylation, and activation of several signaling pathways; thereby, mediating cancer cell growth, proliferation, invasion, metastasis, and inhibition of apoptosis.

The importance of *KIT* in normal melanocyte development is well established¹¹⁻¹³; however, its role as an oncogene and therapeutic target in melanoma has only recently become clear. Although *KIT* is expressed in some melanomas, loss of expression is observed with progression of disease from superficial to invasive to metastatic stages, suggesting that *KIT* possesses tumor suppressive functions.¹⁴⁻¹⁸ Furthermore, 3 phase 2 studies of metastatic melanoma treated with imatinib mesylate, an orally available ATP-competitive inhibitor of several tyrosine kinases including *KIT*, did not demonstrate clinical activity.¹⁹⁻²¹ These trials accrued before the discovery of activating mutations of *KIT* in melanoma and did not select patients based on the presence of *KIT* mutations or amplification.

KIT is an established therapeutic target in cancers with activating mutations of *KIT*, such as gastrointestinal stromal tumors (GIST), and significant benefit is achieved with various small molecule inhibitors of *KIT* including imatinib mesylate.²² Several melanoma cell lines with *KIT* mutations are highly sensitive to imatinib mesylate.²³⁻²⁵ Furthermore, several patients with melanoma harboring *KIT* alterations, including a K642E mutation as well as a 7-codon duplication of exon 11, have been reported to achieve major durable responses to imatinib mesylate.^{26,27}

Given the preclinical and anecdotal clinical activity of imatinib mesylate observed in *KIT* mutant melanoma, we conducted this study to test the hypothesis that inhibition of *KIT* in a molecularly selected subgroup of patients with melanomas harboring mutations or amplification of *KIT* will

result in objective regression and disease control. We further explored whether the identification of functionally relevant *KIT* alterations would allow us to better select patients most likely to respond to *KIT* inhibition.

METHODS

Patients

Between April 23, 2007, and April 16, 2010, 328 patients were enrolled from 1 community and 5 academic oncology centers in the United States for molecular screening and determination of eligibility. Eligible patients included those patients aged 18 years or older with metastatic melanoma arising from acral, mucosal, and body sites with signs of CSD harboring mutations or amplification of *KIT*. Patients required an Eastern Cooperative Oncology Group performance status of 0 (able to be fully active and perform all predisease activities without restriction), 1 (unable to perform physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature, such as light housework or office work), or 2 (ambulatory and capable of all self-care, but unable to perform any work activities),²⁸ life expectancy of 3 months or longer, measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST),²⁹ and adequate bone marrow, hepatic, and renal function. Prior systemic therapy and treated stable brain metastases were permitted.

All patients were informed of the investigational nature of the study and provided written informed consent in accordance with institutional and federal guidelines. The protocol was approved by each center's institutional review board. Race/ethnicity was self-reported by the participants.

Molecular Screening

Tumor specimens were tested for *KIT* mutations and amplification. DNA for mutation analysis was extracted from formalin-fixed, paraffin-embedded specimens as previously published.³⁰ Polymerase chain reaction assays using primers specific for *KIT* exons 9, 11, 13,

17, and 18; *NRAS* exons 1 and 2; *BRAF* exon 15; and *GNAQ* exon 5 were used, followed by Sanger sequencing. Polymerase chain reaction products were purified using ExoSAP-IT (USB Corporation, Cleveland, Ohio) and directly sequenced in the forward and reverse directions using the Applied Biosystems 3730 capillary DNA analyzer (Applied Biosystems, Foster City, California).

Fluorescence in situ hybridization was performed on formalin-fixed, paraffin-embedded sections as previously described.²³ Human BAC clones RP11-722F1 and CTD-3180G20 spanning *KIT* in 4q12 (Invitrogen, Carlsbad, California), reference clones RP11-365H22 (Wellcome Trust Sanger Institute, Hinxton, Cambridge, England) and RP11-799E21 (BACPAC Resources, Oakland, California) for proximal 4q, and RP11-19F13 (Wellcome Trust Sanger Institute) and RP11-461G20 (BACPAC Resources) proximal 4p were used.³¹ BAC DNA was labeled by nick translation with red dUTP (*KIT*), orange dUTP (4q reference), or green dUTP (4p reference) from Enzo Life Sciences Inc, Plymouth Meeting, Pennsylvania. Analysis used a Zeiss Axioplan epifluorescence microscope with motorized stage and Isis 5 imaging software (MetaSystems Group, Waltham, Massachusetts). Amplification was defined as a *KIT*-to-centromere ratio of more than 2.5, with a ratio of more than 10 representing high-level amplification. Polysomy was defined as the presence of discrete red, orange, and green signal groups.

Study Procedures

Patients whose tumors harbored a *KIT* alteration were eligible to receive imatinib mesylate, 400 mg orally twice daily in 6-week cycles until unacceptable toxicity or disease progression. Imatinib mesylate was supplied by the Division of Cancer Treatment and Diagnosis at the National Cancer Institute. Imatinib mesylate was reduced to 400 mg/d in the setting of toxicity, with one further reduction to 300 mg/d permitted. Study participation was discontinued if adverse effects persisted.

Table 1. Frequency of Alterations Identified in *KIT*, *BRAF*, *NRAS*, and *GNAQ* by Melanoma Subtype

Melanoma	No./Total No. (%) of Patients						
	<i>KIT</i>				<i>BRAF</i> Mutation	<i>NRAS</i> Mutation	<i>GNAQ</i> Mutation
	Mutation	Amplification	Both	Either			
Acral (n = 85)	18/84 (21.4)	8/83 (9.6)	6/82 (7.3)	20/84 (23.8)	19/84 (22.6)	13/84 (15.5)	1/80 (1.2)
Mucosal (n = 93)	17/93 (18.3)	14/91 (15.2)	8/91 (8.8)	23/93 (24.7)	8/92 (8.7)	11/92 (12.0)	0/92 (0)
CSD, centrally reviewed (n = 32) ^a	5/32 (15.6)	3/30 (10.0)	2/30 (6.7)	6/32 (18.8)	7/32 (21.9)	0/32 (0)	0/31 (0)
Total	40/209 (19.1)	25/204 (12.2)	16/203 (7.9)	49/209 (23.4)	34/208 (16.3)	24/208 (11.5)	1/203 (0.5%)

Abbreviation: CSD, chronically sun-damaged.

^aAmong the 87 patients with melanoma arising from skin with clinical evidence of CSD, 8 (9.2%) harbored either a mutation or amplification of *KIT*. When limiting assessment to the 32 patients with melanoma arising from sun-damaged skin confirmed histopathologically by central review, only 6 cases harbored a *KIT* mutation or amplification. Overall, 51 cases harboring a mutation or amplification of *KIT* were identified; however, the subset of cases described in this Table includes only 49 such cases.

Safety evaluations were conducted within 14 days of treatment initiation, every 2 weeks for 18 weeks, and every 6 weeks thereafter. Evaluation included physical examination, complete blood cell count, and clinical chemistry panel, including lactate dehydrogenase. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (available at http://www.ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

Radiographic imaging and tumor measurements were performed within 4 weeks of treatment initiation, every 6 weeks for 18 weeks, and every 12 weeks subsequently. Response was judged according to RECIST version 1.0.²⁹ All RECIST responses were confirmed by a central radiologist (J.T.). To be considered durable, changes in tumor measurements were confirmed by repeat radiologic assessment performed no less than 6 weeks after the initial response was observed. Stable disease was defined as a less than 30% decrease or less than 20% increase in the sum of the longest diameters of the target lesions, taking as reference the baseline tumor measurements. Patients receiving 2 or more weeks of imatinib mesylate were evaluable for response. Patients receiving at least 1 week of imatinib mesylate were evaluable for toxicity.

Statistical Analysis

The primary end point of this single-group, open-label, phase 2 study was durable objective response defined as

partial response or complete response according to RECIST version 1.0.²⁹ Secondary end points included time to progression, overall survival, and correlation of molecular alterations and clinical response.

A Simon 2-stage mini-max design³² was used to assess the primary end point of response, with the following parameters: 10% not promising response rate, 30% promising response rate, and .10 type I and II error rates. If 1 or more durable responses were observed in the first 16 evaluable patients, accrual continued until 25 evaluable patients were identified. If 5 or more durable responses were observed, imatinib mesylate would be considered worthy of further testing in this patient population.

Survival time was defined as the time from initiation of imatinib mesylate to the date of death or last follow-up. Time to progression was defined as the time from initiation of imatinib mesylate to the date of progression or last follow-up. Survival distributions were estimated using the Kaplan-Meier method.³³ Comparisons were made by log-rank test. Baseline patient characteristics and adverse events were reported using summary statistics and frequency tables. Adverse events were reported as the most severe manifestation of each event category during any cycle of treatment. Fisher exact test was used to compare molecular alteration and response. Statistical analysis was conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). All significance tests were 2-sided and used a 5% level of significance.

Table 2. Demographic and Baseline Characteristics of the Patients

Characteristic	No. (%) of Patients (n = 28)
Sex	
Female	15 (54)
Male	13 (46)
Age, median (range), y	71 (49-88)
Race/ethnicity	
White	27 (96)
Black	1 (4)
Non-Hispanic or non-Latino	26 (93)
Hispanic or Latino	2 (7)
Clinical melanoma subtype	
Mucosal	13 (46)
Acral	10 (36)
Chronically sun-damaged	5 (18)
Increased lactate dehydrogenase ^a	11 (39)
ECOG performance status	
0	19 (68)
1	8 (28)
2	1 (4)
Prior systemic regimens for metastatic disease	
0	7 (25)
1	14 (50)
≥2	7 (25)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
^aIndicates lactate dehydrogenase level of more than the upper limit of normal.

RESULTS

Molecular Screening

Three hundred twenty-eight patients consented to molecular screening. The flow of patients and tumor testing is shown in eFigure 1 (available at <http://www.jama.com>). Mutation status for *KIT*, *BRAF*, *NRAS*, and *GNAQ*, and *KIT* amplification status was determined in 295 cases, including 85 acral melanomas, 93 mucosal melanomas, and 87 melanomas clinically determined to arise from CSD sites.

and *KIT* alteration identified for each evaluable patient are shown in FIGURE 1. Representative radiographic images of patients achieving responses are shown in FIGURE 2. Because 2 of the 6 responses were transient and not sustained on a follow-up scan performed 6 weeks after the initial response was documented, the predetermined end point of 5 responses of 25 evaluable patients who were treated was not met.

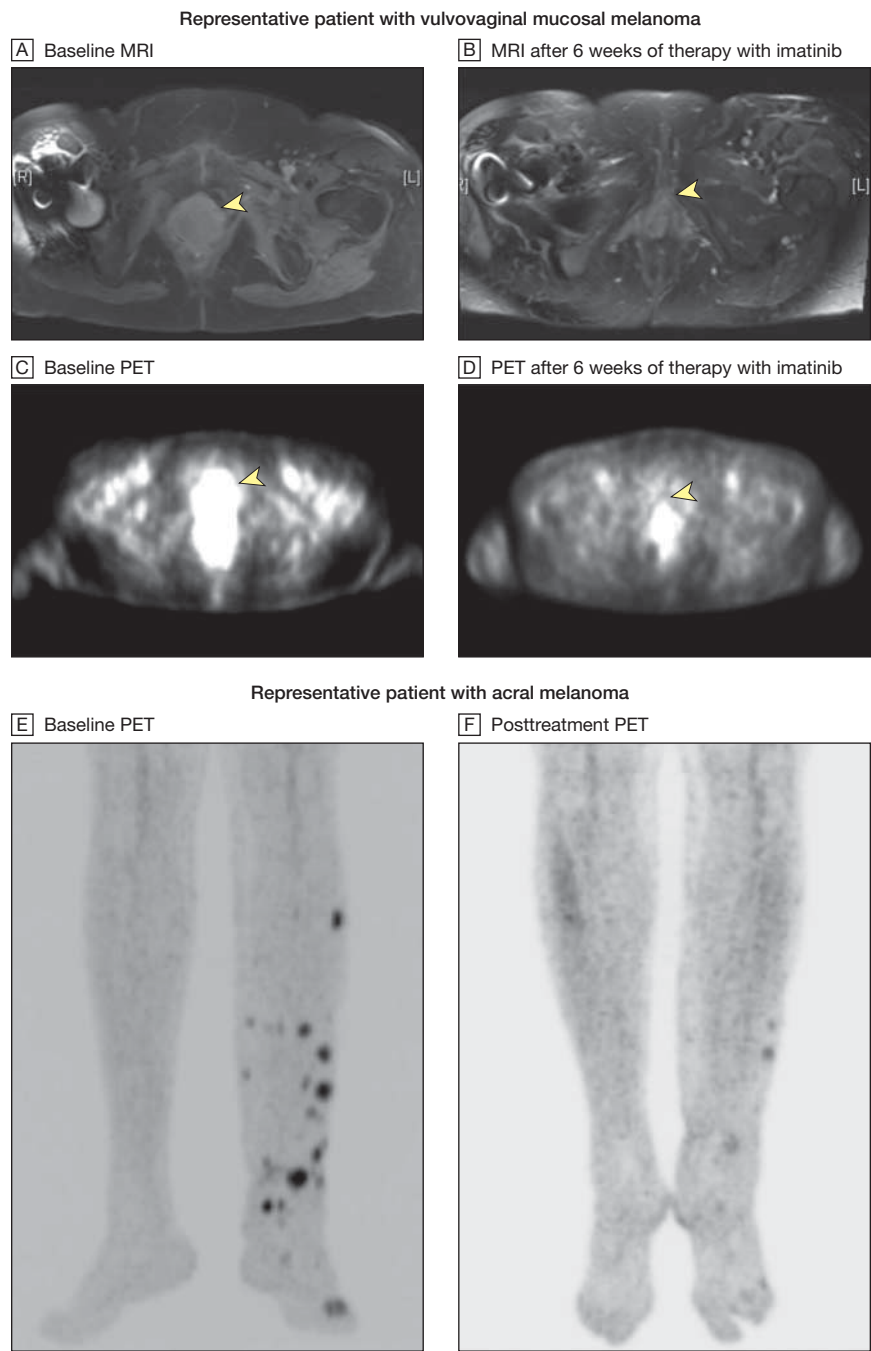
The median time to progression was 12 weeks (interquartile range [IQR], 6-18 weeks; 95% CI, 11-18 weeks). The 4 patients who achieved durable responses maintained disease control for more than 1 year. Durable disease control was observed in patients achieving stable disease, with 2 such patients maintaining stability for more than 6 months. Median survival from the time of initiation of therapy was 46.3 weeks (IQR, 28 weeks-not achieved; 95% CI, 28 weeks-not achieved), with 10 patients (40%) alive at the time of analysis (FIGURE 3).

Five patients underwent optional serial tumor biopsies to determine histopathological and immunohistochemical effects of therapy. One case demonstrating decreased cellularity and reduced tumor proliferation in a clinically responding metastasis compared with both pretreatment sample as well as a clinically progressing lesion is shown in eFigure 3.

Association of Molecular Alterations and Clinical Response

We observed that *KIT* mutations are widely distributed over the coding region as shown in eFigure 2. Many *KIT* mutations identified in our study have not previously been reported in melanoma^{8,9} or GIST^{35,36} and were present only in individual cases, suggesting that some may represent passenger mutations rather than bona fide driver alterations. Specific amino acid changes encountered repeatedly in cancer are likely to be of functional relevance. Interestingly, all 6 responses occurred in tumors with L576P or K642E mutations, the most common mutations in melanoma.^{8,9} The proportion of responders

Figure 2. Radiographic Responses to Imatinib Mesylate



MRI indicates magnetic resonance imaging; PET, positron emission tomography. MRI and PET scans from a representative patient with vulvovaginal mucosal melanoma harboring both an exon 11 L576P mutation and amplification of *KIT* are shown at baseline (yellow arrows, A and C) and after 6 weeks of therapy with imatinib mesylate (yellow arrows, B and D). The arrowhead in A indicates a heterogeneous multilobulated mass distending the entire vagina and extending inferiorly to the introitus. This lesion demonstrates intense fluorodeoxyglucose uptake on PET imaging (arrowhead in C). After 6 weeks of therapy with imatinib mesylate, there was significant shrinkage in the size of this mass with interval resolution of hypermetabolic activity (arrowheads in B and D indicate baseline locations of tumor). This patient ultimately achieved a complete radiographic response to therapy at her week 12 scan. Baseline and posttreatment PET images of a second representative patient with an acral melanoma harboring an exon 11 576P mutation and amplification are shown in E and F. This patient ultimately achieved a complete radiographic and pathological response to therapy at his week 12 scan.

a functionally relevant event. Subgroup analysis reveals a higher response rate in cases with an allelic ratio of more than 1 (71% vs 6%; $P=.002$), with a longer median time to progression (18.0 weeks [IQR, 12.0-95.4 weeks; 95% CI, 11.6-95.4 weeks] vs 11.0 weeks [IQR, 5.0-16.0 weeks; 95% CI, 5.0-12.0 weeks]; $P=.01$) and extended median survival (median not achieved [IQR, 46.5 weeks-not achieved; 95% CI, 34.8 weeks-not achieved] vs 31.3 weeks [IQR, 18.1-80.5 weeks; 95% CI, 18.1-61.5 weeks]; $P=.03$).

COMMENT

These results demonstrate that a subset of melanomas with genetic alterations of *KIT* respond to treatment with imatinib mesylate. Durable responses were observed in 16% (95% CI, 2%-30%) of these patients, with all sustained for more than 1 year. Two additional responses were observed but not sustained on a follow-up scan performed 6 weeks after the initial response was documented. Therefore, this study did not meet its predetermined end point. Nevertheless, the responses achieved in this population preselected based on the presence of *KIT* mutations or amplification compare favorably to that observed in prior trials of molecularly unselected patients,¹⁹⁻²¹ in which response was limited to 1 of 62 evaluable participants treated.

This study additionally highlights the challenges in identifying appropriate patients for treatment with *KIT* inhibition. Seventy-four percent of *BRAF* mutant melanomas harbor a substitution of glutamic acid for valine at amino acid 600 (the V600E mutation).³⁹ By contrast, mutations in *KIT* are more widely distributed over the coding region. Treatment of patients with melanoma harboring the oncogenic V600E *BRAF* mutation with an effective inhibitor of RAF, such as PLX4032 (Plexxikon, RG7204; Roche Pharmaceuticals, Basel, Switzerland), results in tumor response in 81% of cases.⁴⁰ The more modest results in this study suggest that only select *KIT* alterations are truly oncogenic and indicative of an effective therapeutic target.

By using more selective molecular criteria, we may better identify patients who will respond to imatinib mesylate. Response to imatinib mesylate is predicted to be dependent on the region of the protein affected by a mutation, with some mutations affecting the binding affinity of imatinib mesylate to *KIT* as previously demonstrated in *in vitro* and clinical studies of GIST.^{35,37,41} Prior observations in GIST demonstrated the sensitivity of K642E and N822K mutations and the resistance of V654A and D820Y mutations to imatinib mesylate.^{35,41,42} Concordant with these findings, patients with melanoma harboring these resistant mutations progressed, although disease stability and responses were observed in those patients whose tumors harbored K642E and N822K mutations (Figure 1). Imatinib mesylate-resistance in GIST commonly results from the development of secondary *KIT* mutations, including V654A, D820Y, N822K, and A829P.^{35,36} These mutations were identified as primary mutations in several melanomas and may also predict a lower probability of response with imatinib mesylate. Indeed, the best response we observed in such cases was stable disease. Importantly, although an *in vitro* study demonstrated poor sensitivity of a melanoma cell line harboring an L576P mutation to imatinib mesylate,⁴³ we observed dramatic *in vivo* responses in patients with melanomas harboring this mutation.

To separate bona fide driver from passenger alterations of *KIT*, we sought evidence for tumor selection of specific mutations. We observed that imatinib mesylate has greater activity in tumors harboring recurrent *KIT* mutations found in melanoma or GIST, as well as in tumors with a mutant *KIT* allele in greater abundance than the wild-type allele. When combining those patients whose tumors have an allelic ratio of more than 1 with those whose tumors harbor recurrent primary mutations found in GIST or melanoma, we observed a better response rate, time to progression, and overall survival compared with other cases (Figure 3). These criteria may serve as indicators of genetic events relevant to oncogenesis and should be investi-

gated further as predictive markers of response to *KIT* inhibition.

In conclusion, our data show that imatinib mesylate therapy in patients with melanoma harboring specific *KIT* alterations results in clinical responses, consistent with the paradigm of oncogene addiction.⁴⁴ Prediction of response to *KIT* inhibition can be improved beyond what we report herein by identifying tumors that harbor *KIT* alterations of functional relevance.

Author Contributions: Dr Carvajal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Carvajal, Wolchok, Takebe, Bastian, Schwartz.

Acquisition of data: Carvajal, Antonescu, Wolchok, Chapman, Roman, Teitcher, Busam, Chmielowski, Lutzky, Pavlick, Fusco, Cane, Takebe, Vemula, Bastian, Schwartz.

Analysis and interpretation of data: Carvajal, Antonescu, Wolchok, Chapman, Roman, Panageas, Busam, Chmielowski, Lutzky, Vemula, Bouvier, Bastian, Schwartz.

Drafting of the manuscript: Carvajal, Antonescu, Panageas, Bastian, Schwartz.

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Statistical analysis: Carvajal, Panageas.

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Study supervision: Carvajal, Wolchok, Chapman, Takebe, Bastian, Schwartz.

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Online-Only Material: eFigures 1 through 3 and eTables 1 and 2 are available at <http://www.jama.com>.

Additional Contributions: Margaret Leversha, PhD, and Kalyani Chadalavada (both at Memorial Sloan-Kettering Cancer Center, New York, New York), and the Memorial Sloan-Kettering Cancer Center Molecular Cytogenetics Core provided assistance with the conduct of the fluorescence in situ hybridization studies. Dr Leversha and Ms Chadalavada did not receive any compensation for their work on this study.

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