ORIGINAL ARTICLE

Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma

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ABSTRACT

BACKGROUND

Activating mutations in serine–threonine protein kinase B-RAF (BRAF) are found in 50% of patients with advanced melanoma. Selective BRAF-inhibitor therapy improves survival, as compared with chemotherapy, but responses are often short-lived. In previous trials, MEK inhibition appeared to be promising in this population.

METHODS

In this phase 3 open-label trial, we randomly assigned 322 patients who had metastatic melanoma with a V600E or V600K BRAF mutation to receive either trametinib, an oral selective MEK inhibitor, or chemotherapy in a 2:1 ratio. Patients received trametinib (2 mg orally) once daily or intravenous dacarbazine (1000 mg per square meter of body-surface area) or paclitaxel (175 mg per square meter) every 3 weeks. Patients in the chemotherapy group who had disease progression were permitted to cross over to receive trametinib. Progression-free survival was the primary end point, and overall survival was a secondary end point.

RESULTS

Median progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (hazard ratio for disease progression or death in the trametinib group, 0.45; 95% confidence interval [CI], 0.33 to 0.63; P<0.001). At 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the chemotherapy group despite crossover (hazard ratio for death, 0.54; 95% CI, 0.32 to 0.92; P=0.01). Rash, diarrhea, and peripheral edema were the most common toxic effects in the trametinib group and were managed with dose interruption and dose reduction; asymptomatic and reversible reduction in the cardiac ejection fraction and ocular toxic effects occurred infrequently. Secondary skin neoplasms were not observed.

CONCLUSIONS

Trametinib, as compared with chemotherapy, improved rates of progression-free and overall survival among patients who had metastatic melanoma with a BRAF V600E or V600K mutation. (Funded by GlaxoSmithKline; METRIC ClinicalTrials.gov number, NCT01245062.)

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*Members of the MEK versus DTIC or Taxol in Metastatic Melanoma (METRIC) study group are listed in the Supplementary Appendix, available at NEJM.org.

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About 160,000 new cases of melanoma are diagnosed and 48,000 melanoma-related deaths occur worldwide each year.[1] Among cancers in patients under 40 years of age, the incidence of melanoma is second only to that of breast cancer for women and leukemia for men.[2]

Before 2010, no systemic therapy had been shown to improve overall survival among patients with metastatic melanoma, and only modest improvements were observed with interferon as an adjuvant drug.[3] Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and vemurafenib, a selective BRAF inhibitor, have both been shown to improve survival among patients with metastatic melanoma in randomized trials.[4-6]

Activating mutations in serine–threonine protein kinase B-RAF (BRAF), a constituent of the MAP kinase signal-transduction pathway, were first described in 2002 and have been identified in approximately 50% of patients with advanced melanoma.[7,8] The most commonly observed BRAF mutation, V600E, and the next most common, V600K, account for 95% of the BRAF mutations found in all patients with cancer. Activated BRAF phosphorylates and activates MEK proteins (MEK1 and MEK2), which then activate downstream MAP kinases. The MAP kinase pathway is known to regulate proliferation and survival of tumor cells in many cancers.[9] In preclinical models of human melanoma, selective BRAF and MEK inhibitors have inhibited growth and induced cell death in tumors bearing BRAF mutations.[10,11] The use of BRAF inhibitors has been associated with improved rates of progression-free survival and overall survival among patients with BRAF-mutated melanoma.[6]

Trametinib (GSK1120212, GlaxoSmithKline Pharmaceuticals) is an orally available, small-molecule, selective inhibitor of MEK1 and MEK2.[12] At doses that appeared to be nontoxic, trametinib inhibited the growth of human melanoma tumors with the V600E BRAF mutation that were transplanted into mice. In phase 1 and 2 trials, trametinib showed evidence of tumor regression and disease stabilization in patients who had melanoma with a V600E or V600K BRAF mutation.[13,14]

We initiated a randomized, controlled, open-label, phase 3 trial of trametinib when ipilimumab and vemurafenib were still investigational agents. However, the availability of these drugs in clinical trials raised concern that post-protocol therapy with either or both agents might confound a primary end point of overall survival in our study. Therefore, we chose progression-free survival as the primary end point, with the opportunity for patients with disease progression while receiving chemotherapy to cross over to receive trametinib.

METHODS

PATIENTS

Patients who had histologically confirmed, unresectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation were eligible for the study. Mutational status was determined with the use of an allele-specific, investigational polymerase-chain-reaction (PCR) assay performed at Response Genetics. Additional eligibility criteria were an age of at least 18 years, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active) or 1 (ambulatory but restricted in physically strenuous activity),[15] and adequate organ function. Patients could have received one previous chemotherapy regimen for advanced or metastatic melanoma, with the exclusion of BRAF and MEK inhibitors and ipilimumab. Patients with stable brain metastases were allowed to enroll. Patients with a history of clinically significant cardiovascular or interstitial lung disease and those with evidence or a risk of retinal-vein occlusion or central serous retinopathy were excluded. All patients provided written informed consent at screening.

STUDY DESIGN AND TREATMENT

From December 2010 through July 2011, we screened 1022 patients for V600E and V600K BRAF mutations in 103 centers worldwide. The most common reason for exclusion was a negative test for the mutations (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We randomly assigned 322 eligible patients (281 with the V600E mutation, 40 with the V600K mutation, and 1 with both mutations) in a 2:1 ratio to receive oral trametinib (2 mg once daily) or intravenous chemotherapy consisting of either dacarbazine (1000 mg per square meter of body-surface area) or paclitaxel (175 mg per square meter), at the discretion of the investigator, every 3 weeks. Patients were stratified according to the baseline lactate dehy-

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drogenase level (normal or elevated) and status with respect to previous chemotherapy for advanced disease (yes or no).

END POINTS

The primary end point was progression-free survival; secondary end points included overall survival, overall response rate, duration of response, and safety. Treatment continued until disease progression, death, or withdrawal from the study. Patients in the chemotherapy group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review.

Data from the phase 2 study of trametinib showed that the median progression-free survival was longer in the group of patients with the V600E BRAF mutation who did not have brain metastases at enrollment than in the overall study population (5.3 months vs. 4.0 months).[14] Therefore, the primary efficacy analysis was restricted to patients with the V600E BRAF mutation who did not have brain metastases at baseline (amendment 3.0 to the protocol). However, since no significant differences in outcome were observed between the primary efficacy population and the intention-to-treat population, data from the intention-to-treat population are presented.

ASSESSMENTS

Baseline and safety assessments are detailed in the Supplementary Appendix. Tumor assessments were carried out at baseline and at weeks 6, 12, 21, and 30 and then every 12 weeks. Site investigators used the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[16] to assess tumor responses. A blinded, independent central review of tumor assessments was performed.

Adverse events, which were graded on the basis of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, were assessed throughout the study and for 30 days after the end of treatment. Blood samples for determination of plasma levels of trametinib were obtained before the administration of the first dose and on day 1 of cycles 2, 5, and 8.

STUDY OVERSIGHT

The first author and representatives of the sponsor (GlaxoSmithKline) designed the study. Data collection was performed by staff employed at each study site and was monitored by the sponsor. The first two authors wrote the first draft of the manuscript, with support from the last author; all authors had full access to the study data and were involved in the data analysis. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy of the data and the fidelity of the study to the protocol. Editorial support in the form of graphic services was funded by the sponsor. The protocol (which is available at NEJM.org) was approved by the institutional review board at each study center and complied with country-specific regulatory requirements. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

STATISTICAL ANALYSIS

The prespecified number of progression-free survival events was reached in October 2011, and the results reported here are based on data analyses from February 2012. A final overall survival analysis is planned after 80% of patients who underwent randomization have died or have otherwise been lost to follow-up. Efficacy analyses were carried out both in the intention-to-treat population and in the primary efficacy population. The study was designed with a power of at least 99% at a one-sided alpha level of 0.025 to detect a relative improvement of 133% in progression-free survival (hazard ratio for disease progression or death, 0.43) in the trametinib group, as compared with the chemotherapy group. Progression-free survival was defined as the time from randomization to the first documented radiologic progression or death on the basis of the site investigator's assessment.

We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival and used a stratified log-rank test for all comparisons except for subgroup analyses, which were not stratified. Response rates and 95% confidence intervals are reported for the two study groups. We used Fisher's exact test to analyze all between-group comparisons and the Kaplan–Meier method to calculate medians and interquartile ranges to summarize the duration of response. Safety analyses included all patients who had received at least one dose of a study drug and are summarized according to the frequency of adverse events in the total population.

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RESULTS

PATIENTS

Baseline characteristics of the patients were well balanced between the two study groups, although more patients in the trametinib group had M1c disease (characterized by metastasis to sites beyond skin, lymph node, and lung or to any site with an elevated lactate dehydrogenase level) or three or more sites of disease (Table 1).

Table 1. Baseline Demographic and Disease Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Trametinib (N=214)	Chemotherapy (N=108)
Median age — yr (range)	55 (23–85)	54 (21–77)
Male sex — no. (%)	120 (56)	53 (49)
White race — no. (%)	214 (100)	108 (100)
ECOG performance status — no. (%)†		
0	136 (64)	69 (64)
1	78 (36)	39 (36)
Extent of metastatic melanoma — no. (%)‡		
M1a	24 (11)	15 (14)
M1b	35 (16)	22 (20)
M1c	144 (67)	63 (58)
Unresectable IIIC	10 (5)	8 (7)
History of brain metastasis — no. (%)	9 (4)	2 (2)
Disease at ≥3 sites — no. (%)	123 (57)	56 (52)
Lactate dehydrogenase — no. (%)§		
≤ULN	134 (63)	66 (61)
>ULN	77 (36)	42 (39)
Missing data	3 (1)	0
Previous chemotherapy — no. (%)		
No	143 (67)	70 (65)
Yes	71 (33)	38 (35)
Previous immunotherapy — no. (%)¶	68 (32)	30 (28)

* There were no significant differences between the two groups at baseline.
† On the Eastern Cooperative Oncology Group (ECOG) scale, a performance status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction, and a status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
‡ The M1a stage denotes metastasis of the tumor to the skin, subcutaneous tissues, or distant lymph nodes, with a normal lactate dehydrogenase level; M1b denotes metastasis to the lung, with a normal lactate dehydrogenase level; and M1c denotes metastasis to any site, with an elevated lactate dehydrogenase level. In unresectable stage IIIC disease, melanoma has spread to at least three regional lymph nodes or there is intralymphatic dermal metastasis. M staging was missing for one patient in the trametinib group.
§ The upper limit of the normal range (ULN) varied according to the reference values at each study center.
¶ Previous immunotherapy included adjuvant interferon, which accounted for the majority of patients receiving such therapy.

A total of 195 patients (61%) had disease progression or had died at the time of the primary analysis. According to a protocol amendment adopted on February 16, 2012, the independent data and safety monitoring committee and study steering committee concluded that both progression-free survival and overall survival were significantly longer in the trametinib group than in the chemotherapy group and that immediate crossover to trametinib should be permitted.

EFFICACY

There were 322 patients in the intention-to-treat population, of whom 273 (85%) were in the primary efficacy population. The primary efficacy population included patients with the V600E BRAF mutation who did not have brain metastases at baseline.

In the intention-to-treat population, the median duration of progression-free survival was 4.8 months in the trametinib group as compared with 1.5 months in the chemotherapy group (hazard ratio for progression, 0.45; 95% confidence interval [CI], 0.33 to 0.63; P<0.001), as assessed by the site investigators (Fig. 1A), with a slightly greater improvement in progression-free survival as assessed in the independent review (hazard ratio, 0.42; 95% CI, 0.29 to 0.59; P<0.001). The results were similar in the primary efficacy population. There was significant improvement in progression-free survival in all subgroups of patients, except for those with the V600K mutation and those 65 years of age or older (Fig. 1B).

In the intention-to-treat population, there were 35 deaths (16%) in the trametinib group and 29 (27%) in the chemotherapy group at the time of data cutoff. The 6-month overall survival rate in the intention-to-treat population was 81% in the trametinib group and 67% in the chemotherapy group, findings that were identical to those in the primary efficacy population (Fig. 2). The hazard ratio for death in the trametinib group was 0.54 (95% CI, 0.32 to 0.92; P=0.01), even though 51 of 108 patients (47%) in the chemotherapy group crossed over to receive trametinib. Median overall survival had not been reached at the time of this report, and follow-up continues in these cohorts. A total of 8% of patients in the trametinib group and 6% in the chemotherapy group received vemurafenib, and 5% in the trametinib group and no patients in the chemotherapy group received ipilimumab after the study therapy.

In the intention-to-treat analyses, the response

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rate, which was defined as the percentage of patients with a confirmed complete or partial response as assessed according to RECIST by the site investigators, was 22% (95% CI, 17 to 28) in the trametinib group and 8% (95% CI, 4 to 15) in the chemotherapy group (P=0.01) (Table 2). The median duration of response was 5.5 months (95% CI, 4.1 to 5.9) in the trametinib group (in 47 patients) and had not been reached in the chemotherapy group (in 9 patients). The response rates and durations were similar in the primary efficacy population.

ADVERSE EVENTS

Adverse events were assessed in the 310 patients who received at least one dose of a study drug. Adverse events that were reported in at least 15% of the patients in either group, regardless of whether they were considered to be related to the study treatment, are shown in Table 3. The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform; among the patients with rash, less than 8% had grade 3 or 4 rash. A decreased ejection fraction or ventricular dysfunction was observed in 14 patients (7%) in the trametinib group (11 with a decreased ejection fraction and 3 with left ventricular dysfunction). Two patients in the trametinib group had serious grade 3 cardiac-related events that were considered to be drug-related, leading to permanent discontinuation of the study drug.

Ocular events (mostly grade 1 or 2) occurred in 9% of patients in the trametinib group, with blurred vision as the most frequent single ocular event (4%); reversible chorioretinopathy (grade 3) occurred in one patient (<1%). No cases of retinal-vein occlusion had been reported at the time of analysis. No cutaneous squamous-cell carcinomas or hyperproliferative skin lesions were diagnosed while patients were receiving trametinib. Adverse events led to dose interruptions in 35% of patients and to dose reductions in 27% of patients in the trametinib group.

In the chemotherapy group, the most common adverse events were fatigue, nausea, constipation, vomiting, and alopecia. Adverse events led to dose interruptions in 22% of patients and to dose reductions in 10%.

DRUG EXPOSURE

On the basis of in vitro growth-inhibition assays in cell lines of melanoma with the V600E BRAF

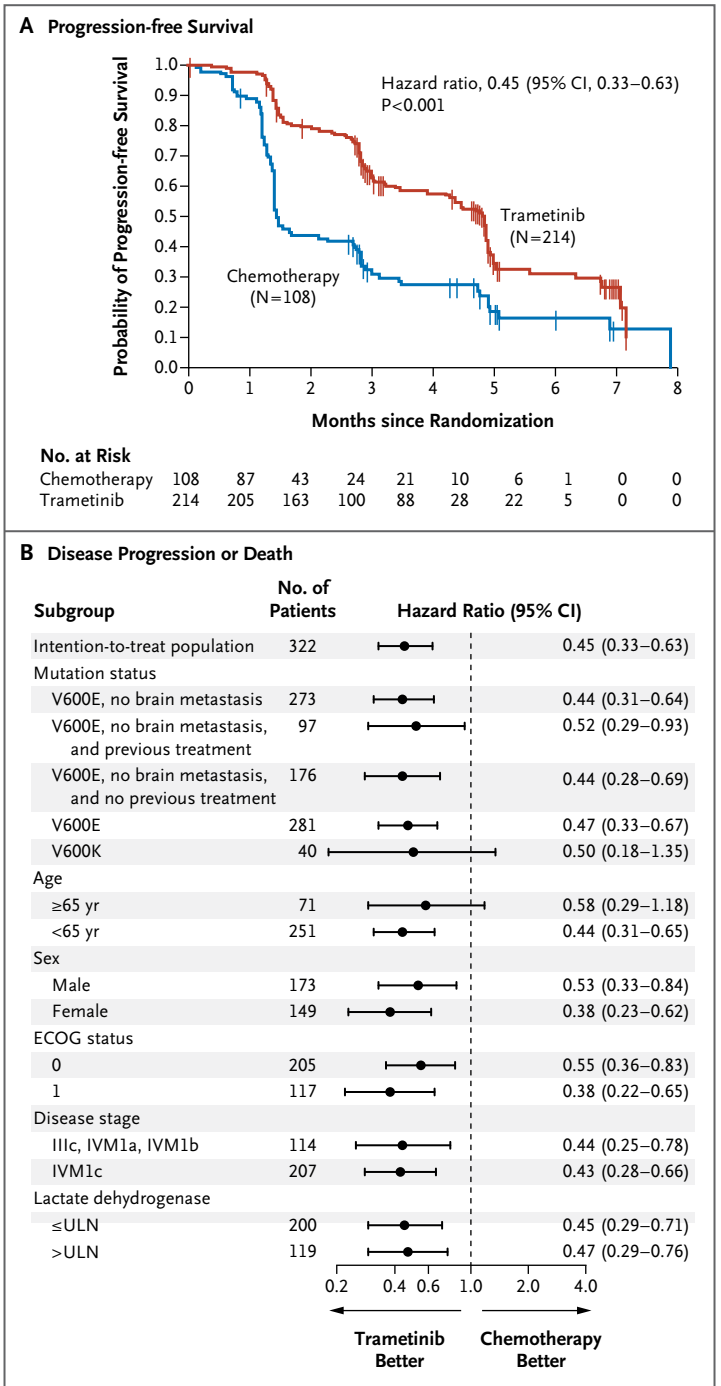

Figure 1. Progression-free Survival and Disease Progression or Death According to Subgroup.

Panel A shows Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population. Panel B shows hazard ratios for disease progression or death in subgroup analyses, according to baseline characteristics. The 273 patients with the V600E BRAF mutation who did not have brain metastases at baseline were evaluated in the primary efficacy analysis. ECOG denotes Eastern Cooperative Oncology Group, and ULN upper limit of the normal range.

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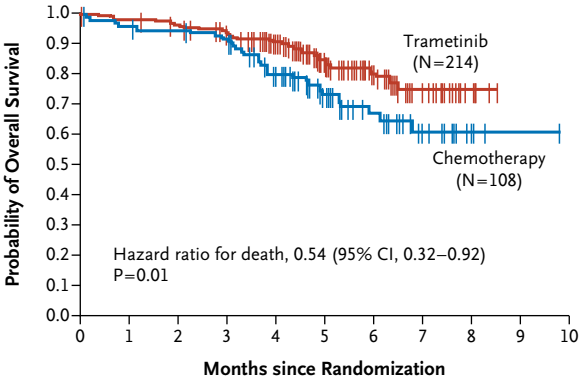

Figure 2. Kaplan–Meier Curves for Overall Survival.
Data are for the intention-to-treat population. The vertical lines indicate censoring of data.

Table 2. Confirmed Response (Intention-to-Treat Population).*

Type of Response	Trametinib (N=214)	Chemotherapy (N=108)
	number of patients (percent)	
Complete response	4 (2)	0
Partial response	43 (20)	9 (8)
Stable disease	119 (56)	34 (31)
Progressive disease	38 (18)	50 (46)
Could not be evaluated†	10 (5)	15 (14)
Complete or partial response	47 (22)	9 (8)

* Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Data regarding the best tumor response, as assessed by the site investigators, are shown for 322 patients.
† Responses could not be evaluated for patients who withdrew consent, were withdrawn by the site investigator, died, or started new anticancer therapy before the first efficacy assessment.

mutation, the target trametinib level after adjustment for the anticipated effects of protein binding in humans was 10.4 ng per milliliter. At the beginning of cycles 2, 5, and 8, the mean (±SD) predose plasma levels of trametinib were 14.5±4.63, 13.3±3.62, and 13.2±4.30 ng per milliliter, respectively.

DISCUSSION

The discovery of activating BRAF mutations in melanoma and other cancers has provided a basis for developing molecularly targeted therapies for this disease. Previously, a selective BRAF inhibitor, vemurafenib, has been associated with improvements in progression-free survival and overall survival, as compared with chemotherapy, among patients with BRAF-mutated melanoma.[6] Our study of the MEK inhibitor trametinib, as compared with chemotherapy, in a similar patient population showed improvements in the same end points. In the intention-to-treat and primary efficacy populations (with the latter representing 85% of the entire study population), we observed reductions of 55% and 56%, respectively, in the risk of disease progression or death in the trametinib group. These improvements were unaffected by adjustment for the small differences in baseline demographic factors on the basis of a Cox regression model. Patients in the chemotherapy group who had disease progression were permitted to cross over to receive trametinib. Even though 51 of 108 patients did so, we observed a 46% reduction in the risk of death among patients receiving trametinib. It is possible that the between-group difference in overall survival might have been even more significant in the absence of crossover.

In a randomized phase 3 trial comparing vemurafenib with chemotherapy in patients with melanoma and the V600E BRAF mutation who had not received previous treatment, the objective response rate was 48%, and approximately 90% of patients had some degree of tumor regression. A 74% reduction in the risk of disease progression and a 63% reduction in the risk of death were observed. With trametinib, 74% of patients had some degree of tumor regression, and 22% had a sufficient degree of sustained tumor regression to qualify as a confirmed objective response according to RECIST (Fig. S2 in the Supplementary Appendix). Although the response rate associated with trametinib appears to be inferior to that with vemurafenib, the two agents appear to provide similar improvements in progression-free and overall survival, as compared with chemotherapy. For both progression-free survival and overall survival, vemurafenib had a numerically greater effect than dacarbazine. Trametinib and vemurafenib would have to be directly compared in a randomized trial to definitively determine whether one drug is superior to the other. The molecular basis for the lesser degree of tumor regression observed with a MEK inhibitor than with a BRAF inhibitor is unknown.

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The safety profile of trametinib differs from that of vemurafenib. Although rash is common with both drugs, the nature of the rash observed with trametinib is papulopustular, as has been reported for other MEK inhibitors,[17] in contrast to the hyperkeratotic, maculopapular rash associated with vemurafenib. Diarrhea and peripheral edema are frequently observed with trametinib, whereas photosensitivity and arthralgia are associated with vemurafenib.[6] Central serous retinopathy and retinal-vein occlusion have been uncommon but worrisome adverse events associated with trametinib.

Notably, no cutaneous squamous-cell carcinomas were observed during the course of treatment with trametinib in our study population. In contrast, treatment-related squamous-cell carcinomas were reported in 18% and 26% of patients in two large trials of vemurafenib.[6,17] This and other differences in toxic effects point to different molecular effects on nonmelanoma tissues. Recent studies suggest that vemurafenib and other BRAF inhibitors can activate the MAP kinase pathway in some normal tissues and have an increased effect in cells that harbor activating RAS mutations.[18-20] RAS normally activates RAF and MEK. In a preclinical model of chemically induced squamous-cell carcinoma, a BRAF inhibitor accelerated the growth of skin lesions. The addition of a MEK inhibitor to a BRAF inhibitor in the same system prevented the appearance of squamous-cell carcinoma.[21]

Although further study will be needed to understand the individual role of BRAF inhibitors versus MEK inhibitors in patients who have melanoma with a V600E or V600K BRAF mutation, both classes of drugs appear to be capable of substantially altering the natural history of metastatic melanoma. Attention has recently turned to the possibility of combining BRAF and MEK inhibitors both to improve efficacy and to reduce toxicity. Preclinical data support an enhanced antitumor effect and the possibility of preventing BRAF-inhibitor–induced cutaneous squamous-cell carcinoma when the two agents are combined. Ongoing clinical trials are exploring the safety and efficacy of this approach. On the basis of emerging evidence that resistance to BRAF inhibitors was associated with reactivation of MEK and ERK, trametinib was administered in a small cohort of patients with resistance to BRAF inhibitors, but no responses were observed.[22,23] MEK-inhibitor therapy, followed by BRAF-inhibitor therapy at the time that resistance emerges, might be an effective sequence, but this hypothesis has not been investigated clinically. Selective BRAF inhibitors appear to be relevant only in the treatment of BRAF-mutated cancers, whereas ex-

Table 3. Adverse Events.*

Adverse Event	Trametinib (N=211)	Chemotherapy (N=99)
	number of patients (percent)	
Rash	121 (57)	10 (10)
Grade 2	40 (19)	3 (3)
Grade 3 or 4†	16 (8)	0
Diarrhea	91 (43)	16 (16)
Grade 2	13 (6)	3 (3)
Grade 3 or 4†	0	2 (2)
Fatigue	54 (26)	27 (27)
Grade 2	11 (5)	7 (7)
Grade 3	8 (4)	3 (3)
Peripheral edema	54 (26)	3 (3)
Grade 2	8 (4)	0
Grade 3	2 (1)	0
Acneiform dermatitis	40 (19)	1 (1)
Grade 2	20 (9)	0
Grade 3	2 (1)	0
Nausea	38 (18)	37 (37)
Grade 2	5 (2)	10 (10)
Grade 3	2 (1)	1 (1)
Alopecia	36 (17)	19 (19)
Grade 2	3 (1)	8 (8)
Grade 3	1 (<1)	0
Hypertension	32 (15)	7 (7)
Grade 2	6 (3)	3 (3)
Grade 3	26 (12)	3 (3)
Constipation	30 (14)	23 (23)
Grade 2	3 (1)	5 (5)
Grade 3	0	1 (1)
Vomiting	27 (13)	19 (19)
Grade 2	3 (1)	4 (4)
Grade 3	2 (1)	2 (2)

* The safety analysis included all patients who underwent randomization and received at least one dose of a study drug (310 patients). Three patients in the trametinib group and 9 patients in the chemotherapy group were not included in the safety population. Listed are the most common adverse events (occurring in ≥15% of patients) of any grade, along with grade 2 or 3 adverse events.

† One patient in the trametinib group had grade 4 rash, and one patient in the chemotherapy group had grade 4 diarrhea.

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tensive preclinical data and limited clinical data suggest that MEK inhibitors may be a component of effective therapy for a broad spectrum of cancers with other oncogenic drivers.

In conclusion, this prospective, randomized trial showed that trametinib, a MEK inhibitor, improved progression-free and overall survival, as compared with chemotherapy, in patients who had melanoma with a V600E or V600K BRAF mutation. Further work will be needed to determine the optimal role for trametinib in the treatment of metastatic melanoma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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