Phase II Study of the MEK1/MEK2 Inhibitor Trametinib in Patients With Metastatic *BRAF*-Mutant Cutaneous Melanoma Previously Treated With or Without a *BRAF* Inhibitor

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See accompanying article on page 499; listen to the podcast by Dr Flaherty at www.jco.org/podcasts

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ABSTRACT

Purpose

BRAF mutations promote melanoma cell proliferation and survival primarily through activation of MEK. The purpose of this study was to determine the response rate (RR) for the selective, allosteric MEK1/MEK2 inhibitor trametinib (GSK1120212), in patients with metastatic *BRAF*-mutant melanoma.

Patients and Methods

This was an open-label, two-stage, phase II study with two cohorts. Patients with metastatic *BRAF*-mutant melanoma previously treated with a *BRAF* inhibitor (cohort A) or treated with chemotherapy and/or immunotherapy (*BRAF*-inhibitor naïve; cohort B) were enrolled. Patients received 2 mg of trametinib orally once daily.

Results

In cohort A ($n = 40$), there were no confirmed objective responses and 11 patients (28%) with stable disease (SD); the median progression-free survival (PFS) was 1.8 months. In cohort B ($n = 57$), there was one (2%) complete response, 13 (23%) partial responses (PRs), and 29 patients (51%) with SD (confirmed RR, 25%); the median PFS was 4.0 months. One patient each with *BRAF* K601E and *BRAF* V600R had prolonged PR. The most frequent treatment-related adverse events for all patients were skin-related toxicity, nausea, peripheral edema, diarrhea, pruritis, and fatigue. No cutaneous squamous cell carcinoma was observed.

Conclusion

Trametinib was well tolerated. Significant clinical activity was observed in *BRAF*-inhibitor-naïve patients previously treated with chemotherapy and/or immunotherapy. Minimal clinical activity was observed as sequential therapy in patients previously treated with a *BRAF* inhibitor. Together, these data suggest that *BRAF*-inhibitor resistance mechanisms likely confer resistance to MEK-inhibitor monotherapy. These data support further evaluation of trametinib in *BRAF*-inhibitor-naïve *BRAF*-mutant melanoma, including rarer forms of *BRAF*-mutant melanoma.

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INTRODUCTION

Mutations in the serine/threonine protein kinase B-Raf (*BRAF*) are common in cutaneous melanoma, occurring in 40% to 60% of patients.¹⁻³ Approximately 70% to 90% of these mutations cause a substitution of glutamic acid for valine (V600E), and an additional 10% to 30% cause a substitution of lysine for valine (V600K); rare *BRAF* mutations occur in approximately 6% to 7% of *BRAF*-mutated melanoma.⁴⁻⁷ *BRAF* mutations constitutively acti-

vate MEK and ERK1/ERK2 proteins, which are downstream of *BRAF* in the mitogen-activated protein kinase (MAPK) pathway.²

Recently, two *BRAF* inhibitors, vemurafenib (PLX4032/RG7204) and dabrafenib (GSK2118436), have demonstrated response rates (RRs) of approximately 50% to 60% and progression-free survival (PFS) benefit over dacarbazine in *BRAF* V600E-mutant melanoma^{3,8,9}; vemurafenib has also shown a superior overall survival (OS).^{3,8,10} These data confirm that *BRAF* V600E-mutated tumors

are responsive to BRAF-inhibitor therapy; however, resistance to BRAF-inhibitor therapy is common and rapidly acquired in the majority of patients.^{8,9} To the best of our knowledge, no MEK inhibitor has demonstrated significant clinical activity in *BRAF*-mutated melanoma in the phase II setting; selumetinib (AZD6244) had an RR of only 10% in *BRAF*-mutant melanoma,¹¹ and PD0325901 was poorly tolerated.^{12,13} In vitro studies and analyses of predose and postprogression tumor biopsies in clinical trials have shown both MEK-dependent and MEK-independent resistance following exposure to a BRAF inhibitor.¹⁴⁻²⁰ Because MEK is the downstream effector of BRAF, MEK inhibition is an attractive mechanism for blocking activation of the MAPK pathway and could also potentially block reactivation of the MAPK pathway in BRAF-inhibitor-resistant disease.¹⁹

Trametinib is a reversible, selective, allosteric inhibitor of MEK1/MEK2 activation and kinase activity, with a half-maximal inhibitory concentration of 0.7 to 14.9 nmol/L for MEK1/MEK2.²¹ In vitro studies have demonstrated that trametinib decreases cell proliferation, causes G1 cell cycle arrest, and induces apoptosis.²¹ In the first-in-human (FIH) study of trametinib (Open-label Study to Investigate the Safety, PK, and Pharmacodynamics of GSK1120212 in Subjects With Solid Tumors or Lymphoma [NCT00687622]), 2 mg administered once daily was selected as the recommended phase II dose on the basis of safety, pharmacokinetic, pharmacodynamic, and efficacy data.²² In this study, trametinib also demonstrated a 33% confirmed RR among 30 patients with *BRAF*-mutant melanoma.²³ Moreover, in six other patients with *BRAF*-mutant melanoma who were previously treated with BRAF-inhibitor therapy, one patient with an unconfirmed partial response (PR) and four patients with stable disease (SD) were observed. These data supported further analysis of trametinib in two patient populations: patients who previously received a BRAF inhibitor and those who did not.

The results of a phase III study demonstrating improved rates of both PFS and OS for trametinib compared with chemotherapy has recently been reported.²⁴ Here we report the results of a multicenter phase II study designed to evaluate the clinical efficacy of trametinib monotherapy in patients with metastatic *BRAF*-mutant melanoma previously treated either with or without a BRAF inhibitor. Long-term follow-up data are also included.

PATIENTS AND METHODS

Patient Selection

Key eligibility criteria included metastatic cutaneous *BRAF*-mutant melanoma (amended later to allow *BRAF* V600E, V600K, or V600D mutations only), 18 years of age or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (amended to 0 to 1), adequate organ function, and one or more prior systemic therapies. Patients with brain metastasis previously treated with surgery or stereotactic radiosurgery and with confirmed SD for ≥ 8 weeks were allowed. Prior MEK-inhibitor therapy, a history of predisposing factors to retinal vein occlusion (RVO) or central serous retinopathy (CSR), and a cardiac symptom or event within 24 weeks were exclusion criteria. All patients provided written informed consent, and the protocol was approved by local ethics committees.

Study Design

This was an open-label, two-cohort, multicenter, phase II study to evaluate the clinical activity of trametinib in patients with *BRAF*-mutant metastatic melanoma (Fig 1). The protocol was approved by the institutional review board at each participating institution. Patients were enrolled onto one of two

Fig 1. Trial design.

cohorts: cohort A, previously treated with a BRAF inhibitor (either vemurafenib or dabrafenib) or cohort B, previously treated with chemotherapy and/or immunotherapy but not with a BRAF inhibitor.

Patients received 2 mg of oral trametinib once daily. Safety assessments and laboratory tests were performed predose on day 15, day 28, and every 4 weeks thereafter; laboratory tests were also performed on day 8. ECGs were obtained predose and every 4 weeks after the first dose. An echocardiogram or multiplegated acquisition scan was performed predose, at week 4, and every 12 weeks thereafter (or more frequently, if clinically indicated). Blood samples for pharmacokinetic analysis were collected on day 15 (predose, 0.5 to 2, 2 to 4, and 4 to 8 hours postdose) and predose at weeks 4, 8, and 12 (Appendix Fig A1, online only).

Disease assessment was performed at baseline and every 8 weeks according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST).²⁵ A planned interim analysis for futility was performed approximately 12 weeks after enrollment of the thirtieth patient in each cohort, which was 4 weeks after the first tumor assessment.

The severity of toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.²⁶ Patients were allowed to enroll on the basis of *BRAF* testing results obtained from local laboratories. However, tumor sample submission to a central laboratory (Response Genetics, Inc [RGI], Los Angeles, CA) was required before enrollment. Tissue submitted to RGI was evaluated by using an allele-specific polymerase chain reaction assay that identifies *BRAF* V600E and V600K mutations. Genotyping reports of *BRAF* V600D from local laboratories and discrepant results between local laboratories and RGI were to be further evaluated by DNA sequence analysis at RGI; no reports of *BRAF* V600D were received.

Statistical Analysis

The primary end point for both cohorts was objective RR as determined by the investigator; each cohort was assessed separately. The null hypothesis was an RR of $\leq 10\%$; the alternative hypothesis was an RR of $\geq 25\%$. To allow early termination for futility, a two-stage Green-Dahlberg design was used.²⁷ If fewer than three responses were observed in the first 30 patients at the interim analysis, enrollment in that cohort would be terminated. If three or more responses were observed, enrollment would continue to 55 patients to achieve the desired type I ($< 5\%$) and type II ($> 90\%$) error rates. PFS was defined as the interval between the date of first dose and the date of disease progression or death, whichever occurred first. PFS and OS were summarized descriptively by using Kaplan-Meier medians and quartiles. Summary statistics were reported for plasma trametinib concentrations by cohort and the time of assessments.

RESULTS

Patient Characteristics

Between December 2009 and December 2010, a total of 97 patients were enrolled (cohort A, n = 40; cohort B, n = 57). Patient baseline characteristics (Table 1) were similar for both cohorts except

for prior therapy due to trial design. Seventy percent were male and all but one had an ECOG performance status of 0 or 1. All patients except one had stage IV melanoma, of which 75% had American Joint Committee on Cancer (AJCC) stage M1c disease. Pre-existent treated brain metastases were reported for 13% of cohort A and 21% of cohort B. The frequency of V600E (81%) and V600K (12%) mutations was

Table 1. Baseline Patient Characteristics

Characteristic	Cohort A (n = 40)		Cohort B (n = 57)		All Patients (N = 97)	
	No.	%	No.	%	No.	%
Age, years,						
Mean	55.6		54.0		54.7	
Median	58.0		54.0		55.0	
Range	23-76		26-79		23-79	
Male sex	25	63	43	75	68	70
ECOG performance status*						
0	19	48	42	74	61	63
1	20	50	15	26	35	36
Stage						
IIIc	0		1	2	1	1
M1a	5	13	7	12	12	12
M1b	6	15	6	11	12	12
M1c	29	73	43	75	72	74
Serum LDH at baseline						
≤ ULN	15	38	32	56	47	48
> ULN	22	55	24	42	46	47
Unknown	3	8	1	2	4	4
No. of prior systemic therapies						
1-2	20	50	50	88	70	72
≥ 3	20	50	7	12	27	28
Chemotherapy	25	63	49	86	74	76
Immunotherapy	17	43	31	54	48	49
Both chemotherapy and immunotherapy†	13	33	23	40	36	37
BRAF mutation status						
V600E	33	83	46	81	79	81
V600K	4	10	8	14	12	12
K601E	0		1	2	1	1
K601E/V600E‡	1	3	0		1	1
V600E/V600K§	1	3	1	2	2	2
V600K/V600R¶	0		1	2	1	1
Unknown	1	3	0		1	1
Prior BRAF inhibitors						
Vemurafenib	23	58	N/A			
Dabrafenib	17	43	N/A			
Duration of prior BRAF inhibitor, weeks						
< 24	19	48	N/A			
≥ 24	19	48	N/A			
Unknown	2	5	N/A			
Best response during prior BRAF inhibitor therapy						
CR	2	5	N/A			
PR	16	40	N/A			
SD	10	25	N/A			
PD	6	15	N/A			
Unknown	6	15	N/A			

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; N/A, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper limit of normal.

*One patient in cohort A had an ECOG status of 2 and was eligible. The protocol was later amended to allow only patients with ECOG status of 0 or 1.

†Three patients in each cohort had prior ipilimumab treatment; all six had prior chemotherapy.

‡One patient had test results for K601E and V600E from different laboratories. DNA sequencing showed the mutation was V600delta; K601E.

§Two patients had different test results for V600E and V600K from different laboratories on the same tumor tissue.

¶One patient had different test results for V600K and V600R from different laboratories on the same tumor tissue.

||One patient was BRAF-mutation positive, but the exact mutation was not known.

Table 2. Clinical Efficacy

Cohort	No. of Patients	Confirmed RR (CR + PR)					Median PFS		Median OS	
		Outcome			RR (%)	95% CI	RR (months)	95% CI	RR (months)	95% CI
		CR	PR	SD						
A	40	0	0	11	0		1.8	1.8 to 2.0	5.8	4.1 to 9.0
B	57	1	13	29	25	14.1 to 37.8	4.0	3.6 to 5.6	14.2	11.3 to N/R
<i>BRAF V600E</i> without prior brain metastases	36	1	9	20	28	14.2 to 45.2	5.3	3.6 to 7.4	N/R	

Abbreviations: CR, complete response; N/R, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate; SD, stable disease.

within the expected range. A *K601E* mutation was identified in two patients; four patients had discrepant results from the same tumor tissue between local laboratories and RGI (Table 1). Three patients in each cohort had received prior ipilimumab treatment; these six patients also had received prior chemotherapy. In cohort A, all patients had received either dabrafenib or vemurafenib before study enrollment. Among these patients, approximately 50% had received BRAF-inhibitor therapy for less than 24 weeks. For cohort A, 50% of the patients received three or more prior therapies, and in cohort B, 38% received chemotherapy and 19% received immunotherapy in the advanced/metastatic setting.

Treatment

The median time receiving study drug was 56 days for cohort A and 120 days for cohort B. Across both arms, 80% of patients discontinued study treatment because of disease progression, and four patients (4%) discontinued study treatment because of adverse events (AEs; two ejection fraction decreases, one intestinal perforation, and one pulmonary embolism).

Efficacy at Interim Analysis

There were no responses at the interim analysis among the first 30 patients enrolled in cohort A; enrollment was therefore terminated due to futility. (Ten additional patients were enrolled because they had given consent before the thirtieth patient was dosed.) Among the 30 patients of cohort B in the first stage, six PRs were observed at the interim analysis. Consequently, enrollment continued toward a target of 55 patients. (Two additional patients were enrolled because they had given consent before the fifty-fifth patient was dosed.)

Overall Efficacy

The median follow-up at the planned analysis was 12 months for cohort A and 10 months for cohort B. Table 2 summarizes the clinical efficacy in both cohorts. None of the 40 patients in cohort A had a confirmed clinical response at the time of data cutoff, although eight patients (20%) experienced tumor reduction (Fig 2A). The best unconfirmed response was one complete response (CR; 3%), one PR (3%), and 11 SD (28%); five patients (13%) received trametinib for ≥ 16 weeks. The patient with a CR at week 8 progressed at week 16, and the patient with a PR, which became a confirmed PR after the data cutoff, was ongoing at week 44; both of these patients had discontinued prior BRAF-inhibitor therapy after less than 24 weeks of treatment because of an AE rather than because of disease progression. In contrast, 36 patients had discontinued BRAF-inhibitor therapy because of disease progression. The median PFS for this cohort was 1.8

months (95% CI, 1.8 to 2.0 months; Fig 3). The median OS for cohort A was 5.8 months (95% CI, 4.1 to 9.0 months).

Among the 57 patients in cohort B, the best confirmed responses were one CR (2%) and 13 PRs (23%), resulting in a best overall RR of 25% (95% CI, 14.1% to 37.8%). The disease control rate (CR + PR + SD/total number of patients) was 75%, and tumor reduction was observed in 37 patients (65%; Fig 2B). Eighteen patients (32%) were treated for ≥ 24 weeks without disease progression. On the basis of this RR, the null hypothesis was rejected in favor of the alternative hypothesis. The median PFS was 4.0 months (95% CI, 3.6 to 5.6 months; Fig 3), and the median duration for response was 5.7 months (95% CI, 3.7 to 9.2 months). Among the 12 patients (21%) with a history of brain metastases, five (42%) had disease progression in the

Fig 2. Best percentage change from baseline in target lesions for (A) cohort A (radiographic scan data was incomplete or unavailable for 5 patients) and (B) cohort B (radiographic scan data was incomplete or unavailable for two patients). Staging was according to the American Joint Committee on Cancer (AJCC) system. (*) Patients with prior brain metastases; (t) patients who discontinued prior BRAF inhibitor because of toxicity; (K) patients with the *V600K* mutation.

Fig 3. Kaplan-Meier estimated survival for all patients by cohort: (A) progression-free survival (PFS) for cohort A, (B) PFS for cohort B, (C) overall survival (OS) for cohort A, and (D) OS for cohort B. The bars represent the date of the last adequate tumor assessment before the data cutoff among patients with censored data without disease progression or death.

brain or the CNS. Subgroup analysis of patients with a *BRAF V600E* mutation and without prior brain metastases showed a confirmed RR of 28% (95% CI, 14.2% to 45.2%) and median PFS of 5.3 months (95% CI, 3.6 to 7.4 months).

There were 10 patients with non-*V600E* mutations in cohort B. Among the eight patients with a *BRAF V600K* mutation, one patient had an unconfirmed PR, and four patients had SD as the best response. The only patient in this cohort with a *BRAF K601E* mutation had a confirmed PR with a PFS of 32 weeks. One patient with discrepant results for *BRAF V600K* (analyzed at a local laboratory) and *BRAF V600R* (sequence analysis at RGI) had a confirmed PR with a PFS of at least 57 weeks.

Overall survival data for cohort B were not mature at the time of data cutoff. However, on the basis of data collected after the original data cutoff, the 6- and 12-month survival rates for all patients enrolled in cohort B, including patients with a *V600K* mutation and patients with prior brain metastases, were 79% (95% CI, 66% to 87%) and 59% (95% CI, 45% to 71%), respectively. The median OS was 14.2 months (95% CI, 11.3 months to upper boundary not reached; Fig 3). The median follow-up time was 20.8 months.

Treatment-Related Toxicity

All 97 patients across both cohorts received at least one dose of trametinib. The most frequent treatment-related AEs across both co-

horts are listed in Table 3. There were no treatment-related deaths and only one grade 4 treatment-related AE (pulmonary embolism). Skin-related toxicity (10%), diarrhea (4%), and peripheral edema (3%) were the only grade ≥ 3 AEs that occurred in more than 2% of the

Table 3. Treatment-Related Adverse Events Occurring in $\geq 10\%$ of Patients (n = 97)

Adverse Event	All Grades		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Overall	89	92	25	26	1	1*
Rash/dermatitis acneiform	73	75	9	9	0	0
Diarrhea	50	52	4	4	0	0
Nausea	29	30	0	0	0	0
Peripheral edema	28	29	3	3	0	0
Pruritis	26	27	1	1	0	0
Fatigue	25	26	2	2	0	0
Dry skin	21	22	0	0	0	0
Vomiting	17	18	0	0	0	0
Abdominal pain	15	15	0	0	0	0
Constipation	14	14	0	0	0	0
Decreased appetite	11	11	1	1	0	0
Dry mouth	11	11	0	0	0	0

*Pulmonary embolism.

patients. CSR was reported in two patients (2%); both were reversible. No cases of RVO were observed. Three patients (3%) had asymptomatic and reversible grade 3 left ventricular ejection fraction reduction. Two patients (2%) experienced reversible asymptomatic grade 3 increase of serum aminotransferases. AEs leading to dose reduction occurred in 15 patients (15%), most frequently for skin-related toxicity. There were no reports of treatment-related cutaneous squamous cell carcinoma. Treatment-related hypertension was reported for six patients (6%); none were grade ≥ 3 . However, blood pressure evaluations demonstrated an overall trend toward increased values.

Trametinib Plasma Concentrations

The mean predose concentrations of trametinib in all patients ranged from 11.6 to 12.6 ng/mL across study visits, with no large differences between cohorts and no trends over the 12-week pharmacokinetics study. The mean concentrations were highest in the 2- to 4-hour collection interval (21.7 ng/mL), consistent with a time-to-peak-concentration of approximately 2 hours. The peak:trough concentration ratio based on mean day 15 concentrations was approximately 1.8, which is consistent with the relatively long half-life of trametinib.²²

DISCUSSION

Since the discovery of frequent *BRAF* mutations in melanoma,² there has been considerable progress in the therapeutic approaches for this disease. Following favorable results in the trametinib FIH study,²² trametinib was further evaluated in this phase II study in patients with *BRAF*-mutant melanoma who had been previously treated either with or without a *BRAF* inhibitor. Vemurafenib had not been approved by the US Food and Drug Administration at the start of this study.

In this study, the patients previously treated with chemotherapy and/or immunotherapy but not with a *BRAF* inhibitor (cohort B) had significant pretreatment with standard therapies and had primarily AJCC stage M1c disease (75%); 21% of the patients in this cohort had a history of treated brain metastases. The confirmed RR (25%), including one CR in a patient with stage M1c disease, and the number of patients with measurable tumor reduction demonstrate substantial clinical activity in this patient population. The RR, median duration of response, and PFS were similar to those of both the FIH²³ and phase III studies.²⁴ Although objective RRs for trametinib are lower than those reported for *BRAF* inhibitors in similar patient populations,^{3,8,9} the estimated 6- and 12-month survival rates and median OS reported here are comparable. The basis for the different RR observed with trametinib and *BRAF* inhibitors is not clear, but it may be because of different modes of action, degree of pathway inhibition, or acquired drug-resistance mechanisms. In this cohort, 54% of the patients received a *BRAF* inhibitor or ipilimumab postprogression, some of whom are still alive more than 1 year after disease progression on trametinib. Objective and durable responses were not limited in this study to *BRAF* V600E or V600K mutations, suggesting that trametinib may be broadly active in *BRAF*-mutant melanoma.

The mean, steady-state, predose trametinib concentrations in this study were generally comparable to those previously observed²² and above the target concentration of 10.4 ng/mL, based on preclinical findings (GlaxoSmithKline, unpublished data). These data suggest that target inhibition is maintained throughout the entire dosing in-

terval and, combined with its unique exposure profile among clinically evaluated MEK inhibitors,²² may explain why trametinib demonstrated a higher RR than those reported for other MEK inhibitors in similar patient populations.^{28,29}

This study demonstrated that trametinib had minimal clinical activity as sequential therapy in patients that had progressed on *BRAF*-inhibitor therapy (cohort A). Only five patients (13%) received trametinib for ≥ 16 weeks. The two patients in this cohort who responded to trametinib were not *BRAF*-inhibitor refractory but were *BRAF*-inhibitor intolerant. The minimal activity in this cohort may be due to several factors, including heavy pretreatment (50% had received three or more prior therapies). Alternatively, acquired *BRAF*-inhibitor resistance mechanisms might also confer resistance to trametinib monotherapy, corroborating data from preclinical modeling.³⁰

Trametinib treatment was well tolerated, with patients experiencing mostly grade 1 or 2 AEs. The majority of patients tolerated a daily dose of 2 mg of trametinib without dose reduction, and only 3% of the patients discontinued trametinib because of treatment-related AEs. The spectrum of AEs was consistent with the class effect of MEK inhibitors. CSR was rarely observed, and there were no RVO events. Skin-related toxicity and diarrhea, the most common AEs, were adequately managed with supportive care only; importantly, there were no reports of treatment-related cutaneous squamous cell carcinoma, commonly seen with *BRAF*-inhibitor treatment. Treatment-related hypertension was observed in six patients (6%) and may be a class effect, since hypertension was also reported in 8.1% of patients administered selumetinib.¹¹ Additional studies will be required to understand trametinib-related hypertension. Importantly, cardiac, ophthalmologic, and hepatic events were uncommon and reversible on interruption of trametinib treatment.

The data presented here demonstrate that trametinib is well tolerated and clinically active in patients with previously treated metastatic *BRAF*-mutant melanoma who have not received or have not progressed on *BRAF*-inhibitor therapy. Activity was broad, with objective responses observed in patients with *BRAF* V600E, V600K, and rare *BRAF* mutations. Additional clinical studies are needed to understand the level of activity in patients with rare *BRAF* mutations and the individual role of trametinib in patients who have melanoma with *BRAF* V600E or V600K mutations. The efficacy and safety results reported here are consistent with those of the phase III study (GSK1120212 vs Chemotherapy in Advanced or Metastatic *BRAF* V600E/K Mutation-positive Melanoma [NCT01245062]), which demonstrated significant improvement in both PFS and OS in patients with *BRAF* V600E- or V600K-mutant metastatic melanoma compared with chemotherapy.²⁴ In addition, the results from this study demonstrate that trametinib monotherapy has minimal clinical activity as sequential therapy in patients with *BRAF*-mutant melanoma who have progressed on *BRAF*-inhibitor therapy. Taken together, these data suggest that trametinib monotherapy could be useful for patients with *BRAF* V600E- or V600K-mutant melanoma, patients who cannot tolerate a *BRAF* inhibitor, and for patients who have melanoma with rare *BRAF* mutations. Sequential therapy with trametinib monotherapy followed by *BRAF* inhibitors or ipilimumab have not been formally evaluated.

Trametinib may also be useful in reducing toxicity and increasing efficacy when combined with a *BRAF* inhibitor in patients who have *BRAF* V600E- or V600K-mutant melanoma.³¹ Phase II

(Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 & GSK1120212 [NCT01072175]) and phase III (A Study Comparing Trametinib and Dabrafenib Combination Therapy to Dabrafenib Monotherapy in Subjects With BRAF-mutant Melanoma [NCT01584648] and Dabrafenib Plus Trametinib vs Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma (COMBI-v) [NCT01597908]) studies comparing trametinib and dabrafenib combination therapy with either dabrafenib or vemurafenib monotherapy in BRAF-mutant melanoma are ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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