ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

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ABSTRACT

BACKGROUND

Combination therapy with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib improved survival in patients with advanced melanoma with *BRAF* V600 mutations. We sought to determine whether adjuvant dabrafenib plus trametinib would improve outcomes in patients with resected, stage III melanoma with *BRAF* V600 mutations.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 870 patients with completely resected, stage III melanoma with *BRAF* V600E or V600K mutations to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy, 438 patients) or two matched placebo tablets (432 patients) for 12 months. The primary end point was relapse-free survival. Secondary end points included overall survival, distant metastasis–free survival, freedom from relapse, and safety.

RESULTS

At a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.47; 95% confidence interval [CI], 0.39 to 0.58; P<0.001). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; P=0.0006), but this level of improvement did not cross the prespecified interim analysis boundary of P=0.000019. Rates of distant metastasis–free survival and freedom from relapse were also higher in the combination-therapy group than in the placebo group. The safety profile of dabrafenib plus trametinib was consistent with that observed with the combination in patients with metastatic melanoma.

CONCLUSIONS

Adjuvant use of combination therapy with dabrafenib plus trametinib resulted in a significantly lower risk of recurrence in patients with stage III melanoma with *BRAF* V600E or V600K mutations than the adjuvant use of placebo and was not associated with new toxic effects. (Funded by GlaxoSmithKline and Novartis; COMBI-AD ClinicalTrials.gov, NCT01682083; EudraCT number, 2012-001266-15.)

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The incidence of cutaneous melanoma has continued to increase in recent years.[1] For early-stage melanoma, surgical resection is the standard treatment and is associated with an excellent long-term prognosis, with 5-year survival rates of 98% for stage I disease and 90% for stage II disease.[1,2] However, patients with stage III disease, who have regional involvement at diagnosis, are at higher risk for recurrence after locoregional resection, and many will ultimately die from metastatic melanoma.[1,3-5]

Checkpoint inhibitor immunotherapies, including those that target programmed death 1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4), and drugs that target the mitogen-activated protein kinase (MAPK) pathway (BRAF and MEK inhibitors and combinations of these drugs) have improved the outcome of patients with metastatic melanoma,[6] but their role as adjuvant therapy is still an area of active investigation.[1] Systemic adjuvant therapies that have been approved by the Food and Drug Administration for the treatment of melanoma include interferon alfa-2b and pegylated interferon, which have shown inconsistent improvements in overall survival along with substantial toxic effects,[7-9] and the CTLA-4 inhibitor ipilimumab.[10] The use of adjuvant ipilimumab has resulted in a significantly higher rate of 5-year survival than placebo (65.4% vs. 54.4%; hazard ratio, 0.72), although ipilimumab has been associated with serious adverse events that have led to early treatment discontinuation in a substantial proportion of patients and with death in 1.1% of patients.[10]

Oncogenic mutations in *BRAF* are found in approximately 40% of melanomas and result in constitutive activation of the MAPK pathway.[11,12] In two independent phase 3 trials (COMBI-d and COMBI-v),[13,14] treatment with the BRAF inhibitor dabrafenib (150 mg twice daily) plus the MEK inhibitor trametinib (2 mg once daily) improved overall survival in patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations.

Given the need for safe and effective adjuvant therapies, we sought to determine whether the combination of dabrafenib and trametinib would improve relapse-free survival, overall survival, distant metastasis–free survival, and freedom from relapse in patients with stage III melanoma with *BRAF* V600E or V600K mutations after complete surgical resection. Here, we report the primary analysis from COMBI-AD, a randomized trial evaluating combination BRAF and MEK inhibition as adjuvant therapy in melanoma.

Methods

Patients

From January 2013 through December 2014, we enrolled patients at 169 sites in 26 countries. Eligible adult patients (≥18 years of age) had undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the American Joint Committee on Cancer, seventh edition[15]) with *BRAF* V600E or V600K mutations. None of the patients had undergone previous systemic anticancer treatment or radiotherapy for melanoma. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). *BRAF* V600 mutation status was confirmed in primary-tumor or lymph-node tissue by a central reference laboratory. All the patients provided written informed consent. Additional details are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Treatments

In this randomized, placebo-controlled, double-blind, phase 3 trial, patients were assigned to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy) or two matched placebo tablets. Patients were stratified according to their *BRAF* mutation status (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). Patients were treated for 12 months in the absence of disease recurrence, unacceptable toxic effects, withdrawal of consent, or death. Follow-up for disease recurrence continued until the first recurrence was observed, and thereafter patients were followed for survival. Dose modifications or interruptions were used for nonhematologic adverse events of grade 2 or higher that could not be managed with routine supportive care.

PRIMARY AND SECONDARY END POINTS

The primary end point was relapse-free survival, defined as the time from randomization to disease recurrence or death from any cause. Secondary end points included overall survival, distant metastasis–free survival (defined as the time from randomization to the date of first distant metastasis or date of death, whichever occurred first), freedom from relapse (defined as the time from randomization to recurrence, with censoring of data for patients who had died from causes other than melanoma or treatment-related toxic effects), and safety. All disease-recurrence analyses were based on investigator assessment. Efficacy analyses included all the patients who had undergone randomization (intention-to-treat population), and safety analyses included all the patients who had received at least one dose of a trial drug (safety population).

ASSESSMENTS

Disease assessments included clinical examination and imaging by means of computed tomography, magnetic resonance imaging, or both. (Additional details are provided in the Supplementary Appendix.) Imaging was performed every 3 months during the first 24 months, then every 6 months until disease recurrence or the completion of the trial. Follow-up for survival began after recurrence and continued through the end of the trial.

Adverse events and laboratory values were assessed at screening, on the date of randomization, at least once per month through month 12, and at every visit for disease-recurrence assessment after month 12. Adverse events and laboratory values were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

TRIAL OVERSIGHT

The trial was sponsored by GlaxoSmithKline; dabrafenib and trametinib were designated as assets of Novartis on March 2, 2015, after which Novartis took over sponsorship of the trial. The trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol (available at NEJM.org) was approved by the institutional review board at each trial center. The trial design was developed jointly by GlaxoSmithKline and the academic authors. Data were collected by investigators at individual study sites and were subsequently transferred to and analyzed by the sponsor (GlaxoSmithKline and Novartis after March 2, 2015). All the authors developed the initial draft of the manuscript and made the decision to submit it for publication; all the authors contributed to subsequent drafts. The authors affirm the accuracy and completeness of the data and adherence of the trial to the protocol. Editorial support was provided by ArticulateScience and was funded by Novartis.

STATISTICAL ANALYSIS

We determined that the enrollment of 870 patients would result in relapse-free survival in approximately 410 patients by the analysis cutoff date (with a two-sided type I error rate of 5%) and would provide a power of more than 90% to detect a hazard ratio of 0.71 (corresponding to a median relapse-free survival of 21 months in the combination-therapy group and 15 months in the placebo group). No interim analysis was performed for efficacy or futility for the primary end point. Overall survival, as the key secondary end point, was to be tested in a hierarchical manner only if the primary end point met the criteria for significance. The overall survival analysis used a preplanned three-look Lan–DeMets group sequential design with an O'Brien–Fleming–type boundary, which was used to determine the significance threshold for the first interim overall survival analysis (two-sided $P=0.000019$).

We used the Kaplan–Meier method to estimate relapse-free survival, overall survival, distant metastasis–free survival, and freedom from relapse and a stratified log-rank test to compare the two trial groups. Hazard ratios with 95% confidence intervals for all time-to-event end points were calculated with the use of the Pike estimator.[16,17] All P values are two-sided. The trial was not powered to detect differences in outcomes on the basis of the type of *BRAF* mutation.

RESULTS

PATIENTS AND TREATMENT

A total of 870 patients underwent randomization, with 438 patients assigned to receive combination therapy with dabrafenib plus trametinib and 432 patients to receive matched placebo tablets for 12 months. The baseline characteristics of the patients were similar in the two groups (Table 1). Among the enrolled patients, 154 (18%) had stage

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dabrafenib plus Trametinib (N=438)	Placebo (N=432)
Median age (range) — yr	50 (18–89)	51 (20–85)
Sex — no. (%)		
Male	195 (45)	193 (45)
Female	243 (55)	239 (55)
BRAF mutation status — no. (%)		
V600E	397 (91)	395 (91)
V600K†	41 (9)	37 (9)
ECOG performance status — no. (%)		
0	402 (92)	390 (90)
1	33 (8)	41 (9)
Unknown	3 (1)	1 (<1)
Disease stage — no. (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
No. of positive lymph nodes — no. (%)		
1	177 (40)	183 (42)
2 or 3	158 (36)	150 (35)
≥4	73 (17)	72 (17)
Unknown	30 (7)	27 (6)
Type of lymph-node involvement — no. (%)		
Microscopic	152 (35)	157 (36)
Macroscopic	158 (36)	161 (37)
Unknown	128 (29)	114 (26)
Primary-tumor ulceration — no. (%)		
Yes	179 (41)	177 (41)
No	253 (58)	249 (58)
Unknown	6 (1)	6 (1)
In-transit metastases — no. (%)‡		
Yes	51 (12)	36 (8)
No	387 (88)	395 (91)
Unknown	0	1 (<1)

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.
† One patient who had both a *BRAF* V600E mutation and a *BRAF* V600K mutation is included in the V600K subgroup.
‡ In-transit metastases are clinically evident cutaneous or subcutaneous metastases identified at a distance of more than 2 cm from the primary melanoma in the region between the primary melanoma and the first echelon of regional lymph nodes.

IIIA disease, 356 (41%) had stage IIIB disease, and 347 (40%) had stage IIIC disease; 13 (1%) had stage III unspecified disease. Of the 870 patients, 792 (91%) had a *BRAF* V600E mutation, and 78 (9%) had a *BRAF* V600K mutation.

As of the data cutoff date for the primary analysis (June 30, 2017), the minimum follow-up time was 2.5 years (median, 2.8 years). The last dose of a trial drug was administered in December 2015, and all the patients had completed the trial treatment at the time of this analysis (Table S1 in the Supplementary Appendix). Follow-up was still occurring in 331 patients (76%) in the combination-therapy group and in 277 patients (64%) in the placebo group; 47 patients (11%) and 62 (14%) patients, respectively, had withdrawn from the trial, and the remaining patients had died (Fig. S1 in the Supplementary Appendix). All scheduled doses of dabrafenib were completed by 272 of 435 patients (63%), all scheduled doses of trametinib by 277 of 435 (64%), and all scheduled doses of placebo by 227 of 432 (53%); the most common reason for premature discontinuation was the occurrence of adverse events in the combination-therapy group (108 patients [25%] for dabrafenib and 104 patients [24%] for trametinib) and disease recurrence in the placebo group (175 patients [41%]). Systemic therapy after recurrence was administered in 28% of the patients in the combination-therapy group and in 42% of those in the placebo group (Table 2). The most common systemic therapies after recurrence were small-molecule targeted therapy (in 14% of the patients in the combination-therapy group and in 32% of those in the placebo group), immunotherapy against PD-1 or programmed death ligand 1 (in 16% in each group), and anti–CTLA-4 immunotherapy (in 12% and 16%, respectively).

EFFICACY

As of the data cutoff, disease recurrence had been reported in 163 of 438 patients (37%) in the combination-therapy group and in 247 of 432 patients (57%) in the placebo group. Investigator-assessed relapse-free survival (primary end point) was significantly longer in the combination-therapy group than in the placebo group, representing a 53% lower risk of relapse (hazard ratio for relapse or death, 0.47; 95% confidence

interval [CI], 0.39 to 0.58; P<0.001 by stratified log-rank test) (Fig. 1A).

At the time of this analysis, 153 deaths had occurred, 60 (14%) in the combination-therapy group and 93 (22%) in the placebo group. The most common cause of death was melanoma (in 54 patients [12%] and 77 [18%], respectively). For all other deaths (6 in the combination-therapy group and 16 in the placebo group), the cause of death was listed as "other" or unknown; among the patients who died from other or unknown causes, melanoma had recurred before death in 5 in the combination-therapy group and in 15 in the placebo group. For the first interim analysis of overall survival, which was performed at the same time as the primary analysis of relapse-free survival, the estimated rate of overall survival was 97% at 1 year, 91% at 2 years, and 86% at 3 years in the combination-therapy group, as compared with rates of 94%, 83%, and 77%, respectively, in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; P=0.0006). Despite this low P value, the between-group difference was not significant because it did not cross the prespecified conservative interim boundary of P=0.000019 (Fig. 1B).

The estimated rates of relapse-free survival were 88% at 1 year, 67% at 2 years, and 58% at 3 years in the combination-therapy group, as compared with rates of 56%, 44%, and 39%, respectively, in the placebo group. At the time of this analysis, median relapse-free survival had not yet been reached in the combination-therapy group (95% CI, 44.5 to not reached) and was 16.6 months (95% CI, 12.7 to 22.1) in the placebo group. The higher rate of relapse-free survival in the combination-therapy group than in the placebo group was consistent across patient subgroups (Fig. 2). At the time of first recurrence, 54 patients (12%) in the combination-therapy group had locoregional recurrence, 7 (2%) had both local and distant recurrence, and 96 (22%) had distant recurrence, as compared with 107 (25%), 7 (2%), and 126 (29%), respectively, in the placebo group.

Fewer patients had distant metastases or died in the combination-therapy group than in the placebo group (110 patients [25%] vs. 152 [35%]; hazard ratio, 0.51; 95% CI, 0.40 to 0.65; P<0.001) (Fig. S2 in the Supplementary Appendix). Two patients (1 in each group) died from causes other than melanoma, and their data were censored in the analysis of freedom from relapse. Thus, results for the analysis of freedom from relapse were very similar to those for relapse-free survival (Fig. S3 in the Supplementary Appendix).

Table 2. Therapy after Melanoma Recurrence (Safety Population).*

Type of Therapy	Dabrafenib plus Trametinib (N=435)	Placebo (N=432)
	no. (%)	
Any anticancer therapy	148 (34)	217 (50)
Surgery	78 (18)	131 (30)
Radiotherapy	60 (14)	72 (17)
Any systemic therapy†	120 (28)	183 (42)
Small-molecule targeted therapy	63 (14)	137 (32)
Any BRAF inhibitor	63 (14)	137 (32)
Dabrafenib	44 (10)	86 (20)
Vemurafenib	29 (7)	59 (14)
Encorafenib	0	16 (4)
Any MEK inhibitor	47 (11)	77 (18)
Trametinib	28 (6)	48 (11)
Cobimetinib	20 (5)	18 (4)
Binimetinib	2 (<1)	15 (3)
Immunotherapy	89 (20)	103 (24)
Anti–PD-1 or PD-L1	71 (16)	68 (16)
Anti–CTLA-4	53 (12)	68 (16)
Interferon	6 (1)	11 (3)
T-VEC	0	1 (<1)
Biologic therapy	1 (<1)	1 (<1)
Chemotherapy	20 (5)	23 (5)
Investigational treatment	6 (1)	19 (4)
Other systemic therapy	2 (<1)	0

* Percentages are based on the safety population rather than on the number of patients who had disease recurrence (163 who received combination therapy with dabrafenib plus trametinib and 247 who received placebo). Patients could have had more than one type of therapy. Data regarding therapy after recurrence were available only if such information was provided to the investigator by the time of the data cutoff and were not available for patients who withdrew from the trial or died shortly after recurrence. CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed death 1, PD-L1 programmed death ligand 1, and T-VEC talimogene laherparepvec.

† The median time from disease recurrence to the initiation of systemic therapy was 7.1 weeks (range, 0 to 136) in the combination-therapy group and 7.3 weeks (range, 0 to 78) in the placebo group.

SAFETY

A total of 435 patients in the combination-therapy group and 432 patients in the placebo group were included in the safety analysis (Fig. S1 in

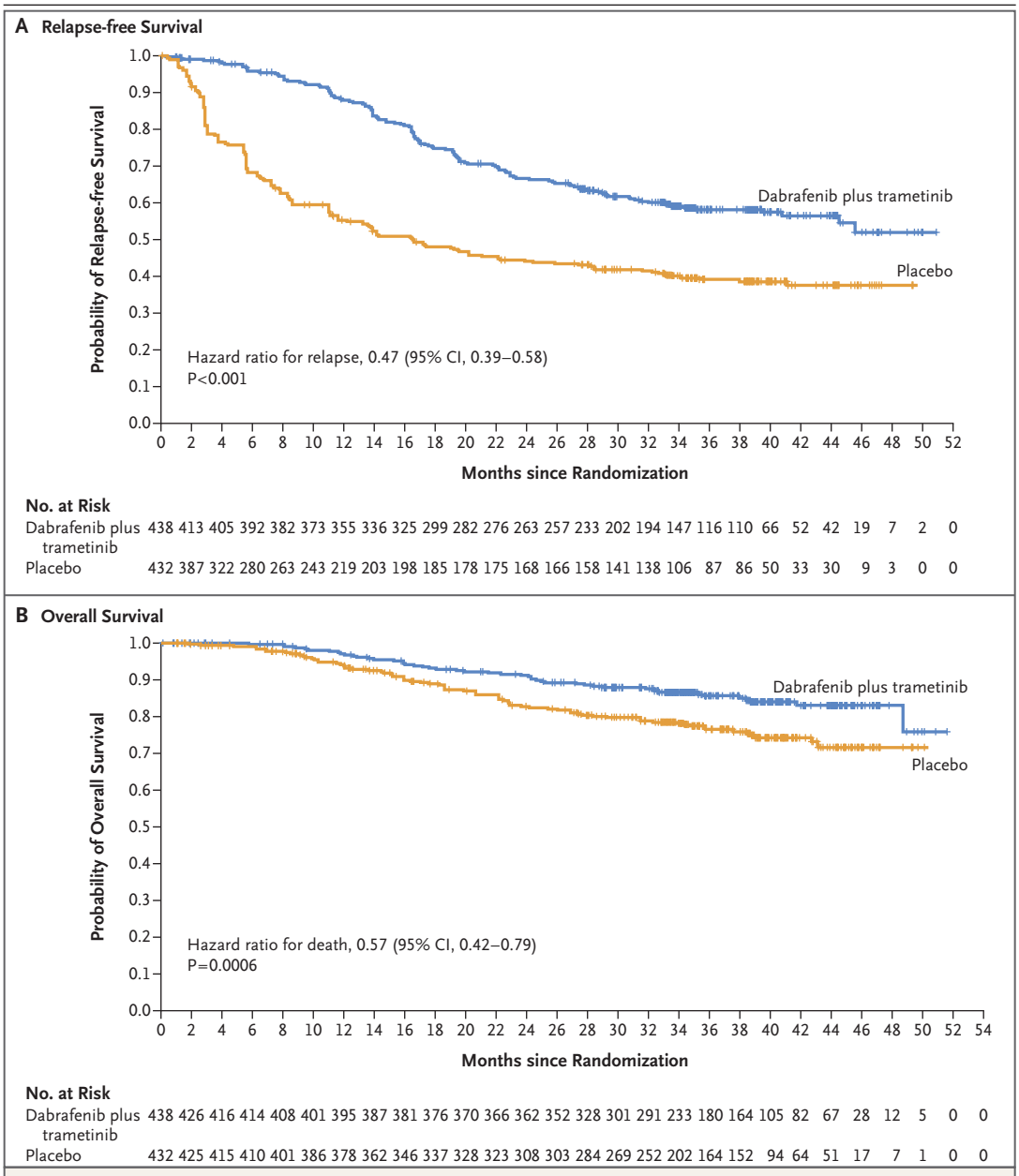

Figure 1. Relapse-free Survival and Overall Survival.

Shown are Kaplan–Meier estimates of relapse-free survival (Panel A) and overall survival (Panel B) among the patients who received combination therapy with dabrafenib plus trametinib and those who received placebo in the intention-to-treat analysis. As of the data cutoff at a median of 2.8 years of follow-up, disease recurrence or death had been reported in 166 of 438 patients (38%) in the combination-therapy group and in 248 of 432 patients (57%) in the placebo group. At the same time, death had been reported in 60 patients (14%) in the combination-therapy group and 93 (22%) in the placebo group, and the median overall survival had not been reached in either group.

the Supplementary Appendix). At least one adverse event was reported in 422 patients (97%) in the combination-therapy group and in 380 patients (88%) in the placebo group. Of the adverse events that occurred in more than 10% of the patients in the combination-therapy group, the most common were pyrexia (any grade, 63%; grade 3 or 4, 5%), fatigue (any grade, 47%; grade 3 or 4, 4%), and nausea (any grade, 40%; grade 3 or 4, <1%) (Table 3). Serious adverse events occurred

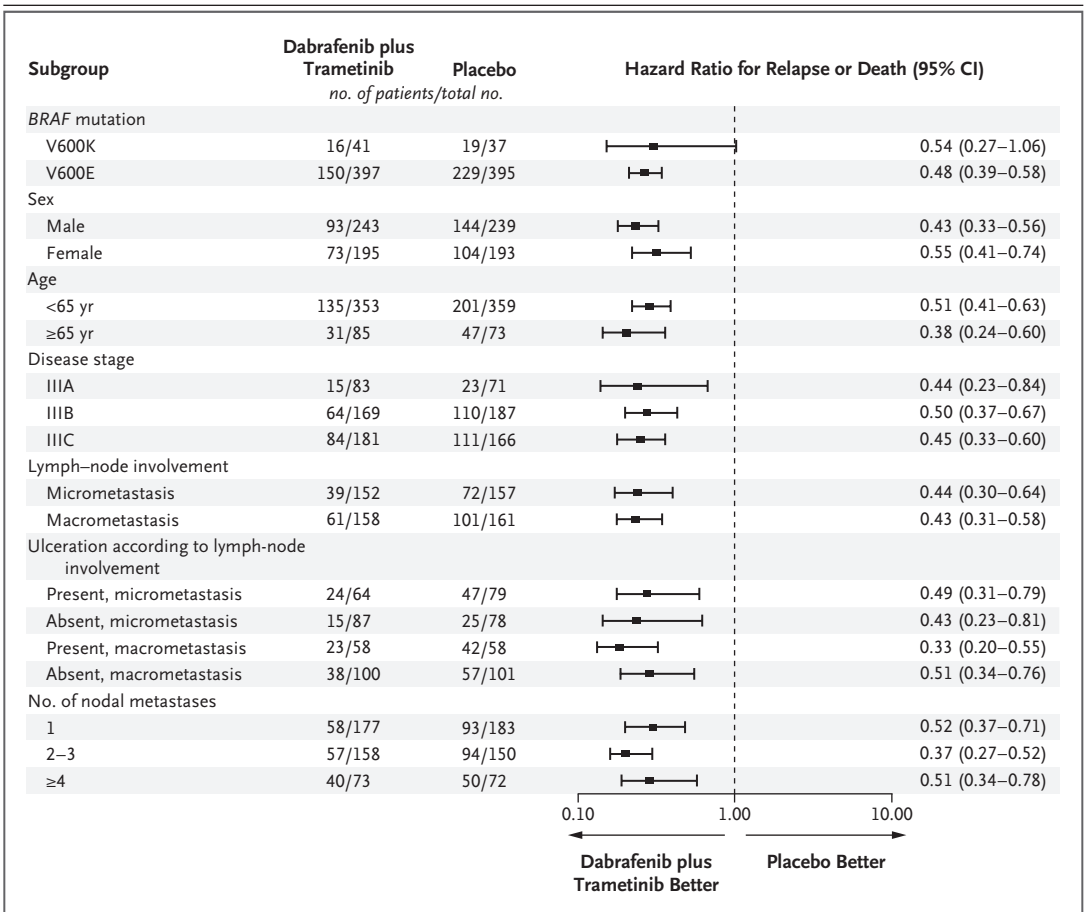

Figure 2. Hazard Ratios for Relapse or Death, According to Subgroup.
The I bars indicate 95% confidence intervals.

in 155 patients (36%) in the combination-therapy group and in 44 patients (10%) in the placebo group. One fatal serious adverse event (pneumonia) was reported in the combination-therapy group. A new primary melanoma was reported in 11 patients (3%) in the combination-therapy group and in 10 (2%) in the placebo group. Cutaneous squamous-cell carcinoma or keratoacanthoma was reported in 8 patients (2%) in the combination-therapy group and in 7 (2%) in the placebo group; basal-cell carcinoma was reported in 19 (4%) and 14 (3%), respectively, and noncutaneous cancers in 10 (2%) and 4 (1%), respectively.

In the combination-therapy group, 114 patients (26%) had adverse events leading to permanent discontinuation of a trial drug, 167 (38%) had adverse events leading to a dose reduction, and 289 (66%) had adverse events leading to a dose interruption, as compared with 12 (3%), 11 (3%), and 65 (15%), respectively, in the placebo group. The median duration of exposure to a trial drug was 11.0 months for both dabrafenib and trametinib and 10.0 months for both placebo tablets. The median daily dose of dabrafenib (283.9 mg; range, 88.5 to 300.0) and trametinib (2.0 mg; range, 0.6 to 2.0) was similar to the intended daily dose (300 mg and 2 mg, respectively).

DISCUSSION

Among patients with stage III melanoma who had undergone resection, the adjuvant use of combination therapy with dabrafenib plus trametinib for 12 months resulted in a 53% lower risk of relapse (the primary end point) than the adjuvant use of placebo at a median follow-up of 2.8 years. At 3 years, the rate of relapse-free survival was 58% in the combination-therapy group and 39% in

Table 3. Adverse Events (Safety Population).*

Adverse Event	Dabrafenib plus Trametinib (N=435)		Placebo (N=432)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (<1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (<1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhea	144 (33)	4 (1)	65 (15)	1 (<1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (<1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Elevated alanine aminotransferase	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza-like illness	67 (15)	2 (<1)	29 (7)	0
Elevated aspartate aminotransferase	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in limb	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)
Peripheral edema	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0
Adverse event leading to dose interruption	289 (66)	NA	65 (15)	NA
Adverse event leading to dose reduction	167 (38)	NA	11 (3)	NA
Adverse event leading to discontinuation of study regimen	114 (26)	NA	12 (3)	NA

* Listed are adverse events that were reported in more than 10% of the patients who received combination therapy with dabrafenib plus trametinib. NA denotes not applicable.

the placebo group. Combination therapy also resulted in higher rates of overall survival, distant metastasis–free survival, and freedom from relapse than placebo, with clinically meaningful lower risks of 43%, 49%, and 53%, respectively. The estimated rate of overall survival at 3 years was 86% in the combination-therapy group and 77% in the placebo group. The between-group difference ($P=0.0006$) did not reach the prespecified threshold of $P=0.000019$ to claim statistical significance in the first interim analysis of overall survival.

Although cross-trial comparisons should be interpreted with caution, these results are favorable in the context of findings from randomized studies of interferon (meta-analysis hazard ratio

for death, 0.89)[7] and ipilimumab (EORTC [European Organization for Research and Treatment of Cancer] 18071 hazard ratio for death, 0.72; 5-year rate of overall survival, 65.4%).[10] In our trial, the proportion of patients who received therapy after disease recurrence was similar in the two groups, which suggests that the higher survival rate in the combination-therapy group resulted from the trial drugs and not from greater access to immunotherapy regimens, given the markedly prolonged time to relapse in the combination-therapy group. There was some imbalance between the two groups with respect to the types of therapy that were administered after recurrence (e.g., a lower rate of BRAF–MEK inhibitor therapy in the combination-therapy group than in the placebo group), which could have had an effect on overall survival outcomes.

The rate of relapse-free survival of 58% in the combination-therapy group at 3 years (hazard ratio for relapse or death, 0.47) was also superior to that in previous randomized melanoma studies evaluating adjuvant interferon (meta-analysis hazard ratio for disease recurrence, 0.82) or ipilimumab (EORTC 18071 hazard ratio, 0.75; 3-year rate of recurrence-free survival, 46.5%).[7,18] Of note, the ipilimumab dose in EORTC 18071 (10 mg per kilogram of body weight) was substantially higher than the currently approved regimen and was associated with a high rate of discontinuation due to adverse events (52% vs. 4% with placebo) and 5 treatment-related deaths due to immune-related adverse events.[18] Furthermore, only 42% of the patients in that trial received one or more doses of ipilimumab in the maintenance phase. Mature data are awaited from the phase 3 E1609 study evaluating adjuvant high-dose interferon alfa-2b versus ipilimumab at doses of 3 mg or 10 mg per kilogram, although the study is not powered to compare efficacy between the two ipilimumab doses.[19] In addition, subgroup analyses in the EORTC 18071 trial of adjuvant ipilimumab versus placebo[10] suggested a potential benefit for adjuvant therapy in patients with stage IIIB or IIIC disease but not those with stage IIIA disease. However, in our trial, the clinical benefit of a combination of dabrafenib plus trametinib was consistent across all subgroups of patients in the analysis, regardless of lymph-node involvement or primary-tumor ulceration.

In our trial, the most common adverse events associated with combination therapy were pyrexia and fatigue, events that were similar to those reported in key trials of dabrafenib plus trametinib in patients with stage IIIC unresectable melanoma or stage IV metastatic melanoma with *BRAF* V600E or V600K mutations.[13,14,20-25] Although the rate of discontinuation of combination therapy because of adverse events in our trial (26%) was somewhat higher than that observed in patients with metastatic disease (14 to 16%),[23,25] this factor could be related to the nature of adjuvant therapy. In contrast with the EORTC 18071 trial of adjuvant ipilimumab,[10] in our trial a majority of the patients completed the scheduled 12 months of combination therapy with a median dose that was close to the scheduled dose for each drug. Furthermore, less than one third of the patients discontinued treatment because of an adverse event. Taken together, these results confirm the acceptable side-effect profile of the combination of dabrafenib plus trametinib as adjuvant therapy.

Regarding the use of a control group in our trial, at the time of enrollment and of the primary analysis, observation was the standard of care after resection of melanoma in most countries. Similar placebo-controlled trials that are currently evaluating targeted therapies or immunotherapies as adjuvant treatment for patients with melanoma include the BRIM8 trial of vemurafenib (ClinicalTrials.gov number, NCT01667419) and the KEYNOTE-054 trial of pembrolizumab (NCT02362594). Other ongoing trials of adjuvant melanoma therapy include ipilimumab as a control drug but differ by the exclusion of patients with stage IIIA melanoma and the inclusion of patients with stage IV disease (i.e., the CheckMate 238 trial of nivolumab or ipilimumab [NCT02388906] and the CheckMate 915 trial of nivolumab combined with ipilimumab or either drug alone [NCT03068455]). Currently, the most effective duration of adjuvant therapy in patients with melanoma is unknown; however, no evidence suggests that a longer treatment duration provides additional clinical benefit. In our trial, adjuvant dabrafenib plus trametinib treatment was planned for 12 months, similar to the regimens in BRIM8, KEYNOTE-054, CheckMate 238,[26] and CheckMate 915.

In conclusion, in this phase 3 trial evaluating a BRAF–MEK inhibitor combination, the adjuvant use of dabrafenib plus trametinib resulted in a significantly lower rate of recurrence than the adjuvant use of placebo in patients with stage III

melanoma with *BRAF* V600E or V600K mutations. In addition, the patients in the combination-therapy group had higher rates of overall and distant metastasis–free survival and freedom from relapse, with no reports of new safety signals.

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APPENDIX

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