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Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

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Abstract: BACKGROUND The BRAF inhibitors vemurafenib and dabrafenib have shown efficacy as monotherapies in patients with previously untreated metastatic melanoma with BRAF V600E or V600K mutations. Combining dabrafenib and the MEK inhibitor trametinib, as compared with dabrafenib alone, enhanced antitumor activity in this population of patients. METHODS In this open-label, phase 3 trial, we randomly assigned 704 patients with metastatic melanoma with a BRAF V600 mutation to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary end point was overall survival. RESULTS At the preplanned interim overall survival analysis, which was performed after 77% of the total number of expected events occurred, the overall survival rate at 12 months was 72% (95% confidence interval [CI], 67 to 77) in the combination-therapy group and 65% (95% CI, 59 to 70) in the vemurafenib group (hazard ratio for death in the combination-therapy group, 0.69; 95% CI, 0.53 to 0.89; P=0.005). The prespecified interim stopping boundary was crossed, and the study was stopped for efficacy in July 2014. Median progression-free survival was 11.4 months in the combination-therapy group and 7.3 months in the vemurafenib group (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.001). The objective response rate was 64% in the combination-therapy group and 51% in the vemurafenib group (P<0.001). Rates of severe adverse events and study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the vemurafenib group. CONCLUSIONS Dabrafenib plus trametinib, as compared with vemurafenib monotherapy, significantly improved overall survival in previously untreated patients with metastatic melanoma with BRAF V600E or V600K mutations, without increased overall toxicity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT01597908.).

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ORIGINAL ARTICLE

Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

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ABSTRACT

BACKGROUND

The BRAF inhibitors vemurafenib and dabrafenib have shown efficacy as monotherapies in patients with previously untreated metastatic melanoma with *BRAF* V600E or V600K mutations. Combining dabrafenib and the MEK inhibitor trametinib, as compared with dabrafenib alone, enhanced antitumor activity in this population of patients.

METHODS

In this open-label, phase 3 trial, we randomly assigned 704 patients with metastatic melanoma with a *BRAF* V600 mutation to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary end point was overall survival.

RESULTS

At the preplanned interim overall survival analysis, which was performed after 77% of the total number of expected events occurred, the overall survival rate at 12 months was 72% (95% confidence interval [CI], 67 to 77) in the combination-therapy group and 65% (95% CI, 59 to 70) in the vemurafenib group (hazard ratio for death in the combination-therapy group, 0.69; 95% CI, 0.53 to 0.89; P=0.005). The prespecified interim stopping boundary was crossed, and the study was stopped for efficacy in July 2014. Median progression-free survival was 11.4 months in the combination-therapy group and 7.3 months in the vemurafenib group (hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.001). The objective response rate was 64% in the combination-therapy group and 51% in the vemurafenib group (P<0.001). Rates of severe adverse events and study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the vemurafenib group.

CONCLUSIONS

Dabrafenib plus trametinib, as compared with vemurafenib monotherapy, significantly improved overall survival in previously untreated patients with metastatic melanoma with *BRAF* V600E or V600K mutations, without increased overall toxicity. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT01597908.)

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The treatment of metastatic melanoma is rapidly evolving. The potent and specific BRAF inhibitors vemurafenib and dabrafenib, as compared with chemotherapy, have significantly improved response rates, along with progression-free and overall survival, in patients with metastatic melanoma with *BRAF* V600E or V600K mutations.[1,2] However, acquired resistance to BRAF inhibitors frequently develops through reactivation of the mitogen-activated protein kinase (MAPK) pathway, resulting in a median progression-free survival of 6 to 8 months.[2-5] In addition, the use of BRAF inhibitors may result in the development of secondary skin tumors, originating from a paradoxical activation of the MAPK pathway in cells without a *BRAF* mutation.[1,6-11] Combining a BRAF inhibitor with a MEK inhibitor addresses the limitations of single-agent BRAF inhibitors and results in a significant delay in the emergence of resistance, with a longer median progression-free survival than with dabrafenib alone, as well as a decreased incidence of BRAF-inhibitor–induced skin tumors.[12-14]

In this open-label, randomized, phase 3 study, we evaluated the effect of combination therapy with dabrafenib plus trametinib versus vemurafenib monotherapy on overall survival in previously untreated patients with unresectable stage IIIC or IV melanoma with *BRAF* V600E or V600K mutations.

Methods

Patients

From June 2012 through October 2013, a total of 1645 patients were screened at 193 centers worldwide. The presence of *BRAF* V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux). Additional key eligibility criteria were measureable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[15] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and higher numbers reflecting greater disability).[16] Patients who had undergone treatment for brain metastases with no increase in lesion size for at least 12 weeks were eligible for enrollment. Additional eligibility criteria are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. Written informed consent was obtained from all study participants.

Study Design and Treatment

Eligible patients were assigned in a 1:1 ratio to receive either a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) or vemurafenib (960 mg orally twice daily). The primary end point was overall survival. Secondary end points included progression-free survival, overall response rate, duration of response, and safety. Crossover was prohibited until the independent data and safety monitoring committee recommended stopping the study early for efficacy. After the recommendation, the study protocol was amended to allow patients in the vemurafenib group to cross over to the combination-therapy group.

Assessment

We conducted tumor assessments according to RECIST, version 1.1,[15] at baseline, every 8 weeks until week 56, and then every 12 weeks until disease progression, death, or withdrawal from the study (Table S1 in the Supplementary Appendix). All responses were confirmed with a scan at least 4 weeks after the first RECIST response. Adverse events were graded by the investigator, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, until day 30 after the discontinuation of study treatment.

Study Oversight

The study was funded by the sponsor, GlaxoSmithKline, and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board or human research ethics committee at each study center. Data were collected at each study site and monitored by the sponsor. The first author wrote the first draft of the manuscript, with support from the last author and representatives of the sponsor. Representatives of the sponsor designed the study, confirmed the accuracy of the data, and compiled the data for analysis. All the authors and sponsor representatives had full access to the study data and were involved in their analysis. No one who was not an author contributed to the writing of the manuscript. Editorial assistance that did not involve writing was provided by SciMentum and funded by the sponsor. All the authors vouch for the accuracy and completeness of the data reported and for the fidelity of the study to the protocol (available at NEJM.org).

STATISTICAL ANALYSIS

We used the Kaplan–Meier method to estimate overall and progression-free survival. We evaluated between-group comparisons using a log-rank test that was stratified for the *BRAF* mutation status (V600E vs. V600K) and the baseline level of lactate dehydrogenase (LDH) (above the upper limit of the normal range vs. the upper limit of the normal range or less). We estimated that 288 events would be required to detect a hazard ratio for death of 0.675 with an alpha level of 0.05 (i.e., an increase in median overall survival from 13.5 months in the vemurafenib group to 20 months in the combination-therapy group). Overall survival was defined as the time from randomization until death from any cause.

A preplanned interim analysis for overall survival was to be conducted when 202 of 288 events that were required for the final analysis (70%) had been observed. Owing to the inherent lag in data entry, the actual number of deaths was 222 at the time of the interim analysis. Per protocol, efficacy boundaries were adjusted on the basis of the actual number of deaths at the time of the interim analysis. The data and safety monitoring committee used the adjusted stopping boundaries (two-sided $P<0.0214$ for the efficacy analysis and $P>0.2210$ for the futility analysis) to review the interim data. The committee recommended stopping for efficacy. As such, the interim summary is considered to be the final analysis of overall survival.

RESULTS

PATIENTS

Of the 1645 patients who underwent screening at 193 centers, 704 underwent randomization, with 352 patients in each group. A total of 68 patients (10%, 34 in each study group) had a *BRAF* V600K mutation. Baseline characteristics of the patients are provided in Table 1. Known prognostic measures were well balanced in the two groups except for sex (59% men in the combination-therapy group vs. 51% in the vemurafenib group). At the date of the analysis, the median follow-up durations were 11 months and 10 months and the median exposure durations were 10 months and 6 months in the combination-therapy group and the vemurafenib group, respectively.

A total of 80 patients in the combination-therapy group and 81 in the vemurafenib group (23% in each group) continued to receive study treatment for at least 15 days after disease progression, according to the protocol, which allowed for treatment after progression on the basis of a request from an investigator for patients who seemed to benefit from the treatment in spite of RECIST progression. The median duration of study treatment after progression was similar in the two study groups and was less than 3 months for the majority of patients, with more patients continuing to receive the combination therapy for 6 to 12 months (9%), as compared with those who continued to receive vemurafenib (1%) (Table S2 in the Supplementary Appendix).

EFFICACY

The interim analysis for overall survival was performed in the intention-to-treat population of 352 patients in each group. At the data-cutoff date of April 17, 2014, the interim analysis was performed after 222 events had occurred. For the overall survival analysis, 100 patients (28%) in the combination-therapy group and 122 (35%) in the vemurafenib group had died (hazard ratio for death in the combination-therapy group, 0.69; 95% confidence interval [CI], 0.53 to 0.89; $P=0.005$) (Fig. 1A). The prespecified stopping boundary ($P<0.0214$) was crossed, and the study was stopped for efficacy on July 14, 2014. A protocol amendment was issued to allow crossover to the combination-therapy group for patients assigned to the vemurafenib group, but no patient had crossed over as of the effective data-freezing date of June 27, 2014.

The median overall survival was 17.2 months for patients in the vemurafenib group and had not been reached for patients in the combination-therapy group (Fig. 1A). The rate of overall survival at 12 months was 72% (95% CI, 67 to 77) in the combination-therapy group and 65% (95% CI, 59 to 70) in the vemurafenib group. The hazard ratios for the variables of V600 mutation type, sex, age (<65 years vs. ≥65 years), baseline LDH level, and ECOG status have been calculated, although these subgroup analyses were not powered to show a significant between-group difference. They all favored the combination-therapy group except for the subgroup of patients with an ECOG score of 1 (hazard ratio, 1.03) (Fig. 1B).

Median progression-free survival was longer in the combination-therapy group than in the vemurafenib group (11.4 months vs. 7.3 months;

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

Characteristic	Dabrafenib plus Trametinib (N=352)	Vemurafenib (N=352)	All Patients (N=704)
Median age (range) — yr	55 (18–91)	54 (18–88)	55 (18–91)
Male sex — no. (%)	208 (59)	180 (51)	388 (55)
Previous immunotherapy — no. (%)†	61 (17)	93 (26)	154 (22)
ECOG score — no./total no. (%)			
0	248/350 (71)	248/352 (70)	496/702 (71)
1	102/350 (29)	104/352 (30)	206/702 (29)
BRAF mutation — no./total no. (%)‡			
V600E	312/346 (90)	317/351 (90)	629/697 (89)
V600K	34/346 (10)	34/351 (10)	68/697 (10)
Tumor stage at screening — no./total no. (%)			
IVM1c	221/351 (63)	208/351 (59)	429/702 (61)
IIIc, IVM1a, or IVM1b	130/351 (37)	143/351 (41)	273/702 (39)
Metastasis stage at screening — no./total no. (%)			
M0	14/351 (4)	26/351 (7)	40/702 (6)
M1a	55/351 (16)	50/351 (14)	105/702 (15)
M1b	61/351 (17)	67/351 (19)	128/702 (18)
M1c	221/351 (63)	208/351 (59)	429/702 (61)
Baseline LDH — no./total no. (%)			
Above ULN	118/351 (34)	114/352 (32)	232/703 (33)
ULN or less	233/351 (66)	238/352 (68)	471/703 (67)
Visceral disease at baseline — no./total no. (%)§			
Yes	278/351 (79)	271/352 (77)	549/703 (78)
No	73/351 (21)	81/352 (23)	154/703 (22)
Number of disease sites at baseline — no./total no. (%)‖			
Fewer than 3	177/351 (50)	201/352 (57)	378/703 (54)
3 or more	174/351 (50)	151/352 (43)	325/703 (46)

* Data are missing in several categories for one patient in each study group because data were either missing or incorrect at baseline. There were no significant differences between the groups at baseline except for sex (P=0.03). ECOG denotes Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, and ULN upper limit of the normal range.

† Previous immunotherapy included interferon-alfa, interferon-gamma, interleukin-2, granulocyte–macrophage colony-stimulating factor, gangliosides, imiquimod, ipilimumab, and investigational antineoplastic vaccine. Interferon and interleukin were classified as biologics in the clinical database. They were reclassified as immunotherapy in this ad hoc analysis.

‡ Six patients in the combination-therapy group and one in the vemurafenib group had both *BRAF* V600E and V600K mutations and thus were excluded from either subgroup.

§ Visceral disease was defined as that affecting the soft internal organs, including the lungs, heart, and the organs of the digestive, excretory, reproductive, and circulatory systems but excluding lymph nodes.

‖ The number of disease sites is the number of unique target and nontarget lesions, as defined by the Response Evaluation Criteria in Solid Tumors and identified by the investigator, not the number of metastases.

hazard ratio, 0.56; 95% CI, 0.46 to 0.69; P<0.001) (Fig. 2A). The hazard ratio for progression-free survival favored combination therapy in all subgroups (Fig 2B).

The objective response rate was 64% (95% CI, 59 to 69) in the combination-therapy group versus 51% (95% CI, 46 to 57) in the vemurafenib group (P<0.001) (Table 2); the median duration

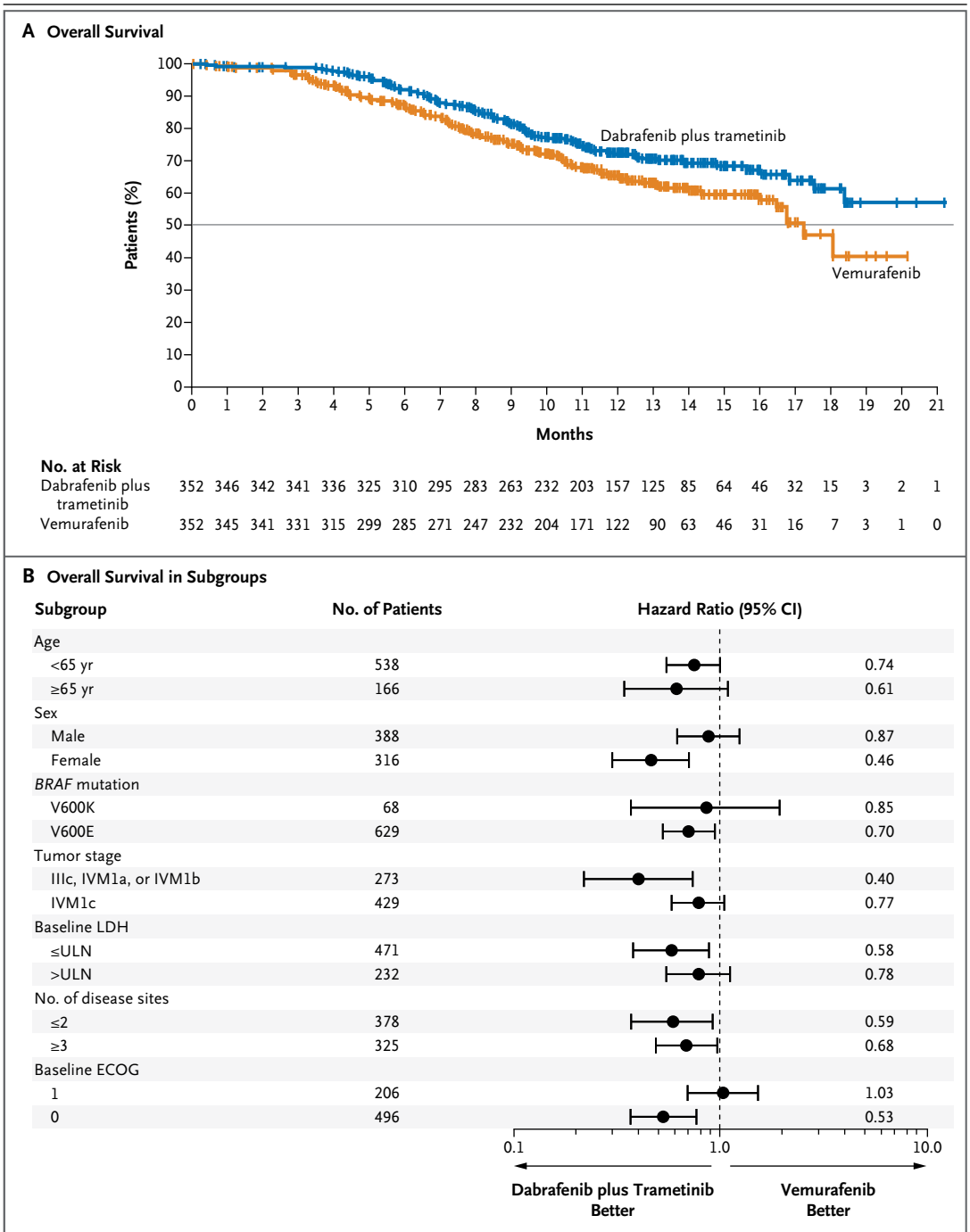
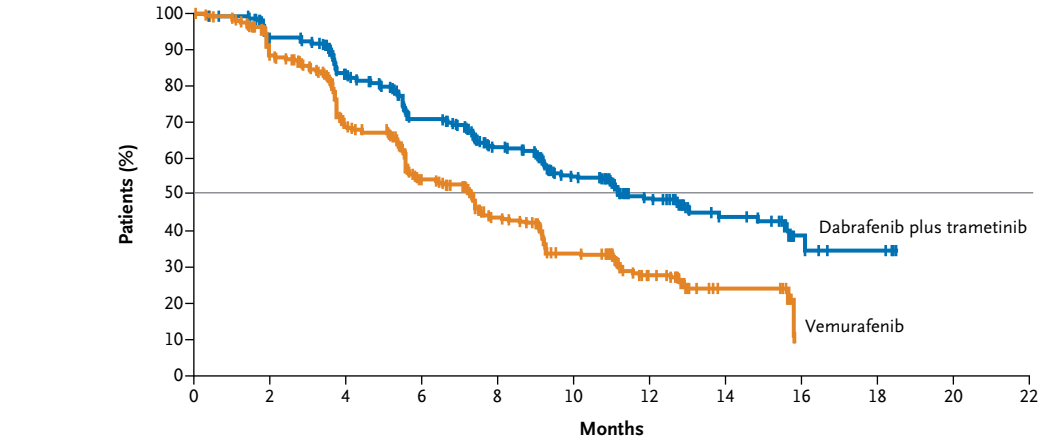


Figure 1. Overall Survival in the Intention-to-Treat Population and Prespecified Subgroups.

Panel A shows Kaplan–Meier estimates of overall survival in the intention-to-treat population among patients receiving combination therapy with dabrafenib plus trametinib versus those receiving vemurafenib monotherapy. The hazard ratio for death in the combination-therapy group was 0.69 (95% confidence interval, 0.53 to 0.89; P=0.005). The tick marks indicate the dates on which data were censored. Panel B shows hazard ratios and 95% confidence intervals for overall survival in prespecified subgroups of patients, according to various baseline characteristics. ECOG denotes Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, and ULN upper limit of the normal range.



No. at Risk

Dabrafenib plus trametinib	352	310	270	228	194	142	83	39	10	7	0	0
Vemurafenib	352	279	214	161	121	83	45	11	0	0	0	0

B Progression-free Survival in Subgroups

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Age		
<65 yr	538	0.57
≥65 yr	166	0.50
Sex		
Male	388	0.65
Female	316	0.44
BRAF mutation		
V600K	68	0.71
V600E	629	0.56
Tumor stage		
IIIc, IVM1a, or IVM1b	273	0.39
IVM1c	429	0.63
Baseline LDH		
≤ULN	471	0.46
>ULN	232	0.72
No. of disease sites		
≤2	378	0.49
≥3	325	0.57
Baseline ECOG		
1	206	0.75
0	496	0.50

Figure 2. Progression-free Survival in the Intention-to-Treat Population and Prespecified Subgroups.

Panel A shows Kaplan–Meier estimates of progression-free survival (as assessed by the site investigators) in the intention-to-treat population among patients receiving combination therapy with dabrafenib plus trametinib versus those receiving vemurafenib monotherapy. The hazard ratio for progression or death in the combination-therapy group was 0.56 (95% confidence interval, 0.46 to 0.69; P<0.001). The tick marks indicate the dates on which data were censored. Panel B shows hazard ratios and 95% confidence intervals for progression-free survival in prespecified subgroups of patients, according to various baseline characteristics.

Table 2. Investigator-Assessed Best Response (Intention-to-Treat Population).*

Response	Dabrafenib plus Trametinib (N=351)	Vemurafenib (N=350)
Type of response — no. (%)		
Complete	47 (13)	27 (8)
Partial	179 (51)	153 (44)
Stable disease	92 (26)	106 (30)
Progressive disease	22 (6)	38 (11)
Not evaluated	11 (3)	26 (7)
Objective response rate		
No. of patients with response (%)†	226 (64)	180 (51)
95% CI	59.1–69.4	46.1–56.8
Duration of response (95% CI) — mo	13.8 (11.0–NR)	7.5 (7.3–9.3)

* Data are missing for one patient in the combination-therapy group and two patients in the vemurafenib group because these patients did not have measurable disease at baseline. NR denotes not reached.

† Included in the objective response are complete and partial responses. P<0.001 for the between-group difference of 13% (95% CI, 6 to 20).

of response was 13.8 months (95% CI, 11.0 to not reached) and 7.5 months (95% CI, 7.3 to 9.3), respectively. In the combination-therapy group, a complete response was reported in 47 patients (13%), as compared with 27 patients (8%) in the vemurafenib group. The response rate for the *BRAF* V600E subgroup was similar to that in the overall population in both study groups: 64% in the combination-therapy group and 52% in the vemurafenib group; in the *BRAF* V600K subgroup, the response rates were 65% and 44%, respectively.

After the discontinuation of study treatment, subsequent anticancer therapy was administered to 20% of the patients in the combination-therapy group and 43% of the patients in the vemurafenib group. The most common therapy after disease progression in the two groups was ipilimumab, which was administered to 12% of the patients in the combination-therapy group and 22% of the patients in the vemurafenib group. Post-trial therapies are listed in Table S3 in the Supplementary Appendix.

ADVERSE EVENTS

The safety analysis included the 699 patients who received at least one dose of a study drug (Table 3, and Table S4 in the Supplementary Appendix). Most patients had adverse events that were deemed by the investigator to be related to the study treatment: 91% in the combination-therapy group and 98% in the vemurafenib group. The rates of permanent treatment discontinuation because of adverse events were similar (13% and 12%, respectively). The most common reasons for discontinuation were pyrexia and decreased ejection fraction (3% for each event) in the combination-therapy group and arthralgia (2%) in the vemurafenib group. Adverse events leading to dose reduction were reported in 33% of patients in the combination-therapy group and 39% of those in the vemurafenib group; adverse events leading to dose interruption occurred in 55% and 56%, respectively. Pyrexia was the most common reason for dose interruption (30%) and dose reduction (14%) in the combination-therapy group. Rash was the most common reason for dose interruption (14%) and dose reduction (11%) in the vemurafenib group.

The most frequent adverse events in the combination-therapy group were pyrexia (53%), nausea (35%), diarrhea (32%), chills (31%), fatigue (29%), headache (29%), and vomiting (29%). In the vemurafenib group, the most frequent adverse events were arthralgia (51%), rash (43%), alopecia (39%), diarrhea (38%), nausea (36%), and fatigue (33%). Skin toxic effects were more frequent in the vemurafenib group than in the combination-therapy group, in particular rash (43% vs. 22%), photosensitivity reaction (22% vs. 4%), hand–foot syndrome (25% vs. 4%), skin papillomas (23% vs. 2%), squamous-cell carcinomas and keratoacanthomas (18% vs. 1%), and hyperkeratosis (25% vs. 4%). Pyrexia was more frequent in the combination-therapy group than in the vemurafenib group (53% vs. 21%).

Grade 3 or 4 adverse events occurred in 52% of the patients in the combination-therapy group and in 63% of those in the vemurafenib group. Three fatal events occurred in each group; all were deemed by the investigator to be unrelated to the study drug. A total of 3 patients in the combination-therapy group died (2 patients from cerebral hemorrhage and 1 from brainstem hemorrhage), as did 3 in the vemurafenib group (1 patient each from acute coronary syndrome, cerebral ischemia, and pleural infection). Rates of noncutaneous cancers were similar in the two groups: 3 patients (1%) in the combination-therapy group and 2 (1%) in the vemurafenib group. A new primary melanoma was reported in 2 (1%) in the combination-therapy group and 7 (2%) in the vemurafenib group. An asymptomatic decrease in cardiac ejection fraction of grade 2 or 3 was reported in 8% of patients in the combination-therapy group and no

Table 3. Adverse Events.*

Event	Dabrafenib plus Trametinib (N=350)		Vemurafenib (N=349)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Clinically significant adverse events occurring in ≥10% of patients				
Any event	343 (98)	167 (48)	345 (99)	198 (57)
Pyrexia‡	184 (53)	15 (4)	73 (21)	2 (1)
Nausea	121 (35)	1 (<1)	125 (36)	2 (1)
Diarrhea	112 (32)	4 (1)	131 (38)	1 (<1)
Chills	110 (31)	3 (1)	27 (8)	0
Vomiting	101 (29)	4 (1)	53 (15)	3 (1)
Arthralgia	84 (24)	3 (1)	178 (51)	15 (4)
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Alopecia	20 (6)	0	137 (39)	1 (<1)
Hand–foot syndrome§	14 (4)	0	87 (25)	1 (<1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (1)
Skin papilloma	6 (2)	0	80 (23)	2 (1)
Photosensitivity reaction	13 (4)	0	78 (22)	1 (<1)
Adverse events of interest occurring in <10% of patients				
Cutaneous squamous-cell carcinoma (including keratoacanthoma)	5 (1)	5 (1)	63 (18)	60 (17)
Decrease in ejection fraction	29 (8)	13 (4)	0	0
Chorioretinopathy	2 (1)	0	1 (<1)	0
Dermatitis acneiform	22 (6)	0	20 (6)	4 (1)

* Included in the safety analysis are 699 patients who received at least one dose of a study drug.
† Grade 4 events occurred in 3 patients (with headache, asthenia, and an elevated aspartate aminotransferase level) in the combination-therapy group and in 5 patients (with hypertension, constipation, an elevated alanine aminotransferase level, and squamous-cell carcinoma) in the vemurafenib group. Grade 5 events occurred in 3 patients (with cerebral hemorrhage in 2 patients and brain-stem hemorrhage in 1 patient) in the combination-therapy group and in 3 patients (with acute coronary syndrome, cerebral ischemia, and pleural infection) in the vemurafenib group.
‡ Pyrexia was defined as a body temperature of 38.5°C or more.
§ The hand–foot syndrome includes the terms palmar–plantar erythrodysesthesia, plantar–palmar hyperkeratosis, and palmoplantar keratoderma.

patients in the vemurafenib group. Two grade 1 chorioretinopathy events were reported in the combination-therapy group and one in the vemurafenib group. In the vemurafenib group, grade 2 retinal-vein occlusion that was reported in 1 patient was considered to be related to the study drug; no retinal-vein occlusion was reported in the combination-therapy group.

DISCUSSION

In our study, patients with previously untreated metastatic melanoma with *BRAF* mutations who received combination therapy with dabrafenib and trametinib, as compared with vemurafenib monotherapy, had a relative reduction of 31% in the risk of death. Together with the previously reported phase 2 and phase 3 trials of dabrafenib plus trametinib, as compared with dabrafenib monotherapy,[12,13] these data provide clear evidence for the benefit of this combination therapy over BRAF monotherapy in prolonging survival. Only modest activity has been observed with single-agent trametinib, or trametinib added to dabrafenib, in patients whose tumors have progressed while they were receiving dabrafenib monotherapy.[17-19] Thus, our study shows that first-line use of both BRAF and MEK inhibitors

resulted in higher response rates and longer durations of response, as well as delayed emergence of tumor resistance, which led to a significant overall survival benefit.

To evaluate a potential influence of subsequent anticancer therapies on the patients' survival, we analyzed the treatments that they received after progression in each group. More patients in the vemurafenib group received subsequent anticancer therapy than in the combination-therapy group (43% vs. 20%). The most common postprogression therapy in the two groups was ipilimumab, which is known to prolong survival in patients with metastatic melanoma.[20,21] The fact that the median duration of exposure to vemurafenib was 4 months shorter than that for the combination therapy might partly explain why more patients in the vemurafenib group received postprogression therapy at this point. However, with more patients in the vemurafenib group having received a therapy that is known to affect overall survival, there is no evidence that differences in postprogression therapy contributed to the survival benefit seen in the combination-therapy group.

Post hoc subgroup analyses showed that the overall survival benefit was found in all prognostic subgroups except for patients with an ECOG score of 1. The hazard ratio for these patients was 1.03, which is surprising, since other known prognostic factors, such as M1c stage, high LDH, and more than three sites of metastases, have hazard ratios that suggest a benefit for the combination therapy, as compared with vemurafenib. To understand the results in this subpopulation of patients, we looked at their subsequent therapies and conducted statistical tests for interactions with other prognostic factors. This observation did not appear to be driven by any specific factor and remains unexplained. Although no definitive conclusions can be drawn for this subgroup, a Cox model showed a hazard ratio for overall survival that was consistent with the results in the overall population, after accounting for the simultaneous effect of prognostic factors corrected for stratification factors.

Progression-free survival was also significantly prolonged among patients receiving the combination therapy, a finding that confirms the results of the COMBI-d phase 3 study, which evaluated progression-free survival in a similar population of patients who were treated with dabrafenib plus trametinib, as compared with dabrafenib alone.[13,22] The results are also consistent with those of another study comparing vemurafenib plus cobimetinib with vemurafenib alone, which showed significant differences in progression-free survival of 9.9 and 6.2 months, respectively.[14]

The objective rate of tumor response was significantly higher in the combination-therapy group than in the vemurafenib group (64% vs. 51%, $P<0.001$), as was the duration of response, with a median duration of response in the combination-therapy group that was almost twice as long as that in the vemurafenib group (13.8 months vs. 7.5 months). Notably, the rate of complete response was also significantly higher in the combination-therapy group than in the vemurafenib group (13% vs. 8%, $P=0.02$) in a post hoc analysis.

The overall safety profile in the combination-therapy group shows that this regimen has frequent low-grade toxicity. The incidences of grade 3 or 4 toxic effects and of adverse effects leading to dose reduction or treatment interruption were similar in the two study groups, with no deaths that were deemed to be related to the study drug. The spectrum of adverse effects differed in the two groups, with the most common cause for treatment modification reported as pyrexia in the combination-therapy group and rash in the vemurafenib group. Pyrexia is usually easily manageable with symptomatic treatment or transient interruption of dabrafenib or both dabrafenib and trametinib, with treatment reinitiation after the patient has been afebrile for a minimum of 24 hours. The education of both patients and physicians regarding pyrexia management is paramount to ensure that this side effect is not prolonged or complicated. A decreased ejection fraction was more frequent with the combination therapy than with vemurafenib (8% vs. 0%), and this side effect has been observed previously with single-agent MEK inhibitors.[14,17]

Skin adverse effects were less frequent in the combination-therapy group, especially the events that are linked to a paradoxical activation of the MAPK pathway, including both benign and malignant skin tumors. This finding is in accordance with preclinical models showing that the addition of MEK inhibitors may down-regulate the BRAF-inhibitor–induced paradoxical activation of the MAPK pathway.[23-27] Thus, secondary resistance and paradoxical activation of the MAPK pathway that occur with BRAF-inhibitor

monotherapy, which translate into rapid tumor relapses and emergence of skin cancers, respectively, were both improved by the combination therapy.

In conclusion, the combination of dabrafenib plus trametinib was superior to vemurafenib monotherapy with regard to all efficacy end points, including overall survival, with no additional overall toxicity.

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

APPENDIX

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