ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

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ABSTRACT

BACKGROUND

Phase 1 and 2 clinical trials of the BRAF kinase inhibitor vemurafenib (PLX4032) have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.

METHODS

We conducted a phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation. Patients were randomly assigned to receive either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg per square meter of body-surface area intravenously every 3 weeks). Coprimary end points were rates of overall and progression-free survival. Secondary end points included the response rate, response duration, and safety. A final analysis was planned after 196 deaths and an interim analysis after 98 deaths.

RESULTS

At 6 months, overall survival was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine (P<0.001 for both comparisons). After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended. Response rates were 48% for vemurafenib and 5% for dacarbazine. Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea, and diarrhea; 38% of patients required dose modification because of toxic effects.

CONCLUSIONS

Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation. (Funded by Hoffmann–La Roche; BRIM-3 ClinicalTrials.gov number, NCT01006980.)

METASTATIC MELANOMA HAS A POOR prognosis, with the median survival for patients with stage IV melanoma ranging from 8 to 18 months after diagnosis, depending on the substage.[1] In the United States last year, 8700 deaths from melanoma were projected, with an estimated rate of death of 2.6 in 100,000.[2] Rates of death from melanoma in Australia and New Zealand are slightly higher (3.5 in 100,000), whereas rates in Western Europe are slightly lower (1.8 in 100,000).[3]

In phase 3 studies, dacarbazine, the only chemotherapeutic agent approved by the Food and Drug Administration for the treatment of metastatic melanoma, was associated with a response rate of 7 to 12% and a median overall survival of 5.6 to 7.8 months after the initiation of treatment.[4-7] Although higher response rates can be achieved with combination chemotherapy, these combinations have not resulted in improved rates of overall survival. Recently, the use of ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) on lymphocytes, has been associated with improved overall survival, as compared with a peptide vaccine,[8] and in combination with dacarbazine has been associated with better overall survival than dacarbazine alone.[9]

Approximately 40 to 60% of cutaneous melanomas carry mutations in *BRAF* that lead to constitutive activation of downstream signaling through the MAPK pathway.[10,11] Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (BRAF V600E), although other activating mutations are known (e.g., BRAF V600K and BRAF V600R).

Vemurafenib (PLX4032) is a potent inhibitor of mutated BRAF.[12] It has marked antitumor effects against melanoma cell lines with the BRAF V600E mutation but not against cells with wild-type BRAF.[12-14] A phase 1 trial established the maximum tolerated dose to be 960 mg twice daily and showed frequent tumor responses.[15] A phase 2 trial involving patients who had received previous treatment for melanoma with the BRAF V600E mutation showed a confirmed response rate of 53%, with a median duration of response of 6.7 months.[16] We conducted a randomized phase 3 trial to determine whether vemurafenib would prolong the rate of overall or progression-free survival, as compared with dacarbazine.

METHODS

PATIENTS

All patients in our study had unresectable, previously untreated stage IIIC or stage IV melanoma that tested positive for the BRAF V600E mutation on real-time polymerase-chain-reaction assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems). The test was performed at one of five central laboratories in the United States, Germany, and Australia. In approximately one third of the patients, *BRAF* was sequenced retrospectively by Sanger and 454 sequencing at a central laboratory. Other inclusion criteria were age of 18 years or older, a life expectancy of 3 months or longer, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active and able to carry on all performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), and adequate hematologic, hepatic, and renal function. Patients were excluded if they had a history of cancer within the past 5 years (except for basal- or squamous-cell carcinoma of the skin or carcinoma of the cervix) or metastases to the central nervous system, unless such metastases had been definitively treated more than 3 months previously with no progression and no requirement for continued glucocorticoid therapy. Concomitant treatment with any other anticancer therapy was not allowed.

The protocol was approved by the institutional review board at each participating institution and was conducted in accordance with the ethical principles of the Declaration of Helsinki and within the Good Clinical Practice guidelines, as defined by the International Conference on Harmonization. All patients provided written informed consent before enrollment.

STUDY DESIGN AND TREATMENT

From January 2010 through December 2010, a total of 2107 patients underwent screening at 104 centers in 12 countries worldwide. The most common reason for screening failure was a negative test for the BRAF V600 mutation. A total of 675 patients were randomly assigned in a 1:1 ratio to receive either vemurafenib (at a dose of 960 mg twice daily orally) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area by intravenous infusion every 3 weeks) (Fig. A in the Supplementary Appendix, available with the full text of this article at NEJM.org). These pa-

tients included 20 with non-V600E mutations (19 with V600K and 1 with V600D), as identified on Sanger and 454 sequencing. Baseline characteristics of the patients were well balanced (Table 1).

Study patients were stratified according to American Joint Committee on Cancer stage (IIIC, M1a, M1b, or M1c), ECOG performance status (0 or 1), geographic region (North America, Western Europe, Australia or New Zealand, or other region), and serum lactate dehydrogenase level (normal or elevated).

Dose reductions for both vemurafenib and dacarbazine were prespecified for intolerable grade 2 toxic effects or worse. The development of cutaneous squamous-cell carcinoma did not require dose modification. The administration of vemurafenib was interrupted until the resolution of the toxic effect to at least grade 1 and restarted at 720 mg twice daily (480 mg twice daily for grade 4 events), with a dose reduction to 480 mg twice daily if the toxic effects recurred. If the toxic effect did not improve to grade 1 or lower or recurred at the 480-mg twice-daily dose, treatment was discontinued permanently. The administration of dacarbazine was interrupted for grade 3 or 4 toxic effects and could be restarted on recovery within 1 week to grade 1 (at full dose) or grade 2 (at 75% dose) or at 75% dose for grade 4 neutropenia or febrile neutropenia. A second dose reduction was allowed, if needed. Antiemetics and granulocyte colony-stimulating factor were administered according to standards at each study center. Treatment was discontinued on disease progression unless continued treatment was in the best interest of the patient in the judgment of the investigator and the sponsor.

ASSESSMENTS

At baseline, patients underwent computed tomography with contrast material or magnetic resonance imaging of the brain, chest, abdomen, pelvis, and other anatomical regions, as clinically indicated. Patients also underwent physical and dermatologic examinations and electrocardiography. Patients were examined every 3 weeks; tumor assessments were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter. Tumor responses were determined by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Electrocardiograms were repeated every other cycle. Blood counts, biochemical analyses, and measurements of lactate dehydrogenase levels were performed at each visit.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Vemurafenib (N = 337)	Dacarbazine (N = 338)
Median age (range) — yr	56 (21–86)	52 (17–86)
Male sex — no. (%)	200 (59)	181 (54)
White race — no. (%)†	333 (99)	338 (100)
Geographic region — no. (%)		
Australia or New Zealand	39 (12)	38 (11)
North America	86 (26)	86 (25)
Western Europe	205 (61)	203 (60)
Other	7 (2)	11 (3)
ECOG performance status — no. (%)‡		
0	229 (68)	230 (68)
1	108 (32)	108 (32)
Extent of metastatic melanoma — no. (%)§		
M1c	221 (66)	220 (65)
M1b	62 (18)	65 (19)
M1a	34 (10)	40 (12)
Unresectable IIIC	20 (6)	13 (4)
Lactate dehydrogenase — no. (%)¶		
≤Upper limit of the normal range	142 (42)	142 (42)
>Upper limit of the normal range	195 (58)	196 (58)

* Percentages may not total 100 because of rounding.
† Race was self-reported.
‡ An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is fully active and able to carry on all predisease activities without restriction; an ECOG performance 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 is characterized by metastasis of the tumor to the skin, subcutaneous tissues, or distant lymph nodes, with a normal lactate dehydrogenase level; M1b by metastasis to the lung, with a normal lactate dehydrogenase level; and M1c by metastasis to any other visceral site or to any site, with an elevated lactate dehydrogenase level. In unresectable stage IIIC disease, melanoma has spread to at least three lymph nodes, which are enlarged because of the cancer.
¶ The upper limit of the normal range varied according to the reference values at each study center.

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Monitoring of adverse events continued for up to 28 days after the last dose of a study drug had been administered or until any ongoing event resolved or stabilized. An independent data and safety monitoring board provided oversight and evaluated interim results on efficacy data.

STUDY OVERSIGHT

The trial was designed jointly by the senior academic authors and representatives of the sponsor, Hoffmann–La Roche. Data were collected by

the sponsor and analyzed in collaboration with the senior academic authors, who vouch for the completeness and accuracy of the data and analyses and for the conformance of this report to the protocol, as amended. The corresponding academic author prepared an initial draft of the manuscript in collaboration with the sponsor. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. The protocol and statistical analysis plan are available at NEJM.org.

STATISTICAL ANALYSIS

The original primary end point was the rate of overall survival. The statistical plan was revised in October 2010 on the basis of phase 1 and 2 efficacy and safety results and after consultation with global regulatory authorities. Under the revised plan, the rates of overall survival and progression-free survival were coprimary end points. The final analysis was planned after 196 deaths, and an interim analysis was planned after 50% of the projected deaths had occurred (Pocock boundary, P≤0.028 at the interim analysis and P≤0.0247 at the final analysis by the log-rank test). According to the revised plan, the final analysis of progression-free survival would be performed at the time of the interim analysis of overall survival. Secondary end points included the confirmed response rate, duration of response, and time to response.

The trial was designed for 680 patients to be randomly assigned to receive either vemurafenib or dacarbazine. The trial had a power of 80% to detect a hazard ratio of 0.65 for overall survival with an alpha level of 0.045 (an increase in median survival from 8 months for dacarbazine to 12.3 months for vemurafenib) and a power of 90% to detect a hazard ratio of 0.55 for progression-free survival with an alpha level of 0.005 (an increase in median survival from 2.5 months for dacarbazine to 4.5 months for vemurafenib). Survival was defined as the time from randomization to death from any cause. Progression-free survival was the time from randomization to documented disease progression or death. We used a two-sided unstratified log-rank test to compare survival rates in the two study groups. Hazard ratios for treatment with vemurafenib, as compared with dacarbazine, were estimated with the use of unstratified Cox regression. We estimated event–time distributions using the Kaplan–Meier method. All reported P values are two-sided, and

confidence intervals are at the 95% level. Descriptive statistics are used for adverse events.

This report is based on data as of December 30, 2010. Efficacy analyses were performed in the intention-to-treat population. In order to ensure adequate follow-up for each efficacy end point, patients could be evaluated for the analysis of overall survival, progression-free survival, and confirmed response if they had undergone randomization at least 2, 9, and 14 weeks, respectively, before the cutoff date. The safety analysis was performed in all patients who received a study drug and who had undergone at least one assessment during the study.

RESULTS

PATIENTS AND TREATMENTS

A total of 118 patients had died at the time of the interim analysis. The data and safety monitoring board determined that both the overall survival and progression-free survival end points had met the prespecified criteria for statistical significance in favor of vemurafenib. The board recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib, and the protocol was amended accordingly on January 14, 2011. Median follow-up for the interim analysis was 3.8 months for patients in the vemurafenib group and 2.3 months for those in the dacarbazine group.

EFFICACY

A total of 672 patients were evaluated for overall survival. The hazard ratio for death in the vemurafenib group was 0.37 (95% confidence interval [CI], 0.26 to 0.55; P<0.001) (Fig. 1A). The survival benefit in the vemurafenib group was observed in each prespecified subgroup, according to age, sex, ECOG performance status, tumor stage, lactate dehydrogenase level, and geographic region (Fig. 1B). At the time of the interim analysis, there were an inadequate number of patients in follow-up beyond 7 months in either study group to provide reliable Kaplan–Meier estimates of the survival curves.[17] At 6 months, overall survival was 84% (95% CI, 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. Further follow-up is required.

Progression-free survival could be evaluated in 549 patients. The hazard ratio for tumor progression in the vemurafenib group was 0.26 (95% CI, 0.20 to 0.33; P<0.001) (Fig. 2A). The esti-
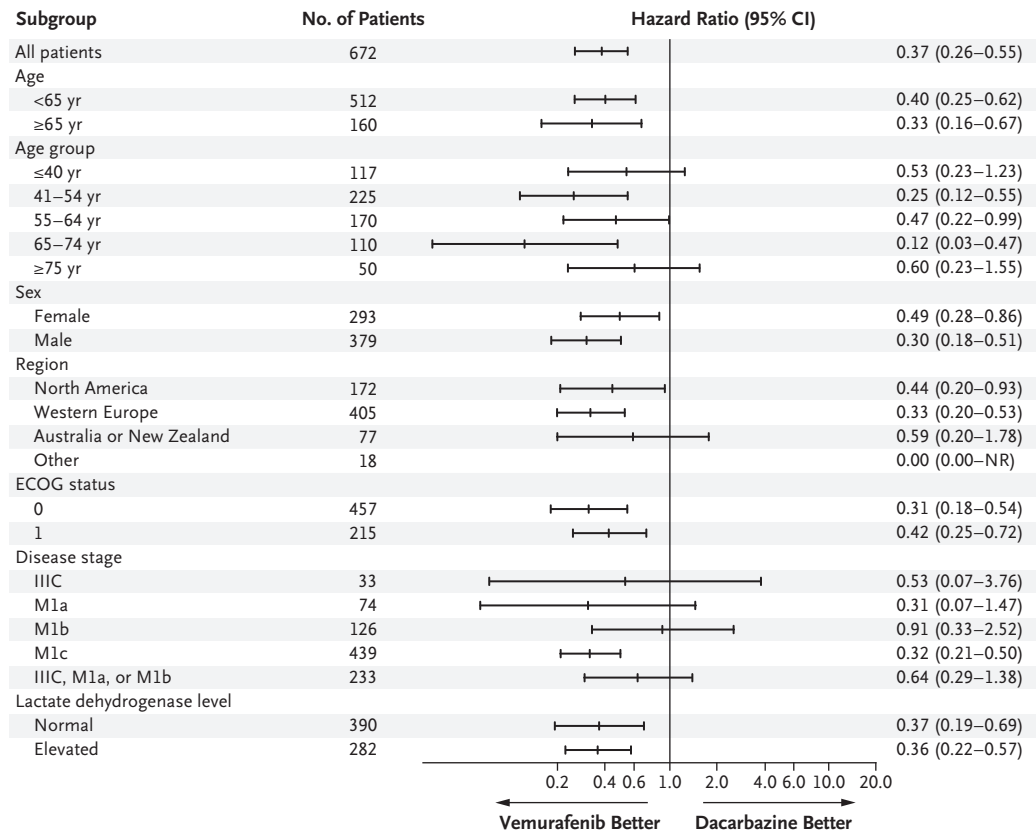
A Overall Survival

Hazard ratio, 0.37; 95% CI, 0.26 to 0.55;
P<0.001

Vemurafenib (N=336)
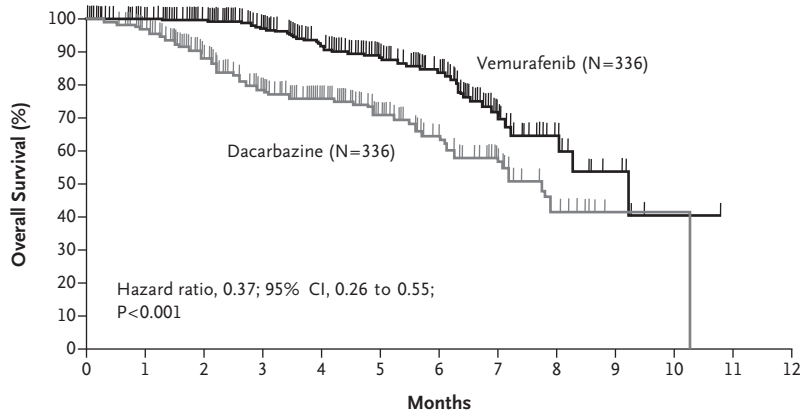
Dacarbazine (N=336)

No. at Risk												
Dacarbazine	336	283	192	137	98	64	39	20	9	1	1	0	0
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1	0	0

B Subgroup Analyses of Overall Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
All patients	672		0.37 (0.26–0.55)
Age			
<65 yr	512		0.40 (0.25–0.62)
≥65 yr	160		0.33 (0.16–0.67)
Age group			
≤40 yr	117		0.53 (0.23–1.23)
41–54 yr	225		0.25 (0.12–0.55)
55–64 yr	170		0.47 (0.22–0.99)
65–74 yr	110		0.12 (0.03–0.47)
≥75 yr	50		0.60 (0.23–1.55)
Sex			
Female	293		0.49 (0.28–0.86)
Male	379		0.30 (0.18–0.51)
Region			
North America	172		0.44 (0.20–0.93)
Western Europe	405		0.33 (0.20–0.53)
Australia or New Zealand	77		0.59 (0.20–1.78)
Other	18		0.00 (0.00–NR)
ECOG status			
0	457		0.31 (0.18–0.54)
1	215		0.42 (0.25–0.72)
Disease stage			
IIIC	33		0.53 (0.07–3.76)
M1a	74		0.31 (0.07–1.47)
M1b	126		0.91 (0.33–2.52)
M1c	439		0.32 (0.21–0.50)
IIIC, M1a, or M1b	233		0.64 (0.29–1.38)
Lactate dehydrogenase level			
Normal	390		0.37 (0.19–0.69)
Elevated	282		0.36 (0.22–0.57)

0.2 0.4 0.6 1.0   2.0   4.0 6.0 10.0 20.0

← Vemurafenib Better   Dacarbazine Better →
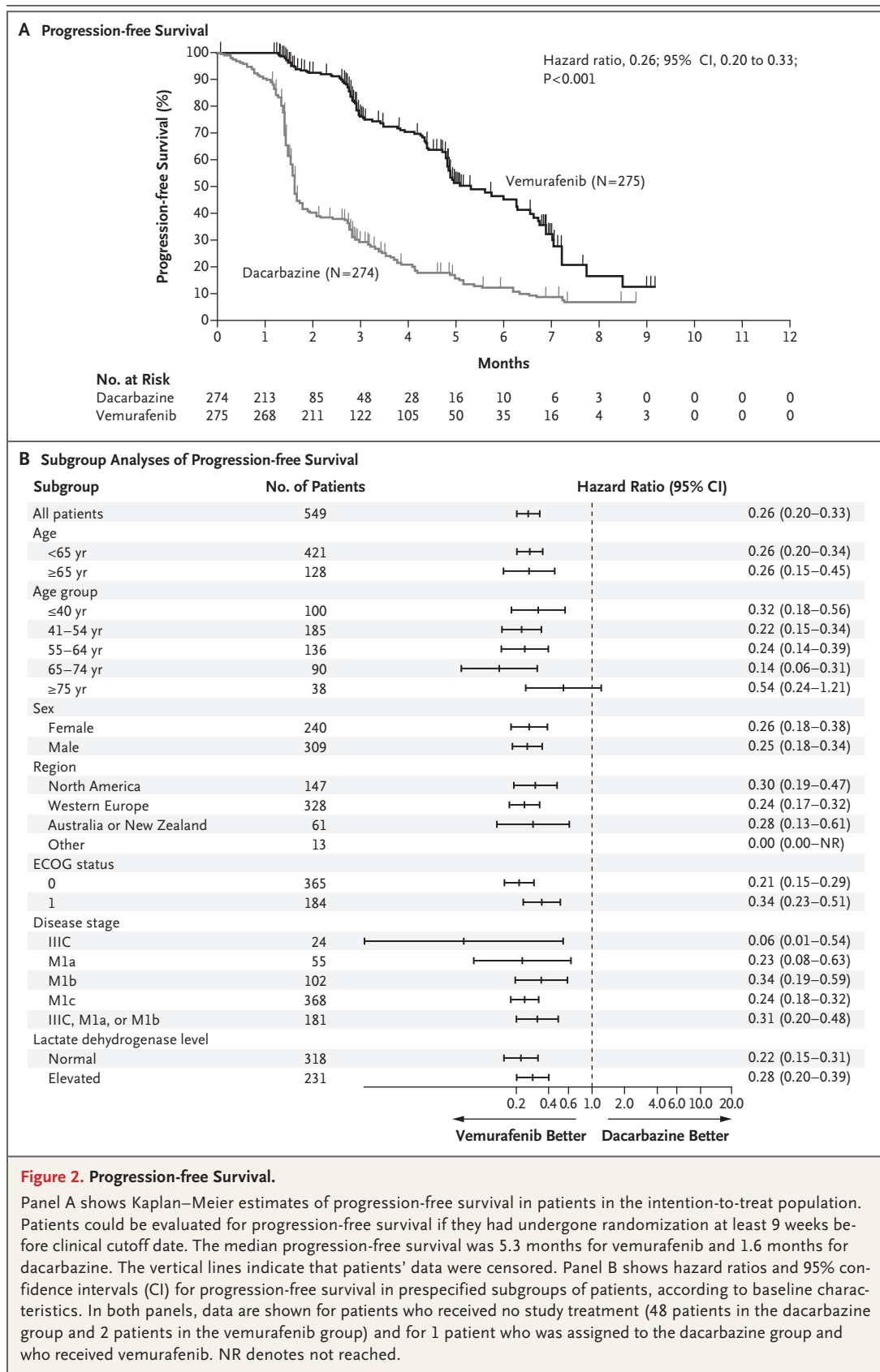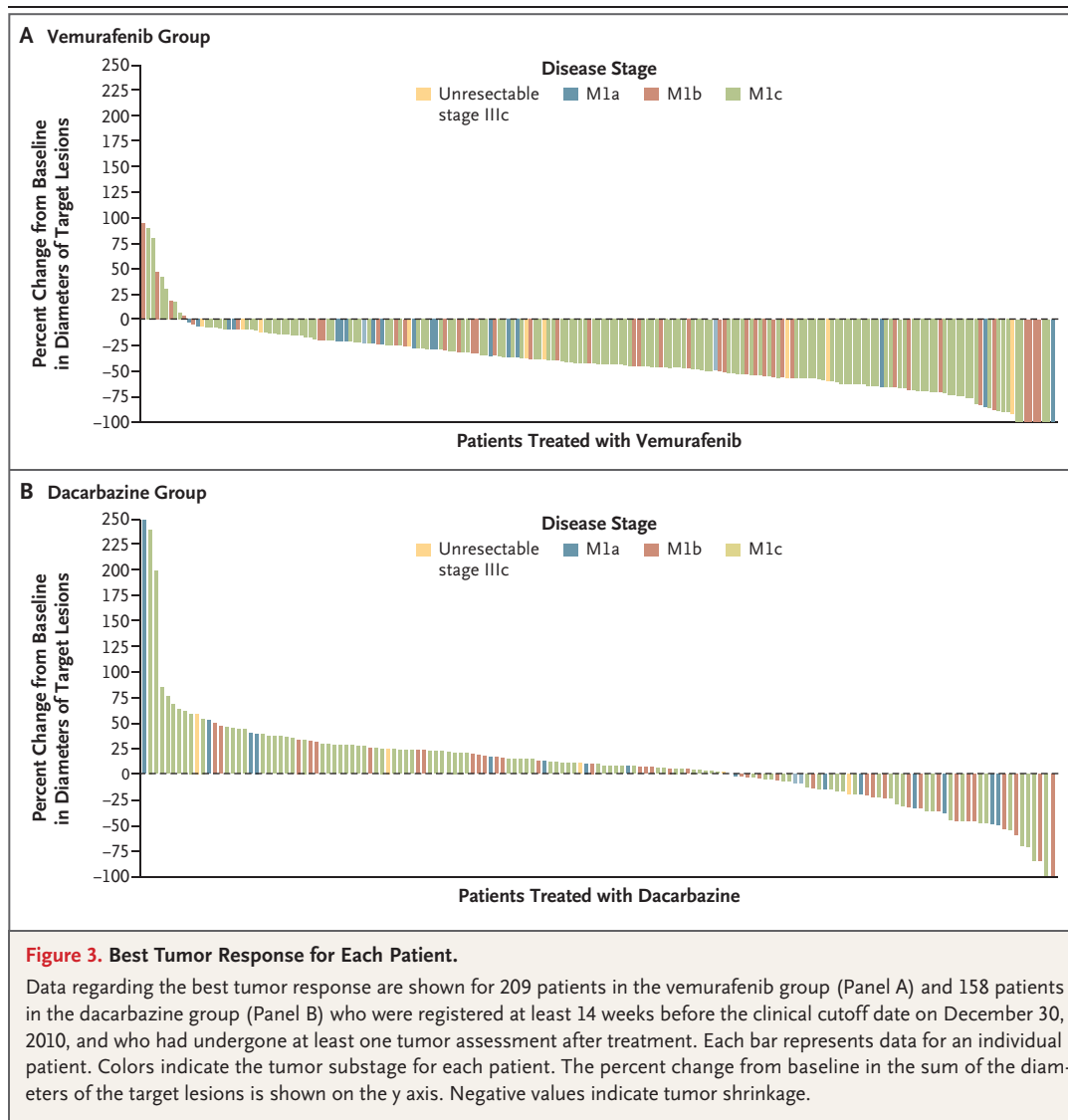
Figure 1. Overall Survival.

Panel A shows Kaplan–Meier estimates of survival in patients in the intention-to-treat population. Patients could be evaluated for overall survival if they had undergone randomization at least 2 weeks before the clinical cutoff date. An inadequate number of patients were evaluated after 7 months of follow-up in either study group to provide reliable Kaplan–Meier estimates of the survival curves. The vertical lines indicate that patients' data were censored. Panel B shows hazard ratios and 95% confidence intervals (CI) for rates of overall survival in prespecified subgroups of patients, according to various baseline characteristics. In both panels, data are shown for patients who received no study treatment (48 patients in the dacarbazine group and 2 patients in the vemurafenib group) and for 1 patient who was assigned to the dacarbazine group but who received vemurafenib. NR denotes not reached.

A Progression-free Survival

Hazard ratio, 0.26; 95% CI, 0.20 to 0.33;
P<0.001

Vemurafenib (N=275)

Dacarbazine (N=274)

No. at Risk												
Dacarbazine	274	213	85	48	28	16	10	6	3	0	0	0	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3	0	0	0

B Subgroup Analyses of Progression-free Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)	
All patients	549		0.26 (0.20–0.33)
Age			
<65 yr	421		0.26 (0.20–0.34)
≥65 yr	128		0.26 (0.15–0.45)
Age group			
≤40 yr	100		0.32 (0.18–0.56)
41–54 yr	185		0.22 (0.15–0.34)
55–64 yr	136		0.24 (0.14–0.39)
65–74 yr	90		0.14 (0.06–0.31)
≥75 yr	38		0.54 (0.24–1.21)
Sex			
Female	240		0.26 (0.18–0.38)
Male	309		0.25 (0.18–0.34)
Region			
North America	147		0.30 (0.19–0.47)
Western Europe	328		0.24 (0.17–0.32)
Australia or New Zealand	61		0.28 (0.13–0.61)
Other	13		0.00 (0.00–NR)
ECOG status			
0	365		0.21 (0.15–0.29)
1	184		0.34 (0.23–0.51)
Disease stage			
IIIC	24		0.06 (0.01–0.54)
M1a	55		0.23 (0.08–0.63)
M1b	102		0.34 (0.19–0.59)
M1c	368		0.24 (0.18–0.32)
IIIC, M1a, or M1b	181		0.31 (0.20–0.48)
Lactate dehydrogenase level			
Normal	318		0.22 (0.15–0.31)
Elevated	231		0.28 (0.20–0.39)

0.2 0.4 0.6 1.0   2.0   4.0 6.0 10.0 20.0

Vemurafenib Better ← → Dacarbazine Better

Figure 2. Progression-free Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival in patients in the intention-to-treat population. Patients could be evaluated for progression-free survival if they had undergone randomization at least 9 weeks before clinical cutoff date. The median progression-free survival was 5.3 months for vemurafenib and 1.6 months for dacarbazine. The vertical lines indicate that patients' data were censored. Panel B shows hazard ratios and 95% confidence intervals (CI) for progression-free survival in prespecified subgroups of patients, according to baseline characteristics. In both panels, data are shown for patients who received no study treatment (48 patients in the dacarbazine group and 2 patients in the vemurafenib group) and for 1 patient who was assigned to the dacarbazine group and who received vemurafenib. NR denotes not reached.

Figure 3. Best Tumor Response for Each Patient.

Data regarding the best tumor response are shown for 209 patients in the vemurafenib group (Panel A) and 158 patients in the dacarbazine group (Panel B) who were registered at least 14 weeks before the clinical cutoff date on December 30, 2010, and who had undergone at least one tumor assessment after treatment. Each bar represents data for an individual patient. Colors indicate the tumor substage for each patient. The percent change from baseline in the sum of the diameters of the target lesions is shown on the y axis. Negative values indicate tumor shrinkage.

mated median progression-free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group. Superior progression-free survival with vemurafenib over dacarbazine was observed in all subgroups that were analyzed (Fig. 2B).

A total of 439 patients (65%) could be evaluated for tumor response on the basis of having undergone randomization at least 14 weeks before the clinical cutoff date of December 30, 2010. In the vemurafenib group, most patients had a detectable decrease in tumor size (Fig. 3A), and 106 of 219 patients (48%; 95% CI, 42 to 55) had a confirmed objective response (including 2 patients with a complete response and 104 with a partial response), with a median time to response

of 1.45 months. Ten patients in the vemurafenib group were later found to have BRAF V600K mutations; of these patients, 4 had a partial response (40%). In the dacarbazine group, a minority of patients had a detectable decrease in tumor size (Fig. 3B), and only 12 of 220 patients (5%; 95% CI, 3 to 9) met the criteria for a confirmed response (all partial responses), with a median time to response of 2.7 months. The difference in confirmed response rates between the two study groups (48% vs. 5%) was highly significant (P<0.001 by the chi-square test).

ADVERSE EVENTS

A total of 618 patients (92%) underwent at least one assessment as of the clinical cutoff date and

Table 2. Adverse Events in 618 Patients.*

Adverse Event	Vemurafenib (N=336)†	Dacarbazine (N=282)
	no. of patients (%)	
Arthralgia		
Grade 2	60 (18)	1 (<1)
Grade 3	11 (3)	2 (<1)
Rash		
Grade 2	33 (10)	0
Grade 3	28 (8)	0
Fatigue		
Grade 2	38 (11)	33 (12)
Grade 3	6 (2)	5 (2)
Cutaneous squamous-cell carcinoma‡		
Grade 3	40 (12)	1 (<1)
Keratoacanthoma§		
Grade 2	7 (2)	0
Grade 3	20 (6)	0
Nausea		
Grade 2	25 (7)	32 (11)
Grade 3	4 (1)	5 (2)
Alopecia		
Grade 2	26 (8)¶	0
Pruritus		
Grade 2	19 (6)	0
Grade 3	5 (1)	0
Hyperkeratosis		
Grade 2	17 (5)	0
Grade 3	4 (1)	0
Diarrhea		
Grade 2	16 (5)	4 (1)
Grade 3	2 (<1)	1 (<1)
Headache		
Grade 2	15 (4)	5 (2)
Grade 3	2 (<1)	0
Vomiting		
Grade 2	9 (3)	14 (5)
Grade 3	4 (1)	3 (1)
Neutropenia		
Grade 2	1 (<1)	4 (1)
Grade 3	0	15 (5)
Grade 4	1 (<1)	8 (3)
Grade 5	0	1 (<1)

* Listed are all adverse events of grade 2 or higher that were reported in more than 5% of patients in either study group.
† One patient in the dacarbazine group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of adverse events.
‡ The criteria for the diagnosis of cutaneous squamous-cell carcinoma were defined in the protocol and were reported as grade 3, according to the National Cancer Institute Common Terminology Criteria for Adverse Events. These events were evaluated by the investigators as grade 1 in one patient and as grade 2 in one patient.
§ Three patients with keratoacanthomas that were assessed by the investigator as grade 1 are included among the grade 2 keratoacanthomas.
¶ In one patient, alopecia that was scored as grade 3 by the investigator was rescored as grade 2 since the Common Terminology Criteria for Adverse Events do not include grade 3 alopecia.

were evaluated for toxic effects. Adverse events of grade 2 or more that were reported in more than 5% of the patients in either study group are shown in Table 2; adverse events of any grade that were reported in more than 5% of the patients are shown in Table A in the Supplementary Appendix. The most common adverse events in the vemurafenib group were cutaneous events, arthralgia, and fatigue; photosensitivity skin reactions of grade 2 or 3 were seen in 12% of the patients, with grade 3 reactions characterized by blistering that often could be prevented with sunblock. As expected, the most common severe toxic effects in the dacarbazine group were fatigue, nausea, vomiting, and neutropenia. Adverse events led to dose modification or interruption in 129 of 336 patients (38%) in the vemurafenib group and in 44 of 282 patients (16%) in the dacarbazine group.

In the vemurafenib group, a cutaneous squamous-cell carcinoma, keratoacanthoma, or both developed in 61 patients (18%). All lesions were treated by simple excision. Pathological analyses of skin-biopsy specimens from these patients are currently being performed by an independent dermatology working group.

DISCUSSION

In our study, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of tumor progression in patients with previously untreated, unresectable stage IIIC or stage IV melanoma with the BRAF V600E mutation, as compared with dacarbazine. Benefit was seen in all subgroups of patients who were included in the analysis, including patients with stage M1c disease or an elevated lactate dehydrogenase level, both of which are associated with particularly poor prognoses.

Recently, ipilimumab, an anti-CTLA4 antibody, was shown to improve overall survival in patients with metastatic melanoma, as compared with a peptide vaccine, although there was only a modest effect on rates of response and progression-free survival.[8] The use of ipilimumab combined with dacarbazine has also been associated with improved rates of survival over dacarbazine alone.[9]

Overall, 48% of the patients who were treated with vemurafenib met the criteria for a confirmed response, although most patients had some tumor shrinkage. This finding was consistent with the confirmed response rates seen in the phase 1 extension cohort[15] and in a recent

phase 2 trial involving previously treated patients.[16] Furthermore, 4 of 10 patients with the BRAF V600K mutation had a response to vemurafenib, indicating that melanomas with this variant are also sensitive to vemurafenib.

The confirmed response rate in the dacarbazine cohort was 5%, which is slightly lower than that in recent phase 3 trials.[4-7] Our study was a randomized trial comparing vemurafenib with dacarbazine in which only patients with BRAF-mutated melanomas were treated. Recent studies have raised the possibility that melanomas with the BRAF V600E mutation are more aggressive[18,19] and less sensitive to chemotherapy[18,20] than BRAF wild-type melanomas. Also, 48 patients (14%) in the dacarbazine group (29 of whom were available for evaluation in this report) did not receive any treatment, most commonly because the patient withdrew consent (Fig. A in the Supplementary Appendix). Patients receiving vemurafenib reported relatively few grade 3 or worse adverse events. Other than cutaneous squamous-cell carcinoma and keratoacanthomas, the most common drug-related grade 3 (or worse) toxic effects were rash, arthralgias, photosensitivity, and fatigue. Overall, 38% of the patients receiving vemurafenib required dose modification because of adverse events.

Among patients treated with vemurafenib, 18% were reported to have at least one squamous-cell carcinoma of the skin or keratoacanthoma. These lesions were excised, and none required dose modification of vemurafenib. These rates are slightly lower than those in the phase 1 and 2 trials of vemurafenib,[15,16] probably because of shorter follow-up in our study. Cutaneous squamous-cell cancer and keratoacanthomas have also been seen in patients treated with sorafenib,[21,22] another compound with inhibitory activity against RAF kinases. No other secondary neoplasia was observed in our patients.

The mechanism of the induction of cutaneous neoplasia is under investigation, but it is speculated to involve the activating effect of vemurafenib on preneoplastic cells in which wild-type BRAF is further primed by upstream pathway activation. Several investigators have shown that vemurafenib and other inhibitors of RAF kinases can potentiate the activity of the MAPK pathway in cells with wild-type BRAF.[23-25] This finding might explain the favorable therapeutic index of vemurafenib in patients who have melanoma with the BRAF V600E mutation but also suggests that vemurafenib could accelerate the growth of some tumors with wild-type BRAF.

An important, related ongoing effort by many research groups is to clarify how melanomas become resistant to vemurafenib. Initial studies from several groups have indicated that the MAPK pathway is reactivated in resistant tumors.[26-28] Although the precise mechanisms of reactivation are still being investigated, gatekeeper mutations in BRAF, which would prevent vemurafenib from binding BRAF, have not been observed.

Our results show that single-agent vemurafenib improved the rates of response and of both progression-free and overall survival, as compared with dacarbazine, in patients with metastatic melanoma with the BRAF V600E mutation. These findings provide a solid foundation for the development of future combination therapies.

APPENDIX

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