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ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

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ABSTRACT

BACKGROUND

Nivolumab was associated with higher rates of objective response than chemotherapy in a phase 3 study involving patients with ipilimumab-refractory metastatic melanoma. The use of nivolumab in previously untreated patients with advanced melanoma has not been tested in a phase 3 controlled study.

METHODS

We randomly assigned 418 previously untreated patients who had metastatic melanoma without a *BRAF* mutation to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The primary end point was overall survival.

RESULTS

At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drug-related adverse events of grade 3 or 4 occurred in 11.7% of the patients treated with nivolumab and 17.6% of those treated with dacarbazine.

CONCLUSIONS

Nivolumab was associated with significant improvements in overall survival and progression-free survival, as compared with dacarbazine, among previously untreated patients who had metastatic melanoma without a *BRAF* mutation. (Funded by Bristol-Myers Squibb; CheckMate 066 ClinicalTrials.gov number, NCT01721772.)

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The global incidence of melanoma continues to rise, and the mortality associated with unresectable or metastatic melanoma remains high.[1] Globally, 132,000 new cases of melanoma are diagnosed and an estimated 48,000 persons die from advanced melanoma each year.[2,3] Ipilimumab has been shown to improve the rate of survival at 2 years, as compared with a vaccine control, among previously treated patients with metastatic melanoma as well as among previously untreated patients who also received dacarbazine.[4,5] BRAF and MEK inhibitors are approved agents that, as monotherapy, have been associated with a survival advantage as compared with chemotherapy, with a median overall survival of 13 to 20 months.[6-8] Although the objective response rate is high with these agents (45 to 53%), the median duration of response is less than 1 year.[6-10]

Recently, a combination of anti-BRAF and anti-MEK agents has been associated with a higher response rate and longer duration of response, as compared with anti-BRAF monotherapies.[11,12] However, the use of these targeted agents, as monotherapy or in combination, is limited to the approximately 40% of patients who have melanoma with a *BRAF* V600 mutation. Dacarbazine is associated with a median overall survival of 5.6 to 7.8 months and remained until recently a commonly used therapy in patients with previously untreated melanoma without a *BRAF* mutation.[5,13] Despite new treatment options, there remains a substantial unmet need for treatments that extend survival and provide a better quality of life.

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation.[14] In a phase 1 study, nivolumab was associated with promising antitumor activity and a favorable safety profile in patients with solid tumors, including advanced melanoma.[15,16] In an open-label, randomized, phase 3 study involving patients with ipilimumab-refractory melanoma, nivolumab was associated with a higher rate of objective response than chemotherapy (32% vs. 11%).[17] Recently, another anti–PD-1 antibody, pembrolizumab, has shown robust clinical activity and has been approved in the United States on the basis of an objective response rate of 24% among patients with advanced melanoma that progressed after ipilimumab, as well as treatment with a BRAF inhibitor if the patient had a *BRAF* V600 mutation.[18] Here, we report the results of a phase 3, randomized, double-blind study conducted to determine whether nivolumab, as compared with dacarbazine, improves overall survival among previously untreated patients who have advanced melanoma without a *BRAF* mutation.

Methods

Patients

Eligible patients had confirmed, unresectable, previously untreated stage III or IV melanoma without a *BRAF* mutation. Other eligibility criteria included an age of 18 years or more, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and 1 indicating mild symptoms), and the availability of tumor tissue from a metastatic or unresectable site for PD-L1 biomarker analysis. Key exclusion criteria were active brain metastases, uveal melanoma, and a history of serious autoimmune disease. Patients who had received adjuvant therapy previously were not excluded.

Study Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive by means of intravenous infusion either 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks, or 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks. Randomization was stratified according to tumor PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c, defined according to the tumor–node–metastasis system of the American Joint Committee on Cancer and the International Union against Cancer). Treatment continued until there was disease progression, as assessed by the investigator, or an unacceptable level of toxic effects. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator (Fig. S1 in the Supplementary

Appendix, available with the full text of this article at NEJM.org).

The primary end point was overall survival. Secondary end points included investigator-assessed progression-free survival, objective response rate, and PD-L1 expression in the tumor as a predictive biomarker of overall survival.

ASSESSMENT

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[19] at 9 weeks after randomization, every 6 weeks thereafter for the first year, and then every 12 weeks until disease progression or treatment discontinuation. Assessments for survival were performed every 3 months. Safety evaluations were performed for patients who received at least one dose of the study treatment, and the severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[20]

STUDY OVERSIGHT

The study protocol, available at NEJM.org with the most recent version of the statistical analysis plan, was approved by the institutional review board at each participating center. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All the patients provided written informed consent to participate in the study. Data were collected by the sponsor, Bristol-Myers Squibb, and analyzed in collaboration with the academic authors. All the authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the first and last authors, with all the authors contributing to subsequent drafts. Medical-writing support, funded by the sponsor, was provided by StemScientific.

A data and safety monitoring committee was established to provide oversight of safety and efficacy considerations. On June 10, 2014, the monitoring committee reviewed an expedited report after noting a potential difference in overall survival during an earlier safety review. Data from the abbreviated report, which was based on an unplanned interim database lock, showed a significant difference in overall survival in favor of nivolumab. As a result, the monitoring committee recommended that the study be unblinded and amended to allow patients enrolled in the dacarbazine group to receive nivolumab. Reported here are the results from the double-blind portion of the study before the amendment (clinical data cutoff on June 24, 2014).

PD-L1 ASSESSMENT

Before randomization, the expression of PD-L1 on the surface of the tumor cells was assessed in a central laboratory with the use of an automated immunohistochemical assay (collaboratively developed by Bristol-Myers Squibb and Dako), as described previously.[21] PD-L1 positivity was defined as at least 5% of tumor cells showing cell-surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was attributed to samples for which tumor cell–surface expression could not be discerned because of melanin content or strong cytoplasmic staining. PD-L1 status was prospectively determined, and the results were used to stratify randomization, which was performed by means of a fully automated interactive voice-response system. Statistical analyses were prespecified to assess the predictive value of PD-L1 expression.

STATISTICAL ANALYSIS

A sample of approximately 410 patients, randomly assigned in a 1:1 ratio to the two treatment groups, was planned. Overall survival and progression-free survival were compared between the two treatment groups with the use of a two-sided log-rank test stratified according to PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c). The hazard ratios for the nivolumab group, as compared with the dacarbazine group, and corresponding confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Survival curves for each treatment group were estimated with the use of the Kaplan–Meier product-limit method. Rates at fixed time points were derived from the Kaplan–Meier estimate, along with their corresponding log-log–transformed 95% confidence interval.

The objective response rate was compared between the two treatment groups with the use of a two-sided Cochran–Mantel–Haenszel test. The efficacy analyses were performed in the

population of patients who underwent randomization (the intention-to-treat population). The safety analyses were performed in the population of patients who received at least one dose of a study drug. At the time of data analysis, 146 patients had died. The boundary for statistical significance, which was based on the Lan–DeMets alpha-spending function with O'Brien and Fleming–type boundaries, required the log-rank P value to be less than 0.0021, corresponding to a 99.79% confidence interval.

RESULTS

PATIENTS AND TREATMENT

From January 2013 through February 2014, a total of 518 patients were enrolled at 80 centers in Europe, Israel, Australia, Canada, and South America. A total of 418 patients underwent randomization: 210 patients were assigned to the nivolumab group and 208 to the dacarbazine group (Fig. S1 in the Supplementary Appendix). One patient randomly assigned to the nivolumab group and 3 randomly assigned to the dacarbazine group were inadvertently enrolled in the study, despite having an ECOG performance-status score of 2; 1 additional patient in the nivolumab group did not report an ECOG performance-status score. Baseline characteristics were balanced between the two groups. A total of 61.0% of patients had stage M1c disease, 36.6% had an elevated lactate dehydrogenase level, and 35.4% had a positive PD-L1 status (Table 1).

At the time of the database lock, 95 of 206 patients (46.1%) treated with nivolumab and 13 of 205 (6.3%) treated with dacarbazine were continuing the study treatment. The most frequent reason for discontinuation was disease progression, in 96 of 206 patients (46.6%) in the nivolumab group and 175 of 205 (85.4%) in the dacarbazine group (Table S1 in the Supplementary Appendix). After the discontinuation of study treatment, 63 of 210 patients (30.0%) in the nivolumab group and 114 of 208 (54.8%) in the dacarbazine group received systemic therapy, most commonly ipilimumab (in 45 of 63 patients and 79 of 114, respectively) (Table S2 in the Supplementary Appendix). All the patients who underwent randomization were followed for up to 16.7 months at the time of database lock on August 5, 2014, which was 5.2 months after the first visit of the last patient who had undergone randomization.

EFFICACY

The median overall survival was not reached in the nivolumab group and was 10.8 months (95% confidence interval [CI], 9.3 to 12.1) in the dacarbazine group. The overall survival rate at 1 year was 72.9% (95% CI, 65.5 to 78.9) in the nivolumab group and 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group. A significant benefit with respect to overall survival was observed in the nivolumab group, as compared with the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001) (Fig. 1A).

The median progression-free survival was 5.1 months (95% CI, 3.5 to 10.8) in the nivolumab group and 2.2 months (95% CI, 2.1 to 2.4) in the dacarbazine group (Fig. 1B). A significant benefit with respect to progression-free survival was observed in the nivolumab group, as compared with the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001).

The objective response rate in the nivolumab group was 40.0% (95% CI, 33.3 to 47.0), which was significantly higher than the rate in the dacarbazine group, which was 13.9% (95% CI, 9.5 to 19.4) (odds ratio, 4.06; P<0.001). The percentage of patients with a complete response was higher with nivolumab than with dacarbazine (7.6% vs. 1.0%) (Fig. 2 and Table 2). Among patients who had a response, the median duration of response was not reached in the nivolumab group and was 6.0 months in the dacarbazine group (95% CI, 3.0 to not reached) (Fig. 2C).

In the nivolumab group, a reduction of 30% or more in the tumor burden in the target lesion, representing an unconventional response pattern sometimes seen with immunotherapies, was achieved or maintained in 17 of 54 patients who were treated beyond progression (8.1% of patients randomly assigned to nivolumab) (Fig. S4A in the Supplementary Appendix). In the dacarbazine group, this unconventional response was achieved or maintained in 8 of the 49 patients who were treated beyond progression (3.8% of patients randomly assigned to dacarbazine) (Fig. S4B in the Supplementary Appendix).

SUBGROUP ANALYSES

Regardless of PD-L1 status, nivolumab-treated patients had improved overall survival, as compared with dacarbazine-treated patients (unadjusted hazard ratio for death among patients with positive PD-L1 status, 0.30 [95% CI, 0.15 to

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nivolumab (N=210)	Dacarbazine (N=208)	Total (N=418)
Age — yr			
Median	64	66	65
Range	18–86	26–87	18–87
Sex — no. (%)			
Male	121 (57.6)	125 (60.1)	246 (58.9)
Female	89 (42.4)	83 (39.9)	172 (41.1)
Geographic region — no. (%)			
Europe or Canada	145 (69.0)	145 (69.7)	290 (69.4)
Israel, Australia, or South America	65 (31.0)	63 (30.3)	128 (30.6)
ECOG performance-status score — no. (%)†			
0	148 (70.5)	121 (58.2)	269 (64.4)
1	60 (28.6)	84 (40.4)	144 (34.4)
2	1 (0.5)	3 (1.4)	4 (1.0)
Metastasis stage — no. (%)‡			
M1c	128 (61.0)	127 (61.1)	255 (61.0)
M0, M1a, or M1b	82 (39.0)	81 (38.9)	163 (39.0)
Lactate dehydrogenase — no. (%)			
≤ULN	120 (57.1)	125 (60.1)	245 (58.6)
>ULN	79 (37.6)	74 (35.6)	153 (36.6)
≤2× ULN	178 (84.8)	177 (85.1)	355 (84.9)
>2× ULN	21 (10.0)	22 (10.6)	43 (10.3)
Not reported	11 (5.2)	9 (4.3)	20 (4.8)
History of brain metastases — no. (%)			
Yes	7 (3.3)	8 (3.8)	15 (3.6)
No	203 (96.7)	200 (96.2)	403 (96.4)
PD-L1 status — no. (%)§			
Positive	74 (35.2)	74 (35.6)	148 (35.4)
Negative or indeterminate	136 (64.8)	134 (64.4)	270 (64.6)
BRAF status — no. (%)			
Mutation	0	0	0
No mutation	202 (96.2)	204 (98.1)	406 (97.1)
Not reported	8 (3.8)	4 (1.9)	12 (2.9)
Prior systemic therapy — no. (%)			
Adjuvant therapy	32 (15.2)	36 (17.3)	68 (16.3)
Neoadjuvant therapy	1 (0.5)	1 (0.5)	2 (0.5)

* There were no significant between-group differences in the baseline characteristics. ULN denotes upper limit of the normal range.

† An Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms, with the patient being ambulatory and capable of all self-care but unable to carry out any work activities. One patient randomly assigned to the nivolumab group and three randomly assigned to the dacarbazine group were inadvertently enrolled in the study, despite having an ECOG performance-status score of 2. One additional patient in the nivolumab group underwent randomization in error without having an ECOG performance-status report.

‡ The metastasis stage was defined according to the tumor–node–metastasis system of the American Joint Committee on Cancer and the International Union against Cancer.

§ A positive status for programmed death ligand 1 (PD-L1) was defined as at least 5% of the tumor cells having cell-surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was attributed to samples for which tumor cell-surface expression could not be discerned because of melanin content or strong cytoplasmic staining.

0.60]; unadjusted hazard ratio for death among those with PD-L1 negative or indeterminate PD-L1 status, 0.48 [95% CI, 0.32 to 0.71]) (Fig. S2 in the Supplementary Appendix). In the nivolumab group, the median overall survival was not reached in either PD-L1 subgroup. In the dacarbazine group, the median overall survival was slightly longer in the subgroup with positive PD-L1 status than in the subgroup with negative or indeterminate PD-L1 status (12.4 vs. 10.2 months) (Fig. S3 in the Supplementary Appendix).

In the two PD-L1 subgroups, nivolumab-treated patients had improved rates of objective response, as compared with dacarbazine-treated patients. In the subgroup with positive PD-L1 status, the objective response rate was 52.7% (95% CI, 40.8 to 64.3) in the nivolumab group versus 10.8% (95% CI, 4.8 to 20.2) in the dacarbazine group. In the subgroup with negative or indeterminate PD-L1 status, the objective response rate was 33.1% (95% CI, 25.2 to 41.7) in the nivolumab group versus 15.7% (95% CI, 10.0 to 23.0) in the dacarbazine group. The survival benefit with nivolumab versus dacarbazine was also observed across prespecified subgroups based on age, sex, metastasis stage, ECOG performance-status score, status with respect to a history of brain metastases, baseline lactate dehydrogenase level, and geographic region (Fig. S2 in the Supplementary Appendix).

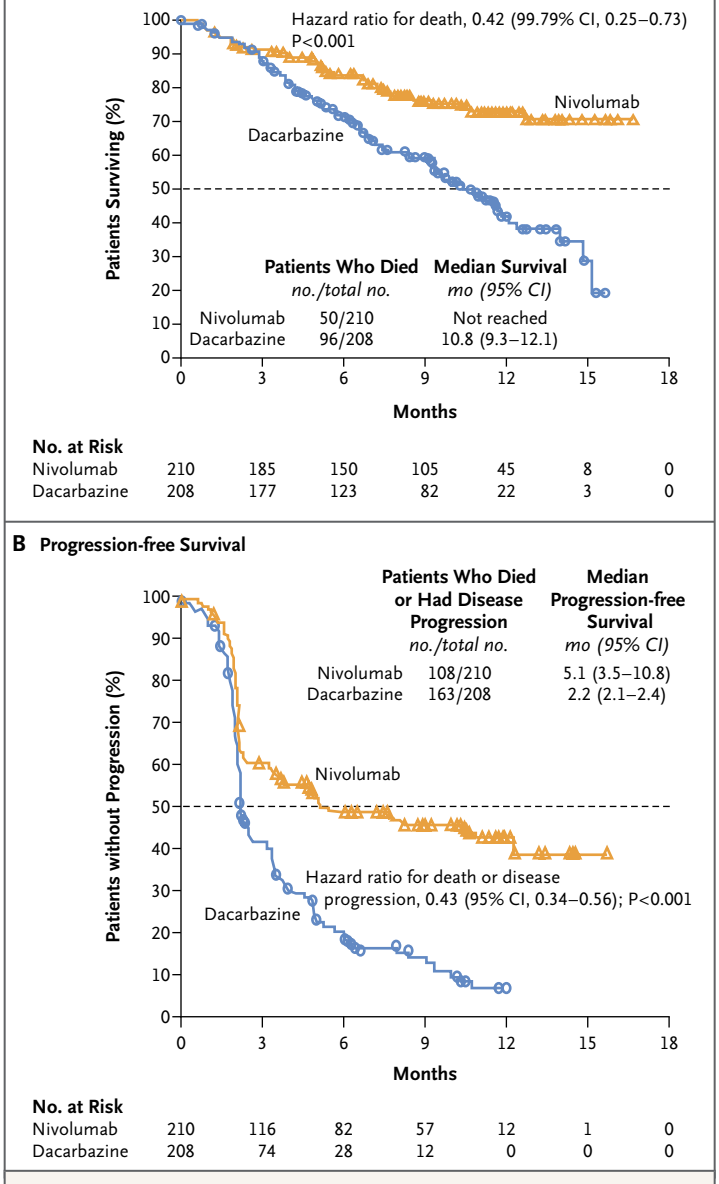

Figure 1. Survival End Points.

Panel A shows the Kaplan–Meier curves for overall survival. The median follow-up for overall survival was 8.9 months in the nivolumab group and 6.8 months in the dacarbazine group. Panel B shows the Kaplan–Meier curves for progression-free survival.

ADVERSE EVENTS

The incidence of treatment-related adverse events of any grade was similar in the nivolumab group and the dacarbazine group (74.3% and 75.6%, respectively). However, treatment-related adverse events of grade 3 or 4 were reported less frequently in the nivolumab group than in the dacarbazine group (11.7% vs. 17.6%) (Table 3, and Table S3 in the Supplementary Appendix). The most common adverse events related to nivolumab treatment were fatigue (in 19.9% of patients), pruritus (in 17.0%), and nausea (in 16.5%). In the dacarbazine group, common treatment-related adverse events were consistent with those in previous reports and included gastrointestinal and hematologic toxic events. The frequency of treatment-related serious adverse events of grade 3 or 4 was similar in the two groups (5.8% in the nivolumab group and 5.9% in the dacarbazine group). The percentage of patients who discontinued the study treatment owing to adverse events was 6.8% in the nivolumab group and 11.7% in the dacarbazine group. No deaths were attributed to study-drug toxicity in either group.

Selected adverse events — defined as those with a potential immunologic cause — were analyzed according to organ category. Grade 3

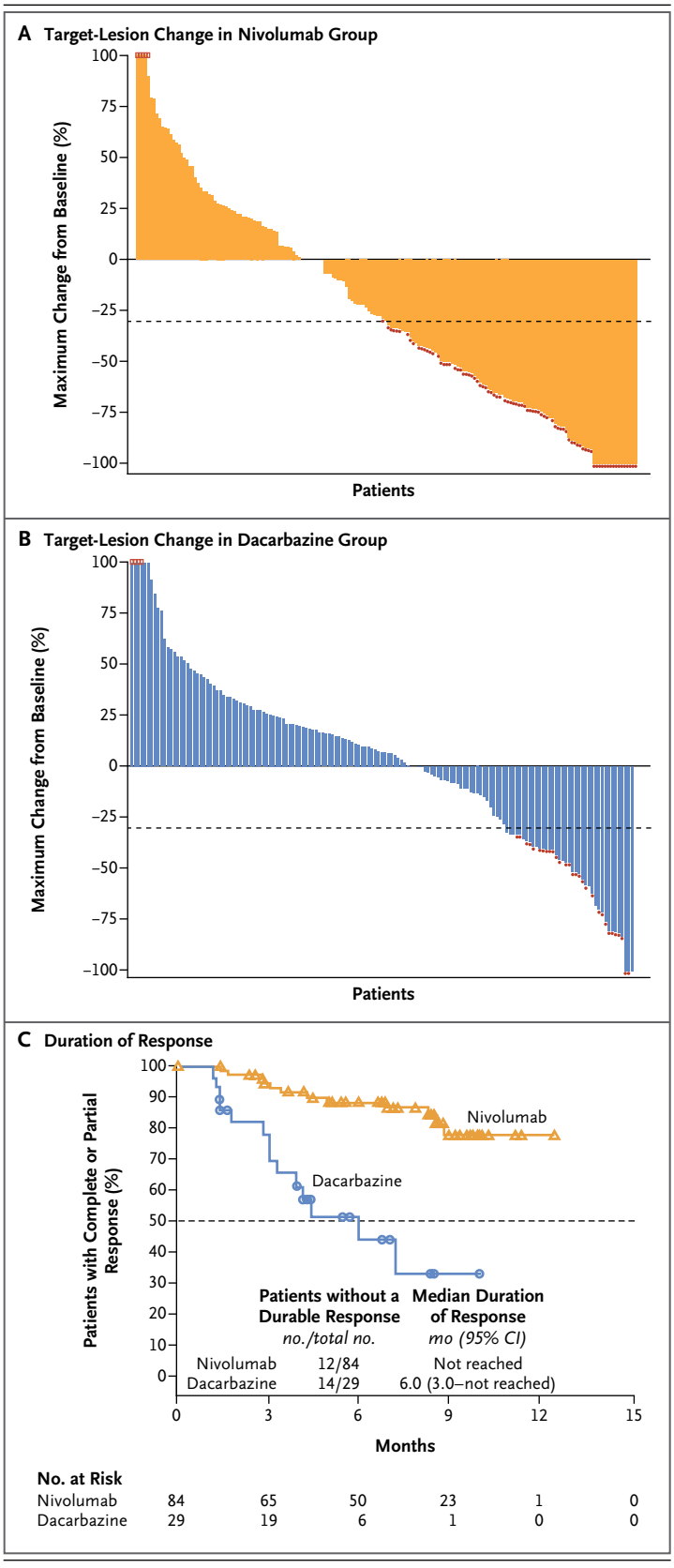

Figure 2. Characteristics of Response.

The waterfall plots show the maximum change from baseline in the sum of the reference diameters of the target lesion in patients receiving nivolumab (Panel A) and those receiving dacarbazine (Panel B). Data are shown for all the patients who had a response that could be evaluated in the target lesion at baseline and who underwent at least one tumor assessment during treatment. The percentage increase was truncated at 100% (red squares). Red dots indicate patients who had a response to treatment according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The dashed lines in Panels A and B indicate a 30% reduction in the tumor burden in the target lesion. Kaplan–Meier curves for the duration of response (Panel C) show that the median duration of response in the 84 patients in the nivolumab group who had a response was not reached; 12 of these patients did not have a durable response. Of the 29 patients in the dacarbazine group who had a response, 14 did not have a durable response. The dashed line in Panel C indicates the median duration of response.

or 4 selected adverse events that were considered to be related to nivolumab treatment were infrequent and included diarrhea and an elevated alanine aminotransferase level (each in 1.0% of patients) (Table S4 in the Supplementary Appendix). The majority of selected adverse events of grade 3 or 4 resolved quickly with a delay in the study treatment, glucocorticoid administration, or both, as recommended in the safety management guidelines for nivolumab (Table S5 in the Supplementary Appendix).

DISCUSSION

This phase 3, double-blind, randomized, controlled study showed an overall survival benefit with nivolumab, an anti–PD-1 antibody. The risk of death decreased by 58% with nivolumab, as compared with dacarbazine, among previously untreated patients with advanced melanoma. The survival benefit was consistent across all the prespecified subgroups, including patients with poor prognostic factors.

The 1-year survival rate associated with nivolumab in this study (73%) is consistent with the results in a phase 1 study[15,16,22] and was significantly higher than the rate associated with dacarbazine. Dacarbazine was chosen as the comparator because, until recently, it was a standard first-line treatment in many countries for patients who had melanoma without a *BRAF*

Table 2. Response to Treatment.*

Response	Nivolumab (N=210)	Dacarbazine (N=208)
Best overall response — no. (%)†		
Complete response	16 (7.6)	2 (1.0)
Partial response	68 (32.4)	27 (13.0)
Stable disease	35 (16.7)	46 (22.1)
Progressive disease	69 (32.9)	101 (48.6)
Could not be determined	22 (10.5)	32 (15.4)
Objective response‡		
No. of patients (% [95% CI])	84 (40.0 [33.3–47.0])	29 (13.9 [9.5–19.4])
Difference — percentage points (95% CI)	26.1 (18.0–34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52–6.54)	
P value	<0.001	
Time to objective response — mo		
Median	2.1	2.1
Range	1.2–7.6	1.8–3.6
Mean	2.6±1.3	2.5±0.7
Duration of response — mo§		
Median (95% CI)	Not reached	6.0 (3.0–not reached)
Range	0.0–12.5	1.1–10.0

* Plus–minus values are means ±SD.
† The best overall response was assessed by the investigator with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1.[19]
‡ Data include patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. The estimate of the difference (the rate in the nivolumab group minus the rate in the dacarbazine group) was based on the Cochran–Mantel–Haenszel method of weighting, with adjustment for PD-L1 status and metastasis stage as entered into the interactive voice-response system. The odds ratio and two-sided P value for an objective response with nivolumab as compared with dacarbazine were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to PD-L1 status and metastasis stage.
§ The median was calculated with the use of the Kaplan–Meier method. Data were censored for the range values because the observations are ongoing. The cutoff date for clinical data was August 5, 2014, with a range of follow-up from 5.2 to 16.7 months.

mutation. In this group of patients, only ipilimumab in combination with dacarbazine has been associated with a survival benefit, as compared with dacarbazine alone, in a phase 3, controlled trial.[5] When the present study was planned in 2012, ipilimumab had not been approved for use as a first-line treatment for advanced melanoma in most regions outside the United States. However, during the course of this study, it was approved for first-line therapy in most regions. Nevertheless, dacarbazine is still used as a first-line therapy for metastatic melanoma in many countries.

An additional phase 3 study (CheckMate 067; ClinicalTrials.gov number, NCT01844505), evaluating both nivolumab monotherapy and combination therapy with nivolumab plus ipilimumab, as compared with ipilimumab alone, in previously untreated patients with melanoma is currently under way. The activity of ipilimumab is probably reflected in the performance of the dacarbazine group in the present study. The median survival in the dacarbazine group (10.8 months) in this study is higher than that previously reported,[5] possibly because 38% of the dacarbazine-treated patients received ipilimumab after stopping the study treatment.

The objective response rate (40%) and duration of response associated with nivolumab that were observed in this study are in line with

Table 3. Adverse Events.*

Event	Nivolumab (N=206)		Dacarbazine (N=205)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients with event (%)			
Any adverse event	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)
Fatigue	41 (19.9)	0	30 (14.6)	2 (1.0)
Pruritus	35 (17.0)	1 (0.5)	11 (5.4)	0
Nausea	34 (16.5)	0	85 (41.5)	0
Diarrhea	33 (16.0)	2 (1.0)	32 (15.6)	1 (0.5)
Rash	31 (15.0)	1 (0.5)	6 (2.9)	0
Vitiligo	22 (10.7)	0	1 (0.5)	0
Constipation	22 (10.7)	0	25 (12.2)	0
Asthenia	21 (10.2)	0	25 (12.2)	1 (0.5)
Vomiting	13 (6.3)	1 (0.5)	43 (21.0)	1 (0.5)
Neutropenia	0	0	23 (11.2)	9 (4.4)
Thrombocytopenia	0	0	21 (10.2)	10 (4.9)
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)
Serious adverse event				
Any event	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)
Treatment-related event	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)

* The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[20]
† The treatment-related adverse events listed here were reported in at least 10% of the patients in either study group.

those in previous reports.[15-17,22] It has generally been accepted that immunotherapy is associated with long-term responses in a subset of patients, whereas targeted therapies, such as BRAF inhibitors, are associated with high response rates and a rapid effect, but the responses are often short-lived.[4-7,9,10,23] The present study shows that nivolumab is associated with a high response rate, a rapid median time to response (2.1 months, which is similar to the time to response for dacarbazine), and a durable response (the median duration of response was not reached, but the duration of follow-up was short). These results are in agreement with the long-term follow-up data from a phase 1 study of nivolumab, which showed a median duration of response of almost 2 years and an objective response rate of 32% among patients with advanced melanoma.[22]

The response rate with a BRAF or MEK inhibitor was recently surpassed by new combination regimens in patients with a *BRAF* V600 mutation[11,12]; however, for patients who have melanoma without a *BRAF* mutation, treatment options beyond ipilimumab are limited. Although the target population of our study was restricted to patients with melanoma who did not have a *BRAF* mutation, previous studies have shown that nivolumab had similar clinical activity regardless of the patient's *BRAF* mutation status.[17,24]

Previous studies, which have used various methodologic approaches, have shown a correlation between PD-L1 expression and objective response in patients with metastatic melanoma treated with anti–PD-1 or anti–PD-L1 antibodies.[21,22,24-28] In our study, given the magnitude of the clinical benefit observed in patients receiving nivolumab versus those receiving dacarbazine, PD-L1 status alone, as assessed with the use of the methods presented here, does not

seem to be useful in the selection of patients for nivolumab treatment. Also, because there was little difference in median overall survival between the two subgroups of dacarbazine-treated patients defined according to PD-L1 status (positive vs. negative or indeterminate), the prognostic role of PD-L1 status remains to be determined.

The safety profile of nivolumab in this study was similar to that observed previously.[15-17,22] The frequency of selected adverse events with a potential immunologic cause was similar to the frequency observed in a previous phase 3 trial,[17] and the events resolved in the majority of our patients.

In conclusion, nivolumab was associated with a significant improvement in overall survival and progression-free survival, as compared with dacarbazine. Nivolumab was associated with a low risk of high-grade toxic effects.

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APPENDIX

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