ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

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ABSTRACT

BACKGROUND

Ipilimumab monotherapy (at a dose of 3 mg per kilogram of body weight), as compared with glycoprotein 100, improved overall survival in a phase 3 study involving patients with previously treated metastatic melanoma. We conducted a phase 3 study of ipilimumab (10 mg per kilogram) plus dacarbazine in patients with previously untreated metastatic melanoma.

METHODS

We randomly assigned 502 patients with previously untreated metastatic melanoma, in a 1:1 ratio, to ipilimumab (10 mg per kilogram) plus dacarbazine (850 mg per square meter of body-surface area) or dacarbazine (850 mg per square meter) plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22. Patients with stable disease or an objective response and no dose-limiting toxic effects received ipilimumab or placebo every 12 weeks thereafter as maintenance therapy. The primary end point was overall survival.

RESULTS

Overall survival was significantly longer in the group receiving ipilimumab plus dacarbazine than in the group receiving dacarbazine plus placebo (11.2 months vs. 9.1 months, with higher survival rates in the ipilimumab–dacarbazine group at 1 year (47.3% vs. 36.3%), 2 years (28.5% vs. 17.9%), and 3 years (20.8% vs. 12.2%) (hazard ratio for death, 0.72; P<0.001). Grade 3 or 4 adverse events occurred in 56.3% of patients treated with ipilimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine and placebo (P<0.001). No drug-related deaths or gastrointestinal perforations occurred in the ipilimumab–dacarbazine group.

CONCLUSIONS

Ipilimumab (at a dose of 10 mg per kilogram) in combination with dacarbazine, as compared with dacarbazine plus placebo, improved overall survival in patients with previously untreated metastatic melanoma. The types of adverse events were consistent with those seen in prior studies of ipilimumab; however, the rates of elevated liver-function values were higher and the rates of gastrointestinal events were lower than expected on the basis of prior studies. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00324155.)

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The survival rate for patients with metastatic melanoma is low, with an expected 2-year survival rate of 10 to 20%.[1-3] Although dacarbazine has never been shown to improve survival in randomized, controlled studies, it has been the drug most frequently compared with new agents or combination therapies in randomized trials involving patients with melanoma.[4,5] High-dose interleukin-2 is associated with durable, complete responses, with a survival benefit, in a small subgroup of patients with metastatic melanoma.[6,7] Ipilimumab, a fully human, IgG1 monoclonal antibody, blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), a negative regulator of T cells, and thereby augments T-cell activation and proliferation.[8-12]

Two separate phase 2 studies support the rationale for the current study. The first phase 2 study, involving 217 patients with previously treated metastatic melanoma, showed a dose-dependent response rate, with the highest rate of response seen in the group receiving ipilimumab at a dose of 10 mg per kilogram of body weight (11.1% in the group receiving 10 mg per kilogram vs. 4.2% and 0% in the groups receiving 3 mg per kilogram and 0.3 mg per kilogram, respectively; P=0.002).[13] In the second, small, randomized, phase 2 study, involving 72 patients, treatment with a combination of dacarbazine (250 mg per square meter of body-surface area per day for 5 days every 3 weeks) and ipilimumab (3 mg per kilogram every 4 weeks for 4 doses) was associated with durable objective responses, with no new adverse events; the rationale for such combinations has been reviewed previously.[14-16] We conducted a phase 3 study to determine whether ipilimumab (at a dose of 10 mg per kilogram) plus dacarbazine, as compared with dacarbazine and placebo, improves overall survival in patients with previously untreated metastatic melanoma.

METHODS

PATIENTS

Eligible patients were at least 18 years of age and had previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction, and 1 indicating 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),[17] and a life expectancy of 16 weeks or more. The baseline serum lactate dehydrogenase level did not affect eligibility. Patients were ineligible if they had received any prior treatment for metastatic disease. Patients who received prior adjuvant therapy were not excluded. Concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids (except for the management of adverse events during the course of the study) was not allowed. Patients were also ineligible if they had evidence of brain metastasis (as confirmed on imaging), primary ocular or mucosal melanoma, or autoimmune disease.

STUDY OVERSIGHT

The protocol was approved by the appropriate institutional review boards or independent ethics committees. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All participating patients gave written informed consent.

The trial was designed jointly by the senior academic authors and the sponsor, Bristol-Myers Squibb. 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. An initial draft of the manuscript was prepared jointly by a writing committee that included five academic authors, the sponsor, and a professional medical writer employed by the sponsor. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. All the authors signed a confidentiality disclosure agreement with the sponsor. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

STUDY DESIGN AND TREATMENT

In this multinational, randomized, double-blind, phase 3 study, patients (stratified according to metastasis stage, study site, and ECOG performance status) were randomly assigned, in a 1:1 ratio, to receive either ipilimumab (at a dose of 10 mg per kilogram) plus dacarbazine (850 mg per square meter) or dacarbazine (850 mg per square meter) plus placebo at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 (induction phase). Treatment was discontinued if

toxic effects associated with the drug or progressive disease was noted during weeks 12 to 24. At week 24, patients with stable disease or an objective response during the induction phase who did not have a dose-limiting adverse event were eligible to enter a maintenance phase in which they received placebo or ipilimumab every 12 weeks until progression of the disease, development of toxic effects, or the end of the study.

In the initial design of the study, 500 patients were to undergo randomization, and progression-free survival was to be the primary end point. Emerging data from other ipilimumab trials suggested that conventional definitions of disease progression and response incompletely reflect overall survival among patients who appear to have a long-term benefit,[18,19] and in an amendment approved by the Food and Drug Administration on October 9, 2008, the primary end point was changed from progression-free survival to overall survival before the treatment assignments were revealed. No change in the size of the study was required, since it was already fully powered to assess overall survival. No interim analysis was conducted. Secondary end points included progression-free survival, the rate of best overall response (defined as the proportion of all randomly assigned patients who had a complete or partial response), the rate of disease control (defined as a complete response, a partial response, or stable disease), the time to a response, the duration of the response, and safety. Responses were defined according to the modified World Health Organization criteria as the sum of the products of bidimensional measurements of target lesions; a complete response is defined by the disappearance of all known lesions, a partial response by a decrease of at least 50% from baseline in the sum of the products of the diameters of index lesions, stable disease by failure to meet the criteria for either partial response or progressive disease, and progressive disease by a 25% increase in an existing lesion or the development of a new lesion. Tumor assessments were performed by the local investigator and by a central independent review committee.

ASSESSMENTS

Radiologic and photographic tumor assessments were performed in all patients at baseline and at week 12, and in patients in whom the disease had not progressed, at weeks 16, 20, and 24 and every 6 weeks through week 48. For patients in whom the disease had not progressed and who remained in the study beyond week 48, tumor assessments were performed every 12 weeks. Patients with progressive disease who entered the follow-up phase were recommended to receive two additional tumor assessments as part of the standard of care. All efficacy end points (except survival) were based on assessments performed by the independent review committee, whose members were not aware of the treatment assignments.

Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Adverse events were reported from the date of the first dose up to and including 70 days after the final dose. The study included two additional safety analyses. One was an analysis of immune-related adverse events (described previously[12]), which were defined as adverse events that were, according to the judgment of the investigator, associated with inflammation. The list of potential inflammation-associated adverse events was defined prospectively, in the protocol, before the database was locked. The other additional safety analysis was an exploratory analysis performed to determine whether specific adverse events were likely to be immune-mediated and associated with ipilimumab treatment. Immune-mediated adverse reactions, identified through retrospective review of the data, were adjudicated by a physician employed by the sponsor, in order to exclude noninflammatory causes of the event, such as infection or tumor progression. The immune-mediated adverse reactions included specific events of clinical interest, such as enterocolitis, hepatitis, dermatitis, neuropathies, or endocrinopathies, including hypophysitis.

STATISTICAL ANALYSIS

All analyses of efficacy were performed as prespecified in the protocol except for the 3-year survival rate, which was analyzed post hoc. The target number of events for the primary analysis was 416 deaths, which we estimated would give the study approximately 90% power to detect a 37% increase in median overall survival to 11 months with ipilimumab plus dacarbazine, with a corresponding hazard ratio for death of 0.727, assuming a total sample of 500 patients (250 randomly assigned to each group) and a median survival of 8 months for the patients receiving dacarbazine plus placebo. For the analysis of overall survival, a log-

rank test was performed, at a two-sided alpha level of 0.05, stratified according to metastasis stage (M0, M1a, M1b, or M1c) and ECOG performance status (0 or 1), as classified at the time of randomization. The final analysis of progression-free survival was conducted on a database that was locked after 416 events had been documented, as originally planned. The hazard ratios for overall survival and progression-free survival with ipilimumab plus dacarbazine as compared with dacarbazine plus placebo, and the associated two-sided 95% confidence intervals, were estimated with the use of a stratified Cox proportional-hazards model. Survival functions were estimated with the use of the Kaplan–Meier method. A hierarchical testing procedure was implemented for a comparison of the treatment groups in the order of the following end points: overall survival, progression-free survival, rate of disease control, and rate of best overall response. Additional details of the methods are provided in the Supplementary Appendix, available at NEJM.org.

RESULTS

PATIENTS AND TREATMENT

Between August 8, 2006, and January 22, 2008, a total of 250 patients were randomly assigned to receive ipilimumab plus dacarbazine (ipilimumab–dacarbazine group) and 252 were randomly assigned to receive dacarbazine plus placebo (dacarbazine group). The baseline characteristics of the patients were balanced between the two groups (Table 1). A total of 92 patients in the ipilimumab–dacarbazine group (36.8%) and 165 patients in the dacarbazine group (65.5%) received all four doses of ipilimumab or placebo. At least one maintenance dose was administered in 43 patients in the ipilimumab–dacarbazine group (17.2%) and 53 in the dacarbazine group (21.0%). The follow-up time between the start of the study (the first visit of the first enrolled patient) and the end of the study (the last visit of the last enrolled patient) was 54 months, and the follow-up time between the time the last patient underwent randomization (the first visit of the last patient) and the end of the study was 36.6 months.

The most frequent reason for discontinuation of the study drug across the entire study was disease progression (in 46.2% of patients in the ipilimumab–dacarbazine group and 77.3% in the dacarbazine group). Discontinuation due to a drug-related adverse event was reported in 89 of the 247 patients in the ipilimumab–dacarbazine group who received at least one dose of the study drug (36.0%) and 10 of the 251 patients in the dacarbazine group who received at least one dose of the study drug (4.0%): 85 of the 247 patients (34.4%) and 10 of the 251 patients (4.0%) in the two groups, respectively, discontinued the study drug because of a drug-related adverse event after receiving treatment in the induction phase; 4 of the 43 patients in the ipilimumab–dacarbazine group who received at least one maintenance dose (9.3%) and none of the 53 patients in the dacarbazine group who received at least one maintenance dose discontinued the therapy after receiving treatment in the maintenance phase.

Therapy after disease progression was balanced between the two groups; 54.7% of the patients in the ipilimumab–dacarbazine group and 59.0% in the dacarbazine group received subsequent therapy. In the ipilimumab–dacarbazine group, 37.7% of the patients received chemotherapy, and 2% immunotherapy; in the dacarbazine group, 34.7% received chemotherapy, and 2% immunotherapy. One patient in the dacarbazine group received the BRAF inhibitor, vemurafenib, at the time of disease progression, but tumors were not routinely assessed for the presence of the BRAF V600E mutation.

EFFICACY

Efficacy analyses were performed on the intention-to-treat population. A survival analysis was performed after 414 deaths occurred, 37 months after the last patient was enrolled. The median overall survival in the ipilimumab–dacarbazine group was 11.2 months (95% confidence interval [CI], 9.4 to 13.6), as compared with 9.1 months (95% CI, 7.8 to 10.5) in the dacarbazine group, with estimated survival rates in the two groups, respectively, of 47.3% and 36.3% at 1 year, 28.5% and 17.9% at 2 years, and 20.8% and 12.2% at 3 years (hazard ratio for death with ipilimumab–dacarbazine, 0.72; $P<0.001$) (Fig. 1A). Ipilimumab was associated with improved overall survival across patient subgroups, including those defined according to age, sex, ECOG performance status, baseline serum lactate dehydrogenase level, and substage of metastatic disease (Fig. 2).

There was a 24% reduction in the risk of progression in the ipilimumab–dacarbazine group as compared with the dacarbazine group (hazard ratio for progression, 0.76; $P=0.006$). The median values for progression-free survival were similar

in the two groups because the first assessment of progression occurred at week 12 after the true median. After the first tumor assessment, the Kaplan–Meier curves separated (Fig. 1B).

The rate of disease control (i.e., a complete or partial response or stable disease) did not differ significantly between the two groups: 33.2% in the ipilimumab–dacarbazine group and 30.2% in the dacarbazine group (P=0.41). The rate of best overall response (i.e., a complete or partial response) was 15.2% in the ipilimumab–dacarbazine group and 10.3% in the dacarbazine group (P=0.09) (Table 2). The median duration of response among all randomly assigned patients with a complete or partial response was 19.3 months (95% CI, 12.1 to 26.1) in the ipilimumab–dacarbazine group and 8.1 months (95% CI, 5.19 to 19.8) in the dacarbazine group (P=0.03) (Fig. 1C). Some patients in the study who were receiving ipilimumab had an improvement from partial response to complete response after 6 months (data not shown). Responses in the presence of new lesions were also observed, although these were not captured as part of the best overall response.

Table 1. Demographic and Baseline Clinical Characteristics of the Patients.*

Characteristic	Ipilimumab plus Dacarbazine (N=250)	Placebo plus Dacarbazine (N=252)
Mean age — yr	57.5	56.4
Sex — no. (%)		
Male	152 (60.8)	149 (59.1)
Female	98 (39.2)	103 (40.9)
ECOG performance status — no. (%)†		
0	177 (70.8)	179 (71.0)
1	73 (29.2)	73 (29.0)
Metastasis stage — no. (%)‡		
M0	6 (2.4)	8 (3.2)
M1a	37 (14.8)	43 (17.1)
M1b	64 (25.6)	62 (24.6)
M1c	143 (57.2)	139 (55.2)
Lactate dehydrogenase — no. (%)		
≤ULN	157 (62.8)	140 (55.6)
>ULN	93 (37.2)	110 (43.7)
Unknown	0	2 (0.8)
Prior adjuvant therapy — no. (%)	66 (26.4)	67 (26.6)

* ULN denotes upper limit of the normal range.
† 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, and 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.[17]
‡ The M1a stage is characterized by metastasis of the tumor to the skin, subcutaneous tissues, or distant lymph nodes, with normal lactate dehydrogenase level; M1b by metastasis to the lung, with normal lactate dehydrogenase level; and M1c by metastasis to any other visceral site or to any site with an elevated lactate dehydrogenase level.

SAFETY

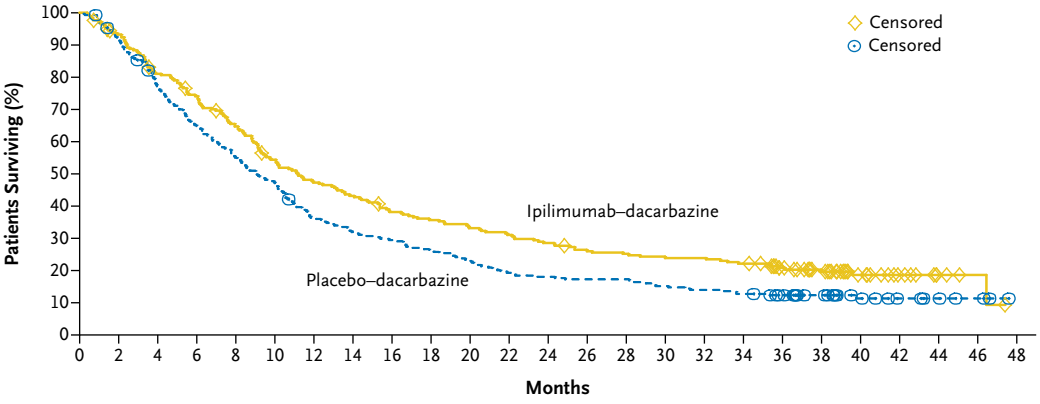
The safety analysis included all patients who underwent randomization and received at least one dose of the assigned study drug (498 patients). The adverse events reported in the safety population are listed in Table 3. Adverse events (all grades) for which there was a higher incidence in the ipilimumab–dacarbazine group than in the dacarbazine group included elevation of alanine aminotransferase levels (in 33.2% of patients vs. 5.6%), elevation of aspartate aminotransferase levels (29.1% vs. 5.6%), diarrhea (36.4% vs. 24.7%), pruritus (29.6% vs. 8.8%), and rash (24.7% vs. 6.8%). Grade 3 or 4 adverse events occurred in 56.3% of patients receiving ipilimumab plus dacarbazine and in 27.5% of patients receiving placebo plus dacarbazine (P<0.001).

No gastrointestinal perforations were reported. No cases of hypophysitis were noted in the ipilimumab–dacarbazine group except for a single case in a patient receiving maintenance therapy that was reported on day 364 (which was outside the protocol-specified reporting window of <70 days after the last dose — a period representing 5 times the half-life of ipilimumab — and was therefore not categorized as an "on-study" event). No drug-related deaths were reported in the ipilimumab–dacarbazine group; one fatal gastrointestinal hemorrhage was reported in the dacarbazine group. Nausea and vomiting (see the table in the Supplementary Appendix) as well as myelosuppression (data not shown), which are common side effects of dacarbazine, were not increased in the ipilimumab–dacarbazine group as compared with the dacarbazine group.

The most common study-drug–related adverse events were those classified as immune-related adverse events, which were seen in 77.7% of the patients treated with ipilimumab plus dacarbazine and 38.2% of the patients treated with dacarbazine and placebo (Table 3). The most common immune-related adverse events in the ipilimumab–dacarbazine group were elevated liver-function values, with grade 3 or 4 elevations in liver-function values noted in 17.4 to 20.7% of the patients.

An alternative characterization of inflammatory events was performed in which noninflammatory causes of the event (e.g., tumor progression or in-

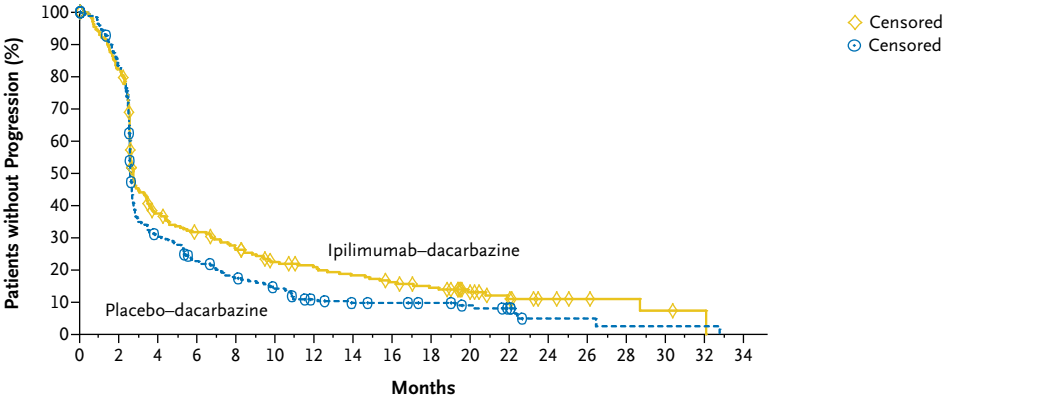
A



No. at Risk

Ipilimumab–dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo–dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

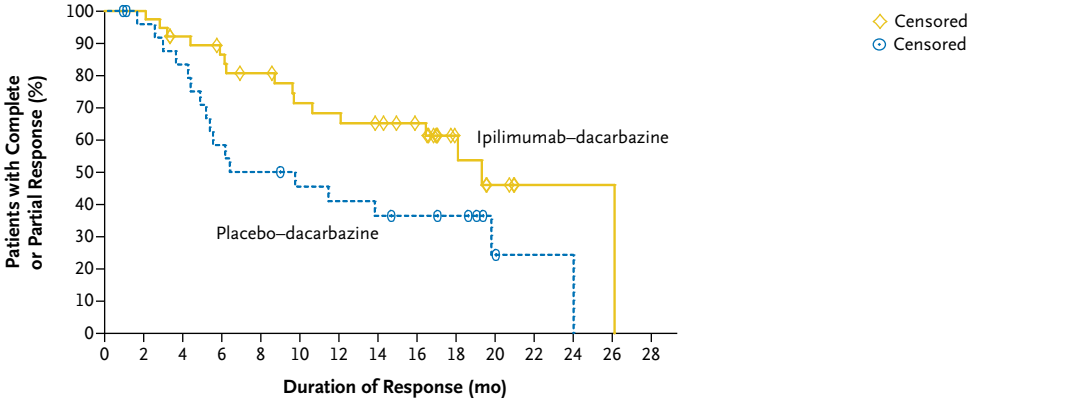
B



No. at Risk

Ipilimumab–dacarbazine	250	199	85	70	57	45	40	35	30	25	16	10	6	4	3	2	1	0
Placebo–dacarbazine	252	205	72	52	39	30	20	16	15	13	10	7	2	2	1	1	1	0

C



No. at Risk

Ipilimumab–dacarbazine	38	38	33	30	27	23	22	20	17	8	4	1	1	1	0
Placebo–dacarbazine	26	23	20	14	12	10	9	8	7	6	2	1	1	0	0

Figure 1 (facing page). Kaplan–Meier Curves for Overall Survival, Progression-free Survival, and Duration of Response.

Overall survival and progression-free survival in the intention-to treat population are shown in Panels A and B, respectively, and the duration of complete or partial response is shown in Panel C.

fection) were ruled out (immune-mediated adverse reactions). Severe (grade 3 or higher) immune-mediated adverse reactions were seen in 38.1% of the patients in the ipilimumab–dacarbazine group and 4.4% of the patients in the dacarbazine group. The most common grade 3 or 4 immune-mediated adverse reaction was immune-mediated hepatitis, which was seen in 78 patients in the ipilimumab–dacarbazine group (31.6%) and in 6 patients in the dacarbazine group (2.4%). Grade 3 or 4 immune-mediated enterocolitis was seen in 12 patients in the ipilimumab–dacarbazine group (4.9%) and no patients in the dacarbazine group. Hepatic immune-mediated adverse reactions were generally reversible with treatment according to established guidelines specified in the research protocol. The proportion of patients who received glucocorticoids or other immunosuppressant agents after the emergence of high-grade immune-mediated hepatitis was 80.8% (63 of 78 patients, including 5 patients who received mycophenolate mofetil) in the ipilimumab–dacarbazine group and 33.3% (2 of 6 patients) in the dacarbazine group. High-grade elevations in liver-function values were normalized in 67.9% of patients in the ipilimumab–dacarbazine group, with a median time to normalization of 9.9 weeks (range, 1.0 to 56.1; interquartile range, 7.0 to 15.0). No patient died

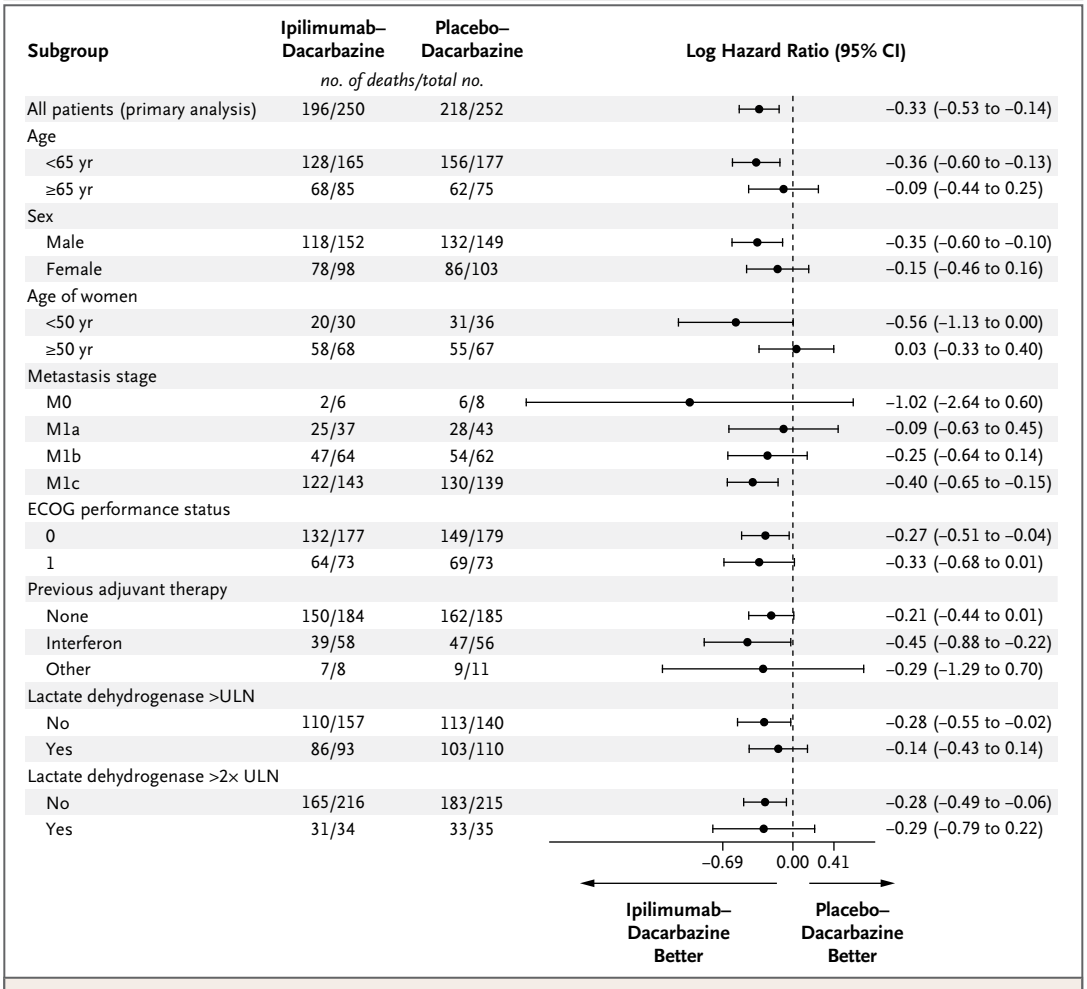


Figure 2. Overall Survival According to Subgroup.

ECOG denotes Eastern Cooperative Oncology Group, and ULN the upper limit of the normal range.

Table 2. Efficacy Results.

End Point	Ipilimumab plus Dacarbazine (N=250)	Placebo plus Dacarbazine (N=252)	Hazard Ratio with Ipilimumab plus Dacarbazine (95% CI)	P Value
Primary end point: overall survival				
No. of deaths	196	218	0.72 (0.59–0.87)	<0.001
Survival — % (95% CI)				
1 yr	47.3 (41.0–53.6)	36.3 (30.4–42.4)		
2 yr	28.5 (22.9–34.2)	17.9 (13.3–22.8)		
3 yr	20.8 (15.7–26.1)	12.2 (8.2–16.5)		
Secondary end points				
Disease progression — no. of events	203	223	0.76 (0.63–0.93)	0.006
Best overall response — no. (%)*	38 (15.2)	26 (10.3)		
Complete response	4 (1.6)	2 (0.8)		
Partial response	34 (13.6)	24 (9.5)		
Stable disease — no. (%)*	45 (18.0)	50 (19.8)		
Progressive disease — no. (%)	111 (44.4)	131 (52.0)		
Response not evaluated — no. (%)†	56 (22.4)	45 (17.9)		

* The rate of disease control (defined as a complete response, a partial response, or stable disease) was 33.2% in the ipilimumab–dacarbazine group and 30.2% in the dacarbazine group (P=0.41).
† To be evaluated for a response, patients had to undergo baseline and follow-up scanning. Owing to early progression, no follow-up scans were available for some patients.

as a result of complications of immune-mediated hepatitis or enterocolitis during the course of the study.

Among the 43 patients who received ipilimumab and the 53 patients who received placebo during the maintenance phase, the most common adverse events (all grades, occurring in >5% of patients in the ipilimumab group) were rash (25.6% vs. 5.7%), pruritus (16.3% vs. 3.8%), diarrhea (14.0% vs. 5.7%), nausea (7.0% vs. 5.7%), and fatigue (9.3% vs. 3.8%). Low-grade increases in liver-function values were noted in 2 patients receiving ipilimumab during the maintenance phase. No high-grade elevations in liver-function values were noted among the patients receiving ipilimumab during the maintenance phase. High-grade adverse events during the maintenance phase were infrequent; among the grade 3 or 4 adverse events noted were colitis and diarrhea (in 1 patient) and rash or pruritus (in 3 patients). No grade 3 or 4 adverse events occurred in patients receiving placebo during the maintenance phase.

DISCUSSION

In this phase 3 study, ipilimumab (at a dose of 10 mg per kilogram), in combination with dacarbazine (at a dose of 850 mg per square meter), as compared with dacarbazine plus placebo, was associated with a significant improvement in overall survival among patients with previously untreated metastatic melanoma. More than 50% of the patients had M1c disease (indicating the presence of visceral metastases, elevated lactate dehydrogenase levels, or both), and more than 35% had baseline elevations in lactate dehydrogenase levels — both of which are associated with poor survival.[20,21] Durable objective responses were observed (median duration of best overall response, 19.3 months in the ipilimumab–dacarbazine group, vs. 8.1 months in the dacarbazine group). Prolonged survival was noted among some patients who were followed for up to 4 years. In the ipilimumab–dacarbazine group, an estimated 28.5% of the patients were alive at 2 years, and an estimated 20.8% at 3 years, as compared with an estimated 17.9% and 12.2%, respectively, in the dacarbazine group.

The rates of some high-grade adverse events in the current study differ from those in previous phase 2 studies of ipilimumab monotherapy (at a dose of 10 mg per kilogram).[13,22-24] The absence of gastrointestinal perforations and the low rates of other grade 3 or 4 gastrointestinal

Table 3. Adverse Events and Immune-Related Adverse Events.*

Adverse Event	Ipilimumab plus Dacarbazine (N=247)			Placebo plus Dacarbazine (N=251)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
All adverse events, regardless of cause†						
Any event	244 (98.8)	99 (40.1)	40 (16.2)	236 (94.0)	45 (17.9)	24 (9.6)
Gastrointestinal: diarrhea	90 (36.4)	10 (4.0)	0	62 (24.7)	0	0
Dermatologic						
Pruritus	73 (29.6)	5 (2.0)	0	22 (8.8)	0	0
Rash	61 (24.7)	3 (1.2)	0	17 (6.8)	0	0
Hepatic						
Increase in alanine aminotransferase	82 (33.2)	40 (16.2)	14 (5.7)	14 (5.6)	2 (0.8)	0
Increase in aspartate aminotransferase	72 (29.1)	36 (14.6)	9 (3.6)	14 (5.6)	3 (1.2)	0
Other						
Pyrexia	91 (36.8)	0	0	23 (9.2)	0	0
Chills	28 (11.3)	0	0	10 (4.0)	0	0
Weight loss	27 (10.9)	1 (0.4)	0	13 (5.2)	1 (0.4)	0
Immune-related adverse events						
Any event	192 (77.7)	78 (31.6)	25 (10.1)	96 (38.2)	8 (3.2)	7 (2.8)
Dermatologic						
Pruritus	66 (26.7)	5 (2.0)	0	15 (6.0)	0	0
Rash	55 (22.3)	3 (1.2)	0	12 (4.8)	0	0
Gastrointestinal						
Diarrhea	81 (32.8)	10 (4.0)	0	40 (15.9)	0	0
Colitis	11 (4.5)	4 (1.6)	1 (0.4)	0	0	0
Hepatic‡						
Increase in alanine aminotransferase	72 (29.1)	37 (15.0)	14 (5.7)	11 (4.4)	2 (0.8)	0
Increase in aspartate aminotransferase	66 (26.7)	34 (13.8)	9 (3.6)	8 (3.2)	1 (0.4)	0
Hepatitis	4 (1.6)	3 (1.2)	0	0	0	0

* The safety analysis included all patients who underwent randomization and received at least one dose of study drug (498 patients). Adverse events and immune-related adverse events were prospectively defined: the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.0, was used for the reporting of adverse events, and a list of events prespecified in the protocol was used to capture immune-related adverse events, which were a subgroup of the reported adverse events. The categories are not mutually exclusive (i.e., one patient could have events in multiple categories).

† A complete list of adverse events that occurred in at least 10% of patients is available in the Supplementary Appendix.

‡ Terms used in the category of hepatic immune-related adverse events are MedDRA preferred terms, as listed by the investigator in case-report forms.

events are in contrast to the results of phase 2 studies involving 325 patients (rate of diarrhea, 4% in this study vs. 11% in the previous studies; rate of colitis, 2% vs. 5%). No cases of hypophysitis were observed during the course of this study, whereas 2% of the patients in the previous studies had high-grade endocrinopathy. The rate of grade 3 or 4 rash was similar (1% in the current study and 2% in the previous studies). However, the rates of high-grade hepatic adverse events in the current study were higher than those in the previous studies (elevated alanine aminotransferase level, 21% vs. 8%; elevated aspartate aminotransferase level, 17% vs. 7%). The apparent shift in the rates of adverse events associated with ipilimumab may be due to its combination with dacarbazine, which is known to cause hepatotoxic effects when it is used as monotherapy.[25-27] The role of systemic glucocorticoids (which were administered to manage hepatic events) in the appar-

ent reduction in gastrointestinal and endocrine events is undefined.

In summary, this trial showed that there was a significant improvement in overall survival among patients with previously untreated metastatic melanoma who received ipilimumab plus dacarbazine as compared with dacarbazine plus placebo. Adverse events other than those typically seen with dacarbazine or ipilimumab therapy were not identified. An increase in liver-function values is an important side effect that was observed more frequently than expected with the combination therapy. Other ipilimumab-associated adverse events (enterocolitis and endocrinopathy) were observed, albeit at a rate that was lower than expected. The key side effects of ipilimumab were managed through adherence to treatment according to well-established guidelines, including the administration of systemic glucocorticoids or other immunosuppressant agents.

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REFERENCES

1. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-66.
2. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1998;16:1743-51.
3. Rusthoven JJ, Quirt IC, Iscoe NA, et al. Randomized, double-blind, placebo-controlled trial comparing the response rates of carmustine, dacarbazine, and cisplatin with and without tamoxifen in patients with metastatic melanoma. J Clin Oncol 1996;14:2083-90.
4. Julia F, Thomas L, Dumontet C, Dalle S. Targeted therapies in metastatic melanoma: toward a clinical breakthrough? Anticancer Agents Med Chem 2010;10:661-5.
5. Agarwala SS. Current systemic therapy for metastatic melanoma. Expert Rev Anticancer Ther 2009;9:587-95.
6. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105-16.
7. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update Cancer J Sci Am 2000;6:Suppl 1:S11-S14.
8. Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. Nat Rev Cancer 2007;7:95-106.
9. O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer 2007;110:2614-27.
10. Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. J Clin Oncol 2008;26:5275-83.
11. Robert C, Ghiringhelli F. What is the role of cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma? Oncologist 2009;14:848-61.
12. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23. [Erratum, N Engl J Med 2010;363:1290.]
13. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11:155-64.
14. Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs 2011;29:489-98.
15. Mokyr MB, Kalinichenko T, Gorelik L, Bluestone JA. Realization of the therapeutic potential of CTLA-4 blockade in low-dose chemotherapy-treated tumor-bearing mice. Cancer Res 1998;58:5301-4.
16. Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nat Rev Immunol 2008;8:59-73.
17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
18. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.
19. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010;102:1388-97.
20. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-206.
21. Bedikian AY, Johnson MM, Warneke CL, et al. Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. Cancer Invest 2008;26:624-33.
22. Weber J, Thompson JA, Hamid O, et al. A randomized, double-blind, placebo controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 2009;15:5591-8.
23. O'Day SJ, Maio M, Chiarion-Sileni V, et al. Efficacy and safety of ipilimumab monotherapy in patients with previously treated, advanced melanoma: a multicenter single-arm phase II study. Ann Oncol 2010;21:1712-7.
24. Schmidt H, Hamid O, Nissan A, et al. Identification of tumor biopsy markers as potential predictors of ipilimumab clinical activity in patients with advanced melanoma. Eur J Cancer Suppl 2009;7:577.
25. Dancygier H, Runne U, Leuschner U, Milbradt R, Classen M. Dacarbazine (DTIC)-induced human liver damage light and electron-microscopic findings. Hepatogastroenterology 1983;30:93-5.
26. Greenstone MA, Dowd PM, Mikhailidis DP, Scheuer PJ. Hepatic vascular lesions associated with dacarbazine treatment. Br Med J (Clin Res Ed) 1981;282:1744-5.
27. Frosch PJ, Czarnetzki BM, Macher E, Grundmann E, Gottschalk I. Hepatic failure in a patient treated with dacarbazine (DTIC) for malignant melanoma. J Cancer Res Clin Oncol 1979;95:281-6.