ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

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ABSTRACT

BACKGROUND

Nivolumab and ipilimumab are immune checkpoint inhibitors that have been approved for the treatment of advanced melanoma. In the United States, ipilimumab has also been approved as adjuvant therapy for melanoma on the basis of recurrence-free and overall survival rates that were higher than those with placebo in a phase 3 trial. We wanted to determine the efficacy of nivolumab versus ipilimumab for adjuvant therapy in patients with resected advanced melanoma.

METHODS

In this randomized, double-blind, phase 3 trial, we randomly assigned 906 patients (≥15 years of age) who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma to receive an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks (453 patients) or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks (453 patients). The patients were treated for a period of up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was recurrence-free survival in the intention-to-treat population.

RESULTS

At a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% (95% confidence interval [CI], 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group (hazard ratio for disease recurrence or death, 0.65; 97.56% CI, 0.51 to 0.83; P<0.001). Treatment-related grade 3 or 4 adverse events were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any adverse event in 9.7% and 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment.

CONCLUSIONS

Among patients undergoing resection of stage IIIB, IIIC, or IV melanoma, adjuvant therapy with nivolumab resulted in significantly longer recurrence-free survival and a lower rate of grade 3 or 4 adverse events than adjuvant therapy with ipilimumab. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; CheckMate 238 ClinicalTrials.gov number, NCT02388906; Eudra-CT number, 2014-002351-26.)

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*A complete list of the CheckMate 238 collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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Ipilimumab (Yervoy, Bristol-Myers Squibb), a human IgG1 monoclonal antibody against cytotoxic T-lymphocyte antigen 4, and nivolumab (Opdivo, Bristol-Myers Squibb), a human IgG4 monoclonal antibody against programmed death 1 (PD-1), are approved for monotherapy and combination therapy in several countries worldwide for the treatment of patients with metastatic melanoma on the basis of the results of phase 3 randomized trials.[1-4] In 2015, the Food and Drug Administration approved ipilimumab as adjuvant therapy in patients with resected stage III melanoma on the basis of recurrence-free survival in a randomized, placebo-controlled, phase 3 trial.[5] In that trial, at 5 years of follow-up, the use of ipilimumab resulted in a higher rate of overall survival than placebo (65.4% vs. 54.4%), along with a higher rate of distant metastasis–free survival.[6] Quality-of-life analysis supported the benefit of ipilimumab treatment despite a rate of grade 3 or 4 immune-related adverse events of 42%.[6,7] Nonetheless, by 5 years, more than half of all ipilimumab-treated patients had had a relapse and more than one third had died.

Further improvement in the outcome for patients with stage III disease is needed. Patients with resected stage IV melanoma, a population that is generally excluded from phase 3 trials of adjuvant therapy, are in need of treatments that improve their survival. The outcome in patients with resected stage IV disease is determined according to tumor substage, and the rates of recurrence-free and overall survival are generally lower than those among patients with stage IIIC disease.[8] A better outcome is predicted by such factors as nonvisceral disease sites, the involvement of fewer organs, and a longer time until the diagnosis of metastatic disease.[9]

PD-1–blocking antibodies have shown a favorable safety profile with better efficacy and durability than those reported with ipilimumab in unresectable stage IV melanoma.[10,11] Because PD-1 blockade acts primarily within the tumor microenvironment,[12] the possibility of providing benefit as adjuvant therapy in patients with microscopic disease required formal exploration.[13] Nivolumab has been assessed in a small, single-group study as adjuvant therapy in patients with resected stage IIIC and IV melanoma, and results showed favorable rates of relapse-free and overall survival.[14] Here, we report efficacy and safety data from a prespecified interim analysis of a randomized, double-blind, phase 3 trial (CheckMate 238) evaluating nivolumab versus ipilimumab in patients with resected stage IIIB, IIIC, or IV melanoma.

Methods

Patients

Eligible patients were 15 years of age or older and had stage IIIB, IIIC, or IV melanoma, according to the 2009 classification of the American Joint Committee on Cancer (AJCC), seventh edition[8] (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All the patients had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability) and histologically confirmed melanoma with metastases to regional lymph nodes or distant metastases that had been surgically resected. Complete regional lymphadenectomy or resection was required within 12 weeks before randomization. Patients with resected brain metastases were eligible to participate in the trial. Key exclusion criteria included ocular or uveal melanoma, a history of autoimmune disease, previous nonmelanoma cancer without complete remission for more than 3 years, systemic use of glucocorticoids, and previous systemic therapy for melanoma. A complete list of inclusion and exclusion criteria is provided in the protocol, available at NEJM.org.

Trial Design and Regimen

From March 30, 2015, to November 30, 2015, we enrolled patients at 130 centers in 25 countries. Registration was performed centrally by Bristol-Myers Squibb, the trial sponsor. Randomization was stratified according to disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c, according to the AJCC criteria) and status regarding programmed death ligand 1 (PD-L1) (negative or intermediate vs. positive) on the basis of a 5% cutoff with PD-L1 staining only of tumor cells, preferably in the most recently resected lesion. (Nivolumab blocks the binding of PD-1 by its ligand PD-L1, which can restore the immune function of T cells.) Clinical investigators and those collecting or analyzing the data were unaware of trial-group assignments.

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

Characteristic	Nivolumab (N=453)	Ipilimumab (N=453)
Sex — no. (%)		
Male	258 (57.0)	269 (59.4)
Female	195 (43.0)	184 (40.6)
Median age (range) — yr	56 (19–83)	54 (18–86)
Disease stage — no. (%)		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or not reported	4 (1.0)	0
Type of lymph-node involvement in stage III — no./total no. (%)		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
Not reported	25/369 (6.8)	18/366 (4.9)
Tumor ulceration in stage III — no./total no. (%)		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
Not reported	15/369 (4.1)	15/366 (4.1)
Metastasis status in stage IV — no./total no. (%)		
M1a	50/82 (61.0)	51/87 (58.6)
M1b	12/82 (14.6)	15/87 (17.2)
M1c	20/82 (24.4)	21/87 (24.1)
Tumor PD-L1 expression — no. (%)		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
Could not be determined or not reported	26 (5.7)	13 (2.9)
BRAF status — no. (%)		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
Not reported	69 (15.2)	45 (9.9)

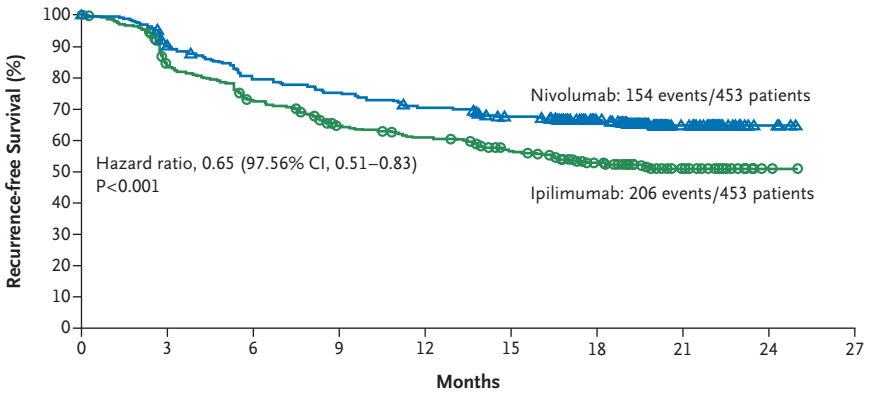
* Percentages may not total 100 because of rounding. PD-L1 denotes programmed death ligand 1.

Patients were assigned in a 1:1 ratio to receive an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks, along with corresponding matching placebo (Fig. S1 in the Supplementary Appendix). Treatment was administered for up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The rules regarding the withholding of a treatment dose and the management of immune-related adverse events are described in the protocol.

TRIAL END POINTS

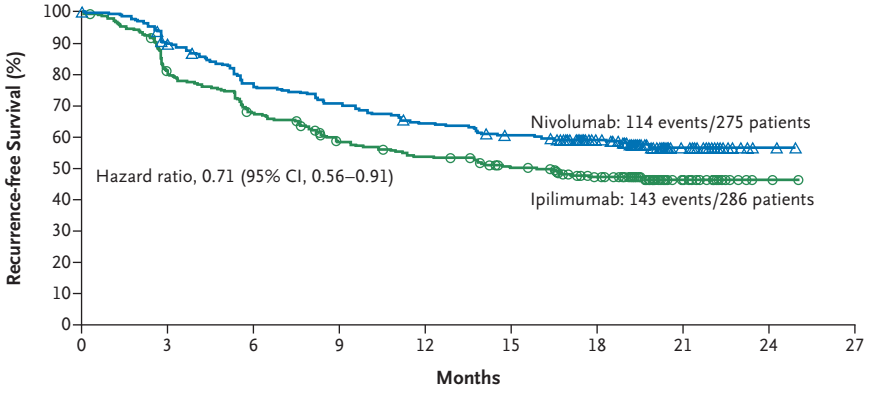
The primary end point was recurrence-free survival in the intention-to-treat population. Secondary end points included overall survival, safety and side-effect profiles, recurrence-free survival according to tumor PD-L1 expression, and health-related quality of life. Distant metastasis–free survival was an exploratory end point.

A Intention-to-Treat Population



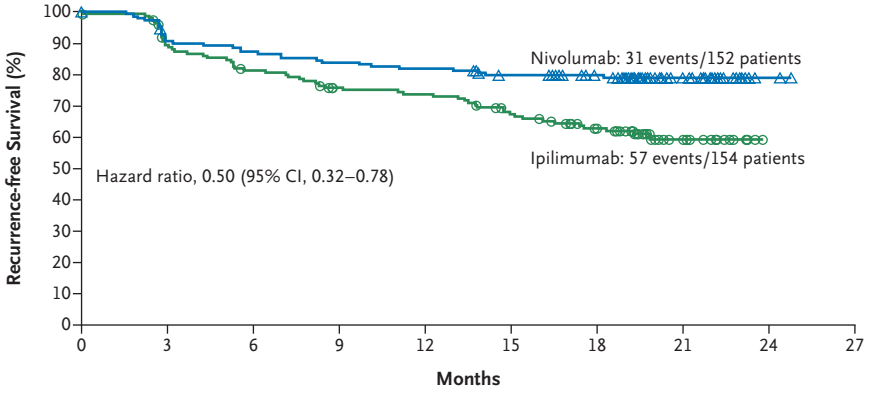
No. at Risk										
Nivolumab	453	399	353	332	311	291	249	71	5	0
Ipilimumab	453	364	314	269	252	225	184	56	2	0

B PD-L1 Expression of Less Than 5%



No. at Risk										
Nivolumab	275	242	204	189	171	159	129	41	3	0
Ipilimumab	286	219	184	153	139	124	100	31	2	0

C PD-L1 Expression of 5% or More



No. at Risk										
Nivolumab	152	135	130	125	122	114	105	26	2	0
Ipilimumab	154	133	120	108	105	93	78	21	0	0

Figure 1 (facing page). Recurrence-free Survival in the Intention-to-Treat Population and According to Tumor PD-L1 Expression.

Panel A shows Kaplan–Meier estimates of recurrence-free survival in the intention-to-treat population. Patients were followed for a minimum of 18 months. At 12 months, the rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group. In addition, significantly longer recurrence-free survival was observed in the nivolumab group than in the ipilimumab group. Among the patients who were evaluated for tumor expression of programmed death ligand 1 (PD-L1), the 12-month rate of recurrence-free survival was 64.3% in the nivolumab group and 53.7% in the ipilimumab group among those with PD-L1 expression of less than 5% (Panel B) and 81.9% and 73.8%, respectively, among those with PD-L1 expression of 5% or more (Panel C). CI denotes confidence interval.

ASSESSMENTS

All the patients were to be assessed for recurrence every 12 weeks for the first 2 years after randomization and every 6 months thereafter until 5 years had elapsed. At each staging visit, the assessments included a physical examination, computed tomography (of the chest, abdomen, and pelvis), and magnetic resonance imaging or computed tomography of the brain. Other imaging was performed if indicated. Recurrent lesions were histologically confirmed whenever possible. The first date that recurrence was observed was used in the analysis, regardless of the imaging method that was used.

Recurrence-free survival was defined as the time from randomization until the date of the first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause. Data regarding adverse events were collected for each group according to the Common Terminology Criteria for Adverse Events, version 4.0. Immune-related selected adverse events were determined on the basis of a prespecified list of terms from the *Medical Dictionary for Regulatory Activities*, which was updated according to each new version. Health-related quality of life was assessed at baseline, at weeks 5, 7, 11, 17, 25, 37, and 49, and then at two follow-up visits (the first 30 days after the last dose and the second approximately 84 days after the first follow-up) with the use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire, version 3,[15] and the European Quality of Life–5 Dimensions (EQ-5D) summary index and visual-analogue scale.[16] Additional descriptions of assessment methods are provided in the Methods section in the Supplementary Appendix.

TRIAL OVERSIGHT

The protocol and amendments for this trial were reviewed by the institutional review board or ethics committee at each trial site. The trial was conducted in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All the patients provided written informed consent before enrollment. The trial was designed by the senior academic authors and representatives of the sponsor, Bristol-Myers Squibb. Data were collected by the sponsor and analyzed in collaboration with all the authors. Ono Pharmaceutical provided funding but was not involved in the trial design, final data collection, or analysis.

A data and safety monitoring committee provided oversight of safety and efficacy and assessed the conduct of the trial in light of an acceptable risk–benefit profile for nivolumab and ipilimumab. The committee also reviewed the formal interim analysis of recurrence-free survival, after which the results were disclosed to the sponsor. The first draft of the manuscript was written by the first author, and all the authors contributed to subsequent drafts and provided final approval before submission for publication. Writing and other editorial assistance was provided by Stem-Scientific and funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and the analyses reported and also confirm adherence to the protocol.

STATISTICAL ANALYSIS

A sample of 800 patients was planned for a final analysis of recurrence-free survival that was time-driven (rather than event-driven) at a minimum of 36 months of follow-up for all patients. Recruitment was rapid owing to high unmet need, and approximately 900 patients who had already signed consent forms underwent randomization. Although 507 events of recurrence-free survival were initially anticipated, we revised that number to 450 for the final analysis on the basis of the distribution of patients according to AJCC disease stage, a slower event rate, a higher cure rate, and a higher rate of early withdrawal from the trial. We determined that the occurrence

of 450 events would provide a power of 85% to detect a hazard ratio for disease recurrence or death of 0.75 (under the 0.83 cutoff for significance) with an overall two-sided type I error rate of 0.05. A protocol amendment mandated the performance of an interim analysis at 18 months of follow-up for all the patients. For that analysis (presented here), 360 of the 450 events (80%) had occurred. The stopping boundary was derived on the basis of the 360 events with the use of a Lan–DeMets alpha spending function with O'Brien–Fleming boundaries. The critical hazard ratio was 0.78 with an adjusted alpha level of 0.0244 (two-sided). No adjustments for multiple inferences were used in the analysis except for the primary analysis of recurrence-free survival, which was adjusted for the interim analysis. Additional descriptions of statistical methods are provided in the Methods section in the Supplementary Appendix.

The main analyses of the efficacy end points included all the patients who had undergone randomization, according to the intention-to-treat principle. Safety was assessed in patients who had received at least one dose of a trial drug in an analysis that included events that were reported between the receipt of the first dose and 30 days after the last dose of a trial drug.

RESULTS

PATIENTS

A total of 906 patients underwent randomization, and 905 were treated (Fig. S2 in the Supplementary Appendix). At the clinical data cutoff of May 15, 2017, the minimum follow-up was 18 months (median, 19.5) for all the patients. The demographic and other baseline characteristics of the patients were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix). At the time of this analysis, all 905 treated patients were no longer receiving the trial drug. The median number of doses was 24 (range, 1 to 26) in the nivolumab group and 4 (range, 1 to 7) in the ipilimumab group. A total of 397 patients had completed 1 year of treatment: 275 of 452 patients (60.8%) in the nivolumab group and 122 of 453 patients (26.9%) in the ipilimumab group (Fig. S2 in the Supplementary Appendix). Overall, subsequent anticancer therapy (including radiotherapy, surgery, and systemic therapy) was administered in 129 patients (28.5%) in the nivolumab group and in 171 (37.7%) in the ipilimumab group (Table S4 in the Supplementary Appendix).

EFFICACY

Intention-to-Treat Population

At the time of this report, the median recurrence-free survival had not been reached in either treatment group. At 12 months, the rate of recurrence-free survival was 70.5% (95% confidence interval [CI], 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group; at 18 months, the corresponding rates were 66.4% (95% CI, 61.8 to 70.6) and 52.7% (95% CI, 47.8 to 57.4). Treatment with nivolumab also showed benefit on the basis of investigator assessment; the use of nivolumab resulted in significantly longer recurrence-free survival than the use of ipilimumab, with recurrence or death reported by investigators in 154 of 453 patients (34.0%) and in 206 of 453 patients (45.5%), respectively (hazard ratio for disease recurrence or death, 0.65; 97.56% CI, 0.51 to 0.83; P<0.001) (Fig. 1A).

Tumor PD-L1 Expression

Prespecified subgroup analyses of recurrence-free survival according to tumor PD-L1 expression showed hazard ratios favoring the nivolumab group, consistent with the primary analysis; however, these analyses were not adjusted for multiple comparisons. Among the patients with PD-L1 expression of less than 5%, the 12-month recurrence-free survival rate was 64.3% (95% CI, 58.3 to 69.7) in the nivolumab group and 53.7% (95% CI, 47.6 to 59.4) in the ipilimumab group (Fig. 1B). Among those with PD-L1 expression of 5% or more, the 12-month recurrence-free survival rate was 81.9% (95% CI, 74.7 to 87.2) in the nivolumab group and 73.8% (95% CI, 65.9 to 80.1) in the ipilimumab group (Fig. 1C).

Disease Stage and Other Subgroup Analyses

The median recurrence-free survival had not been reached in patients with stage III or stage IV disease in the nivolumab group. Patients with either stage of disease in the ipilimumab group had less benefit than those in the nivolumab group. Among the patients with stage IIIB or IIIC disease, the 12-month recurrence-free survival rate was 72.3% (95% CI, 67.4 to 76.7) in the nivolumab group and 61.6% (95% CI, 56.3 to 66.5) in the ipilimumab group (Fig. 2A). Among those with stage IV disease, the 12-month recurrence-free survival rate

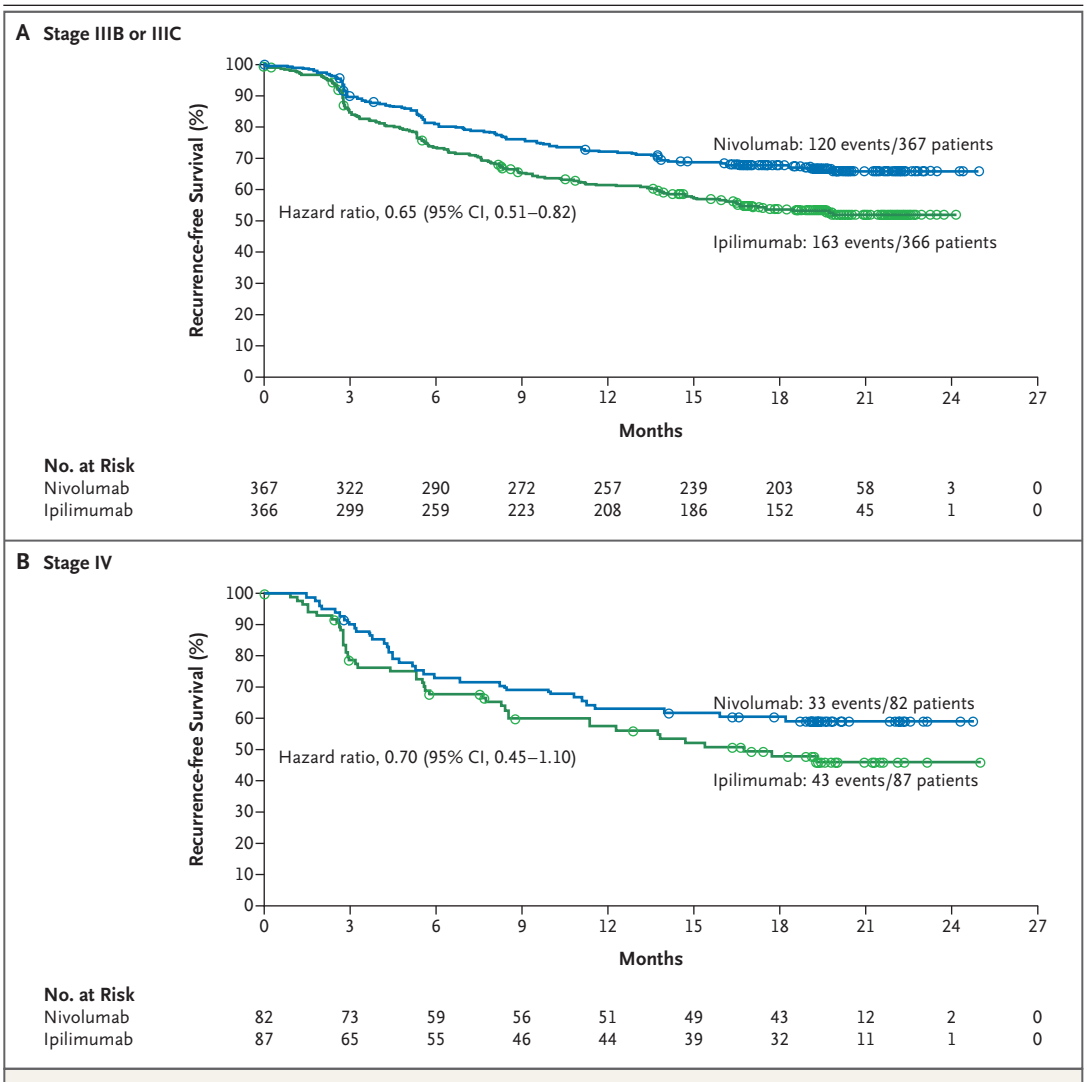


Figure 2. Recurrence-free Survival, According to Disease Stage.

Shown are Kaplan–Meier 12-month estimates of recurrence-free survival in patients with stage IIIB or IIIC disease (72.3% in the nivolumab group and 61.6% in the ipilimumab group) (Panel A) and stage IV disease (63.0% and 57.5%, respectively) (Panel B).

was 63.0% (95% CI, 51.6 to 72.5) in the nivolumab group and 57.5% (95% CI, 46.0 to 67.4) in the ipilimumab group (Fig. 2B). The use of nivolumab resulted in significantly longer recurrence-free survival than the use of ipilimumab, with recurrence or death reported in 120 of 367 patients (32.7%) in the nivolumab group and in 163 of 366 patients (44.5%) in the ipilimumab group among those with stage IIIB or IIIC disease (hazard ratio, 0.65; 95% CI, 0.51 to 0.82) and in 33 of 82 patients (40.2%) in the nivolumab group and in 43 of 87 patients (49.4%) in the ipilimumab group among those with stage IV disease (hazard ratio, 0.70; 95% CI, 0.45 to 1.10). In addition, a benefit for nivolumab was observed with respect to recurrence-free survival in nearly every subgroup tested, including those defined according to age, sex, disease stage, microscopic versus macroscopic nodal disease, ulceration status of the primary tumor, and *BRAF* status (Fig. 3). (*BRAF* is a known driver oncogene that is mutated in a substantial proportion of melanomas.)

Distant Metastasis

The median distant metastasis–free survival was not reached in either treatment group. Longer dis-

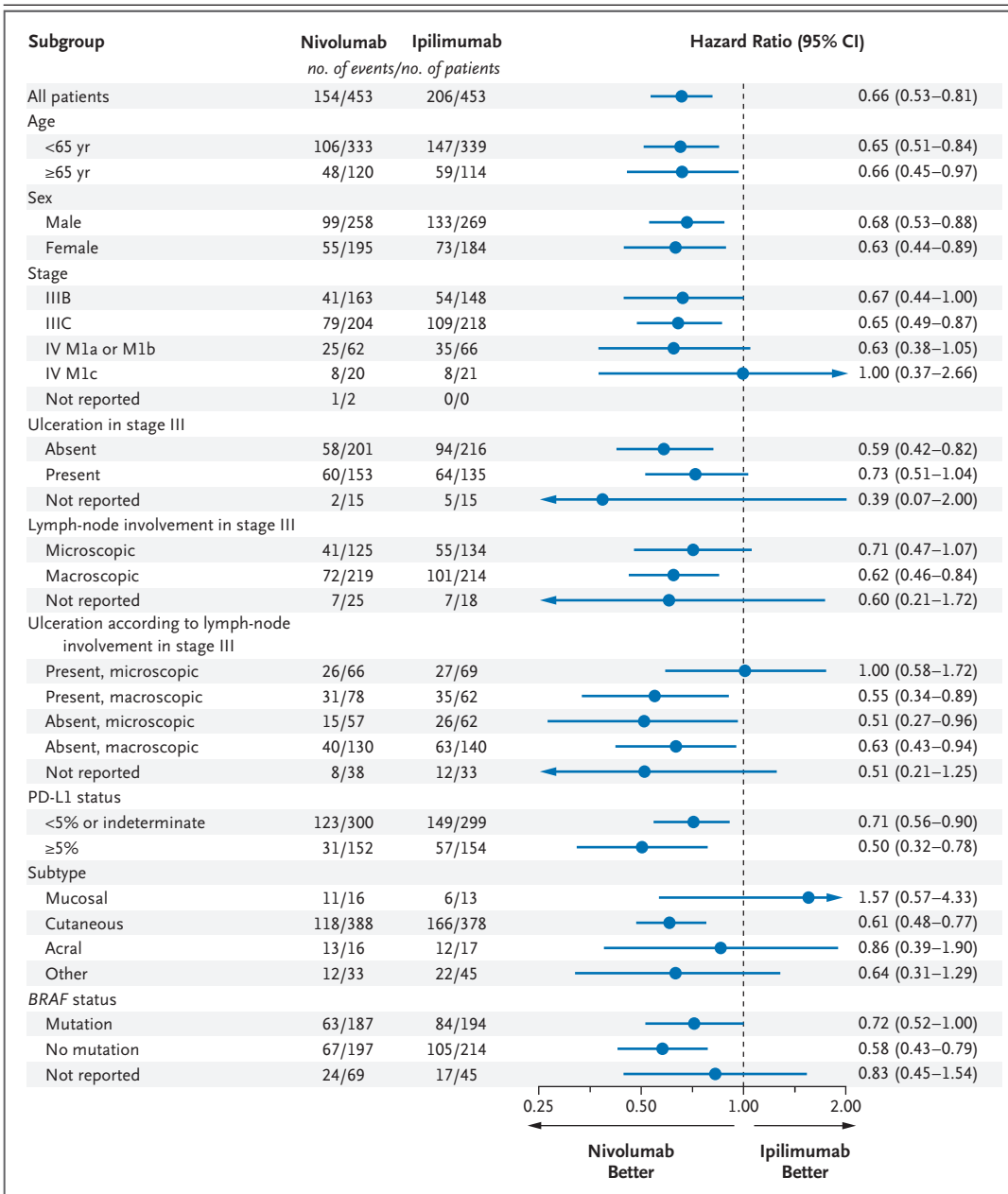


Figure 3. Subgroup Analysis of Disease Recurrence or Death.

Shown is a forest plot of hazard ratios for disease recurrence or death among prespecified subgroups of patients in the nivolumab group and the ipilimumab group. The hazard ratios were not stratified according to the randomization factors of disease stage and PD-L1 status, as was done in the primary analyses. The horizontal lines indicate 95% confidence intervals.

tant metastasis–free survival was observed in the nivolumab group than in the ipilimumab group, with events reported in 93 of 369 patients (25.2%) and in 115 of 366 patients (31.4%), respectively (hazard ratio for distant metastasis or death, 0.73; 95% CI, 0.55 to 0.95) (Fig. S3 in the Supplementary Appendix).

SAFETY

Adverse events of any cause were reported in 96.9% of the patients in the nivolumab group and in 98.5% of those in the ipilimumab group (Table 2). Grade 3 or 4 adverse events that investigators deemed to be related to a trial drug were reported in 14.4% of the patients in the nivolumab

Table 2. Adverse Events*

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Treatment-related adverse event†	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

* The safety population included all the patients who had received at least one dose of a trial drug. Listed are events that were reported between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† The investigators determined whether adverse events were related to a trial drug. The events that are listed here were reported in at least 10% of the patients in either treatment group.

group and in 45.9% of those in the ipilimumab group. The rate of serious adverse events of any grade was 17.5% in the nivolumab group and 40.4% in the ipilimumab group. During the trial, adverse events of any grade that resulted in the discontinuation of a trial drug were reported in 9.7% of the patients in the nivolumab group and in 42.6% of those in the ipilimumab group; grade 3 or 4 adverse events that resulted in such discontinuation were reported in 4.6% and 30.9% of the patients, respectively. In addition, adverse events leading to discontinuation that were related to a trial drug, as determined by investigators, were less frequent in the nivolumab group than in the ipilimumab group (7.7% vs. 41.7%). There were 2 deaths (0.4%) from toxic effects (marrow aplasia and colitis, both of which occurred more than 100 days after the last dose) in the ipilimumab group and no treatment-related deaths in the nivolumab group. Selected adverse events involving the skin, gastrointestinal tract, liver, and lungs that were deemed to be related to a trial drug were less frequent in the nivolumab group than in the ipilimumab group (Table S5 in the Supplementary Appendix). The median time until the onset of select adverse events that were deemed to be related to a trial drug was generally shorter among patients receiving ipilimumab; the time until the resolution of such events was similar in the two groups, with the exception of skin disorders, which took longer to resolve in the nivolumab group (Table S6 in the Supplementary Appendix).

QUALITY OF LIFE

Quality-of-life scores in the two groups remained close to baseline values without any clinically meaningful changes with respect to the score on the EORTC QLQ-C30 Global Health Status or on any of the individual scales, as well as to scores on the EQ-5D utility index and the EQ-5D visual-analogue scale (Fig. S4 in the Supplementary Appendix).

DISCUSSION

Among patients with stage IIIB, IIIC, or IV melanoma, the adjuvant use of nivolumab resulted in a significantly longer recurrence-free survival than the use of ipilimumab at 12 months. In addition, longer distant metastasis–free survival was observed in the nivolumab group than in the ipilimumab group, although this comparison was performed as an exploratory analysis. At the time of this analysis, all the patients in the trial had finished treatment with a minimum follow-up of 18 months.

The results from the prespecified subgroup analyses according to PD-L1 status showed a benefit for nivolumab as compared with ipilimumab, a benefit that was also seen in all subgroups, including those defined according to age, sex, disease stage, microscopic versus macroscopic nodal disease, ulceration status of the primary tumor, and *BRAF* status, although these comparisons were not adjusted for multiple comparisons.[17,18] In an ongoing analysis, we are investigating biomarkers for both nivolumab and ipilimumab using cryopreserved samples of peripheral-blood cells and serum obtained during the trial.

Patients appeared to benefit more from nivolumab than from ipilimumab regardless of PD-L1 status. Among the patients with tumor PD-L1 expression of less than 5%, recurrence was reported in 114 of 275 patients in the nivolumab group and in 143 of 286 patients in the ipilimumab group (hazard ratio, 0.71); among those with tumor PD-L1 expression of 5% or more, recurrence events were reported in 31 of 152 patients in the nivolumab group and in 57 of 154 patients in the ipilimumab group (hazard ratio, 0.50) (Fig. 1B and 1C). As was previously shown in patients with metastatic disease, we found that patients who received nivolumab as adjuvant therapy after tumor resection derived benefit regardless of *BRAF* status. The mature results of the BRIM8 and COMBI-AD trials of adjuvant therapy involving patients with stage III melanoma, in which vemurafenib and dabrafenib plus trametinib, respectively, are being investigated against placebo, are expected later this year and may also provide additional options for patients with *BRAF* mutations.

In our trial, the rate of recurrence-free survival at 1 year in the ipilimumab group was 60.8%. That finding was consistent with the rate in the EORTC 18071 trial (63.5%), in which the same ipilimumab dose was used for 3 years; that trial included patients with stage IIIA melanoma in addition to those with stages IIIB and IIIC but excluded patients with stage IV melanoma.[5] Recent data from an interim analysis of the E1609 trial of adjuvant therapy, in which patients with resected stage III melanoma received either 3 mg or 10 mg of ipilimumab per kilogram, suggested that the rates of recurrence-free survival at both 12 months and 18 months were generally higher than those with ipilimumab in our trial, but the patient population of E1609 also had a lower risk of recurrence (no stage IV M1c).[19] In contrast to these studies, our trial included patients with stage IV disease. Although in the nivolumab group, the rate of recurrence-free survival was higher among patients with stage III disease than among those with stage IV disease, the patients with stage IV disease also benefited, with a 12-month rate of recurrence-free survival of 63.0% with nivolumab, as compared with 57.5% with ipilimumab (Fig. 2).

In the safety analysis, nivolumab was associated with lower rates of adverse events that were deemed to be related to treatment (particularly, grade 3 or 4 adverse events, serious adverse events, adverse events leading to discontinuation, and selected adverse events) than ipilimumab. Such grade 3 or 4 adverse events occurred in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group and led to discontinuation in 3.5% and 30.0%, respectively. Although the two treatment groups remained close to baseline values with respect to measures of quality of life, during the first 12 weeks of ipilimumab induction, there were lower quality-of-life scores in the ipilimumab group than in the nivolumab group, but the difference was not seen as clinically important.

The recurrence-free survival benefit observed in the EORTC 18071 trial comparing ipilimumab with placebo translated into a significant overall survival benefit. It is unclear whether longer follow-up will lead to a similar survival benefit with nivolumab relative to ipilimumab in our trial, since the data are not yet mature. In addition, the possibility of crossover after relapse owing to the availability of ipilimumab, nivolumab, and pembrolizumab for the treatment of metastatic disease in North America, Australia, and Europe during the trial period may complicate the interpretation of survival data.

The recently published results of the second Multicenter Selective Lymphadenectomy Trial, which suggest that patients with stage III melanoma with microscopic nodal disease may no longer need to undergo completion lymphadenectomy after a positive sentinel-node biopsy, may alter the applicability of our results to future patients.[20] In our trial, all the patients with stage III nodal disease underwent completion lymphadenectomy; 28% of the patients with stage III disease in the nivolumab group and 30% of those in the ipilimumab group had microscopic disease. In addition, it is possible that the early reporting of recurrence-free survival could add potential bias in an overestimation of the treatment effect of nivolumab. However, many other melanoma trials that were stopped early have shown consistency between the interim findings and the final results. Given the substantial benefit that is provided by PD-1 antibodies used in combination or as monotherapy in patients with metastatic disease, an additional question is whether adjuvant checkpoint blockade after resection is necessary or should be reserved with the hope of equal benefit for patients who have a relapse with unresectable disease after surgery for stage III or IV melanoma.

In conclusion, we found that adjuvant therapy with nivolumab among patients with resected stage IIIB, IIIC, or IV melanoma resulted in significantly longer recurrence-free survival and a better safety profile than adjuvant therapy with ipilimumab.

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APPENDIX

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