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Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial

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PURPOSE Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1+IPI3) is approved for first-line treatment of patients with advanced melanoma in several countries. We conducted a phase IIIb/IV study (CheckMate 511) to determine if nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3+IPI1) improves the safety profile of the combination.

PATIENTS AND METHODS Patients (N = 360) age 18 years or older with previously untreated, unresectable stage III or IV melanoma were randomly assigned 1:1 to NIVO3+IPI1 or NIVO1+IPI3 once every 3 weeks for four doses. After 6 weeks, all patients received NIVO 480 mg once every 4 weeks until disease progression or unacceptable toxicity. The primary end point was a comparison of the incidence of treatment-related grade 3 to 5 adverse events (AEs) between groups. Secondary end points included descriptive analyses of objective response rate, progression-free survival, and overall survival. The study was not designed to formally demonstrate noninferiority of NIVO3+IPI1 to NIVO1+IPI3 for efficacy end points.

RESULTS At a minimum follow-up of 12 months, incidence of treatment-related grade 3 to 5 AEs was 34% with NIVO3+IPI1 versus 48% with NIVO1+IPI3 ($P = .006$). In descriptive analyses, objective response rate was 45.6% in the NIVO3+IPI1 group and 50.6% in the NIVO1+IPI3 group, with complete responses in 15.0% and 13.5% of patients, respectively. Median progression-free survival was 9.9 months in the NIVO3+IPI1 group and 8.9 months in the NIVO1+IPI3 group. Median overall survival was not reached in either group.

CONCLUSION The CheckMate 511 study met its primary end point, demonstrating a significantly lower incidence of treatment-related grade 3-5 AEs with NIVO3+IPI1 versus NIVO1+IPI3. Descriptive analyses showed that there were no meaningful differences between the groups for any efficacy end point, although longer follow up may help to better characterize efficacy outcomes.

ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Combined inhibition of programmed death 1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) with nivolumab and ipilimumab has demonstrated efficacy in several tumor types at different dosing schedules.¹⁻⁵ In patients with advanced melanoma, nivolumab combined with ipilimumab was first evaluated in a phase I dose-escalation study.^{6,7} This study showed that nivolumab 1 mg/kg plus ipilimumab 3 mg/kg led to higher rates of objective response and greater aggregate clinical activity than did nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, albeit with a higher incidence of treatment-related adverse events (AEs).⁶ On the basis of these findings, we selected nivolumab

1 mg/kg plus ipilimumab 3 mg/kg as the dosing regimen for additional clinical evaluation.

In patients with previously untreated, advanced melanoma, results of the phase II CheckMate 069^{8,9} and phase III CheckMate 067^{1,2} trials demonstrated a significant improvement in objective response rate (ORR) and progression-free survival (PFS) with nivolumab plus ipilimumab versus ipilimumab alone. Follow-up analyses from the CheckMate 067 trial showed a significant improvement in overall survival (OS) for nivolumab plus ipilimumab compared with ipilimumab alone.² Recently, updated data from the CheckMate 067 trial showed 4-year OS rates of 53%, 46%, and 30% in the nivolumab plus

ipilimumab, nivolumab alone, and ipilimumab alone groups, respectively.¹⁰

In both the CheckMate 069 and 067 studies, nivolumab was administered at 1 mg/kg and ipilimumab at 3 mg/kg, once every 3 weeks for four doses, followed by nivolumab monotherapy at 3 mg/kg once every 2 weeks. Results of these studies led to the approval of the combination as a first-line treatment in patients with advanced melanoma. In the initial report from CheckMate 067, at a minimum follow-up of 9 months, treatment-related grade 3 and 4 AEs were reported in 55% of patients who received combination therapy, 16% who received nivolumab alone, and 27% who received ipilimumab alone, which led to the discontinuation of treatment in 29%, 5%, and 13% of patients, respectively.¹ The phase IIIb/IV CheckMate 511 study was conducted to determine whether nivolumab 3 mg/kg plus ipilimumab 1 mg/kg improves the safety profile of the approved dosing regimen in patients with advanced melanoma.

PATIENTS AND METHODS

Patients

Eligible patients were age 18 years or older with unresectable stage III or stage IV melanoma (per American Joint Committee on Cancer staging system 7th edition), an Eastern Cooperative Oncology Group performance status of 0 or 1, no prior systemic therapy for metastatic melanoma (prior adjuvant or neoadjuvant therapy was permitted if completed 6 weeks or more before random assignment), measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, and tumor tissue available for biomarker analyses. Patients with active brain metastases, ocular melanoma, or autoimmune disease that required systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of random assignment were excluded.

The trial was conducted in accordance with Good Clinical Practices as defined by the International Conference on Harmonization. The study was conducted in compliance with the protocol approved by the institutional review boards of each study center. All patients provided written, informed consent before enrollment.

Study Design and Treatment

This phase IIIb/IV, randomized, double-blind study was conducted at 57 sites in 13 countries. Patients were randomly assigned 1:1 and stratified by programmed death ligand 1 (PD-L1) status (5% or more v less than 5% tumor cell surface expression) and M stage (M0/M1a/M1b v M1c; Data Supplement). In part 1 of the study, patients received either nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3+IPI1) or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1+IPI3) once every 3 weeks for four doses. NIVO was administered first as a 30-minute infusion, and after a 30-minute waiting period was followed by IPI as a 30-minute

infusion. Patients who discontinued combination therapy as a result of toxicity did not enter the maintenance phase (part 2 of the study) in which open-label NIVO was administered as a 30-minute infusion at a flat dose of 480 mg once every 4 weeks until disease progression or unacceptable toxicity. The maintenance phase began 6 weeks after the last combination dose. Dose delays as a result of toxicity were permitted, but dose reductions for either drug were not allowed.

Assessments

The primary end point was to evaluate the rate of treatment-related grade 3 to 5 AEs in patients who received NIVO3+IPI1 and NIVO1+IPI3. Secondary end points included ORR, PFS, OS, and health-related quality of life (HRQoL) in both treatment groups. Exploratory end points included duration of response, time to response, and overall safety and tolerability.

AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), assessed from the first dose of study therapy to 30 days after the last dose. Safety was based on the frequency of deaths, AEs, serious AEs, and AEs leading to treatment discontinuation. In addition, analyses of select AEs—that is, those with a potential immunologic cause—were included incidence, time to onset, and time to resolution with immune-modulating medications. All treated patients were evaluated for investigator-assessed response according to RECIST v1.1 at 12 weeks after random assignment, 8 weeks thereafter for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation. Tumor PD-L1 expression was assessed in pretreatment biopsy specimens at a central laboratory using a validated, automated immunohistochemical assay (PD-L1 IHC 28-8 pharmDx; Dako, Carpinteria, CA) as described previously.¹

HRQoL was assessed with the use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30) and the three-level version of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire, as described previously.¹¹ Analysis of HRQoL outcomes was performed on all treated patients who had a baseline assessment and at least one subsequent assessment on study. A clinically meaningful change from baseline score was defined as 10 for QLQ-C30 Global Health Status,¹² 0.08 for the EQ-5D utility index,¹³ and 7 for the EQ-5D Visual Analog Scale.¹³ For all assessments, a higher score represents a better quality of life.

Statistical Analysis

Statistical powering for the primary end point of treatment-related grade 3 to 5 AEs assumed that 340 total patients would be treated, 170 in each group. Given a two-sided α of .05, 340 patients would provide 80% power to show a statistically significant difference assuming a rate of 40% in the NIVO3+IPI1 group versus 55% in the NIVO1+IPI3

group. A difference of 15% was considered clinically meaningful and is consistent with results from the CheckMate 067^{1,2} and CheckMate 069^{8,9} studies. As the primary end point was a safety analysis that included all treated patients, secondary efficacy end points also included all treated patients. The study was not designed or powered to formally demonstrate noninferiority of NIVO3+IPI1 to NIVO1+IPI3 for the secondary end points; thus, efficacy data are for descriptive purposes only and were not adjusted for multiplicity. We calculated ORR and corresponding 95% CI using the Clopper-Pearson method and compared the two groups using a two-sided Cochran-Mantel-Haenszel test, stratified by PD-L1 and M stage. We estimated PFS and OS using the Kaplan-Meier method.

RESULTS

Patient Characteristics and Drug Exposure

Patients were enrolled from April 4, 2016, to March 27, 2017. Results presented here are from a database lock on June 1, 2018, with a minimum patient follow-up of 12 months. Median follow-up was 18.8 months in the NIVO3+IPI1 group and 18.6 months in the NIVO1+IPI3

group. A total of 360 patients were randomly assigned, with 180 treated in the NIVO3+IPI1 group and 178 in the NIVO1+IPI3 group; 119 (66.1%) of 180 patients and 100 (56.2%) of 178 patients completed combination therapy in the NIVO3+IPI1 and NIVO1+IPI3 groups, respectively (Fig 1). The most common reason for discontinuation of combination therapy was study drug toxicity—17.2% in the NIVO3+IPI1 group and 28.1% in the NIVO1+IPI3 group.

Baseline characteristics were generally well balanced between the two groups, with the exception of a higher percentage of patients with elevated lactate dehydrogenase (LDH) levels in the NIVO3+IPI1 group (Table 1). In the initial treatment period (part 1), patients in both groups received a median of four doses of NIVO (range, one to four doses) and four doses of IPI (range, one to four doses); 123 (68.3%) of 180 patients in the NIVO3+IPI1 group and 102 (57.3%) of 178 patients in the NIVO1+IPI3 group received all four doses of the combination. Median duration of therapy was 4.4 months and 2.3 months, respectively. During part 2 of the treatment period, 102 patients (56.7%) in the NIVO3+IPI1 group and 75 patients (42.1%) in the NIVO1+IPI3 group received NIVO maintenance therapy, with a median of 15.0 doses (range, one to 23 doses) and

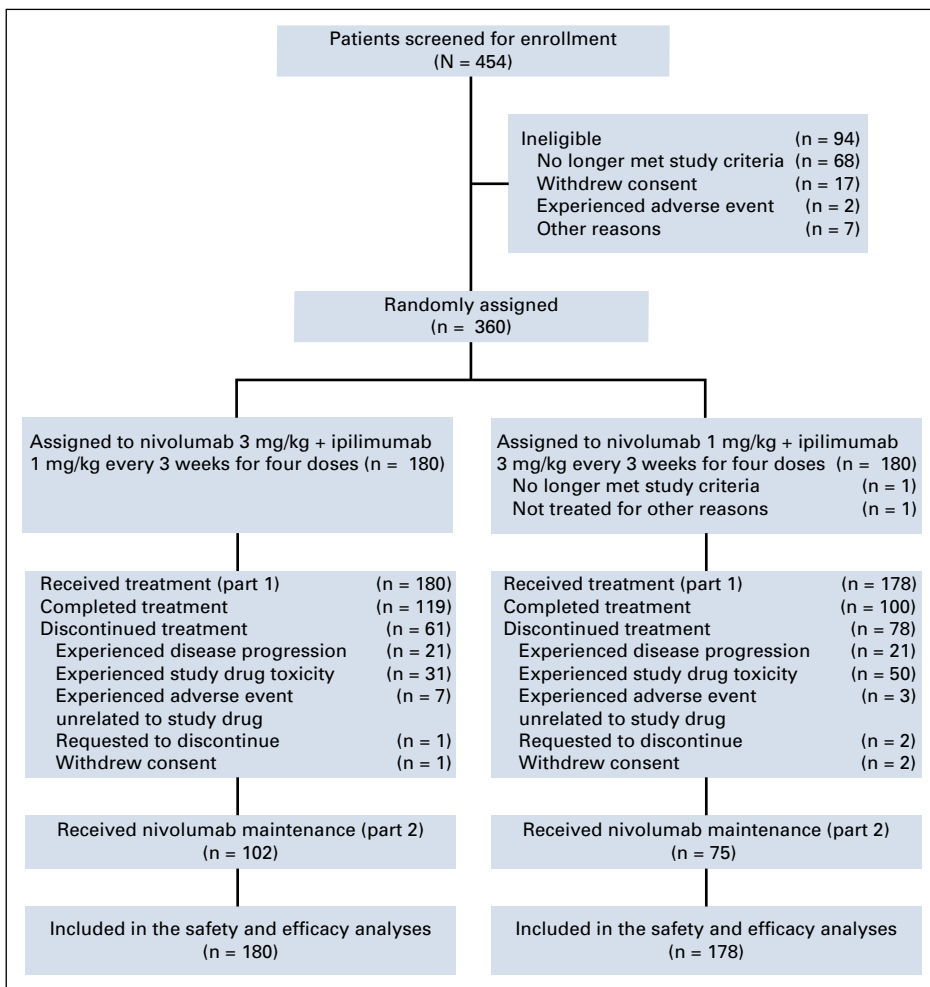


FIG 1. CONSORT diagram. Patient disposition as of June 1, 2018.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Patients

Characteristic	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Age, years		
Median (range)	58.5 (19-85)	58.5 (26-85)
< 65	115 (63.9)	120 (67.4)
≥ 65 to < 75	48 (26.7)	43 (24.2)
≥ 75	17 (9.4)	15 (8.4)
Sex		
Male	105 (58.3)	101 (56.7)
Female	75 (41.7)	77 (43.3)
ECOG PS		
0	129 (71.7)	133 (74.7)
1	51 (28.3)	43 (24.2)
≥ 2	0	2 (1.1)
M-stage at study entry		
M0/M1a/M1b	77 (42.8)	76 (42.7)
M1c	103 (57.2)	102 (57.3)
LDH level		
≤ ULN	102 (56.7)	114 (64.0)
> ULN	77 (42.8)	64 (36.0)
≤ 2× ULN	156 (86.7)	164 (92.1)
> 2× ULN	23 (12.8)	14 (7.9)
Not reported	1 (0.6)	0
History of brain metastases		
Yes	4 (2.2)	5 (2.8)
No	176 (97.8)	173 (97.2)
PD-L1 status, %		
≥ 5	59 (32.8)	60 (33.7)
< 5	120 (66.7)	117 (65.7)
Not reported	1 (0.6)	1 (0.6)
BRAF status		
Wild type	86 (47.8)	90 (50.6)
Mutant	77 (42.8)	73 (41.0)
Not reported	17 (9.4)	15 (8.4)
Prior adjuvant therapy	23 (12.8)	27 (15.2)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

16.0 doses (range, one to 23 doses), respectively. Median duration of therapy in part 2 of the study was 14.7 months in both groups. Subsequent systemic therapy was received by 43 patients (23.9%) in the NIVO3+IPI1 group and 41 patients (23.0%) in the NIVO1+IPI3 group.

Safety

Incidence of treatment-related grade 3 to 5 AEs was significantly lower in the NIVO3+IPI1 group (61 [33.9%] of

180 patients; 95% CI, 27.0% to 41.3%) compared with the NIVO1+IPI3 group (86 [48.3%] of 178 patients; 95% CI, 40.8% to 55.9%; $P = .006$; Table 2). Grade 5 treatment-related AEs were reported in one patient in the NIVO3+IPI1 group (rhabdomyolysis and autoimmune myocarditis). One patient in the NIVO1+IPI3 group experienced treatment-related grade 2 hypophysitis and died 23 days after onset following an episode of sepsis. The investigator reported that hypophysitis and probable encephalitis contributed to the patient's death. Grade 3 and 4 serious AEs were reported in 33.9% of patients in the NIVO3+IPI1 group and 47.8% in the NIVO1+IPI3 group, with treatment-related grade 3 and 4 AEs leading to discontinuation in 16.7% and 27.5% of patients, respectively (Table 2).

Rates of most treatment-related AEs were lower in the NIVO3+IPI1 group (Table 3); however, the overall lower incidence of treatment-related grade 3 and 4 AEs in the NIVO3+IPI1 group compared with the NIVO1+IPI3 group was primarily a result of lower rates of hepatic (7.2% v 16.3%), GI (6.1% v 10.7%), and endocrine (2.8% v 7.3%) AEs (Data Supplement). Median time to the onset of treatment-related select AEs of any grade ranged from 5.1 weeks to 15.7 weeks in the NIVO3+IPI1 group and from 2.4 weeks to 9.1 weeks in the NIVO1+IPI3 group (Data Supplement). Skin AEs occurred early relative to other AE categories, whereas renal and pulmonary AEs occurred later after treatment initiation. Most select AEs were manageable and resolved with immune-modulating medications (Data Supplement). For endocrine AEs of any grade, 30% and 40% resolved in the NIVO3+IPI1 and NIVO1+IPI3 groups, respectively, although unresolved AEs were manageable with sustained hormone-replacement therapy. Infusion-related reactions of any grade occurred in nine patients (5.0%) in the NIVO3+IPI1 group and in four patients (2.2%) in the NIVO1+IPI3 group.

Among patients who received NIVO maintenance therapy, treatment-related AEs of any grade were reported in 78.4% in the NIVO3+IPI1 group and in 80.0% in the NIVO1+IPI3 group (Data Supplement). Treatment-related AEs of grade 3 and 4 were reported in 17.6% and 16.0% of patients in the NIVO3+IPI1 and NIVO1+IPI3 groups and led to discontinuation in 5.9% and 2.7%, respectively. There were no reported deaths as a result of study drug toxicity during maintenance therapy.

Efficacy

In descriptive analyses, investigator-assessed ORR was 45.6% (95% CI, 38.1% to 53.1%) in the NIVO3+IPI1 group and 50.6% (95% CI, 43.0% to 58.1%) in the NIVO1+IPI3 group, with complete responses in 15.0% and 13.5% of patients, respectively (Table 4). Median time to response was approximately 2.8 months in both

TABLE 2. Safety Summary

Variable	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Treatment-related grade 3-5 AEs (95% CI), %	33.9 (27.0 to 41.3)	48.3 (40.8 to 55.9)
Difference (95% CI), %	-14.4 (-24.5 to -4.3)	
<i>P</i>	.006	
Treatment-related AEs	154 (85.6)	167 (93.8)
Grade 3 and 4	60 (33.3)	86 (48.3)
Grade 5	1 (0.6)	0
Serious AEs of any cause	86 (47.8)	113 (63.5)
Grade 3 and 4	61 (33.9)	85 (47.8)
Grade 5	6 (3.3)	3 (1.7)
Treatment-related AEs leading to discontinuation	43 (23.9)	59 (33.1)
Grade 3 and 4	30 (16.7)	49 (27.5)
Grade 5	1 (0.6)	0

NOTE. Data are presented as No. (%) unless otherwise indicated. Data include AEs reported between the first dose and 30 days after the last dose of study therapy.

Abbreviations: AE, adverse event; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg.

groups. At the time of the current analysis, 63 (76.8%) of 82 responses in the NIVO3+IPI1 group and 68 (75.6%) of 90 responses in the NIVO1+IPI3 group were ongoing. Median duration of response was not reached in either group. Median reduction in tumor volume was -41.3% and -55.9% in the NIVO3+IPI1 and NIVO1+IPI3 groups, respectively (Data Supplement). ORR was similar between NIVO3+IPI1 and NIVO1+IPI3 across patient subgroups, including baseline LDH levels, *BRAF* mutation status, and PD-L1 status, although no definitive conclusions can be made from these analyses (Data Supplement).

TABLE 3. Treatment-Related AEs That Occurred in at Least 10% of Patients

AE	NIVO3+IPI1 (n = 180)		NIVO1+IPI3 (n = 178)	
	Any Grade	Grade 3 and 4	Any Grade	Grade 3 and 4
Any treatment-related AE	154 (85.6)	60 (33.3)	167 (93.8)	86 (48.3)
Diarrhea	47 (26.1)	5 (2.8)	55 (30.9)	11 (6.2)
Fatigue	44 (24.4)	1 (0.6)	39 (21.9)	1 (0.6)
Pruritus	43 (23.9)	1 (0.6)	47 (26.4)	0
Rash	31 (17.2)	0	47 (26.4)	0.6
Asthenia	29 (16.1)	0	42 (23.6)	3 (1.7)
Hypothyroidism	25 (13.9)	0	36 (20.2)	0
Nausea	32 (12.2)	0	33 (18.5)	5 (2.8)
Hyperthyroidism	19 (10.6)	0	31 (17.4)	3 (1.7)
Decreased appetite	19 (10.6)	0	19 (10.7)	3 (1.7)
Vitiligo	19 (10.6)	0	11 (6.2)	0
ALT increased	16 (8.9)	3 (1.7)	32 (18.0)	8 (4.5)
AST increased	14 (7.8)	1 (0.6)	27 (15.2)	5 (2.8)
Pyrexia	14 (7.8)	0	35 (19.7)	2 (1.1)
Headache	13 (7.2)	0	25 (14.0)	0
Dry mouth	11 (6.1)	1 (0.6)	21 (11.8)	1 (0.6)
Vomiting	9 (5.0)	1 (0.6)	22 (12.4)	3 (1.7)

NOTE. Data are presented as No. (%). Data include AEs reported between the first dose and 30 days after the last dose of study therapy.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg.

TABLE 4. Investigator-Assessed Response

Response	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Best overall response, No. (%)		
Complete response	27 (15.0)	24 (13.5)
Partial response	55 (30.6)	66 (37.1)
Stable disease	21 (11.7)	21 (11.8)
Progressive disease	62 (34.4)	47 (26.4)
Unknown	15 (8.3)	20 (11.2)
ORR (95% CI), %	45.6 (38.1 to 53.1)	50.6 (43.0 to 58.1)
<i>P</i>	0.35	
Median time to response, months (range)	2.83 (2.0-17.9)	2.79 (2.3-10.5)
No. of ongoing responses/No. of responders (%)	63/82 (76.8)	68/90 (75.6)
Median duration of response, months	NR	NR

Abbreviations: NIVO1+IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; NIVO3+IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; NR, not reached; ORR, objective response rate.

Survival outcomes seemed to be similar between the two treatment groups (Fig 2). Median PFS was 9.92 months in the NIVO3+IPI1 group and 8.94 months in the NIVO1+IPI3 group (HR, 1.06; 95% CI, 0.79 to 1.42). Twelve-month PFS rates were 47.2% and 46.4% in the NIVO3+IPI1 and NIVO1+IPI3 groups, respectively (Fig 2A). Median OS was not reached in either group (HR, 1.09; 95% CI, 0.73 to 1.62). Twelve-month OS rates were 79.7% and 81.0% in

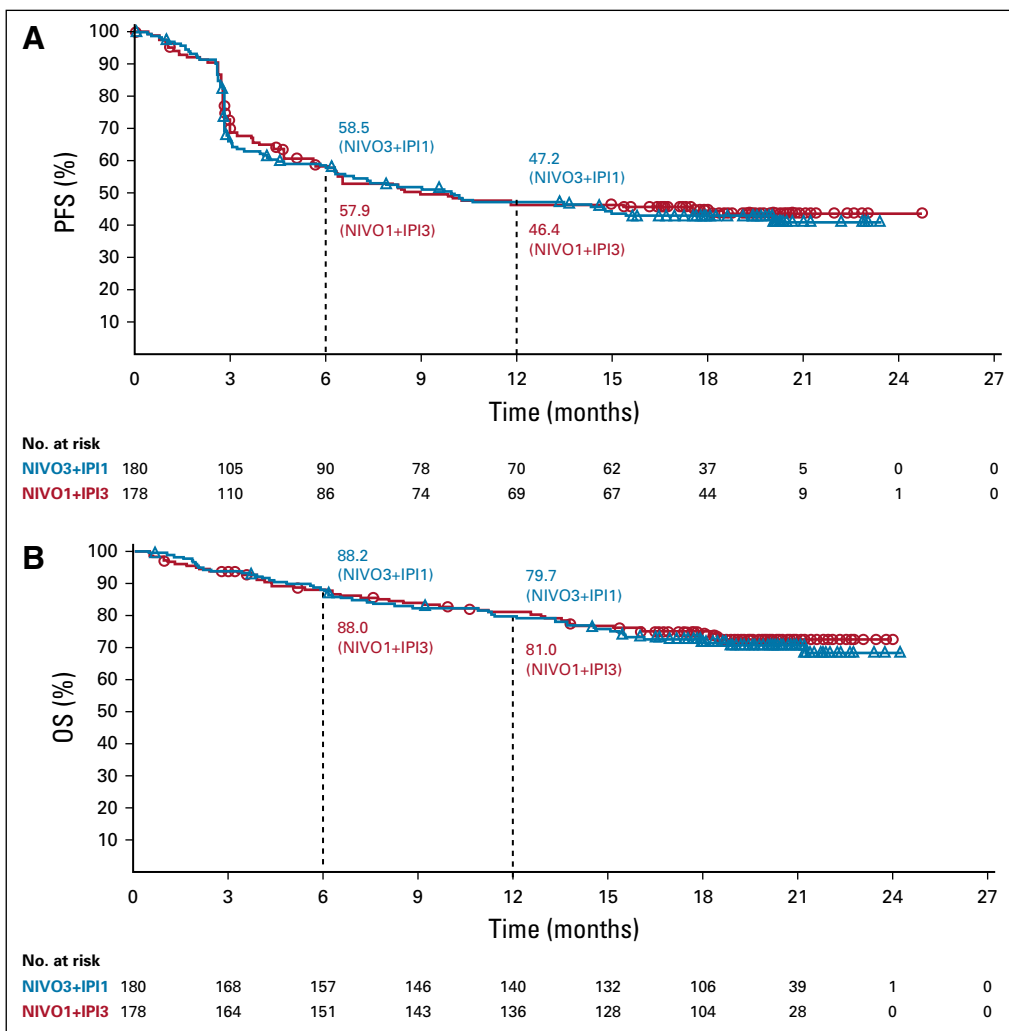


FIG 2. Kaplan-Meier plot of (A) progression-free survival (PFS) and (B) overall survival (OS) in patients who received NIVO3+IPI1 (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) or NIVO1+IPI3 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg). Symbols indicate censored observations. Median PFS was 9.92 months in the NIVO3+IPI1 group and 8.94 months in the NIVO1+IPI3 group (hazard ratio, 1.06; 95% CI, 0.79 to 1.42). Median OS was not reached in either group (hazard ratio, 1.09; 95% CI, 0.73 to 1.62).

the NIVO3+IPI1 and NIVO1+IPI3 groups, respectively (Fig 2B).

HRQoL

Quality of life as measured by the European Organization for Research and Treatment of Cancer QLQ-C30 Global Health Status remained stable through week 40 in both groups, with no mean change in score from baseline reaching a clinically meaningful difference at any time point in either group (Data Supplement). Similarly, health status as measured by the EQ-5D utility index remained stable through week 40 in both groups, with no mean change in score from baseline reaching a minimally important difference at any time point in either group. For the EQ-5D Visual Analog Scale, we observed a clinically meaningful improvement in the NIVO3+IPI1 group from week 24 through week 40, whereas an improvement from baseline in the NIVO1+IPI3 group was only observed at week 28.

DISCUSSION

The CheckMate 511 study met its primary end point, demonstrating a significantly lower incidence of treatment-related grade 3 to 5 AEs with NIVO3+IPI1 compared with the approved regimen, NIVO1+IPI3, in patients with previously untreated, advanced melanoma. On the basis of descriptive analyses, there were no clinically meaningful differences between groups for ORR, PFS, or OS at the time of the current analysis. Analyses of HRQoL demonstrated little to no impact of NIVO3+IPI1 or NIVO1+IPI3 on quality of life in a clinically meaningful way.

Our results showed that duration of therapy during combination treatment was longer for NIVO3+IPI1 treatment than for NIVO1+IPI3, which is consistent with the higher rate of discontinuation as a result of treatment-related AEs in the NIVO1+IPI3 group. Despite discontinuation because of AEs, analyses from the CheckMate 069 and 067 studies have demonstrated that patients who discontinued NIVO1+IPI3 as a result of an AE can still derive benefit without additional treatment.^{10,14} The lower rate of discontinuation as a result of treatment-related AEs in the NIVO3+IPI1 group led to more patients entering the NIVO maintenance phase than in the NIVO1+IPI3 group. For those who entered the maintenance phase, duration of therapy and the number of NIVO doses received were similar in both groups.

The overall lower incidence of treatment-related AEs in the NIVO3+IPI1 group compared with the NIVO1+IPI3 group was a result of lower rates of several treatment-related grade 3 and 4 AEs, particularly diarrhea, colitis, increased ALT and AST, and endocrine AEs. For endocrine AEs, such as hypophysitis, a lower incidence may lead to fewer patients requiring long-term hormone-replacement therapy. Of interest, the incidence of treatment-related grade 3 and 4 AEs with NIVO1+IPI3 in CheckMate 511 was lower than that initially reported with NIVO1+IPI3 in CheckMate 067 (48%

v 55%).¹ It is hypothesized that this apparent difference is because of improved management of AEs with the combination as a result of earlier recognition and management of events and greater experience among investigators with established management guidelines.

In a recent meta-analysis of a WHO pharmacovigilance database and records from seven academic centers, toxicity-related deaths with anti-PD-1/anti-CTLA-4 combination therapies were most commonly a result of colitis and myocarditis.¹⁵ In CheckMate 511, one grade 5 treatment-related AE of myocarditis was reported in the NIVO3+IPI1 group, but no case of colitis had a fatal outcome. Of note, rates of grade 3 and 4 colitis at 2.2% in the NIVO3+IPI1 group and 4.5% in the NIVO1+IPI3 group were lower than that observed in other studies of the combination.^{2,7,9,10} During maintenance therapy with NIVO 480 mg once every 4 weeks, as recently approved in the United States and European Union, a manageable safety profile was observed in both groups with no new safety signals and no deaths as a result of study drug toxicity.

We reported an initial analysis of secondary efficacy end points which were descriptive according to the study design. Our results show that efficacy measures were largely consistent between groups. ORR was numerically lower in the NIVO3+IPI1 group compared with the NIVO1+IPI3 group, but the small 5% difference was not statistically significant. PFS and OS were similar between groups in CheckMate 511 and were consistent with results from CheckMate 067; however, as shown in CheckMate 067 with NIVO1+IPI3 and NIVO alone,^{2,10} longer follow-up may differentiate survival outcomes between groups in CheckMate 511. Recently, results of the phase II Optimal Neoadjuvant Combination Scheme of Ipilimumab and Nivolumab study were reported that evaluated two dosing regimens of IPI plus NIVO in patients with resected stage III melanoma before complete lymph node dissection. A lower incidence of grade 3 and 4 immune-related AEs was reported in patients who received 2× IPI 1 mg/kg + NIVO 3 mg/kg than in patients who received 2× IPI 3 mg/kg + NIVO 1 mg/kg (20% v 40%), but with a similar pathologic response rate (77% v 80%).¹⁶ These results suggest that NIVO combined with a lower dose of IPI may be appropriate for neoadjuvant treatment of melanoma.

Dual inhibition of CTLA-4 and PD-1 continues to demonstrate durable, long-term immunologic memory and clinical benefit for patients with advanced melanoma. In a recent 4-year update of data from the CheckMate 067 study, 53% of patients who were treated with NIVO1+IPI3 were alive, and among these patients, 71% were off study therapy and had not received subsequent systemic therapy at the time of the analysis.¹⁰ A complete response was achieved by 21% of patients who were treated with NIVO1+IPI3 in this study.¹⁰ Whereas the results of the CheckMate 511 study provide evidence for the safety of NIVO in combination with a lower dose of IPI, long-term survival outcomes are

supported by data with NIVO1+IPI3 in CheckMate 067.¹⁰ Moreover, NIVO1+IPI3 has demonstrated clinical benefit in patients with *BRAF*-mutated tumors,^{2,10} elevated LDH levels,^{2,10} brain metastases,^{17,18} and mucosal melanoma¹⁹ and may thus be considered as a first-line treatment of these patients.

The CheckMate 511 study was the first large, randomized trial, to our knowledge, to evaluate low-dose IPI in combination with the approved dose of an anti-PD-1 agent in advanced melanoma. Results of this study demonstrate that the safety profile of NIVO3+IPI1 is superior to that of NIVO1+IPI3, which is consistent with the results of other

studies in earlier stages of melanoma. Whereas the analyses of efficacy end points are descriptive, this study provides important information for health care providers to consider regarding the benefit–risk profile of anti-PD-1 agents combined with IPI, particularly in certain populations—such as, elderly patients. Patients in CheckMate 511 will continue to be observed to assess long-term overall survival.

Data Sharing

Bristol-Myers Squibb's policy on data sharing may be found online.²⁰

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT**Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial**

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