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Survival Outcomes in Patients With Previously Untreated *BRAF* Wild-Type Advanced Melanoma Treated With Nivolumab Therapy

Three-Year Follow-up of a Randomized Phase 3 Trial

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IMPORTANCE This analysis provides long-term follow-up in patients with *BRAF* wild-type advanced melanoma receiving first-line therapy based on anti–programmed cell death 1 receptor inhibitors.

OBJECTIVE To compare the 3-year survival with nivolumab vs that with dacarbazine in patients with previously untreated *BRAF* wild-type advanced melanoma.

DESIGN, SETTING, AND PARTICIPANTS This follow-up of a randomized phase 3 trial analyzed 3-year overall survival data from the randomized, controlled, double-blind CheckMate 066 phase 3 clinical trial. For this ongoing, multicenter academic institution trial, patients were enrolled from January 2013 through February 2014. Eligible patients were 18 years or older with confirmed unresectable previously untreated stage III or IV melanoma and an Eastern Cooperative Oncology Group performance status of 0 or 1 but without a *BRAF* mutation.

INTERVENTIONS Patients were treated until progression or unacceptable toxic events with nivolumab (3 mg/kg every 2 weeks plus dacarbazine-matched placebo every 3 weeks) or dacarbazine (1000 mg/m^2 every 3 weeks plus nivolumab-matched placebo every 2 weeks).

MAIN OUTCOME AND MEASURE Overall survival.

RESULTS At minimum follow-ups of 38.4 months among 210 participants in the nivolumab group (median age, 64 years [range, 18-86 years]; 57.6% male) and 38.5 months among 208 participants in the dacarbazine group (median age, 66 years [range, 25-87 years]; 60.1% male), 3-year overall survival rates were 51.2% (95% CI, 44.1%-57.9%) and 21.6% (95% CI, 16.1%-27.6%), respectively. The median overall survival was 37.5 months (95% CI, 25.5 months–not reached) in the nivolumab group and 11.2 months (95% CI, 9.6-13.0 months) in the dacarbazine group (hazard ratio, 0.46; 95% CI, 0.36-0.59; $P < .001$). Complete and partial responses, respectively, were reported for 19.0% (40 of 210) and 23.8% (50 of 210) of patients in the nivolumab group compared with 1.4% (3 of 208) and 13.0% (27 of 208) of patients in the dacarbazine group. Additional analyses were performed on outcomes with subsequent therapies. Treatment-related grade 3/4 adverse events occurred in 15.0% (31 of 206) of nivolumab-treated patients and in 17.6% (36 of 205) of dacarbazine-treated patients. There were no deaths due to study drug toxic effects.

CONCLUSIONS AND RELEVANCE Nivolumab led to improved 3-year overall survival vs dacarbazine in patients with previously untreated *BRAF* wild-type advanced melanoma.

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Supplemental content

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The programmed cell death 1 (PD-1) receptor inhibitors nivolumab and pembrolizumab have demonstrated superior efficacy compared with chemotherapy or the cytotoxic T-lymphocyte-associated antigen 4 inhibitor ipilimumab in advanced melanoma, with a lower incidence of treatment-related grade 3/4 adverse events (AEs).[1-6] In phase 2 and phase 3 trials, the combination of nivolumab and ipilimumab has demonstrated significantly longer progression-free survival and a higher objective response rate compared with ipilimumab alone.[1,7-9]

Emerging evidence shows encouraging long-term survival outcomes for patients with advanced melanoma who received first-line therapy based on anti-PD-1 receptor inhibitors. The randomized, controlled, double-blind CheckMate 066 clinical trial was one of the first phase 3 studies to evaluate anti-PD-1 therapy in advanced melanoma and compared nivolumab with dacarbazine in patients with previously untreated melanoma without *BRAF* mutation.[3] The primary results were previously reported from that study, which demonstrated a significant improvement in the 1-year survival rate (73% with nivolumab vs 42% with dacarbazine), progression-free survival (5.1 months with nivolumab vs 2.2 months with dacarbazine), and objective response rate (40% with nivolumab vs 14% with dacarbazine).[3] In this follow-up of a randomized phase 3 trial, we report 3-year overall survival data from the CheckMate 066 trial. This ongoing, multicenter academic institution trial enrolled patients from January 2013 through February 2014.

Key Points

Question What were 3-year outcomes with nivolumab vs dacarbazine in patients with previously untreated *BRAF* wild-type advanced melanoma?

Findings In this follow-up of a randomized phase 3 trial, 3-year overall survival rates for nivolumab and dacarbazine were 51.2% and 21.6%, respectively, with median overall survival of 37.5 months and 11.2 months, respectively. Treatment-related grade 3/4 adverse events were reported in 15.0% (31 of 206) of nivolumab-treated patients and in 17.6% (36 of 205) of dacarbazine-treated patients.

Meaning Nivolumab led to improved 3-year overall survival vs dacarbazine in patients with previously untreated *BRAF* wild-type advanced melanoma, with no new safety signals observed.

Methods

Patients and Treatment

The CheckMate 066 trial design and patient eligibility criteria have been previously reported.[3] In brief, eligible patients were 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1 and had histologically confirmed unresectable previously untreated stage III or IV melanoma but without a *BRAF* mutation.[3] Patients were randomly assigned 1:1 to receive either nivolumab (3 mg/kg intravenously every 2 weeks plus dacarbazine-matched placebo intravenously every 3 weeks) or dacarbazine (1000 mg/m^2 intravenously every 3 weeks plus nivolumab-matched placebo intravenously every 2 weeks).[3] Patients were treated until progression or unacceptable toxic effects occurred but could be treated beyond initial progression defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guideline[10] if considered by a trial investigator to be experiencing clinical benefit and tolerating study drug. Patients must have discontinued therapy when further progression was documented. A protocol amendment on July 9, 2014, after unmasking of the study and based on recommendations of the data monitoring committee, allowed patients who discontinued dacarbazine to cross over to receive nivolumab in an open-label extension phase, in which they were treated until progression or unacceptable toxic effects. The study protocol was approved by the institutional review board at each participating center. The study was conducted in accord with the Declaration of Helsinki[11] and the International Conference on Harmonisation Guideline for Good Clinical Practice. Trial Protocol is available in Supplement 1.

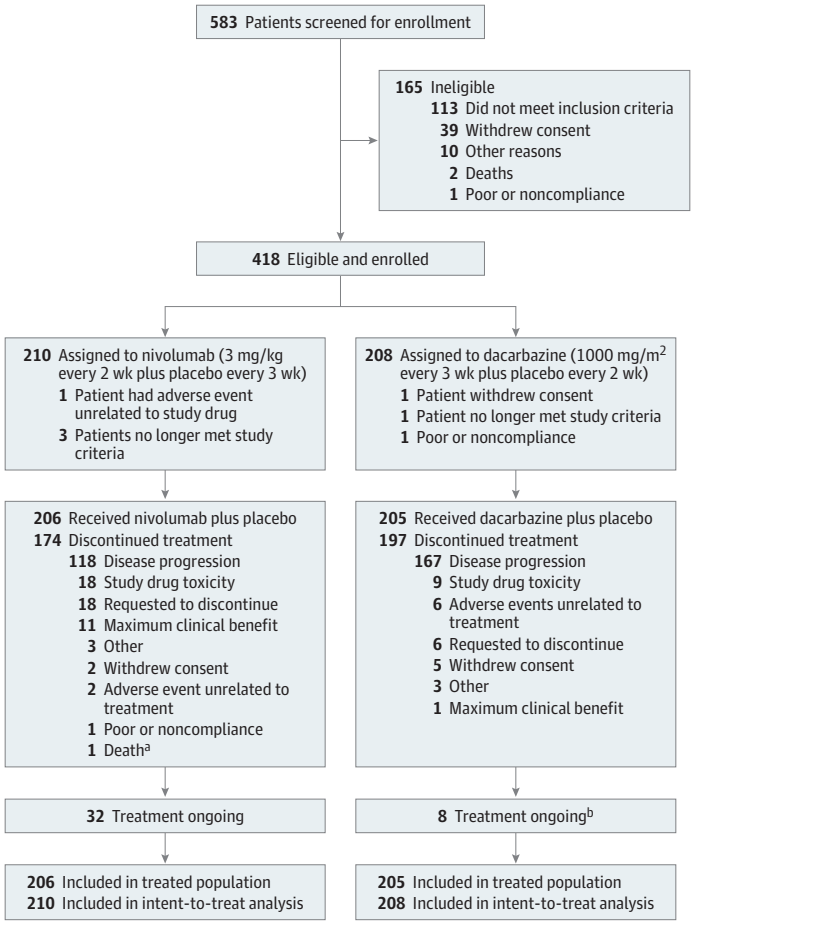
Assessments

Tumor response was assessed by the investigators on computed tomography or magnetic resonance imaging scan in accord with RECIST version 1.1 at the following time points: within 28 days before the first dose (baseline), 9 weeks from randomization, every 6 weeks thereafter for the first year, and then every 12 weeks until disease progression or discontinuation of treatment. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[12] Exposure-adjusted evaluation of AEs over time was performed for patients receiving nivolumab, in which incidence rate per 100 person-years of exposure was reported as event count times 100 per person-years of exposure. Tumor expression of programmed cell death 1 ligand 1 (PD-L1) was assessed in pretreatment samples at a central laboratory by use of a validated, automated immunohistochemical assay (PD-L1 IHC 28-2 pharmDx; Dako) as previously described.[13]

Outcomes

The primary end point was overall survival. Secondary end points included investigator-assessed progression-free survival and objective response, as well as tumor PD-L1 expression as a predictive biomarker of overall survival. A post hoc analysis was conducted to assess outcomes in patients who discontinued study treatment and received subsequent therapy, including nivolumab to subsequent therapy that included any ipilimumab (nivolumab to ipilimumab), dacarbazine to subsequent therapy that included any nivolumab (dacarbazine to nivolumab), and dacarbazine to subsequent therapy that included any ipilimumab (dacarbazine to ipilimumab). Overall survival was available for these 3 patient groups because of a protocol amendment (May 6, 2015) allowing survival data to be requested outside of the protocol-defined window. Response data were also collected for patients who received any ipilimumab therapy after discontinuation of nivolumab.

Figure 1. Trial Profile



[a] Reported as sudden death, cause unknown.

[b] Seven patients crossed over to nivolumab; 1 remains on dacarbazine.

Statistical Analysis

Overall survival and progression-free survival were compared between the 2 treatment groups with the use of a 2-sided log-rank test stratified according to PD-L1 status and metastasis stage. The hazard ratios for the nivolumab group compared with the dacarbazine group and corresponding 95% CIs were estimated with the use of a stratified Cox proportional hazards model. Survival curves for each treatment group were estimated with the use of the Kaplan-Meier product-limit method. Rates at fixed time points were derived from the Kaplan-Meier estimate, along with their corresponding 95% CIs that were log-log transformed.

The 95% CIs for binomial proportions were derived using the Clopper-Pearson method. The differences in objective response rates between the 2 treatment groups, along with their 2-sided 95% CIs, were estimated using the Cochran-Mantel-Haenszel method. Efficacy analyses were performed in the randomized (intent-to-treat) population, whereas safety analyses were performed in all patients who received at least 1 dose of study drug. The threshold for statistical significance was based on the number of deaths (269 at the time of the analysis) using the Lan-DeMets α spending function with O'Brien-Fleming boundaries. We performed all statistical analyses with a software program (SAS, version 9.2; SAS Institute Inc).

Results

A total of 418 patients were randomized to receive either nivolumab (n = 210) or dacarbazine (n = 208) (**Figure 1**); 4 patients in the nivolumab group and 3 patients in the dacarbazine group did not receive treatment. In the nivolumab group, the median age of patients was 64 years (range, 18-86 years), with 57.6% (121 of 210) male; in the dacarbazine group, the median age of patients was 66 years (range, 25-87 years), with 60.1% (125 of 208) male (**Table 1**). Baseline characteristics were balanced between the 2 treatment groups,[3] although a higher percentage of patients in the nivolumab group had an Eastern Cooperative Oncology Group performance status of 0 (70.5% [148 of 210] vs 58.2% [121 of 208]) (Table 1). Among randomized patients, 57.6% (121 of 210) in the nivolumab group and 76.4% (159 of 208) in the dacarbazine group received subsequent treatment. In the nivolumab and dacarbazine groups, respectively, subsequent treatment included radiotherapy (25.7% [54 of 210]

Table 1. Baseline Characteristics

Variable	Nivolumab (n = 210)	Dacarbazine (n = 208)
Age, median (range), y	64 (18-86)	66 (25-87)
Sex, No. (%)		
Male	121 (57.6)	125 (60.1)
Female	89 (42.4)	83 (39.9)
ECOG performance status, No. (%)[a]		
0	148 (70.5)	121 (58.2)
1	60 (28.6)	84 (40.4)
M stage, No. (%)		
M0/M1a/M1b	82 (39.0)	81 (38.9)
M1c	128 (61.0)	127 (61.1)
Baseline LDH level, No. (%)		
≤ULN	120 (57.1)	125 (60.1)
>ULN	79 (37.6)	74 (35.6)
Not reported	11 (5.2)	9 (4.3)
PD-L1 tumor expression, No. (%)[b]		
Positive, ≥5% expression	59 (28.1)	61 (29.3)
Negative or indeterminate	151 (71.9)	147 (70.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

[a] One patient in the nivolumab group and 3 patients in the dacarbazine group were inadvertently enrolled in the study, despite having an ECOG performance status score of 2. In addition, a patient was randomized to the nivolumab group without having an ECOG performance status report.

[b] In the present analysis, tumor PD-L1 expression was assessed using an analytically validated immunohistochemical assay, whereas a verified assay was used in the original study analysis.[3]

and 30.8% [64 of 208]), surgery (15.2% [32 of 210] and 16.3% [34 of 208]), and systemic therapy (46.2% [97 of 210] and 63.5% [132 of 208]) (eTable 1 in Supplement 2).

At a minimum follow-up of 38.4 months in the nivolumab group and 38.5 months in the dacarbazine group (database lock, June 22, 2017), the median overall survival was 37.5 months (95% CI, 25.5 months-not reached [NR]) with nivolumab and 11.2 months (95% CI, 9.6-13.0 months) with dacarbazine (hazard ratio, 0.46; 95% CI, 0.36-0.59; $P < .001$) (**Figure 2**A). Three-year overall survival rates were 51.2% (95% CI, 44.1%-57.9%) and 21.6% (95% CI, 16.1%-27.6%) in the nivolumab and dacarbazine groups, respectively.

As of the data cutoff, 63.8% (134 of 210) of patients in the nivolumab group had disease progression or had died compared with 82.7% (172 of 208) of patients in the dacarbazine group. The median progression-free survival was 5.1 months (95% CI, 3.5-12.2 months) in the nivolumab group and 2.2 months (95% CI, 2.1-2.5 months) in the dacarbazine group (hazard ratio, 0.42; 95% CI, 0.33-0.53; $P < .001$) (Figure 2B), with 3-year progression-free survival rates of 32.2% (95% CI, 25.6%-39.0%) and 2.9% (95% CI, 0.7%-8.1%), respectively.

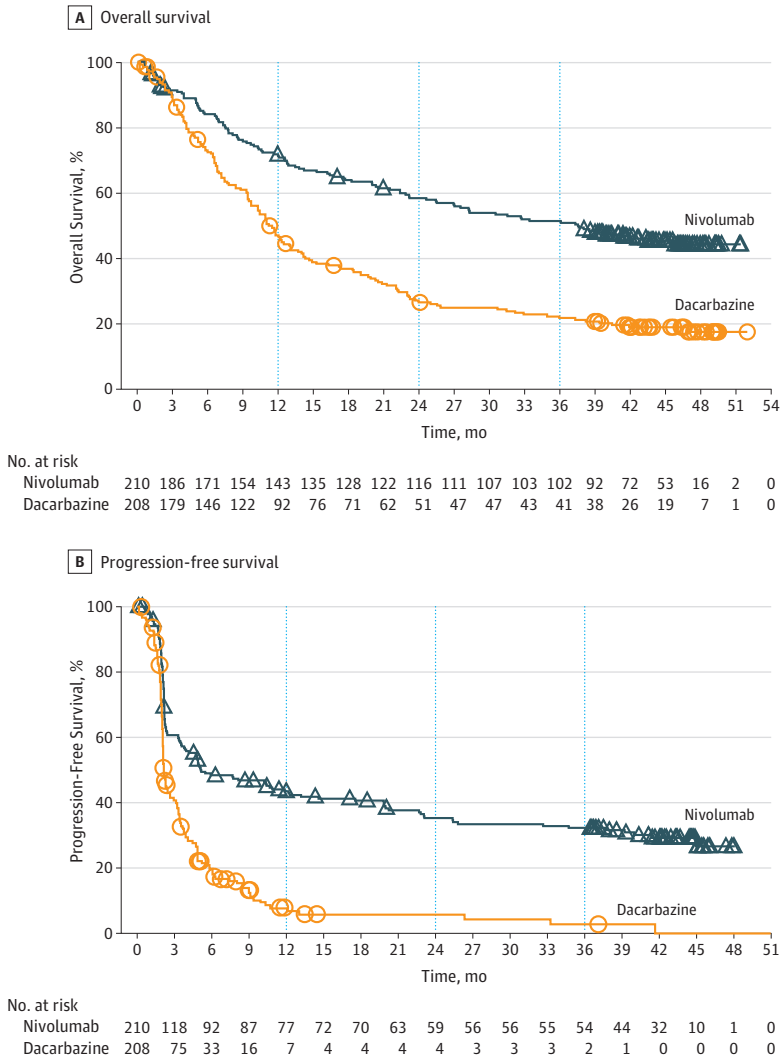
In a prespecified subgroup analysis, we investigated survival outcomes by PD-L1 tumor expression. In patients with PD-L1 expression of at least 5%, the median overall survival was not reached (95% CI, 42.4-NR) in the nivolumab group and was 9.7 months (95% CI, 6.7-13.5 months) in the dacarbazine group; for those with PD-L1 expression less than 5%, the median overall survival with nivolumab was 28.2 months (95% CI, 18.2-38.5 months) and with dacarbazine was 11.6 months (95% CI, 9.3-13.0 months) (eFigure 1 in Supplement 2). Similarly, regardless of PD-L1 expression, patients in the nivolumab group had numerically longer progression-free survival compared with patients in the dacarbazine group (eFigure 1 in Supplement 2).

A significantly higher proportion of patients achieved objective responses in the nivolumab group (42.9% [90 of 210]) compared with the dacarbazine group (14.4% [30 of 208]) (**Table 2** and eFigure 2 in Supplement 2). The median duration of response had not been reached in the nivolumab group (95% CI, 38.2-NR) and was 6.0 months (95% CI, 3.9-24.3 months) in the dacarbazine group. A complete response and a partial response, respectively, were reported for 19.0% (40 of 210) and 23.8% (50 of 210) of patients in the nivolumab group compared with 1.4% (3 of 208) and 13.0% (27 of 208) of patients in the dacarbazine group (Table 2). The median time to both complete response and partial response was 2.1 months with nivolumab and was 2.9 and 2.2 months, respectively, with dacarbazine. Among the 40 patients (19.0%) who achieved a complete response in the nivolumab group, 25.0% (n = 10) had lactate dehydrogenase exceeding upper limit of normal, 57.5% (n = 23) had stage M1c disease, 30.0% (n = 12) had at least 3 organs involved, and 52.5% (n = 21) had tumor PD-L1 expression of at least 5%. In the nivolumab group, 66.7% (60 of 90) of patients had ongoing responses at the time of the last assessment (Table 2 and eFigure 3 in Supplement 2). Most of the responses lasted more than 160 weeks after the start of treatment, and almost half were in patients who had discontinued nivolumab. In addition, 3 initial responses occurred after 74 weeks. In the dacarbazine group, 36.7% (11 of 30) of patients had ongoing responses at the time of the last assessment (eFigure 3 in Supplement 2).

In a post hoc analysis of overall survival for patients who discontinued study therapy and received subsequent systemic therapy, the median overall survival from randomization was 21.5 months (95% CI, 14.2-28.3 months) for the nivolumab to ipilimumab group, 35.4 months (95% CI, 22.4 months-NR) for the dacarbazine to nivolumab group, and 17.4 months (95% CI, 11.7-22.1 months) for the dacarbazine to ipilimumab group (eFigure 4 in Supplement 2). The median overall survival from the start of subsequent therapy was 8.8 months (95% CI, 7.1-14.3 months) for the nivolumab to ipilimumab group, 16.5 months (95% CI, 7.5 months-NR) for the dacarbazine to nivolumab group, and 10.6 months (95% CI 7.8-17.4 months) for the dacarbazine to ipilimumab group. Among the 68 patients who discontinued nivolumab and received subsequent therapy that included ipilimumab (92.6% [63 of 68] discontinued nivolumab because of disease progression), the objective response rate from the start of subsequent ipilimumab was 10.3% (7 of 68) (eTable 2 in Supplement 2); the median time between the last nivolumab dose and the first ipilimumab dose was 1.0 month (range, 0.0-26.9 months).

Treatment-related grade 3/4 AEs were reported in 15.0% (31 of 206) of nivolumab-treated patients and in 17.6% (36 of 205) of dacarbazine-treated patients, which led to discontinu-

Figure 2. Survival Outcomes



A, Kaplan-Meier curves of overall survival for the intent-to-treat population. For nivolumab, the overall survival rate at 1 year was 71%; 2 years, 58%; and 3 years, 51%. For dacarbazine, the overall survival rate at 1 year was 46%; 2 years, 26%; and 3 years, 22%. B, Kaplan-Meier curves of investigator-assessed disease progression (in accord with Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) for the intent-to-treat population. For nivolumab, the the progression-free survival rate at 1 year was 43%; 2 years, 35%; and 3 years, 32%. For dacarbazine, the progression-free survival rate at 1 year was 7%; 2 years, 6%; and 3 years, 3%.

ation in 4.9% (10 of 206) and 2.0% (4 of 205) of patients, respectively (**Table 3**). There were no deaths due to study drug toxic effects in either group. Exposure-adjusted treatment-related AEs were investigated as incidence rate per 100 person-years (event count times 100 per person-years of exposure) in 6-month increments through 36 months. For this report, AEs that occurred in at least 3 different time points are presented (eTable 3 and eFigure 5 in Supplement 2). Most of the observed AEs occurring in at least 3 time points had a larger exposure-adjusted incidence early in treatment that decreased over time.

Discussion

This analysis represents a long-term follow-up of patients with previously untreated *BRAF* wild-type advanced melanoma who received an anti-PD-1 agent in a phase 3 trial. With 3 years of follow-up, nivolumab treatment resulted in improved overall survival compared with dacarbazine (median, 37.5 vs 11.2 months, respectively). Previously demonstrated improvements in progression-free survival and higher objective response rates with nivolumab vs dacarbazine, regardless of tumor PD-L1 expression, were maintained at the 3-year follow-up. Collectively, our results showed durable responses and long-term survival with nivolumab monotherapy, with no new AEs developing at late time points.

The median overall survival had not been reached in the nivolumab group at the time of the initial report (up to 16.7 months of follow-up)[3] but was 37.5 months at the time of the present analysis, with 51.2% (95% CI, 44.1%-57.9%) of patients alive. In the phase 1b KEYNOTE-001 study,[14] the 3-year overall survival rate with pembrolizumab monotherapy was 45% in treatment-naive patients and 40% in the overall population. In the phase 3 KEYNOTE-006 study,[15,16] which also enrolled previously untreated and previously treated patients, pembrolizumab-treated patients had survival rates of 55% at 2 years and 50% at 33 months (median overall survival, 32.3

months [with a 33.9-month median follow-up]). In contrast to the present study, patients with and without a *BRAF* mutation were included in KEYNOTE-001 and KEYNOTE-006. The CheckMate 067 trial[8] also included patients with *BRAF* wild-type and *BRAF*-mutant melanoma, with a 3-year median overall survival of 37.6 months and a survival rate of 52% observed with nivolumab monotherapy. These findings demonstrate consistency in survival outcomes with anti-PD-1 monotherapy across studies, regardless of *BRAF* mutation status. Nivolumab plus ipilimumab from CheckMate 067 was associated with a 3-year overall survival rate of 58%, with the median not yet reached.[8]

Compared with the initial analysis,[3] our 3-year results demonstrate an increase in the objective response rate with nivolumab (40.0% [84 of 210] vs 42.9% [90 of 210]). In addition, compared with previous analyses,[3,17] our results show an increase in the number of patients who achieved a complete response (16 [7.6%] at 1 year, 22 [11.0%] at 2 years, and 40 [19.0%] at 3 years). Time to response was generally similar between nivolumab and dacarbazine, but the median duration of response with nivolumab was longer compared with dacarbazine (NR vs 6 months, respectively). In addition, responses to nivolumab were long-lasting in many patients who discontinued treatment, with most patients who stopped treatment still alive and without disease progression at the time of the last assessment. Patients who achieved a complete response in the nivolumab group had, in general, good prognostic factors, although 25.0% (10 of 40) had elevated lactate dehydrogenase level, 57.5% (23 of 40) had stage M1c disease, and 30.0% (12 of 40) had at least 3 organ sites involved. However, achievement of an objective response with an immune checkpoint inhibitor is not necessarily required for long-term survival.[18] Indeed, our results showed that the percentage of patients surviving to 3 years was higher than the percentage who achieved an objective response.

Table 2. Response to Treatment

Variable	Nivolumab (n = 210)	Dacarbazine (n = 208)
Objective response, No. (%) [95% CI]	90 (42.9) [36.1-49.8]	30 (14.4) [9.9-19.9]
Odds ratio (95% CI) for comparison	4.50 (2.80-7.27)	NA
P value for comparison	<.001	NA
Best overall response, No. (%)		
Complete response	40 (19.0)	3 (1.4)
Partial response	50 (23.8)	27 (13.0)
Stable disease	28 (13.3)	43 (20.7)
Progressive disease	70 (33.3)	104 (50.0)
Unable to determine	22 (10.5)	31 (14.9)
Duration of response		
Ongoing responders, No./total No. (%)	60/90 (66.7)	11/30 (36.7)
Median (95% CI), mo	NR (38.2-NR)	6.0 (3.9-24.3)

Abbreviations: NA, not applicable; NR, not reached.

Limitations

One limitation across studies is the use of subsequent therapies, which likely affected survival outcomes in the present analysis. The median overall survival from randomization was longer and 3-year survival rates were higher for nivolumab compared with dacarbazine when either was followed by subsequent therapy that included ipilimumab. These results indicate that patients can benefit from subsequent ipilimumab, regardless of prior therapy. Survival outcomes may also have been affected by the allowance of nivolumab treatment beyond progression in some patients, as suggested by the findings of prior analysis.[19]

Conclusions

The results of this 3-year follow-up analysis provided evidence for a durable survival benefit with nivolumab monotherapy in patients with previously untreated *BRAF* wild-type advanced melanoma. Improved rates of complete response and longer progression-free survival, as well as overall survival, demonstrated durable benefit with nivolumab monotherapy beyond 1 year. Novel combinations under evaluation using anti-PD-1 therapies as the backbone have the potential to further improve outcomes in patients with advanced melanoma.

Table 3. Adverse Events (AEs) Among 206 Nivolumab Patients and 205 Dacarbazine Patients Included in the Treated Population

	No. (%)			
	Nivolumab (n = 206)		Dacarbazine (n = 205)	
Variable	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Treatment-related AE	160 (77.7)	31 (15.0)	159 (77.6)	36 (17.6)
Treatment-related AE leading to discontinuation[a]	18 (8.7)	10 (4.9)	8 (3.9)	4 (2.0)
Treatment-related select AEs[b]	123 (59.7)	14 (6.8)	65 (31.7)	3 (1.5)
Pruritus	49 (23.8)	1 (0.5)	11 (5.4)	0
Diarrhea	39 (18.9)	1 (0.5)	35 (17.1)	1 (0.5)
Rash	38 (18.4)	1 (0.5)	6 (2.9)	0
Vitiligo	34 (16.5)	0	1 (0.5)	0
Erythema	17 (8.3)	0	4 (2.0)	0
Hypothyroidism	13 (6.3)	0	2 (1.0)	0
Infusion-related reaction	11 (5.3)	0	8 (3.9)	0

[a] Adverse events that led to discontinuation in more than 1 patient in the nivolumab group were colitis, diarrhea, increased alanine aminotransferase level, and pneumonitis (n = 2 for all); only diarrhea led to discontinuation in more than 1 patient in the dacarbazine group (n = 2).

[b] Listed are AEs that were reported in at least 5% of the patients in any study group.

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Correction: This article was corrected on December 6, 2018, to fix an instance of the incorrect treatment group in the Results and data errors in the legend for Figure 2.

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