original reports abstract

Five-Year Outcomes With Nivolumab in Patients With Wild-Type *BRAF* Advanced Melanoma

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PURPOSE The CheckMate 066 trial investigated nivolumab monotherapy as first-line treatment for patients with previously untreated *BRAF* wild-type advanced melanoma. Five-year results are presented herein.

PATIENTS AND METHODS In this multicenter, double-blind, phase III study, 418 patients with previously untreated, unresectable, stage III/IV, wild-type *BRAF* melanoma were randomly assigned 1:1 to receive nivolumab 3 mg/kg every 2 weeks or dacarbazine 1,000 mg/m^2 every 3 weeks. The primary end point was overall survival (OS), and secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety.

RESULTS Patients were followed for a minimum of 60 months from the last patient randomly assigned (median follow-up, 32.0 months for nivolumab and 10.9 months for dacarbazine). Five-year OS rates were 39% with nivolumab and 17% with dacarbazine; PFS rates were 28% and 3%, respectively. Five-year OS was 38% in patients randomly assigned to dacarbazine who had subsequent therapy, including nivolumab (n = 37). ORR was 42% with nivolumab and 14% with dacarbazine; among patients alive at 5 years, ORR was 81% and 39%, respectively. Of 42 patients treated with nivolumab who had a complete response (20%), 88% (37 of 42) were alive as of the 5-year analysis. Among 75 nivolumab-treated patients alive and evaluable at the 5-year analysis, 83% had not received subsequent therapy; 23% were still on study treatment, and 60% were treatment free. Safety analyses were similar to the 3-year report.

CONCLUSION Results from this 5-year analysis confirm the significant benefit of nivolumab over dacarbazine for all end points and add to the growing body of evidence supporting long-term survival with nivolumab monotherapy. Survival is strongly associated with achieving a durable response, which can be maintained after treatment discontinuation, even without subsequent systemic therapies.

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INTRODUCTION

Before the advent of checkpoint inhibitors and targeted therapy, advanced melanoma had a poor prognosis and a 5-year survival rate of < 10%.[1] The programmed cell death 1 (PD-1) receptor inhibitors nivolumab and pembrolizumab have demonstrated superior efficacy compared with ipilimumab (a cytotoxic T-lymphocyte–associated protein 4 inhibitor)[2,3] in patients with treatment-naive advanced melanoma. Both nivolumab and pembrolizumab, as well as nivolumab plus ipilimumab combination, are approved therapies for advanced melanoma first-line treatment.[4,5] Recent results of pembrolizumab and nivolumab 5-year analyses (monotherapy and combined with ipilimumab) have highlighted the clear advantage of these treatments in advanced melanoma compared with ipilimumab.[2,3] Furthermore, most patients in these phase III studies ceased therapy by 2 years and derive ongoing benefit after treatment discontinuation, an apparently consistent finding in checkpoint inhibitor trials.[2,3,6]

In patients with wild-type *BRAF* melanoma, targeted anti–BRAF ± MEK therapies are not indicated; checkpoint inhibitors are the only therapies that have demonstrated an overall survival (OS) benefit, and these trials were conducted before widespread access of first-line ipilimumab outside the United States. CheckMate 066 is the only randomized phase III study to have evaluated first-line anti–PD-1 therapy with nivolumab versus standard chemotherapy (dacarbazine) in patients with treatment-naive *BRAF* wild-type advanced melanoma.[7,8] This seminal study demonstrated the superiority of nivolumab over dacarbazine in these patients in terms of response and survival outcomes. In a 3-year analysis of CheckMate 066, median OS was 37.5 months with nivolumab and 11.2 months with dacarbazine, with 3-year OS rates of 52% and 22%, respectively.[8]

ASSOCIATED CONTENT

Data Supplement
Protocol

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

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CONTEXT

Key Objective

The study objective was to investigate end points, including post-therapy, at a 5-year follow-up of nivolumab treatment in patients with metastatic melanoma.

Knowledge Generated

These 5-year results confirm advantages of nivolumab versus dacarbazine for all end points observed previously, including survival across patient subgroups and survival after treatment discontinuation. Subsequent treatment with nivolumab after dacarbazine led to similar median overall survival compared with primary nivolumab treatment.

Relevance

Results of long-term survival and durable response, even after treatment discontinuation, of nivolumab in patients with metastatic melanoma adds to the growing knowledge base of programmed cell death 1 inhibitors to help to inform treatment decisions for clinicians.

Herein, we provide an analysis of the CheckMate 066 trial at 5 years in the overall patient population as well as in important patient subgroups. We also investigate characteristics, outcomes, and the long-term safety of patients alive at 5 years.

PATIENTS AND METHODS

Patients

Patient eligibility criteria were previously published.[7] In brief, patients with previously untreated, histologically confirmed, unresectable stage III or IV wild-type *BRAF* melanoma who were at least 18 years of age with an Eastern Cooperative Oncology Group performance status ≤ 1 were eligible.

The trial was conducted in accordance with Good Clinical Practices as defined by the International Council for Harmonisation. The study was conducted in compliance with the protocol, which was approved by each study center institutional review board. All patients provided written informed consent before enrollment.

Study Design and Treatment

In this multicenter, double-blind, phase III trial, patients were randomly assigned 1:1 to receive placebo-matched nivolumab 3 mg/kg intravenously every 2 weeks or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks per stratification according to programmed death-ligand 1 (PD-L1) status (≥ 5% *v* < 5% or indeterminate) and metastasis stage (M0, M1a, or M1b *v* M1c according to American Joint

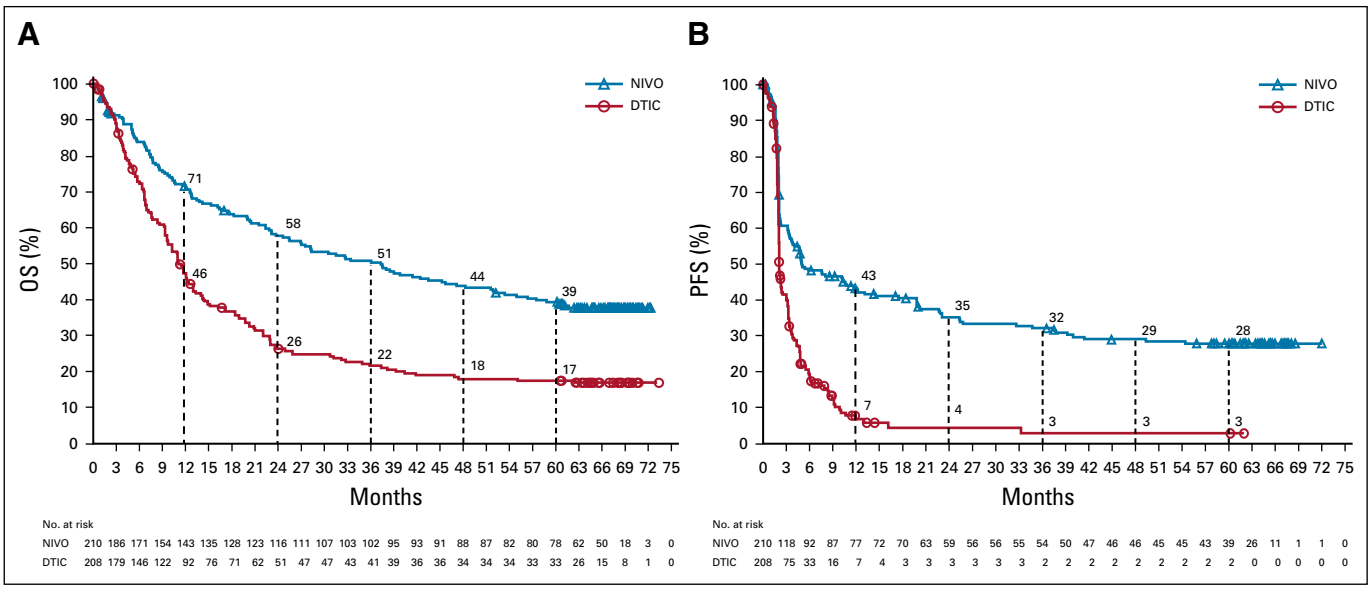

FIG 1. Kaplan-Meier plot of (A) overall survival (OS) and (B) progression-free survival (PFS) in patients who received nivolumab (NIVO) or dacarbazine (DTIC). Median survival time was 37.3 months (95% CI, 25.4 to 51.6 months) in the NIVO group and 11.2 months (95% CI, 9.6 to 13.0 months) in the DTIC group. Median time to progression or death was 5.1 months (95% CI, 3.5 to 12.2 months) in the NIVO group and 2.2 months (95% CI, 2.1 to 2.5 months) in the DTIC group. Rates at earlier time points are based on 5-year analysis and, therefore, may differ slightly from those available for previous reports.

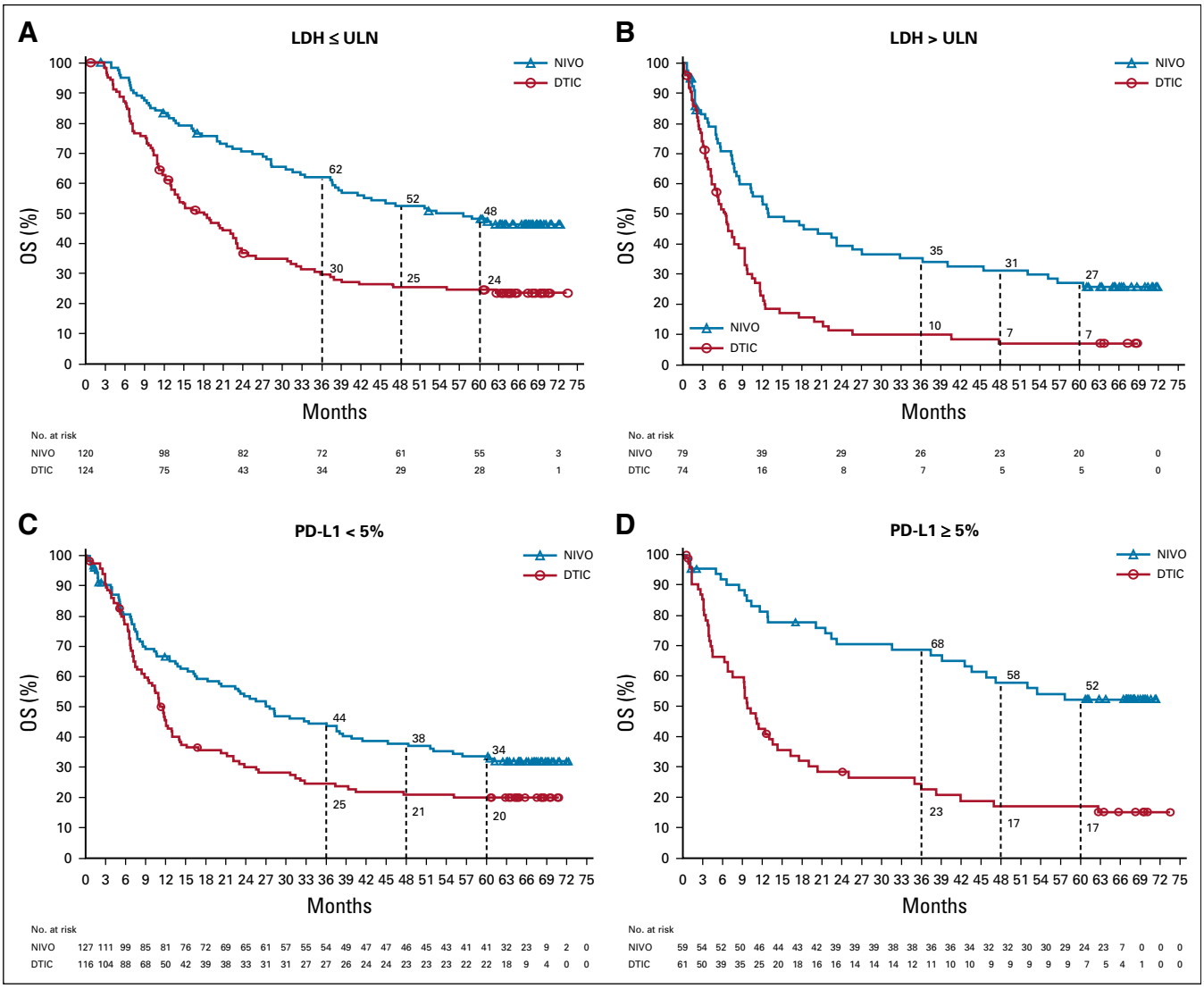

FIG 2. Kaplan-Meier plot of overall survival (OS) in patients who received nivolumab (NIVO) or dacarbazine (DTIC) with (A) lactate dehydrogenase (LDH) ≤ the upper limit of normal (ULN), (B) LDH > ULN, (C) programmed death-ligand 1 (PD-L1) < 5%, and (D) PD-L1 ≥ 5%. For LDH ≤ ULN, median survival time was 53.4 months (95% CI, 37.6 months to not reached [NR]) in the NIVO group and 18.4 months (95% CI, 13.0 to 22.9 months) in the DTIC group, and for LDH > ULN, median survival time was 12.8 months (95% CI, 8.4 to 25.5 months) in the NIVO group and 6.5 months (95% CI, 4.2 to 8.4 months) in the DTIC group. For PD-L1 < 5%, median survival time was 27.5 months (95% CI, 18.2 to 38.0 months) in the NIVO group and 11.6 months (95% CI, 9.3 to 13.0 months) in the DTIC group, and for PD-L1 ≥ 5%, median survival time was NR (95% CI, 42.4 months to NR) in the NIVO group and 9.7 months (95% CI, 6.7 to 13.5 months) in the DTIC group.

Committee on Cancer Staging Manual, Seventh Edition).[9] Patients were treated until progression or unacceptable toxicity and could be treated beyond initial progression per investigator. The trial was reported early on the basis of recommendation of the data safety monitoring committee, which led to a July 9, 2014, protocol amendment that allowed dacarbazine-treated patients to cross over to receive on-study open-label nivolumab until progression or unacceptable toxicity. Additional trial details are available in the Data Supplement (online only) and as previously published.[7,8]

Assessments

The primary end point was OS. Secondary and exploratory end points included progression-free survival (PFS), objective response rate (ORR), PD-L1 biomarker expression, quality of life, and safety. Tumor response was investigator assessed in accordance with RECIST version 1.1. Adverse event (AE) severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Tumor PD-L1 expression was assessed at a central laboratory as described previously.[9]

Post hoc survival analyses of outcomes in patients who discontinued study treatment and received subsequent therapy were conducted. The status of patients who were alive and still being followed at the 5-year analysis was also evaluated.

Statistical Analysis

Treatment groups for OS and PFS were compared using a two-sided log-rank test, with hazard ratios (HRs) and corresponding 95% CIs for the nivolumab group versus the dacarbazine group estimated using a stratified Cox proportional hazards model.[7,8] Survival curves were generated using the Kaplan-Meier product limit method; fixed time point rates and 95% CIs were derived from the Kaplan-Meier estimate. Additional information is provided in the Data Supplement. All statistical analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC). A post hoc sensitivity analysis was performed to determine the average restricted mean survival time (RMST) difference between treatment groups at 5 years.

RESULTS

Patients

From January 2013 through February 2014, 418 patients were enrolled and randomly assigned to nivolumab (n = 210) or dacarbazine (n = 208). Baseline characteristics were published previously[7,8] and were well balanced between treatment groups (Data Supplement). Among patients alive at 5 years (n = 111), baseline characteristics

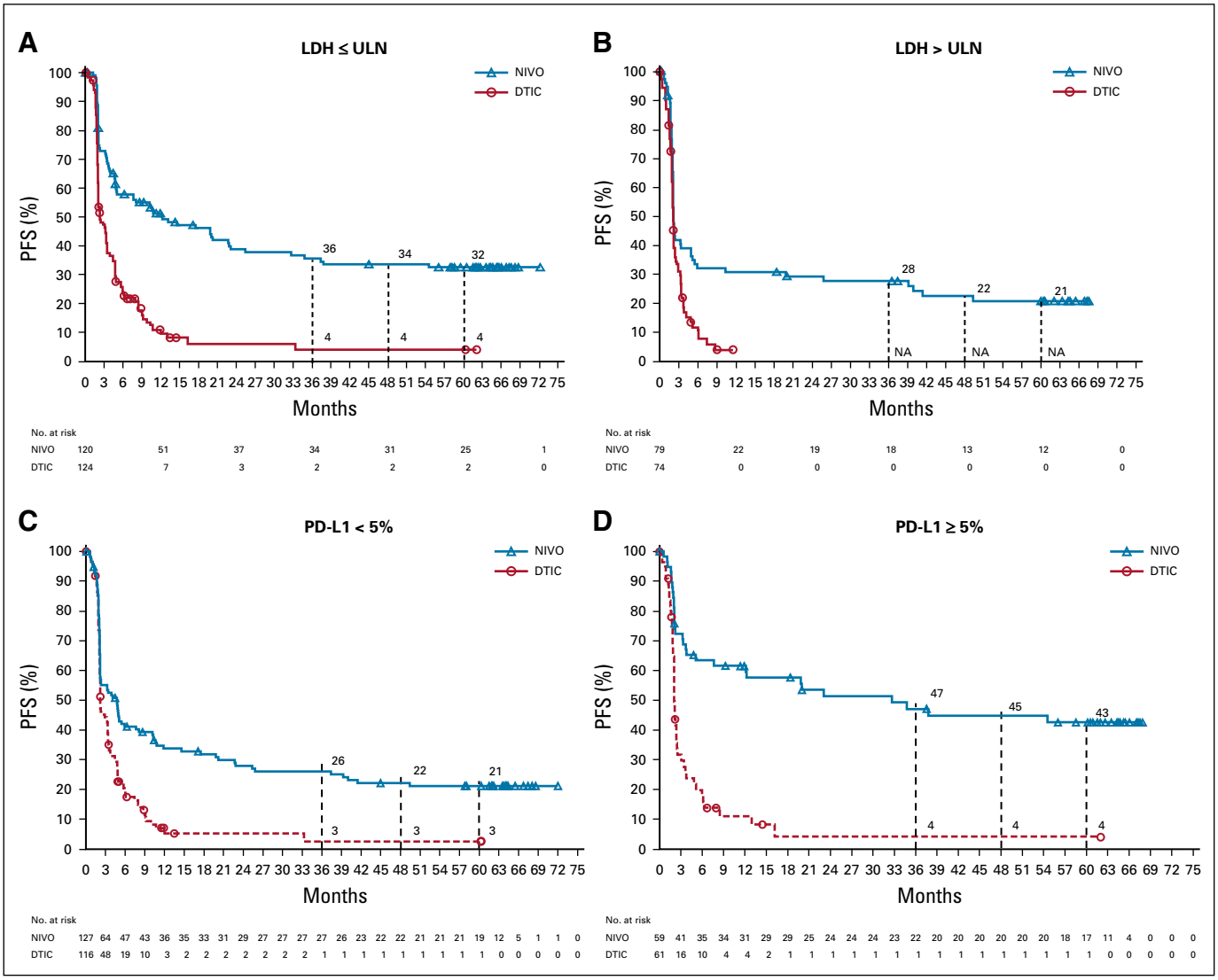

FIG 3. Kaplan-Meier plot of progression-free survival (PFS) in patients who received nivolumab (NIVO) or dacarbazine (DTIC) with (A) lactate dehydrogenase (LDH) ≤ the upper limit of normal (ULN), (B) LDH > ULN, (C) programmed death-ligand 1 (PD-L1) < 5%, and (D) PD-L1 ≥ 5%. For LDH ≤ ULN, median time to progression or death was 12.2 months (95% CI, 5.0 to 22.8 months) in the NIVO group and 2.4 months (95% CI, 2.1 to 3.4 months) in the DTIC group, and for LDH > ULN, median time to progression or death was 2.1 months (95% CI, 2.0 to 3.3 months) in the NIVO group and 2.1 months (95% CI, 1.9 to 2.4 months) in the DTIC group. For PD-L1 < 5%, median time to progression or death was 4.7 months (95% CI, 2.2 to 7.6 months) in the NIVO group and 2.2 months (95% CI, 2.1 to 3.3 months) in the DTIC group, and for PD-L1 ≥ 5%, median time to progression or death was 32.7 months (95% CI, 5.1 months to not reached) in the NIVO group and 2.1 months (95% CI, 2.0 to 2.4 months) in the DTIC group.

TABLE 1. Response to Treatment: All Patients and Patients Alive at 5 Years of Follow-Up

	Nivolumab, No. (%)		Dacarbazine, No. (%)	
Variable	**All Patients**	**Alive at 5 Years**	**All Patients**	**Alive at 5 Years**
No. of patients	210	78	208	33
Objective response rate	89 (42)	63 (81)	30 (14)	13 (39)
95% CI	36 to 49	ND	10 to 20	ND
Odds ratio (95% CI)	4.43 (2.75 to 7.13)	ND	—	—
P	< .0001	ND	—	—
Best overall response				
Complete response	42 (20)	37 (47)	3 (1)	3 (9)
Partial response	47 (22)	26 (33)	27 (13)	10 (30)
Stable disease	30 (14)	5 (6)	42 (20)	6 (18)
Progressive disease	68 (32)	8 (10)	105 (50)	14 (42)
Unevaluable	23 (11)	2 (3)	31 (15)	0

Abbreviation: ND, not determined.

were similar to those of the total population (Data Supplement). The population alive at 5 years had a lower proportion of patients with poor prognostic factors compared with the total population: M1c disease was 53% *v* 60% of patients in the nivolumab arm and 42% *v* 61% in the dacarbazine arm, respectively, and lactate dehydrogenase (LDH) above the upper limit of normal (ULN) was 26% *v* 38% for the nivolumab arm and 15% *v* 36% for the dacarbazine arm, respectively.

The minimum follow-up (database lock April 9, 2019) was 60 months from the last patient randomly assigned. With a median follow-up of 32.0 months for nivolumab and 10.9 months for dacarbazine, 75 (36%) of 206 nivolumab-treated patients were still on study *v* 30 (15%) of 205 dacarbazine-treated patients; 17 (8%) of 206 patients *v* one (< 1%) of 205 patients were still receiving study treatment (Data Supplement). The most common reasons for nivolumab treatment discontinuation were disease progression (58%), patient request (11%), study drug toxicity (9%), and maximum clinical benefit (8%); for dacarbazine, these were disease progression (85%), maximum clinical benefit (4%), and study drug toxicity (4%).

In the nivolumab and dacarbazine groups, 48% and 65% of total patients received subsequent systemic therapy, respectively; 39% and 53% of patients received subsequent immunotherapy. Ipilimumab was the most common subsequent immunotherapy received (in 34% and 44% of total patients, respectively), followed by pembrolizumab (10% and 14%) and nivolumab (5% and 18%; Data Supplement). The median time from random assignment to subsequent systemic therapy (excluding patients who died and never received subsequent therapy [40 and 61 patients, respectively]) was 22.2 months (95% CI, 11.2 to 42.1 months) for nivolumab and 3.8 months (95% CI, 3.5 to 4.7 months) for dacarbazine.

Efficacy

With 291 death events (nivolumab, 126; dacarbazine, 165), median survival time was 37.3 months (95% CI, 25.4 to 51.6 months) and 11.2 months (95% CI, 9.6 to 13.0 months), with 5-year OS rates of 39% and 17%, respectively, and an HR of 0.5 (95% CI, 0.40 to 0.63; $P < .0001$; Fig 1A). In addition, the RMST analysis showed that at 5 years, there was an average survival time difference of 14.3 months (95% CI, 9.9 to 18.7 months) for nivolumab (34.8 months; 95% CI, 31.5 to 38.1 months) over dacarbazine (20.5 months; 95% CI, 17.6 to 23.4 months). With 307 progression (or death) events (nivolumab, 136; dacarbazine, 171), median time to progression (or death) was 5.1 months (95% CI, 3.5 to 12.2 months) in the nivolumab group and 2.2 months (95% CI, 2.1 to 2.5 months) in the dacarbazine group, with 5-year PFS rates of 28% and 3%, respectively, and an HR of 0.4 (95% CI, 0.33 to 0.54; $P < .0001$; Fig 1B).

OS and PFS were evaluated in patient subgroups of clinical interest. In patients with normal LDH (n = 244), OS rates at 5 years were 48% with nivolumab and 24% with dacarbazine and 27% and 7% in patients with LDH > ULN (n = 153), respectively (Figs 2A and B). In patients with PD-L1 < 5% (n = 243), OS rates at 5 years were 34% with nivolumab and 20% with dacarbazine, and in patients with PD-L1 ≥ 5% (n = 120), rates were 52% and 17%, respectively (Figs 2C and D). In patients with normal LDH, PFS rates at 5 years were 32% with nivolumab and 4% with dacarbazine, and in patients with LDH > ULN, rates were 21% and 0%, respectively (Figs 3A and B). In patients with PD-L1 < 5%, PFS rates at 5 years were 21% with nivolumab and 3% with dacarbazine, and in patients with PD-L1 ≥ 5%, rates were 43% and 4%, respectively (Figs 3C and D).

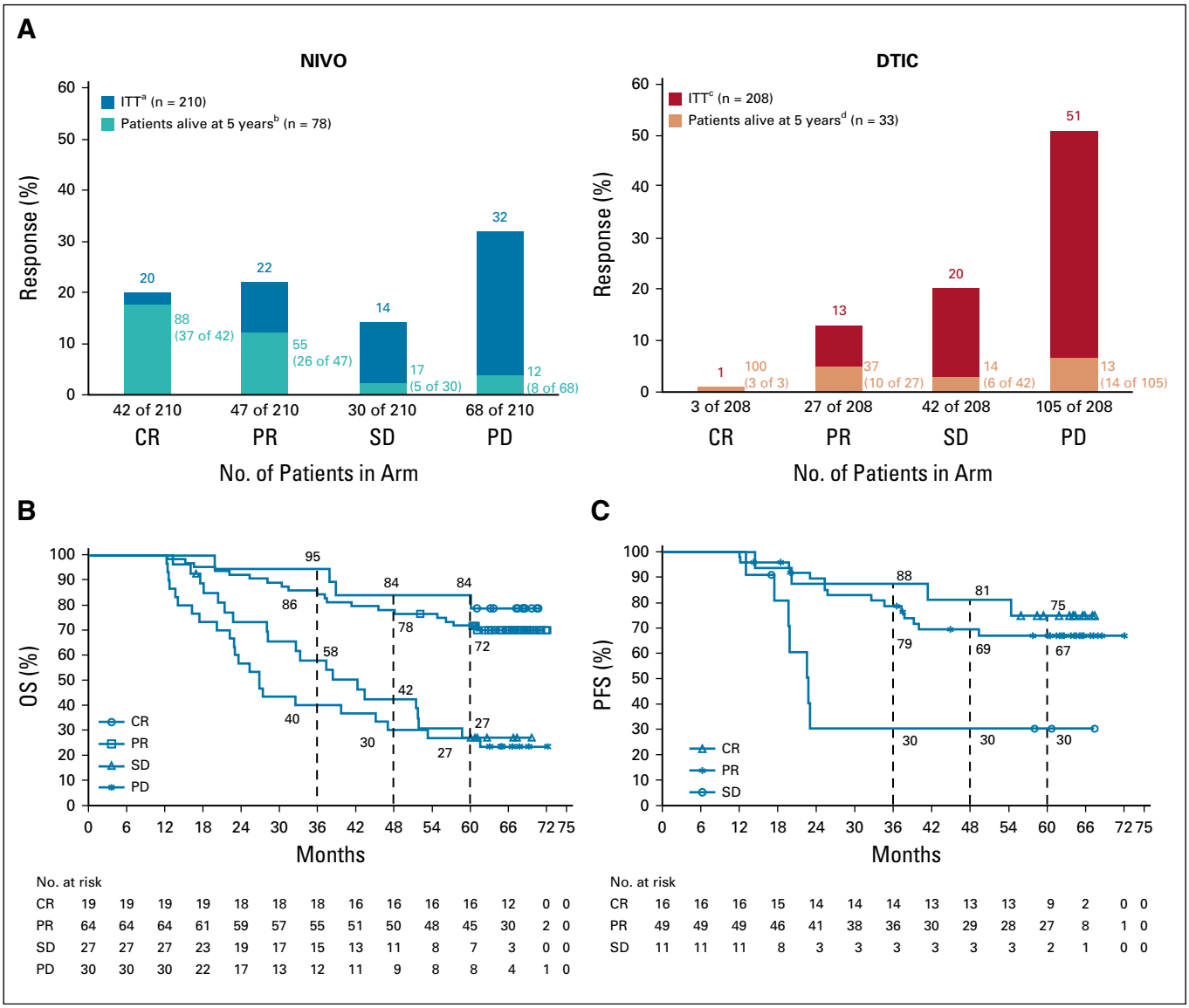

FIG 4. (A) Response to treatment in all patients and proportion alive at 5 years of follow-up and Kaplan-Meier plots of (B) overall survival (OS) and (C) progression-free survival (PFS) from landmark 12-month analyses by individual response in patients on nivolumab (NIVO). Median survival time was not reached (NR) in patients with a complete response (CR) or partial response (PR), 42.4 months (95% CI, 28.19 to 52.01 months) in patients with stable disease (SD), and 26.9 months (95% CI, 22.34 to 47.11 months) in patients with progressive disease (PD). Median time to progression or death was NR (95% CI, 54.44 months to NR) in patients with a CR, NR in patients with a PR, and 22.8 months (95% CI, 17.51 months to NR) in patients with SD. [a]Intention to treat (ITT; NIVO): objective response rate (ORR), 42%; response in patients not evaluable, 23 (11%) of 210. [b]Patients alive at 5 years (NIVO): ORR, 80%; response in patients not evaluable, two (3%) of 78. [c]ITT (DTIC): ORR, 14%; response in patients not evaluable, 31 (15%) of 208. [d]Patients alive at 5 years (DTIC): ORR, 39%; response in patients not evaluable, zero of 33.

Among all patients, the ORR was 42% with nivolumab (89 of 210 patients) and 14% with dacarbazine (30 of 208 patients; Table 1). Median time to an objective response was 2.1 months (range, 1.2-26.7 months) with nivolumab and 2.2 months (range, 1.8-12.9 months) with dacarbazine; median duration of response was not reached (95% CI, 47.2 months to not reached) and 6 months (95% CI, 3.9 to 30.4 months), respectively. In the nivolumab group, 27 (30%) of 89 patients had a response ≥ 60 months; no responder in the dacarbazine group had a duration of response ≥ 5 years. In patients alive at 5 years of follow-up, the ORR was 81% with nivolumab (63 of 78 patients) and 39% with dacarbazine (13 of 33 patients). In patients alive at 5 years who did not receive subsequent systemic therapy, the ORR was 92% for nivolumab (48 of 52 patients), with 56% of patients (29 of 52) having a complete response (CR). For dacarbazine, only two patients (both with a CR) were alive at 5 years and did not receive any subsequent treatment. In all patients randomly assigned to nivolumab, 42 (20%) of 210 had a best response of CR and 37 (88%)

of those 42 patients were alive at 5 years; 55% of the patients with a PR (26 of 47) were alive at 5 years (Fig 4A). OS and PFS were also investigated in a landmark 12-month analysis in the nivolumab group according to individual response. The 5-year OS rate was 84% in patients with a CR, 72% in patients with a partial response (PR), 27% in patients with stable disease (SD), and 27% in patients with progressive disease (Fig 4B). Five-year PFS rates were 75%, 67%, and 30% in patients with a CR, PR, or SD, respectively (Fig 4C).

Survival was also analyzed according to subsequent therapy use (Data Supplement). In 71 patients randomly assigned to nivolumab who received subsequent therapy that included ipilimumab, the 5-year OS rate was 13%. For patients initially randomly assigned to dacarbazine who received subsequent therapy that included nivolumab (37 patients; 18%), the 5-year OS rate was 38%; for dacarbazine patients who received subsequent therapy that included ipilimumab, the 5-year OS rate was 23%.

At the time of the 5-year analysis, 75 patients (36%) and 30 patients (15%) randomly assigned to nivolumab and dacarbazine, respectively, were alive and still being followed in the study (Data Supplement). Of the 75 nivolumab-treated patients alive and being followed at 5 years, 62 (83%) had not yet received subsequent therapy: 17 (23%) were still on study therapy and 45 (60%) were treatment free (off study therapy without having received subsequent systemic therapy). In addition, at the time of the analysis, 55 nivolumab-treated patients and five dacarbazine-treated patients who were alive at 5 years and were still being followed had not progressed (Data Supplement). Of the 55 nivolumab-treated patients, 96% had not yet received subsequent therapy, which comprised 74% who were treatment free and 22% who were still on study therapy.

Safety

In this long-term analysis, safety analyses were similar to previous reports.[7,8] Grade 3/4 treatment-related AEs were reported in 16% and 18% of nivolumab- and dacarbazine-treated patients, respectively; grade 3/4 treatment-related AEs that led to discontinuation were reported in 5% and 2% of patients, respectively (Data Supplement). Of patients on treatment for ≥ 3 years, 21 (50%) of 42 in the nivolumab group reported treatment-related AEs at 5 years that were not reported at the 3-year analysis; treatment-related AEs reported in > 2% of patients were fatigue (n = 3), increased amylase (n = 2), increased lipase (n = 2), and pruritus (n = 2; Data Supplement). In patients who experienced nivolumab-related vitiligo (n = 34), the ORR was 71%; the one patient with vitiligo in the dacarbazine arm had a PR. There were no treatment-related deaths in either treatment group since the previous analysis.

DISCUSSION

This 5-year survival analysis from the seminal phase III Checkmate 066 trial showed a continued substantial benefit for nivolumab versus dacarbazine in patients with *BRAF* wild-type advanced melanoma, with a 50% reduction in the hazard of death (HR, 0.5; 95% CI, 0.40 to 0.63; $P < .0001$) and a 60% reduction in the hazard of progression or death (HR, 0.4; 95% CI, 0.33 to 0.54; $P < .0001$). The first data analysis largely replaced dacarbazine with nivolumab as a first-line treatment option for these patients, showing an unprecedented benefit in favor of nivolumab with a 58% reduction in the hazard of death with nivolumab versus dacarbazine (HR, 0.42; 99.79% CI, 0.25 to 0.73; $P < .001$).[7] The 3-year analysis showed a similar benefit, with a 54% reduction in the hazard of death (HR, 0.46; 95% CI, 0.36 to 0.59; $P < .001$).[8]

Results of this long-term analysis, including the RMST analysis difference of 14.3 months, confirm the impressive clinical advantages, including long-term OS conferred by therapy with nivolumab versus dacarbazine. Of note, subsequent treatment that included nivolumab among patients initially treated with dacarbazine was associated with a median OS similar to that of nivolumab-treated patients in the total population (35.9 months [95% CI, 25.0 months to not reached] and 37.3 months [95% CI, 25.4 to 51.6 months], respectively). However, obvious selection bias precludes a strict comparison between the patient populations, and patients in the dacarbazine arm must have survived long enough to access nivolumab, a good prognostic marker in itself.

These 5-year survival results align with those recently reported for the CheckMate 067 trial that investigated nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in patients with treatment-naive advanced melanoma.[2,3,10] In the subgroup of patients in CheckMate 067 with *BRAF* wild-type melanoma treated with nivolumab monotherapy, 5-year OS and PFS rates were 43% and 32%, respectively, which is comparable to the 39% and 28% rates reported here. In the phase I KEYNOTE-001 study, in a mixed population of patients with *BRAF* wild-type and mutant melanoma, the 5-year OS and PFS rates for treatment-naive patients who received pembrolizumab was 41% and 29%, respectively.[10] In the phase III KEYNOTE-006 study, the 5-year OS rate for treatment-naive patients who received pembrolizumab was 43% (no PFS was reported).[3] When an anti–PD-1 agent is combined with ipilimumab, as in CheckMate 067, a numerically greater survival benefit (52% at 5 years) was observed but with increased toxicity to some patients.[2,5,11,12] Thus, it would be critically useful to have reliable predictive parameters to guide patient selection, but to date, this has not been the case.

These 5-year analyses reinforce the efficacy of nivolumab across all patient subgroups. OS and PFS were similarly

reduced in patients with LDH > ULN in both the nivolumab and the dacarbazine groups, suggesting that LDH is more of a prognostic factor than a predictive factor for both agents. In contrast, both OS and PFS rates were higher in patients with PD-L1 expression ≥ 5% *v* < 5% who were treated with nivolumab but not dacarbazine, suggesting that PD-L1 may have some effect on clinical outcomes with nivolumab but not with dacarbazine. Despite this, those with PD-L1 < 5% still benefited more from nivolumab compared with dacarbazine.

An important attribute of treatment with immune checkpoint inhibitors is the opportunity for patients to remain progression free after therapy discontinuation. This is a major advantage over other melanoma treatment options, such as *BRAF*-targeted therapy, where patients have a higher risk of relapse after discontinuing compared with this trial and other studies of anti–PD-1 monotherapy.[13] Recent results of the Checkmate 067 trial conducted in patients alive and still in follow-up at 5 years showed that 74% of patients treated with nivolumab plus ipilimumab and 58% treated with nivolumab alone were treatment free. It is noteworthy that in the combination arm, the most frequent reason for stopping treatment in the total population was toxicity (44% *v* 14% in the nivolumab arm).[2] In the current study, 60% of patients (45 of 75) treated with nivolumab were alive and being followed at 5 years treatment free and 9% of patients in the total population discontinued treatment because of toxicity, consistent with the nivolumab results from CheckMate 067; moreover, 41 (91%) of those 45 patients had not experienced progression. Although the CheckMate 066 study did not include a plan to stop nivolumab after confirmed CR, 16 patients were reported to have discontinued treatment because of maximum clinical benefit. In addition, among the 78 patients alive at 5 years, 37 (47%) had a CR as best response, with 29 (78%) of 37 never having received subsequent systemic therapy. On the basis of our collective clinical experience, it is possible that some patients with a durable CR could be cured of their metastatic melanoma. Currently, there are ongoing studies that are examining the role of cessation of anti–PD-1 therapy at response versus continuation to 2 years.[14]

The results here show that the probability of being alive at 5 years depends on the type of response achieved: Those with CR do better than those with PR long term, the former making up a near majority of patients alive at 5 years (47%). Long-term survival without subsequent therapy might also be explained by misclassified patients. Indeed, in our clinical experience and as supported by reports in the published literature, it is possible that response in some patients will be classified as a PR when it is actually a CR (ie, if RECIST continued to detect target lesions that were nonviable sequelae of previous metastases).[15] This is only a potential hypothesis and not an observation that has been documented in this study. Fluorodeoxyglucose positron emission tomography and/or pathologic verification can be useful in detecting true CRs.[16,17] A related phenomenon has been demonstrated in the context of neoadjuvant immunotherapy given for short durations, with significant pathologic responses observed in tumors that did not significantly decrease in size according to RECIST version 1.1.[18]

The 5-year results of CheckMate 066 presented here add to the growing body of evidence supporting long-term survival with PD-1 inhibitors. Such long-term survival seems associated with achieving a durable response to treatment and can be maintained after treatment discontinuation (even without subsequent systemic therapies) and without new long-term safety concerns. Future studies that investigate predictive parameters to identify patients who may achieve treatment-free status are warranted.

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Five-Year Outcomes With Nivolumab in Patients With Wild-Type *BRAF* Advanced Melanoma

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