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ORIGINAL REPORT

Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial

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ABSTRACT

Purpose

Until recently, limited options existed for patients with advanced melanoma who experienced disease progression while receiving treatment with ipilimumab. Here, we report the coprimary overall survival (OS) end point of CheckMate 037, which has previously shown that nivolumab resulted in more patients achieving an objective response compared with chemotherapy regimens in ipilimumab-refractory patients with advanced melanoma.

Patients and Methods

Patients were stratified by programmed death-ligand 1 expression, *BRAF* status, and best prior cytotoxic T-lymphocyte antigen-4 therapy response, then randomly assigned 2:1 to nivolumab 3 mg/kg intravenously every 2 weeks or investigator's choice chemotherapy (ICC; dacarbazine 1,000 mg/m^2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m^2 every 3 weeks). Patients were treated until they experienced progression or unacceptable toxicity, with follow-up of approximately 2 years.

Results

Two hundred seventy-two patients were randomly assigned to nivolumab (99% treated) and 133 to ICC (77% treated). More nivolumab-treated patients had brain metastases (20% *v* 14%) and increased lactate dehydrogenase levels (52% *v* 38%) at baseline; 41% of patients treated with ICC versus 11% of patients treated with nivolumab received anti–programmed death 1 agents after randomly assigned therapy. Median OS was 16 months for nivolumab versus 14 months for ICC (hazard ratio, 0.95; 95.54% CI, 0.73 to 1.24); median progression-free survival was 3.1 months versus 3.7 months, respectively (hazard ratio, 1.0; 95.1% CI, 0.78 to 1.436). Overall response rate (27% *v* 10%) and median duration of response (32 months *v* 13 months) were notably higher for nivolumab versus ICC. Fewer grade 3 and 4 treatment-related adverse events were observed in patients on nivolumab (14% *v* 34%).

Conclusion

Nivolumab demonstrated higher, more durable responses but no difference in survival compared with ICC. OS should be interpreted with caution as it was likely impacted by an increased dropout rate before treatment, which led to crossover therapy in the ICC group, and by an increased proportion of patients in the nivolumab group with poor prognostic factors.

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INTRODUCTION

There have been major advances in the treatment of advanced melanoma, with the development of agents that have changed clinical practice.[1,2] Ipilimumab, an antibody to cytotoxic T-lymphocyte-associated-antigen-4 (CTLA-4), was the first therapy to demonstrate a survival improvement in metastatic melanoma in a phase III randomized clinical trial[3,4]; however, more than one half of patients do not derive benefit from ipilimumab.[5] The combination of mitogen-activated protein kinase pathway inhibitors, including

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vemurafenib and cobimetinib, or dabrafenib and trametinib, is associated with a high response rate and increased survival compared with chemotherapy[6,7]; however, the use of BRAF inhibitors is restricted to approximately 50% of patients with melanoma who harbor *BRAF*^{V600} mutations, and most patients develop resistance to these inhibitors.[6,8] Treatment options are needed when disease progression occurs with ipilimumab and BRAF inhibitor–based therapy. CheckMate 037 investigated treatments in patients with advanced melanoma who experienced progression on ipilimumab and a BRAF inhibitor (if *BRAF* mutated). At trial initiation, ipilimumab and vemurafenib were the only approved agents for the treatment of advanced melanoma that had demonstrated prolongation of overall survival (OS) in phase III registration studies,[3,9] and no single chemotherapeutic agents were considered a standard of care for second-line therapy.

Nivolumab, a human IgG4 monoclonal antibody, inhibits the programmed death 1 (PD-1) immune checkpoint protein.[10] Nivolumab and another PD-1 inhibitor, pembrolizumab, have shown increased efficacy compared with ipilimumab in metastatic melanoma[11,12] and have now been approved for treatment. Combination nivolumab plus ipilimumab is also approved for metastatic melanoma and has demonstrated an unprecedented 2-year OS rate of 63.8%.[13]

Here, we report updated results of the phase III, randomized, open-label study, CheckMate 037, which previously demonstrated that nivolumab resulted in more patients achieving an objective response compared with chemotherapy in patients with metastatic melanoma who experienced progression after treatment with ipilimumab (plus a BRAF inhibitor, if *BRAF*-mutation positive).[14] The coprimary end point of OS is presented here, as well as updated results for objective response rate (ORR), progression-free survival (PFS), and safety.

PATIENTS AND METHODS

Eligibility Criteria

Patients were at least age 18 years with histologically confirmed, unresectable stage IIIC or IV metastatic melanoma and Eastern Cooperative Oncology Group performance status 0 or 1.[14] Patients with *BRAF* wild-type metastatic melanoma must have experienced progression after treatment with anti–CTLA-4, and patients with *BRAF*^{V600} mutation must have experienced progression after treatment with anti–CTLA-4 and a BRAF inhibitor. Key exclusion criteria included active brain metastases; prior treatment with anti–PD-1, anti–programmed death ligand 1 (PD-L1), or anti–PD-L2; grade 4 toxicity or use of infliximab during previous ipilimumab treatment; and primary ocular melanoma.[14]

Study Design and Treatment

The study design and treatments have been previously described.[14] In this randomized, controlled, open-label phase III trial, patients were randomly assigned 2:1 to nivolumab 3 mg/kg intravenously every 2 weeks or investigator's choice chemotherapy (ICC), which consisted of dacarbazine 1,000 mg/m^2 every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m^2 every 3 weeks. This was an open-label design study because the different toxicity profiles of the comparators made the study infeasible to blind. Patients were stratified by PD-L1 expression, *BRAF* status, and best response to prior CTLA-4 therapy, and were treated until progression or unacceptable toxicity. Patients who experienced clinical benefit and who tolerated nivolumab were allowed to continue beyond progression per investigator.

Coprimary end points were the proportion of patients who achieved an objective response per independent radiologic review committee and OS comparison of nivolumab versus ICC. Secondary end points included PFS comparison per independent radiologic review committee assessment, evaluation of PD-L1 expression as a predictive biomarker for ORR and OS, and evaluation of health-related quality of life as assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). Exploratory objectives included assessment of overall safety and tolerability as well as changes in health status by the European Quality of Life-5 Dimensions (EuroQoL EQ-5D).

The study protocol was approved by institutional review boards of the participating centers and performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Written patient consent was obtained before the start of the study and a data monitoring committee was established for oversight.

Efficacy and Safety Assessments

Tumor response and progression were assessed by using Response Evaluation Criteria in Solid Tumors (v1.1; RECIST).[15] Radiographic assessments were performed at baseline and week 9 after random assignment, every 6 weeks for the first year, and then every 12 weeks until disease progression, death, or study withdrawal. End point definitions are available in the Data Supplement. PD-L1 expression was measured via PD-L1 immunohistochemistry assay (Dako, Burlingame, CA) as previously described.[16]

Deaths, adverse events (AEs), serious AEs, AEs that led to discontinuation, and select AEs—with time to onset and resolution—are summarized for all treated patients. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Health-related quality of life was assessed at baseline, every cycle (ICC), or every other cycle (nivolumab) for the first 6 months, then every 6 weeks and at follow-up and survival visits; assessments were EORTC QLQ-C30 version 3[17] and EuroQoL EQ-5D summary index and visual analog scale.[18]

Statistical Analysis

Efficacy end points were based on the intent-to-treat population. Approximately 390 patients were to be randomly assigned with an α allocation of 0.1% and OS with an α allocation of 4.9%. At least 260 deaths were required to provide 90% power to detect a hazard ratio (HR) of 0.65 with an overall two-sided type I error of 4.9%; 263 deaths occurred by the database lock. Final OS α boundary was 0.0446 (or adjusted 95.54% CI) for OS and 0.049 for PFS when OS was statistically significant. Time-to-event distribution—PFS, time to response, duration of response—was estimated by using the Kaplan-Meier technique. Median and 95% CIs were estimated on the basis of the Brookmeyer and Crowley methodology. Rates at fixed time points were derived from the Kaplan-Meier estimate along with their corresponding transformed 95% CIs. CIs for binomial proportions were derived by using the Clopper-Pearson method.

RESULTS

Patients and Treatment

From December 21, 2012, to January 10, 2014, 631 patients were enrolled from 90 sites in 14 countries; 405 patients were randomly assigned, with 268 treated in the nivolumab group and 102 in the ICC group (Fig 1). A higher proportion of patients who were randomly assigned to ICC did not receive treatment compared with patients who were randomly assigned to nivolumab (23% *v* 2%; Fig 1 and Data Supplement). Patient demographics have been reported[14] and were generally balanced, with the exception

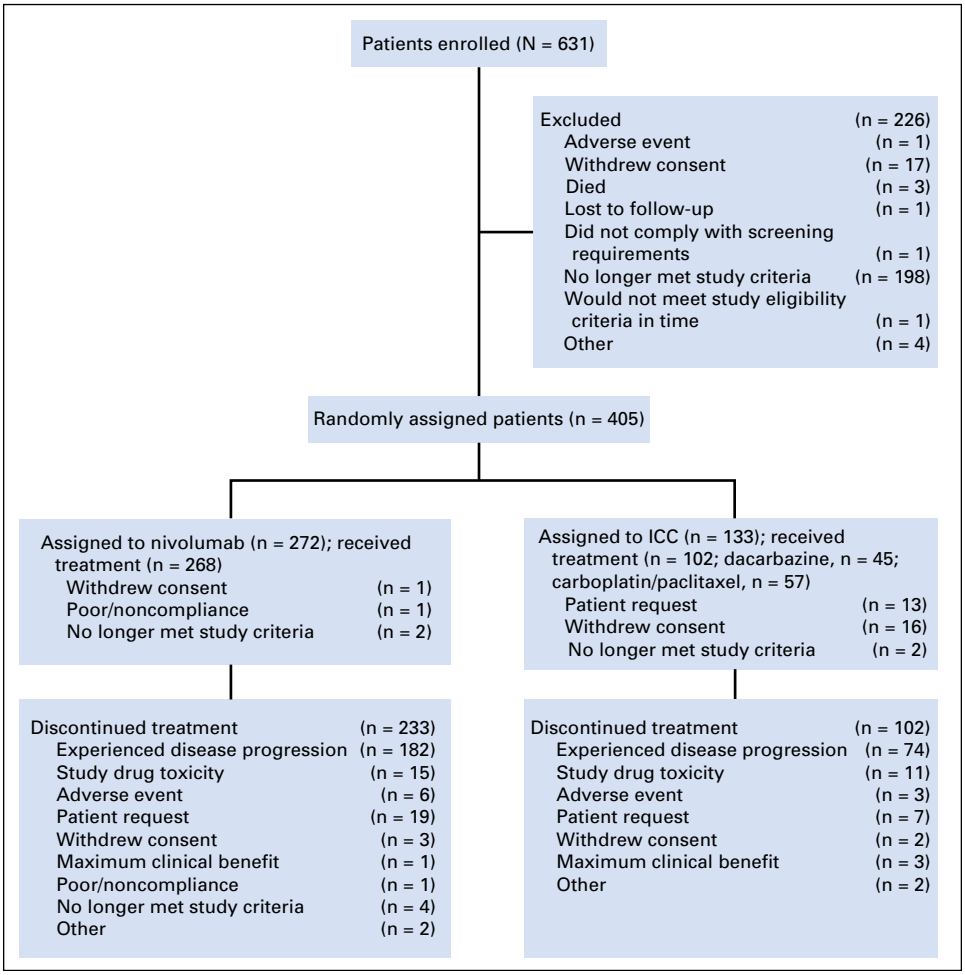

Fig 1. Trial design. ICC, investigator's choice chemotherapy.

that a larger proportion of patients on nivolumab versus ICC had brain metastases (20% *v* 14%) and increased lactate dehydrogenase levels (52% *v* 38%; Table 1).

With a database lock of March 29, 2016, and follow-up of approximately 2 years, median duration of therapy was 4.7 months (95% CI, 3.3 to 6.0) for nivolumab and 2.0 months (95% CI, 1.6 to 2.8) for ICC. More patients received systemic therapy after randomly assigned therapy in the ICC arm (83 [62%] of 133) compared with the nivolumab arm (109 [40%] of 272; Data Supplement). Specifically, anti–PD-1 therapy was administered to 54 (41%) of 133 patients in the ICC group versus 29 (11%) of 272 patients in the nivolumab group, and ipilimumab to 14 (11%) and 13 (5%) patients in the ICC and nivolumab groups, respectively (Data Supplement). As case report forms for this study did not adequately capture all post–random assignment/poststudy therapy, the 41% of patients in the ICC arm who received anti–PD-1 therapy is likely underestimated.

Efficacy

In the randomly assigned population, median OS was 15.7 months (95% CI, 12.9 to 19.9) for the nivolumab group versus 14.4 months (95% CI, 11.7 to 18.2) for ICC (HR, 0.95; 95.54% CI, 0.73 to 1.24; Fig 2A). Survival rates at 1 year were 58.9% (95% CI, 52.8% to 64.5%) in the nivolumab group and 55.1% (95% CI, 46.1% to 63.3%) for ICC; 2-year rates were 38.7% (95% CI, 32.8% to 44.5%) and 33.9% (95% CI, 25.8% to 42.1%), respectively. Nivolumab had a higher rate of death compared with ICC in the first 3 months, which may be a result of group imbalance in poor prognostic factors. A multivariable analysis demonstrated that Eastern Cooperative Oncology Group performance status (HR, 0.64; 95% CI, 0.49 to 0.83; 0 *v* 1), brain metastases (HR, 0.61; 95% CI, 0.45 to 0.83; no *v* yes), and elevated lactate dehydrogenase (HR, 0.60; 95% CI, 0.46 to 0.78; $\leq$ upper limit of normal *v* $>$ upper limit of normal) were all associated with shorter survival, and there were more patients in the nivolumab group for two of these three factors. No notable differences in OS were observed in prespecified subgroup analysis, although an HR of $>$ 1.10 was observed for patients with *BRAF* mutation, those younger than 65 years, those with a history of brain metastases, and those with PD-L1 expression $<$ 5% (Data Supplement).

Given the higher number of ICC patients who received subsequent systemic treatment, OS was investigated in a sensitivity analysis by censoring at the start of the PD-1/PD-L1 therapy that was received after assigned therapy in the ICC group. In contrast to the main OS analysis, this assessment was performed only in the treated patient population. With the recognition of possible selection bias in these patients, an OS difference was observed with a median OS of 16.4 months (95% CI, 12.9 to 20.3) for the nivolumab group and 11.8 months (95% CI, 9.9 to 14.4) for the ICC group (HR, 0.81; 95% CI, 0.59 to 1.1; Fig 2B).

Table 1. Baseline Characteristics of Patients

Characteristic	Nivolumab (n = 272)	ICC (n = 133)
Age, median (range), years	59 (23-88)	62 (29-85)
Sex		
Male	176 (65)	85 (64)
Female	96 (35)	48 (36)
ECOG performance status		
0	162 (60)	84 (63)
1	110 (40)	48 (36)
Stage M1c at study entry	203 (75)	102 (77)
AJCC stage IV at study entry	261 (96)	131 (99)
History of brain metastases	55 (20)	18 (14)
Lactate dehydrogenase > ULN	140 (52)	51 (38)
Pretreatment PD-L1 positive (5% cutoff)	134 (49)	67 (50)
BRAF mutant	60 (22)	29 (22)
No prior anti–CTLA-4 benefit	173 (64)	86 (65)
No. of previous systemic treatments		
1	76 (28)	34 (26)
2	139 (51)	68 (51)
> 2	57 (21)	31 (23)

NOTE. Data are presented as No. (%) unless otherwise noted. Adapted from Weber et al,[14] with permission from Elsevier.

Abbreviations: AJCC, American Joint Committee on Cancer; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; ICC, investigator's choice chemotherapy; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

Both ORR and median duration of response in the updated results were notably higher for nivolumab versus ICC at 27% versus 10% and 32 months versus 13 months, respectively (Table 2). Results were similar to those observed in the previous analysis, although duration of response was now reached for the nivolumab group; however, time to response for nivolumab versus ICC is similar at 2.2 months versus 2.1 months currently and 2.1 months versus 3.5 months previously.[14] In addition, nivolumab demonstrated more durable responses than did ICC; 69% of responses in the nivolumab group compared with 62% in the ICC group were ongoing at the end of the study period for individual patients (Fig 3). There was no improvement in PFS for nivolumab compared with ICC; median PFS was 3.1 months (95% CI, 2.3 to 3.5) for nivolumab versus 3.7 months (95% CI, 2.3 to 5.3) for ICC (HR, 1.0; 95.1% CI, 0.78 to 1.436; Fig 4), which was decreased compared with the earlier analysis that reported median PFS at 4.7 months (95% CI, 2.3 to 6.5) versus 4.2 months (95% CI, 2.1 to 6.3).[14]

There were more patients in the nivolumab group who had quantifiable PD-L1 expression data (248 [91%] of 272 patients) compared with the ICC group (99 [74%] of 133 patients). In all PD-L1 expression subgroups tested, ORR was numerically higher for the nivolumab group relative to the ICC group (Data Supplement). In addition, a similar ORR was observed with ICC in all subgroups, whereas ORR increased with increasing PD-L1 expression in the nivolumab group. In a post hoc analysis that explored the association between response and the expression of PD-L1 across the continuum of expression (0% to 100%), no optimal threshold for PD-L1 expression was identified that could be used to select patients for nivolumab treatment.

Safety

Any-grade, treatment-related AEs occurred in 77% and 82% of patients in the nivolumab and ICC groups, respectively, including grade 3 and 4 AEs (14% and 34%, respectively; Table 3). The most common treatment-related AE in both groups was fatigue at 32% for nivolumab and 39% for ICC; AEs were similar to those reported previously.[14] Any-grade, treatment-related AEs led to discontinuation in 5% of patients treated with nivolumab and 11% with ICC. Treatment-related AEs that led to discontinuation in two or more patients were increased ALT and pancreatitis (two patients each) in the nivolumab group and peripheral neuropathy (three patients), arthralgia (two patients), anemia (two patients), and thrombocytopenia (two patients) in the ICC group.

The most common treatment-related select AEs—AEs with a potential immunologic cause—in the nivolumab group were skin (38%) followed by GI (18%) and hepatic (11%; Data Supplement), as opposed to the previous analysis in which the third most common AE was endocrine (7.8%).[14] Time to onset for patients with select AEs in the nivolumab group was shortest for hypersensitivity at

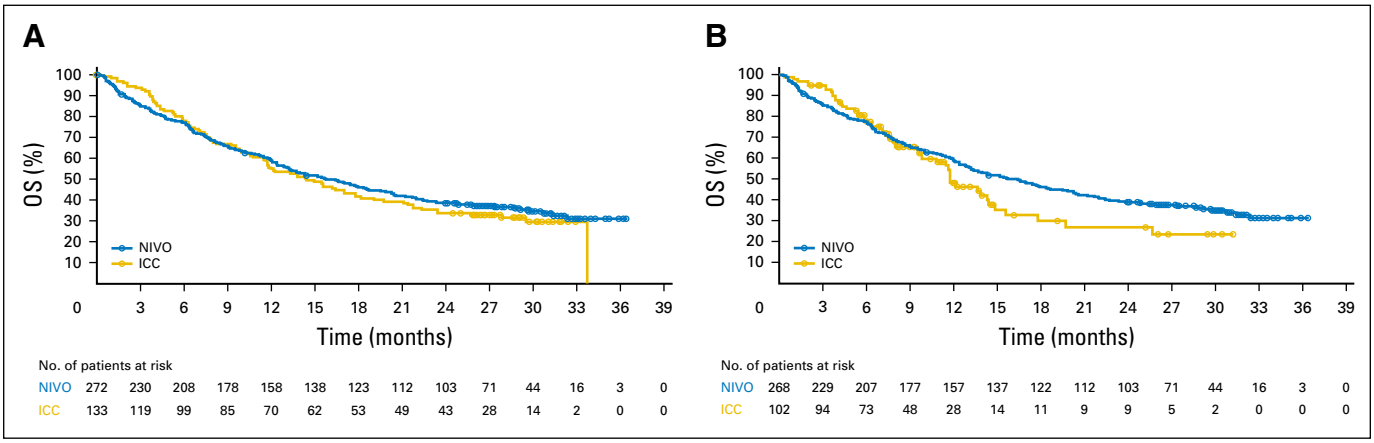

Fig 2. (A and B) Overall survival (OS) in all randomly assigned patients and OS censoring at the start of programmed death 1 (PD-1) or programmed death-ligand 1 (PD-L1) agent after assigned therapy in investigator's choice chemotherapy (ICC). (A) Kaplan-Meier curves for OS in all randomly assigned patients. Median OS was 15.7 months (95% CI, 12.9 to 19.9) in the nivolumab (NIVO) group and 14.4 months (95% CI, 11.7 to 18.2) in the ICC group (hazard ratio for death, 0.95; 95.54% CI, 0.73 to 1.24; $P = .716$). (B) Kaplan-Meier curves for OS in all treated patients censoring at the start of PD-1 or PD-L1 agent after assigned therapy in ICC. Median OS was 16.4 months (95% CI, 12.9 to 20.3) in the NIVO group and 11.8 months (95% CI, 9.9 to 14.4) in the ICC group (hazard ratio for death, 0.81; 95.54% CI, 0.59 to 1.11).

Table 2. Response to Treatment via IRRC Analysis

Response	IRRC	
	Nivolumab (n = 272)	ICC (n = 133)
Best overall response,* No. (%)		
Complete response	17 (6)	1 (1)
Partial response	57 (21)	12 (9)
Stable disease	55 (20)	37 (28)
Progressive disease	113 (42)	36 (27)
Unable to determine	30 (11)	47 (35)
Objective response†		
No. of patients (%; 95% CI)	74 (27; 22 to 33)	13 (10; 5 to 16)
Difference in ORR (95% CI)	17 (10 to 24)	
Median time to objective response (95% CI), months	2.2 (1.4 to 7.4)	2.1 (1.9 to 5.1)
Median duration of response (95% CI), months	31.9 (25.9 to 31.9)	12.8 (3.0 to NR)

Abbreviations: ICC, investigator's choice chemotherapy; IRRC, independent radiologic review committee; NR, not reached; ORR, overall response rate.
*RECIST v1.1.
†Complete response plus partial response.

4.1 weeks, followed by skin at 6.1 weeks; a range of 46% to 86% of patients resolved, with the shortest time to resolution being 0.1 weeks for hypersensitivity and the longest being 29.1 weeks for endocrine AEs (Data Supplement). Although categorized as resolved, most patients with endocrine AEs continued to receive hormone therapy. Overall, 137 (51%) patients in the nivolumab group and 35 (34%) patients in the ICC group were managed with immune-modulating agents, the most common being topical corticosteroids (24% and 5%, respectively) and systemic corticosteroids (36% and 20%, respectively).

A total of 244 patients died during the study within 30 days of the last dose: 172 (64%) in the nivolumab group and 72 (71%) in the ICC group. Most deaths—165 of (96%) 172 and 69 of (96%) 72, respectively—were a result of disease progression.

Quality of Life

Quality of life in patients on nivolumab remained unchanged for all EORTC QLQ-C30 individual scales during the treatment course, with no score reaching minimal important difference (≥ 10 points). EORTC QLQ-C30 Global Health Status changes from baseline are shown in the Data Supplement. No clinically significant improvement was observed for either the EuroQoL EQ-5D utility index or the EuroQoL EQ-5D visual analog scale for nivolumab. At 12 weeks, the ICC group demonstrated a clinically significant decrease in the EuroQoL EQ-5D utility index.

DISCUSSION

Here, we report OS in nivolumab-treated patients with metastatic melanoma who experienced progression after treatment with ipilimumab (plus a BRAF inhibitor, if *BRAF*-mutation positive). Consistent with the initial report, the proportion of patients who achieved an objective response was higher for nivolumab than for ICC and responses were more durable.[14] Responses were also consistent with those observed with pembrolizumab treatment in a similar patient population[19]; however, no survival or PFS difference was observed for nivolumab compared with ICC. The safety profile of nivolumab versus ICC was consistent with the original findings, with less toxicity observed for nivolumab compared with ICC.[14] The majority of nivolumab treatment-related AEs were low grade and manageable using recommended treatment algorithms. Grade 3 and 4 treatment-related AEs were reported in 31% of ICC patients compared with 14% of nivolumab-treated patients.

In patients with advanced melanoma who have experienced progression on ipilimumab and a BRAF inhibitor (if *BRAF* mutated), both nivolumab and pembrolizumab have shown ORR benefit over ICC.[14,19] Median pembrolizumab OS was reported at 13.4 months (95% CI, 11.0 to 16.4) for 2 mg/kg, which did not achieve a significant difference compared with chemotherapy.[20] Median OS reported in the current study was higher for both nivolumab and ICC at 15.7 months and 14.4 months, respectively, and was not statistically different, similar to the pembrolizumab study.

The standard of care for melanoma in many countries has evolved since trial initiation, with anti–PD-1 as monotherapy and

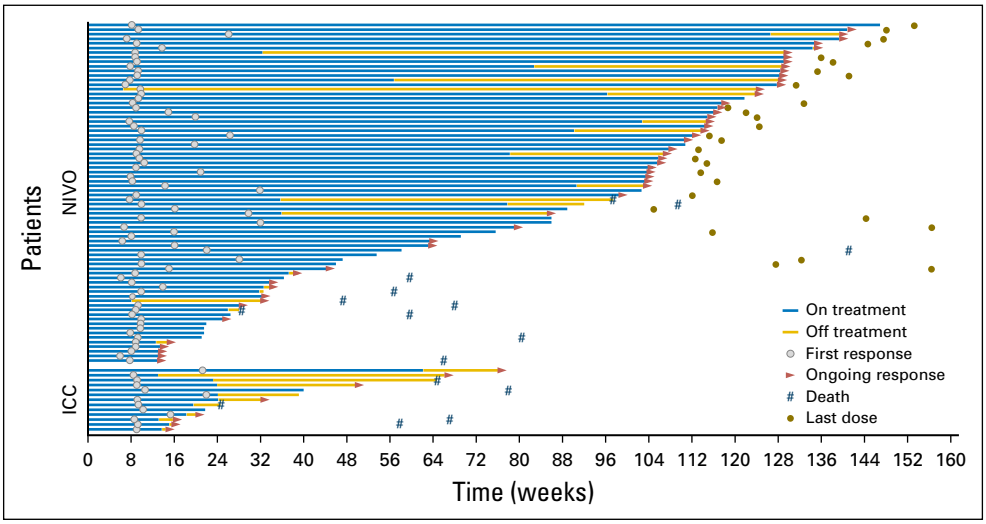

Fig 3. Duration of response per independent radiologic review committee. Swimmer plots show time to first response and duration of response, as defined by RECIST v1.1, for responders who received nivolumab (NIVO) or investigator's choice chemotherapy (ICC).

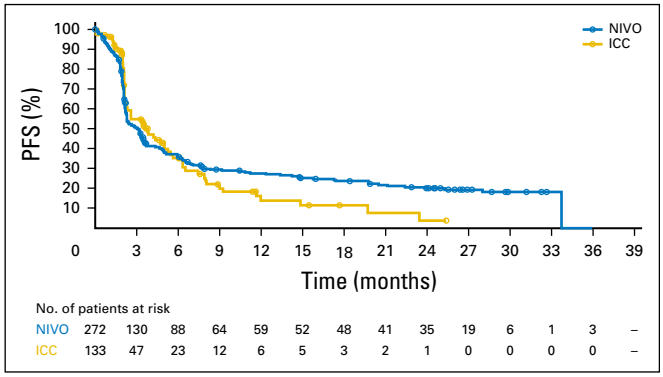

Fig 4. Progression-free survival (PFS) by independent radiologic review committee (IRRC) assessment. Kaplan-Meier curves for PFS in all randomly assigned patients by IRRC assessment. Median PFS was 3.1 months (95% CI, 2.3 to 3.5) in the nivolumab (NIVO) group and 3.7 (95% CI, 2.3 to 5.3) in the investigator's choice chemotherapy (ICC) group (hazard ratio for death or disease progression, 1.03; 95.1% CI, 0.78 to 1.436).

in combination with anti–CTLA-4 becoming first-line options, making first-line ipilimumab treatment obsolete. However, there are still cases in which treatment with ipilimumab is used for patients with advanced melanoma, particularly in areas of the world where anti–PD-1 therapy is not available as first-line therapy. In addition, because patients are living longer, second-line treatment after ipilimumab is important. Many patients treated with ipilimumab do not achieve a response, ultimately experience progression after treatment, or need to discontinue treatment because of immune-related toxicity.[21] In addition, approximately 50% of patients who are treated with BRAF and MEK inhibitors will experience progression as a result of mitogen-activated protein kinase resistance within 12 months of therapy.[22,23] These results, along with similar data with pembrolizumab, demonstrate that these patients can be treated effectively with anti–PD-1 therapy.

The current study showed that durable objective responses were achieved with nivolumab, but no survival difference. Several confounding factors likely impacted OS, which suggests that the results need to be interpreted with caution. A primary factor was the open-label design of the trial with crossover potential for patients to enter a PD-1/PD-L1 antibody trial or receive approved agents after experiencing progression in the ICC arm. Indeed, 41% of patients in the ICC group versus 11% in the nivolumab group received a subsequent anti–PD-1/PD-L1 agent. In patients who were treated, a numeric survival difference was observed between treatment groups with censoring at the start of anti–PD-1/PD-L1 treatment after assigned therapy in the ICC group; however, this was a sensitivity analysis and there is possible bias associated with these types of analyses. In addition, a high proportion of patients who were randomly assigned to ICC compared with those who were randomly assigned to nivolumab (23% *v* 1%) dropped out as soon as the random assignment occurred before receiving assigned chemotherapy treatments. Many of these patients went on to receive pembrolizumab in available phase I studies, which may have skewed the results.

Differences in patient population general health could also affect the survival curves. Two indicators of poor prognosis—brain metastases and elevated lactate dehydrogenase—were more frequent in the nivolumab group compared with the ICC group. In addition, systemic corticosteroids were used to manage immune-related AEs in 36% of patients in the nivolumab group. This may be attributed, in part, to the increased frequency of poor prognostic factors in this treatment group and may

Table 3. AEs

Event	Nivolumab (n = 268)		ICC (n = 102)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any AE	266 (99)	126 (47)	98 (96)	46 (45)
AEs leading to discontinuation	39 (15)	29 (11)	16 (16)	3 (3)
Treatment-related AEs leading to discontinuation	13 (5)	12 (4)	11 (11)	2 (2)
Treatment-related AEs in > 5% patients	206 (77)	37 (14)	84 (82)	35 (34)
Fatigue	86 (32)	3 (1)	40 (39)	4 (4)
Pruritus	59 (22)	0	1 (1)	0
Diarrhea	49 (18)	1 (< 1)	16 (16)	2 (2)
Rash	36 (13)	1 (< 1)	5 (5)	0
Nausea	33 (12)	0	38 (37)	2 (2)
Vitiligo	29 (11)	0	0	0
Arthralgia	22 (8)	0	13 (13)	1 (1)
Anemia	20 (8)	3 (1)	24 (24)	5 (5)
Increased AST	20 (8)	2 (1)	2 (2)	0
Hypothyroidism	19 (7)	0	0	0
Maculopapular rash	19 (7)	1 (< 1)	2 (2)	0
Decreased appetite	18 (7)	0	15 (15)	0
Increased ALT	16 (6)	3 (1)	1 (1)	0
Asthenia	15 (6)	0	7 (7)	0
Dry skin	15 (6)	0	0	0
Dyspnea	15 (6)	0	7 (7)	0
Pyrexia	14 (5)	0	5 (5)	1 (1)

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; ICC, investigator's choice chemotherapy.

have had a detrimental effect on efficacy in nivolumab-treated patients.

ORR of 10% and median PFS of 3.7 months for the ICC group are similar to a previous study of patients with advanced melanoma who experienced progression on dacarbazine and whose ORR was 11% and PFS was 17.9 weeks after treatment with carboplatin plus paclitaxel.[24] This consistency reinforces the impact of the increased ORR of 27% versus 10% for nivolumab compared with ICC in the current study.

In conclusion, although there were no survival differences between nivolumab and ICC treatments, nivolumab treatment after progression on ipilimumab with or without a BRAF inhibitor does provide a higher rate of response and more durable responses. Some situations may still exist that necessitate the use of ipilimumab as first-line therapy and nivolumab provides a safer option with a better maintained quality of life for patients who have experienced failure with prior systemic therapies compared with cytotoxic chemotherapy. The OS outcome may have been impacted by the increased dropout rate before treatment and increased systemic therapy received after assigned therapy in the ICC group, as well as an increased proportion of patients with poor prognostic factors in the nivolumab group. Despite the lack of survival advantage, nivolumab remains an effective option for PD-1 inhibitor–naive patients who experienced failure with ipilimumab and a BRAF inhibitor if *BRAF* mutated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: David Minor, Sandra D'Angelo, Jeffrey Weber
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