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Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Programmed cell death 1 (PD-1) is an inhibitory receptor expressed by activated T cells that downmodulates effector functions and limits the generation of immune memory. PD-1 blockade can mediate tumor regression in a substantial proportion of patients with melanoma, but it is not known whether this is associated with extended survival or maintenance of response after treatment is discontinued.

Patients and Methods
Patients with advanced melanoma (N = 107) enrolled between 2008 and 2012 received intravenous nivolumab in an outpatient setting every 2 weeks for up to 96 weeks and were observed for overall survival, long-term safety, and response duration after treatment discontinuation.

Results
Median overall survival in nivolumab-treated patients (62% with two to five prior systemic therapies) was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. Among 33 patients with objective tumor regressions (31%), the Kaplan-Meier estimated median response duration was 2 years. Seventeen patients discontinued therapy for reasons other than disease progression, and 12 (71%) of 17 maintained responses off-therapy for at least 16 weeks (range, 16 to 56+ weeks). Objective response and toxicity rates were similar to those reported previously; in an extended analysis of all 306 patients treated on this trial (including those with other cancer types), exposure-adjusted toxicity rates were not cumulative.

Conclusion
Overall survival following nivolumab treatment in patients with advanced treatment–refractory melanoma compares favorably with that in literature studies of similar patient populations. Responses were durable and persisted after drug discontinuation. Long-term safety was acceptable. Ongoing randomized clinical trials will further assess the impact of nivolumab therapy on overall survival in patients with metastatic melanoma.

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INTRODUCTION

Melanoma harbors one of the highest somatic mutation frequencies among human cancers.[1] Although the diversity of genetic alterations in melanoma creates challenges for targeted therapies, it provides a common denominator for immunotherapy, namely, the creation of tumor-specific antigens recognizable by the immune system. The adaptive immune system has powerful anticancer potential, with a broad capacity and exquisite specificity to respond to diverse tumor antigens. It also demonstrates considerable plasticity and a memory component, making immunotherapy unique among all cancer treatment modalities. Evidence suggests that a properly educated immune system can provide a self-perpetuating mechanism to eliminate or durably control melanoma and other cancers.[2] The clinical translation of cancer immunotherapy has recently accelerated as advances in molecular immunology have elucidated mechanistic pathways that subvert antitumor immunity. These include dysfunctional T-cell signaling,[3] suppressive regulatory cells,[4] and key "immune checkpoints" that regulate the outcome of lymphocyte engagement with antigen-presenting cells and tumor cells.[5,6] In

particular, immune checkpoints, which serve to downmodulate the intensity of adaptive immune responses and protect normal tissues from collateral damage, can be co-opted by cancer cells to evade immune attack, which provides a spectrum of potential new targets for cancer immunotherapy.

The recent clinical success of anti-CTLA-4 (CD152) (ipilimumab) in improving survival in patients with advanced melanoma was achieved by blocking a prototypical T-cell checkpoint. This innovation established a therapeutic role for targeting immune inhibitory receptors and ligands and fueled efforts to explore the clinical effects of inhibiting other molecules in the CD28 and B7 families.[7,8] Programmed cell death 1 (PD-1) is a key inhibitory receptor expressed by activated T and B cells. Its binding with programmed cell death ligand 1 (PD-L1 [B7-H1]) and PD-L2 (B7-DC), expressed on antigen-presenting cells and human cancers, delivers a negative signal to lymphocytes.[9-12] In the first-in-human study of the PD-1 immune checkpoint inhibitor nivolumab (BMS-936558, MDX-1106, ONO-4538), an acceptable safety profile and durable objective tumor regressions were observed in patients with advanced solid tumors, including melanoma.[13,14] On the basis of these findings, this study of a multidose nivolumab regimen was undertaken. We have reported preliminary findings showing that approximately 20% to 30% of patients with advanced treatment–refractory melanoma, non–small-cell lung cancer, or kidney cancer experienced objective tumor regressions.[15] We now report overall survival outcomes in patients with melanoma who received nivolumab. Response characteristics, including durability and persistence after treatment discontinuation, and the long-term safety profile are presented in patients with a minimum of 14 months and up to 4.3 years since treatment initiation.

PATIENTS AND METHODS

Study Design

This dose-escalation, cohort expansion study evaluated the antitumor activity and safety of nivolumab, a fully human immunoglobulin G4 monoclonal antibody blocking PD-1 in patients with advanced cancers, including melanoma and non–small-cell lung, kidney, colorectal, and castration-resistant prostate cancer. Study design and methods, including the protocol, amendments, and detailed statistical analysis plan, were previously published.[15] The study was approved by local institutional review boards, and all patients or their legal representatives gave written informed consent before enrollment. Nivolumab was administered intravenously once every 2 weeks in an outpatient setting in 8-week treatment cycles at 1, 3, or 10 mg/kg during dose escalation. After completion of dose escalation, each dose cohort was expanded to accrue approximately 16 patients with advanced melanoma. Following a 6.5-month hiatus for protocol amendment, additional melanoma cohorts randomly assigned to 0.1, 0.3, and 1.0 mg/kg were enrolled. In patients with melanoma receiving 0.1 or 0.3 mg/kg who had progressive disease, intrapatient dose escalation to 1.0 mg/kg was permitted. On the basis of observed objective responses, the protocol was further amended to evaluate overall survival.

Tumors were reassessed radiographically following each treatment cycle. Treatment continued up to 96 weeks (12 cycles), until patients experienced confirmed complete response, unacceptable toxicity, or progressive disease or until they withdrew consent. In clinically stable patients, treatment could be continued beyond initial disease progression pending subsequent confirmation of progression, consistent with proposed immune response criteria.[16] Patients with stable disease or an ongoing objective response (complete or partial) at the end of treatment were observed for up to 1 year and were offered re-treatment for 1 additional year if disease progressed.

Clinical and laboratory safety assessments were conducted on all treated patients at regular intervals during therapy and were reported up to 70 days following the last drug administration. Adverse event severity was graded on the basis of the National Cancer Institute's Common Terminology Criteria for Adverse Events, v3.0.[17]

Patients

Eligibility criteria have been previously described.[15] Patients with melanoma arising from any primary site, including ocular, were required to have measurable disease by RECIST (Response Evaluation Criteria in Solid Tumors) v1.0[18] with modification. Those with brain metastases were eligible if lesions had been treated and were clinically stable for at least 8 weeks. Patients must have received at least one but not more than five prior systemic cancer therapies. Those with a history of autoimmune disease, prior therapy with T-cell modulating antibodies (eg, anti–PD-1, anti–PD-L1, anti–CTLA-4), conditions requiring immunosuppression, chronic infections, or history of other invasive cancers within the previous 2 years were excluded.

Statistical Analysis

Baseline characteristics, response rates, adverse events, and survival results for all patients with melanoma (N = 107) are reported here as of March 5, 2013. Interim response rates for 94 patients and adverse events for 104 patients were previously reported as of February 2012.[15] Tumor measurements were collected by investigators, and individual best responses were centrally assessed by the sponsor per modified RECIST v1.0. Objective response and stable disease rates with CIs were estimated by using the Clopper-Pearson method. Time-to-event end points, including progression-free survival, overall survival, survival rates, and response duration, were estimated by using the Kaplan-Meier method, with CIs based on Greenwood's formula. Survival data were collected retrospectively. Progression-free survival estimates take into account all deaths, including four that occurred during the follow-up for survival. Adverse events were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1. Categories of select adverse events with potential immunologic etiologies, defined as adverse events that require more frequent monitoring or intervention with immune suppression or hormone replacement, were based on a prespecified list of MedDRA Terms (Data Supplement). An exposure-adjusted analysis of select adverse events that was based on the event rate per 100 person-years of nivolumab exposure was conducted for all 306 treated patients, including those with melanoma and non–small-cell lung, kidney, colorectal, and castration-resistant prostate cancer.[15]

RESULTS

Patient Characteristics

In all, 107 patients with melanoma initiated treatment with nivolumab from November 2008 through January 2012. Baseline characteristics are presented in the Data Supplement. Of note, 62% had received at least two prior systemic treatments for melanoma, 78% had a visceral metastatic lesion, and 36% had an increased lactate dehydrogenase level in the blood, a factor associated with adverse prognosis in patients with advanced melanoma.

Overall and Progression-Free Survival

We undertook a retrospective analysis of overall survival in patients with advanced melanoma receiving nivolumab that was based on preliminary findings of durable tumor regression in these patients.[15] All patients initiated treatment at least 14 months before this analysis. The estimated median overall survival was 16.8 months (95% CI, 12.5 to 31.6 months; Table 1 and Fig 1A). One- and 2-year survival

Table 1. Clinical Activity of Nivolumab in Melanoma by Dose Level

	ORR*			Duration of Response (weeks)†		Stable Disease ≥24 Weeks			PFS (months)		OS (months)	
Dose (mg/kg)	n/N	%	95% CI	Median	Individual Responses	n/N	%	95% CI	Median	95% CI	Median	95% CI
All doses	33/107	30.8	22.3 to 40.5	104	—	7/107	6.5	2.7 to 13.0	3.7	1.9 to 9.1	16.8	12.5 to 31.6
0.1‡	6/17	35.3	14.2 to 61.7	NR§	24.1, 24.1, 34.3, 44.1+, 48.1+, 48.7+	0	0	0	3.6	1.7 to 9.1	16.2	8.6 to NE
0.3‡	5/18	27.8	9.7 to 53.5	NR§	18.4, 44.4+, 64.6+, 65.1+, 66.3+	1/18	5.6	0.1 to 27.3	1.9	1.8 to 9.3	12.5	7.7 to NE
1	11/35	31.4	16.9 to 49.3	104	32.4, 32.4, 43.0+, 64.1+, 74.1+, 80.1+, 82.1+, 99.4, 100.9+, 104.1, 108.1+	5/35	14.3	4.8 to 30.3	9.1	1.8 to 24.7	25.3	14.6 to NE
3	7/17	41.2	18.4 to 67.1	75.9	40.1+, 40.4, 48.1, 56.1, 95.7, 106.7+, 115.4+	1/17	5.9	0.1 to 28.7	9.7	1.9 to 16.4	20.3	8.2 to NE
10	4/20	20.0	5.7 to 43.7	112	73.9, 78.3+, 111.7, 117.0+	0	0	0	3.7	1.7 to 20.5	11.7	7.2 to 37.8

Abbreviations: NE, not estimable; n/N, No. of patients/total No. of patients; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

*Objective response rates {[(CR + PR) ÷ N] × 100} have been calculated on the basis of confirmed responses with CIs calculated by using the Clopper-Pearson method. Individual patient responses were adjudicated per Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 with modification. One complete response was noted.

†Kaplan-Meier estimate, time from first response to time of documented progression, death, or for censored data (denoted by "+"), time to last tumor assessment.

‡Five patients with tumor progression received dose-escalation from 0.1 to 1.0 mg/kg, and six patients received dose-escalation from 0.3 to 1.0 mg/kg. None of these patients responded to therapy.

§The time point at which the probability that responder's progress drops below 50% has not been reached because of insufficient number of events and/or follow-up.

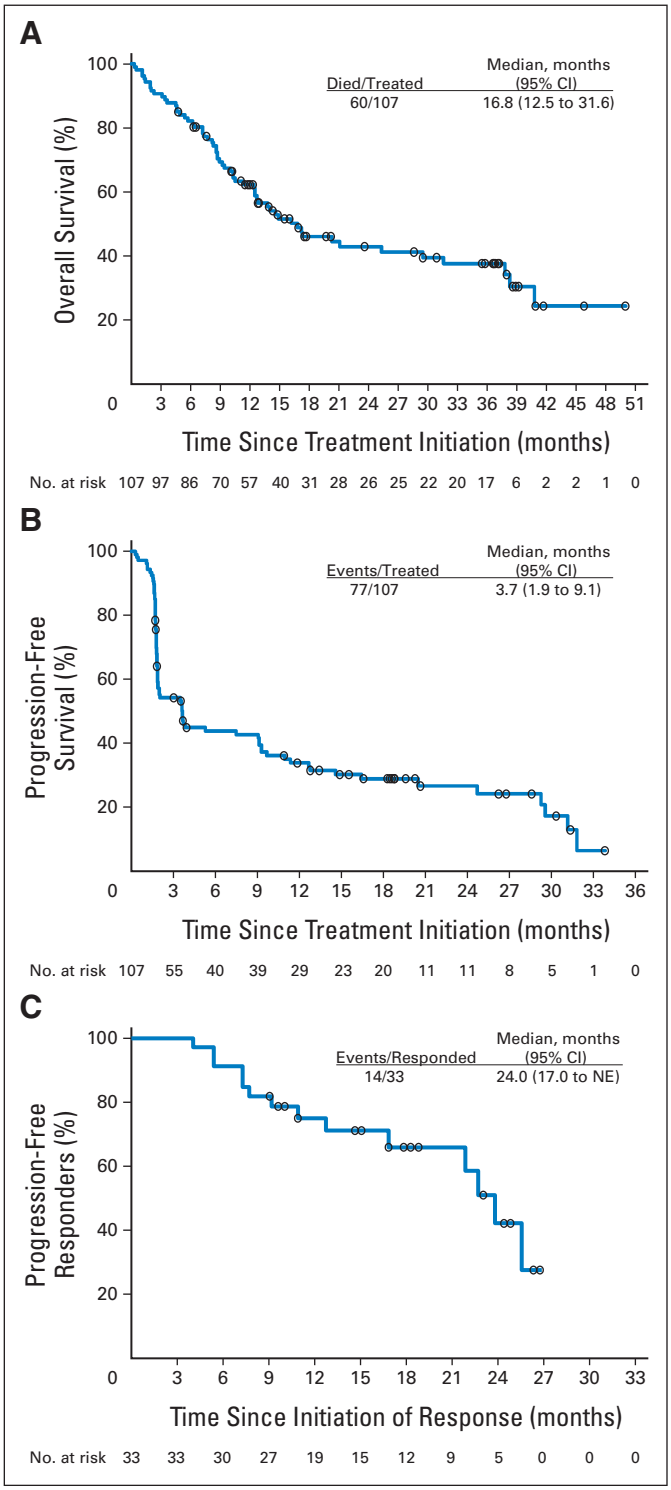

Fig 1. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival in 107 nivolumab-treated patients with melanoma and (C) response duration in 33 objective responders. Analysis includes patients from all dose cohorts. (A) Patients with melanoma had 1- and 2-year overall survival rates of 62% and 43% and a median overall survival of 16.8 months. (B) Progression-free survival rates were 36% and 27% at 1 and 2 years, and the median was 3.7 months. (C) The median duration of response in 33 responding patients was 24 months. Open circles indicate censored events defined for progression-free survival as the time to the last tumor assessment before the date of data analysis for patients without disease progression or death, and for overall survival as the time to the last known alive date before the date of data analysis for patients without a death. NE, not estimable.

rates were 62% (95% CI, 53% to 72%) and 43% (95% CI, 32% to 53%), respectively (Fig 1A). Median progression-free survival was 3.7 months (95% CI, 1.9 to 9.1 months), with 1- and 2-year progression-free survival rates of 36% (95% CI, 27% to 46%) and 27% (95% CI, 17% to 36%), respectively (Table 1 and Fig 1B). Both the overall and progression-free survival curves appeared to flatten beyond the median, although verification of this observation will require longer follow-up.

Response Rate and Duration

Objective responses were observed in 31% of patients (33 of 107) with melanoma, and an additional 7% of patients (seven of 107) experienced stable disease lasting for 24 weeks or more (Table 1). Durable responses were observed across all nivolumab doses tested within a 2-log range (0.1 to 10 mg/kg). Changes in the sum of target lesion dimensions compared with baseline are shown in Figure 2A. Unconventional response patterns that did not meet RECIST criteria (eg, persistent reduction in target lesions in the presence of new lesions or regression following initial progression)[16] were observed in four patients (4%); three of them received nivolumab at 1 mg/kg (Fig 2B), and a fourth received 10 mg/kg. Among 11 patients who experienced disease progression following treatment with nivolumab at 0.1 or 0.3 mg/kg, none responded following dose escalation to 1.0 mg/kg.

In 33 patients with objective responses, the Kaplan-Meier estimated median duration of response was 2 years (Fig 1C). Nineteen of 33 responses (58%) were ongoing at the time of data analysis (Table 1 and Fig 2C). Fifteen responses (45%) occurred rapidly and were documented at the first tumor assessment 8 weeks after starting treatment (Fig 2B-C). Tumor regression was observed at various anatomic sites and in primary and metastatic lesions, as exemplified in Figures 3 and 4. Seventeen of 33 patients stopped therapy for reasons other than disease progression during response and were observed; 12 (71%) of 17 maintained their responses for at least 16 weeks off-drug (16 to 56+ weeks), and eight of the 12 had responses ongoing at the time of analysis. Figure 4 shows an example of continued regression in multiple metastatic lesions after nivolumab discontinuation.

Safety

The maximum-tolerated dose of nivolumab was not reached within the tested dose range. With extended observation since our initial report (median time on treatment, 22 weeks; range, 2 to 122 weeks), the spectrum and severity of treatment-related adverse events remained stable (Table 2 and Data Supplement).[15] The most common events of any grade that occurred in patients with melanoma were fatigue (32%), rash (23%), and diarrhea (18%). Twenty-four (22%) of 107 patients with melanoma experienced grade 3 to 4 treatment-related adverse events. Select adverse events with potential immune-related causality, previously termed "immune-related adverse events" or "adverse events of special interest,"[15] were also analyzed (categorized in the Data Supplement). Treatment-related select adverse events of any grade were observed in 58 (54%) of 107 patients with melanoma, the most common of which included skin disorders (36%), GI events (18%), and endocrinopathies (13%; Data Supplement). Grade 3 to 4 treatment-related select events were seen in five patients (5%). There were no drug-related deaths in the population of patients

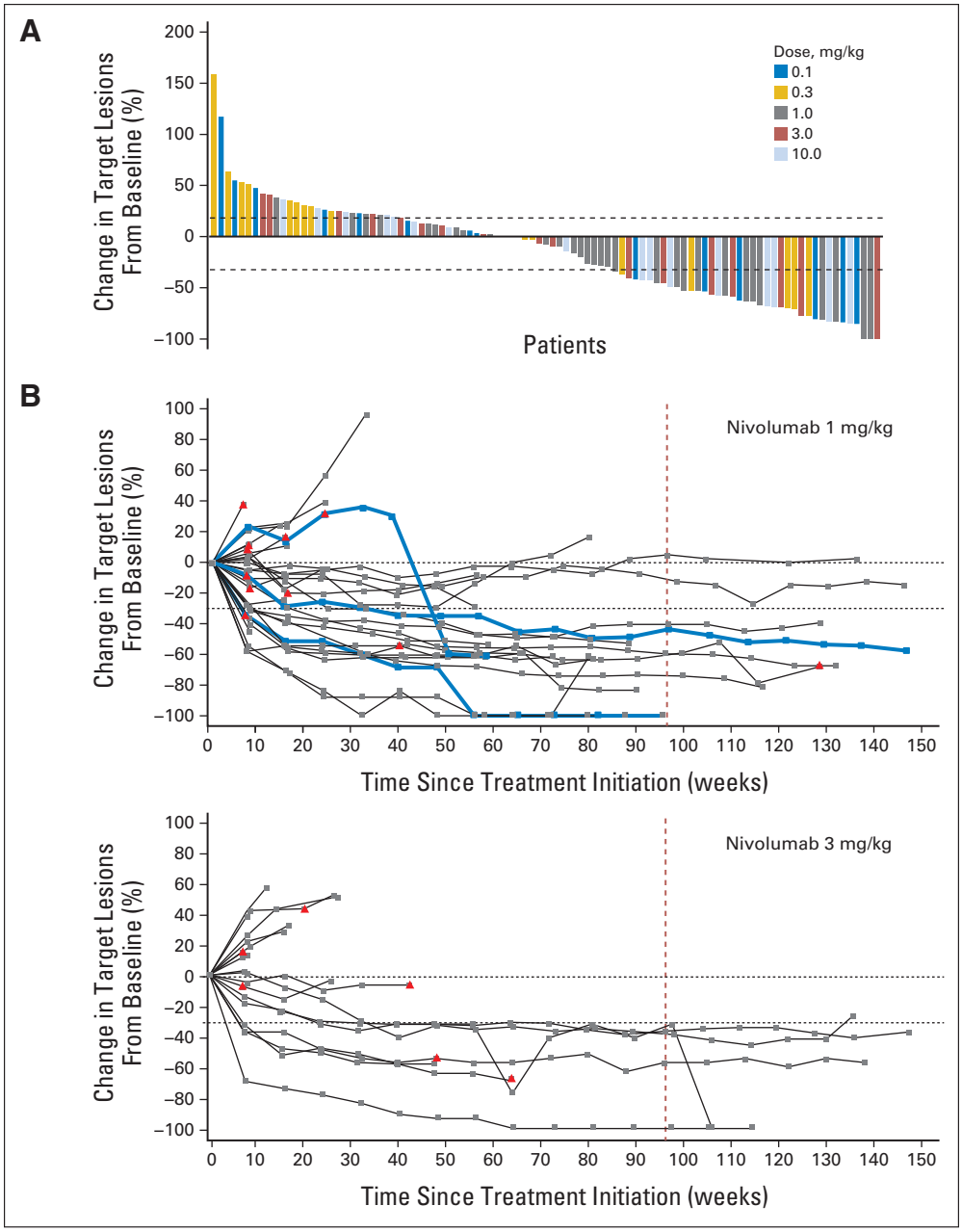

Fig 2. Characteristics of tumor regression in patients with melanoma receiving nivolumab therapy. (A) Maximum reduction or minimum increase in the sum of target lesion measurements compared with baseline in all treated patients with tumor measurements during treatment (n = 97). Responses were observed at all dose levels. Horizontal line at +20% indicates the threshold for defining progressive disease according to RECIST. Horizontal line at −30% indicates threshold for defining objective response (partial tumor regression) in the absence of new lesions or nontarget disease progression according to RECIST. (B) Response kinetics in patients receiving nivolumab at 1 mg/kg (n = 31) or 3 mg/kg (n = 17). Baseline tumor measurements are standardized to zero. Tumor burden is measured as the sum of the longest diameters of target lesions. Triangles indicate first occurrence of a new lesion. Vertical line at 96 weeks indicates the protocol-defined maximum duration of continuous nivolumab therapy. Horizontal line at −30% marks the threshold for defining objective response (partial tumor regression) according to RECIST. Blue curves indicate three unconventional immune-related response patterns in the 1 mg/kg dose cohort that did not meet RECIST criteria (eg, persistent reduction in target lesions in the presence of new lesions or regression following initial progression). Objective responses, unconventional responses, and stable disease persisted following treatment discontinuation in some patients. (Continued on next page.)

with melanoma, although there were three mortalities following treatment-related adverse events in the overall patient population (1%; two patients with non–small-cell lung cancer and one with colorectal cancer) associated with pneumonitis. Taking into account multiple adverse events occurring in individual patients, we analyzed the select adverse event rate as adjusted for person-years of nivolumab treatment in the total patient population, including those with melanoma and those with other solid tumors (N = 306; Data Supplement). Notably, with up to 2 years of safety monitoring for some patients, most adverse events occurred within the first 6 months of therapy, and cumulative toxicities were not observed with prolonged drug exposure.

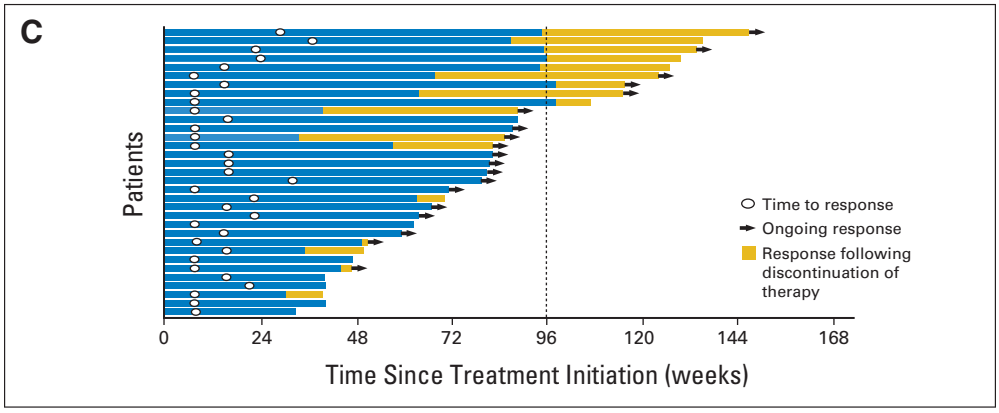

Fig 2. Continued. (C) Durability of tumor regressions in patients with melanoma who had objective responses to nivolumab therapy according to conventional RECIST criteria. Among 107 patients, 33 (31%) responded, including six (35%) of 17 who received nivolumab at 0.1 mg/kg, five (28%) of 18 at 0.3 mg/kg, 11 (31%) of 35 at 1 mg/kg, seven (41%) of 17 at 3 mg/kg, and four (20%) of 20 at 10 mg/kg. Blue bars indicate the time to and duration of response while on treatment; gold bars indicate response duration after treatment discontinuation; open circles indicate first evidence of objective response; arrows indicate ongoing response at time of analysis. Vertical line at 96 weeks indicates maximum planned duration of continuous nivolumab therapy. Reasons for treatment discontinuation with ongoing response included investigator-assessed complete response (n = 2), attainment of maximum treatment duration (n = 5), adverse events (n = 6), and other (eg, withdrew consent or investigator decision [n = 4]).

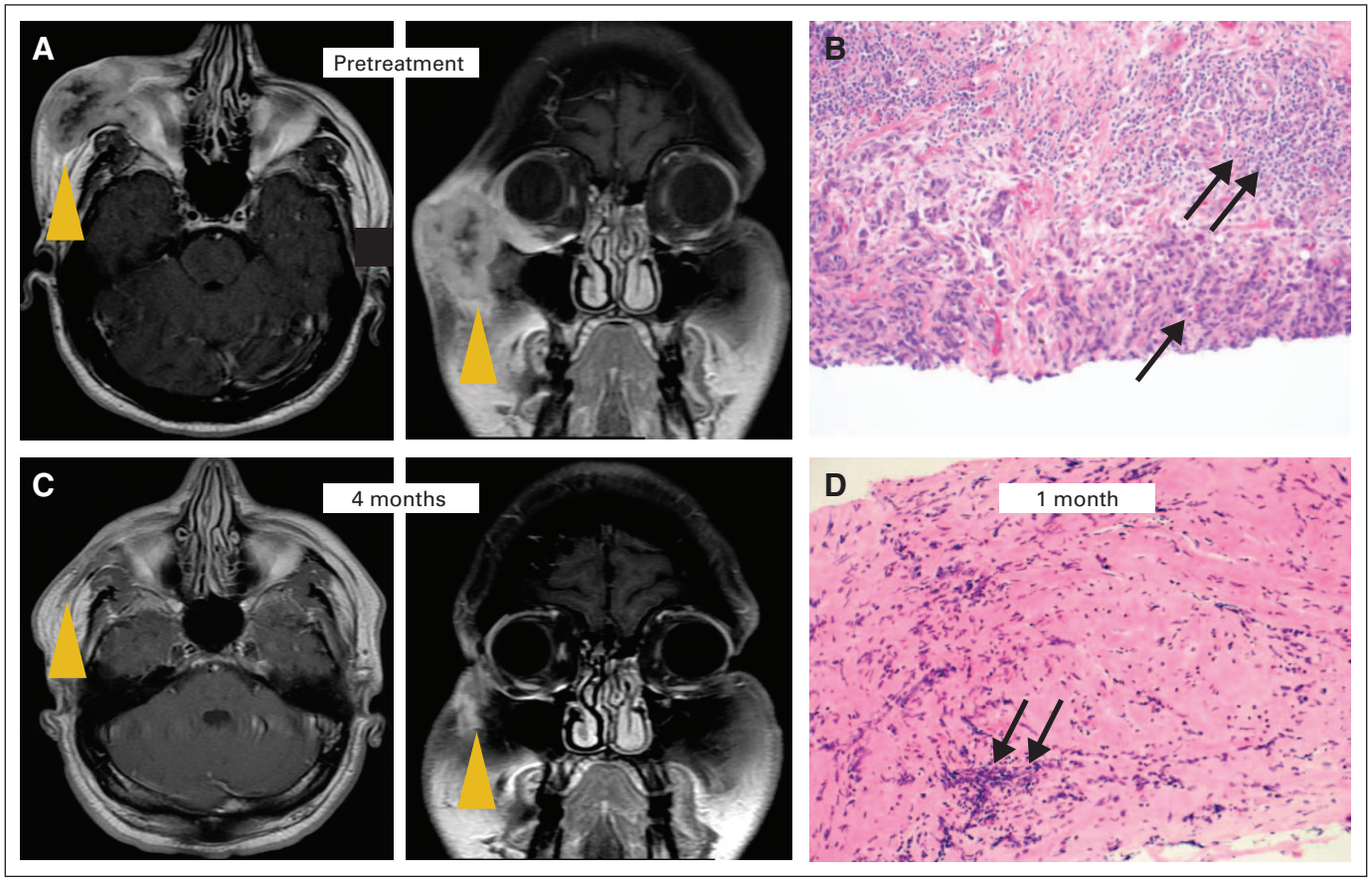

Fig 3. Partial response of locally advanced unresectable primary melanoma to nivolumab therapy in a 34-year-old man with xeroderma pigmentosum. Tumor had progressed through prior treatment with high-dose interleukin-2. (A) Pretreatment magnetic resonance imaging scans show right facial tumor eroding the zygomatic bone and extending into the orbit (gold arrows). (B) Immediate pretreatment core-needle tumor biopsy of the facial mass shows melanoma cells (single arrow) adjacent to infiltrating lymphocytes (double arrows). (C) A partial response was observed after 4 months (two cycles) of nivolumab therapy at 0.3 mg/kg every 2 weeks. This patient remains in partial response 2 years after treatment initiation. (D) Post-treatment core-needle biopsy shows fibrosis and infiltrating lymphocytes (double arrows); no tumor was present in this specimen. Hematoxylin and eosin stain; original magnification, ×200.

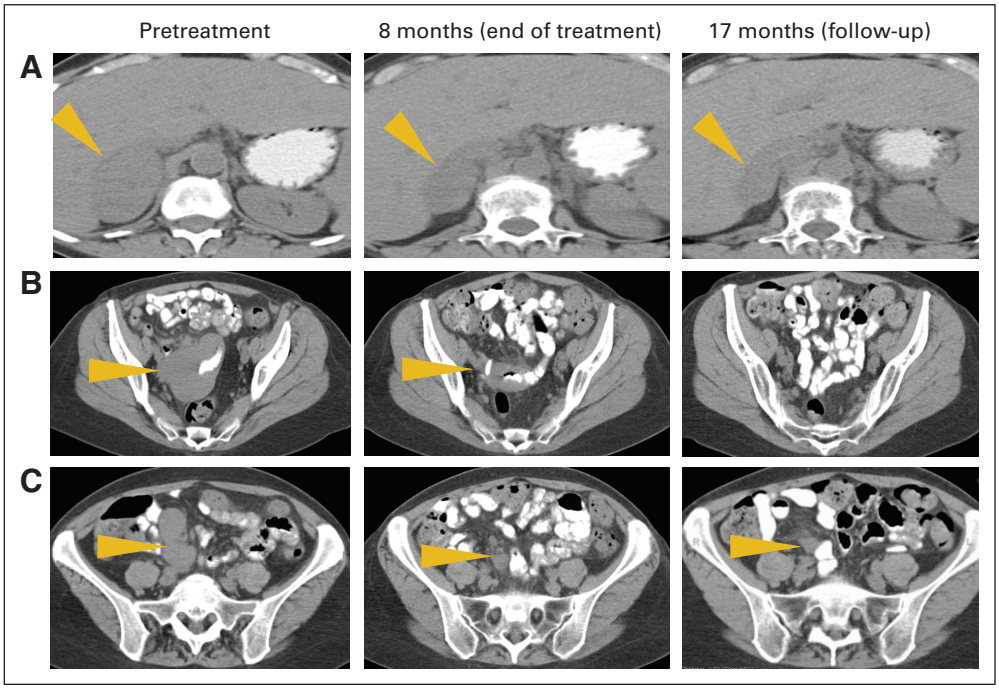

Fig 4. Partial response of metastatic melanoma to nivolumab, with continued tumor regression after drug discontinuation. This 59-year-old woman previously had experienced disease progression following high-dose interleukin-2, temozolomide, and sorafenib therapies. She received nivolumab 10 mg/kg every 2 weeks and achieved a partial tumor regression at 2 months. Treatment was discontinued at 8 months (four treatment cycles) as a result of exacerbation of an upper extremity neuropathy. Tumor regression continued after drug discontinuation. Computed tomographic scanning was performed with oral contrast but without intravenous contrast dye. Gold arrows indicate melanoma metastases involving (A) the right adrenal gland, (B) small bowel, and (C) mesenteric lymph nodes.

DISCUSSION

The critical role of the PD-1pathway in suppressing antitumorimmunity, first revealed in laboratory models, has now been validated in clinical studies. Monotherapy with drugs blocking PD-1 (nivolumab, MK-3475 [lambrolizumab])[15,19] or its major ligand PD-L1 (BMS-936559, MPDL3280A)[20,21] can mediate rapid and durable regressions in patients with advanced treatment–refractory solid tumors, including epithelial cancers not traditionally viewed as immune responsive. These findings have established the PD-1 pathway as a new therapeutic focus in oncology.[22] This study presents the longest follow-up to date in patients with melanoma treated with a PD-1 pathway inhibitor, nivolumab, and allows us to assess for the first time survival outcomes and the durability of clinical activity mediated by this therapeutic approach. In addition to persistence of conventional responses and unconventional (immune-related) responses in patients receiving this therapy, the follow-up presented here assesses response maintenance after treatment discontinuation and treatment-associated toxicity as a function of time on therapy.

In the context of published clinical experience with similar patient populations, the survival outcomes associated with nivolumab therapy in melanoma in this early-phase study are particularly important. Overall survival rates of 62% at 1 year and 43% at 2 years were achieved, with a median overall survival of 16.8 months. In a recent phase III trial enrolling patients with melanoma who had at least one prior treatment for metastatic disease, ipilimumab increased median overall survival from 6.4 to 10.1 months compared with a gp100 peptide vaccine.[8] In phase II trials of ipilimumab in previously treated patients, median overall survivals of 8.7 to 11.4 months were observed in patients receiving 3 or 10 mg/kg, with 1-year and 2-year survival rates of 39% to 49% and 24% to 33%, respectively.[23] Treatment with selective BRAF and MEK inhibitors is restricted to patients with mutation-positive melanomas, which are found almost exclusively in tumors of cutaneous origin. In contrast, the trial of nivolumab described here enrolled patients regardless of anatomic site of melanoma origin or oncogene mutational status. The median overall survival in previously treated patients with *BRAF*-mutant melanoma enrolled onto a large phase II trial of vemurafenib was 15.9 months, and the 1-year survival rate was 58%; among 53% of patients with objective tumor regressions, the median response duration was 6.7 months.[24] Treatment of a similar patient population with the MEK inhibitor trametinib in those who had not previously received a BRAF inhibitor resulted in a median overall survival of 14.2 months and estimated 1-year survival of 59%; among the 25% of patients with objective tumor regressions, the median response duration was 5.7 months.[25] Of interest, PD-1 blockade has been reported to be effective in melanoma regardless of *BRAF* mutational status.[19,26] Despite the limitations of cross-study comparisons, this information suggests that nivolumab therapy may have a favorable impact on the survival of patients with advanced melanoma.

Notably, overall survival in patients with melanoma who received nivolumab was considerably longer than progression-free survival. Both survival curves appear to flatten after 1 year of follow-up. This mirrors observations reported for ipilimumab,[8] suggesting that early disease progression in some patients receiving immune checkpoint blockade can evolve to durable disease stabilization or regression. These findings suggest that progression-free survival may underestimate the efficacy of immunomodulatory agents such as nivolumab.[27]

We report here that 31% of patients with melanoma experienced confirmed objective tumor regressions when they were given nivolumab therapy, and 7% had disease stabilization lasting at least 6 months. In addition, 4% of patients manifested unconventional immune-related response patterns.[28] The apparent durability of clinical activity in nivolumab-treated patients is remarkable, because this has generally not been observed with chemotherapy or small molecule kinase inhibitors to date but has been seen to a

Table 2. Treatment-Related Adverse Events That Occurred in at Least 3% of the Total Population of Patients With Melanoma

Treatment-Related Adverse Event	Patients (N = 107)			
	All Grades		Grades 3 to 4	
	No.	%	No.	%
Any adverse event*†	90	84.1	24	22.4
General disorders				
Fatigue	34	31.8	2	1.9
Pyrexia	5	4.7	0	0
Pain	4	3.7	0	0
Skin and subcutaneous tissue disorders				
Rash	25	23.4	0	0
Pruritus	14	13.1	0	0
Vitiligo	10	9.3	0	0
Dermatitis acneiform	6	5.6	0	0
Photosensitivity reaction	4	3.7	0	0
GI disorders				
Diarrhea	19	17.8	2	1.9
Nausea	9	8.4	1	0.9
Abdominal pain	8	7.5	2	1.9
Dry mouth	7	6.5	1	0.9
Vomiting	5	4.7	1	0.9
Musculoskeletal disorders				
Arthralgia	7	6.5	0	0
Myalgia	4	3.7	0	0
Metabolism and nutrition disorders				
Decreased appetite	7	6.5	0	0
Hyperuricemia	4	3.7	1	0.9
Hypophosphatemia	4	3.7	1	0.9
Blood and lymphatic system disorders				
Lymphopenia	7	6.5	3	2.8
Investigations				
Blood thyroid-stimulating hormone increased	6	5.6	1	0.9
Weight decreased	6	5.6	0	0
Alanine aminotransferase increased	5	4.7	0	0
Hemoglobin decreased	5	4.7	1	0.9
Platelet count decreased	5	4.7	1	0.9
Aspartate aminotransferase increased	4	3.7	0	0
WBC count decreased	4	3.7	0	0
Endocrine disorders				
Hypothyroidism	6	5.6	1	0.9
Procedural complications				
Infusion-related reaction	6	5.6	0	0
Respiratory disorders				
Cough	4	3.7	0	0
Vascular disorders				
Flushing	4	3.7	0	0
Hypotension	4	3.7	0	0

NOTE. Treatment-related adverse events are reported according to the nivolumab dose cohort in the Data Supplement.
*Treatment-related adverse events that were reported in less than 3% of the total melanoma population included pneumonitis, colitis, and renal failure (two each; 2%) and hepatitis, hypophysitis, thyroiditis, uveitis, and tubulointerstitial nephritis (one each; 1%).
†The numbers reported within a column may not add up to the total number reported under any adverse event, because patients who had more than one adverse event were counted for each event but were counted only once for any adverse event. Data for only those events that were reported in at least 3% of the treated patient population are presented.

lesser degree in some patients with advanced melanoma receiving immunotherapies including ipilimumab and high-dose interleukin 2.[5,8] Among 33 patients with objective responses to nivolumab, the median response duration was 2 years. Unconventional responses also appeared to be long-lasting and may contribute to overall survival outcomes.

Beyond durability, a distinguishing feature of response to nivolumab therapy is the maintenance of response status after treatment discontinuation. The persistence of partial tumor regressions and stable disease following nivolumab discontinuation in the absence of any other systemic cancer therapy is not commonly seen with chemotherapy or kinase inhibitors and suggests that PD-1 blockade may

reset the immune equilibrium between tumor and host. If PD-1 blockade served only to reverse inhibition of effector T-cell functions in the tumor microenvironment, tumors might be expected to re-engage this pathway and progress after drug discontinuation. Instead, our findings are consistent with a mechanism by which an effective tumor-selective immune memory response may have been established in some patients, similar to immune memory against specific infectious organisms after antigen exposure.[29] In other responding patients, persistent radiographic abnormalities may represent residual scarring rather than viable tumor (Fig 3), leading to an underestimation of true complete response rates. Further research will be needed to define mechanisms underlying the persistence of nivolumab-mediated tumor regressions after drug discontinuation and to explain disease recurrence following prolonged regression. Another implication worthy of further study is that the immune response unleashed by PD-1 blockade may adapt dynamically as the tumor evolves to mitigate the development of treatment resistance.

The acceptable long-term safety profile of nivolumab supports its continued development in the outpatient setting. Importantly, the exposure-adjusted toxicity rate in the total study population, including 306 patients with melanoma or other solid tumors who initiated therapy at least 14 months before data analysis, was not cumulative. Although the optimal duration of continuous nivolumab treatment is not yet known, this finding reduces potential concerns about the extended administration of anti–PD-1 therapy. In contrast, toxicities associated with chemotherapy typically accumulate with ongoing treatment. Select adverse events with potential immune-related causation are consistent with nivolumab's immunologic mechanism of action and include disorders of the lung, GI tract, skin, endocrine system, and kidney. The occurrence rate of grade 3 to 4 pneumonitis in 1% of all 306 patients receiving nivolumab on this study is lower than rates typically reported for some chemotherapies, tyrosine kinase inhibitors, and lung irradiation.[30-32] High-grade pneumonitis was not observed in any of the 107 patients with melanoma treated on this trial. Nivolumab-associated pneumonitis can be managed by drug discontinuation, corticosteroids, and other immune suppressive agents; however, vigilance and a multidisciplinary approach are needed.

Although nivolumab monotherapy may have an impact on the survival of patients with melanoma and other cancers,[33,34] preclinical evidence suggests that synergistic treatment combinations based on PD-1 pathway blockade could have even more potent effects. The apparently favorable therapeutic index of nivolumab as monotherapy supports its testing in treatment combinations. The clinical activity of nivolumab combined with ipilimumab, whose mechanism of action is distinct from that of nivolumab,[35] has been reported in melanoma,[36] and the potential advantage of this combination over monotherapy with either agent is being explored in a phase III trial (NCT01844505). In addition, combination trials with chemotherapy (NCT01454102), kinase inhibitors (NCT01472081), cancer vaccines (NCT01176461, NCT01176474), and other immune-modulating therapies (anti-killer inhibitory receptor, NCT01714739; interleukin-21, NCT01629758) are ongoing in patients with a variety of solid tumor types. Tumor cell expression of PD-L1 has been hypothesized as a molecular marker that may be associated with response to PD-1 or PD-L1 blockade.[15,21] Clinical trials incorporating molecular analyses to further explore the association of PD-L1 expression with clinical outcome and to profile the complex tumor immune microenvironment in patients treated with nivolumab may reveal additional therapeutic cotargets.[37,38] Innovative, rational treatment combinations based on preclinical evidence may be needed to realize the full therapeutic potential of PD-1 blockade.

In summary, these results suggest that nivolumab may have an impact on overall survival in patients with advanced melanoma with an acceptable long-term safety profile. Controlled phase III trials in melanoma with prospective survival end points (NCT01673867, NCT01721772, NCT01642004, NCT01668784, and NCT01721746) are currently underway.

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GLOSSARY TERMS

antigen: a substance that promotes, or is the target of, an immune response.

CTLA4 (CD152): receptor on activated T cells that binds B7 molecules with a higher affinity than CD28, downregulating T-cell responses by inhibiting CD28 signaling.

immunotherapy: a therapeutic approach that uses cellular and/or humoral elements of the immune system to fight a disease.

interleukin-2 (IL-2): a cytokine that stimulates proliferation of activated T cells and, at high doses, is used as antitumor therapy in metastatic renal cell carcinoma.

monoclonal antibody: an antibody that is secreted from a single clone of an antibody-forming cell. Large quantities of monoclonal antibodies are produced from hybridomas, which are produced by fusing single antibody-forming cells to tumor cells. The process is initiated with initial immunization against a particular antigen, stimulating the production of antibodies targeted to different epitopes of the antigen. Antibody-forming cells are subsequently isolated from the spleen. By fusing each antibody-forming cell to tumor cells, hybridomas can each be generated with a different specificity and targeted against a different epitope of the antigen.

RECIST (Response Evaluation Criteria in Solid Tumors): a model proposed by the Response Evaluation Criteria Group by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment.

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