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ORIGINAL REPORT

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

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See accompanying editorial on page 986; listen to the podcast by Dr Gulley at www.jco.org.podcasts

A B S T R A C T

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

Dose (mg/kg)	ORR*			Duration of Response (weeks)†		Stable Disease ≥24 Weeks			PFS (months)		OS (months)	
	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.
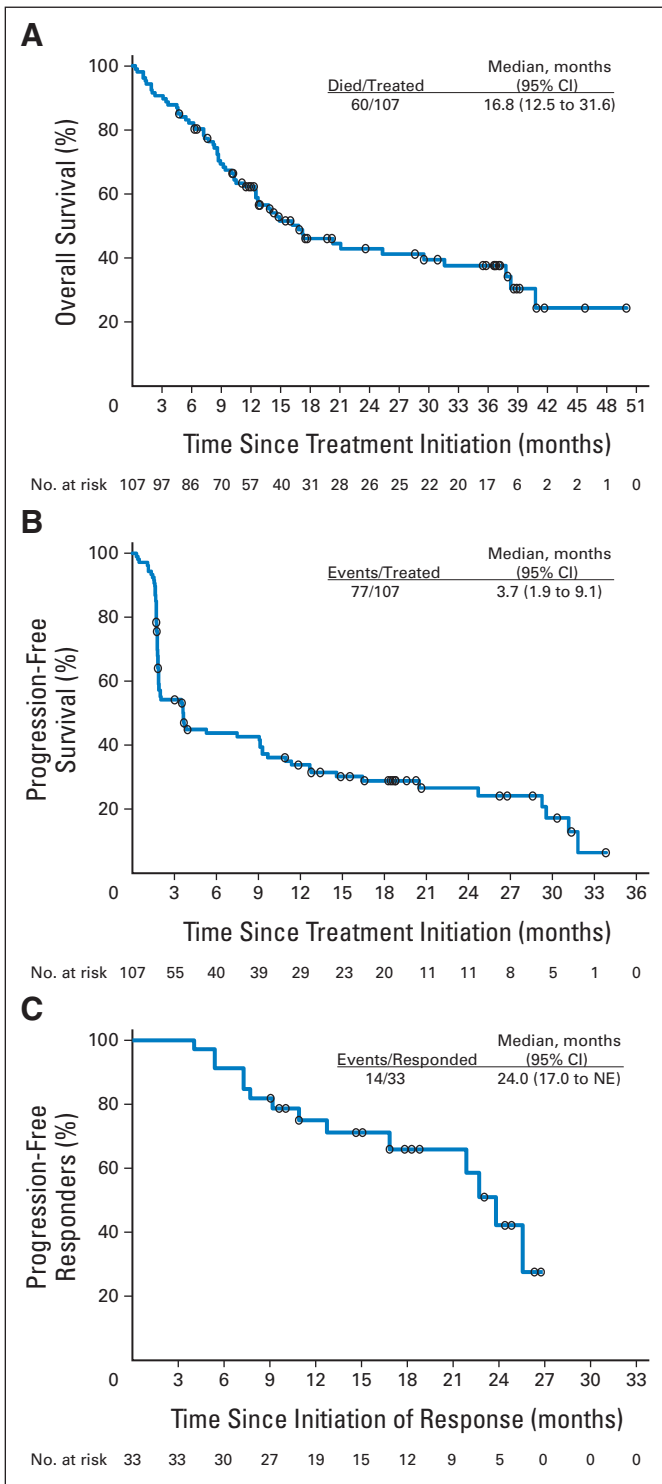
Fig 1. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival in 107 nivolumab-treated patients with melanoma and (C) response duration in 33 objective responders. Analysis includes patients from all dose cohorts. (A) Patients with melanoma had 1- and 2-year overall survival rates 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
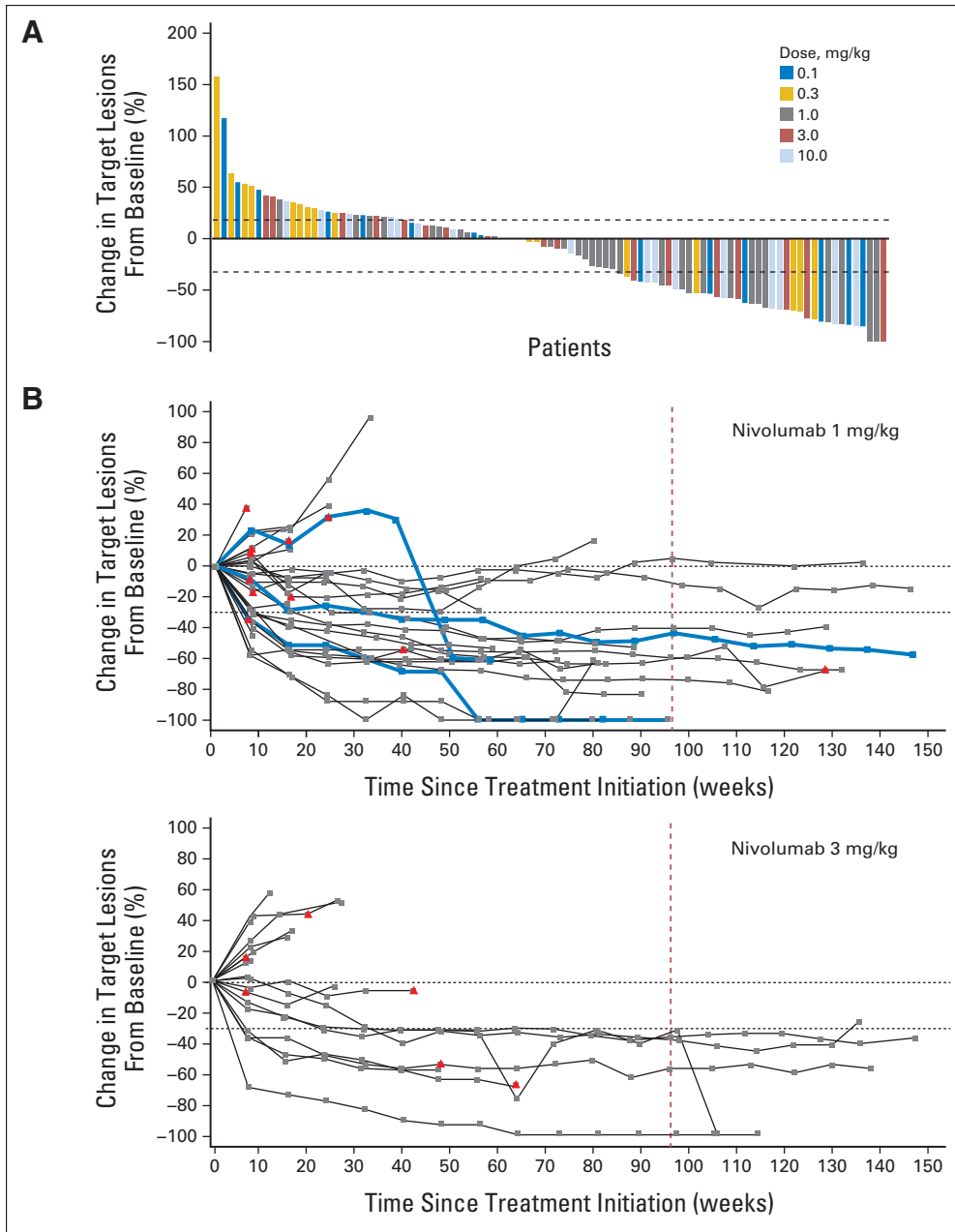
Fig 2. Characteristics of tumor regression in patients with melanoma receiving nivolumab therapy. (A) Maximum reduction or minimum increase in the sum of target lesion measurements compared with baseline in all treated patients with tumor measurements during treatment (n = 97). Responses were observed 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.

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