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Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Purpose—Nivolumab is a fully human immunoglobulin G4 programmed death–1 immune

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Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial

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checkpoint inhibitor antibody that restores T-cell immune activity. This phase II trial assessed the antitumor activity, dose-response relationship, and safety of nivolumab in patients with metastatic renal cell carcinoma (mRCC).

Patients and Methods—Patients with clear-cell mRCC previously treated with agents targeting the vascular endothelial growth factor pathway were randomly assigned (blinded ratio of 1:1:1) to nivolumab 0.3, 2, or 10 mg/kg intravenously once every 3 weeks. The primary objective was to evaluate the dose-response relationship as measured by progression-free survival (PFS); secondary end points included objective response rate (ORR), overall survival (OS), and safety.

Results—A total of 168 patients were randomly assigned to the nivolumab 0.3- (n = 60), 2- (n = 54), and 10-mg/kg (n = 54) cohorts. One hundred eighteen patients (70%) had received more than one prior systemic regimen. Median PFS was 2.7, 4.0, and 4.2 months, respectively (*P* = .9). Respective ORRs were 20%, 22%, and 20%. Median OS was 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months), respectively. The most common treatment-related adverse event (AE) was fatigue (24%, 22%, and 35%, respectively). Nineteen patients (11%) experienced grade 3 to 4 treatment-related AEs.

Conclusion—Nivolumab demonstrated antitumor activity with a manageable safety profile across the three doses studied in mRCC. No dose-response relationship was detected as measured by PFS. These efficacy and safety results in mRCC support study in the phase III setting.

INTRODUCTION

An understanding of the mechanisms involved in the pathogenesis of renal cell carcinoma (RCC) led to development of treatment options that inhibit vascular endothelial growth factor (VEGF)–mediated signaling or the mammalian target of rapamycin pathway.[1,2] Although these treatment options have demonstrated progression-free survival (PFS) benefit, most patients with metastatic RCC (mRCC) eventually experience progression,[1-3] underscoring the need for treatment options with novel mechanisms of action that could potentially result in improved efficacy and a survival advantage.

Multiple resistance mechanisms, including systemic dysfunction in T-cell signaling[4-7] and exploitation of immune checkpoints,[8] evolve in tumors, helping them evade specific immune responses despite the presentation of tumor antigens to the immune system.[8] Recent understanding of these host-tumor immune interactions has given rise to novel antibodies directed against immune checkpoint proteins.[9,10]

Nivolumab is a fully human immunoglobulin (Ig) G4 programmed death (PD)–1 immune check-point inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2—a mechanism that normally leads to down-regulation of cellular immune response.[11-13] By inhibiting this interaction, nivolumab can enhance T-cell function in vitro, which may result in antitumor activity.[14] In a phase I study that included patients with mRCC, nivolumab demonstrated objective responses and a manageable safety profile; no maximum-tolerated dose was identified (0.1 to 10 mg/kg every 3 weeks).[15] Herein, we report the results of a randomized phase II trial that evaluated three doses of nivolumab to

identify a potential dose-response relationship and assess the activity and safety of nivolumab in patients with mRCC.

PATIENTS AND METHODS

Study Design and Treatment

This was a blinded, randomized, multicenter phase II trial. Previously treated patients were randomly assigned at a ratio of 1:1:1 to receive nivolumab 0.3, 2, or 10 mg/kg administered intravenously every 3 weeks. Randomization was stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) risk group[16] (favorable *v* intermediate *v* poor) and number of prior treatment regimens (one *v* more than one) in the metastatic setting.

Nivolumab was provided by the sponsor (Bristol-Myers Squibb, Lawrenceville, NJ; Ono Pharmaceutical Company, Osaka City, Japan) and administered as a 60-minute intravenous infusion on day 1 of each treatment cycle. No dose escalations or reductions were allowed. Dose delay of up to 3 weeks was permitted for management of adverse events (AEs). Treatment was continued until disease progression or intolerance or until stopped for other protocol-defined reasons. Treatment beyond first progression was allowed in patients continuing to tolerate nivolumab and exhibiting investigator-assessed clinical benefit at the time of progression.

The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines[17] and approved by the institutional review board or independent ethics committee of each center. Each institutional review board or independent ethics committee comprised a review panel that was responsible for ensuring protection of the rights, safety, and well-being of human participants involved in the study and was adequately constituted to provide assurance of that protection. All patients provided written informed consent before enrollment, based on ethical principles outlined in the Declaration of Helsinki.[18]

Patients

Patients eligible for study inclusion had histologic confirmation of RCC with a clear-cell component and measurable disease defined by RECIST (version 1.1) and had received prior treatment with at least one antiangiogenic therapy (eg, VEGF tyrosine kinase inhibitors, monoclonal antibodies) in the metastatic setting. Previous treatment with cytokines, cytotoxic drugs, or other targeted agents was permitted but not required. Other key inclusion criteria included disease progression during or after last therapy received and within 6 months of enrollment, Karnofsky performance status ≥ 70%, available tumor tissue for correlative studies, and adequate bone marrow, renal, and hepatic function.

Exclusion criteria included active CNS metastases, autoimmune disease, previous therapy with a T-cell costimulation or checkpoint inhibitor, or treatment with more than three prior treatment regimens in the metastatic setting.

End Points and Assessments

The primary end point was comparison of PFS across each of the three dose arms (0.3, 2, and 10 mg/kg) to assess whether a dose-response relationship exists. Secondary end points included assessment of PFS, objective response rate (ORR), time to response, duration of response, overall survival (OS), and AE rate. Exploratory end points included evaluation of immune-related PFS (based on immune-related RECIST [version 1.1][19]; Appendix Table A1, online only) and ORR (definitions provided in Appendix, online only), and tumor PD-L1 expression to explore associations between expression in tumors and clinical outcome.

Tumor assessments were performed at baseline and every 6 weeks from random assignment for the first 12 months and every 12 weeks thereafter, until disease progression or treatment discontinuation (whichever occurred later). Tumor response was based on investigator assessment using RECIST (version 1.1). After treatment discontinuation, patients were observed every 3 months for survival.

Safety was assessed at every clinic visit. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[20]

PD-L1 protein expression was measured in archival tumor tissue (or fresh, pretreatment tissue if archival material was not available) by immunohistochemistry using a rabbit antihuman PD-L1 monoclonal antibody (clone 28-8; subsequently developed as part of an automated PD-L1 assay by Dako Denmark A/S, Glostrup, Denmark).[21] Blinded scoring was completed by two independent pathologists. PD-L1 positivity was defined by membrane staining of ≥ 5% of tumor cells. A cutoff of ≥ 1% for positivity was also assessed. Patients with multiple specimens were considered PD-L1 positive if any specimen met this criterion.[22,23]

Statistical Analyses

PFS was defined as time from random assignment to date of investigator-assessed clinical or radiographic progression or death. With a target number of PFS events set at 116, it was calculated that the study objective could be met with ≥ 150 patients to provide ≥ 90% power to detect a dose-response relationship across the three treatment arms (assuming median PFS was 4.0, 5.7, and 8.1 months for arms 0.3, 2, and 10 mg/kg, respectively, derived using exponential distribution assumption, where treatment difference of hazard ratio [HR] of 0.7 was assumed between two consecutive doses and 4 months assumed for smallest dose based on historical data). With approximately 150 patients, it was expected that accrual would be completed after 10 months, and final analysis of PFS could be conducted 19 months from the start of the study.

Evaluation of a dose-response relationship as measured by PFS was performed using a two-sided 20%-level log-rank trend test stratified by MSKCC risk group and number of prior treatment regimens in the metastatic setting. The HRs and two-sided 80% CIs of the nivolumab 0.3,2,and 10 mg/kg doses relative to each other dose were estimated using the Cox proportional hazards model,[24] stratified by MSKCC risk group and number of prior therapies, with randomized treatment arm as the single covariate.

Analysis of ORR was performed based on best overall response (RECIST [version 1.1]; investigator assessed). For each treatment group, ORR was estimated along with exact 80% CI using the Clopper-Pearson method.[25] The dose-response relationship was evaluated using a two-sided 20%-level Cochran-Armitage test.[26,27]

Median OS and 80% CI for each treatment group were estimated using Kaplan-Meier methodology.[28] OS was defined as the time from random assignment to date of death. *P* values for secondary or exploratory end point analyses were not controlled for multiplicity and were conducted for descriptive purposes only. Data cutoffs were May 15, 2013, for the primary PFS and ORR analyses and March 5, 2014, for OS and response duration.

RESULTS

Patient Population

Between May 2011 and January 2012, 168 patients from 39 participating sites in the United States, Canada, Finland, and Italy were randomly assigned: 60 to the nivolumab 0.3-mg/kg arm and 54 patients each to the nivolumab 2- and 10-mg/kg arms. The efficacy population (N = 168) included all randomly assigned patients, and the safety population (n = 167) included all patients who received at least one dose of nivolumab (Fig 1).

Baseline characteristics were balanced among treatment groups (Table 1). In total, 70% (n = 118) had received more than one prior systemic regimen for mRCC, and 25% (n = 42) met MSKCC poor-risk criteria.

Efficacy

Median PFS was 2.7 months (80% CI, 1.9 to 3.0 months), 4.0 months (80% CI, 2.8 to 4.2 months), and 4.2 months (80% CI, 2.8 to 5.5 months) for the 0.3-, 2-, and 10-mg/kg groups, respectively (Table 2; Fig 2A), and no dose-response relationship for PFS was detected (stratified trend test *P* = .9). When immune-response PFS was assessed as an exploratory end point, median immune-response PFS was 4.3 months (80% CI, 2.8 to 6.9 months), 5.4 months (80% CI, 4.2 to 7.1 months), and 6.9 months (80% CI, 4.4 to 8.5 months) in the 0.3-, 2-, and 10-mg/kg treatment groups, respectively (test for trend *P* = .6; Appendix Table A2, online only).

ORR was 20% (n = 12), 22% (n = 12), and 20% (n = 11) in the 0.3-, 2-, and 10-mg/kg groups, respectively (exact Cochran-Armitage trend test *P* = 1.0; Table 2). Median time to achieving an objective response was 2.8 months (range, 1.3 to 5.6 months) in the 0.3-mg/kg group (n = 12), 3.0 months (range, 1.4 to 6.9 months) in the 2-mg/kg group (n = 12), and 2.8 months (range, 1.2 to 10 months) in the 10-mg/kg group (n = 11). Median duration of response was not reached (NR) in the 0.3-mg/kg (80% CI, NR to NR) and 2-mg/kg groups (80% CI, 4.2 months to NR) and 22.3 months (80% CI, 4.8 months to NR) in the 10-mg/kg group. Of patients who responded to treatment, 75% (nine of 12) in the 0.3-mg/kg group, 50% (six of 12) in the 2-mg/kg group, and 45% (five of 11) in the 10-mg/kg group were ongoing responders (Fig 3). Forty percent (14 of 35) were responding at 24 months from start of study therapy (of the remainder, 14 had stopped responding, and seven were ongoing responders who had not yet reached the 24-month mark).

Median OS was 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months) in the 0.3-, 2-, and 10-mg/kg groups, respectively (Fig 2B), with a minimum follow-up of 24 months. HRs for OS in the 2- and 10-mg/kg groups compared with the 0.3-mg/kg group were 0.8 (80% CI, 0.6 to 1.1) and 0.9 (80% CI, 0.6 to 1.2), respectively. OS analyses by MSKCC risk group and by number of prior therapies are shown in Figures 4A and 4B.

Treatment Administered and Safety

Median number of doses received was 6.0 (range, one to 29), 7.5 (range, one to 32), and 8.0 (range, one to 31) in the 0.3-, 2-, and 10-mg/kg groups, respectively. Dose delay occurred in 41% (n = 24), 43% (n = 23), and 39% (n = 21) of patients, respectively.

The percentage of patients treated beyond progression (patients with at least one nivolumab dose received > 6 weeks after date of RECIST [version1.1] progression) was 17% (n = 10) in the 0.3-mg/kg group, 22% (n = 12) in the 2-mg/kg group, and 26% (n = 14) in the 10-mg/kg group. Median number of doses received after progression was 4.5, 7.5, and 8.5 in the 0.3-, 2-, and 10-mg/kg treatment groups, respectively. In some patients who continued treatment beyond initial progression, sustained reductions and/or stabilization in the size of target lesions were observed (Appendix Fig A1, online only).

Most of the 167 patients (n = 122; 73%) experienced treatment-related AEs (any grade); 19 (11%) experienced a grade 3 to 4 event (Table 3). Incidence of treatment-related AEs of any grade was similar across dose arms: 75%, 67%, and 78% in the 0.3-, 2-, and 10-mg/kg groups, respectively. Grade 3 to 4 events occurred in 5%, 17%, and 13% of patients in the 0.3-, 2-, and 10-mg/kg groups, respectively. Fatigue was the most common treatment-related AE in each group (24%, 22%, and 35% of patients, respectively). Incidence of hypersensitivity was higher in the nivolumab 10-mg/kg group than in the lower-dose groups; none of these events were grade 3 to 4. No grade 3 to 4 pneumonitis events were reported (Table 3). Systemic corticosteroids for the management of AEs (regardless of causality) were administered to nine (15%), 10 (19%), and 18 (33%) patients in the 0.3-, 2-, and 10-mg/kg groups, respectively.

Treatment-related AEs leading to discontinuation of study drug occurred in 7% (n = 11) of patients (2% [n = 1], 11% [n = 6], and 7% [n = 4] in 0.3-, 2-, and 10-mg/kg groups, respectively). The most common reason for treatment-related discontinuation was an elevated level of serum AST, occurring in two patients. Types of treatment-related AEs leading to discontinuation in each group included cardiac disorders (0.3-mg/kg group, n = 1 patient), endocrine disorders (2-mg/kg group, n = 2 patients), and nervous system and respiratory or thoracic disorders (10-mg/kg group, n = 2 patients each). No treatment-related deaths were reported.

PD-L1 Expression

As an exploratory end point, efficacy parameters were assessed according to PD-L1–expression status at a 5% cutoff. In total, 107 of 168 patients (64%) were PD-L1 quantifiable. Of these, 29 (27%) had PD-L1 expression ≥ 5%, and 78 (73%) had expression < 5%. Median PFS was 4.9 months in the PD-L1 ≥ 5% subgroup versus 2.9 months in the

PD-L1 < 5% subgroup (Appendix Table A3, online only); ORR was 31% in the PD-L1 ≥ 5% subgroup and 18% in the PD-L1 < 5% subgroup (Appendix Table A3, online only); median OS was NR in the PD-L1 ≥ 5% subgroup and 18.2 months in the PD-L1 < 5% subgroup (Appendix Table A3, online only). When a cutoff ≥ 1% for PD-L1 expression was used to define PD-L1 positivity, median PFS, ORR, and OS were similar in PD-L1–positive (n = 43) and PD-L1–negative patients (n = 64; data not shown).

DISCUSSION

Nivolumab demonstrated antitumor activity in this randomized, dose-ranging phase II trial. ORR was similar by treatment arm, ranging from 20% to 22% and including patients with ongoing, durable objective responses. At data cutoff, 40% of the 35 objective responders were still responding ≥ 24 months from start of nivolumab therapy.

No dose-response relationship was observed. Seventy percent of patients had received more than one prior systemic regimen, including 40% who had received two or three prior antiangiogenic drugs and approximately one third who had received prior everolimus. In our study, nivolumab treatment resulted in a median PFS of up to 4.2 months (10-mg/kg dose arm) when assessed by conventional RECIST criteria. Median OS values observed in our study were numerically higher than those reported in pivotal phase III trials in mRCC.[29-32] Median OS was 15.2 months (95% CI, 12.8 to 18.3 months) with axitinib and 16.5 months (95% CI, 13.7 to 19.2 months) with sorafenib as second-line treatment (both in patients who experienced progression on sunitinib) in the AXIS (Axitinib Versus Sorafenib) trial[31] and 11 months (95% CI, 8.6 to 13.5 months) with sorafenib as third-line therapy in the GOLD (Global Oncologic Learnings for Dovitinib) trial.[32] In RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily), median OS for everolimus was 14.8 months (95% CI not stated).[30] Cross-study comparisons should be interpreted cautiously, because differences in trial design influence the results. Nevertheless, they can be used to generate hypotheses. Our data suggest that nivolumab may produce a greater improvement in OS than that observed in previous trials.[29-32] Also, comparison of OS results among arms suggests that a higher dose could be an important factor in achieving a longer OS. Although longer OS was observed in patients with MSKCC favorable-risk score and in those who had received only one line of prior therapy, robust results were seen across all risk groups and lines of therapy.

The OS benefit observed in our study was of a greater degree than would have been predicted from the PFS results and may be related to the immunostimulatory mechanism of action of nivolumab. Tumor kinetics could initially outpace the time required for immune-cell activation to occur. In addition, immune-cell infiltration of the tumor might mimic progression. Together, these phenomena may lead to the detection of transient progression that could negatively affect the assessment of PFS, but not OS. Similar findings have been observed with ipilimumab and nivolumab in patients with malignant melanoma.[33] Results from the phase III trial (Clinicaltrials.gov identifier NCT01668784) might help us to further understand this relationship.

A modified version of RECIST, the immune-related response criteria, was proposed to more adequately address the delayed and mixed responses observed with immunotherapy.[19] Using these immune-related criteria, median PFS values for the three study arms were longer, compared with those based on standard RECIST assessment. Treatment beyond RECIST-defined progression was allowed in this study and may be an important strategy for extending OS. Also, our data show that although response to treatment was higher in patients with greater PD-L1 expression (≥ 5%), those with lower PD-L1 expression (< 5%) also had meaningful responses. These PD-L1 outcome data were assessed as an exploratory end point but are consistent with earlier published observations.[15,34] New strategies to assess response and improve outcomes are important to maximize benefit for patients treated with novel immunotherapy agents such as nivolumab.

The safety profile of nivolumab was manageable in all treatment groups (Appendix Table A4, online only) and consistent with that reported in the phase I trial.[15] The frequency of treatment-related AEs was similar across groups, and treatment-related AEs were primarily low grade in severity. Cases of drug-related pneumonitis associated with fatal outcome were observed in the phase I trial in other tumor types,[15] but no high-grade pneumonitis was observed in our trial.

Findings from our dose-ranging study, coupled with analyses of safety and efficacy across tumor types from a large phase I study,[15] support the selection of nivolumab 3 mg/kg intravenously every 2 weeks as the monotherapy dosing regimen for further study. Our results add to a growing body of evidence supporting the efficacy of nivolumab immunotherapy in mRCC.[15,34,35] There are a number of ongoing studies that will further elucidate this evidence, including a phase III trial comparing nivolumab versus everolimus using an OS primary end point in patients with mRCC pretreated with antiangiogenic therapy (Clinicaltrials.gov identifier NCT01668784). Encouraging antitumor activity was observed in a phase IB trial evaluating the combination of nivolumab and ipilimumab in patients with mRCC.[36] A phase III trial using OS as a primary end point is under way to evaluate this combination in the first-line setting (Clinicaltrials.gov identifier NCT02231749).

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Appendix

Immune-Related Response Criteria

The immune-related response criteria are based on the conventional RECIST (version 1.1; Appendix Table A1), with the following major modifications: requirement to confirm progression ≥ 4 weeks after scan indicating initial progression and not scoring new small nontarget lesions as evidence of progression (instead, net tumor burden is used to gauge progression).[19] Immune-related progression-free survival (PFS) was defined in the same

way as PFS, and analysis was conducted similar to the analysis of PFS. Median immune-related PFS and hazard ratios along with 80% CIs were estimated.

Immune-Related Responses

Immune-related response assessment criteria were applied by the sponsor to investigator-assessed tumor measurements. Median immune-related PFS was 4.3 (80% CI, 2.8 to 6.9), 5.4 (80% CI, 4.2 to 7.1), and 6.9 months (80% CI, 4.4 to 8.5) in the nivolumab 0.3-, 2-, and 10-mg/kg groups, respectively (Appendix Table A2). Immune-related objective response rate was 20%, 22%, and 26% in the nivolumab 0.3-, 2-, and 10-mg/kg groups, respectively (Appendix Table A2), similar to the corresponding objective response rate (Table 2).

Table A1

Immune-Related RECIST (version 1.1) Definitions

Target Lesion Response	Nontarget Lesion Response	New Measurable Lesions	New Nonmeasurable Lesions	Change in Tumor Burden (%)	Overall Immu
CR	CR	Any	Any	–100	
PR	Any	Any	Any	≤ –30	
				> –30 to < 20	
				≥ 20	
SD	Any	Any	Any	> –30 to < 20	
				≥ 20	
PD	Any	Any	Any	≥ 20	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

[*] Including measurable new lesions when present.

Table A2

Exploratory End Points Based on Immune-Related RECIST (version 1.1) Criteria

	Nivolumab Arm (mg/kg)					
	0.3 (n = 60)		2 (n = 54)		10 (n = 54)	
Parameter	No.	%	No.	%	No.	%
Immune-related PFS						
Events	35	58	33	61	31	57
Median, months	4.3		5.4		6.9	
80% CI	2.8 to 6.9		4.2 to 7.1		4.4 to 8.5	
6-month rate, %	0.4		0.5		0.5	
80% CI	0.3 to 0.5		0.4 to 0.6		0.5 to 0.6	
HR[*]						
2 *v* 0.3 mg/kg			0.9			
80% CI			0.7 to 1.2			
10 *v* 0.3 mg/kg			0.9			

	Nivolumab Arm (mg/kg)					
	0.3 (n = 60)		2 (n = 54)		10 (n = 54)	
Parameter	No.	%	No.	%	No.	%
80% CI			0.6 to 1.2			
10 *v* 2 mg/kg			1.0			
80% CI			0.7 to 1.4			
Trend test *P*[†]			.6			
Immune-related ORR						
Events[‡]	12	20	12	22	14	26
Exact 80% CI	13.4 to 28.2		15.0 to 31.1		18.2 to 35.1	
Stratified odds ratio						
2 *v* 0.3 mg/kg			1.2			
80% CI			0.6 to 2.3			
10 *v* 0.3 mg/kg			1.3			
80% CI			0.7 to 2.6			
10 *v* 2 mg/kg			1.3			
80% CI			0.7 to 2.6			
Trend test *P*[§]			.5			

Abbreviations: HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival.

[*] Stratified Cox proportional hazards model.

[†] Stratified log-rank trend test with 20% significance level (two sided).

[‡] Using same definition of PFS as for primary end point but accounting for assessment that occurred after initiation of subsequent anticancer therapy.

[§] Complete plus partial responses per immune-related RECIST (version 1.1) criteria (sponsor assessment).

Table A3

Summary of Efficacy Results According to PD-L1 Expression Status (prototype assay) at 5% Cutoff (randomly assigned patients[*])

	PD-L1 Expression			
	< 5% (n = 78)		≥ 5% (n = 29)	
Parameter	No.	%	No.	%
PFS	64	82	22	76
Median, months	2.9		4.9	
95% CI	2.1 to 4.2		1.4 to 7.8	
ORR	14	18	9	31
95% CI	10.2 to 28.3		15.3 to 50.8	
OS	47	60	13	45
Median, months	18.2		NR	
95% CI	12.7 to 26.0		13.4 to NR	

Abbreviations: NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival.

[*] Data for 61 patients were not available or missing from analysis.

Table A4

Nivolumab Select AEs

Category	Preferred Term
Endocrine events	Adrenal insufficiency
	Adrenal suppression
	Blood corticotrophin decreased
	Blood corticotrophin increased
	Secondary adrenocortical insufficiency
	Diabetes mellitus
	Latent autoimmune diabetes in adults
	Hypophysitis
	Autoimmune thyroiditis
	Blood thyroid-stimulating hormone decreased
	Blood thyroid-stimulating hormone increased
	Hyperthyroidism
	Hypothyroidism
	Thyroid function test abnormal
	Thyroiditis
	Thyroxine decreased
	Thyroxine free decreased
	Thyroxine free increased
	Thyroxine increased
	Tri-iodothyronine uptake increased
GI events	Colitis
	Diarrhea
	Enteritis
	Enterocolitis
	Frequent bowel movements
	GI perforation
Hepatic events	Acute hepatic failure
	ALT increased
	AST increased
	Bilirubin conjugated increased
	Blood bilirubin increased
	Hepatic enzyme increased
	Hepatic failure
	Hepatitis
	Hyperbilirubinemia
	Liver disorder
	Liver function test abnormal
	Transaminases increased
Infusion reactions events	Anaphylactic reaction

Category	Preferred Term
	Hypersensitivity
	Infusion-related reaction
Pulmonary events	Acute respiratory distress syndrome
	Acute respiratory failure
	Interstitial lung disease
	Lung infiltration
	Pneumonitis
Renal events	Blood creatinine increased
	Creatinine renal clearance decreased
	Hypercreatininemia
	Nephritis
	Nephritis allergic
	Renal failure
	Renal failure acute
	Renal tubular necrosis
	Tubulointerstitial nephritis
Skin events	Blister
	Dermatitis
	Dermatitis exfoliative
	Drug eruption
	Eczema
	Erythema
	Exfoliative rash
	Palmar-plantar erythrodysesthesia syndrome
	Photosensitivity reaction
	Pruritus
	Pruritus allergic
	Pruritus generalized
	Psoriasis
	Rash
	Rash erythematous
	Rash generalized
	Rash macular
	Rash maculopapular
	Rash papular
	Rash pruritic
	Skin exfoliation
	Skin irritation
	Urticaria

Abbreviation: AE, adverse event.

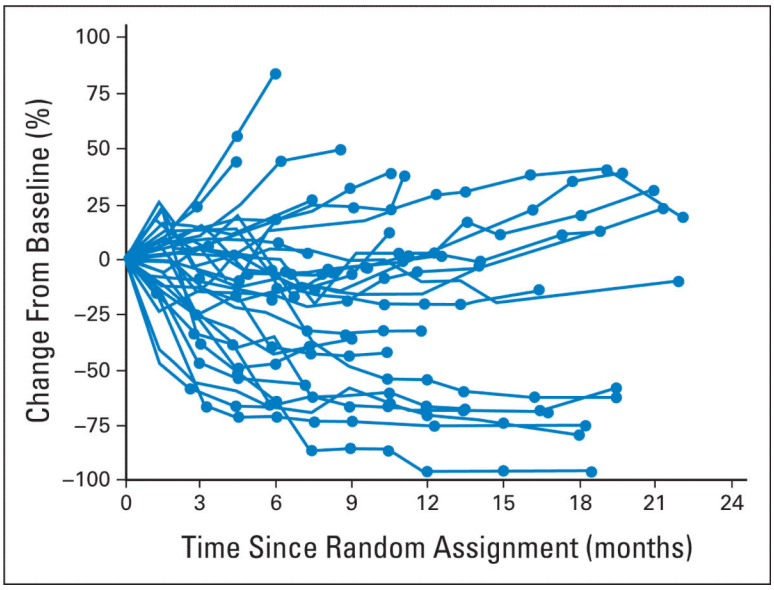

Fig A1.

Changes in measurable lesions from study baseline in patients treated beyond progression (n = 36 [0.3 mg/kg, n = 10; 2 mg/kg, n = 12; 10 mg/kg, n = 14]). Circles represent assessments that occurred after initial progression.

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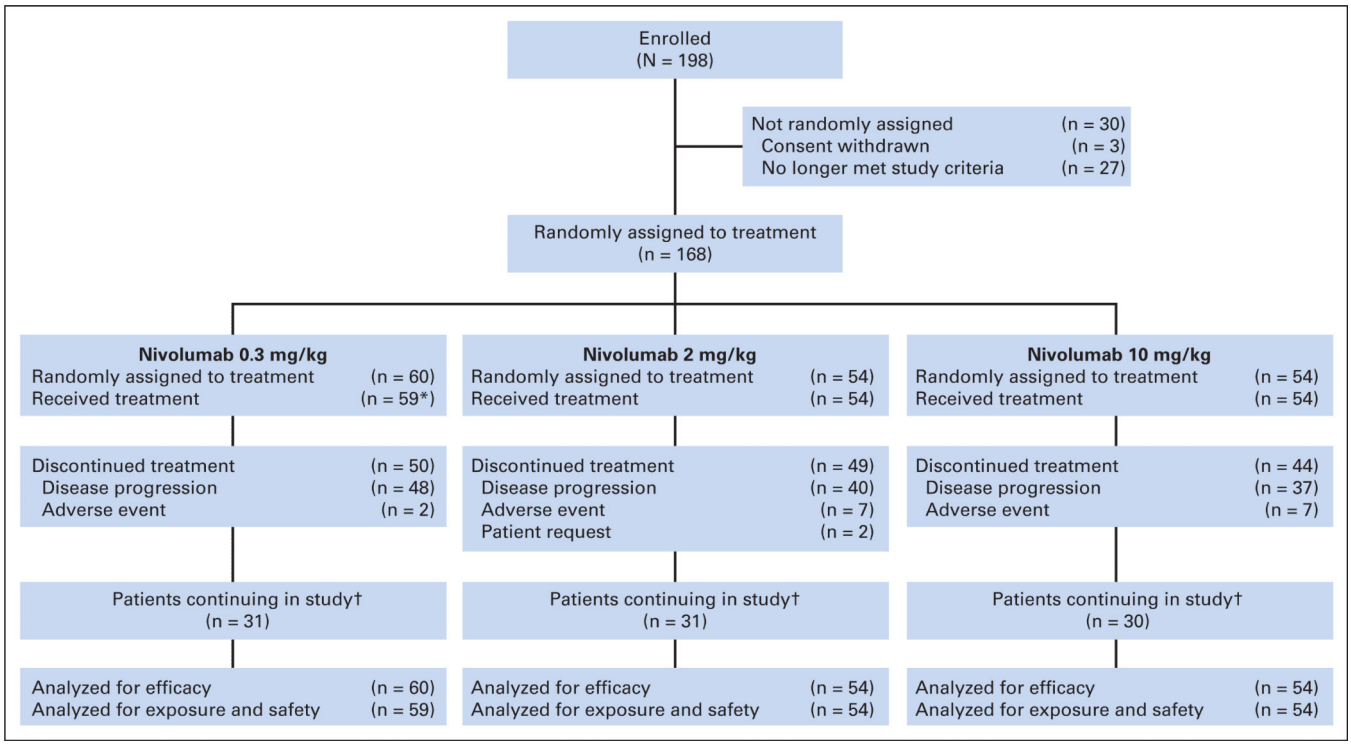

Fig 1.

Patient disposition (as of May 15, 2013, data cutoff). (*) One patient not treated; no longer met study criteria. (†) Includes patients continuing in treatment period and patients in follow-up period.

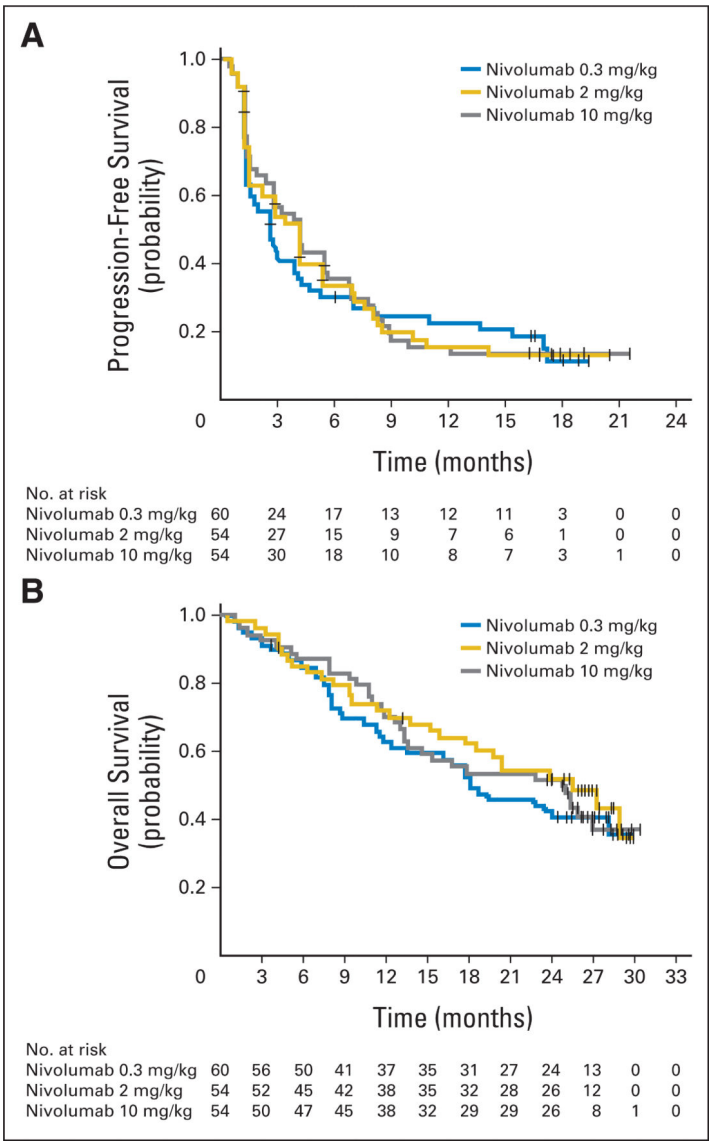

Fig 2.

(A) Progression-free and (B) overall survival by treatment arm (randomly assigned patients). Tick marks represent censored observations.

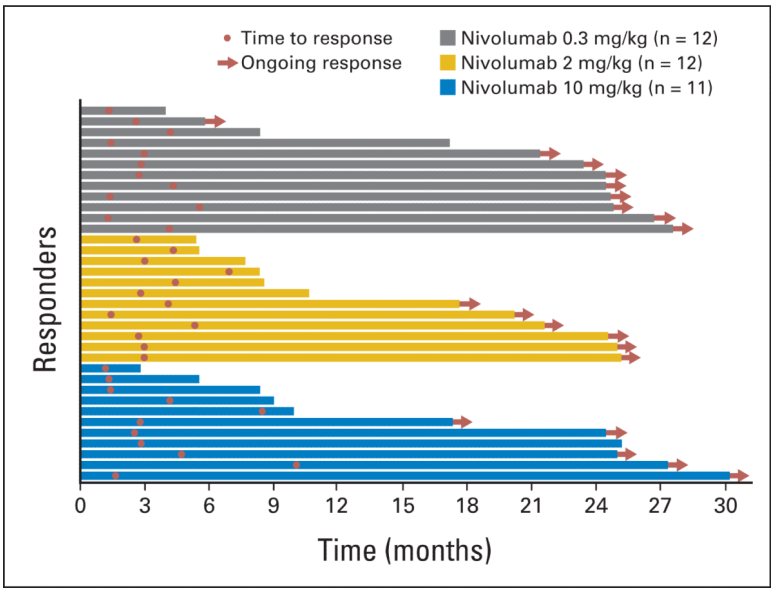

Fig 3.

Duration of response in patients who achieved objective response by dose treatment arm. Based on data cutoff date of March 5, 2014.

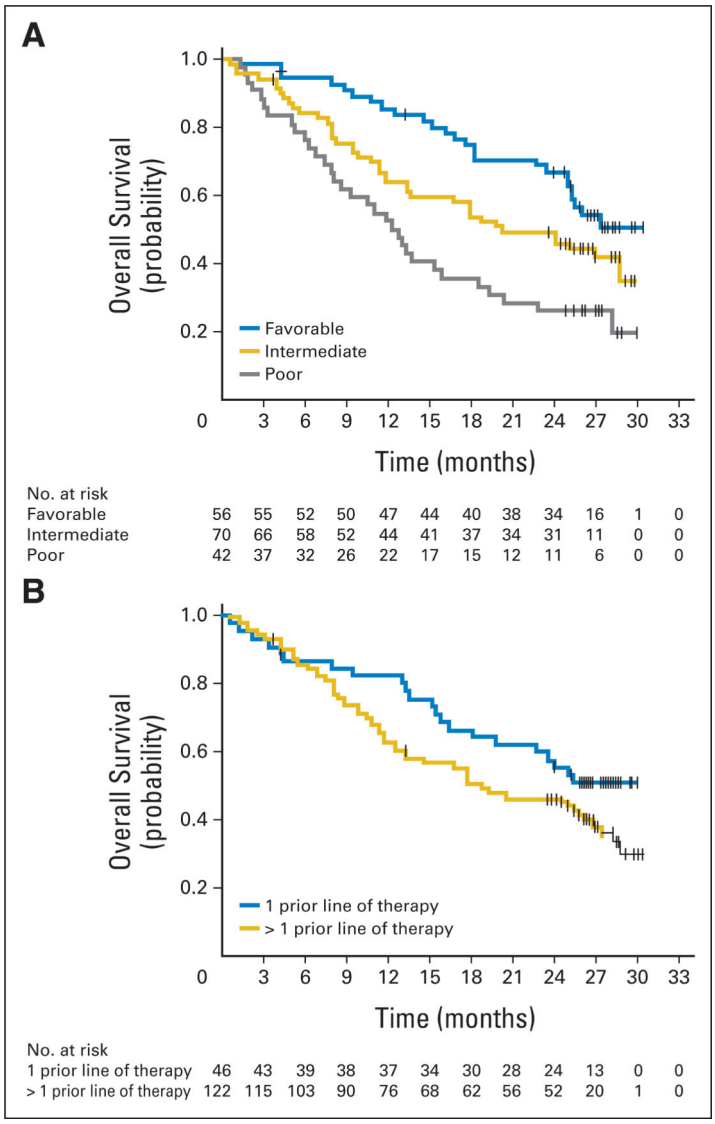

Fig 4.

Overall survival (randomly assigned patients) by (A) Memorial Sloan-Kettering Cancer Center risk group and (B) number of prior therapies in advanced or metastatic setting. Tick marks represent censored observations.

Table 1

Baseline Demographic and Clinical Characteristics (randomly assigned patients)

	Nivolumab Arm (mg/kg)							
	0.3 (n = 60)		2 (n = 54)		10 (n = 54)		Total (N = 168)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age, years								
Mean	61		61		61		61	
SD	9		8		10		9	
Sex								
Male	41	68	40	74	40	74	121	72
Female	19	32	14	26	14	26	47	28
MSKCC risk group[*]								
Favorable	20	33	18	33	18	33	56	33
Intermediate	26	43	22	41	22	41	70	42
Poor	14	23	14	26	14	26	42	25
Karnofsky performance status, %[†]								
70 or 80	22	37	30	56	25	46	77	46
90 or 100	38	63	24	44	28	52	90	54
No. of evaluable sites[‡]								
1	13	22	5	9	12	22	30	18
≥ 2	47	78	49	91	42	78	138	82
Site of lesion (> 20% in any group)[‡§]								
Lung	46	77	39	72	39	72	124	74
Lymph node	29	48	35	65	34	63	98	58
Liver	15	25	13	24	19	35	47	28
Skin/soft tissue	18	30	11	20	11	20	40	24
Adrenal	8	13	19	35	10	19	37	22
Prior radiotherapy	18	30	21	39	22	41	61	36
Prior surgery	58	97	53	98	54	100	165	98
No. of prior systemic regimens in metastatic setting								
1	16	27	16	30	18	33	50	30
2	20	33	19	35	23	43	62	37
≥ 3	24	40	19	35	13	24	56	33
No. of prior systemic antiangiogenic regimens in metastatic setting								
1	34	57	35	65	35	65	104	62
2	22	37	16	30	18	33	56	33
3	4	7	3	6	1	2	8	5
Common prior systemic therapies in metastatic setting[‖]								
Sunitinib	46	77	42	78	37	69	125	74
Everolimus	21	35	18	33	18	33	57	34
Pazopanib	15	25	18	33	13	24	46	27

	Nivolumab Arm (mg/kg)							
	0.3 (n = 60)		2 (n = 54)		10 (n = 54)		Total (N = 168)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Interleukin-2	15	25	11	20	12	22	38	23
Sorafenib	13	22	8	15	10	19	31	19

Abbreviations: MSKCC, Memorial Sloan-Kettering Cancer Center; SD, standard deviation.

[*] Interactive voice response system source.

[†] One patient (1.9%) in 10-mg/kg group had deviation to Karnofsky performance status < 70%.

[‡] Including target and nontarget lesions.

[§] Patients could have lesions at more than one site.

[//] > 20% of patients in any group.

Table 2

Summary of Efficacy Results (randomly assigned patients)

	Nivolumab Arm (mg/kg)					
	0.3 (n = 60)		2 (n = 54)		10 (n = 54)	
Parameter	**No.**	**%**	**No.**	**%**	**No.**	**%**
Primary End Point						
PFS						
Median, months	2.7		4.0		4.2	
80% CI	1.9 to 3.0		2.8 to 4.2		2.8 to 5.5	
6-month rate, %	0.3		0.3		0.4	
80% CI	0.2 to 0.4		0.2 to 0.4		0.3 to 0.4	
HR[a]						
2 *v* 0.3 mg/kg			1.0			
80% CI			0.7 to 1.3			
10 *v* 0.3 mg/kg			1.0			
80% CI			0.8 to 1.3			
10 *v* 2 mg/kg			1.0			
80% CI			0.8 to 1.3			
Trend test *P*[b]			.9			
Secondary End Points						
Best objective response[c]						
CR	1	2	1	2	0	0
PR	11	18	11	20	11	20
SD	22	37	23	43	24	44
PD	24	40	18	33	17	32
Not evaluable	2[d]	3	1[e]	2	2[f]	4
ORR[g]	12	20	12	22	11	20
Exact 80% CI	13.4 to 28.2		15.0 to 31.1		13.4 to 29.1	
Stratified odds ratio						
2 *v* 0.3 mg/kg			1.2			
80% CI			0.6 to 2.4			
10 *v* 0.3 mg/kg			0.9			
80% CI			0.4 to 1.8			
10 *v* 2 mg/kg			0.9			
80% CI			0.4 to 1.8			
Trend test *P*[h]			1.0			

Abbreviations: CR, complete response; HR, hazard ratio; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Stratified Cox proportional hazards model.

[b] Stratified log-rank trend test with 20% significance level (two sided).

[c] Per RECIST (version 1.1) criteria (investigator assessment).

[d] Never treated (n = 1), and death before disease assessment (n = 1).

[e] Early discontinuation because of toxicity.

[f] Death before disease assessment.

[g] CR plus PR per RECIST (version 1.1) criteria (investigator assessment).

[h] Exact Cochran-Armitage trend test with 20% significance level (two sided).

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Table 3

Treatment-Related AEs

	Nivolumab Arm (mg/kg)											
	0.3 (n = 59)				2 (n = 54)				10 (n = 54)			
	Any Grade		Grade 3 to 4		Any Grade		Grade 3 to 4		Any Grade		Grade 3 to 4	
AE	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any treatment-related AE	44	75	3	5	36	67	9	17	42	78	7	13
Treatment-related AEs occurring in ≥ 10% of patients in any group												
Fatigue	14	24	0	0	12	22	0	0	19	35	0	0
Nausea	6	10	1	2	7	13	1	2	7	13	0	0
Pruritus	6	10	0	0	5	9	1	2	6	11	0	0
Rash	5	9	0	0	4	7	0	0	7	13	0	0
Appetite decreased	2	3	0	0	7	13	0	0	2	4	0	0
Diarrhea	2	3	0	0	6	11	0	0	8	15	0	0
Dry mouth	2	3	0	0	3	6	0	0	6	11	0	0
Arthralgia	1	2	0	0	4	7	0	0	8	15	1	2
Dry skin	1	2	0	0	3	6	0	0	7	13	0	0
Hypersensitivity	1	2	0	0	1	2	0	0	9	17	0	0
Treatment-related select AEs*												
Skin	13	22	0	0	12	22	2	4	15	28	0	0
Pruritus	6	10	0	0	5	9	1	2	6	11	0	0
Rash	5	9	0	0	4	7	0	0	7	13	0	0
Endocrine	4	7	0	0	6	11	2	4	8	15	0	0
Hypothyroidism	2	3	0	0	4	7	1	2	4	7	0	0
GI	3	5	0	0	6	11	1	2	8	15	0	0
Diarrhea	2	3	0	0	6	11	0	0	8	15	0	0
Pulmonary	3	5	0	0	2	4	0	0	4	7	0	0
Pneumonitis	3	5	0	0	2	4	0	0	3	6	0	0
Hepatic	2	3	1	2	4	7	2	4	3	6	0	0
AST increased	2	3	1	2	4	7	1	2	2	4	0	0
ALT increased	2	3	1	2	2	4	1	2	3	6	0	0

AE	Nivolumab Arm (mg/kg)											
	0.3 (n = 59)				2 (n = 54)				10 (n = 54)			
	Any Grade		Grade 3 to 4		Any Grade		Grade 3 to 4		Any Grade		Grade 3 to 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Renal	1	2	0	0	0	0	0	0	1	2	0	0
Blood creatinine increased	1	2	0	0	0	0	0	0	1	2	0	0

Abbreviation: AE, adverse event.

* Defined as AE with potential immune-mediated etiology, which may require special monitoring and specific unique interventions. Full listing of preferred terms for each select AE category is provided in online-only Appendix Table A4.