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ORIGINAL REPORT

Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Programmed death 1 is an immune checkpoint that suppresses antitumor immunity. Nivolumab, a fully human immunoglobulin G4 programmed death 1 immune checkpoint inhibitor antibody, was active and generally well tolerated in patients with advanced solid tumors treated in a phase I trial with expansion cohorts. We report overall survival (OS), response durability, and long-term safety in patients with non–small-cell lung cancer (NSCLC) receiving nivolumab in this trial.

Patients and Methods
Patients (N = 129) with heavily pretreated advanced NSCLC received nivolumab 1, 3, or 10 mg/kg intravenously once every 2 weeks in 8-week cycles for up to 96 weeks. Tumor burden was assessed by RECIST (version 1.0) after each cycle.

Results
Median OS across doses was 9.9 months; 1-, 2-, and 3-year OS rates were 42%, 24%, and 18%, respectively, across doses and 56%, 42%, and 27%, respectively, at the 3-mg/kg dose (n = 37) chosen for further clinical development. Among 22 patients (17%) with objective responses, estimated median response duration was 17.0 months. An additional six patients (5%) had unconventional immune-pattern responses. Response rates were similar in squamous and nonsquamous NSCLC. Eighteen responding patients discontinued nivolumab for reasons other than progressive disease; nine (50%) of those had responses lasting > 9 months after their last dose. Grade 3 to 4 treatment-related adverse events occurred in 14% of patients. Three treatment-related deaths (2% of patients) occurred, each associated with pneumonitis.

Conclusion
Nivolumab monotherapy produced durable responses and encouraging survival rates in patients with heavily pretreated NSCLC. Randomized clinical trials with nivolumab in advanced NSCLC are ongoing.

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INTRODUCTION

Progress in the treatment of advanced non–small-cell lung cancer (NSCLC) over the last decade has been modest.[1] Although molecularly targeted therapies have significantly affected the small proportion of patients whose tumors harbor epidermal growth factor receptor (*EGFR*) mutations[2,3] or anaplastic lymphoma kinase (*ALK*) gene rearrangements,[4] the majority of patients with advanced NSCLC die within 1 year of diagnosis. Clearly, a plateau has been reached with chemotherapy, with some enhancement of benefit from the addition of bevacizumab, an antiangiogenesis agent targeting vascular endothelial growth factor.[5] Additional molecularly targeted agents have been evaluated in clinical trials with limited success, and efforts are currently focusing on identifying biomarkers in tumor or blood to predict benefit from such therapies.

Programmed death 1 (PD-1) is an immune checkpoint receptor expressed on activated T cells, which normally serves to dampen the immune

response to protect against excessive inflammation and the development of autoimmunity.[6,7] However, in the setting of malignancy, PD-1 signaling, driven primarily by adaptive expression of programmed death ligand 1 (PD-L1) within the tumor, inactivates primed T cells that recognize tumor-specific antigens, allowing tumor growth and metastasis.[8-10] PD-1 pathway blockade with monoclonal antibodies offers a novel approach to restoring T cell–mediated antitumor immunity, with the potential for application across a broad population of patients with NSCLC.

The tolerability and activity of nivolumab, a fully human immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody,[11] were previously reported in patients with NSCLC, melanoma, and renal cell carcinoma treated in a phase I multidose clinical trial.[12] We now report overall survival (OS) outcomes in the population of patients with NSCLC, in addition to further characterizing response duration and the long-term safety profile of nivolumab.

PATIENTS AND METHODS

Trial Design

This phase I dose-escalation cohort expansion trial evaluated the safety and clinical activity of nivolumab in patients with advanced NSCLC, melanoma, and kidney, colorectal, and castration-resistant prostate cancer. Detailed methods, including the study protocol and statistical analysis plan, have been previously published.[12] Nivolumab was administered intravenously as a 1-hour infusion every 2 weeks in 8-week treatment cycles in an outpatient setting. During dose escalation, patients with all cancer types received 1-, 3-, or 10-mg/kg doses of nivolumab; during cohort expansion, patients with NSCLC were stratified for squamous versus nonsquamous cell histology and randomly assigned to receive 1-, 3-, or 10-mg/kg doses of nivolumab. Patients continued treatment for up to 96 weeks (12 cycles) or until unacceptable toxicity, confirmed complete response, confirmed disease progression, or withdrawal of consent. In the absence of clinical deterioration, patients could continue treatment after initial disease progression to allow for patterns of response consistent with immune-related response criteria (ie, persistent reduction in target lesions in presence of new lesions or regression of target lesions after initial growth).[13] Patients with stable disease or ongoing complete or partial responses at the end of the 96-week treatment period could restart nivolumab at the time of confirmed disease progression, if this occurred within 1 year of completing initial therapy, and continue treatment for up to 1 year.

The study protocol was approved by local institutional review boards, and the study was conducted in accordance with international standards of good clinical practice. All patients or their legal representatives provided written informed consent before enrollment.

Patients

Patients eligibility criteria were as follows: pathologically confirmed advanced NSCLC, age $\geq$ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (before implementation of amendment 4 in October 2010, ECOG performance status of 0 to 2 was allowed), adequate organ function, and one to five prior systemic treatment regimens for advanced NSCLC. Patients also had to have experienced progression through at least one platinum- or taxane-based regimen and have at least one measurable lesion by RECIST (version 1.0).[14] Patients with treated brain metastases stable for at least 8 weeks were eligible. Exclusion criteria included autoimmune disease, prior therapy with T cell–modulating antibodies (eg, anti–CTLA-4, anti–PD-1, and anti–PD-L1), conditions requiring immunosuppressive medications, history of infection by HIV, and active infection by hepatitis B or C viruses.

Evaluation

All treated patients were evaluated for safety by laboratory tests, physical examination, and adverse event assessment at screening, every 2 weeks during therapy, and up to 70 days after receiving the last dose of nivolumab. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 15.1). The severity of adverse events was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[15] Select adverse events, defined as adverse events with potential immunologic etiologies that require more frequent monitoring or intervention with immune suppression or hormone replacement, were identified based on a sponsor-derived prespecified list of Medical Dictionary for Regulatory Activities terms in seven categories.[16]

Tumor status was assessed radiographically at screening and after each 8-week treatment cycle. The objective response rate (ORR; percentage of patients with confirmed complete or partial responses among all treated patients) was the primary parameter of clinical activity. The protocol was amended after all patients were enrolled so that survival data could be collected. After completion of the treatment and follow-up periods, survival status was assessed approximately every 3 months either by office visits or telephone calls until study completion. Baseline characteristics of age, sex, ECOG performance status, histology, and number of prior therapies were collected for all patients; *EGFR* and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) tumor mutation status were also collected from the study sites when available.

Statistical Analysis

Efficacy analysis, including OS results for all patients, is reported as of September 2014. Baseline characteristics and the safety analysis are reported as of March 2013. Associations between clinical activity and various baseline characteristics were explored by estimating the ORR by baseline characteristic subgroups and by plots of changes in tumor burden for selected characteristics (eg, by prior therapy or mutation status).

RESULTS

Patient Characteristics

From November 2008 through January 2012, 129 patients with NSCLC were enrolled across 12 sites in the United States. Patients had a median age of 65 years, and 98% had an ECOG performance status of 0 or 1; 42% and 57% had squamous and nonsquamous NSCLC, respectively (Table 1). NSCLC histology was unknown in one patient. Patients were heavily pretreated; 54% had received three or more prior systemic treatments for advanced NSCLC. As of September 2014, 129 patients were evaluated for clinical activity, with a median follow-up of 39 months (range, 32 to 66 months).

Clinical Activity

Median OS was 9.9 months (95% CI, 7.8 to 12.4) for all 129 patients with NSCLC (Table 2; Fig 1A). In 37 patients receiving nivolumab 3 mg/kg, the dose currently being used for phase III trials, median OS was 14.9 months (95% CI, 7.3 to 30.3). Median OS was 9.2 months in both the 1- and 10-mg/kg cohorts (Table 2; Fig 1B). In the total population of patients with NSCLC, across all dose levels, 1-, 2-, and 3-year survival rates were 42% (95% CI, 33 to 50), 24% (95% CI, 17 to 33), and 18% (95% CI, 11 to 25), respectively. At the 3-mg/kg dose, 1-, 2-, and 3-year OS rates were 56% (95% CI, 38 to 71), 42% (95% CI, 24 to 58), and 27% (95% CI, 12 to 43), respectively. Median OS and survival rates were similar in patients with squamous and nonsquamous histologies (Table 2; Data Supplement). Median progression-free survival (PFS) across doses was 2.3 months (95% CI, 1.8 to 3.7), with PFS rates at 6 months, 1 year, and 2 years of 33%, 22%, and 9%, respectively (Data Supplement).

Table 1. Baseline Characteristics and Prior Therapy of All Treated Patients With NSCLC

Characteristic	All Treated Patients (N = 129) No.	%
Age, years		
Median	65	
Range	38-85	
Sex		
Male	79	61.2
Female	50	38.8
Tumor cell histology		
Squamous	54	41.9
Nonsquamous	74	57.4
Unknown	1	0.8
ECOG performance status[17]		
0 or 1	127	98.4
2*	2	1.6
No. of prior systemic treatment regimens		
1-2	59	45.7
≥ 3	70	54.3
Nature of prior therapy		
Platinum-based chemotherapy	128	99.2
Tyrosine kinase inhibitor	36	27.9
Surgery†	85	65.9
Radiotherapy†	75	58.1
Hormonal, immunologic, or biologic therapy	16	12.4
Other	9	7.0
EGFR tumor mutation status		
Mutant	12	9.3
Wild type	56	43.4
Unknown‡	61	47.3
KRAS tumor mutation status		
Mutant	21	16.3
Wild type	36	27.9
Unknown‡	72	55.8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell cancer.

*One patient was enrolled before protocol amendment 4, which changed eligibility requirements from ECOG performance status of 0-2 to 0-1. Second patient was enrolled without evaluation of ECOG performance status at screening and had ECOG performance status of 2 at time of first nivolumab treatment.

†Surgery and radiotherapy were not considered to be systemic therapies.

‡*EGFR* or *KRAS* mutational testing were not required for entry into this trial; 41 (67%) of 61 patients with unknown *EGFR* tumor status and 43 (60%) of 72 patients with unknown *KRAS* tumor status had squamous cell histology; these patients likely were not tested for *EGFR* or *KRAS* mutations, because squamous non–small-cell lung cancer rarely harbors *EGFR* or *KRAS* mutations.[18-20]

An ORR of 17% was observed across all doses (Table 2). Patients with squamous and nonsquamous histologies had similar ORRs (17% and 18%, respectively). ORRs by dose were 3% (1 mg/kg), 24% (3 mg/kg), and 20% (10 mg/kg). For the 110 patients randomly assigned to the 1-, 3-, and 10-mg/kg doses, ORR was 3%, 22.2%, and 19.5%, respectively, and OS was 9.2, 14.9, and 8.6 months, respectively, similar to the overall population. Six (5%) of 129 patients had unconventional immune-pattern responses (Data Supplement) and were not considered responders in the calculation of ORR. OS for these patients was 7.3, 11.2, 16.7, 26.7, 34.5+ (ongoing), and 54.3+ months as of the September 2014 data analysis. Stable disease lasting at least 24 weeks was observed in an additional 10% of patients.

Among the 22 patients with objective responses, the Kaplan-Meier estimated median duration of response was 17.0 months (range, 1.4+ to 36.8+ months; Table 2 and Data Supplement). Eleven (50%) responses were documented at the first 8-week tumor assessment (Figs 1C and 1D). Median PFS of the 22 responders was 20.6 months (95% CI, 11.4 to not reached; range, 4.7+ to 40.3+ months; Fig 1D). At the time of data analysis, responses were ongoing in 41% (nine of 22) of the responders. Among 18 responders who discontinued nivolumab therapy for reasons other than disease progression (completion of maximum cycles, n = 7; adverse events, n = 8; withdrawal of consent, n = 2; other, n = 1), 50% (nine) had responses for more than 9 months after the end of therapy (range, 9.2 to 16.4+ months). Figure 2 shows an example of an ongoing response in a patient with widely metastatic chemotherapy-refractory squamous NSCLC.

Analysis of predefined patient subgroups revealed similar ORRs (Table 3). Best changes in tumor burden presented by number of prior therapies and by *EGFR* and *KRAS* tumor mutation status are shown in the Data Supplement. Exploratory analysis by tumor PD-L1 expression, using an automated immunohistochemistry assay (Dako North America, Carpinteria, CA), on archived tumor samples from 68 patients found no clear association between PD-L1 expression and response or survival (Data Supplement).[21] An additional exploratory analysis conducted retrospectively by select sites of response by smoking exposure in 80 evaluable patients found ORR was higher in patients with a smoking history of more than 5 pack-years (30%; n = 66) than in those with a history of 5 pack-years or less (no responses; n = 14).[22]

Safety

In the dose-escalation portion of this trial, the maximum-tolerated dose was not reached at the highest planned dose of 10 mg/kg. Subsequently, the 1-, 3-, and 10-mg/kg cohorts were expanded in patients with NSCLC. At the time of the March 2013 safety analysis, the median duration of therapy was 13.6 weeks (range, 2 to 104 weeks). Among the treated patients with NSCLC, 71% had experienced treatment-related adverse events of any grade (Data Supplement). The most common were fatigue (24%), decreased appetite (12%), and diarrhea (10%). Eighteen patients (14%) experienced grade 3 to 4 treatment-related adverse events, and the most common was fatigue (3%; Data Supplement). The spectrum, incidence, and severity of the treatment-related adverse events were similar for the NSCLC population (N = 129) and the total patient population (N = 306).[23]

Treatment-related select adverse events of any grade were observed in 41% of 129 patients with NSCLC, and the most common included skin, GI, and pulmonary events (16%, 12%, and 7%, respectively; Table 4). Four patients (3%) had treatment-related grade ≥ 3 pneumonitis, including one with grade 5 pneumonitis (Data Supplement). Three treatment-related deaths occurred among patients with NSCLC, each associated with pneumonitis (two with unresolved grade 4 pneumonitis, and one with grade 5 pneumonitis). Two of the deaths occurred early in the trial, and the third occurred after the March 2013 safety analysis (descriptions provided in Data Supplement). No clear relationships between the occurrence of pneumonitis and dose level or treatment duration were noted.

Table 2. Clinical Activity of Nivolumab in Patients With NSCLC*

Dose (mg/kg)	ORR† No. of Patients	ORR† %	ORR† 95% CI	Duration of Response (months)‡§ Median	Duration of Response (months)‡§ Range	OS (months)§‖ Median	OS (months)§‖ 95% CI	OS Rate§ 1 Year %	1 Year 95% CI	1 Year No. at Risk	2 Years %	2 Years 95% CI	2 Years No. at Risk	3 Years %	3 Years 95% CI	3 Years No. at Risk
NSCLC¶																
All doses	22 of 129	17.1	11.0 to 24.7	17.0	1.4+ to 36.8+	9.9	7.8 to 12.4	42	33 to 50	48	24	17 to 33	26	18	11 to 25	12
1	1 of 33	3.0	0.1 to 15.8	14.7	14.7 to 14.7	9.2	5.3 to 11.1	33	17 to 49	9	15	5 to 30	4	15	5 to 30	1
3	9 of 37	24.3	11.8 to 41.2	17.0	3.7+ to 32.6+	14.9	7.3 to 30.3	56	38 to 71	17	42	24 to 58	11	27	12 to 43	5
10	12 of 59	20.3	11.0 to 32.8	19.1	1.4+ to 36.8+	9.2	5.2 to 12.4	38	26 to 50	22	20	11 to 31	11	14	7 to 25	6
Squamous NSCLC																
All doses	9 of 54	16.7	7.9 to 29.3	NR#	3.7 to 36.8+	9.2	7.3 to 12.5	41	27 to 54	20	24	14 to 37	12	19	9 to 32	6
1	0 of 15	0	0	0	0	8.0	2.4 to 13.3	29	9 to 52	4	14	2 to 37	2	0	0	0
3	4 of 18	22.2	6.4 to 47.6	NR#	3.7+ to 32.6+	9.5	5.3 to NE	49	23 to 71	7	35	13 to 58	5	28	9 to 51	3
10	5 of 21	23.8	8.2 to 47.2	19.1	3.7 to 36.8+	10.5	4.9 to 16.7	43	22 to 62	9	24	9 to 43	5	18	5 to 37	3
Nonsquamous NSCLC																
All doses	13 of 74	17.6	9.7 to 28.2	14.2	1.4+ to 29.9	10.1	5.7 to 13.7	42	30 to 53	27	23	14 to 34	13	16	8 to 26	6
1	1 of 18	5.6	0.1 to 27.3	14.7	14.7 to 14.7	9.9	5.3 to 22.5	36	15 to 58	5	15	3 to 36	2	15	3 to 36	1
3	5 of 19	26.3	9.1 to 51.2	13.6	5.6 to 17.0	18.2	5.2 to 30.8	62	37 to 80	10	48	22 to 69	6	24	6 to 48	2
10	7 of 37	18.9	8.0 to 35.2	18.3	1.4+ to 29.9	7.4	4.5 to 11.0	34	19 to 49	12	16	6 to 30	5	12	4 to 26	3

Abbreviations: NE, not estimable; NR, not reached; NSCLC, non–small-cell cancer; ORR, objective response rate; OS, overall survival.
*September 2014 data analysis.
†Percentage of patients with confirmed complete or partial responses among all treated patients. CIs were calculated using Clopper-Pearson method. Individual patient responses were adjudicated per RECIST (version 1.0).
‡Time from date of first documented complete or partial response to time of documented progression, death, or last tumor assessment for censored data (denoted by +).
§Time-to-event end points (duration of response, OS, and OS rate) were estimated using Kaplan-Meier method. CIs for medians were calculated using Brookmeyer and Crowley method, and CIs for survival rates were calculated using Greenwood formula.
‖Time from date of first treatment to date of death resulting from any cause or last tumor assessment for those patients who were alive at date of data analysis.
¶One patient with unknown histology.
#Time point at which probability that responder's progress drops below 50% not reached because of insufficient No. of events and/or follow-up.

DISCUSSION

Current second-line therapies for advanced NSCLC generate ORRs of 7% to 9%, with median OS of approximately 8 months and 1-year survival rates of 30%.[24-26] The only third-line therapy approved for use in NSCLC is erlotinib, an EGFR tyrosine kinase inhibitor, with an ORR of 9% in a pooled population of patients, unselected for *EGFR*-mutant NSCLC, who had received one or two prior therapies for advanced NSCLC.[26] Limited data exist supporting the use of chemotherapy after progression through two lines of chemotherapy for advanced NSCLC.[27,28] Guidelines of the American Society of Clinical Oncology and the National Clinical Cancer Network currently do not recommend more than two lines of chemotherapy for advanced NSCLC, after which erlotinib, best supportive care alone, or clinical trial consideration is recommended.[29,30]

Unlike chemotherapy or tyrosine kinase inhibitors, immune checkpoint inhibitors aim to restore antitumor immunity, allowing the destruction of malignant cells with the potential for durable clinical benefit persisting long after cessation of therapy. By blocking the PD-1 inhibitory receptor, nivolumab releases immune suppression of primed tumor-specific T cells, enabling such cells to carry out their cytotoxic functions. The PD-1 receptor seems to be a clinically relevant target in NSCLC, demonstrated here by an ORR to nivolumab monotherapy of 17%, lasting for a median of 17.0 months among patients with heavily pretreated advanced NSCLC. The ORR in the subgroup of patients receiving three or more prior therapies for advanced NSCLC was 21%, similar to the ORR for the entire population of patients with NSCLC. This differs from chemotherapy, where response rates decrease with subsequent lines of therapy.[31] Median OS of 9.9 months and 1-, 2-, and 3-year survival rates of 42%, 24%, and 18% with nivolumab surpass expectations of second- and third-line chemotherapies, taking into account the caveats of a phase I dose-escalation/expansion trial design. This effect seemed to vary by dose, with an ORR of 24%, median OS of 14.9 months, and 1-, 2-, and 3-year survival rates of 56%, 45%, and 27%, respectively, in the 3-mg/kg dose cohort.

Response rates to nivolumab were similar across most patient subgroups despite dose, including those with squamous and nonsquamous NSCLC. Activity in squamous cell carcinoma was consistent with a recent report from a trial evaluating nivolumab in 117 patients who received at least two prior lines of chemotherapy for advanced squamous NSCLC, where ORR was 15%, with a 1-year survival rate of 41%.[32] Responses were seen in patients with *EGFR*– and *KRAS*–wild type and *EGFR*- and *KRAS*-mutant NSCLC; however, low patient numbers in each subset preclude association of mutation status with clinical outcomes after nivolumab therapy. Tumor PD-L1 status did not seem to predict response or survival; however, evaluable specimens were available for only half of the patients and were archival (most collected before systemic therapies received before nivolumab; updated data to be reported separately). Because tumor PD-L1

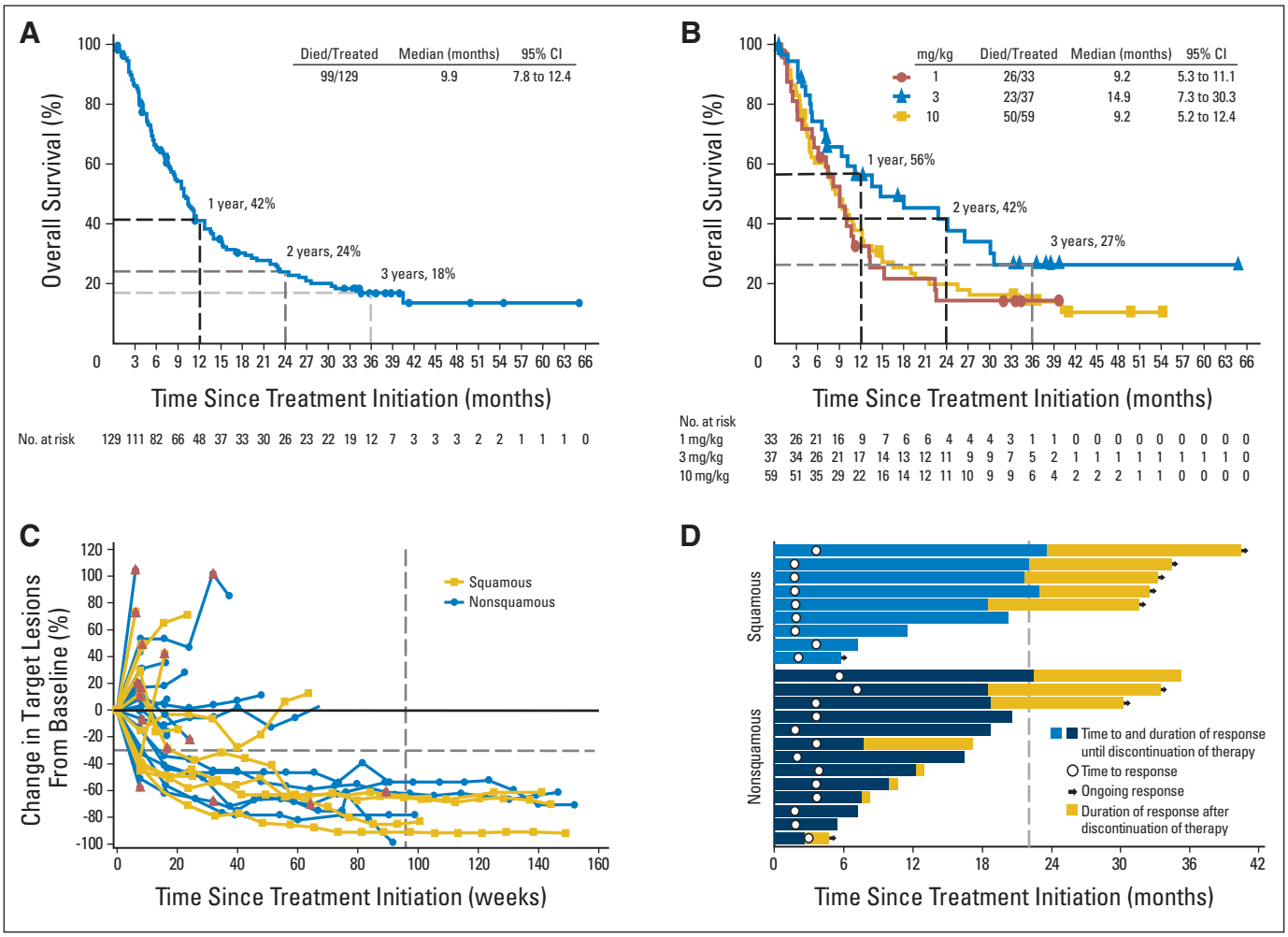

Fig 1. Clinical activity in patients with non–small-cell lung cancer (NSCLC) receiving nivolumab. Kaplan-Meier curves of overall survival (OS) for (A) total patient population (N = 129) and (B) patients who received nivolumab 1 (n = 33), 3 (n = 37), or 10 mg/kg (n = 59). Symbols indicate censored events, defined for OS as time to last known date alive before date of data analysis, for patients without death. (C) Tumor burden kinetics in patients with NSCLC treated with nivolumab 3 mg/kg (n = 37). Baseline tumor measurements are standardized to zero. Tumor burden was measured as sum of longest diameters of target lesions compared with baseline. Red triangles indicate first occurrence of new lesion. Horizontal dashed line at −30% indicates threshold for defining objective response (partial tumor regression) in absence of new lesions or nontarget disease progression, according to RECIST (version 1.0); vertical dashed line at 96 weeks indicates protocol-defined maximum duration of continuous nivolumab therapy. (D) Characteristics of objective responses in patients with squamous cell histology (n = 9) and nonsquamous cell histology (n = 13) treated with nivolumab. Vertical dashed line at 22 months indicates maximum planned duration of continuous nivolumab therapy. Eighteen responders discontinued nivolumab therapy for reasons other than disease progression, including: completion of maximum cycles (n = 7), adverse events (n = 8), withdrawal of consent (n = 2), and other (n = 1).

expression may vary over time and be induced by other anticancer therapy, results here may not be truly reflective of immediate pre-nivolumab tumor PD-L1 status. Analysis by smoking history suggested higher responses rates to nivolumab in former and current smokers, which is consistent with prior reports from trials evaluating nivolumab and other anti–PD-1 and anti–PD-L1 antibodies.[31,33-35] One potential explanation for this finding is the expected higher mutational load in smoking-associated lung cancer, leading to more tumor neoantigens and increased immunogenicity.[36]

The durability of response after discontinuation of nivolumab, coupled with the unconventional responses observed in some patients in this trial, underscores the unique mechanisms of action of immunotherapy compared with standard therapies for NSCLC. Among 18 RECIST responders who discontinued nivolumab for reasons other than disease progression, nine (50%) had responses lasting more than 9 months after their last dose at the time of data analysis. In addition to objective responses by RECIST, 5% of patients experienced immune-related radiographic responses—that is, persistent reduction in target lesions in the presence of new lesions or regression of target lesions after initial growth. Unconventional response patterns such as these will require clinicians to alter their approach to and assessment of patients receiving immunotherapy (eg, potentially continuing therapy in face of radiographic progression in patient who is medically stable without decline of performance status).

Nivolumab therapy was generally well tolerated, with 14% of patients experiencing grade 3 to 4 treatment-related adverse events. Toxicities did not seem to be cumulative.[16] Select adverse events with immune-based etiologies were generally low grade, and those at higher grades were manageable in most cases with drug discontinuation, immune suppressive agents (steroids or, rarely, infliximab),

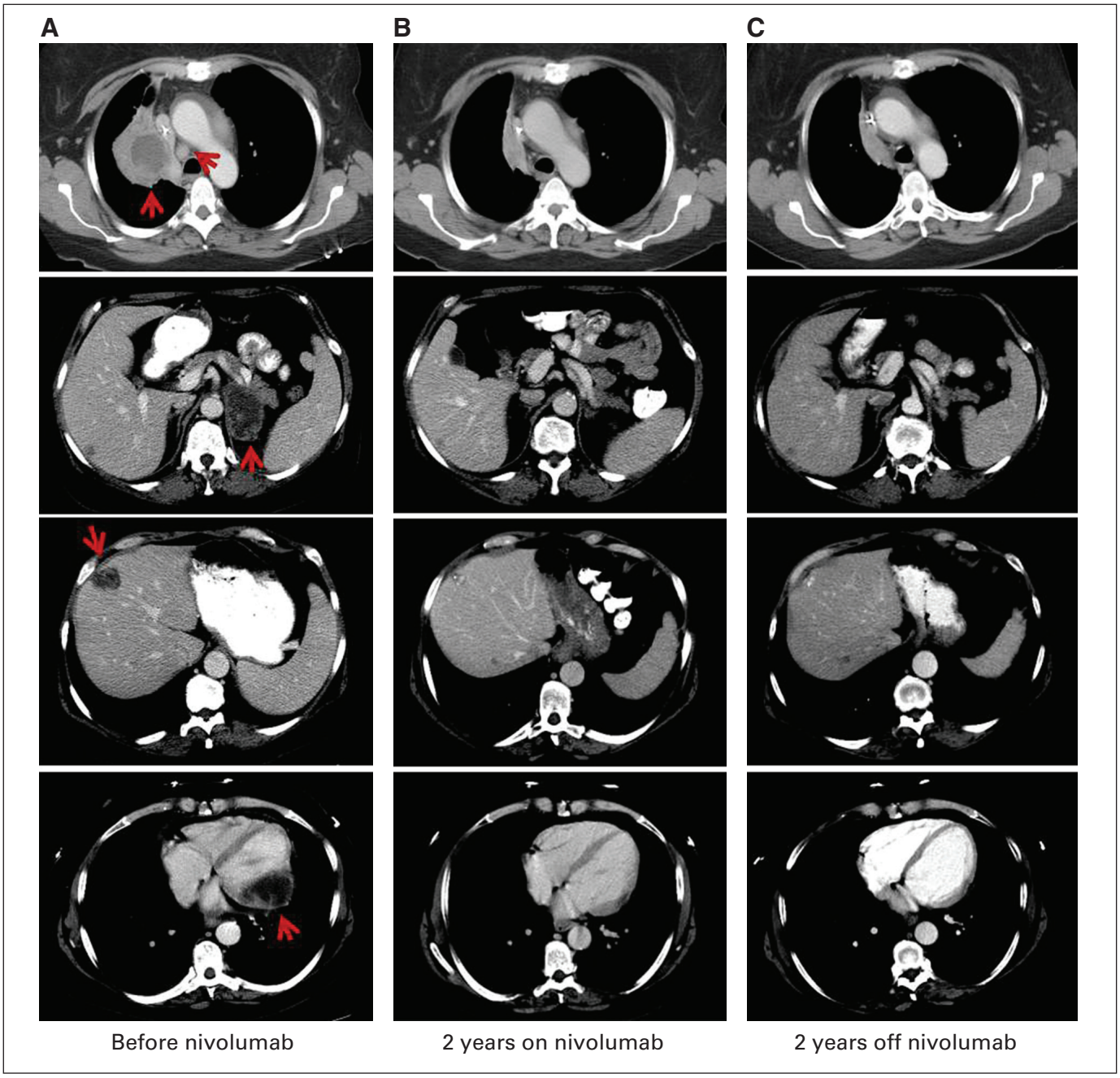

Fig 2. Partial response of patient with metastatic squamous non–small-cell lung cancer (NSCLC) treated with nivolumab, with sustained response after drug discontinuation. Female former smoker age 57 years had widely metastatic chemotherapy-refractory squamous NSCLC after four lines of systemic therapy for stage IV disease. She received 10-mg/kg dose of nivolumab every 2 weeks and achieved partial response after 16 weeks of treatment (two cycles). Response was sustained through 96-week course of nivolumab and, as of September 2014, was ongoing 50 months after initiation of nivolumab treatment and 26 months after drug discontinuation. Computer tomography imaging shows NSCLC metastases (A) before nivolumab, (B) after 2 years with nivolumab, and (C) 2 years after stopping nivolumab therapy, involving lung and mediastinal lymph node (upper row), adrenal gland (second row), liver (third row), and myocardium (bottom row). Arrows indicate locations of metastatic disease.

and/or hormone replacement. Three treatment-related deaths occurred among patients with NSCLC, all associated with pneumonitis, including one that occurred after the date of the last safety analysis. It should be noted that two of the fatal cases occurred early in the trial, before pneumonitis was recognized as a toxicity of treatment with nivolumab. Currently, guidelines are in place to facilitate early identification and management of pneumonitis.[37] For grade 1 to 2 pneumonitis, nivolumab therapy is delayed, with administration of steroids for grade 2 pneumonitis. In select cases, rechallenge with nivolumab can be considered after resolution of pneumonitis. For grade 3 to 4 pneumonitis, nivolumab therapy is discontinued, with administration of steroids and additional immune suppressive agents as needed.

On the basis of the encouraging results seen in this large phase I trial, phase III clinical trials are further evaluating nivolumab in

Table 3. ORRs by Baseline Characteristic Subgroups*

Subgroup	ORR†		
	No. of Patients	%	95% CI
Age, years			
< 70	15 of 90	16.7	9.6 to 26.0
≥ 70	7 of 39	17.9	7.5 to 33.5
Sex			
Male	13 of 79	16.5	9.1 to 26.5
Female	9 of 50	18.0	8.6 to 31.4
ECOG performance status[17]			
0	3 of 27	11.1	2.4 to 29.2
1-2‡	19 of 102	18.6	11.6 to 27.6
Tumor cell histology			
Squamous	9 of 54	16.7	7.9 to 29.3
Nonsquamous	13 of 74	17.6	9.7 to 28.2
No. of prior therapies			
1-2	7 of 59	11.9	4.9 to 22.9
≥ 3	15 of 70	21.4	12.5 to 32.9
Prior TKI therapy			
Yes	4 of 36	11.1	3.1 to 26.1
No	18 of 93	19.4	11.9 to 28.9
EGFR tumor status			
Mutant	2 of 12	16.7	2.1 to 48.4
Wild type	11 of 56	19.6	10.2 to 32.4
Unknown	9 of 61	14.8	7.0 to 26.2
KRAS tumor status			
Mutant	3 of 21	14.3	3.0 to 36.3
Wild type	9 of 36	25.0	12.1 to 42.2
Unknown	10 of 72	13.9	6.9 to 24.1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
*September 2013 data analysis.
†Percentage of patients with confirmed complete or partial responses compared with total No. of treated patients. CIs were calculated using Clopper-Pearson method. Individual patient responses were adjudicated per RECIST (version 1.0).
‡Only two patients had ECOG performance status of 2.

Table 4. Treatment-Related Select AEs Occurring in All Treated Patients in NSCLC Population*

Select AE	All Patients (N = 129)			
	Any Grade†		Grades 3 to 4	
	No.	%	No.	%
Any AE	53	41.1	6	4.7
Skin	20	15.5	0	0
GI	15	11.6	1	0.8
Pulmonary	9‡§	7.0§	3‡	2.3
Endocrinopathies	8	6.2	0	0
Hepatic	6	4.7	1	0.8
Infusion reaction	5	3.9	1	0.8
Renal	4	3.1	0	0

Abbreviations: AE, adverse event; NSCLC, non–small-cell cancer.
*Select AEs were those requiring more frequent monitoring or intervention with immune suppression or hormone replacement, based on prespecified list of Medical Dictionary for Regulatory Activities terms.[16] March 2013 data analysis.
†Grades 1 to 5.
‡Eight patients had pneumonitis (grades 1 to 2, n = 5; grades 3 to 4, n = 3), and one patient had grade 2 interstitial lung disease.
§Two additional patients had treatment-related grade 2 pneumonitis, which occurred before date of safety analysis, but they were not included, because these data were not available until after this analysis. Third patient had treatment-related grade 5 pneumonitis (detailed in Data Supplement) but was not included because event occurred after date of safety analysis.

patients with NSCLC. The dose of nivolumab 3 mg/kg administered intravenously every 2 weeks was chosen for these phase III trials based on pharmacokinetic exposure, safety, and efficacy data from all patients enrolled onto this study. Two phase III clinical trials comparing standard-of-care docetaxel with nivolumab in patients with previously treated advanced NSCLC completed accrual in late 2013. One trial enrolled patients with nonsquamous NSCLC,[38] whereas the other enrolled patients with squamous NSCLC[39]; both are powered to detect a difference in OS. In each of these trials, secondary end points include OS and ORR by PD-L1 tumor status. Another phase III trial was recently initiated, comparing standard first-line platinum-based doublet chemotherapy with nivolumab in patients with treatment-naive advanced PD-L1–positive NSCLC. This trial is supported by results in a PD-L1–positive NSCLC subset from an ongoing phase I trial evaluating nivolumab as first-line therapy for advanced NSCLC.[40,41]

Additional phase I, II, and III clinical trials are currently evaluating other anti–PD-1 or anti–PD-L1 antibodies and have shown encouragingly consistent activity in patients with advanced NSCLC.[36,42-46] Efforts are now focusing on evaluating potential predictive biomarkers, such as tumor expression of PD-L1, to select populations most likely to benefit from antibodies targeting the PD-1 axis. Clinical trials evaluating combinations of nivolumab and other PD-1 axis inhibitors with chemotherapy, targeted therapy, epigenetic therapy, and other immunotherapies are also underway or being planned and hold promise for fully realizing the potential of immunotherapy in NSCLC.

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

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Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

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